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Airway and Lung Remodelling in Chronic Pulmonary Obstructive Disease: A Role for Muscarinic Receptor Antagonists?

Michael Roth

ABSTRACT

Lung tissue remodelling in chronic inflammatory lung diseases has long been regarded as a follow-up event to inflammation. Recent studies have indicated that, although airway and lung tissue remodelling is often independent of inflammation, it precedes or causes inflammation. None of the available therapies has a significant effect on airway and lung tissue remodelling in asthma, bronchiectasis, fibrosis and chronic obstructive pulmonary disease (COPD). The goal of stopping or reversing lung tissue remodelling is difficult, as the term summarizes the net effect of independent events, including (1) cell proliferation, (2) cell volume increase, (3) cell migration, (4) modified deposition and metabolism of specific extracellular matrix components, and (5) local action of infiltrated inflammatory cells. The extracellular matrix of the lung has a very high turnover, and thus small changes may accumulate to significant structural pathologies, which seem to be irreversible. The most important question is ‘why are pathological changes of the lung structure irreversible and resistant to drugs?’ Many drugs have the potential to reduce remodelling mechanisms in vitro but fail in clinical trials. New evidence suggests that muscarinic receptor inhibitors have the potential to improve lung function through modifying tissue remodelling. However, the role of muscarinic receptors in lung remodelling, especially their supportive role for other remodelling driving factors, needs to be further investigated. The focus of this review is the role of muscarinic receptors in lung tissue remodelling as it has been reported in the human lung.

Pharmacological Approaches to the Management of Binge Eating Disorder

Kimberly A. Brownley, Christine M. Peat, Maria La Via, Cynthia M. Bulik

ABSTRACT

In the USA, binge eating disorder (BED) is the most common eating disorder, with a lifetime prevalence of ~3.5 % in adult women, 2.0 % in adult men, and 1.6 % in adolescents. BED is characterized by frequent episodes of binge eating that are accompanied by a sense of loss of control over eating and result in marked psychological distress. BED is highly co-morbid with obesity and with depression and other psychiatric conditions, and it is associated with substantial role impairment. Currently, there are no US FDA-approved pharmacological treatments for BED. Animal and human studies implicate underlying dysregulation in dopamine, opioid, acetylcholine, and serotonin neurocircuitry within brain reward regions in the pathogenesis and maintenance of BED. To date, the efficacy of various agents that target these and other neurotransmitter systems involved in motivated feeding behavior, mood regulation, and impulse control have been investigated in the treatment of BED. Several antidepressant and anticonvulsant agents have demonstrated efficacy in reducing binge eating frequency, but only in limited cases have these effects resulted in patients achieving abstinence, which is the primary goal of treatment; they also range from less (fluvoxamine) to more (topiramate) effective in achieving weight loss that is both clinically meaningful and significantly greater than placebo. Collectively, the literature on pharmacological treatment approaches to BED is limited in that very few agents have been studied in multiple, confirmatory trials with adequate follow up, and almost none have been evaluated in large patient samples that are diverse with respect to age, sex, and ethnicity. In addition, prior trials have not adequately addressed, through study design, the high placebo response commonly observed in this patient population. Several novel agents are in various phases of testing, and recent animal studies focusing on glutamate-signaling circuits linking the amygdala to the lateral hypothalamus offer new avenues for exploration and potential therapeutic development.
SGLT2 inhibitors for the Treatment of Type 2 Diabetes Mellitus

André J. Scheen

ABSTRACT

Inhibitors of sodium–glucose co-transporter type 2 (SGLT2) are proposed as a novel approach for the management of type 2 diabetes mellitus (T2DM). Several compounds are already available in many countries (dapagliflozin, canagliflozin, empagliflozin and ipragliflozin) and some others are in a late phase of development. The available SGLT2 inhibitors share similar pharmacokinetic characteristics, with a rapid oral absorption, a long elimination half-life allowing once-daily administration, an extensive hepatic metabolism mainly via glucuronidation to inactive metabolites, the absence of clinically relevant drug–drug interactions and a low renal elimination as parent drug. SGLT2 co-transporters are responsible for reabsorption of most (90 %) of the glucose filtered by the kidneys. The pharmacological inhibition of SGLT2 co-transporters reduces hyperglycaemia by decreasing renal glucose threshold and thereby increasing urinary glucose excretion. The amount of glucose excreted in the urine depends on both the level of hyperglycaemia and the glomerular filtration rate. Results of numerous placebo-controlled randomised clinical trials of 12–104 weeks duration have shown significant reductions in glycated haemoglobin (HbA1c), resulting in a significant increase in the proportion of patients reaching HbA1c targets, and a significant lowering of fasting plasma glucose when SGLT2 inhibitors were administered as monotherapy or in addition to other glucose-lowering therapies including insulin in patients with T2DM. In head-to-head trials of up to 2 years, SGLT2 inhibitors exerted similar glucose-lowering activity to metformin, sulphonylureas or sitagliptin. The durability of the glucose-lowering effect of SGLT2 inhibitors appears to be better; however, this remains to be more extensively investigated. The risk of hypoglycaemia was much lower with SGLT2 inhibitors than with sulphonylureas and was similarly low as that reported with metformin, pioglitazone or sitagliptin. Increased renal glucose elimination also assists weight loss and could help to reduce blood pressure. Both effects were very consistent across the trials and they represent some advantages for SGLT2 inhibitors when compared with other oral glucose-lowering agents. The pharmacodynamic response to SGLT2 inhibitors declines with increasing severity of renal impairment, and prescribing information for each SGLT2 inhibitor should be consulted regarding dosage adjustments or restrictions in moderate to severe renal dysfunction. Caution is also recommended in the elderly population because of a higher risk of renal impairment, orthostatic hypotension and dehydration, even if the absence of hypoglycaemia represents an obvious advantage in this population. The overall effect of SGLT2 inhibitors on the risk of cardiovascular disease is unknown and will be evaluated in several ongoing prospective placebo-controlled trials with cardiovascular outcomes. The impact of SGLT2 inhibitors on renal function and their potential to influence the course of diabetic nephropathy also deserve more attention. SGLT2 inhibitors are generally well-tolerated. The most frequently reported adverse events are female genital mycotic infections, while urinary tract infections are less commonly observed and generally benign. In conclusion, with their unique mechanism of action that is independent of insulin secretion and action, SGLT2 inhibitors are a useful addition to the therapeutic options available for the management of T2DM at any stage in the natural history of the disease. Although SGLT2 inhibitors have already been extensively investigated, further studies should even better delineate the best place of these new glucose-lowering agents in the already rich armamentarium for the management of T2DM.
Umeclidinium/Vilanterol: A Review of Its Use as Maintenance Therapy in Adults with Chronic Obstructive Pulmonary Disease
Hannah A. Blair, Emma D. Deeks

ABSTRACT
Umeclidinium/vilanterol (Anoro® Ellipta™; Laventair™) is an inhaled fixed-dose combination of a long-acting muscarinic receptor antagonist and a long-acting β2-adrenoceptor agonist. It is available in several countries, including Japan, the USA, Canada and those of the EU, where it is indicated for oral inhalation in adults with chronic obstructive pulmonary disease (COPD). Umeclidinium/vilanterol is administered once daily using the Ellipta™ multi-dose dry powder inhaler, which is regarded as easy to use. Umeclidinium/vilanterol (62.5/25 µg once daily, equivalent to a delivered dose of 55/22 µg once daily) was effective and well tolerated in adult patients with COPD participating in large, multicentre trials of up to 24 weeks’ duration. Umeclidinium/vilanterol improved pulmonary function to a significantly greater extent than placebo and each of the individual components. Moreover,umeclidinium/vilanterol was significantly more effective than once-daily tiotropium monotherapy and a twice-daily fixed combination of salmeterol/fluticasone propionate at improving pulmonary function. Umeclidinium/vilanterol also had beneficial effects on dyspnoea, use of rescue medication, exacerbations, health-related quality of life and, in one study, exercises endurance. Umeclidinium/vilanterol is generally well tolerated in patients with COPD, with the most common adverse events in clinical trials being headache and nasopharyngitis. Umeclidinium/vilanterol was not associated with a clinically relevant increased risk of cardiovascular adverse events in patients with COPD, when data from several clinical trials were pooled. Thus, inhaled umeclidinium/vilanterol extends the treatment options currently available for the maintenance treatment of adults with COPD and has the convenience of once-daily administration.

Alectinib: A Review of Its Use in Advanced ALK-Rearranged Non-Small Cell Lung Cancer
Kate McKeage

ABSTRACT
Alectinib (Alecensa®) is a second-generation, orally active, potent and highly selective inhibitor of anaplastic lymphoma kinase (ALK). Alectinib is approved for the treatment of ALK fusion-gene positive, unresectable, advanced or recurrent non-small cell lung cancer (NSCLC) in Japan, where it has been given orphan drug designation. Approval was based on a phase 1–2 study in ALK inhibitor-naive patients with ALK-rearranged advanced NSCLC who received twice-daily alectinib 300 mg. In the phase 2 portion, 93.5 % of patients achieved an objective response. Treatment response was rapid, with a partial response achieved in two-thirds of patients within 3 weeks (cycle 1). Patient follow-up is ongoing, and after approximately 2 years, 19.6 % of patients had achieved a complete response, and the 2-year progression-free survival rate is 76 %. During treatment with alectinib (median follow-up approximately 8 months), there was no progression of CNS lesions among patients with known CNS metastases at baseline (although prior radiation therapy may have confounded results). In preclinical models, alectinib was active against most ALK fusion-gene mutations related to crizotinib resistance, and preliminary results from clinical trials indicate efficacy in crizotinib-refractory NSCLC. Alectinib was generally well tolerated in clinical trials, and there were no treatment-related grade 4 adverse events or deaths. The most common grade 3 treatment-related adverse events were decreased neutrophil counts and increased creatinine phosphokinase. While more data are needed to confirm the efficacy of alectinib and to evaluate its activity in crizotinib-resistant disease, the drug provides a very promising option for the treatment of ALK-rearranged advanced NSCLC.
Delamanid: A Review of Its Use in Patients with Multidrug-Resistant Tuberculosis
Hannah A. Blair, Lesley J. Scott

ABSTRACT
Delamanid (Deltyba®), a nitroimidazo-oxazole derivative, is a new anti-tuberculosis (TB) drug which exhibits potent in vitro and in vivo antitubercular activity against drug-susceptible and -resistant strains of Mycobacterium tuberculosis. It is approved in several countries, including Japan and those of the EU, for use as part of an appropriate combination regimen in adults with multidrug-resistant tuberculosis (MDR-TB) when an effective treatment regimen cannot otherwise be composed due to resistance or tolerability. In a robust phase II trial in adult patients with MDR-TB, oral delamanid 100 mg twice daily for 2 months plus an optimized background regimen improved sputum culture conversion rates to a significantly greater extent than placebo. In a 6-month extension study, long-term (≤8 months) treatment with delamanid was associated with a higher incidence of favourable outcomes (i.e. cured or completed all treatment) than short-term (≤2 months) treatment, with an accompanying reduction in unfavourable outcomes as defined by the WHO (i.e. pre-specified proportion of TB-positive sputum cultures, death or treatment discontinuation for ≥2 months without medical approval). Delamanid was not associated with clinically relevant drug-drug interactions, including with antiretroviral drugs and those commonly used in treating TB. Delamanid was generally well tolerated in patients with MDR-TB, with gastrointestinal adverse events and insomnia reported most commonly. Although the incidence of QT interval prolongation was higher with delamanid-based therapy, it was not associated with clinical symptoms such as syncope and arrhythmia. In conclusion, delamanid is a useful addition to the treatment options currently available for patients with MDR-TB.

Dextromethorphan/Quinidine: A Review of Its Use in Adults with Pseudobulbar Affect
Lily P. H. Yang, Emma D. Deeks

ABSTRACT
Fixed-dose dextromethorphan/quinidine capsules (Nuedexta®) utilize quinidine to inhibit the metabolism of dextromethorphan, enabling high plasma dextromethorphan concentrations to be reached without using a larger dose of the drug. The drug combination is the first treatment to be approved for pseudobulbar affect (PBA), a condition of contextually inappropriate/exaggerated emotional expression that often occurs in adults with neurological damage conditions, such as amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), stroke, traumatic brain injury, Alzheimer’s disease or Parkinson’s disease. Dextromethorphan/quinidine at the recommended dosages of 20/10 or 30/10 mg twice daily reduced the rate of PBA episodes and improved PBA severity in a 12-week, double-blind, placebo-controlled trial in adults with ALS or MS (STAR), with further improvements in the severity of the condition observed in a 12-week open-label extension phase. Dextromethorphan/quinidine 20/10 mg twice daily also improved PBA secondary to dementia in a cohort of a 12-week noncomparative trial (PRISM II). The drug combination was generally well tolerated in these studies, with no particular safety or tolerability concerns. Although longer-term efficacy and tolerability data for dextromethorphan/quinidine 20/10 or 30/10 mg twice daily would be beneficial, current evidence indicates that it is a useful option in the treatment of adults with PBA.
Ferric Carboxymaltose: A Review of Its Use in Iron Deficiency

Gillian M. Keating

ABSTRACT

Ferric carboxymaltose (Ferinject®, Injectafer®) is an intravenous iron preparation approved in numerous countries for the treatment of iron deficiency. A single high dose of ferric carboxymaltose (up to 750 mg of iron in the US and 1,000 mg of iron in the EU) can be infused in a short time frame (15 min). Consequently, fewer doses of ferric carboxymaltose may be needed to replenish iron stores compared with some other intravenous iron preparations (e.g., iron sucrose). Ferric carboxymaltose improved self-reported patient global assessment, New York Heart Association functional class and exercise capacity in patients with chronic heart failure and iron deficiency in two randomized, placebo-controlled trials (FAIR-HF and CONFIRM-HF). In other randomized controlled trials, ferric carboxymaltose replenished iron stores and corrected anaemia in various populations with iron-deficiency anaemia, including patients with chronic kidney disease, inflammatory bowel disease or heavy uterine bleeding, postpartum iron-deficiency anaemia and perioperative anaemia. Intravenous ferric carboxymaltose was generally well tolerated, with a low risk of hypersensitivity reactions. It was generally better tolerated than oral ferrous sulfate, mainly reflecting a lower incidence of gastrointestinal adverse effects. The most common laboratory abnormality seen in ferric carboxymaltose recipients was transient, asymptomatic hypophosphataemia. The higher acquisition cost of ferric carboxymaltose appeared to be offset by lower costs for other items, with the potential for cost savings. In conclusion, ferric carboxymaltose is an important option for the treatment of iron deficiency.

Nintedanib: First Global Approval

Paul L. McCormack

ABSTRACT

Nintedanib (Ofev®) is an orally available, small, multiple receptor tyrosine kinase inhibitor developed by Boehringer Ingelheim for the treatment of idiopathic pulmonary fibrosis (IPF) and cancer. Nintedanib received its first global approval in the US in October 2014 for the treatment of IPF. Nintedanib has received a positive opinion from the European Medicines Agency’s Committee for Medicinal Products for Human Use for the treatment of IPF, and for the second-line treatment in combination with docetaxel of locally advanced, metastatic or locally recurrent non-small cell lung cancer of adenocarcinoma tumour histology. Phase 3 development programmes are also underway for colorectal cancer and ovarian cancer. Phase 2 investigation is being conducted for a variety of other solid tumours, including hepatocellular carcinoma, mesothelioma, prostate cancer, glioblastoma, renal cell carcinoma and endometrial carcinoma. This article summarizes the milestones in the development of nintedanib leading to this first approval for IPF.
Targeted Therapy for Chronic Lymphocytic Leukemia: Current Status and Future Directions
Jon E. Arnason, Jennifer R. Brown

ABSTRACT
The majority of patients with chronic lymphocytic leukemia (CLL) respond to chemo-immunotherapy. However, long-term remission remains elusive and the majority of patients will die of complications related to CLL. In this review we discuss the recent developments in targeted therapy for CLL. Targeted therapy has evolved beyond the cell surface targeting of CD20 with rituximab. Our review focuses on the evolution of antibody therapy in CLL, strategies to target effector T cells to the tumor, inhibition of the B-cell receptor signaling pathway, and finally targeting the mediators of apoptosis. With our improved understanding of the biology of CLL, the evolution of targeted therapy has resulted in significant clinical responses in patients who are refractory to traditional treatment options and holds the potential for a future where we can manage this disease without chemotherapy.

Catechol-O-Methyltransferase Inhibitors in Parkinson’s disease
Thomas Müller

ABSTRACT
Inhibitors of catechol-O-methyltransferase (COMT) are commonly used as an adjunct to levodopa in patients with Parkinson’s disease (PD) for the amelioration of wearing-off symptoms. This narrative review aims to discuss the role of COMT inhibitors on peripheral levodopa metabolism and continuous brain delivery of levodopa, and to describe their metabolic properties. Oral application of levodopa formulations with a dopa decarboxylase inhibitor (DDI) results in fluctuating levodopa plasma concentrations, predominantly due to the short half-life of levodopa and its slowing of gastric emptying. Following transport across the blood–brain barrier and its metabolic conversion to dopamine, these peripheral ‘ups and downs’ of levodopa are reflected in fluctuating dopamine levels in the synaptic cleft between presynaptic and postsynaptic dopaminergic neurons of the nigrostriatal system. As a result, pulsatile postsynaptic dopaminergic stimulation takes place and results in the occurrence of motor complications, such as wearing-off and dyskinesia. More continuous plasma behaviour was observed after the combination of levodopa/DDI formulations with COMT inhibitors. These compounds also weaken a levodopa/DDI-related homocysteine increase, as biomarker for an impaired methylation capacity, which is involved in an elevated oxidative stress exposure. These findings favour the concept of chronic levodopa/DDI application with concomitant inhibition of COMT and monoamine oxidase, since deamination of dopamine via this enzyme also generates free radicals. This triple combination is suggested as standard levodopa application in patients with PD who need levodopa, if they will tolerate it.
Alipogene Tiparvovec: A Review of Its Use in Adults with Familial Lipoprotein Lipase Deficiency
Lesley J. Scott

ABSTRACT
Alipogene tiparvovec (Glybera®; AMT-011, AAV1-LPLS447X) is an adeno-associated virus serotype 1-based gene therapy for adult patients with familial lipoprotein lipase (LPL) deficiency (LPLD) and suffering from severe or multiple pancreatitis attacks despite dietary fat restrictions. It is administered as a one-time series of intramuscular injections in the legs. LPLD, a rare autosomal recessive disorder, results in hyperchylomicronaemia and severe hypertriglyceridaemia, which in turn, are associated with an increased risk of clinical complications, the most debilitating of which is recurrent severe and potentially life-threatening pancreatitis. In clinical studies (n = 27 patients), one-time administration of alipogene tiparvovec was associated with significant reductions in plasma triglyceride levels during the 12 or 14 week study period post administration. Although triglyceride levels returned to pre-treatment levels within 16–26 weeks after administration, patients had sustained improvements in postprandial chylomicron metabolism, with sustained expression of functional copies of the LPLS477X gene and of biologically active LPL in skeletal muscle. Moreover, after up to 6 years’ follow-up post administration, there were clinically relevant reductions in the incidence of documented pancreatitis and acute abdominal pain events consistent with pancreatitis. Alipogene tiparvovec was generally well tolerated, with most adverse events being localized, transient, mild to moderate injection-site reactions. This article reviews the pharmacology of alipogene tiparvovec and its efficacy and safety in adults with LPLD.

Simeprevir: A Review of Its Use in Patients with Chronic Hepatitis C Virus Infection
Mark Sanford

ABSTRACT
Simeprevir (Olysio™; Galexos™; Sovriad®) is an orally-administered NS3/4A protease inhibitor for use in combined drug regimens against chronic hepatitis C virus (HCV) infection. This article reviews studies relevant to the EU simeprevir label. In proof-of-concept studies, simeprevir had potent antiviral activity against all HCV genotypes, except genotype 3. In trials in patients with chronic HCV genotype 1 infection, week-12 sustained virological response (SVR12) rates in treatment-naïve patients and prior relapers were significantly higher with simeprevir plus peginterferon-a/ribavirin (PR) [79–89 %] than with placebo plus PR (36–62 %). In prior partial/null responders, the SVR12 rate with simeprevir plus PR (54 %) was noninferior to that with telaprevir plus PR (55 %). Simeprevir plus PR was also efficacious in patients with HCV genotype 1/HIV-1 co-infection. In prior null responders without severe liver fibrosis (cohort 1) and treatment-naïve patients with severe liver fibrosis (cohort 2) treated with simeprevir plus sofosbuvir, the SVR12 rate for the two cohorts combined was 92 %. In patients with chronic HCV genotype 4 infection, the SVR12 rates with simeprevir plus PR were 83, 87 and 40 % in treatment-naïve patients, prior relapers and prior null responders, respectively. Grade 3–4 adverse event, serious adverse event and treatment withdrawal rates with simeprevir plus PR were similar to those with placebo plus PR. Skin rashes with simeprevir were mostly mild or moderate; serious photosensitivity reactions occur, but are rare. Simeprevir is efficacious and generally well tolerated in patients with chronic HCV genotypes 1 and 4 infection. Studies of simeprevir in interferon-free regimens and in other subpopulations with HCV infections will be of interest.
Droxidopa: A Review of Its Use in Symptomatic Neurogenic Orthostatic Hypotension
Gillian M. Keating

ABSTRACT
The norepinephrine prodrug droxidopa (NORTHERA™) is approved in the US for the treatment of orthostatic dizziness, lightheadedness, or the ‘feeling that you are about to black out’ in adults with symptomatic neurogenic orthostatic hypotension associated with primary autonomic failure (e.g. Parkinson’s disease, multiple system atrophy or pure autonomic failure), dopamine β-hydroxylase deficiency or nondiabetic autonomic neuropathy. This article reviews the clinical efficacy and tolerability of droxidopa in symptomatic neurogenic orthostatic hypotension, as well as summarizing its pharmacological properties. Oral droxidopa was effective in the shorter-term treatment of patients with symptomatic neurogenic orthostatic hypotension, with improvements seen in symptoms, the impact of symptoms on daily activities and standing systolic blood pressure. More data are needed to confirm the longer-term efficacy of droxidopa. Droxidopa was generally well tolerated, although patients should be monitored for supine hypertension.

Silodosin: A Review of Its Use in the Treatment of the Signs and Symptoms of Benign Prostatic Hyperplasia
Gillian M. Keating

ABSTRACT
Silodosin is a highly selective α1A-adrenoceptor antagonist indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH). Oral silodosin had a rapid onset of effect in men with lower urinary tract symptoms (LUTS) associated with BPH, with improvements seen in voiding and storage symptoms, maximum urinary flow rate and health-related quality of life in well-designed, 12-week trials. Silodosin was noninferior to tamsulosin in terms of improving LUTS associated with BPH. The efficacy of silodosin was maintained in 9-month extension studies and was also seen in a phase IV study conducted in a real-world setting. Silodosin was generally well tolerated and was associated with a low risk of orthostatic hypotension. Abnormal ejaculation was the most commonly reported adverse event, although few patients discontinued treatment with silodosin because of this adverse event. In conclusion, silodosin is a useful option for the treatment of LUTS associated with BPH.

Pirfenidone: A Review of Its Use in Idiopathic Pulmonary Fibrosis
Esther S. Kim, Gillian M. Keating

ABSTRACT
Pirfenidone (Esbriet®) is an orally administered, synthetic, pyridone compound that is approved for the treatment of adults with mild to moderate idiopathic pulmonary fibrosis (IPF) in the EU, and for the treatment of IPF in the USA. This article summarizes pharmacological, efficacy and tolerability data relevant to the use of pirfenidone in these indications. In the randomized, double-blind, placebo-controlled, multinational CAPACITY trials in patients with mild to moderate IPF, a significant reduction in the rate of decline in forced vital capacity (FVC) was seen with pirfenidone versus placebo in study 004 but not in study 006. Pirfenidone also reduced the rate of decline in FVC to a significantly greater extent than placebo in the randomized, double-blind, multinational ASCEND trial in this patient population. In addition, pirfenidone showed a significant treatment effect on the 6-min walking test distance and progression-free survival in the ASCEND trial and in a pooled analysis of the CAPACITY trials. Pirfenidone had a manageable tolerability profile in all three studies. Gastrointestinal and skin-related events (e.g. nausea, rash, photosensitivity reaction), which were the most commonly occurring treatment-emergent adverse events, were generally mild to moderate in severity.
Olaparib: First Global Approval
Emma D. Deeks

ABSTRACT
Olaparib (Lynparza™) is an oral, small molecule, poly (ADP-ribose) polymerase inhibitor being developed by AstraZeneca for the treatment of solid tumours. The primary indication that olaparib is being developed for is BRCA mutation-positive ovarian cancer. A capsule formulation of the drug has received approval for use in this setting in the EU and USA, and a tablet formulation is in global phase III trials (including in the USA, EU, Australia, Brazil, Canada, China, Israel, Japan, Russia and South Korea). In addition, phase III trials in breast, gastric and pancreatic cancer are underway/planned, and phase I/II investigation is being conducted in other malignancies, including prostate cancer, non-small cell lung cancer, Ewing’s sarcoma and advanced cancer. This article summarizes the milestones in the development of olaparib leading to this first approval for ovarian cancer.

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Pre-Exposure Prophylaxis to Prevent HIV Infection: Current Status, Future Opportunities and Challenges
Douglas S. Krakower, Kenneth H. Mayer

ABSTRACT
As the global incidence of HIV exceeds 2 million new infections annually, effective interventions to decrease HIV transmission are needed. Randomized, placebo-controlled studies have demonstrated that daily oral antiretroviral pre-exposure prophylaxis (PrEP) with a fixed-dose combination tablet containing tenofovir disoproxil fumarate and emtricitabine can significantly reduce HIV incidence among diverse at-risk populations. In these studies, the efficacy of PrEP was correlated with levels of adherence. Official guidelines recommend provision of PrEP to people at greatest risk of HIV acquisition, and demonstration projects suggest that high levels of uptake and adherence are possible outside of controlled studies. However, several potential barriers to implementing PrEP remain. These challenges include low awareness and utilization of PrEP by at-risk individuals, uncertainty about adherence in ‘real-world’ settings, the majority of healthcare providers being untrained in PrEP provision, limited data about potential adverse effects from long-term use of tenofovir–emtricitabine, high costs of PrEP medications, and stigma associated with PrEP use and the behaviors that would warrant PrEP. Innovative pharmacologic chemoprophylactic approaches could provide solutions to some of these challenges. Less-than-daily oral dosing regimens and long-acting injectable medications could reduce pill burdens and facilitate adherence, and local delivery of PrEP medications to genital compartments via gels, rings and films may limit systemic drug exposure and potential toxicities. As the portfolio of chemoprophylactic agents and delivery systems expands to meet the diverse sexual health needs and product preferences of individuals who may benefit from PrEP, it is hoped that antiretroviral chemoprophylaxis could become an acceptable, feasible, and highly effective addition to existing HIV prevention strategies.
Tedizolid: A Novel Oxazolidinone with Potent Activity against Multidrug-Resistant Gram-Positive Pathogens

George G. Zhanel, Riley Love, Heather Adam, Alyssa Golden, Sheryl Zelenitsky

ABSTRACT

Tedizolid phosphate is a novel oxazolidinone prodrug (converted to the active form tedizolid by phosphatases in vivo) that has been developed and recently approved (June 2014) by the United States FDA for the treatment of acute bacterial skin and skin structure infections (ABSSSIs) caused by susceptible Gram-positive pathogens, including methicillin-resistant Staphylococcus aureus (MRSA). Tedizolid is an oxazolidinone, but differs from other oxazolidinones by possessing a modified side chain at the C-5 position of the oxazolidinone nucleus which confers activity against certain linezolid-resistant pathogens and has an optimized C- and D-ring system that improves potency through additional binding site interactions. The mechanism of action of tedizolid is similar to other oxazolidinones and occurs through inhibition of bacterial protein synthesis by binding to 23S ribosomal RNA (rRNA) of the 50S subunit of the ribosome. As with other oxazolidinones, the spontaneous frequency of resistance development to tedizolid is low. Tedizolid is four- to eightfold more potent in vivo than linezolid against all species of staphylococci, enterococci, and streptococci, including drug-resistant phenotypes such as MRSA and vancomycin-resistant enterococci (VRE) and linezolid-resistant phenotypes. Importantly, tedizolid demonstrates activity against linezolid-resistant bacterial strains harboring the horizontally transmissible cfr gene, in the absence of certain ribosomal mutations conferring reduced oxazolidinone susceptibility. With its half-life of approximately 12 h, tedizolid is dosed once daily. It demonstrates linear pharmacokinetics, has a high oral bioavailability of approximately 90%, and is primarily excreted by the liver as an inactive, non-circulating sulphate conjugate. Tedizolid does not require dosage adjustment in patients with any degree of renal dysfunction or hepatic dysfunction. Studies in animals have demonstrated that the pharmacodynamic parameter most closely associated with the efficacy of tedizolid is fAUC0–24h/MIC. In non-neutropenic animals, a dose-response enhancement was observed with tedizolid and lower exposures were required compared to neutropenic cohorts. Two Phase III clinical trials have demonstrated non-inferiority of a once-daily tedizolid 200 mg dose for 6–10 days versus twice-daily 600 mg linezolid for the treatment of ABSSSIs. Both trials used the primary endpoint of early clinical response at 48–72 h; however, one trial compared oral formulations while the other initiated therapy with the parenteral formulation and allowed oral sequential therapy following initial clinical response. Throughout its development, tedizolid has demonstrated that it is well tolerated and animal studies have shown a lower propensity for neuropathies with long-term use than its predecessor linezolid. Data from the two completed Phase III clinical trials demonstrated that the studied tedizolid regimen (200 mg once daily for 6 days) had significantly less impact on hematologic parameters as well as significantly less gastrointestinal treatment-emergent adverse effects (TEAEs) than its comparator linezolid. As with linezolid, tedizolid is a weak, reversible MAO inhibitor; however, a murine head twitch model validated to assess serotonergic activity reported no increase in the number of head twitches with tedizolid even at doses that exceeded the Cmax in humans by up to 25-fold. Tyramine and pseudoephedrine challenge studies in humans have also reported no meaningful MAO-related interactions with tedizolid. With its enhanced in vitro activity against a broad-spectrum of Gram-positive aerobic bacteria, convenient once-daily dosing, a short 6-day course of therapy, availability of both oral and intravenous routes of administration, and an adverse effect profile that appears to be more favorable than linezolid, tedizolid is an attractive agent for use in both the hospital and community settings. Tedizolid is currently undergoing additional Phase III clinical trials for the treatment of hospital-acquired bacterial pneumonia (HABP) and ventilated nosocomial pneumonia (VNP).
ABSTRACT

Background: While a variety of intervention options have been described for pemphigus vulgaris, the optimal treatment strategy has not been established.

Objectives: The objective of this systematic review is to assess the literature on the efficacy and safety of interventions for the treatment of pemphigus vulgaris.

Data Sources: Five electronic databases were searched, including The Cochrane Skin Group’s Specialized Register, The Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, MEDLINE and Latin American and Caribbean Health science Information database (LILACS). Five trial registers as well as reference lists of included RCTs were also searched.

Study Eligibility Criteria: Any published randomised controlled trial (RCT) on intervention for pemphigus vulgaris was included, provided the diagnosis of pemphigus vulgaris was confirmed with appropriate clinical features, histopathology and immunofluorescence studies. Studies which included forms of pemphigus other than pemphigus vulgaris were excluded.

Interventions: Altogether 18 RCTs were identified including 16 distinct interventions.

Study Appraisal and Synthesis Methods: Included studies were assessed for patient selection, methods of randomisation, blinding, follow-up and selective reporting.

Results: Current evidence is incomplete and inconclusive. The interventions which appear promising, but will require further evaluation include adjuvant mycophenolate mofetil (MMF), azathioprine, intravenous immunoglobulins (IVIG), sulfasalazine and pentoxifylline, infliximab, epidermal growth factor and pimecrolimus. Interventions with inconclusive evidence include high (120–180 mg) versus low (45–60 mg) prednisone dosage, pulsed dexamethasone, cyclophosphamide, dexamethasone–cyclophosphamide pulse therapy (DCP), cyclosporine, dapsone, etanercept, acyclovir and tacrolimus.

Limitations: Our review is limited by the small number of high-quality RCTs and variety of outcome measures, precluding the performing of a meta-analysis.
Obinutuzumab: A Review of Its Use in Patients with Chronic Lymphocytic Leukaemia

Sheridan M. Hoy

ABSTRACT

Obinutuzumab (Gazyva®; Gazyvaro®) is an intravenously administered, glycoengineered, humanized, type II, anti-CD20 monoclonal antibody of the IgG1 subclass. It is available in the EU and the USA as combination therapy with oral chlorambucil in adults with previously untreated chronic lymphocytic leukaemia (CLL). In a multinational phase III study in this patient population, obinutuzumab plus chlorambucil significantly prolonged progression-free survival compared with oral chlorambucil alone and intravenous rituximab plus oral chlorambucil. Significant advantages with obinutuzumab plus chlorambucil over chlorambucil alone and rituximab plus chlorambucil were also observed in event-free survival, the time to a new anti-leukaemia treatment and overall response. The overall survival benefit with obinutuzumab plus chlorambucil is as yet unclear, although the most recent analysis suggests a benefit over chlorambucil alone. In the phase III study, obinutuzumab plus chlorambucil had a manageable tolerability profile in accordance with what would be expected for an anti-CD20 antibody. Neutropenia and infusion-related reactions were the most frequently reported grade 3 or higher treatment-emergent adverse events. In the majority of patients, infusion-related reactions were mild to moderate in severity and occurred predominantly during the first infusion and were managed by slowing or temporarily halting the infusion. Thus, current evidence suggests that obinutuzumab plus chlorambucil is a welcome addition to the treatment options currently available for adults with previously untreated CLL and is recommended by the National Comprehensive Cancer Network guidelines as the preferred first option for some, including those with comorbidities.

Ruxolitinib: A Review of Its Use in Patients with Myelofibrosis

Greg L. Plosker

ABSTRACT

Ruxolitinib (Jakavi®, Jakafi®) is an orally administered inhibitor of Janus kinases (JAK) 1 and 2 used in the management of patients with myelofibrosis. Clinical trials with ruxolitinib, notably the phase III COMFORT-I and -II studies and their extensions, have demonstrated marked and durable clinical benefits in terms of reductions in splenomegaly and disease-related symptoms in patients with intermediate-2 or high-risk myelofibrosis. Ruxolitinib was also associated with improvements in health-related quality of life and functioning. Despite the crossover of patients in control groups to ruxolitinib, results of the COMFORT studies and their extensions indicate a survival advantage for patients randomized to ruxolitinib. The beneficial effects of ruxolitinib were observed across subgroups of myelofibrosis patients, including those not harbouring the JAK2V617F mutation. Improvements in splenomegaly and disease-related symptoms were also observed in a trial in Japanese/Asian patients with myelofibrosis and in myelofibrosis patients with a low baseline platelet count. Dose-related anaemia and thrombocytopenia were common in clinical trials with ruxolitinib, but rarely led to discontinuation of therapy and were managed with dosage modifications and/or transfusions of packed red blood cells. In addition to the USA and EU, ruxolitinib is now approved in a number of other countries, including Japan, and remains the only approved drug for the treatment of myelofibrosis, although various other agents are undergoing investigation. Appropriate monitoring and dosage titration are important to achieve optimal clinical benefits of ruxolitinib. Further research, including studies evaluating ruxolitinib-based combination therapy, may also help to optimise treatment.
Tacrolimus prolonged release (Ensvarsu®; henceforth referred to as tacrolimus PR) is a new, once-daily, prolonged-release tacrolimus formulation, utilizing a drug delivery technology designed to enhance the bioavailability of drugs with low water solubility by creating a solid solution of the drug. This article reviews the pharmacological properties of tacrolimus PR and its clinical efficacy and tolerability in adult kidney and liver transplant recipients. In phase III trials, tacrolimus PR was noninferior to tacrolimus immediate release (IR; twice daily) in both de novo and stable, previously treated kidney transplant recipients, and had a similar tolerability profile. Preliminary efficacy data from phase II trials in de novo and stable, previously treated liver transplant recipients imply that tacrolimus PR is effective in these patient groups; however, more data would be of interest. Pharmacokinetic analyses demonstrated that tacrolimus PR is associated with a higher bioavailability, reduced peak-trough concentration fluctuation ratio, lower mean values for percentage degree of fluctuation and percentage degree of swing, and a longer time to maximum concentration than tacrolimus IR. Tacrolimus PR is a promising addition to the treatment options available for kidney and liver transplant recipients.

Blinatumomab: First Global Approval
Mark Sanford

ABSTRACT
Blinatumomab (BLINCYTO™) is a novel, bispecific T-cell engaging antibody that binds cluster of differentiation (CD) 19 antigens on blast cells while also binding and activating the CD3/T cell receptor complex, causing cell lysis. The antibody is being developed by Amgen as a treatment for haematological cancers that originate from B cell lines. Blinatumomab was approved by the US FDA in December 2014 for the treatment of adults with Philadelphia chromosome (Ph)-negative relapsed/refractory B-cell precursor acute lymphoblastic leukaemia (BCP-ALL). It is awaiting approval for this indication in the EU and is in phase III development in various countries. This article summarizes the milestones in the development of blinatumomab leading to its first approval for the treatment of Ph-negative BCP-ALL.

Secukinumab: First Global Approval
Mark Sanford, Kate McKeage

ABSTRACT
Secukinumab (Cosentyx™) is a fully human monoclonal antibody against interleukin-17A, formulated for intravenous and subcutaneous administration. It received its first global approval in Japan on 26 December 2014 for the treatment of psoriasis and psoriatic arthritis in adults who are not adequately responding to systemic therapies (except for biologic agents). In the USA and the EU, secukinumab was approved in early 2015 for the treatment of patients with moderate-to-severe plaque psoriasis. Secukinumab is also being investigated in patients with ankylosing spondylitis and rheumatoid arthritis. This article summarizes the milestones in the development of secukinumab leading to its first approval for the treatment of adult patients with psoriasis and psoriatic arthritis.
Preventive Analgesia and Novel Strategies for the Prevention of Chronic Post-Surgical Pain

Hance Clarke, Michael Poon, Aliza Weinrib, Rita Katzenelson, Kirsten Wentlandt

ABSTRACT

Chronic post-surgical pain (CPSP) is a serious complication of major surgery that can impair a patient’s quality of life. The development of CPSP is a complex process which involves biologic, psychosocial, and environmental mechanisms that have yet to be fully understood. Currently perioperative pharmacologic interventions aim to suppress and prevent sensitization with the aim of reducing pain and analgesic requirement in acute as well as long-term pain. Despite the detrimental effects of CPSP on patients, the body of literature focused on treatment strategies to reduce CPSP remains limited and continues to be understudied. This article reviews the main pharmacologic candidates for the treatment of CPSP, discusses the future of preventive analgesia, and considers novel strategies to help treat acute post-operative pain and lessen the risk that it becomes chronic. In addition, this article highlights important areas of focus for clinical practice including: multimodal management of CPSP patients, psychological modifiers of the pain experience, and the development of a Transitional Pain Service specifically designed to manage patients at high risk of developing chronic post-surgical pain.

Identification and Management of Alcohol Withdrawal Syndrome

Antonio Mirrijello, Cristina D’Angelo, Anna Ferrulli, Gabriele Vassallo

ABSTRACT

Symptoms of alcohol withdrawal syndrome (AWS) may develop within 6–24 h after the abrupt discontinuation or decrease of alcohol consumption. Symptoms can vary from autonomic hyperactivity and agitation to delirium tremens. The gold-standard treatment for AWS is with benzodiazepines (BZDs). Among the BZDs, different agents (i.e., long-acting or short-acting) and different regimens (front-loading, fixed-dose or symptom-triggered) may be chosen on the basis of patient characteristics. Severe withdrawal could require ICU admission and the use of barbiturates or propofol. Other drugs, such as α2-agonists (clonidine and dexmedetomidine) and β-blockers can be used as adjunctive treatments to control neuroautonomic hyperactivity. Furthermore, neuroleptic agents can help control hallucinations. Finally, other medications for the treatment for AWS have been investigated with promising results. These include carbamazepine, valproate, sodium oxybate, baclofen, gabapentin and topiramate. The usefulness of these agents are discussed.

The Role of Pre-Transplant Induction Regimens and Autologous Stem Cell Transplantation in the Era of Novel Targeted Agents

Francesca Gay, Federica Cavallo, Antonio Palumbo

ABSTRACT

Outcome of patients with multiple myeloma (MM) has greatly improved with the use of autologous stem cell transplantation (ASCT) and new agents, such as immunomodulatory drugs (thalidomide and lenalidomide) and proteasome inhibitors (bortezomib). When compared to conventional chemotherapy, high-dose melphalan with ASCT significantly improved response rates and progression-free survival, while overall survival benefit was not consistent across all trials. ASCT is considered the standard treatment for patients who are younger than 65 years and who do not have limiting comorbidities. New, effective agents have been introduced as part of induction, consolidation and maintenance treatments within ASCT and in combinations with chemotherapy for patients not eligible for ASCT. The remarkable results obtained with these regimens are questioning the role of ASCT for newly diagnosed MM patients. This article aims to delineate the role of ASCT in the era of novel agents based on the results of recent clinical trials.
Clinical Efficacy and Safety of Cilostazol: A Critical Review of the Literature
Kelly C. Rogers, Carrie S. Oliphant, Shannon W. Finks

ABSTRACT

Cilostazol is a unique antiplatelet agent that has been commercially available for over two decades. As a phosphodiesterase III inhibitor, it reversibly inhibits platelet aggregation yet also possesses vasodilatory and antiproliferative properties. It has been widely studied in a variety of disease states, including peripheral arterial disease, cerebrovascular disease, and coronary artery disease with percutaneous coronary intervention. Overall, cilostazol appears to be a promising agent in the management of these disease states with a bleeding profile comparable to placebo; even when combined with other antiplatelet agents, cilostazol does not appear to increase the rate of bleeding. Despite the possible benefit of cilostazol, its use is limited by tolerability as some patients often report drug discontinuation due to headache, diarrhea, dizziness, or increased heart rate. To date, it has been predominantly studied in the Asian population, making it difficult to extrapolate these results to a more diverse patient population. This paper discusses the evolving role of cilostazol in the treatment of vascular diseases.

Posaconazole: A Review of the Gastro-Resistant Tablet and Intravenous Solution in Invasive Fungal Infections
Kate McKeage

ABSTRACT

Posaconazole (Noxafil®) is a triazole antifungal agent with an extended spectrum of antifungal activity. It is approved for the prophylaxis of invasive fungal infections in patients with neutropenia or in haematopoietic stem cell transplant recipients undergoing high-dose immunosuppressive therapy for graft-versus-host disease, and for the treatment of fungal infections. The efficacy and good tolerability of posaconazole oral suspension administered three or four times daily is well established. However, in order to overcome pharmacokinetic limitations associated with the suspension, a new gastro-resistant tablet and intravenous (IV) solution were developed. This article reviews the pharmacokinetic properties of the new posaconazole formulations and briefly summarizes efficacy data relating to the suspension. The pharmacokinetic advantages of the posaconazole gastro-resistant tablet compared with the suspension formulation include less interpatient variability, better systemic availability enabling once-daily administration, and absorption that is unaffected by changes in gastric pH or motility; in addition the tablets may be taken with or without food. The posaconazole tablet achieves higher and more consistent mean plasma concentrations than the suspension and, therefore, it is the preferred option to optimize efficacy in the prophylaxis or treatment of invasive fungal disease. The posaconazole IV solution provides an option for these same indications in patients who are unable to receive oral formulations.
Fluticasone Furoate/Vilanterol: a Review of Its Use in Patients with Asthma

Yahiya Y. Syed

ABSTRACT

Fluticasone furoate/vilanterol (Relvar®) is a once-daily, fixed combination of an inhaled corticosteroid (ICS) and a long-acting β2-adrenoreceptor agonist (LABA), delivered via a dry powder inhaler (Ellipta®). It is approved for the treatment of asthma in the EU and Japan, and is the first once-daily ICS/LABA to be available for this indication. Fluticasone furoate is an enhanced-affinity glucocorticoid receptor agonist, with potent anti-inflammatory activity. Vilanterol produces rapid and prolonged bronchodilation. In phase III trials in adolescents and adults with various levels of asthma uncontrolled on ICS and/or ICS/LABA, fluticasone furoate/vilanterol 100/25 or 200/25 µg once daily (approved dosages in the EU) significantly improved pulmonary function compared with placebo or equivalent dosages of fluticasone furoate alone (in some trials) or fluticasone propionate. In similar trials, fluticasone furoate/vilanterol 100/25 µg once daily was as effective as fluticasone propionate/salmeterol 250/50 µg twice daily in improving pulmonary function and significantly reduced the risk of severe asthma exacerbation relative to fluticasone furoate alone. In clinical trials, fluticasone furoate/vilanterol was generally well tolerated with fewer than 15 % of patients experiencing treatment-related adverse events, the most common of which were oral/oropharyngeal candidiasis, dysphonia, extrasystoles and cough. The tolerability profile of fluticasone furoate/vilanterol was generally similar to that of fluticasone propionate/salmeterol. Thus, fluticasone furoate/vilanterol is an effective and generally well tolerated ICS/LABA option for the treatment of uncontrolled asthma.

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Naloxegol: A Review of Its Use in Patients with Opioid-Induced Constipation

Karly P. Garnock-Jones

ABSTRACT

Oral naloxegol (Movantik™, Moventig®), a peripherally acting μ-opioid receptor antagonist, inhibits opioid binding in μ-opioid receptors in the gastrointestinal tract. This article reviews the pharmacological properties of naloxegol and its clinical efficacy and tolerability in patients with opioid-induced constipation. It demonstrated clinical efficacy and was well tolerated in placebo-controlled trials in patients with non-cancer pain and opioid-induced constipation, including those with an inadequate response to laxatives, and was well tolerated in a long-term safety study. As a PEGylated naloxone derivative, naloxegol is associated with significant improvements in spontaneous bowel movements, while maintaining levels of opioid-related analgesia (a result of its reduced ability to cross the blood-brain barrier). Naloxegol is a useful option in the treatment of opioid-induced constipation.

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Vonoprazan: First Global Approval

Karly P. Garnock-Jones

ABSTRACT

Vonoprazan (Takecab®) is an orally bioavailable potassium-competitive acid blocker (P-CAB) being developed by Takeda for the treatment and prevention of acid-related diseases. The drug is approved in Japan for the treatment of acid-related diseases, including erosive oesophagitis, gastric ulcer, duodenal ulcer, peptic ulcer, gastro-oesophageal reflux, reflux oesophagitis and Helicobacter pylori eradication. Phase III development is underway for the prevention of recurrence of duodenal and gastric ulcer in patients receiving aspirin or NSAID therapy. Phase I development was conducted in the UK for gastro-oesophageal reflux; however, no further development has been reported. This article summarizes the milestones in the development of vonoprazan leading to this first approval for acid-related diseases.
Febuxostat: A Review of Its Use in the Treatment of Hyperuricaemia in Patients with Gout

James E. Frampton

ABSTRACT

Febuxostat (Adenuric®, Uloric®, Feburic®) is an orally-active, potent, non-purine, selective xanthine oxidase inhibitor. In the EU, it is indicated in adults for the treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred. Unlike allopurinol, the prototypical xanthine oxidase inhibitor that is the cornerstone therapy for chronic gout, febuxostat does not require dosage adjustment in patients with mild or moderate renal impairment. In randomized, double-blind studies, 6–12 months’ treatment with febuxostat at dosages approved for use in the EU (80 and 120 mg/day) was significantly more effective in lowering serum uric acid (sUA) levels in patients with hyperuricaemia and gout than allopurinol at dosages commonly prescribed in practice (100–300 mg/day); febuxostat demonstrated greater urate-lowering efficacy than allopurinol in patients with renal impairment. In open-label extension studies, 3–5 years’ treatment with febuxostat maintained a target sUA level of <6.0 mg/dL in most patients; sustained reduction in sUA level was associated with near elimination of gout flares and improved tophus status. Febuxostat therapy was generally well tolerated during clinical development; frequently reported adverse events included liver function abnormalities, diarrhoea and rash. Cardiovascular (CV) events were the most common serious adverse events; the comparative safety of febuxostat and allopurinol is being examined further in large, ongoing trials in patients with gout who already have, or are at risk of developing, CV disease. In conclusion, febuxostat is a well established anti hyperuricaemic agent that provides an effective alternative to allopurinol for the management of chronic gout.

Retention in Care and Medication Adherence: Current Challenges to Antiretroviral Therapy Success

Carol W. Holtzman, Kathleen A. Brady, Baligh R. Yehia

ABSTRACT

Health behaviors such as retention in HIV medical care and adherence to antiretroviral therapy (ART) pose major challenges to reducing new HIV infections, addressing health disparities, and improving health outcomes. Andersen’s Behavioral Model of Health Service Use provides a conceptual framework for understanding how patient and environmental factors affect health behaviors and outcomes, which can inform the design of intervention strategies. Factors affecting retention and adherence among persons with HIV include patient predisposing factors (e.g., mental illness, substance abuse), patient-enabling factors (e.g., social support, reminder strategies, medication characteristics, transportation, housing, insurance), and healthcare environment factors (e.g., pharmacy services, clinic experiences, provider characteristics). Evidence-based recommendations for improving retention and adherence include (1) systematic monitoring of clinic attendance and ART adherence; (2) use of peer or paraprofessional navigators to re-engage patients in care and help them remain in care; (3) optimization of ART regimens and pharmaceutical supply chain management systems; (4) provision of reminder devices and tools; (5) general education and counseling; (6) engagement of peer, family, and community support groups; (7) case management; and (8) targeting patients with substance abuse and mental illness. Further research is needed on effective monitoring strategies and interventions that focus on improving retention and adherence, with specific attention to the healthcare environment.
Kidney transplant is the preferred treatment of pediatric end-stage renal disease. One of the most challenging aspects of pediatric kidney transplant is the prevention and treatment of antibody-mediated rejection (ABMR), which is one of the main causes of graft dysfunction and early graft loss. Most challenges are similar to those faced in adult kidney transplants; however, factors unique to the pediatric realm include naivety of the immune system and the small number of studies and randomized controlled trials available when considering pharmacological treatment options. Here, we present a case of ABMR in a pediatric patient and a review of the pathophysiology, diagnosis, and management of ABMR. ABMR in pediatric kidney transplant continues to be a frustrating condition to treat because (1) there still remain many unidentified potential antigens leading to ABMR, (2) children and adults are at different stages of their immune system development, and, thus, (3) the full pathophysiology of alloimmunity is still not completely understood, and (4) the efficacy and safety of treatment in adults may not be directly translated to children. As we continue to gain a better understanding towards the precise alloimmune mechanism that drives a particular ABMR, we can also improve pharmacotherapeutic choices. With continued research, they will become more precise in treating a particular mechanism versus using a broad scope of immunosuppression such as steroids. However, there is much more to be uncovered, such as identifying more non-human leukocyte antigens and their role in alloimmunity, determining the exact mechanism of adults achieving complete operational tolerance, and understanding the difference between pediatric and adult transplant recipients. Making strides towards a better understanding of these mechanisms will lead to continued efficacy and safety in treatment of pediatric ABMR.

Drug Therapy of Apparent Treatment-Resistant Hypertension: Focus on Mineralocorticoid Receptor Antagonists

Apparent treatment-resistant hypertension (aTRH) is defined as blood pressure (BP) >140/90 mmHg despite three different antihypertensive drugs including a diuretic. aTRH is associated with an increased risk of cardiovascular events, including stroke, chronic renal failure, myocardial infarction, congestive heart failure, aortic aneurysm, atrial fibrillation, and sudden death. Preliminary studies of renal nerve ablation as a therapy to control aTRH were encouraging. However, these results were not confirmed by the Symplicity 3 trial. Therefore, attention has refocused on drug therapy. Secondary forms of hypertension and associated conditions such as obesity, sleep apnea, and primary aldosteronism are common in patients with aTRH. The pivotal role of aldosterone in the pathogenesis of aTRH in many cases is well recognized. For patients with aTRH, the Joint National Committee-8, the European Society of Hypertension, and a recent consensus conference recommend that a diuretic, ACE inhibitor, or angiotensin receptor blocker and calcium channel blocker combination be used to maximally tolerated doses before starting a ‘fourth-line’ drug such as a mineralocorticoid receptor (MR) antagonist. Although the best fourth-line drug for aTRH has not been extensively investigated, a number of studies summarized here show that an MR antagonist is effective in reducing BP when added to the standard multi-drug regimen.
An Update on Pharmacological, Pharmacokinetic Properties and Drug–Drug Interactions of Rotigotine Transdermal System in Parkinson’s disease and Restless Legs Syndrome

Jan-Peer Elshoff, Willi Cawello, Jens-Otto Andreas, Francois-Xavier Mathy

ABSTRACT

This narrative review reports on the pharmacological and pharmacokinetic properties of rotigotine, a non-ergolinic D3/D2/D1 dopamine receptor agonist approved for the treatment of early- and advanced-stage Parkinson’s disease (PD) and moderate to severe restless legs syndrome (RLS). Rotigotine is formulated as a transdermal patch providing continuous drug delivery over 24 h, with a plasma concentration profile similar to that of administration via continuous intravenous infusion. Absolute bioavailability after 24 h transdermal delivery is 37 % of the applied rotigotine dose. Following a single administration of rotigotine transdermal system (24-h patch-on period), most of the absorbed drug is eliminated in urine and feces as sulphated and glucuronidated conjugates within 24 h of patch removal. The drug shows a high apparent volume of distribution (>2500 L) and a total body clearance of 300–600 L/h. Rotigotine transdermal system provides dose-proportional pharmacokinetics up to supratherapeutic dose rates of 24 mg/24 h, with steady-state plasma drug concentrations attained within 1–2 days of daily dosing. The pharmacokinetics of rotigotine transdermal patch are similar in healthy subjects, patients with early- or advanced-stage PD, and patients with RLS when comparing dose-normalized area under the plasma concentration–time curve (AUC) and maximum plasma drug concentration (Cmax), as well as half-life and other pharmacokinetic parameters. Also, it is not influenced in a relevant manner by age, sex, ethnicity, advanced renal insufficiency, or moderate hepatic impairment. No clinically relevant drug–drug interactions were observed following co-administration of rotigotine with levodopa/carbidopa, domperidone, or the CYP450 inhibitors cimetidine or omeprazole. Also, pharmacodynamics and pharmacokinetics of an oral hormonal contraceptive were not influenced by rotigotine co-administration. Rotigotine was generally well tolerated, with an adverse event profile consistent with dopaminergic stimulation and use of a transdermal patch. These observations, combined with the long-term efficacy demonstrated in clinical studies, support the use of rotigotine as a continuous non-ergot D3/D2/D1 dopamine receptor agonist in the treatment of PD and RLS.

Abacavir/Dolutegravir/Lamivudine Single-Tablet Regimen: A Review of Its Use in HIV-1 Infection

Sarah L. Greig, Emma D. Deeks

ABSTRACT

A fixed-dose, single-tablet regimen comprising the integrase strand transfer inhibitor (INSTI) dolutegravir and the nucleos (t) ide reverse transcriptase inhibitors (NRTIs) abacavir and lamivudine (abacavir/dolutegravir/lamivudine; Triumeq®) is now available for the treatment of HIV-1 infection. In a randomized, double-blind, phase III trial in antiretroviral therapy (ART)-naive adults (SINGLE), once-daily dolutegravir plus abacavir/lamivudine had noninferior efficacy to once-daily efavirenz/tenofovir disoproxil fumarate (tenofovir DF)/emtricitabine with regard to establishing and sustaining virological suppression over 144 weeks, and subsequent superiority testing significantly favoured dolutegravir plus abacavir/lamivudine. This outcome was predominantly driven by more favourable rates of discontinuation due to adverse events versus the efavirenz/tenofovir DF/emtricitabine group. These data were generally supported by findings from other phase III trials in ART-naïve adults receiving dolutegravir plus either abacavir/lamivudine or tenofovir DF/emtricitabine (SPRING-2 and FLAMINGO). Dolutegravir plus abacavir/lamivudine is generally well tolerated, with a tolerability profile that appears to be more favourable than efavirenz/tenofovir DF/emtricitabine. In the SINGLE trial, there were no major treatment-emergent INSTI or NRTI resistance-associated mutations in dolutegravir plus abacavir/lamivudine recipients with protocol-defined virological failure, indicating a high genetic barrier to resistance. Thus, triple combination therapy with abacavir, dolutegravir and lamivudine is an effective, generally well tolerated option for the management of HIV-1 infection, with the convenient once-daily fixed-dose tablet providing the first single-tablet regimen option without tenofovir DF.
Daclatasvir: A Review of Its Use in Adult Patients with Chronic Hepatitis C Virus Infection
Paul L. McCormack

ABSTRACT
Daclatasvir (Daklinza®) is an inhibitor of hepatitis C virus (HCV) NS5A protein. It is a new, oral, direct-acting antiviral with potent pangenotypic activity. This article provides a narrative review of the efficacy and tolerability of daclatasvir in combination with other agents in the treatment of patients with chronic HCV infection and summarizes its pharmacological properties. Since daclatasvir has a different mechanism of action to other current direct-acting antivirals, it provides additive or synergistic antiviral activity when used in combination. It produces high sustained virological response rates when used in combination with peginterferon-α plus ribavirin in patients chronically infected with HCV genotypes 1–4, and provides even higher response rates when used in an interferon-free, all-oral combination with sofosbuvir, with or without ribavirin. Daclatasvir has a moderately high genetic barrier to resistance, is effective during short-term treatment over 12 weeks and has a tolerability profile similar to that of placebo. In conclusion, daclatasvir is a highly effective and well tolerated, oral, once-daily, direct-acting antiviral for use in combination therapy in adult patients chronically infected with HCV.

Eltrombopag: A Review of Its Use in Patients with Severe Aplastic Anaemia
Paul L. McCormack

ABSTRACT
Eltrombopag (Promacta®) is an orally active thrombopoietin receptor agonist recently approved in the US for the treatment of patients with severe aplastic anaemia who have had an insufficient response to immunosuppressive therapy. This article reviews the efficacy and tolerability of eltrombopag in this indication and overviews its pharmacological properties. Eltrombopag does not compete with thrombopoietin and binds to a different site on the receptor, producing additive effects. It stimulates haematopoietic stem cells and promotes haematopoietic recovery in patients with aplastic bone marrow. Eltrombopag increased platelet counts and can also increase red blood cell and neutrophil counts. In patients with severe aplastic anaemia refractory to prior immunosuppressive therapy, oral eltrombopag at dosages ≤150 mg once daily for 12–16 weeks produced a haematological response in at least one cell lineage in 40 % of patients. Trilineage responses were achieved in nearly one-half of the responders during extended treatment. In robust responders, stable haematological counts were maintained after eltrombopag discontinuation. Eltrombopag was generally well tolerated, with increased liver transaminases as the only dose-limiting toxicity. Clonal cytogenetic abnormalities were observed in 19 % of patients and dysplasia in 5 % of patients.
Sucroferric Oxyhydroxide: A Review in Hyperphosphataemia in Chronic Kidney Disease Patients Undergoing Dialysis
Sarah L. Greig, Greg L. Plosker

ABSTRACT

Sucroferric oxyhydroxide (Velphoro®), an iron-based oral phosphate binder, is available for the control of serum phosphorus levels in patients with chronic kidney disease (CKD) on dialysis. In a pivotal phase III trial, sucroferric oxyhydroxide 1000–3000 mg/day for 24 weeks was noninferior to sevelamer carbonate 4800–14,400 mg/day with regard to lowering serum phosphorus levels. Additionally, sucroferric oxyhydroxide at maintenance dosages was significantly more effective than low dosage sucroferric oxyhydroxide (250 mg/day) with regard to maintaining controlled serum phosphorus levels during weeks 24–27 of treatment. Sucroferric oxyhydroxide had a numerically lower mean daily pill burden and better treatment adherence than sevelamer carbonate. Treatment with sucroferric oxyhydroxide was generally well tolerated over 24 weeks’ treatment, with the most frequently reported treatment-emergent adverse events being mild, transient diarrhoea and discoloured faeces. In a 28-week extension study, the efficacy and tolerability profile of sucroferric oxyhydroxide remained similar to sevelamer carbonate for up to 52 weeks. In conclusion, sucroferric oxyhydroxide is a valuable treatment option for hyperphosphataemia in CKD patients on dialysis, providing an effective and generally well tolerated non-calcium-based phosphate binder therapy with a lower pill burden than sevelamer carbonate and the potential for improved treatment adherence.

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Palbociclib: First Global Approval
Sohita Dhillon

ABSTRACT

Palbociclib (Ibrance®) is an oral, reversible, selective, small-molecule inhibitor of cyclin-dependent kinases (CDK) 4 and CDK6 developed by Pfizer for the treatment of cancer. CDKs are important modulators of cell cycle entry and progression in response to growth signals, and inhibition of these kinases with palbociclib could enhance the activity of other anticancer drugs in tolerable regimens. Palbociclib, in combination with letrozole, was recently approved in the US for the first-line treatment of advanced breast cancer. Phase III development is underway worldwide investigating its use as first-line treatment in advanced breast cancer, as well as treatment of recurrent or advanced breast cancer and high-risk, early-stage breast cancer. A phase II trial is underway in the USA for non-small cell lung cancer under a US National Cancer Institute-funded research collaboration, and several phase I and II investigations are being conducted for various other solid tumour types and haematological malignancies. This article summarizes the milestones in the development of palbociclib leading to this first approval for use in postmenopausal women with estrogen-positive, human epidermal growth factor receptor (HER) 2-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease.
**ABSTRACT**

Lenvatinib (Lenvima™) is a multitargeted receptor kinase inhibitor that inhibits the kinase activities of vascular endothelial-derived growth factor receptors 1, 2 and 3, fibroblast growth factor receptors 1, 2, 3 and 4, platelet-derived growth factor receptor α, RET and KIT. In addition to their role in normal cellular function, these kinases have been implicated in pathogenic angiogenesis, tumour growth and cancer progression. Lenvatinib is being developed by Eisai Co. Ltd for the treatment of solid tumours, primarily for differentiated thyroid cancer, and other malignancies. A capsule formulation of the drug has received approval in the USA for use in locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer. Lenvatinib is in pre-registration for this indication in the EU, Australia, Brazil, Canada, Japan, South Korea, Russia, Singapore and Switzerland, and is in phase 3 development in Argentina, Chile and Thailand. Lenvatinib has orphan designation in the EU and Japan for use in differentiated thyroid cancer. In addition, an ongoing global, phase 3 trial is evaluating the use of lenvatinib as first-line treatment in unresectable hepatocellular carcinoma. This article summarizes the milestones in the development of lenvatinib leading to this first approval in locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer.

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**The Role of Anti-PD-1/PD-L1 Agents in Melanoma: Progress to Date**

Katy K. Tsai, Adil I. Daud

**ABSTRACT**

The discovery of immune inhibitory checkpoints has revolutionized the approach to the systemic treatment of cancer. The programmed death 1 (PD-1) inhibitory checkpoint, in particular, has played a key role in understanding how certain cancers can evade immune surveillance. Blocking the interaction between the PD-1 receptor and its primary ligand (PD-L1) has demonstrated remarkable anti-cancer activity, and has led to the recent accelerated approval of two anti-PD-1 drugs for use in unresectable and metastatic melanoma in the USA. Results of these therapeutic advances have solidified the role of immunotherapy in the treatment of melanoma, results that may be applicable to the treatment of other cancers. In this review, we discuss the role of the PD-1 pathway in the immune system and the anti-cancer mechanism of action of inhibiting the PD-1/PD-L1 interaction. We also review the efficacy and safety data of currently approved and in-development anti-PD-1 agents, and explore the next steps to further improve patient outcomes.

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**Clinical Association between Pharmacogenomics and Adverse Drug Reactions**

Zhi-Wei Zhou, Xiao-Wu Chen, Kevin B. Sneed, Yin-Xue Yang, Xueji Zhang, Zhi-Xu

**ABSTRACT**

Adverse drug reactions (ADRs) are a major public health concern and cause significant patient morbidity and mortality. Pharmacogenomics is the study of how genetic polymorphisms affect an individual’s response to pharmacotherapy at the level of a whole genome. This article updates our knowledge on how genetic polymorphisms of important genes alter the risk of ADR occurrence after an extensive literature search. To date, at least 244 pharmacogenes identified have been associated with ADRs of 176 clinically used drugs based on PharmGKB. At least 28 genes associated with the risk of ADRs have been listed by the Food and Drug Administration as pharmacogenomic biomarkers. With the availability of affordable and reliable testing tools, pharmacogenomics looks promising to predict, reduce, and minimize ADRs in selected populations.
Clinically significant depression is present in one of every four people with type 2 diabetes mellitus (T2DM). Depression increases the risk of the development of T2DM and the subsequent risks of hyperglycemia, insulin resistance, and micro- and macrovascular complications. Conversely, a diagnosis of T2DM increases the risk of incident depression and can contribute to a more severe course of depression. This linkage reflects a shared etiology consisting of complex bidirectional interactions among multiple variables, a process that may include autonomic and neurohormonal dysregulation, weight gain, inflammation, and hippocampal structural alterations. Two recent meta-analyses of randomized controlled depression treatment trials in patients with T2DM concluded that psychotherapy and antidepressant medication (ADM) were each moderately effective for depression and that cognitive behavior therapy (CBT) had beneficial effects on glycemic control. However, the number of studies (and patients exposed to randomized treatment) included in these analyses is extremely small and limits the certainty of conclusions that can be drawn from the data. Ultimately, there is no escaping the paucity of the evidence base and the need for additional controlled trials that specifically address depression management in T2DM. Future trials should determine both the effects of treatment and the change in depression during treatment on measures of mood, glycemic control, and medical outcome.

Ledipasvir/Sofosbuvir: A Review of Its Use in Chronic Hepatitis C

Gillian M. Keating

ABSTRACT

The single-tablet regimen of the hepatitis C virus (HCV) NS5A inhibitor ledipasvir and the HCV NS5B polymerase inhibitor sofosbuvir (ledipasvir/sofosbuvir; Harvoni®) was recently approved in the US and the EU. The phase III ION trials included treatment-naïve (ION-1 and -3) or treatment-experienced (ION-2) patients with chronic HCV genotype 1 infection (≈20 % of patients in ION-1 and -2 had cirrhosis, whereas no patient in ION-3 had cirrhosis). A sustained virological response 12 weeks’ post-treatment (SVR12) was seen in 99 % of treatment-naïve patients receiving ledipasvir/sofosbuvir for 12 weeks in ION-1, with no additional benefit conferred by the addition of ribavirin or extending the treatment duration to 24 weeks. Moreover, in ION-3, an 8-week regimen achieved an SVR12 rate of 94 % overall and 97 % in the subgroup of patients with a baseline HCV RNA level of <6 million IU/mL. SVR12 rates of 94 and 99 % were seen in treatment-experienced patients who received ledipasvir/sofosbuvir for 12 and 24 weeks in ION-2. Data also support the use of ledipasvir/sofosbuvir in chronic HCV genotype 4 infection, in HCV and HIV co-infection and, in combination with ribavirin, in patients with chronic HCV genotype 1 or 4 infection who have decompensated cirrhosis or are liver transplant recipients and in chronic HCV genotype 3 infection. Oral ledipasvir/sofosbuvir was generally well tolerated. In conclusion, ledipasvir/sofosbuvir is an important new single-tablet regimen that represents a significant advance in the treatment of chronic hepatitis C.
Modified Regulatory Pathways to Approve Generic Drugs in the US and a Systematic Review of Their Outcomes

Aaron S. Kesselheim, Jennifer M. Polinski, Lisa A. Fulchino, Danielle L. Isaman

ABSTRACT

Background: Generic drugs are approved on the basis of pharmaceutical equivalence and bioequivalence. Some drug products have unique structural or functional attributes, necessitating modified approaches to bioequivalence determinations.

Objective: The aim of this systematic review was to identify studies that evaluated laboratory or clinical outcomes of six drugs approved via modified bioequivalence approaches.

Data Sources: We conducted a systematic review of articles published through February 2014 in MEDLINE, EMBASE, and International Pharmaceutical Abstracts related to six recent drugs subject to modified regulatory approaches: venlafaxine extended release tablet (Effexor XR), acarbose (Precose), enoxaparin (Lovenox), vancomycin capsules (Vancocin), sodium ferric gluconate (Ferrlecit), and calcitonin salmon nasal spray (Miacalcin NS). We included all empirical evaluations (whether in vivo or in vitro) and excluded case studies, qualitative analyses, and pharmacoeconomic evaluations. Studies were summarized and evaluated on their methodological quality and assessed for bias using the Cochrane Risk of Bias Assessment Tool. Articles were divided into studies of US FDA-approved generics and non-FDA-approved generics available in non-US locations.

Data Extraction: We extracted drug(s) studied, study design, setting, sample size, population characteristics, study endpoints and results, and source of funding.

Data Synthesis: After retrieving 1408 articles and searching through the full text of 106 articles, we found 26 articles that met our inclusion criteria—8 examining FDA-approved versions and 18 examining non-FDA-approved versions. Among FDA-approved generics, five studies of enoxaparin showed minor variations in biologic activities of unclear clinical importance, and no publications involved acarbose, venlafaxine ER, or vancomycin capsules. Among non-FDA-approved generics, nine studies of enoxaparin supported generic bioequivalence, despite three showing minor variations in drug activity. Four of six studies of venlafaxine ER supported generic bioequivalence, while two found a lack of bioequivalence with a Canadian generic version of the drug. Most studies were either highly susceptible to bias (12/26) or were not able to be assessed for bias (13/26), in part because eight studies were abstracts/posters without full reports.

Conclusions: Pharmaceutical manufacturers sometimes raise scientific concerns related to potential generic versions of their drugs; however, in the six cases we reviewed, these companies did not follow up the pre-approval concerns they raised with any methodologically rigorous post-approval testing using clinical endpoints. Despite their pre-approval controversy, experience with these generic drugs provides reassurance of their clinical interchangeability. Systematized post-approval study of certain generic drug bioequivalence determinations is needed.
Albiglutide: A Review of Its Use in Patients with Type 2 Diabetes Mellitus  
Hannah A. Blair, Gillian M. Keating

**ABSTRACT**

Albiglutide (Eperzan®, Tanzeum®), administered subcutaneously once weekly, is a glucagon-like peptide (GLP)-1 receptor agonist approved for the treatment of type 2 diabetes mellitus in several countries. Albiglutide has a longer half-life than native GLP-1, since it is resistant to degradation by the dipeptidyl peptidase-4 enzyme. As an incretin mimic, albiglutide enhances glucose-dependent insulin secretion, suppresses inappropriate glucagon secretion, delays gastric emptying and reduces food intake. Several phase III clinical trials have demonstrated the efficacy of albiglutide in terms of improving glycaemic control in patients with inadequately controlled type 2 diabetes, including its use as monotherapy or add-on therapy to other antidiabetic agents (e.g. metformin, sulfonylureas, thiazolidinediones and insulins). In addition to improving glycaemic control, albiglutide had beneficial effects on bodyweight. These improvements in glycaemic control and reductions in bodyweight were maintained during long-term treatment (up to 3 years). Albiglutide was generally well tolerated in clinical trials, with mild to moderate gastrointestinal adverse events seen most commonly. Albiglutide has a convenient once-weekly administration regimen and a low risk of hypoglycaemia (except when used in combination with agents that may be associated with hypoglycaemia, such as sulfonylureas or insulin). Thus, albiglutide is an effective and generally well tolerated treatment option for patients with inadequately controlled type 2 diabetes.

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Olodaterol: A Review of Its Use in Chronic Obstructive Pulmonary Disease  
Emma D. Deeks

**ABSTRACT**

Olodaterol (Striverdi® Respimat®) is an inhaled long-acting β2-adrenoceptor agonist (LABA) indicated as a once-daily maintenance bronchodilator therapy in adults with COPD. Several well-designed phase III trials have assessed use of the drug over 6 or 48 weeks in this patient population. In these studies, once-daily olodaterol improved lung function relative to placebo over 48 weeks of treatment, with such improvements being achieved and maintained within the 24-h dosage interval, supporting its once-daily administration. In addition, combined analyses of 48-week trials indicated that olodaterol reduces rescue medication use and may also improve dyspnoea and health-related quality of life, and crossover studies showed improvements in exercise endurance after 6 weeks of treatment with the drug. Pooled analyses of crossover studies assessing 24-h bronchodilation after 6 weeks of therapy indicated that once-daily olodaterol has a 24-h bronchodilatory profile generally similar to that of once-daily tiotropium bromide and twice-daily formoterol. Olodaterol was generally well tolerated and had an acceptable cardiovascular and respiratory adverse event profile. However, further longer-term and active comparator-controlled studies would be beneficial, including trials powered to assess COPD exacerbations.
Finafloxacin: First Global Approval
Kate McKeage

ABSTRACT
Finafloxacin is a fluoroquinolone antimicrobial agent that exhibits optimum efficacy in slightly acidic environments. It is being developed by MerLion Pharmaceuticals to treat serious bacterial infections associated with an acidic environment, including urinary tract infections and Helicobacter pylori infections. An otic suspension of finafloxacin (Xtoro™), developed by Alcon (a division of Novartis), was recently approved in the USA for the treatment of acute otitis externa, and a Common Technical Document for this indication was also filed in Canada. Oral and/or intravenous formulations are in phase I and II evaluation in uncomplicated urinary tract infections (Germany and Singapore), complicated urinary tract infections and pyelonephritis (Germany and Poland) and H. pylori infection (Germany). This article summarizes the milestones in the development of finafloxacin leading to this first approval for otitis externa.

Panobinostat: First Global Approval
Karly P. Garnock-Jones

ABSTRACT
Novartis has developed oral and intravenous formulations of panobinostat (Farydak®), a histone deacetylase (HDAC) inhibitor, for the treatment of cancer. HDACs have important roles in maintaining chromatin structure and in regulating gene expression, including that of tumour suppressor genes, and thus represent valid targets in the search for cancer therapeutics. Oral panobinostat is approved in the US, as combination therapy with bortezomib and dexamethasone in patients with recurrent multiple myeloma who have received at least two prior treatment regimens, including bortezomib and an immunomodulatory agent. Regulatory submissions have been made for the use of combination therapy with panobinostat in patients with recurrent multiple myeloma in the EU and Japan. Panobinostat is in various stages of clinical development worldwide for a range of haematological and solid tumours. This article summarizes the milestones in the development of panobinostat leading to this first approval for multiple myeloma.

Safinamide: First Global Approval
Emma D. Deeks

ABSTRACT
Safinamide (Xadago®) is an oral α-aminoamide derivative developed by Newron for the treatment of Parkinson’s disease (PD). The drug has both dopaminergic properties (highly selective and reversible inhibition of monoamine oxidase-B) and non-dopaminergic properties (selective sodium channel blockade and calcium channel modulation, with consequent inhibition of excessive glutamate release). Safinamide is approved in the EU, Iceland, Lichtenstein and Norway, as an add-on therapy to stable-dose levodopa, alone or in combination with other PD therapies in mid- to late-stage fluctuating PD patients; regulatory submissions have also been filed in the USA and Switzerland for its use in this indication. Additional submissions have been made in the USA, Iceland, Lichtenstein, Norway and Switzerland for early-stage PD. Safinamide has also undergone phase II investigation in PD patients with drug-induced dyskinesia (France, Germany, Austria, Canada and South Africa) or cognitive impairment (USA and Spain). This article summarizes the milestones in the development of safinamide leading to its first approval for PD.
Targeting High-Density Lipoproteins: Increasing De Novo Production versus Decreasing Clearance
Arshag D. Mooradian, Michael J. Haas

ABSTRACT

Although cardiovascular mortality has been decreasing in industrialized countries, there continues to be a substantial residual risk; thus, novel therapeutic agents and new targets of therapy have been sought. One highly plausible therapeutic target is high-density lipoprotein (HDL). HDL is a key player in reverse cholesterol transport and possesses a slew of other cardioprotective properties; however, recent trials with agents known to increase HDL levels have generally not shown any reduction in cardiovascular events. Further analysis of these trials suggest that fibrates have consistently reduced some cardiovascular outcomes, at least in the subgroup of patients with high serum triglycerides and low HDL cholesterol (HDLc) levels. Since fibrates, unlike niacin or cholesterol ester transfer protein inhibitors, increase HDLc level mostly through the stimulation of apolipoprotein A-I production, it is suggested that the quality and functionality of HDL are enhanced when de novo synthesis rather than inhibition of turnover is the mechanism of increasing HDL level. In this communication, the evidence for and against the cardioprotective properties of HDL is reviewed and the contemporary clinical trials are discussed.

Antisense Approach to Inflammatory Bowel Disease: Prospects and Challenges
Irene Marafini, Davide Di Fusco, Emma Calabrese, Silvia Sedda, Francesco Pallone

ABSTRACT

Despite the great success of anti-tumour necrosis factor-based therapies, the treatment of Crohn’s disease (CD) and ulcerative colitis (UC) still remains a challenge for clinicians, as these drugs are not effective in all patients, their efficacy may wane with time, and their use can increase the risk of adverse events and be associated with the development of new immune-mediated diseases. Therefore, new therapeutic targets are currently being investigated both in pre-clinical studies and in clinical trials. Among the technologies used to build new therapeutic compounds, the antisense oligonucleotide (ASO) approach is slowly gaining space in the field of inflammatory bowel diseases (IBDs), and three ASOs have been investigated in clinical trials. Systemic administration of alicaforsen targeting intercellular adhesion molecule-1, a protein involved in the recruitment of leukocytes to inflamed intestine, was not effective in CD, even though the same compound was of benefit when given as an enema to UC patients. DIMS0150, targeting nuclear factor (NF) κB-p65, a transcription factor that promotes pro-inflammatory responses, was very promising in pre-clinical studies and is currently being tested in clinical trials. Oral mongersen, targeting Smad7, an intracellular protein that inhibits transforming growth factor (TGF)-β1 activity, was safe and well tolerated by CD patients, and the results of a phase II clinical trial showed the efficacy of the drug in inducing clinical remission in patients with active disease. In this leading article, we review the rationale and the clinical data available regarding these three agents, and we discuss the challenge of using ASOs in IBD.
ABSTRACT
Tumour biomarker status is being used more and more frequently to guide treatment decisions in patients with metastatic colorectal cancer (mCRC). Continued cycles of hypothesis generation and biomarker testing in retrospective, prospective–retrospective and prospective analyses from studies of the epidermal growth factor (EGFR)-targeted monoclonal antibodies (mAbs), panitumumab and cetuximab, have resulted in improved patient selection in mCRC. Initial data suggested EGFR-targeted mAb treatment should be limited to patients with KRAS exon 2 wild-type (WT) tumours, but the availability of tumour samples from large phase III studies permitted evaluation of additional potential biomarkers of activity for these agents. Subsequent analyses further refined the target population to those patients whose tumours were WT for KRAS and NRAS exons 2, 3 and 4 (i.e., those with RAS WT status). Here, we review key clinical data for panitumumab in mCRC across the lines of treatment, assessing in detail the impact of more comprehensive RAS selection on patient outcomes.

Disease Modification in Epilepsy: From Animal Models to Clinical Applications
Melissa L. Barker-Haliski, Dan Friedman, Jacqueline A. French, H. Steve White
ABSTRACT
Several relevant animal models of epileptogenesis and biomarkers have emerged for evaluating the antiepileptogenic potential of an investigational drug. Although several promising candidate compounds and approaches have been identified in these preclinical models, no treatment has yet successfully navigated the path from preclinical efficacy to clinical validation. Until such an agent can move from preclinical proof of concept to clinical success, the need remains to continually develop and optimize preclinical models and clinical trial design in an effort to guide potential clinical investigations. This review describes several available models of disease modification and/or epileptogenesis, preclinical studies in these models and potential biomarkers useful for evaluating the efficacy of a potential therapeutic agent in the preclinical setting. The results that emerge from such efforts may then guide the clinical evaluation of a candidate compound. This review discusses some of the known limitations and hurdles to moving compounds found effective in these models to clinical practice, in the hope that knowledge of this information will facilitate the design and conduct of clinical studies and effectively facilitate the identification of a first-in-class disease-modifying or antiepileptogenic agent.

Alogliptin: A Review of Its Use in Patients with Type 2 Diabetes Mellitus
Gillian M. Keating
ABSTRACT
The dipeptidyl peptidase-4 inhibitor alogliptin (Nesina®, Vipidia®) is approved in numerous countries worldwide for the treatment of type 2 diabetes mellitus. Fixed-dose combinations of alogliptin/metformin (Kazano®, Vipdomet®) and alogliptin/pioglitazone (Oseni®, Incresync®) are also available. This article reviews the clinical efficacy and tolerability of oral alogliptin in the treatment of type 2 diabetes. Results of randomized controlled trials demonstrated that oral alogliptin improved glycaemic control when administered as monotherapy, as dual therapy in combination with metformin, pioglitazone, a sulfonylurea, voglibose or insulin, or as triple therapy in combination with metformin plus pioglitazone. Alogliptin was generally well tolerated in patients with type 2 diabetes and was weight neutral, with a low risk of hypoglycaemia. Results of the large, well designed EXAMINE trial revealed that alogliptin was not associated with an increased risk of major cardiovascular events in patients with type 2 diabetes and recent acute coronary syndrome. In conclusion, alogliptin is a useful option for the treatment of patients with type 2 diabetes.
Ibrutinib: A Review of Its Use in Patients with Mantle Cell Lymphoma or Chronic Lymphocytic Leukaemia

Esther S. Kim, Sohita Dhillon

ABSTRACT

Ibrutinib (Imbruvica®) is a first-in-class, potent, orally administered, covalent inhibitor of Bruton’s tyrosine kinase (BTK) that inhibits B-cell antigen receptor signalling downstream of BTK. Oral ibrutinib is indicated for the treatment of patients with relapsed/refractory mantle cell lymphoma (MCL) or chronic lymphocytic leukaemia (CLL) and for the treatment of patients with CLL and a chromosome 17 deletion (del 17p) or TP53 mutation. This article summarizes pharmacological, efficacy and tolerability data relevant to the use of ibrutinib in these indications. In clinical studies, ibrutinib induced a high overall response rate in patients with relapsed/refractory MCL (phase II study). In addition, ibrutinib significantly prolonged progression-free survival and significantly improved the partial response rate and overall survival in patients with relapsed/refractory CLL (RESONATE study), including in those with del 17p, a subgroup with a poor prognosis. Ibrutinib had an acceptable tolerability profile in these studies with <10 % of patients discontinuing treatment because of adverse events. Given its efficacy and tolerability, once-daily, oral ibrutinib is an emerging treatment option for patients with relapsed/refractory MCL or CLL and CLL patients with del 17p or TP53 mutation.

Vorapaxar: A Review of Its Use in the Long-Term Secondary Prevention of Atherothrombotic Events

James E. Frampton

ABSTRACT

Vorapaxar (Zontivity®) is a first-in-class, potent and orally-active protease-activated receptor 1 (PAR-1) antagonist that blocks thrombin-mediated platelet activation without interfering with thrombin-mediated fibrin deposition. The long-term efficacy of once-daily vorapaxar added to standard antiplatelet therapy (aspirin with or without clopidogrel) in the secondary prevention of atherothrombotic events in patients with a history of myocardial infarction (MI), ischaemic stroke or peripheral arterial disease was investigated in the large, multinational TRA 2°P-TIMI 50 trial. Compared with placebo, vorapaxar significantly reduced the risk of the composite endpoints of cardiovascular (CV) death, MI or stroke, and CV death, MI, stroke or urgent coronary revascularization in the overall trial population. Vorapaxar also significantly reduced the risk of these composite endpoints in the subgroup of patients with prior MI (the largest qualifying disease cohort) and the subset of post-MI patients with no history of stroke or transient ischaemic attack (TIA). Vorapaxar significantly increased the risk of GUSTO moderate and/or severe bleeding in the overall trial population and all key subgroups (including post-MI patients with no history of stroke or TIA). Vorapaxar also significantly increased the risk of intracranial haemorrhage (ICH) in the overall trial population and the subgroup of patients with prior stroke, but not the subgroup of post-MI patients or the subset of post-MI patients with no history of stroke or TIA. Based on these results, vorapaxar has been approved in the EU as an adjunctive treatment for the secondary prevention of atherothrombotic events in patients with prior MI who do not have a history of stroke, TIA or ICH.
Tiotropium Respimat®: A Review of Its Use in Asthma Poorly Controlled with Inhaled Corticosteroids and Long-Acting β₂-Adrenergic Agonists

Kate McKeage

ABSTRACT

Tiotropium bromide (Spiriva®) solution for inhalation via the Respimat® Soft Mist™ inhaler is a long-acting anticholinergic agent approved in the EU for the add-on maintenance treatment of asthma in adults currently receiving maintenance therapy with an inhaled corticosteroid (ICS) (≥800 µg budesonide per day or equivalent) and a long-acting β2-adrenergic agonist (LABA) and who have experienced at least one severe exacerbation in the previous year. Tiotropium Respimat® added to maintenance ICS/LABA treatment significantly improved lung function after 6 months’ treatment and extended the time to the first asthma exacerbation in two well-designed, replicate, phase III trials in patients with poorly controlled asthma despite treatment with an ICS (≥800 µg budesonide/day or equivalent) and a LABA. Tiotropium Respimat® was also associated with a reduced incidence of severe asthma exacerbations and an increase in the median time to asthma worsening. The drug was well tolerated in asthma patients throughout 48 weeks’ treatment, with a generally similar incidence of serious adverse events in tiotropium Respimat® and placebo treatment groups.

Isavuconazonium: First Global Approval

Paul L. McCormack

ABSTRACT

Isavuconazonium (Cresemb®) is a water-soluble prodrug of the triazole antifungal isavuconazole (BAL 4815), a 14-α-demethylase inhibitor, under development by Basilea Pharmaceutica International Ltd and Astellas Pharma Inc. Isavuconazonium, in both its intravenous and oral formulations, was approved for the treatment of invasive aspergillosis and invasive mucormycosis (formerly termed zygomycosis) in the US in March 2015. Isavuconazonium is under regulatory review in the EU for invasive aspergillosis and mucormycosis. It is also under phase III development worldwide for the treatment of invasive candidiasis and candidaemia. This article summarizes the milestones in the development of isavuconazonium leading to the first approval for invasive aspergillosis and mucormycosis.


Treatment of Hepatitis C in Patients with Cirrhosis: Remaining Challenges for Direct-Acting Antiviral Therapy

Avik Majumdar, Matthew T. Kitson, Stuart K. Roberts

ABSTRACT

Chronic hepatitis C virus (HCV) infection is a major global health concern, resulting in significant morbidity and mortality. Treatment using interferon-based therapy in patients with HCV-related cirrhosis has been problematic due to toxicity and poor tolerability. Furthermore, interferon therapy is contraindicated in those with advanced cirrhosis or clinical decompensation, who are arguably the group most in need of viral eradication. The arrival of the direct-acting antiviral (DAA) era has resulted in the development of well-tolerated and highly effective interferon-free drug regimens that promise to dramatically change the therapeutic landscape for those with advanced HCV-related liver disease, including patients with clinical decompensation or pre-liver transplantation. Many successful DAA combinations have emerged; however, a number of challenges remain including the establishment of the optimal treatment duration, the ideal combination of drug classes and determining the role of ribavirin. Moreover, the identification of treatment-experienced patients with genotype 3 HCV cirrhosis as a difficult-to-treat subgroup is a significant impediment to overcome, as are those who have failed prior DAA therapy.
Targeting Interferons in Systemic Lupus Erythematosus: Current and Future Prospects
Alexis Mathian, Miguel Hie, Fleur Cohen-Aubart, Zahir Amoura

ABSTRACT
Systemic lupus erythematosus (SLE) is a chronic autoimmune disease of unknown aetiology that can be debilitating and life threatening. As new insights are gained into the underlying pathology of SLE, there have been an unprecedented number of new agents under development to treat the disease via a diverse range of targets. One such class of emerging agents target interferon (IFN) signalling. In this article, we review the preclinical evidence that the inhibition of the secretion and downstream effectors of both IFN-α and IFN-γ may be effective for the treatment of SLE. The primary agents that are currently in clinical development to treat SLE via the targeting of interferon pathways are monoclonal neutralising antibodies (Mab) that bind to and neutralise IFN-γ (AMG 811), IFN-α (sifalimumab, rontalizumab and AGS-009) or its receptor (anifrolumab), and IFN-α kinoid, which is a drug composed of inactivated IFN-α molecules coupled to the keyhole limpet haemocyanin protein. Phase I and II trials have demonstrated acceptable short-term safety with no increase in severe viral infections or reactivation, favourable pharmacokinetic profiles and an inhibition of IFN-associated gene overexpression; however, the impact of these drugs on disease activity must still be assessed in phase III clinical trials.

The Expanding Role of Somatostatin Analogs in Gastroenteropancreatic and Lung Neuroendocrine Tumors
Mauro Cives, Jonathan Strosberg

ABSTRACT
Somatostatin analogs (SSAs) were initially developed as antisecretory agents used for the control of hormonal syndromes associated with neuroendocrine tumors (NETs). In recent years, accumulating evidence has also supported their role as antiproliferative agents in well or moderately differentiated NETs. The phase III PROMID trial demonstrated that octreotide long-acting repeatable (LAR) can significantly prolong time to progression among patients with metastatic midgut NETs. More recently, the randomized CLARINET trial reported a significant improvement in progression-free survival in a heterogeneous population of patients with gastroenteropancreatic (GEP)-NETs treated with depot lanreotide. Octreotide and lanreotide target somatostatin receptor subtypes in a similar fashion, and appear to be clinically interchangeable; however, comparative noninferiority trials have not been performed.

Dinutuximab: First Global Approval
Sohita Dhillon

ABSTRACT
United Therapeutics Corporation and the National Cancer Institute are developing dinutuximab (Unituxin™; ch14.18), a monoclonal antibody targeting GD2, for the treatment of neuroblastoma. GD2 is a glycolipid found on the surface of tumour cells, which is overexpressed in neuroblastoma. Dinutuximab, an IgG1 human/mouse chimeric switch variant of murine monoclonal antibody 14G2a, binds to GD2 and induces antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity. The US FDA has recently approved the use of dinutuximab combination therapy for the treatment of high-risk neuroblastoma in paediatric patients. The marketing authorization application for dinutuximab is under regulatory review in the EU, and phase I–III development is underway in several other countries. This article summarizes the milestones in the development of dinutuximab leading to this first approval for use (in combination with granulocyte macrophage colony-stimulating factor, interleukin-2 and 13-cis retinoic acid) in the treatment of paediatric patients with high-risk neuroblastoma who achieve at least partial response to prior first-line multiagent, multimodality therapy.
ABSTRACT

Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) of the phenylacetic acid class with anti-inflammatory, analgesic, and antipyretic properties. Contrary to the action of many traditional NSAIDs, diclofenac inhibits cyclooxygenase (COX)-2 enzyme with greater potency than it does COX-1. Similar to other NSAIDs, diclofenac is associated with serious dose-dependent gastrointestinal, cardiovascular, and renal adverse effects. Since its introduction in 1973, a number of different diclofenac-containing drug products have been developed with the goal of improving efficacy, tolerability, and patient convenience. Delayed- and extended-release forms of diclofenac sodium were initially developed with the goal of improving the safety profile of diclofenac and providing convenient, once-daily dosing for the treatment of patients with chronic pain. New drug products consisting of diclofenac potassium salt were associated with faster absorption and rapid onset of pain relief. These include diclofenac potassium immediate-release tablets, diclofenac potassium liquid-filled soft gel capsules, and diclofenac potassium powder for oral solution. The advent of topical formulations of diclofenac enabled local treatment of pain and inflammation while minimizing systemic absorption of diclofenac. SoluMatrix diclofenac, consisting of submicron particles of diclofenac free acid and a proprietary combination of excipients, was developed to provide analgesic efficacy at reduced doses associated with lower systemic absorption. This review illustrates how pharmaceutical technology has been used to modify the pharmacokinetic properties of diclofenac, leading to the creation of novel drug products with improved clinical utility.

Budesonide MMX®: A Review of Its Use in Patients with Mild to Moderate Ulcerative Colitis

Sheridan M. Hoy

ABSTRACT

Budesonide MMX® (Cortiment®; Uceris®) is a novel once-daily oral formulation of budesonide using Multi Matrix (MMX®) colonic delivery technology to permit the release of budesonide at a controlled rate throughout the colon. It is available in the USA for the induction of remission in patients with active, mild to moderate ulcerative colitis, and in various European countries for the induction of remission in patients with active, mild to moderate ulcerative colitis where 5-aminosalicylic acid (5-ASA) therapy is not sufficient. In three 8-week multinational, phase III studies in patients with active, mild to moderate ulcerative colitis, once-daily budesonide MMX® 9 mg, as monotherapy (CORE I and II studies) or add-on therapy to 5-ASAs (CONTRIBUTE), was significantly more effective than placebo in inducing combined clinical and endoscopic remission. In an 8-week extension of the CORE I study, the efficacy of budesonide MMX® 9 mg monotherapy was demonstrated among patients who completed the CORE I study, but did not achieve clinical remission. In phase III studies, the tolerability profile of budesonide MMX® 9 mg as monotherapy or add-on therapy to 5-ASAs was generally similar to that of placebo. Adverse events were generally mild or moderate in intensity, with exacerbation, relapse or worsening of ulcerative colitis, headache, nausea, abdominal pain and nasopharyngitis the most frequently reported following budesonide MMX® 9 mg monotherapy. Although final data from the CONTRIBUTE study are awaited, current evidence suggests budesonide MMX® 9 mg extends the treatment options currently available for patients with active, mild to moderate ulcerative colitis.
Memantine is an uncompetitive N-methyl-d-aspartate (NMDA) receptor antagonist that is a well-established treatment option for moderate to severe dementia of the Alzheimer’s type, either alone or in combination with cholinesterase inhibitors. The immediate-release (IR) formulations of memantine (tablets and oral solution) have been available in numerous countries, including the USA, for more than a decade and are administered orally twice daily at a maximum recommended total daily dosage of 20 mg/day. The memantine extended-release (ER) (Namenda XR®) 28 mg once-daily capsule formulation was approved in the USA in 2010 and became available more recently. The potential advantages of memantine ER over the IR formulation include a more convenient dosage regimen and lower pill burden that may improve adherence to therapy; also, memantine ER capsules may be opened and the contents sprinkled on applesauce for patients who have difficulty swallowing. Memantine ER provides a higher total daily dosage than the recommended memantine IR regimen and pharmacokinetic data indicate greater exposure with the ER formulation, but the clinical implications of this are unclear, as the two formulations have not been assessed in a comparative clinical trial. The efficacy of memantine ER 28 mg once daily was demonstrated in a large, multinational, phase III trial, which showed that the addition of memantine ER to ongoing oral cholinesterase inhibitors improved key outcomes compared with cholinesterase inhibitor monotherapy, including measures of cognition and global status, which were the co-primary endpoints of the study. The most common adverse events were headache, diarrhoea and dizziness.

Liraglutide: A Review of Its Use in the Management of Obesity

Lesley J. Scott

ABSTRACT

Globally, obesity has reached epidemic proportions and poses an ever increasing burden from a societal and healthpayer perspective. Although lifestyle interventions are fundamental in its management, in the real world setting most obese or overweight adults require adjunctive pharmacotherapy to achieve clinically relevant reductions in bodyweight (i.e. a ≥5 % reduction). Subcutaneous liraglutide (Saxenda®) 3 mg once daily is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic bodyweight management in adults with an initial body mass index (BMI) of ≥30 kg/m² (obese) or a BMI of ≥27 kg/m² (overweight) and at least one bodyweight-related comorbidity (e.g. hypertension, dyslipidaemia, type 2 diabetes mellitus or obstructive sleep apnoea (OSA)). In phase III trials (32 or 56 weeks’ duration) in these populations, subcutaneous liraglutide was associated with clinically relevant reductions in fasting bodyweight and was generally well tolerated. Liraglutide was significantly more effective than placebo in terms of reductions in fasting bodyweight and waist circumference, and improvements in some biomarkers of cardiovascular risk. Improvements in bodyweight were maintained after up 2 years of liraglutide therapy. In nondiabetic adults with moderate to severe OSA, liraglutide improved apnoea-hypopnoea index scores at 32 weeks, which was largely driven by significant reductions in bodyweight. In the absence of head-to-head trials, the relative position of individual anti-obesity drugs remains to be fully determined. In the meantime, liraglutide is an emerging option, as an adjunct to a reduced-calorie diet and increased physical activity, for chronic bodyweight management in obese adults and overweight adults with at least one bodyweight-related comorbidity.
Diquafosol Ophthalmic Solution 3%: A Review of Its Use in Dry Eye
Gillian M. Keating

ABSTRACT
Diquafosol ophthalmic solution 3% (Diquas®) is a P2Y2 receptor agonist that promotes tear fluid and mucin secretion and is currently approved in Japan and South Korea for the treatment of dry eye. In randomized, double-blind, multicentre trials in patients with dry eye, significantly greater improvements in fluorescein and rose bengal staining scores were seen with diquafosol ophthalmic solution 3% than with placebo, and diquafosol ophthalmic solution 3% was noninferior to sodium hyaluronate ophthalmic solution 0.1% in terms of the improvement in the fluorescein staining score and more effective than sodium hyaluronate ophthalmic solution 0.1% in terms of the improvement in the rose bengal staining score. The efficacy of diquafosol ophthalmic solution 3% in the treatment of dry eye was maintained in the longer term, with improvements also seen in subjective dry eye symptoms, and was also shown in a real-world setting. Diquafosol ophthalmic solution 3% also demonstrated efficacy in various specific dry eye disorders, including aqueous-deficient dry eye, short tear film break-up time dry eye, obstructive meibomian gland dysfunction, dry eye following laser in situ keratomeileusis surgery and dry eye following cataract surgery, as well as in contact lens wearers and visual display terminal users. Diquafosol ophthalmic solution 3% was generally well tolerated in patients with dry eye, with eye irritation the most commonly reported adverse event.

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Anti-Obesity Pharmacotherapy: The Intercontinental Regulatory Divide
Andrew J. Krentz, Ken Fujioka, Marcus Hompesch

ABSTRACT
Obesity, while recognized as a pressing global public health issue, does not present an immediate threat to life. Accordingly, weight-reducing medication is required to be exceptionally safe [1]. Since the 1960s, several agents have been withdrawn in the USA or Europe because of toxicity issues (Table 1) [2]. Two events in particular helped change the regulatory and marketing landscape concerning the development, registration, and commercialization of weight-reducing drugs. The first was the suspension in 2008 by the European Medicines Agency (EMA) of marketing authorization for the cannabinoid receptor type 1 inverse agonist rimonabant following reports of psychiatric adverse events including suicidal ideation [3]. The second was the demise of sibutramine, a serotonin–norepinephrine reuptake inhibitor, in 2010 in response to the results of a post-marketing safety trial that demonstrated an increased risk of non-fatal myocardial infarction and stroke in patients with pre-existing cardiovascular disease.

The New Era of Drug Therapy for Obesity: The Evidence and the Expectations
Ben J. Jones, Stephen R. Bloom

ABSTRACT
There is an urgent need for effective pharmacological therapies to help tackle the growing obesity epidemic and the healthcare crisis it poses. The past 3 years have seen approval of a number of novel anti-obesity drugs. The majority of these influence hypothalamic appetite pathways via dopaminergic or serotoninergic signalling. Some are combination therapies, allowing lower doses to minimize the potential for off-target effects. An alternative approach is to mimic endogenous satiety signals using long-lasting forms of peripheral appetite-suppressing hormones. There is also considerable interest in targeting thermogenesis by brown adipose tissue to increase resting energy expenditure. Obesity pharmacotherapy has seen several false dawns, but improved understanding of the pathways regulating energy balance, and better-designed trials, give many greater confidence that recently approved agents will be both efficacious and safe.
Pharmacological Approaches to Delaying Disability Progression in Patients with Multiple Sclerosis
Heinz Wiendl, Sven G. Meuth

ABSTRACT
In individuals with multiple sclerosis, physical and cognitive disability progression are clinical and pathophysiological hallmarks of the disease. Despite shortcomings, particularly in capturing cognitive deficits, the Expanded Disability Status Scale is the assessment of disability progression most widely used in clinical trials. Here, we review treatment effects on disability that have been reported in large clinical trials of disease-modifying treatment, both among patients with relapsing–remitting disease and among those with progressive disease. However, direct comparisons are confounded to some degree by the lack of consistency in assessment of disability progression across trials. Confirmed disability progression (CDP) is a more robust measure when performed over a 6-month than a 3-month interval, and reduction in the risk of 6-month CDP in phase III trials provides good evidence for the beneficial effects on disability of several high-efficacy treatments for relapsing–remitting disease. It is also becoming increasingly clear that therapies effective in relapsing–remitting disease have little impact on the course of progressive disease. Given that the pathophysiological mechanisms, which lead to the long-term accrual of physical and cognitive deficits, are evident at the earliest stages of disease, it remains a matter of debate whether the most effective therapies are administered early enough to afford patients the best long-term outcomes.

Use of Non-Vitamin K Antagonist Oral Anticoagulants in Special Patient Populations with Nonvalvular Atrial Fibrillation: A Review of the Literature and Application to Clinical Practice
Julie Kalabalik, Gail B. Rattering, Jesse Sullivan, Malgorzata Slugocki

ABSTRACT
Atrial fibrillation is a commonly encountered arrhythmia associated with increased risk for thromboembolic events. Anticoagulation is necessary to decrease the risk of ischemic stroke. Traditionally, warfarin has been the only oral pharmacotherapeutic option for long-term anticoagulation in patients with nonvalvular atrial fibrillation (NVAF). Recently, non-vitamin K antagonist oral anticoagulants (NOAC), including dabigatran, rivaroxaban, apixaban, and edoxaban, have become available as alternatives for warfarin in the prevention of stroke in patients with NVAF. Recently published atrial fibrillation guidelines contain new recommendations for risk stratification tools in determining the need for anticoagulant therapy and incorporate NOAC pharmacotherapy options for stroke prevention in patients with NVAF. NOACs offer several advantages over warfarin, including the elimination of routine laboratory monitoring, fewer drug and food interactions, and rapid therapeutic onset and offset. However, the lack of antidote in the case of serious bleeding and lack of data for long-term use in patient populations at risk for bleeding is problematic. Older adults are at high risk for thromboembolic and bleeding events as a result of anticoagulation and require special consideration when selecting anticoagulant therapy. The risk of drug accumulation and bleeding is concerning in the presence of renal impairment. The objective of this review is to provide the clinician with an update on the use of NOACs for NVAF, focusing on older adults and patients with renal impairment in light of recently published atrial fibrillation guidelines. Available data on using NOACs in coronary artery stenting, cardioversion, and ablation are also reviewed.
Management Strategies for Clopidogrel Hypersensitivity
Craig J. Beavers, Nicolas W. Carris, Kathryn M. Ruf

ABSTRACT
Clopidogrel is a cornerstone of dual antiplatelet therapy. Hypersensitivity reactions potentially limit the use of this treatment and present a significant clinical challenge. The authors have developed recommendations for the management of clopidogrel hypersensitivity with consideration for the etiology, pathophysiology, and critical evaluation of potential management strategies. The clopidogrel hypersensitivity reaction is complex in mechanism and presents generally around day 5 of treatment. Generalized reactions are most common, but the reaction may also be localized or systemic. Screening patients for hypersensitivity is not always possible because the type IV delayed reaction is not detected reliably by conventional skin prick, intradermal challenge, or patch testing. Proposed strategies for management of clopidogrel hypersensitivity include treatment of the reaction with corticosteroids, clopidogrel desensitization, substituting an alternative P2Y12 inhibitor, or clopidogrel avoidance. The safety, efficacy, and cost of each potential strategy must be considered when managing a patient with clopidogrel hypersensitivity.

Regorafenib: A Review of Its Use in Patients with Advanced Gastrointestinal Stromal Tumours
Matt Shirley, Gillian M. Keating

ABSTRACT
Regorafenib (Stivarga®) is an orally administered small molecule inhibitor of multiple protein kinases, including kinases involved in oncogenesis and tumour angiogenesis. It was initially approved for use in patients with previously treated metastatic colorectal cancer. Based on the findings of the phase III GRID clinical trial, approval for regorafenib has been expanded to include the treatment of advanced gastrointestinal stromal tumours (GISTs) following the failure of imatinib and sunitinib. In the GRID trial, regorafenib significantly improved progression-free survival and was associated with a significantly higher disease control rate than placebo. No significant between-group difference was observed in overall survival (OS) in the trial; however, the high proportion of patients who crossed over from placebo to regorafenib likely impacted the OS analysis. Regorafenib has an acceptable tolerability profile, with most adverse events being manageable with dose modification and/or supportive measures. The most commonly reported drug-related adverse events among patients receiving regorafenib in the GRID trial were hand-foot skin reaction, hypertension, diarrhoea and fatigue.

Extended-Cycle Levonorgestrel/Ethinylestradiol and Low-Dose Ethinylestradiol (Seasonique®): A Review of Its Use as an Oral Contraceptive
Celeste B. Burness

ABSTRACT
A 91-day extended-cycle oral contraceptive (OC) consisting of levonorgestrel/ethinylestradiol 150/30 μg for 84 days and ethinylestradiol 10 μg for 7 days (Seasonique®) has recently been approved for the prevention of pregnancy in adult women in the EU. This regimen allows for a reduction in the number of withdrawal bleeding episodes to four per year, compared with 13 episodes per year with conventional 28-day regimens. Seasonique® was effective in preventing pregnancy in a large (n = 1006), noncomparative trial of healthy, sexually active women. In this trial, the overall Pearl index (pregnancies per 100 woman-years of use) in women aged 18–35 years (n = 621) was 0.76 and the Pearl index for method-failure (compliant use) was 0.26. Scheduled (withdrawal) bleeding and/or spotting remained fairly constant over time, with a mean of 2 days of bleeding and 1 day of spotting per each 91-day cycle. Unscheduled bleeding and unscheduled spotting was highest during the first few cycles of use and decreased thereafter.
Ombitasvir/Paritaprevir/Ritonavir plus Dasabuvir: A Review in Chronic HCV Genotype 1 Infection

Emma D. Deeks

ABSTRACT

A fixed-dose tablet comprising ombitasvir (an NS5A replication complex inhibitor), paritaprevir (an NS3/4A protease inhibitor) and ritonavir (a cytochrome P450 inhibitor) taken in combination with dasabuvir (an NS5B polymerase inhibitor) is indicated for the treatment of chronic hepatitis C virus (HCV) genotype 1 infection in several countries, including the USA (copackaged as Viekira Pak™) and those of the EU (Viekirax® and Exviera®). In phase II and III trials, this interferon-free regimen, taken ± ribavirin, provided high rates of sustained virological response 12 weeks post-treatment in adults with chronic HCV genotype 1a or 1b infection, including those with compensated cirrhosis, liver transplants or HIV-1 co-infection. The regimen was generally well tolerated, with nausea, insomnia, asthenia, pruritus, other skin reactions and fatigue being among the most common tolerability issues. Thus, ombitasvir/paritaprevir/ritonavir plus dasabuvir is an effective interferon-free, direct-acting antiviral regimen for use ± ribavirin in a broad range of adults chronically infected with HCV genotype 1.

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Pasireotide in Acromegaly: A Review

Kate McKeage

ABSTRACT

Pasireotide (Signifor®, Signifor® LAR) is a somatostatin analogue recently approved for the treatment of acromegaly. Unlike the first-generation agents, octreotide and lanreotide, which bind preferentially to somatostatin receptor (SSTR)-2, pasireotide binds to multiple SSTRs. This article reviews the clinical use and summarizes the pharmacological properties of intramuscular pasireotide in the treatment of acromegaly. The efficacy of pasireotide 40 mg every 28 days was superior to that of intramuscular octreotide 20 mg every 28 days with regard to biochemical control in a 12-month, phase III trial in medically naive patients. Similarly, in a 6-month, phase III trial in patients with acromegaly inadequately controlled with somatostatin analogues for at least 6 months, the efficacy of pasireotide 40 or 60 mg was superior to that of continued octreotide 30 mg or lanreotide autogel 120 mg (each drug was administered once every 28 days) with regard to biochemical control. The tolerability profile of intramuscular pasireotide is generally similar to that of first-generation agents, except for a higher incidence of hyperglycaemia-related adverse events with pasireotide. In clinical trials, the risk of developing pasireotide-associated hyperglycaemia was numerically greater in patients categorized as diabetic or prediabetic at baseline than in those with normal glucose tolerance. Careful monitoring of glycaemic status is required prior to and during pasireotide treatment and antidiabetic therapy should be commenced as indicated. Thus, in the treatment of acromegaly, pasireotide may be a more effective somatostatin analogue than other approved agents of the same class; however, the increased risk of hyperglycaemia needs to be considered and proactively managed.
Modulating Bone Resorption and Bone Formation in Opposite Directions in the Treatment of Postmenopausal Osteoporosis
Natasha M. Appelman-Dijkstra, Socrates E. Papapoulos

ABSTRACT
Bone remodeling, the fundamental process for bone renewal, is targeted by treatments of osteoporosis to correct the imbalance between bone resorption and bone formation and reduce the risk of fractures and associated clinical consequences. Currently available therapeutics affect bone resorption and bone formation in the same direction and either decrease (inhibitors of bone resorption) or increase (parathyroid hormone [PTH] peptides) bone remodeling. Studies of patients with rare bone diseases and genetically modified animal models demonstrated that bone resorption and bone formation may not necessarily be coupled, leading to identification of molecular targets in bone cells for the development of novel agents for the treatment of osteoporosis. Application of such agents to the treatment of women with low bone mass confirmed that bone resorption and bone formation can be modulated in different directions and so far two new classes of therapeutics for osteoporosis have been defined with distinct mechanisms of action. Such treatments, if combined with a favorable safety profile, will offer new therapeutic options and will improve the management of patients with osteoporosis.

Treatment of ALK-Rearranged Non-Small Cell Lung Cancer: Recent Progress and Future Directions
Laird Cameron, Benjamin Solomon

ABSTRACT
Rearrangements of the anaplastic lymphoma kinase (ALK) gene originally discovered nearly 20 years ago in the context of anaplastic large cell lymphoma were identified as oncogenic drivers in a subset of non-small cell lung cancers (NSCLCs) in 2007. These ALK gene rearrangements are present in 3–5 % of NSCLC patients, typically younger, never or light smokers with adenocarcinomas. Crizotinib is a first-in-class ALK tyrosine kinase inhibitor with significant activity in ALK-positive NSCLC that received accelerated US Food and Drug Administration approval for treatment of ALK-positive NSCLC in 2011, just 4 years after identification of ALK rearrangements in this setting. Subsequently, two phase III trials have shown crizotinib to have a tolerable toxicity profile and to be superior to standard chemotherapy for the first- or second-line treatment of advanced ALK-positive lung cancer and numerous countries have approved its use. Despite initial responses, acquired resistance to crizotinib invariably leads to disease progression. Mechanisms of resistance have been described to include ALK tyrosine kinase mutations, activation of bypass signalling pathways and pharmacokinetic failure of crizotinib. Several next-generation ALK inhibitors, including ceritinib and alectinib, are in clinical development and show efficacy in both the crizotinib naive and crizotinib refractory settings.

Aflibercept: A Review of Its Use in Diabetic Macular Oedema
Gillian M. Keating

ABSTRACT
Aflibercept (Eylea®) is an anti-vascular endothelial growth factor agent indicated for intravitreal use in the treatment of diabetic macular oedema. In patients with diabetic macular oedema, significantly greater improvements from baseline to week 52 in visual acuity were seen with intravitreal aflibercept versus macular laser photocoagulation in the phase III VISTA-DME and VIVID-DME trials, and versus intravitreal bevacizumab or ranibizumab in those with worse visual acuity at baseline (i.e. Early Treatment Diabetic Retinopathy Study letter score of <69) in the phase III PROTOCOL-T trial. Intravitreal aflibercept was generally well tolerated in patients with diabetic macular oedema. In conclusion, intravitreal aflibercept is an important new treatment for diabetic macular oedema.
Therapeutic Use of Metformin in Prediabetes and Diabetes Prevention
Ulrike Hostalek, Mike Gwilt, Steven Hildemann

ABSTRACT

People with elevated, non-diabetic, levels of blood glucose are at risk of progressing to clinical type 2 diabetes and are commonly termed ‘prediabetic’. The term prediabetes usually refers to high–normal fasting plasma glucose (impaired fasting glucose) and/or plasma glucose 2 h following a 75 g oral glucose tolerance test (impaired glucose tolerance). Current US guidelines consider high–normal HbA1c to also represent a prediabetic state. Individuals with prediabetic levels of dysglycaemia are already at elevated risk of damage to the microvasculature and macrovasculature, resembling the long-term complications of diabetes. Halting or reversing the progressive decline in insulin sensitivity and β-cell function holds the key to achieving prevention of type 2 diabetes in at-risk subjects. Lifestyle interventions aimed at inducing weight loss, pharmacologic treatments (metformin, thiazolidinediones, acarbose, basal insulin and drugs for weight loss) and bariatric surgery have all been shown to reduce the risk of progression to type 2 diabetes in prediabetic subjects. However, lifestyle interventions are difficult for patients to maintain and the weight loss achieved tends to be regained over time. Metformin enhances the action of insulin in liver and skeletal muscle, and its efficacy for delaying or preventing the onset of diabetes has been proven in large, well-designed, randomised trials, such as the Diabetes Prevention Program and other studies. Decades of clinical use have demonstrated that metformin is generally well-tolerated and safe. We have reviewed in detail the evidence base supporting the therapeutic use of metformin for diabetes prevention.

Controversies around Epidemiology, Diagnosis and Treatment of Clostridium difficile Infection
Fawziah Marra, Karen Ng

ABSTRACT

Clostridium difficile infection is a major public health problem. However, in recent years the epidemiology, risk factors, diagnosis, and treatment of C. difficile infection have undergone a significant change. The incidence of C. difficile has increased, not only in the healthcare sector but also in the community. Hospital-acquired infection and community-acquired disease have different risk factors, with the latter occurring in children and younger individuals without a history of antibiotic use or previous infections. From a clinician’s perspective, a quick efficient diagnosis is required for patient treatment; however, the old method of using enzyme immunoassays is insensitive and not very specific. Recent literature around diagnostic testing for C. difficile infection suggests using PCR or a two-step algorithm to improve sensitivity and specificity. More failures and recurrence with metronidazole have led to treatment algorithms suggesting its use for mild infections and switching to vancomycin if there is no clinical improvement. Alternatively, if signs and symptoms suggest severe infection, then oral vancomycin is recommended as a first-line agent. The addition of a new but costly agent, fidaxomicin, has seen some disparity between the European and North American guidelines with regard to when it should be used. Lastly, rapid developments and good results with fecal microbial transplantation have also left clinicians wondering about its place in therapy. This article reviews the literature around some of the recent controversies in the field of C. difficile infection.
Dexmedetomidine: A Review of Its Use for Sedation in the Intensive Care Setting
Gillian M. Keating

ABSTRACT
Dexmedetomidine (Dexdor®) is a highly selective α2-adrenoceptor agonist. It has sedative, analgesic and opioid-sparing effects and is suitable for short- and longer-term sedation in an intensive care setting. In the randomized, double-blind, multicentre MIDEX and PRODEX trials, longer-term sedation with dexmedetomidine was noninferior to midazolam and propofol in terms of time spent at the target sedation range, as well as being associated with a shorter time to extubation than midazolam or propofol, and a shorter duration of mechanical ventilation than midazolam. Patients receiving dexmedetomidine were also easier to rouse, more co-operative and better able to communicate than patients receiving midazolam or propofol. Dexmedetomidine had beneficial effects on delirium in some randomized, controlled trials (e.g. patients receiving dexmedetomidine were less likely to experience delirium than patients receiving midazolam, propofol or remifentanil and had more delirium- and coma-free days than patients receiving lorazepam). Intravenous dexmedetomidine had an acceptable tolerability profile; hypotension, hypertension and bradycardia were the most commonly reported adverse reactions. In conclusion, dexmedetomidine is an important option for sedation in the intensive care setting.

Nintedanib: A Review of Its Use in Patients with Idiopathic Pulmonary Fibrosis
Gillian M. Keating

ABSTRACT
Nintedanib (Ofev®) inhibits receptor tyrosine kinases implicated in the pathogenesis of idiopathic pulmonary fibrosis (IPF). This article reviews the efficacy and tolerability of oral nintedanib in the treatment of IPF, as well as summarizing its pharmacological properties. In the randomized, double-blind, multinational, 12-month INPULSIS-1 and -2 trials in patients with IPF, nintedanib significantly reduced the decline in forced vital capacity versus placebo, indicating a slowing of disease progression. The time to first acute exacerbation was significantly increased with nintedanib in INPULSIS-2, but not in INPULSIS-1, and significantly less deterioration in health-related quality of life was seen with nintedanib in INPULSIS-2, but not in INPULSIS-1. Nintedanib had an acceptable tolerability profile in patients with IPF; gastrointestinal adverse events (diarrhoea, nausea, vomiting) were reported most commonly. In conclusion, nintedanib is an important new option for the treatment of IPF.

Exenatide Extended-Release: An Updated Review of Its Use in Type 2 Diabetes Mellitus
Yahiya Y. Syed, Paul L. McCormack

ABSTRACT
Exenatide extended-release (exenatide ER) [Bydureon®] is a glucagon-like peptide-1 receptor agonist, approved for the treatment of type 2 diabetes mellitus. It is injected subcutaneously by patients once weekly, with no dose titration required. This article updates an earlier review of exenatide ER in the management of type 2 diabetes, focusing on recently published data. In randomized, controlled trials, adjunctive exenatide ER 2 mg once weekly for 24–30 weeks significantly improved glycaemic control and reduced bodyweight in patients with inadequately controlled type 2 diabetes despite diet plus exercise and/or oral antihyperglycaemic drugs (OADs). These beneficial effects of exenatide ER were maintained after up to 6 years of treatment. In patients receiving one or more OADs, addition of exenatide ER provided better glycaemic control than an immediate-release formulation of exenatide (exenatide twice daily), sitagliptin, pioglitazone, insulin glargine or insulin detemir, and was slightly less effective than liraglutide. In patients treated with diet plus exercise alone, adjunctive exenatide ER was noninferior to metformin and superior to sitagliptin, but was not noninferior to pioglitazone. Exenatide ER was generally well tolerated, with a low inherent risk of hypoglycaemia. The most common adverse events were mild to moderate gastrointestinal events, injection-site reactions and headache.
Trelagliptin: First Global Approval
Kate McKeage

ABSTRACT
Trelagliptin (Zafatek®) is an orally active dipeptidyl peptidase (DPP)-4 inhibitor developed by Takeda and approved in Japan for the treatment of type 2 diabetes mellitus (T2DM). Unlike other approved agents of its class, which are usually administered once daily, trelagliptin can be administered once weekly. Phase II development of trelagliptin was discontinued in the USA and EU, as Takeda considered that the costs associated with obtaining approval in these markets were prohibitive. This article summarizes the milestones in the development of trelagliptin leading to this first approval for T2DM.

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New and Emerging Treatments for Cystic Fibrosis
Peter J. Barry, Andrew M. Jones

ABSTRACT
Recently, a significant number of additional key medications have become licensed in Europe for the treatment of patients with cystic fibrosis (CF), including a number of inhaled antibiotics, such as nebulised aztreonam and dry powder versions of colistin and tobramycin for inhalation; dry powder inhaled mannitol, an agent to improve airway hydration and aid airway clearance; and ivacaftor, an oral therapy that directly acts on dysfunctional CFTR to correct the basic defect encountered in CF patients with the G551D CF gene mutation. The marked success of ivacaftor both in clinical trials and in post-licensing evaluation studies in treating patients with G551D and other gating mutations has greatly encouraged the ongoing development of similar therapies that can directly target the underlying cause of CF. Other therapies, including a number of anti-infectives, anti-inflammatories and replacement pancreatic enzymes, are currently undergoing clinical studies. This article reviews those treatments that have been recently licensed for CF and highlights some of the exciting emerging therapies presently under evaluation in clinical trials. In addition, it discusses some of the potential challenges being encountered by research and clinical teams in developing and delivering treatments for this condition.

Recombinant Human Parathyroid Hormone (1–84): A Review in Hypoparathyroidism
Esther S. Kim, Gillian M. Keating

ABSTRACT
Full-length recombinant human parathyroid hormone [rhPTH (1–84); Natpara®] is approved in the USA as an adjunct to calcium and vitamin D therapy for control of hypocalcaemia in patients with hypoparathyroidism. This article reviews the clinical efficacy and tolerability of rhPTH (1–84) in hypoparathyroidism and summarizes its pharmacological properties. In a pivotal phase III trial, subcutaneous rhPTH (1–84) was effective in maintaining albumin-corrected total serum calcium levels while reducing/eliminating the need for oral calcium and active vitamin D. rhPTH (1–84) had a generally acceptable tolerability profile in this trial, with <3 % of patients discontinuing treatment because of adverse events. Commonly occurring adverse reactions included hypocalcaemia, hypercalcaemia and hypercalciuria. As the first PTH replacement therapy for hypoparathyroid patients with hypocalcaemia, rhPTH (1–84) is an effective regimen, has generally acceptable tolerability and represents an important advance for the management of hypoparathyroidism.
Current and Emerging Therapeutic Strategies for the Treatment of Meibomian Gland Dysfunction (MGD)

Adam R. Thode, Robert A. Latkany

ABSTRACT

Meibomian gland (MG) dysfunction (MGD) is a multifactorial, chronic condition of the eyelids, leading to eye irritation, inflammation and ocular surface disease. Initial conservative therapy often includes a combination of warm compresses in addition to baby shampoo or eyelid wipes. The practice of lid hygiene dates back to the 1950s, when selenium sulfide-based shampoo was first used to treat seborrhoeic dermatitis of the eyelids. Today, tear-free baby shampoo has replaced dandruff shampoo for MGD treatment and offers symptom relief in selected patients. However, many will not achieve significant improvement on this therapy alone; some may even develop an allergy to the added dyes and fragrances in these products. Other manual and mechanical techniques to treat MGD include MG expression and massage, MG probing and LipiFlow®. While potentially effective in patients with moderate MGD, these procedures are more invasive and may be cost prohibitive. Pharmacological treatments are another course of action. Supplements rich in omega-3 fatty acids have been shown to improve both MGD and dry eye symptoms. Tea tree oil, specifically the terpenin-4-ol component, is especially effective in treating MGD associated with Demodex mites. Topical antibiotics, such as azithromycin, or systemic antibiotics, such as doxycycline or azithromycin, can improve MGD symptoms both by altering the ocular flora and through anti-inflammatory mechanisms. Addressing and treating concurrent ocular allergy is integral to symptom management. Topical N-acetylcysteine and topical cyclosporine can both be effective therapeutic adjuncts in patients with concurrent dry eye. A short course of topical steroid may be used in some severe cases, with monitoring for steroid-induced glaucoma and cataracts. While the standard method to treat MGD is simply warm compresses and baby shampoo, a more tailored approach to address the multiple aetiologies of the disease is suggested.

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Current Treatment of Dyslipidemia: A New Paradigm for Statin Drug Use and the Need for Additional Therapies

Richard Kones, Umme Rumana

ABSTRACT

Coronary heart disease (CHD) is the leading cause of death in most countries, with the high prevalence currently driven by dual epidemics of obesity and diabetes. Statin drugs, the most effective, evidence-based agents to prevent and treat this disease, have a central role in management and are advised in all published guidelines. The 2013 American College of Cardiology/American Heart Association (ACC/AHA) cholesterol and assessment guidelines (‘new ACC/AHA guidelines’) emphasized global cardiovascular (CV) risk reduction as opposed to targeting low-density lipoprotein-cholesterol (LDL-C) levels, stressed the use of stents in two dose intensities, utilized a new risk calculator using pooled cohort equations, and lowered the risk cutoff for initiation of statin therapy. Although there were major strengths of the new ACC/AHA guidelines, substantial controversy followed their release, particulars of which are discussed in this review. They were generally regarded as improvements in an ongoing transition using evidenced-based data for maximum patient benefit. Several guidelines, other than the ACC/AHA guidelines, currently provide practitioners with choices, some depending on practice locations. Cholesterol control with statin drugs is used in all paradigms. However, some patients respond inadequately, approximately 15 % are intolerant, and other factors prevent attaining cholesterol goals in as many as 40 % of patients. Even after treatment, substantial residual risk for ongoing major events remains. Another readily available modality that can rival statin drugs in effectiveness is vast improvement in diet and lifestyle within the general population; however, despite great effort, existing programs to implement such changes have failed. Hence, despite unrivaled success, there is great need for additional drugs to prevent and treat CHD, whether as monotherapy or in combination with statin drugs.
ABSTRACT

Since their introduction, statin (HMG-CoA reductase inhibitor) drugs have advanced the practice of cardiology to unparalleled levels. Even so, coronary heart disease (CHD) still remains the leading cause of death in developed countries, and is predicted to soon dominate the causes of global mortality and disability as well. The currently available non-statin drugs have had limited success in reversing the burden of heart disease, but new information suggests they have roles in sizeable subpopulations of those affected. In this review, the status of approved non-statin drugs and the significant potential of newer drugs are discussed. Several different ways to raise plasma high-density lipoprotein (HDL) cholesterol (HDL-C) levels have been proposed, but disappointments are now in large part attributed to a preoccupation with HDL quantity, rather than quality, which is more important in cardiovascular (CV) protection. Niacin, an old drug with many antiatherogenic properties, was re-evaluated in two imperfect randomized controlled trials (RCTs), and failed to demonstrate clear effectiveness or safety. Fibrates, also with an attractive antiatherosclerotic profile and classically used for hypertriglyceridemia, lacks evidence-based proof of efficacy, save for a subgroup of diabetic patients with atherogenic dyslipidemia. Omega-3 fatty acids fall into this category as well, even with an impressive epidemiological evidence base. Omega-3 research has been plagued with methodological difficulties yielding tepid, uncertain, and conflicting results; well-designed studies over longer periods of time are needed. Addition of ezetimibe to statin therapy has now been shown to decrease levels of low-density lipoprotein (LDL) cholesterol (LDL-C), accompanied by a modest decrease in the number of CV events, though without any improvement in CV mortality. Importantly, the latest data provide crucial evidence that LDL lowering is central to the management of CV disease. Of drugs that inhibit cholesteryl ester transfer protein (CETP) tested thus far, two have failed and two remain under investigation and may yet prove to be valuable therapeutic agents. Monoclonal antibodies to proprotein convertase subtilisin/kexin type 9, now in phase III trials, lower LDL-C by over 50% and are most promising. These drugs offer new ability to lower LDL-C in patients in whom statin drug use is, for one reason or another, limited or insufficient. Mipomersen and lomitapide have been approved for use in patients with familial hypercholesterolemia, a more common disease than appreciated. Anti-inflammatory drugs are finally receiving due attention in trials to elucidate potential clinical usefulness. All told, even though statins remain the standard of care, non-statin drugs are poised to assume a new, vital role in managing dyslipidemia.
ABSTRACT

Coronary artery disease and acute myocardial infarction still represent the leading cause of mortality in developed countries. Therefore, great efforts have been made in the last decades to improve reperfusion strategies and adjunctive antithrombotic therapies. In fact, despite optimal epicardial recanalisation, a large proportion of patients still experience impaired reperfusion and in-stent thrombosis. The adjunctive use of glycoprotein (GP) IIb-IIIa inhibitors may certainly contribute to the reduction of such complications, especially when administered in the early phase of infarction. In fact, in this phase a larger platelet composition of the thrombus and the presence of a larger amount of viable myocardium, as compared to a delayed phase, may increase the benefits from this therapy and counterbalance the potential higher risk of bleeding. A large body of evidence has been accumulated on the benefits from GP IIb-IIIa inhibitors in terms of prevention of stent thrombosis, and benefits in mortality, especially among high-risk patients and as upstream strategy. Therefore, based on current available data, GP IIb-IIIa inhibitors can be recommended as early as possible (upstream strategy) among high-risk patients, such as those with advanced Killip class or anterior myocardial infarction (MI), and those presenting within the first three hours. Even though it is not universally accepted, in our opinion this strategy should be implemented in a pre-hospital setting (in ambulance) or at first hospital admission (Emergency Room or Coronary Care Unit, irrespective of whether they are in the spoke or hub hospitals). Peri-procedural intracoronary administration of GP IIb-IIIa inhibitors has not provided additional benefits as compared to intravenous administration and therefore cannot be recommended. Even though the vast majority of trials have been conducted with abciximab, several meta-analyses comparing small molecules (mainly high-dose tirofiban rather than eptifibatide) versus abciximab showed similar angiographic and clinical results between the molecules. Several recent investigations and meta-analyses have documented the higher risk of stent thrombosis associated with bivalirudin as compared to unfractionated heparin (UFH). Being that these results are independent from the use of GP IIb-IIIa inhibitors, UFH should still remain the anticoagulation therapy of choice in ST-segment elevation myocardial infarction (STEMI) patients. Minimisation of bleeding complications by extensive use of the radial approach, in the setting of STEMI, may further contribute to the adoption of a more aggressive antithrombotic and antiplatelet therapy incorporating the use of GP IIb-IIIa inhibitors. The establishment of dedicated networks for STEMI, and the large STEMI campaign, will certainly contribute to increase the proportion of patients presenting at first medical contact within the early phase (3 h) of infarction and therefore highly suitable for a more aggressive pharmacoinvasive approach with upstream administration of GP IIb-IIIa inhibitors. In fact, although the current therapeutic targets of increased rates of timely reperfusion, mainly by primary percutaneous coronary intervention (PCI), has been achieved, a deep look into the future in the fight against MI will certainly put aborting infarction as the major desirable target to be achieved.

Eluxadoline: First Global Approval
Karly P. Garnock-Jones

ABSTRACT

Eluxadoline (Viberzi™), developed by Actavis (now Allergan), is an orally administered, first-in-class compound that functions as both a μ-opioid receptor agonist and a δ-opioid receptor antagonist, and is indicated for the treatment of diarrhoea-predominant irritable bowel syndrome (IBS-D) in adults. The agent was originally developed by Janssen Pharmaceutica. Eluxadoline has been approved in the US, and submissions to other global authorities are being contemplated or planned. This article summarizes the milestones in the development of eluxadoline leading to this first approval for IBS-D.
ABSTRACT

Acamprosate (Campral®, Aotal®, Regtect®) is one of a limited number of pharmacological treatment options approved as an adjunct to psychosocial interventions to facilitate the maintenance of abstinence in alcohol-dependent patients. It has been used in Europe, the USA and other countries for many years and was recently approved for this indication in Japan. In several randomized, double-blind, placebo-controlled trials (without active comparators), acamprosate in conjunction with psychosocial therapy for 3–12 months was generally significantly better than placebo plus psychosocial interventions in improving various key outcomes, including the proportion of patients who maintained complete abstinence from alcohol (complete abstinence rate), the mean cumulative abstinence duration, the percentage of alcohol-free days and the median time to first drink. Acamprosate as an adjunct to psychosocial interventions also demonstrated efficacy in some randomized, active-comparator trials of similar duration. Although results were not always consistent across individual trials, overall findings were generally favourable for acamprosate in a recent meta-analysis, which showed that alcohol-consumption outcomes were similarly improved with acamprosate or naltrexone. Acamprosate is generally well tolerated, has a low propensity for drug interactions and may be used without dosage adjustment in patients with mild to moderate hepatic impairment, although dosage adjustments or contraindications are recommended in patients with renal impairment. Thus, the use of acamprosate as an adjunct to psychosocial interventions in alcohol-dependent patients provides modest but potentially valuable improvements in alcohol-consumption outcomes and is generally well tolerated.

Naltrexone ER/Bupropion ER: A Review in Obesity Management

Sarah L. Greig, Gillian M. Keating

ABSTRACT

Oral naltrexone extended-release/bupropion extended-release (naltrexone ER/bupropion ER; Contrave®, Mysimba™) is available as an adjunct to a reduced-calorie diet and increased physical activity in adults with an initial body mass index (BMI) of ≥30 kg/m2 (i.e. obese) or a BMI of ≥27 kg/m2 (i.e. overweight) in the presence of at least one bodyweight-related comorbidity, such as type 2 diabetes mellitus, hypertension or dyslipidaemia. In 56-week phase III trials in these patient populations, oral naltrexone ER/bupropion ER 32/360 mg/day was significantly more effective than placebo with regard to percentage bodyweight reductions from baseline and the proportion of patients who achieved bodyweight reductions of ≥5 and ≥10 %. Significantly greater improvements in several cardiometabolic risk factors were also observed with naltrexone ER/bupropion ER versus placebo, as well as greater improvements in glycated haemoglobin levels in obese or overweight adults with type 2 diabetes. Naltrexone ER/bupropion ER was generally well tolerated in phase III trials, with nausea being the most common adverse event. Thus, naltrexone ER/bupropion ER 32/360 mg/day as an adjunct to a reduced-calorie diet and increased physical activity, is an effective and well tolerated option for chronic bodyweight management in obese adults or overweight adults with at least one bodyweight-related comorbidity.
Dalbavancin: A Review in Acute Bacterial Skin and Skin Structure Infections

Lesley J. Scott

ABSTRACT

Intravenous dalbavancin (Dalvance™; Xydalba™) is approved for use in adult patients with acute bacterial skin and skin structure infections (ABSSSI), with the recommended regimen being a 1000 mg dose followed 1 week later by a 500 mg dose. In the multinational DISCOVER 1 and 2 trials in adult patients with ABSSSI, dalbavancin treatment was noninferior to vancomycin (for ≥3 days with an option to switch to oral linezolid to complete a 10- to 14-day course) in terms of early clinical success rates (assessed 48–72 h after initiation of treatment; primary endpoint required by the FDA to assess noninferiority in registration trials of ABSSSI). Clinical response rates were also similar in both treatment groups at the end of treatment (day 14–15), irrespective of geographic region or baseline characteristics, including by infection type, diabetes mellitus status, systemic inflammatory response syndrome status, causative pathogen and renal function. Dalbavancin was generally well tolerated, with adverse events generally being of mild to moderate intensity and transient. With its broad spectrum of activity against clinically relevant Gram-positive pathogens and its favourable pharmacokinetic profile that permits a convenient two-dose, once-weekly regimen with no requirement for therapeutic drug monitoring, dalbavancin is a promising emerging option for the treatment of ABSSSI in adult patients.

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Navigating the Challenges of Endocrine Treatments in Premenopausal Women with ER-Positive Early Breast Cancer

Marco Colleoni, Elisabetta Munzone

ABSTRACT

Endocrine therapy is a key component of adjuvant treatment for premenopausal patients with endocrine-responsive tumors. It is commonly well tolerated, although side effects are a main concern in the selection of treatment options. Tamoxifen is still considered an adequate endocrine therapy in a large group of premenopausal patients (e.g. lower-risk patient, presence of co-morbidities, patient preference). Results of the SOFT and TEXT trials addressing new adjuvant endocrine treatment options in premenopausal patients were recently presented. Overall, in the SOFT study the premenopausal population did not benefit from the addition of ovarian function suppression (OFS). Nevertheless, for women at sufficient risk of recurrence to receive adjuvant chemotherapy and who maintained premenopausal estradiol, the addition of OFS to tamoxifen reduced the risk of recurrence. The magnitude of the effect was larger in younger patients. Moreover, in the SOFT and TEXT trials, adjuvant treatment with exemestane plus OFS, as compared with tamoxifen plus OFS, significantly improved disease-free survival, breast cancer-free interval and distant disease-free survival. However, premenopausal patients include heterogeneous subsets of women and tumors where costs and benefits of adjuvant endocrine therapy should be properly weighted. Issues specific for premenopausal patients, related to desire for pregnancy, family planning, safety, quality of life and subjective side effects, should be a priority in the therapeutic algorithm. Therefore, selecting the best-tolerated agent can enhance adherence to therapies and reduce the impact on quality of life and health status for these younger patients.
Emerging Agents for the Treatment of Advanced, Imatinib-Resistant Gastrointestinal Stromal Tumors: Current Status and Future Directions

Sebastian Bauer, Heikki Joensuu

ABSTRACT

Imatinib is strongly positioned as the recommended first-line agent for most patients with advanced gastrointestinal stromal tumor (GIST) due to its good efficacy and tolerability. Imatinib-resistant advanced GIST continues to pose a therapeutic challenge, likely due to the frequent presence of multiple mutations that confer drug resistance. Sunitinib and regorafenib are approved as second- and third-line agents, respectively, for patients whose GIST does not respond to imatinib or who do not tolerate imatinib, and their use is supported by large randomized trials. ATP-mimetic tyrosine kinase inhibitors provide clinical benefit even in heavily pretreated GIST suggesting that oncogenic dependency on KIT frequently persists. Several potentially useful tyrosine kinase inhibitors with distinct inhibitory profiles against both KIT ATP-binding domain and activation loop mutations have not yet been fully evaluated. Agents that have been found promising in preclinical models and early clinical trials include small molecule KIT and PDGFRA mutation-specific inhibitors, heat shock protein inhibitors, histone deacetylase inhibitors, allosteric KIT inhibitors, KIT and PDGFRA signaling pathway inhibitors, and immunological approaches including antibody-drug conjugates. Concomitant or sequential administration of tyrosine kinase inhibitors with KIT signaling pathway inhibitors require further evaluation, as well as rotation of tyrosine kinase inhibitors as a means to suppress drug-resistant cell clones.

Expert Consensus on the Management of Adverse Events from EGFR Tyrosine Kinase Inhibitors in the UK

R. Califano, N. Tariq, S. Compton, D. A. Fitzgerald, C. A. Harwood, R. Lal

ABSTRACT

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) such as gefitinib, erlotinib, and afatinib are standard-of-care for first-line treatment of EGFR-mutant advanced non-small cell lung cancer (NSCLC). These drugs have a proven benefit in terms of higher response rate, delaying progression and improvement of quality of life over palliative platinum-based chemotherapy. The most common adverse events (AEs) are gastrointestinal (GI) (diarrhoea and stomatitis/mucositis) and cutaneous (rash, dry skin and paronychia). These are usually mild, but if they become moderate or severe, they can have a negative impact on the patient’s quality of life (QOL) and lead to dose modifications or drug discontinuation. Appropriate management of AEs, including prophylactic measures, supportive medications, treatment delays and dose reductions, is essential. A consensus meeting of a UK-based multidisciplinary panel composed of medical and clinical oncologists with a special interest in lung cancer, dermatologists, gastroenterologists, lung cancer nurse specialists and oncology pharmacists was held to develop guidelines on prevention and management of cutaneous (rash, dry skin and paronychia) and GI (diarrhoea, stomatitis and mucositis) AEs associated with the administration of EGFR-TKIs. These guidelines detail supportive measures, treatment delays and dose reductions for EGFR-TKIs. Although the focus of the guidelines is to support healthcare professionals in UK clinical practice, it is anticipated that the management strategies proposed will also be applicable in non-UK settings.
Nebivolol is a highly selective β1-adrenergic receptor antagonist with a pharmacologic profile that differs from those of other drugs in its class. In addition to cardioselectivity mediated via β1 receptor blockade, nebivolol induces nitric oxide-mediated vasodilation by stimulating endothelial nitric oxide synthase via β3 agonism. This vasodilatory mechanism is distinct from those of other vasodilatory β-blockers (carvedilol, labetalol), which are mediated via α-adrenergic receptor blockade. Nebivolol is approved for the treatment of hypertension in the US, and for hypertension and heart failure in Europe. While β-blockers are not recommended within the current US guidelines as first-line therapy for treatment of essential hypertension, nebivolol has shown comparable efficacy to currently recommended therapies in lowering peripheral blood pressure in adults with hypertension with a very low rate of side effects. Nebivolol also has beneficial effects on central blood pressure compared with other β-blockers. Clinical data also suggest that nebivolol may be useful in patients who have experienced erectile dysfunction while on other β-blockers. Here we review the pharmacological profile of nebivolol, the clinical evidence supporting its use in hypertension as monotherapy, add-on, and combination therapy, and the data demonstrating its positive effects on heart failure and endothelial dysfunction.

Non-Alcoholic Steatohepatitis: Limited Available Treatment Options but Promising Drugs in Development and Recent Progress Towards a Regulatory Approval Pathway

Claudia Filozof, Barry J. Goldstein, Richard N. Williams, Arun Sanyal

The prevalence of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) is increasing world-wide in parallel to the increase of the obesity epidemic. Insulin resistance (IR) and the accumulation of triglyceride-derived toxic lipid metabolites play a key role in its pathogenesis. Multiple biomarkers are being evaluated for the non-invasive diagnosis of NASH. However, a percutaneous liver biopsy is still the gold standard method; the minimal diagnostic criteria include the presence of >5 % macrovesicular steatosis, inflammation, and liver cell ballooning. Several pharmaceutical agents have been evaluated for the treatment of NASH; however, no single therapy has been approved so far. Due to the increasing prevalence and the health burden, there is a high need to develop therapeutic strategies for patients with NASH targeting both those with early-stage disease as well as those with advanced liver fibrosis. There are unique challenges in the design of studies for these target populations. Collaborative efforts of health authorities, medical disease experts, and the pharmaceutical industry are ongoing to align options for a registrational pathway. Several companies pursuing different mechanisms of action are nearing the end of phase II with their candidates. This manuscript reviews those compounds with a variety of mode of actions that have been evaluated and/or are currently being tested with the goal of achieving a NAFLD/NASH indication.
Apremilast (Otezla®) is an oral phosphodiesterase 4 inhibitor indicated for the twice-daily treatment of adults with psoriasis and psoriatic arthritis (PsA). Its use in these patient populations has been assessed in two phase III clinical trial programmes (ESTEEM and PALACE). At 16 weeks in the two ESTEEM trials, apremilast reduced the severity and extent of moderate to severe plaque psoriasis, including nail, scalp and palmoplantar manifestations, versus placebo in adults, with these benefits generally being sustained over 52 weeks of treatment. Similarly, in three PALACE trials (PALACE 1–3), apremilast improved the signs and symptoms of PsA relative to placebo at 16 weeks in adults with active disease despite treatment with conventional synthetic and/or biologic disease-modifying anti-rheumatic drugs. These PsA benefits were generally sustained for up to 104 weeks of treatment; skin involvement, enthesitis and dactylitis also improved with the drug. Apremilast was generally well tolerated, with the most common adverse events being diarrhoea and nausea in the first year of treatment (usually occurring in the first 2 weeks after the first dose and resolving within 4 weeks) and nasopharyngitis and upper respiratory tract infection with continued treatment. Although further longer-term and comparative efficacy and tolerability data would be beneficial, the current clinical data indicate that apremilast is an effective and well tolerated option for the management of psoriasis and PsA in adults.

Collagenase Clostridium Histolyticum: A Review in Peyronie’s Disease

Sohita Dhillon

ABSTRACT

Collagenase Clostridium Histolyticum (CCH) (Xiaflex®, Xiapex®) intralvesional injection is a mixture of class I (AUX-I) and class II (AUX-II) clostridial collagenases. It is indicated for the treatment of adult men with Peyronie’s disease with a palpable plaque and curvature deformity of ≥30° at the start of therapy. This article reviews the efficacy and tolerability of CCH in this indication and briefly summarizes its pharmacology. CCH treatment significantly improved penile curvature deformity and reduced patient-reported bother associated with Peyronie’s disease in the 52-week, double-blind, phase III IMPRESS I and II studies. Treatment benefit with CCH was also seen in 36-week, open-label studies, providing further support for its efficacy. CCH was generally well tolerated in patients with Peyronie’s disease, with most treatment-related adverse events being of mild or moderate severity. Serious treatment-related adverse events (penile haematoma or corporal ruptures) were reported in <1 % of CCH recipients in clinical studies. Although further studies assessing the long-term effects of CCH intralvesional injection are needed, current evidence indicates that this is a minimally invasive, effective and generally well tolerated treatment option for patients with Peyronie’s disease.
Nivolumab: A Review in Advanced Melanoma
Lesley J. Scott

ABSTRACT
An improved understanding of cancer genetics and immune regulatory pathways, including those associated with evasion of immune surveillance by tumours, has culminated in the development of several targeted therapies. One such strategy that acts to negate evasion of immune surveillance by tumours is inhibition of the programmed cell death receptor-1 (PD-1) checkpoint pathway. Intravenous nivolumab (Opdivo®), a PD-1 checkpoint inhibitor, is approved or in pre-registration in various countries for use in adult patients with advanced melanoma, with the recommended monotherapy dosage being a 60-min infusion of 3 mg/kg once every 2 weeks. In well-designed multinational trials, as monotherapy or in combination with ipilimumab (a cytotoxic T-lymphocyte antigen 4 checkpoint inhibitor), nivolumab significantly improved clinical outcomes and had a manageable tolerability profile in adult patients with advanced melanoma with or without BRAF mutations. Nivolumab monotherapy was associated with a higher objective response rate (ORR) than chemotherapy in treatment-experienced patients and a higher ORR and prolonged progression-free survival (PFS) and overall survival than dacarbazine in treatment-naive patients. In combination with ipilimumab, nivolumab was associated with an improved ORR and prolonged PFS compared with ipilimumab monotherapy in treatment-naive patients. In addition, nivolumab monotherapy significantly prolonged PFS and improved ORRs compared with ipilimumab monotherapy. The optimal combination regimen for immune checkpoint inhibitors remains to be fully elucidated, with various combination regimens and different sequences of individual immunotherapies currently being investigated in ongoing clinical trials. Given the significant improvements in outcomes associated with nivolumab in clinical trials, nivolumab monotherapy or combination therapy is a valuable first-line or subsequent treatment option for adult patients with unresectable or metastatic melanoma, irrespective of BRAF mutation status.

Cangrelor: A Review in Percutaneous Coronary Intervention
Gillian M. Keating

ABSTRACT
Cangrelor (Kengreal®, Kengreal™) is an intravenously administered P2Y12 receptor inhibitor. It is direct-acting and reversible, with a very rapid onset and offset of action. The randomized, double-blind, multinational, phase III CHAMPION PHOENIX trial compared the efficacy of intravenous cangrelor with that of oral clopidogrel in patients requiring percutaneous coronary intervention (PCI) for stable angina pectoris, a non-ST-segment elevation acute coronary syndrome or ST-segment elevation myocardial infarction (MI). The primary composite efficacy endpoint of death from any cause, MI, ischaemia-drive revascularization or stent thrombosis in the 48 h following randomization occurred in significantly fewer cangrelor than clopidogrel recipients. The rate of severe or life-threatening non-coronary artery bypass graft-related, GUSTO-defined bleeding at 48 h did not significantly differ between cangrelor and clopidogrel recipients. In conclusion, intravenous cangrelor is an important new option for use in patients undergoing PCI who have not been treated with oral P2Y12 inhibitors.
Aflibercept is a recombinant fusion protein that acts as a soluble decoy receptor for vascular endothelial growth factor (VEGF), a key regulator of angiogenesis. It binds to all isoforms of VEGF-A as well as VEGF-B and placental growth factor, and, thus, prevents them from binding to and activating their cognate receptors. In the USA and EU, intravenously administered aflibercept in combination with an infusion of leucovorin, fluorouracil and irinotecan (FOLFIRI) is approved for the treatment of patients with metastatic colorectal cancer that is resistant to or has progressed after treatment with an oxaliplatin-containing regimen. The efficacy of aflibercept in this indication was assessed in a multinational, pivotal phase 3 trial (VELOUR), in which the approved regimen of aflibercept 4 mg/kg every 2 weeks plus FOLFIRI significantly prolonged median overall survival by 1.44 months compared with FOLFIRI alone (primary endpoint). The addition of aflibercept also significantly prolonged progression-free survival and significantly increased the objective response rate compared with FOLFIRI alone. Addition of aflibercept to FOLFIRI was associated with anti-VEGF-related adverse events and an increased incidence of FOLFIRI-related adverse events, but the tolerability of the combination was generally acceptable in this pre-treated population. The most common grade 3 or 4 adverse events with aflibercept plus FOLFIRI included neutropenia, diarrhoea and hypertension. In conclusion, aflibercept plus FOLFIRI is a useful treatment option for patients with metastatic colorectal cancer previously treated with an oxaliplatin-containing regimen, with or without bevacizumab.

ABSTRACT

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Leveraging Cancer Therapeutics for the HIV Cure Agenda: Current Status and Future Directions

Mark N. Polizzotto, Grace Chen, Randall L. Tressler, Catherine Godfrey

Despite effective antiretroviral therapy (ART) and undetectable HIV RNA in the plasma, latent replication-competent HIV persists indefinitely in long-lived cells. Cessation of ART results in rebound of HIV from these persistent reservoirs. While this was thought to be an insurmountable obstacle to viral eradication, recent cases suggest otherwise. To date one patient has been “cured” of HIV and several others have been able to interrupt ART without viral rebound for prolonged periods. These events have sparked renewed interest in developing strategies that will allow eradication of HIV in infected individuals. We review the current knowledge of HIV latency and the viral reservoir, describe the potential utility of emerging cancer therapeutics in HIV cure research with an emphasis on pathways implicated in reservoir persistence, and outline opportunities and challenges in the context of the current clinical trial and regulatory environment.
Diabetic Macular Edema: Options for Adjunct Therapy
Pilar Calvo, Beatriz Abadia, Antonio Ferreras, Oscar Ruiz-Moreno, Guayente Verdes

ABSTRACT

Diabetes mellitus (DM) is a chronic disease that affects 387 million people worldwide. Diabetic retinopathy (DR), a common complication of DM, is the main cause of blindness in the active population. Diabetic macular edema (DME) may occur at any stage of DR, and is characterized by vascular hyperpermeability accompanied by hard exudates within the macula. Medical and surgical therapies have dramatically reduced the progression of DR, and timely intervention can reduce the risk of severe vision loss by more than 90%. In 2012, intravitreal ranibizumab became the first antivascular endothelial growth factor (anti-VEGF) agent approved for DME and, since then, many reports of the use of ranibizumab for DME have been promising. Randomized, prospective, multicenter clinical trials—most notably, RESOLVE, READ-2, RISE/RIDE, RESTORE, DRCR.net protocol I, and RETAIN—reported improvements in best-corrected visual acuity and decreased central retinal thickness as measured with optical coherence tomography in patients with DME. Similar treatment benefits have also been noted in clinical trials evaluating intravitreal aflibercept and bevacizumab (DAVINCI, VISTA/VIVID, and BOLT) and more recently DRCR.net protocol T. Intravitreal steroids (dexamethasone intravitreal implant and fluocinolone acetonide), particularly in refractory cases, also play a significant role in the management of DME (MEAD/CHAMPLAIN and FAMOUS/FAME studies). In summary, over the last 5 years, blocking VEGF and inflammation has been shown to improve visual outcomes in patients with macular edema due to DM, revolutionizing the treatment of center-involved DME and establishing a new standard of care.

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A Practical Approach to the Management of Radiation-Induced Hemorrhagic Cystitis
Xavier Liem, Fred Saad, Guila Delouya

ABSTRACT

Radiation-induced hemorrhagic cystitis (HC) is a complication of pelvic radiotherapy, mainly for prostate and uterine cancers. In the acute phase, patients feel urinary urgency and bladder pain. This phase is reversible after radiotherapy. In the chronic stage, an irritative syndrome is coupled with hematuria during the 2–10 years following radiotherapy. Cystoscopy shows white and frosted mucosa with telangiectasia. The incidence is estimated at 5% or less. It is suggested that the radiation oncologist reviews the dosimetry plan to validate that the lesions coincide with significant radiation exposure confirming diagnosis of radiation-induced HC. The treatment for HC is first symptomatic, with bladder lavage, clot evacuation, coagulation via cystoscopy and blood transfusions if necessary. Subsequently, hyaluronic acid bladder instillation can be done with little toxicity. Hyperbaric oxygen therapy delivers pure oxygen to patients in a pressurized cabin, promoting angio-neogenesis and lowering hypoxia to the irradiated tissues. The clinical response rate is estimated to be around 80%. Nevertheless, this approach is limited by the low availability, and length of treatment. While surgery remains an effective treatment for HC, it is the last option because of the high morbidity and mortality risks. Prospective studies need to be conducted to identify and evaluate new interventions, particularly for HC.
Use of Integrase Inhibitors in HIV-Infected Children and Adolescents
Walter Dehority, Jacobo Abadi, Andrew Wiznia, Rolando M. Viani

ABSTRACT
Resistance to antiretroviral drugs is an increasingly prevalent challenge affecting both the adult and pediatric HIV-infected populations. Though data on the safety, pharmacokinetics, and efficacy of newer antiretroviral agents in children typically lags behind adult data, newer agents are becoming available for use in HIV-infected children who are failing to respond to or are experiencing toxicities with traditional antiretroviral regimens. Integrase strand transfer inhibitors are one such new class of antiretrovirals. Raltegravir has been US Food and Drug Administration (FDA) approved for use in patients over the age of 4 weeks. Elvitegravir is a second member of this class, and has the potential for use in children but does not yet have a Pediatric FDA indication. Dolutegravir, a second-generation integrase inhibitor, is approved for those older than 12 years. This review summarizes the use of integrase inhibitors in children and adolescents, and highlights the results of recent clinical trials.

Pharmacotherapy for Status Epilepticus
Eugen Trinka, Julia Höfle, Markus Leitinger, Francesco Brigo

ABSTRACT
Status epilepticus (SE) represents the most severe form of epilepsy. It is one of the most common neurologic emergencies, with an incidence of up to 61 per 100,000 per year and an estimated mortality of 20%. Clinically, tonic-clonic convulsive SE is divided into four subsequent stages: early, established, refractory, and super-refractory. Pharmacotherapy of status epilepticus, especially of its later stages, represents an “evidence-free zone,” due to a lack of high-quality, controlled trials to inform clinical decisions. This comprehensive narrative review focuses on the pharmacotherapy of SE, presented according to the four-staged approach outlined above, and providing pharmacological properties and efficacy/safety data for each antiepileptic drug according to the strength of scientific evidence from the available literature. Data sources included MEDLINE and back-tracking of references in pertinent studies. Intravenous lorazepam or intramuscular midazolam effectively control early SE in approximately 63–73% of patients. Despite a suboptimal safety profile, intravenous phenytoin or phenobarbital are widely used treatments for established SE; alternatives include valproate, levetiracetam, and lacosamide. Anesthetics are widely used in refractory and super-refractory SE, despite the current lack of trials in this field. Data on alternative treatments in the later stages are limited. Valproate and levetiracetam represent safe and effective alternatives to phenobarbital and phenytoin for treatment of established SE persisting despite first-line treatment with benzodiazepines. To date there are no class I data to support recommendations for most antiepileptic drugs for established, refractory, and super-refractory SE. Limiting the methodologic heterogeneity across studies is required and high-class randomized, controlled trials to inform clinicians about the best treatment in established and refractory status are needed.
Insulin Degludec/Liraglutide: A Review in Type 2 Diabetes
Sarah L. Greig, Lesley J. Scott

ABSTRACT

Insulin degludec/liraglutide (Xultophy®), a fixed-ratio combination of an ultra-long-acting insulin analogue and a glucagon-like protein-1 (GLP-1) receptor agonist, is available in the EU for the management of inadequately controlled type 2 diabetes. Once-daily subcutaneous insulin degludec/liraglutide as add-on therapy to oral antidiabetics was effective and generally well tolerated in adults with inadequately controlled type 2 diabetes in several well designed 26-week phase III trials. In insulin-naive patients, add-on insulin degludec/liraglutide provided significantly greater improvements in glycated haemoglobin (HbA1c) levels than add-on insulin degludec, liraglutide or placebo, or unchanged GLP-1 receptor agonists (i.e. liraglutide or exenatide). In the extension of one of these trials, the efficacy of add-on insulin degludec/liraglutide was maintained for a total of 52 weeks. In insulin-experienced patients, add-on insulin degludec/liraglutide was significantly more effective with regard to improvements in HbA1c levels than add-on insulin degludec (at equivalent doses) or ongoing insulin glargine therapy. Add-on insulin degludec/liraglutide was associated with a lower incidence of confirmed hypoglycaemia than add-on insulin degludec in insulin-naive patients or ongoing insulin glargine in insulin-experienced patients, and a lower initial rate of nausea than add-on liraglutide. Thus, once-daily subcutaneous insulin degludec/liraglutide is a useful add-on therapy option for adult patients with inadequately controlled type 2 diabetes.

13-Valent Pneumococcal Conjugate Vaccine: A Review of Its Use in Adults
Greg L. Plosker

ABSTRACT

The 13-valent pneumococcal conjugate vaccine (Prevenar 13®, Prevnar 13®) [PCV13] consists of 13 serotype-specific polysaccharides of Streptococcus pneumoniae (pneumococcus), each covalently conjugated to a non-toxic immunogenic carrier protein. PCV13 has a well established immunogenicity and tolerability profile in adults, particularly those ≥50 years of age. Results of CAPiTAT, a randomized, double-blind, placebo-controlled trial in >84,000 older adults aged ≥65 years, showed that PCV13 was effective in preventing vaccine-type pneumococcal community-acquired pneumonia (CAP), vaccine-type pneumococcal nonbacteraemic (noninvasive) CAP and vaccine-type invasive pneumococcal disease (IPD). These findings, along with changes in pneumococcal serotype distribution and epidemiology of pneumococcal disease, prompted the US Advisory Committee on Immunization Practices (ACIP) to recommend PCV13 in series with 23-valent pneumococcal polysaccharide vaccine (PPVS23) for all adults aged ≥65 years. PCV13 also has a role in preventing pneumococcal disease (pneumonia and IPD) in younger adults with immunocompromising conditions and potentially in those with other underlying medical conditions that increase the risk of pneumococcal disease.
Empagliflozin/Linagliptin: A Review in Type 2 Diabetes

Esther S. Kim, Emma D. Deeks

ABSTRACT

Empagliflozin/linagliptin (Glyxambi®) is a once-daily sodium glucose co-transporter type 2 (SGLT2) inhibitor and dipeptidyl peptidase (DPP)-4 inhibitor fixed-dose combination product that is approved in the USA as an adjunct to diet and exercise in adults with type 2 diabetes (T2D) when treatment with both empagliflozin and linagliptin is appropriate. This article reviews the clinical efficacy and tolerability of oral empagliflozin/linagliptin in patients with T2D and summarizes the pharmacological properties of the agents. Results of two randomized controlled trials of 52 weeks’ duration in adults with T2D demonstrated that empagliflozin/linagliptin improved glycaemic control significantly more than linagliptin when administered as initial therapy (whereas results vs. empagliflozin were mixed in this setting) and significantly more than linagliptin or empagliflozin when administered as an add-on therapy to metformin. In addition to glycaemic control, empagliflozin/linagliptin provided significant weight loss compared with linagliptin in both trials. Empagliflozin/linagliptin was generally well tolerated in patients with T2D, with a low risk of hypoglycaemia and no reports of exacerbations of, or hospitalizations for, heart failure during the trials. As the first SGLT2 inhibitor/DPP-4 inhibitor fixed-dose combination available, empagliflozin/linagliptin is a useful new option for patients with T2D.

Sonidegib: First Global Approval

Celeste B. Burness

ABSTRACT

Sonidegib (Odomzo™) is an orally bioavailable, small molecule, Smoothened (SMO) receptor antagonist that is being developed by Novartis for the treatment of cancer. SMO is a G protein-coupled receptor-like molecule that is essential for the actions of the Hedgehog family of secreted proteins, which play a critical role in the development and homeostasis of many organs and tissues. Oral sonidegib is approved in Switzerland for the treatment of adult patients with advanced basal cell carcinoma (BCC) and in the US and EU for the treatment of adult patients with locally advanced BCC that has recurred following surgery or radiation therapy, or those who are not candidates for surgery or radiation therapy. Submissions to other global authorities are being contemplated or planned. Additionally, phase I/II investigation is being conducted in other malignancies, including multiple myeloma, medulloblastoma, myelofibrosis, ovarian cancer, prostate cancer, breast cancer, chronic myeloid leukaemia, myelodysplastic syndromes, oesophageal cancer and pancreatic cancer. This article summarizes the milestones in the development of sonidegib leading to the first approvals for advanced and locally advanced BCC.

Evolocumab: First Global Approval

Anthony Markham

ABSTRACT

Evolocumab (Repatha™) is a fully human monoclonal antibody developed by Amgen that has been approved as a treatment for hypercholesterolaemia in the EU, and is awaiting approval in the USA and Japan. It specifically binds proprotein convertase subtilisin/kexin type 9 (PCSK9)—a negative regulator of low-density lipoprotein (LDL)-receptors—thereby improving the ability of the liver to bind LDL-cholesterol (LDL-C), leading to reduced LDL-C blood levels. The drug reduces LDL-C levels in patients with hypercholesterolaemia when used as monotherapy or in conjunction with a statin. This article summarizes the milestones in the development of evolocumab leading to this approval for the treatment of adults with primary hypercholesterolaemia (homozygous familial and non-familial) or mixed dyslipidaemia as an adjunct to diet with or without a statin and/or other lipid lowering therapies, and in adults and adolescents aged ≥12 years with homozygous familial hypercholesterolaemia in combination with other lipid lowering therapies.
ABSTRACT

Chronic obstructive pulmonary disease (COPD) guidelines and strategies suggest escalating treatment, mainly depending on the severity of airflow obstruction. However, some de-escalation of therapy in COPD would be appropriate, although we still do not know when we should switch, step-up or step-down treatments in our patients. Unfortunately, trials comparing different strategies of step-up and step-down treatment (e.g. treatment initiation with one single agent and then further step-up if symptoms are not controlled versus initial use of double or triple therapy, possibly with lower doses of the individual components, or the role of N-acetylcysteine in combination therapy for a step-down approach) are still lacking. In general, there is a large and often inappropriate use of the inhaled corticosteroid (ICS)/long-acting β2-agonist (LABA) combination. However, the withdrawal of the ICS in COPD patients at low risk of exacerbation can be safe, provided that patients are under regular treatment with long-acting bronchodilators. Maximising the treatment in patients with a degree of clinical instability by including an ICS in the therapeutic regimen is useful to control the disease, but may not be needed during periods of clinical stability. In patients with severe but stable COPD, the withdrawal of the ICS from triple therapy [LABA + long-acting muscarinic antagonist (LAMA) + ICS] is possible, but not when the patient has been hospitalised for an acute exacerbation of COPD. We must still establish how long we should wait before withdrawing the ICS. It is still unclear whether the same is true when only the LABA or the LAMA is withdrawn while continuing treatment with the other bronchodilator and the ICS. In any case, we strongly believe that it is always better to avoid a therapeutic step-up progression when it is not needed rather than being forced subsequently into a step-down approach in which the outcome is always unpredictable.

New and Emerging Agents for the Treatment of Hemophilia: Focus on Extended Half-Life Recombinant Clotting Proteins

Margaret V. Ragni

ABSTRACT

Hemophilia A and B are X-linked disorders caused by deficient or defective clotting factor VIII (FVIII) or IX factor (FIX) proteins, and characterized by spontaneous or traumatic bleeding into joints and muscles. Previous use of plasma and plasma-derived clotting factors that lacked appropriate viral inactivation steps in manufacturing led to significant morbidity associated with transfusion-transmitted HIV and hepatitis C virus (HCV). The development of recombinant proteins revolutionized their treatment, and, with no new HIV or HCV infection via clotting proteins for nearly 30 years, greatly improved their lifespan, which now approaches that of the general population, and with the same risks for aging complications. Novel long-acting factor proteins are being licensed to extend FVIII and FIX half-life, thereby reducing infusion frequency and potentially bleed frequency and associated morbidity. Further, novel therapeutics which take advantage of new technologies, including siRNA, monoclonal antibody, and small peptide inhibition technologies, have the potential to simplify treatment and improve outcomes for those with inhibitors.
Anticancer Drug Delivery: An Update on Clinically Applied Nanotherapeutics
Sophie Marchal, Amélie El Hor, Marie Millard, Véronique Gillon, Lina Bezdetnaya

ABSTRACT
The development of chemotherapy using conventional anticancer drugs has been hindered due to several drawbacks related to their poor water solubility and poor pharmacokinetics, leading to severe adverse side effects and multidrug resistance in patients. Nanocarriers were developed to palliate these problems by improving drug delivery, opening the era of nanomedicine in oncology. Liposomes have been by far the most used nanovectors for drug delivery, with liposomal doxorubicin receiving US FDA approval as early as 1995. Antibody drug conjugates and promising drug delivery systems based on a natural polymer, such as albumin, or a synthetic polymer, are currently undergoing advanced clinical trials or have received approval for clinical applications. However, despite attractive results being obtained in preclinical studies, many well-designed nanodrugs fell short of expectations when tested in patients, evidencing the gap between nanoparticle design and their clinical translation. The aim of this review is to evaluate the extent of nanotherapeutics used in oncology by providing an insight into the most successful concepts. The reasons that prevent nanodrugs from expanding to clinic are discussed, and the efforts that must be taken to take full advantage of the great potential of nanomedicine are highlighted.

Current Strategies to Reduce Gastrointestinal Bleeding Risk Associated with Antiplatelet Agents
Parth J. Parekh, Edward C. Oldfield IV, David A. Johnson

ABSTRACT
Antiplatelet agents remain the cornerstone in the primary and secondary therapeutic intervention for cardiovascular disease. Some patients may be subjected to a year or more of dual antiplatelet therapy to reduce the risk of subsequent cardiovascular events. Patients on antiplatelet therapy have an increased risk of gastrointestinal bleeding; however, not all patients benefit from concomitant acid suppressive therapy. This review will provide an overview of the pharmacology of antiplatelet agents and outline patient risk profiles that ought to be considered when considering prophylactic therapy to reduce gastrointestinal toxicity. In addition, we discuss the current risk-reduction strategies intended to mitigate against the potential for related gastroduodenal injury.

Direct Oral Anticoagulants for the Prevention of Stroke in Patients with Nonvalvular Atrial Fibrillation: Understanding Differences and Similarities
Paul P. Dobesh, John Fanikos

ABSTRACT
The presence of atrial fibrillation (AF), the most common sustained cardiac arrhythmia, significantly increases the risk for stroke. Current guidelines recommend that the vitamin K antagonist warfarin or direct oral anticoagulants (DOACs), such as the approved direct thrombin inhibitor dabigatran and the approved direct factor Xa inhibitors apixaban, rivaroxaban, and edoxaban, should be used for thromboprophylaxis in patients with nonvalvular AF at risk for stroke or systemic embolic events (SEE). Warfarin, the mainstay of stroke prevention in AF, increases the risk of major bleeding. Furthermore, warfarin therapy comes with several limitations including frequent monitoring and the need for dose adjustments, unpredictable pharmacokinetics and pharmacodynamics, and the potential for significant drug-drug and food-drug interactions. The DOACs were developed to overcome these limitations while maintaining or surpassing warfarin’s efficacy and safety profiles. All four DOACs have similar or better efficacy and safety compared with warfarin and are therefore valuable alternatives for the prevention of stroke and SEE in patients with nonvalvular AF. Understanding the subtle differences in the DOACs’ pharmacology, phase 3 study designs, and trial outcomes will allow for a more tailored approach in selecting the right oral anticoagulant for each patient.
Roflumilast: A Review in COPD

Karly P. Garnock-Jones

ABSTRACT

Roflumilast (Daliresp®, Daxas®) is a selective phosphodiesterase 4 (PDE4) inhibitor that decreases systemic and pulmonary inflammation and improves disease symptoms in patients with severe chronic obstructive pulmonary disease (COPD). This article reviews the pharmacological properties of roflumilast and its clinical efficacy and tolerability in patients with COPD. Roflumilast is an effective treatment in patients with moderate to severe COPD; it improves lung function and is generally associated with a lower risk of exacerbation, particularly in patients with more severe disease and/or chronic bronchitis, cough and sputum. It is generally well tolerated; the most common adverse event was diarrhoea. While associated with an increased risk of psychiatric adverse events and weight loss, roflumilast is not associated with an increased risk of respiratory disease and infection, and may decrease the risk of cardiovascular adverse events. Roflumilast is a useful addition to the treatment options for patients with COPD.

Perampanel: A Review in Drug-Resistant Epilepsy

James E. Frampton

ABSTRACT

Perampanel (Fycompa®), an orally-active, selective, noncompetitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist, is a first-in-class antiepileptic drug (AED) offering the convenience of once-daily administration. In the EU and US, perampanel is approved in patients with epilepsy aged ≥12 years for the adjunctive treatment of primary generalized tonic-clonic seizures (GTCS) and partial-onset seizures (POS; with or without secondary generalization). In phase III trials of 17 or 19 weeks’ duration, add-on perampanel ≤12 mg/day significantly improved seizure control in patients aged ≥12 years who were experiencing either primary GTCS or POS (with or without secondary generalization), despite ongoing treatment with stable dosages of one to three AEDs. Improvements in seizure control were maintained for up to 2 years in extensions of these core studies. Perampanel also provided sustained seizure control for up to 4 years in an extension of two phase II studies in patients aged ≥18 years with drug-resistant POS. Adjunctive perampanel therapy was generally well tolerated. Treatment-emergent adverse events were most commonly CNS-related (e.g. dizziness, somnolence, fatigue and irritability) and dose-related; however, most were of mild to moderate intensity. Clinical experience with perampanel is accumulating, although comparative studies and pharmacoeconomic data that could assist in positioning it relative to other AEDs that are approved and/or recommended as adjunctive therapy are lacking. Nonetheless, on the basis of its overall clinical profile and unique mechanism of action, perampanel is a useful additional adjunctive treatment option for patients with drug-resistant POS, with or without secondary generalization, and primary GTCS.
Eliglustat: A Review in Gaucher Disease Type 1
Lesley J. Scott

ABSTRACT
Oral eliglustat (Ceredo®) is approved in several countries for the long-term treatment of adults with Gaucher disease type 1 (GD1) who are cytochrome P450 (CYP) 2D6 extensive metabolizers (EMs), intermediate metabolizer (IMs) or poor metabolizers (PMs) [these three CYP categories encompass >90% of individuals]. Eliglustat is a potent, selective inhibitor of glucosylceramide synthase, the rate-limiting enzyme in the synthesis of certain glycosphingolipids, and thus, reduces the rate of biosynthesis of glycosphingolipids to counteract the catabolic defect (i.e. substrate reduction therapy). In the 9-month phase 3 ENGAGE trial, eliglustat significantly improved haematological endpoints and reduced organomegaly compared with placebo in treatment-naive adults with GD1, with the bone marrow burden score (a marker of Gaucher cell infiltration) and GD1 biomarkers also improving from baseline in eliglustat recipients. After 12 months in the phase 3 ENCORE trial, oral eliglustat was noninferior to intravenous miglurecrose [an enzyme replacement therapy (ERT)] in maintaining disease stability in adults who had stable disease after receiving ERT for ≥3 years. During long-term treatment with eliglustat (≤4 years) in the extension period of each of these pivotal trials and a phase 2 trial, patients experienced sustained improvements in visceral, haematological and skeletal endpoints, with no new safety concerns identified. Further clinical experience will help to more definitively establish the position of eliglustat treatment in adults with GD1. In the meantime, with its convenient oral regimen, eliglustat is an emerging alternative therapy to ERT for the long-term treatment of adults with GD1 who are CYP2D6 EMs, IMs or PMs.

AFREZZA® (insulin human) Inhalation Powder: A Review in Diabetes Mellitus
Esther S. Kim, Greg L. Plosker

ABSTRACT
Afrezza® (insulin human) inhalation powder is a rapid-acting Technosphere® insulin (TI) administered via a breath-powered oral inhaler to patients with diabetes requiring prandial insulin. TI, a dry powdered formulation of recombinant human insulin adsorbed onto a proprietary carrier, is designed to deliver insulin to the deep lung, at the level of the alveoli, where it is absorbed into the systemic circulation. In a randomized, open-label, multinational, phase III trial (trial 171) in type 1 diabetes (T1DM) patients, prandial TI via the Gen2 inhaler provided noninferior glycated haemoglobin (HbA1c) lowering compared with prandial subcutaneous insulin aspart. Although TI was associated with less HbA1c lowering, it provided significantly lower fasting plasma glucose levels and significantly less hypoglycaemia and bodyweight gain compared with insulin aspart. In a randomized, double-blind, placebo-controlled, multinational, phase III trial (trial 175) in type 2 diabetes (T2DM) patients, prandial TI via the Gen2 inhaler provided superior HbA1c lowering compared with inhaled placebo. Cough was the most commonly occurring non-hypoglycaemia adverse event across both studies. In a pooled analysis of tolerability data from phase II and III studies, the most commonly occurring non-hypoglycaemia adverse events in T1DM and T2DM patients were cough and throat pain/irritation. However, cough was generally mild, dry and decreased over time. In addition, treatment with TI was associated with positive patient-reported outcomes. Insulin human inhalation powder is an effective and generally well-tolerated agent for the prandial treatment of hyperglycaemia in T1DM and T2DM patients and may provide a solution to insulin initiation barriers such as injection phobia, concerns of bodyweight gain and concerns of hypoglycaemia.
Brexpiprazole: First Global Approval
Sarah L. Greig

ABSTRACT
Brexpiprazole (Rexulti®) is an atypical antipsychotic that has been developed by Otsuka Pharmaceutical Co. Ltd and H. Lundbeck A/S as an oral treatment for several psychiatric disorders. Brexpiprazole is a novel serotonin-dopamine activity modulator that acts as a partial agonist of serotonin 1A (5-HT1A) and dopamine D2 receptors, as well as a potent antagonist of 5-HT2A receptors and noradrenergic α1B and α2C receptors. In July 2015, brexpiprazole received its first approval in the USA for use as an adjunctive treatment of major depressive disorder (MDD) and the treatment of schizophrenia. In several countries, brexpiprazole is in development for MDDs, schizophrenia, post-traumatic stress disorder and agitation in patients with dementia of the Alzheimer’s type. This article summarizes the milestones in the development of brexpiprazole leading to its first global approval in MDD and schizophrenia.

Alirocumab: First Global Approval
Anthony Markham

ABSTRACT
Alirocumab (Praluent®) is a fully human monoclonal antibody developed by Regeneron Pharmaceuticals and Sanofi that has been approved in the US as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolaemia (HeFH) or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-C. It specifically binds proprotein convertase subtilisin/kexin type 9 (PCSK9)—a down regulator of liver low-density lipoprotein (LDL)-receptors—thereby increasing the ability of the liver to bind LDL-cholesterol (LDL-C) and reducing levels of LDL-C in blood. It has been shown to reduce LDL-C levels in patients with hypercholesterolaemia, including HeFH, both as monotherapy and in conjunction with statin therapy. This article summarizes the milestones in the development of alirocumab leading to this first approval.

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Overactive Bladder and the β3-Adrenoceptor Agonists: Current Strategy and Future Prospects
Ilias Giarenis, Dudley Robinson, Linda Cardozo

ABSTRACT
Overactive bladder (OAB) is a clinical syndrome describing the symptom complex of urgency, with or without urgency incontinence, and is usually associated with frequency and nocturia. It is a common, under-diagnosed and therefore under-treated condition that can have a detrimental effect on physical functioning and psychological well-being. Initial treatment of OAB includes lifestyle advice, behavioural modifications, bladder retraining and pelvic floor muscle training, usually in combination with antimuscarinic agents. The β3-adrenoceptor agonist mirabegron is the first of a new class of drugs that are now competing with the more established antimuscarinics for the treatment of OAB. Our review focuses on the mode of action, efficacy and tolerability of mirabegron. The place of β3-adrenoceptor agonists in the treatment algorithm of OAB is discussed, considering the adverse events associated with antimuscarinics. Drug therapy tailored to different population groups appears a promising future prospect. Development of other β3-adrenoceptor agonists is expected, and combination therapy regimens might revolutionise the treatment of OAB.
Challenges in the Diagnosis and Treatment of Homozygous Familial Hypercholesterolemia

Matthew K. Ito, Gerald F. Watts

ABSTRACT

Homozygous familial hypercholesterolemia (HoFH) is a rare, genetic disorder characterized by an absence or impairment of low-density lipoprotein receptor (LDLR) function resulting in significantly elevated low-density lipoprotein cholesterol (LDL-C) levels. The cholesterol exposure burden beginning in utero greatly increases the risk for atherosclerotic cardiovascular disease (ASCVD) and premature death. The genetic heterogeneity of HoFH results in a wide range of LDL-C levels among both untreated and treated patients. Diagnosis of HoFH should, therefore, be based on a comprehensive evaluation of clinical criteria and not exclusively LDL-C levels. As treatment goals, the European Atherosclerosis Society and International FH Foundation suggest target LDL-C levels of <100 mg/dL (<2.5 mmol/L) in adults or <70 mg/dL (<1.8 mmol/L) in adults with clinical coronary artery disease or diabetes. The National Lipid Association (NLA) recommends that LDL-C levels be reduced to <100 mg/dL (<2.5 mmol/L) or by at least ≥50% from pretreatment levels. Conventional therapy combinations that lower atherogenic lipoproteins levels in the blood, such as statins, ezetimibe, bile acid sequestrants and niacin, as well as lipoprotein apheresis, are usually unable to reduce LDL-C levels to recommended targets. Two recently approved agents that reduce lipoprotein synthesis and secretion by the liver are lomitapide, a microsomal triglyceride transfer protein inhibitor, and mipomersen, an apolipoprotein B antisense oligonucleotide. The newly approved inhibitor of proprotein convertase subtilisin/kexin type 9 (PCSK9), evolocumab, also shows promise for the management of FH. Because of the extremely high risk for ASCVD, HoFH patients should be identified early.

Management of Hematologic Malignancies: Special Considerations in Pregnant Women

Odelia Amit, Merav Barzilai, Irit Avivi

ABSTRACT

The diagnosis and management of hematologic malignancy during pregnancy is a significant challenge. This is due to both medical and ethical considerations regarding when and how to treat this special sub-group of patients. Recurring uncertainties remain around appropriate imaging techniques, timing and dosage of chemotherapy, and timing of delivery. In this article we examine and summarize current literature in this field to assist physicians in their understanding and management of this patient group. Special attention has been given to diagnostic and staging procedures, risks associated with chemotherapy at different stages of gestation, and chemotherapy-dose adaption during pregnancy. In addition, recommended guidelines for management of lymphoma, leukemia, and planning delivery are discussed. A multidisciplinary team approach is critical for patient care, as is shared decision making with the patient and family.
Prognostic and Predictive Value of RAS Gene Mutations in Colorectal Cancer: Moving Beyond KRA8 Exon 2

Nele Boeckx, Marc Peeters, Guy Van Camp, Patrick Pauwels, Ken Op de Beeck

ABSTRACT

The advent of anti-EGFR (epidermal growth factor receptor) therapy resulted in significant progress in the treatment of metastatic colorectal cancer patients. However, many patients do not respond to this therapy or develop acquired resistance within a few months after the start of treatment. Since 2008, anti-EGFR therapy is restricted to KRAS wild-type patients as it has been shown that KRAS exon 2-mutated patients do not respond to this therapy. Still, up to 60% of KRAS exon 2 wild-type patients show primary resistance to this treatment. Recently, several studies investigating the predictive and prognostic role of RAS mutations other than in KRAS exon 2 demonstrated that patients with these mutations are not responding to therapy. However, the role of these mutations has long been questioned as The National Comprehensive Cancer Network Guidelines in Oncology and the European Medicines Agency indications had already been changed in order to restrict anti-EGFR therapy to all RAS wild-type colorectal cancer patients, while the Food and Drug Administration guidelines remained unchanged. Recently, the Food and Drug Administration guidelines have also been changed, which implies the importance of RAS mutations beyond KRAS exon 2 in colorectal cancer. In this review, we discuss the most important studies regarding the predictive and prognostic role of RAS mutations other than in KRAS exon 2 in order to demonstrate the importance of these RAS mutations in patients with metastatic colorectal cancer treated with anti-EGFR therapy.

Targeting Chromatin-Mediated Transcriptional Control of Gene Expression in Non-Small Cell Lung Cancer Therapy: Preclinical Rationale and Clinical Results

Alice Pasini, Angelo Delmonte, Anna Tesi, Daniele Calistri, Emanuele Giordano

ABSTRACT

Targeting chromatin-mediated transcriptional control of gene expression is nowadays considered a promising new strategy, transcending conventional anticancer therapy. As a result, molecules acting as DNA demethylating agents or histone deacetylase inhibitors (HDACi) have entered the clinical arena in the last decade. Given the evidence suggesting that epigenetic regulation is significantly involved in lung cancer development and progression, the potential of epigenetically active compounds to modulate gene expression and reprogram cancer cells to a less aggressive phenotype is, at present, a promising strategy. Accordingly, a large number of compounds that interact with the epigenetic machinery of gene expression regulation are now being developed and tested as potential antitumor agents, either alone or in combination with standard therapy. The preclinical rationale and clinical data concerning the pharmacological modulation of chromatin organization in non-small cell lung cancer (NSCLC) is described in this review. Although preclinical data suggest that a pharmacological treatment targeting the epigenetic machinery has relevant activity over the neoplastic phenotype of NSCLC cells, clinical results are disappointing, leading only to short periods of disease stabilization in NSCLC patients. This evidence calls for a significant rethinking of strategies for an effective epigenetic therapy of NSCLC. The synergistic effect of concurrent epigenetic therapies, use at low doses, the priming of current treatments with previous epigenetic drugs, and the selection of clinical trial populations based on epigenetic biomarkers/signatures appear to be the cornerstones of a mature therapeutic strategy aiming to establish new regimens for reprogramming malignant cells and improving the clinical history of affected patients.
Ruxolitinib: A Review in Polycythaemia Vera
Kate McKeage

**ABSTRACT**
Ruxolitinib (Jakavi®, Jakafi®) is an orally administered, first-in-class Janus Kinase (JAK) 1 and 2 inhibitor that was recently approved for the treatment of patients with polycythaemia vera (PV) who have responded inadequately to or are intolerant of hydroxyurea. By inhibiting JAK 1 and 2, ruxolitinib reduces hyperactive JAK-signal transducers and activators of transcription (STAT) signalling that is implicated in the pathogenesis of PV. This article briefly reviews the pharmacology of the drug, focusing on its clinical use in patients with PV. In the phase III RESPONSE trial in PV patients who had an inadequate response to or unacceptable adverse effects from hydroxyurea, ruxolitinib was superior to best available therapy in reducing haematocrit without phlebotomy and reducing spleen size after 32 weeks of treatment. Ruxolitinib was also associated with reducing leukocyte and platelet counts and improving symptoms. Patient follow-up demonstrated that response to ruxolitinib was durable, including preliminary results after up to 80 weeks of treatment. The drug is generally well tolerated, although mild to moderate anaemia, thrombocytopenia and lymphopenia were common in the RESPONSE trial. These effects can usually be managed with dosage modification and did not lead to therapy discontinuation in the RESPONSE trial.

Saxagliptin: A Review in Type 2 Diabetes
Sohita Dhillon

**ABSTRACT**
Saxagliptin (Onglyza®) is a highly potent, reversible, competitive dipeptidyl peptidase-4 inhibitor indicated for the treatment of patients with type 2 diabetes. Numerous well-designed clinical studies and their extensions showed that saxagliptin as monotherapy or as dual or triple combination therapy with other antihyperglycaemics improved glyaemic control and was generally well tolerated in patients with type 2 diabetes during ≤2 years’ therapy. Saxagliptin was generally weight-neutral and had a low risk of hypoglycaemia (unless coadministered with agents that may be associated with hypoglycaemia, such as sulfonylureas or insulin). In addition, at a median follow-up of 2.1 years in the large SAVOR-TIMI 53 study, with the exception of a 27 % greater risk of hospitalization for heart failure, the addition of saxagliptin to standard of care neither reduced nor increased the rate of ischemic cardiovascular events in at-risk patients. Although further long-term data will be beneficial, current evidence indicates that saxagliptin is a useful option for the treatment of patients with type 2 diabetes.

Tolvaptan: A Review in Autosomal Dominant Polycystic Kidney Disease
Hannah A. Blair, Gillian M. Keating

**ABSTRACT**
Tolvaptan (Jinarc®) is a highly selective vasopressin V2 receptor antagonist indicated for use in patients with autosomal dominant polycystic kidney disease (ADPKD). Tolvaptan is the first pharmaceutical agent to be approved in Europe for delaying the progression of ADPKD in adults with stage 1–3 chronic kidney disease at initiation of treatment. In the large phase III TEMPO 3:4 trial in adults with ADPKD, 3 years’ treatment with oral tolvaptan significantly reduced growth in total kidney volume and slowed renal function decline relative to placebo. Tolvaptan was also associated with a significantly lower rate of events for the composite secondary endpoint of time to investigator-assessed clinical progression relative to placebo, an effect that was largely attributable to reductions in the risk of worsening renal function and the risk of worsening kidney pain. Many of the most common adverse events in the tolvaptan group were related to its aquarectic mechanism of action (e.g. polyuria, nocturia, polydipsia and thirst). Tolvaptan was also associated with idiosyncratic elevations of liver enzymes which were reversible on discontinuation of the drug.
A once-daily preservative-free fixed combination ophthalmic solution containing tafluprost 0.0015 % and timolol 0.5 % (hereafter referred to as tafluprost/timolol) [Taptiqom®] has been developed to lower intraocular pressure (IOP) whilst avoiding damage to the ocular surface associated with preservatives such as benzalkonium chloride. Tafluprost/timolol is available in various EU countries for the reduction of IOP in adults with open-angle glaucoma or ocular hypertension who are insufficiently responsive to topical monotherapy with β-adrenergic receptor antagonists or prostaglandin analogues and require a combination therapy, and who would benefit from preservative-free eye drops. In two multinational, phase III studies, tafluprost/timolol was superior to monotherapy with either preservative-free tafluprost 0.0015 % once daily or preservative-free timolol 0.5 % twice daily, and noninferior to concomitant therapy with preservative-free tafluprost 0.0015 % once daily plus preservative-free timolol 0.5 % twice daily in lowering IOP in adults with open-angle glaucoma or ocular hypertension. Tafluprost/timolol was well tolerated in these studies, with a tolerability profile consistent with that of its individual components and with no new adverse reactions observed. Thus, preservative-free fixed combination tafluprost/timolol is an effective treatment option for the reduction of IOP in adults with open-angle glaucoma or ocular hypertension, providing a useful alternative for those patients who would benefit from preservative-free eye drops.

Flibanserin: First Global Approval
Emma D. Deeks

Flibanserin (Addyi™) is chemically described as a benzimidazole and is being developed by Sprout Pharmaceuticals for the treatment of hypoactive sexual desire disorder (HSDD). The drug has a high affinity for serotonin 5-HT1A and 5-HT2A receptors (5-HT1A agonist/5-HT2A antagonist) and is believed to treat HSDD by increasing levels of dopamine and noradrenaline and lowering levels of serotonin in the brain. Flibanserin has been approved in the USA for the treatment of premenopausal women with acquired, generalized HSDD. Earlier phase III development of the agent for HSDD in the EU and Canada had been discontinued by Boehringer Ingelheim, following regulatory feedback. Boehringer Ingelheim had also evaluated flibanserin for the treatment of depression but, due to displaying very mild antidepressant activity, its development in this indication was discontinued. This article summarizes the milestones in the development of flibanserin leading to its first approval for HSDD.

Cobimetinib: First Global Approval
Karly P. Garnock-Jones

Genentech (a subsidiary of Roche) and Exelixis are developing cobimetinib, an orally available small molecule, for the treatment of various cancers, including malignant melanoma and breast cancer. Cobimetinib inhibits the MEK (mitogen-activated protein kinase) component of the MAPK/ERK signalling pathway, which is frequently over-activated in human tumours. The product has been approved in Switzerland in combination with vemurafenib for the treatment of patients with unresectable or metastatic BRAF V600 mutation-positive melanoma, and is under regulatory review for the same indication in several countries, including the USA and the EU. This article summarizes the milestones in the development of cobimetinib leading to this first approval for unresectable or metastatic BRAF V600 mutation-positive melanoma.
Maintenance Therapy for Colorectal Cancer: Which Regimen and Which Patients?
Sameh Mikhail, Tanios Bekaii-Saab

ABSTRACT
The introduction of therapeutic agents such as irinotecan, oxaliplatin, and more recently biologic agents such as vascular endothelial growth factor and epidermal growth factor receptor (EGFR) inhibitors has significantly improved survival of patients with metastatic colorectal cancer. These novel agents have also contributed to added toxicities. Therefore, several studies have evaluated the role of maintenance therapy with less intensive regimens in patients who experienced stable disease or treatment response following induction therapy as a strategy to reduce toxicity and improve quality of life. The success of such strategies, however, requires assurance that their survival would not be compromised. We therefore reviewed studies that have explored the various strategies of treatment de-escalation with an emphasis on survival and toxicity outcomes. Recent studies evaluated the role of maintenance therapy with chemotherapy only, chemotherapy plus bevacizumab, bevacizumab only, and EGFR inhibitors. Current evidence suggests that maintenance strategies offer significant benefit to patients by providing continuous clinical benefit while minimizing the risks associated with continuous therapy. Strategies to improve selection of patients for maintenance therapy versus identifying subgroups of patients that will benefit from a chemotherapy-free interval need to continue to be studied. Finally, as our understanding of the molecular and genetic drivers of colorectal cancer continues to expand, refining these strategies to include more target-specific agents should become more routine.

Pharmacologic Targeting of Regulatory T Cells for Solid Organ Transplantation: Current and Future Prospects
Kassem Safa, Sindhu Chandran, David Wojciechowski

ABSTRACT
The last three decades have witnessed significant advances in the development of immunosuppressive medications used in kidney transplantation leading to a remarkable gain in short-term graft function and outcomes. Despite these major breakthroughs, improvements in long-term outcomes lag behind due to a stalemate between drug-related nephrotoxicity and chronic rejection typically due to donor-specific antibodies. Regulatory T cells (Tregs) have been shown to modulate the alloimmune response and can exert suppressive activity preventing allograft rejection in kidney transplantation. Currently available immunosuppressive agents impact Tregs in the alloimmune milieu with some of these interactions being deleterious to the allograft while others may be beneficial. Variable effects are seen with common antibody induction agents such that basiliximab, an IL-2 receptor blocker, decreases Tregs while lymphocyte depleting agents such as antithymocyte globulin increase Tregs. Calcineurin inhibitors, a mainstay of maintenance immunosuppression since the mid-1980s, seem to suppress Tregs while mammalian targets of rapamycin (less commonly used in maintenance regimens) expand Tregs. The purpose of this review is to provide an overview of Treg biology in transplantation, identify in more detail the interactions between commonly used immunosuppressive agents and Tregs in kidney transplantation and lastly describe future directions in the use of Tregs themselves as therapy for tolerance induction.
Pharmacologic Management of Advanced Cervical Cancer: Antiangiogenesis Therapy and Immunotherapeutic Considerations

Teresa C. Longoria, Krishnansu S. Tewari

ABSTRACT

As a consequence of disparities in access to and utilization of preventative healthcare, the incidence and death rates from cervical cancer remain substantial in the face of indisputable evidence that screening saves lives. While disparities persist, there will be an urgent need for research into the treatment of advanced forms of this disease. In this review, we explore the evolution of the treatment of metastatic, recurrent, and persistent cervical cancer from cytotoxic agents to targeted therapy. We discuss why targeted therapies are unlikely to produce sustained responses alone but may be more successful in combination with immunotherapies. We also provide a rationale for the potential next phase in treatment of this challenging disease—combined therapy with antiangiogenic agents and immune checkpoint inhibitors. In doing so, we highlight recent paradigm shifts within cancer therapeutics, including the shift in focus from the tumor cell itself to the tumor microenvironment, and from stimulating the immune system to inhibiting the inhibitors of an adequate immune response.

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Laparoscopic Surgery: A Narrative Review of Pharmacotherapy in Pain Management

Sari Sjövall, Merja Kokki, Hannu Kokki

ABSTRACT

Laparoscopic surgery is widespread, and an increasing number of surgeries are performed laparoscopically. Early pain after laparoscopy can be similar or even more severe than that after open surgery. Thus, proactive pain management should be provided. Pain after laparoscopic surgery is derived from multiple origins; therefore, a single agent is seldom sufficient. Pain is most effectively controlled by a multimodal, preventive analgesia approach, such as combining opioids with non-opioid analgesics and local anaesthetics. Wound and port site local anaesthetic injections decrease abdominal wall pain by 1–1.5 units on a 0–10 pain scale. Inflammatory pain and shoulder pain can be controlled by NSAIDs or corticosteroids. In some patient groups, adjuvant drugs, ketamine and α2-adrenergic agonists can be helpful, but evidence on gabapentinoids is conflicting. In the present review, the types of pain that need to be taken into account while planning pain management protocols and the wide range of analgesic options that have been assessed in laparoscopic surgery are critically assessed. Recommendations to the clinician will be made regarding how to manage acute pain and how to prevent persistent postoperative pain.

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Axitinib: A Review in Advanced Renal Cell Carcinoma

Gillian M. Keating

ABSTRACT

Axitinib (Inlyta®) is a potent, selective inhibitor of vascular endothelial growth factor receptor-1, -2 and -3. This article reviews the clinical efficacy and tolerability of axitinib in patients with previously-treated advanced renal cell carcinoma (RCC), as well as summarizing its pharmacological properties. Axitinib was effective in the second-line treatment of advanced RCC, according to the results of the pivotal, phase III AXIS trial. Median progression-free survival (PFS) was significantly prolonged with axitinib versus sorafenib (primary endpoint; independent review committee assessment); this PFS benefit was seen in patients who had received prior treatment with cytokines or sunitinib. The objective response rate was also significantly higher with axitinib than with sorafenib, with no significant between-group difference in median overall survival. Axitinib had a manageable tolerability profile in the AXIS trial, with the most commonly reported treatment-related adverse events including diarrhoea, hypertension, fatigue, decreased appetite, nausea, dysphonia, hand-foot syndrome and hypothyroidism. In conclusion, axitinib is an important option in previously-treated patients with advanced RCC.
Oritavancin: A Review in Acute Bacterial Skin and Skin Structure Infections
Yahiya Y. Syed, Lesley J. Scott

ABSTRACT
Oritavancin (Orbactiv®) is a new generation lipoglycopeptide approved for use in adult patients with acute bacterial skin and skin structure infections (ABSSSI). It is administered as a single 1200 mg intravenous infusion over 3 h. In phase 3 trials in adult patients with ABSSSI, oritavancin was noninferior to vancomycin in terms of a composite outcome (cessation of spreading or reduction in the size of the baseline lesion, absence of fever and no rescue antibacterials required; primary endpoint) assessed at an US FDA-recommended early timepoint of 48–72 h after initiation of treatment. Oritavancin was also noninferior to vancomycin in terms of a ≥20 % reduction in the baseline lesion size at the early timepoint and clinical cure rate 7–14 days after the end of treatment. Oritavancin was generally well tolerated in the phase 3 trials, with most treatment-emergent adverse reactions being mild in severity. The most common adverse events occurring in oritavancin recipients were nausea, headache, vomiting, limb and subcutaneous abscesses, and diarrhoea. Oritavancin offers a number of potential advantages, including a convenient single dose treatment that may shorten or eliminate hospital stays, a reduction in healthcare resource utilization and cost, no need for dosage adjustment in patients with mild to moderate hepatic or renal impairment, no need for therapeutic drug monitoring, and elimination of compliance concerns. Therefore, oritavancin is a useful treatment option for adults with ABSSSI.

Vilazodone: A Review in Major Depressive Disorder in Adults
Paul L. McCormack

ABSTRACT
Vilazodone (Viibryd®) exhibits the combined properties of a selective serotonin reuptake inhibitor (SSRI) and a serotonin 5-HT1A receptor partial agonist, and is approved in the US for the treatment of major depressive disorder (MDD) in adults. In four randomized, double-blind, clinical trials, oral vilazodone 20 or 40 mg once daily for 8 or 10 weeks reduced from baseline (improved) the Montgomery-Åsberg Depression Rating Scale (MADRS) total score significantly more than placebo in adult patients with MDD. In these trials, significantly greater reductions in MADRS total score with vilazodone compared with placebo were seen from either week 1, week 2 (two trials) or week 6. In a noncomparative study, MADRS total scores continued to improve throughout therapy for up to 1 year. Vilazodone was generally well tolerated, with the most common treatment-emergent adverse events being mild or moderate diarrhoea, nausea and headache. Vilazodone had only limited adverse effects on sexual function or bodyweight. Therefore, vilazodone is an effective agent for treating MDD in adults.

Nivolumab: A Review in Advanced Squamous Non-Small Cell Lung Cancer
Gillian M. Keating

ABSTRACT
Nivolumab (Opdivo®; Nivolumab BMSTM™) was the first programmed death (PD)-1 immune checkpoint inhibitor to be approved for use in advanced, squamous non-small cell lung cancer (NSCLC) following prior chemotherapy. In the pivotal CheckMate 017 trial, intravenous nivolumab 3 mg/kg every 2 weeks was associated with significantly better overall survival and progression-free survival and a significantly higher overall response rate than intravenous docetaxel in the second-line treatment of advanced, squamous NSCLC. Nivolumab was also better tolerated than docetaxel in CheckMate 017, and its adverse event profile (which included immune-mediated adverse events) was manageable. In conclusion, nivolumab represents an important advance in previously-treated, advanced, squamous NSCLC.
Sebelipase Alfa: First Global Approval
Matt Shirley

ABSTRACT
Sebelipase alfa (Kanuma™) is a recombinant human lysosomal acid lipase (LAL) developed by Synageva BioPharma Corp. (now Alexion Pharmaceuticals, Inc.) for long-term enzyme replacement therapy in patients with LAL deficiency. The agent, administered by intravenous infusion once weekly or once every other week, acts to replace the deficient enzyme activity in patients with LAL deficiency, reducing lysosomal lipid accumulation, and thereby improving disease-related abnormalities such as dyslipidaemia and liver abnormalities. Sebelipase alfa received its first global approval, in the EU, in August 2015 for long-term enzyme replacement therapy in patients of all ages with LAL deficiency. Regulatory submissions have also been filed in the USA, Mexico and Japan for use in this indication. This article summarizes the milestones in the development of sebelipase alfa leading to this first approval for the treatment of LAL deficiency.

Rolapitant: First Global Approval
Yahiya Y. Syed

ABSTRACT
Rolapitant (Varubi™) is an orally active neurokinin-1 receptor antagonist developed by TESARO and approved in the USA for use in combination with other antiemetic agents for the prevention of delayed chemotherapy-induced nausea and vomiting (CINV) in adults. Unlike other approved agents in this class, rolapitant does not interact with cytochrome P450 (CYP) enzyme CYP3A4. It also has a long elimination half-life which means that a single dose could prevent CINV during the entire at-risk period (0–120 h). An intravenous formulation of rolapitant is under clinical development in the USA. Phase II development of rolapitant in postoperative nausea and vomiting, and cough appears to have been discontinued. This article summarizes the milestones in the development of rolapitant leading to the first approval for the prevention of CINV.

Omarigliptin: First Global Approval
Celeste B. Burness

ABSTRACT
Omarigliptin [Marizev® (Japan)] is a small-molecule dipeptidyl peptidase-4 (DPP-4) inhibitor developed by Merck for the oral treatment of type 2 diabetes (T2DM). Unlike the majority of other approved agents of its class, which are usually administered once daily, omarigliptin can be administered once weekly. Once-weekly omarigliptin has received its first global approval in this indication in Japan, for use in adults. Phase III clinical development of the product is underway in several other countries. This article summarizes the milestones in the development of omarigliptin leading to this first approval for the treatment of T2DM.
ABSTRACT

Methotrexate is the most common disease-modifying antirheumatic drug (DMARD) used in the treatment of rheumatoid arthritis (RA). Current evidence supports its efficacy in the treatment of RA, resulting in improved short-term disease control and long-term outcomes in terms of radiographic progression. Oral methotrexate has traditionally been used first-line due to various reasons, including ease of administration, low cost and easy availability. A methotrexate dose of >15 mg/week is generally required for disease control but oral methotrexate may be only partially effective or poorly tolerated in some patients. The rationale for using subcutaneous (SC) methotrexate is based on its improved bioavailability at higher doses and better tolerability in some patients who have side effects when receiving oral methotrexate. Current guidance advocates ‘treating to target’, with the aim of inducing remission in RA patients. In some patients, this can be achieved using methotrexate alone or in combination with other traditional DMARDs. Patients who have not responded to two DMARDs, including methotrexate, are eligible for biological therapy as per current National Institute for Health and Care Excellence (NICE) guidance in the UK. Biological treatments are expensive and using SC methotrexate can improve disease control in RA patients, thus potentially avoiding or delaying the requirement for future biological treatment.

Intrathecal Analgesia for Chronic Refractory Pain: Current and Future Prospects

Catherine Smyth, Nadera Ahmadzai, Jason Wentzell, Ashley Pardoe, Andrew Tse

ABSTRACT

The intrathecal drug-delivery system (IDDS) is one mode of infusing analgesic medications directly into the cerebrospinal fluid in close proximity to their site of action. This modality has been employed in patients with refractory pain either due to malignant or non-malignant causes for over 30 years. Unfortunately, and despite the number of years it has been in use, there is still a scarcity of rigorous evidence to guide its integration into clinical practice. Current best evidence is inconclusive as to the comparative effectiveness and harms of the IDDS relative to routine medical care of patients. There are far more systematic reviews than high-quality primary comparative studies of the IDDS vs. conventional pain treatment. Existing clinical practice recommendations are best viewed as expert opinion with competing interests. This article will review the existing literature for indications, contraindications, consensus statements, different technologies, and complications of the IDDS. Although approved analgesics for IDDS delivery are limited to morphine and ziconotide, many other analgesics, alone or in combination, are routinely used in this setting. This review will also focus on the pharmacology, clinical efficacy, and safety of intrathecal medications extensively used in clinical practice; including agents approved, unapproved, and under development.
Thrombocytopenia (platelet count <150 × 109/L) often complicates chronic liver disease, impeding optimal management of these patients. The prevalence of this manifestation ranges from 6 % among non-cirrhotic patients with chronic liver disease to 70 % among patients with liver cirrhosis. It has also been shown that the severity of liver disease is associated with both prevalence and level of thrombocytopenia. Its development is often multifactorial, although thrombopoietin is thought to be a major factor. The discovery of and ability to clone thrombopoietin led to new treatment opportunities for this clinical manifestation. This review discusses data on the three most important thrombopoietin receptor agonists: eltrombopag, avatrombopag, and romiplostim. Currently, only eltrombopag is approved for usage among patients with thrombocytopenia and chronic hepatitis C virus infection in order to initiate and maintain interferon-based antiviral treatment. Nevertheless, the optimal management of hematologic abnormalities among patients with chronic liver disease, and its risk for bleeding complications, is still a matter of discussion. Thrombocytopenia definitely contributes to hemostatic defects but is often counterbalanced by the enhanced presence of procoagulant factors. Therefore, a thorough assessment of the patient’s risk for thrombotic events is essential when the use of thrombopoietin receptor agonists is considered among patients with chronic liver disease and thrombocytopenia.

Recent Advances in the Development of Antineoplastic Agents Derived from Natural Products
Matthew Trendowski

ABSTRACT
Through years of evolutionary selection pressures, organisms have developed potent toxins that coincidentally have marked antineoplastic activity. These natural products have been vital for the development of multiagent treatment regimens currently employed in cancer chemotherapy, and are used in the treatment of a variety of malignancies. Therefore, this review catalogs recent advances in natural product-based drug discovery via the examination of mechanisms of action and available clinical data to highlight the utility of these novel compounds in the burgeoning age of precision medicine. The review also highlights the recent development of antibody-drug conjugates and other immunotoxins, which are capable of delivering highly cytotoxic agents previously deemed too toxic to elicit therapeutic benefit preferentially to neoplastic cells. Finally, the review examines natural products not currently used in the clinic that have novel mechanisms of action, and may serve to supplement current chemotherapeutic protocols.
**ABSTRACT**

Nanoparticle albumin-bound paclitaxel (Abraxane®) [hereafter referred to as nab-paclitaxel] is a taxane developed to avoid some of the toxicities associated with solvent-bound (sb) paclitaxel. Nab-paclitaxel, in combination with carboplatin, is indicated for the first-line treatment of non-small cell lung cancer (NSCLC) in patients who are not candidates for curative surgery and/or radiation therapy. This article summarizes pharmacological, efficacy and tolerability data relevant to the use of nab-paclitaxel in this indication. Compared with sb-paclitaxel plus carboplatin, nab-paclitaxel plus carboplatin significantly improved the objective response rate (ORR), but did not prolong progression-free survival or overall survival (OS), in the overall population of patients with advanced NSCLC in a multinational phase III trial. The nab-paclitaxel regimen also provided benefit over the sb-paclitaxel regimen in certain patient subgroups, including patients with squamous cell histology (in terms of ORR) and patients who were elderly (in terms of OS). Nab-paclitaxel plus carboplatin had a manageable tolerability profile with some benefits over sb-paclitaxel plus carboplatin, including lower rates of grade ≥3 neutropenia, peripheral neuropathy, arthralgia and myalgia, although was associated with more grade ≥3 anaemia and thrombocytopenia. Given its efficacy and tolerability, intravenous nab-paclitaxel plus carboplatin is a valuable first-line treatment option for patients with advanced NSCLC.

**Edoxaban: A Review in Deep Vein Thrombosis and Pulmonary Embolism**

Matt Shirley, Sohita Dhillon

**ABSTRACT**

Edoxaban (Lixiana®, Savaysa®) is an oral, direct factor Xa inhibitor which has recently been approved for use in the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) [collectively, venous thromboembolism (VTE)] and for the prevention of recurrent VTE. This article reviews the pharmacological properties of edoxaban as well as its tolerability and therapeutic efficacy in the treatment and prevention of recurrent VTE events. As demonstrated in the pivotal Hokusai-VTE phase III trial, once-daily edoxaban after initial treatment with heparin was non-inferior to standard therapy with heparin/warfarin in preventing recurrent VTE events and was associated with a significantly lower risk of clinically relevant bleeding than the traditional therapy. Edoxaban shares the advantages of other direct oral anticoagulants (DOACs) over traditional therapies, including the lack of requirement for routine coagulation monitoring, a rapid onset and offset of action, and few drug-drug interactions. It offers the convenience of once-daily dosing, can be taken without regard to food and allows for a dose reduction in patients with certain clinical features, such as moderate renal impairment or low body weight. In conclusion, edoxaban represents an effective and potentially safer alternative to traditional vitamin K antagonist therapy for the treatment and prevention of recurrent VTE. Its recent approval expands the range of DOAC agents for recurrent VTE, further facilitating treatment individualization.
Cariprazine: First Global Approval
Paul L. McCormack

ABSTRACT
Cariprazine (Vraylar™) is an oral atypical antipsychotic originated by Gedeon Richter. It is a potent dopamine D3 and D2 receptor partial agonist, which preferentially binds to the D3 receptor. Cariprazine also has partial agonist activity at serotonin 5-HT1A receptors. In September 2015, cariprazine received its first global approval in the USA for the treatment of schizophrenia and for the acute treatment of manic or mixed episodes associated with bipolar I disorder. It is also in development in a variety of countries for the treatment of schizophrenia with predominant negative symptoms (phase III), as adjunctive therapy for major depressive disorder (phase II/III) and for the treatment of bipolar depression (phase II). This article summarizes the milestones in the development of cariprazine leading to this first approval for schizophrenia and manic or mixed episodes associated with bipolar I disorder.

Evogliptin: First Global Approval
Paul L. McCormack

ABSTRACT
Evogliptin (Suganon™) is an orally bioavailable, selective dipeptidyl peptidase-4 (DPP-4; CD26 antigen) inhibitor being developed by Dong-A ST for the treatment of type 2 diabetes mellitus. DPP-4 inhibitors control glucose levels by preventing the breakdown of the incretin hormones glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), which stimulate insulin secretion in response to the increased levels of glucose in the period following meals. In October 2015, evogliptin received its first global approval in South Korea for blood glucose control in patients with type 2 diabetes mellitus. This article summarizes the milestones in the development of evogliptin leading to this first approval for type 2 diabetes mellitus.

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The Challenges of Interstitial Cystitis: Current Status and Future Prospects
Samuel Belknap, Eric Blalock, Deborah Erickson

ABSTRACT
Interstitial cystitis/bladder pain syndrome (IC/BPS) is a syndrome of unpleasant bladder sensations and lower urinary tract symptoms. The three main proposed etiologies are bladder urothelial dysfunction, bladder inflammation (possible neurogenic), and neuropathic pain. Despite decades of basic and clinical research, IC/BPS remains difficult to treat. A variety of treatments are used, each aimed towards one etiology. For example, glycosaminoglycans are thought to improve the urothelial permeability barrier, anti-inflammatory agents are used to decrease general inflammation, and mast cell stabilizers and/or antagonists of mast cell products are used in the treatment of neurogenic inflammation. In the (unfortunately frequent) event that a treatment fails, possible reasons are that (1) the clinician is aiming towards the wrong etiology for that patient (i.e., the treatment is off target) or (2) the correct etiology is being targeted, but the treatment is not ameliorating it (i.e., the treatment is sub-therapeutic). This is a crucial distinction, because an off-target treatment should be abandoned, but a sub-therapeutic treatment should be escalated. Currently, our inability to make this crucial distinction is the greatest obstacle to effective treatment. An important future advance would be to identify urine or serum biomarkers specific to each etiologic target. Then, each biomarker could be used to select appropriate patients for each treatment and monitor the treatment’s effect on its intended target.
Disease-Modifying Drugs in Parkinson’s disease
Ariane Park, Mark Stacy

ABSTRACT
Despite an increased understanding of the pathogenesis of Parkinson’s disease (PD), and a number of drugs designed to ameliorate symptoms, finding an effective neuroprotective therapy remains elusive. For decades now, several promising agents targeting different pathways have been explored as potential treatments that could help slow disease progression, but these have met with limited success. There are hurdles to overcome, particularly given that there is no exact animal model of PD and also no reliable biomarkers for PD. Without biomarkers, it is not possible to demonstrate, in the context of a clinical trial, that an intervention prevents neuronal degeneration. However, given the compelling scientific rationale of several compounds, an unrelenting pursuit continues. There have been hundreds of human studies looking at neuroprotection in PD. This article will briefly summarize several of the neuroprotective treatments that have been evaluated in large clinical trials, and will also outline some of the newer therapies that are currently being explored.

Lipoglycopeptide Antibacterial Agents in Gram-Positive Infections: A Comparative Review
Françoise Van Bambéke

ABSTRACT
Oritavancin, telavancin, and dalbavancin are recently marketed lipoglycopeptides that exhibit remarkable differences to conventional molecules. While dalbavancin inhibits the late stages of peptidoglycan synthesis by mainly impairing transglycosylase activity, oritavancin and telavancin anchor in the bacterial membrane by the lipophilic side chain linked to their disaccharidic moiety, disrupting membrane integrity and causing bacteriolysis. Oritavancin keeps activity against vancomycin-resistant enterococci, being a stronger inhibitor of transpeptidase than of transglycosylase activity. These molecules have potent activity against Gram-positive organisms, most notably staphylococci (including methicillin-resistant Staphylococcus aureus and to some extent vancomycin-intermediate S. aureus), streptococci (including multidrug-resistant pneumococci), and Clostridia. All agents are indicated for the treatment of acute bacterial skin and skin structure infections, and telavancin, for hospital-acquired and ventilator-associated bacterial pneumonia. While telavancin is administered daily at 10 mg/kg, the remarkably long half-lives of oritavancin and dalbavancin allow for infrequent dosing (single dose of 1200 mg for oritavancin and 1000 mg at day 1 followed by 500 mg at day 8 for dalbavancin), which could be exploited in the future for outpatient therapy. Among possible safety issues evidenced during clinical development were an increased risk of developing osteomyelitis with oritavancin; taste disturbance, nephrotoxicity, and risk of corrected QT interval prolongation (especially in the presence of at-risk co-medications) with telavancin; and elevation of hepatic enzymes with dalbavancin. Interference with coagulation tests has been reported with oritavancin and telavancin. These drugs proved non-inferior to conventional treatments in clinical trials but their advantages may be better evidenced upon future evaluation in more severe infections.
Complicated Intra-Abdominal Infections: The Old Antimicrobials and the New Players
Young R. Lee, Danni McMahan, Catherine McCall, Gregory K. Perry

ABSTRACT
Complicated intra-abdominal infections (cIAIs) are an important cause of morbidity and mortality worldwide. They are diagnosed when the initial abdominal organ infection has spread into the peritoneal space. Successful treatment relies on adequate source control and appropriate empiric antimicrobial therapy. Inappropriate antimicrobial therapy may result in poor patient outcomes and increases in healthcare costs. Current guidelines recommend several single and combination antimicrobial regimens; however, empiric antimicrobial treatment has been complicated by the increasing rates of resistant organisms, especially the extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae. Additionally, the overuse of carbapenems to combat these resistant pathogens has contributed to the rise of carbapenemase-producing microorganisms, especially Klebsiella pneumoniae. This increasing resistance has prompted the development of novel antimicrobials like ceftazidime–avibactam and ceftolozane–tazobactam, whose activity extends to ESBL-producing microorganisms. Furthermore, the optimal duration of antimicrobial therapy is still unknown, and further research is necessary to find a definitive answer. This review will focus on antimicrobial therapies recommended by the current guidelines, the individual properties of these agents, appropriate duration of therapy, recent clinical trials, and place in therapy of the antimicrobial agents recently approved for the treatment of cIAIs.

Adalimumab: A Review in Chronic Plaque Psoriasis
Celeste B. Burness, Kate McKeage

ABSTRACT
Adalimumab (Humira®) is a fully human monoclonal antibody against tumour necrosis factor (TNF), formulated for subcutaneous administration. It is well established in the treatment of adults with moderate-to-severe chronic plaque psoriasis and has recently received approval in the EU for the treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age. In a phase III trial in paediatric patients, a significantly greater proportion of patients receiving adalimumab 0.8 mg/kg (to a maximum of 40 mg) every other week (eow) achieved a ≥75 % improvement from baseline in Psoriasis Area and Severity Index than those receiving methotrexate after 16 weeks of treatment. In adults, well-designed randomized clinical trials demonstrated that adalimumab 40 mg eow effectively reduced the signs and symptoms of psoriasis and improved dermatology-specific and general measures of health-related quality of life, with these benefits sustained during long-term treatment. Adalimumab was generally well tolerated, compared with placebo or methotrexate, during clinical trials in paediatric and adult patients with chronic plaque psoriasis. Thus, adalimumab remains an important treatment strategy in adults with moderate-to-severe chronic plaque psoriasis and provides a promising new systemic treatment option for children and adolescents from 4 years of age with severe psoriasis.
Netupitant/Palonosetron: A Review in the Prevention of Chemotherapy-Induced Nausea and Vomiting
Gillian M. Keating

ABSTRACT
An oral fixed combination of netupitant/palonosetron (NEPA; Akynzeo®) is available for use in the prevention of acute and delayed chemotherapy-induced nausea and vomiting (CINV). Netupitant is a highly selective neurokinin-1 receptor antagonist and palonosetron is a serotonin 5-HT3 receptor antagonist with a distinct pharmacological profile. Complete response rates during the delayed, acute and overall phases were significantly higher with single-dose netupitant 300 mg plus palonosetron 0.5 mg than with single-dose palonosetron 0.5 mg in cycle 1 of cisplatin-based highly emetogenic chemotherapy (HEC) in a phase II trial and with single-dose netupitant/palonosetron 300/0.5 mg than with single-dose palonosetron 0.5 mg in cycle 1 of anthracycline–cyclophosphamide (AC) moderately emetogenic chemotherapy (MEC) in a phase III trial; the greater efficacy of netupitant/palonosetron was maintained over repeated cycles of AC MEC in the phase III trial. In another phase III trial, netupitant/palonosetron 300/0.5 mg was effective over repeated cycles of non-AC MEC or HEC. Netupitant/palonosetron was well tolerated, with no cardiac safety concerns. The convenience of administering netupitant/palonosetron as a single dose in a fixed combination has the potential to improve adherence to CINV prevention guidelines. In conclusion, netupitant/palonosetron is an important option to consider in the prevention of acute and delayed CINV in patients receiving MEC or HEC.

Lacosamide: A Review in Focal Seizures in Patients with Epilepsy
Lesley J. Scott

ABSTRACT
Lacosamide (Vimpat®) is a functionalized amino acid available orally (as a solution or tablets) and as an intravenous infusion for use as monotherapy (only in the USA) or adjunctive therapy for the treatment of focal seizures in adult and adolescent (aged ≥17 years in the USA) patients with epilepsy. As adjunctive therapy to other antiepileptic drugs (AEDs), lacosamide provided effective seizure control and was generally well tolerated in adults and adolescents (aged ≥16 years) in randomized clinical trials and in the real-world setting. In clinical trials, adjunctive lacosamide provided significantly greater reductions in 28-day seizure rates than adjunctive placebo, with these benefits maintained after up to 8 years of therapy in open-label extension studies. Moreover, patients were effectively switched from oral to short-term intravenous adjunctive therapy at the same dosage, which may be particularly beneficial in situations where oral therapy is not suitable. Conversion to lacosamide monotherapy was superior to a historical-control cohort in patients with focal seizures converting from previous AED therapy. In the absence of head-to-head comparisons with other AEDs, the exact position of lacosamide relative to other AEDs remains to be fully determined. In the meantime, oral and intravenous lacosamide provides a useful option as monotherapy (only in the USA) or adjunctive therapy for the treatment of focal seizures in adult and adolescent (aged ≥17 years in the USA) patients with epilepsy.
Idarucizumab: First Global Approval
Celeste B. Burness

ABSTRACT
Idarucizumab (Praxbind®) is a fully humanized, monoclonal antibody fragment developed by Boehringer Ingelheim as a specific antidote to reverse the anticoagulant effect of the direct oral thrombin inhibitor dabigatran etexilate (Pradaxa®). Idarucizumab received its first global approval, in the USA, in October 2015 for use in adult patients treated with dabigatran etexilate when rapid reversal of its anticoagulant effects is required for emergency surgery/urgent procedures or in life-threatening or uncontrolled bleeding. Regulatory applications have been submitted in Canada and in the EU, where it has received a positive opinion from the European Medicines Agency’s Committee for Medicinal Products for Human Use. This article summarizes the milestones in the development of idarucizumab leading to this first approval for reversing the anticoagulant effects of dabigatran in adults.

Mepolizumab: First Global Approval
Gillian M. Keating

ABSTRACT
Mepolizumab (Nucala®) is a fully humanized monoclonal antibody against interleukin-5 (IL-5) that is being developed by GlaxoSmithKline. Subcutaneous mepolizumab is approved in the USA for the add-on maintenance treatment of patients aged ≥12 years with severe asthma and an eosinophilic phenotype, and is awaiting approval in the EU. Mepolizumab blocks IL-5 and reduces blood and sputum eosinophil counts in patients with asthma. In the phase III MENSA trial in patients with recurrent asthma exacerbations and evidence of eosinophilic inflammation despite high-dose inhaled glucocorticoid therapy, mepolizumab significantly reduced the annualized exacerbation rate. In the phase III SIRIUS trial, mepolizumab had an oral glucocorticoid-sparing effect in patients with severe eosinophilic asthma requiring systemic glucocorticoid maintenance therapy. This article summarizes the milestones in the development of mepolizumab leading to this first approval for severe asthma with an eosinophilic phenotype.

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