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Combined Angiotensin Receptor Modulation in the Management of Cardio-Metabolic Disorders

Ludovit Paulis, Sébastien Foulquier, Pawel Namsolleck, Chiara Recarti

ABSTRACT

Cardiovascular and metabolic disorders, such as hypertension, insulin resistance, dyslipidemia or obesity are linked with chronic low-grade inflammation and dysregulation of the renin–angiotensin system (RAS). Consequently, RAS inhibition by ACE inhibitors or angiotensin AT1 receptor (AT1R) blockers is the evidence-based standard for cardiovascular risk reduction in high-risk patients, including diabetics with albuminuria. In addition, RAS inhibition reduces the new onset of diabetes mellitus. Yet, the high and increasing prevalence of metabolic disorders, and the high residual risk even in properly treated patients, calls for additional means of pharmacological intervention. In the past decade, the stimulation of the angiotensin AT2 receptor (AT2R) has been shown to reduce inflammation, improve cardiac and vascular remodeling, enhance insulin sensitivity and increase adiponectin production. Therefore, a concept of dual AT1R/AT2R modulation emerges as a putative means for risk reduction in cardio-metabolic diseases. The approach employing simultaneous RAS blockade (AT1R) and RAS stimulation (AT2R) is distinct from previous attempts of double intervention in the RAS by dual blockade. Dual blockade abolishes the AT1R-linked RAS almost completely with subsequent risk of hypotension and hypotension-related events, i.e. syncope or renal dysfunction. Such complications might be especially prominent in patients with renal impairment or patients with isolated systolic hypertension and normal-to-low diastolic blood pressure values. In contrast to dual RAS blockade, the add-on of AT2R stimulation does not exert significant blood pressure effects, but it may complement and enhance the anti-inflammatory and antifibrotic/de-stiffening effects of the AT1R blockade and improve the metabolic profile. Further studies will have to investigate these putative effects in particular for settings in which blood pressure reduction is not primarily desired.

Targeted Therapies for Advanced Oesophagogastric Cancer: Recent Progress and Future Directions

Kate Young, Ian Chau

ABSTRACT

The genomic landscape of oesophagogastric (OG) cancer is highly complex. The recent elucidation of some of the pathways involved has suggested a number of novel targets for therapy. This therapy is urgently required as with conventional chemotherapy regimens patients with advanced OG cancer still have a median overall survival of under a year. This review outlines the rationale for the current treatment of OG cancer with chemotherapy and describes both previously conducted and ongoing clinical trials of novel agents in this area. The targets and associated treatments discussed include HER-2, EGFR, VEGF, c-Met, FGFR-2, PI3K, mTOR and IGF-1. To date only two targeted treatments, trastuzumab and ramucirumab, have become part of the treatment paradigm for OG cancer, partly due to difficulties in defining predictive biomarkers in this disease. However, there are a number of promising drugs in the pipeline and this article seeks to describe these and other potential novel approaches including targeting DNA repair deficiencies and the immune system.
Non-Infectious Uveitis: Optimising the Therapeutic Response
Archana Airody, Greg Heath, Susan Lightman, Richard Gale

ABSTRACT
Non-infectious uveitis mainly affects the working-age population and can contribute to significant social and economic burden. It comprises a heterogeneous group of conditions with varied aetiology. Precise and early diagnosis, excluding masquerade syndromes, is the key to early therapeutic intervention. Treatment should be appropriately selected according to the anatomical sites of inflammation, the diagnosis and known prognosis, and whether there is a systemic inflammatory drive. Corticosteroids in the form of local or systemic therapy form the mainstay of treatment; however, due to unacceptable side effects, the need for long-term use or suboptimal response, corticosteroid-sparing medications may need to be considered early on in the management of non-infectious uveitis. With newer insights into the immunopathology of uveitis and the availability of biologic agents, treatment can be tailored according to individual needs. Many patients have systemic involvement, and hence a multidisciplinary approach is often required to achieve the best outcome in an individual. Patient involvement in the management of non-infectious uveitis, ensuring compliance, and continual monitoring of both the treatment and therapeutic response are the key to achieving optimal outcomes.

Insulin Aspart in the Management of Diabetes Mellitus: 15 Years of Clinical Experience
Kjeld Hermansen, Mette Bohl, Anne Grethe Schioldan

ABSTRACT
Limiting excessive postprandial glucose excursions is an important component of good overall glyemic control in diabetes mellitus. Pharmacokinetic studies have shown that insulin aspart, which is structurally identical to regular human insulin except for the replacement of a single proline amino acid with an aspartic acid residue, has a more physiologic time–action profile (i.e., reaches a higher peak and reaches that peak sooner) than regular human insulin. As expected with this improved pharmacokinetic profile, insulin aspart demonstrates a greater glucose-lowering effect compared with regular human insulin. Numerous randomized controlled trials and a meta-analysis have also demonstrated improved postprandial control with insulin aspart compared with regular human insulin in patients with type 1 or type 2 diabetes, as well as efficacy and safety in children, pregnant patients, hospitalized patients, and patients using continuous subcutaneous insulin infusion. Studies have demonstrated that step-wise addition of insulin aspart is a viable intensification option for patients with type 2 diabetes failing on basal insulin. Insulin aspart has shown a good safety profile, with no evidence of increased receptor binding, mitogenicity, stimulation of anti-insulin antibodies, or hypoglycemia compared with regular human insulin. In one meta-analysis, there was evidence of a lower rate of nocturnal hypoglycemia compared with regular human insulin and, in a trial that specifically included patients with a history of recurrent hypoglycemia, a significantly lower rate of severe hypoglycemic episodes. The next generation of insulin aspart (faster-acting insulin aspart) is being developed with a view to further improving on these pharmacokinetic/pharmacodynamic properties.
ABSTRACT

HIV-1-infected patients with suppressed plasma viral loads often require changes to their antiretroviral (ARV) therapy to manage drug toxicity and intolerance, to improve adherence, and to avoid drug interactions. In patients who have never experienced virologic failure while receiving ARV therapy and who have no evidence of drug resistance, switching to any of the acceptable US Department of Health and Human Services first-line therapies is expected to maintain virologic suppression. However, in virologically suppressed patients with a history of virologic failure or drug resistance, it can be more challenging to change therapy while still maintaining virologic suppression. In these patients, it may be difficult to know whether the discontinuation of one of the ARVs in a suppressive regimen constitutes the removal of a key regimen component that will not be adequately supplanted by one or more substituted ARVs. In this article, we review many of the clinical scenarios requiring ARV therapy modification in patients with stable virologic suppression and outline the strategies for modifying therapy while maintaining long-term virologic suppression.

Prucalopride: A Review in Chronic Idiopathic Constipation

Karly P. Garnock-Jones

ABSTRACT

Prucalopride (Resolor®), a highly selective serotonin 5-HT4 receptor agonist, is indicated in the European Economic Area for the treatment of adults with chronic idiopathic constipation (CIC) in whom laxatives have failed to provide adequate relief. This article reviews the pharmacological properties of prucalopride and its clinical efficacy and tolerability in patients with CIC. In five well-designed, 12-week trials in patients with CIC, oral prucalopride 2 mg/day was significantly more effective than placebo at improving bowel function, including the number of bowel movements and a range of other constipation symptoms, as well as health-related quality of life and patient satisfaction; however, no significant differences in bowel function measures were observed between prucalopride and placebo in a 24-week trial. Oral PEG-3350 + electrolytes reconstituted powder was found to be noninferior but not superior to prucalopride according to primary endpoint data from a 4-week, controlled-environment trial. Prucalopride was generally well tolerated in clinical trials; the most common adverse events were headache, diarrhoea, nausea and abdominal pain. No cardiovascular safety issues have arisen with prucalopride treatment. Although further long-term and comparative data would be beneficial, prucalopride provides an additional treatment option for patients with CIC.
Sumatriptan/Naproxen Sodium: A Review in Migraine

Yahiya Y. Syed

ABSTRACT

Sumatriptan/naproxen sodium (Treximet®) is a fixed-dose combination of a serotonin 5-HT1B/1D receptor agonist (sumatriptan) and an NSAID (naproxen sodium), approved in the USA for the acute treatment of migraine with or without aura in adolescents and adults. In a randomized, phase 3 trial in adolescents, significantly more sumatriptan/naproxen sodium than placebo recipients were pain-free at 2 h. Similarly, in a pair of randomized phase 3 trials in adults, significantly more sumatriptan/naproxen sodium than placebo recipients had relief from migraine symptoms at 2 h, and the combination was more effective than individual components in terms of sustained (2–24 h) pain-free response rate. Sumatriptan/naproxen sodium was generally well tolerated, with ≤11% of adolescents and ≤22% of adults reporting treatment-related adverse events in the key clinical trials. The most common adverse reactions were nasopharyngitis, hot flushes and muscle tightness in adolescents, and dizziness, pain or pressure sensations, nausea, somnolence, dry mouth, dyspepsia and paraesthesia in adults. Based on current data, sumatriptan/naproxen sodium is a useful option for the acute treatment of migraine in adolescents and adults. The fixed-dose combination may reduce pill burden and improve adherence in some patients.

Capsaicin 8 % Patch: A Review in Peripheral Neuropathic Pain

Celeste B. Burness, Paul L. McCormack

ABSTRACT

The capsaicin 8% patch (QUTENZA®) is an adhesive patch containing a high concentration (8 % w/w) of synthetic capsaicin, a selective agonist of transient receptor potential vanilloid 1 channel. It is approved for treatment of peripheral neuropathic pain in adults either alone or in combination with other medicinal products for pain in the EU; it is only approved to treat postherpetic neuralgia (PHN) in the USA. In patients with painful diabetic peripheral neuropathy (PDPN), a single 30-min application of the capsaicin 8% patch significantly improved pain relief and sleep quality compared with placebo in a 12-week double-blind trial. In a 52-week, randomized trial, up to seven consecutive 30-min treatments with the capsaicin 8% patch (≤7 treatments each at least 8 weeks apart) plus standard of care therapy was associated with sustained pain relief and no negative neurological safety consequences compared with standard of care. In two randomized trials, a single 60-min application of the capsaicin 8% patch reduced pain scores significantly more than a low-concentration (0.04 %) capsaicin control patch in patients with PHN. Capsaicin 8% patch treatment was noninferior to pregabalin (optimized dosage) in a randomized trial in patients with nondiabetic peripheral neuropathic pain. Results in two trials in patients with HIV-AN were equivocal, with a significant improvement in pain intensity observed in one trial, but not in the other. The capsaicin 8% patch was associated with expected, transient, capsaicin-related application-site adverse events such as erythema and pain.
ABSTRACT

Tiotropium/olodaterol (Stiolto™ Respimat®, Spiolto™ Respimat®) is a fixed-dose combination of the long-acting antimuscarinic agent tiotropium bromide (hereafter referred to as tiotropium) and the long-acting β2-adrenoreceptor agonist olodaterol delivered via the Respimat® Soft Mist™ inhaler. It is indicated for the maintenance treatment of airflow obstruction in adults with COPD. Several randomized, phase III studies of 6–52 weeks’ duration evaluated the efficacy of once-daily tiotropium/olodaterol in patients with GOLD stage 2–3 or 2–4 COPD. Tiotropium/olodaterol maintenance therapy improved lung function to a greater extent than the individual components or placebo and provided clinically meaningful improvements in health-related quality of life and dyspnoea in 12- and 52-week studies. Tiotropium/olodaterol consistently improved 24-h lung function in 6-week studies, providing greater benefits than the monotherapies, placebo or twice-daily fixed-dose fluticasone propionate/salmeterol. Inspiratory capacity and exercise endurance were also improved with tiotropium/olodaterol following 6 or 12 weeks’ treatment. The tolerability profile of tiotropium/olodaterol in the phase III studies was generally similar to that of the component monotherapies. The most common adverse events and serious adverse events during 52 weeks’ therapy were respiratory in nature, with COPD exacerbation, unsurprisingly, reported most frequently with tiotropium/olodaterol and component monotherapies. Although additional data assessing the effect of tiotropium/olodaterol on exacerbations and comparative studies with other recommended therapies are needed to definitively position tiotropium/olodaterol, current evidence indicates that tiotropium/olodaterol is a useful treatment option for patients with COPD.

Talimogene Laherparepvec: First Global Approval

Sarah L. Greig

ABSTRACT

Talimogene laherparepvec (Imlygic™) is an oncolytic viral therapy that is being developed by BioVex (a subsidiary of Amgen) for the intralesional treatment of various cancers, including malignant melanoma. Talimogene laherparepvec is a genetically modified, live, attenuated, herpes simplex virus type 1 that is designed to promote an antitumour response through selective viral replication in tumour cells and stimulation of systemic antitumour immunity. In October 2015, talimogene laherparepvec was the first genetically modified oncolytic viral therapy to be approved in the USA for the local treatment of unresectable cutaneous, subcutaneous and nodal lesions in patients with melanoma recurrent after initial surgery, although it has not been shown to improve overall survival or have an effect on visceral metastases. Talimogene laherparepvec has been recommended for approval in adults with unresectable metastatic melanoma in the EU, and is being evaluated in several countries for use as neoadjuvant or combination therapy in malignant melanoma; it is also in development for soft tissue sarcoma and liver cancer in the USA. This article summarizes the milestones in the development of talimogene laherparepvec leading to this first approval in malignant melanoma.
Antidepressant Drugs for Postsurgical Pain: Current Status and Future Directions
Ian Gilron

ABSTRACT

Current treatments for postsurgical pain are often inadequate and adverse effects are substantial such that residual pain and/or side effects impair recovery. The recognition of analgesic efficacy with antidepressant drugs for chronic pain suggests the potential for efficacy in acute postsurgical pain. As reviewed here, current evidence suggests that approximately half of previous trials suggest efficacy of various antidepressants for acute postoperative pain. However, most trials are older with deficiencies including: lack of designation of a primary outcome, no assessment of movement-evoked pain, small size and limited safety assessment. Only one of three trials addressing prevention of chronic postsurgical pain suggested any efficacy; however, the evidence base for this indication is limited. Thus, current evidence does not yet support routine use of any one specific antidepressant for treatment of acute, or prevention of chronic, postsurgical pain. However, limitations in available trials are such that one cannot yet rule out the possibility that one or more antidepressant drugs may provide benefit in specific populations. Therefore, future larger trials should explore optimal dosing and duration of antidepressant treatment, procedure specificity, safety evaluation, and assessment of movement-evoked pain.

Therapies to preserve β-Cell Function in Type 1 Diabetes
Johnny Ludvigsson

ABSTRACT

In spite of modern techniques, the burden for patients with type 1 diabetes mellitus will not disappear, and type 1 diabetes will remain a life-threatening disease causing severe complications and increased mortality. We have to learn of ways to stop the destructive process, preserve residual insulin secretion or even improve the disease via β-cell regeneration. This will give a milder disease, a more stable metabolism, simpler treatment and perhaps even cure. Therapies based on single drugs have not shown sufficient efficacy; however, there are several treatments with encouraging efficacy and no apparent, or rather mild, adverse events. As the disease process is heterogeneous, treatments have to be chosen to fit relevant subgroups of patients, and step by step efficacy can possibly be improved by the use of combination therapies. Thus immunosuppressive therapies like anti-CD3 and anti-CD20 monoclonal antibodies might be combined with fusion proteins such as etanercept [tumor necrosis factor (TNF)-α inhibitor] and/or abatacept (CTLA4-Ig) early after onset to stop the destructive process, supported by β-cell protective agents. The effect may be prolonged by using autoantigen therapy [glutamate decarboxylase (GAD) proinsulin], and by adding agents facilitating β-cell regeneration [e.g. glucagon-like peptide-1 (GLP-1)] there should be a good chance to make the disease milder, perhaps leading to cure in some patients.
Systemic sclerosis is a devastating multisystem rheumatologic condition that is characterized by autoimmunity, tissue fibrosis, obliterative vasculopathy and inflammation. Clinical presentation and course of the condition vary greatly, which complicates both diagnosis and corresponding treatment. In this regard, recent advances in disease understanding, both clinically and biochemically, have led to newer classification criteria for systemic sclerosis that are more inclusive than ever before. Still, significant disease modifying therapies do not yet exist for most patients. Therefore, organ-based management strategies are employed and research has been directed within this paradigm focusing on either the most debilitating symptoms, such as Raynaud’s phenomenon, digital ulcers and cutaneous sclerosis, or life-threatening organ involvement such as interstitial lung disease and pulmonary arterial hypertension. The current trends in systemic sclerosis diagnosis, evidence-based treatment recommendations and potential future directions in systemic sclerosis treatment are discussed.

ABSTRACT

Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease characterized by recurrent inflammatory nodules mostly located in the armpits and groin. Over the years multiple treatments for HS have been proposed; however, to date a cure is still lacking. In this update we provide an overview of most drug treatments reported on for HS, where possible with their mode of action and side effects. In mild cases, clindamycin lotion or resorcinol cream have proven effective. Tetracyclines are a first-line systemic option in more widespread or severe cases, followed by the combination of clindamycin and rifampicin. However, the recurrence rate is high after discontinuation of clindamycin plus rifampicin combination therapy. Long-term treatment with retinoids, especially acitretin is feasible, although teratogenicity has to be taken into account in females of reproductive age. Multiple anti-inflammatory drugs have been suggested for HS, such as dapsone, fumarates or cyclosporine. However, their effectiveness in HS is based on small case series with varying results. If most common treatments have failed, biologics (e.g., infliximab or adalimumab) are the next step. Although not addressed in this review, surgical interventions are often needed to achieve remission.

ABSTRACT
Ceftolozane/Tazobactam: A Review in Complicated Intra-Abdominal and Urinary Tract Infections
Lesley J. Scott

ABSTRACT
Globally, the increasing prevalence of multidrug-resistant pathogens continues to pose major problems in healthcare systems and, at least in part, is driving an initiative to develop new antibacterials, such as ceftolozane (a cephalosporin β-lactam). Adding a β-lactamase inhibitor (e.g. tazobactam) to a β-lactam extends its spectrum of activity against β-lactamase-producing microorganisms (a key mechanism of resistance to β-lactams). Ceftolozane/tazobactam (Zerbaxa™), a β-lactam/β-lactamase inhibitor combination, is indicated for the treatment of adults with complicated intra-abdominal infections (cIAI) or complicated urinary tract infections (cUTI), including pyelonephritis. In multinational, phase 3 noninferiority trials, intravenous ceftolozane/tazobactam was an effective and generally well tolerated treatment in patients with cIAI or cUTI. In the ASPECT-cIAI trial, ceftolozane/tazobactam plus metronidazole was noninferior to meropenem in terms of clinical cure rates at the test-of-cure (TOC) visit, with clinical cure rates in subgroup analyses consistent with those in the primary analysis. In the ASPECT-cUTI trial, ceftolozane/tazobactam was superior to levofloxacin in terms of composite cure rates (clinical cure plus microbiological eradication) at the TOC visit. Further clinical experience should help to more definitively position ceftolozane/tazobactam in the treatment of cIAI and cUTI, including in patients with renal impairment. In the meantime, given its very good in vitro activity against extended-spectrum β-lactamase-producing Enterobacteriaceae and drug-resistant Pseudomonas aeruginosa isolates, ceftolozane/tazobactam provides a potential alternative to currently approved antibacterials for empirical treatment of cIAI and cUTI in adults.

Dimethyl Fumarate: A Review in Relapsing-Remitting MS
Emma D. Deeks

ABSTRACT
Dimethyl fumarate (Tecfidera®) is an oral disease-modifying agent indicated for the twice-daily treatment of relapsing forms of multiple sclerosis (MS) and relapsing-remitting MS (RRMS). It displays immunomodulating and neuroprotective properties, both of which may contribute to its efficacy in these settings. In two phase III trials of 2 years’ duration (DEFINE and CONFIRM), twice-daily dimethyl fumarate reduced clinical relapse (both the proportion of patients with MS relapse and the annualized relapse rate), as well as MRI measures of disease activity, versus placebo in adults with RRMS; the drug also reduced disability progression relative to placebo in one of the two studies (DEFINE). Dimethyl fumarate had an acceptable tolerability profile in these trials, with the most common tolerability issues being flushing and gastrointestinal events, which appear to be largely manageable. In the DEFINE and CONFIRM extension (ENDORSE), a minimum of 5 years of treatment with the drug was associated with continued benefit and no new/worsening tolerability signals. Although additional active comparator data are needed, dimethyl fumarate is an effective twice-daily treatment option for use in adults with RRMS, with the convenience of oral administration and an acceptable long-term tolerability profile.
Hypophosphatasia (HPP) is a rare inheritable disease that results from loss-of-function mutations in the ALPL gene encoding tissue-nonspecific alkaline phosphatase (TNSALP). Therapeutic options for treating the underlying pathophysiology of the disease have been lacking, with the mainstay of treatment being management of symptoms and supportive care. HPP is associated with significant morbidity and mortality in paediatric patients, with mortality rates as high as 100% in perinatal-onset HPP and 50% in infantile-onset HPP. Subcutaneous asfotase alfa (Strensiq®), a first-in-class bone-targeted human recombinant TNSALP replacement therapy, is approved in the EU for long-term therapy in patients with paediatric-onset HPP to treat bone manifestations of the disease. In noncomparative clinical trials in infants and children with paediatric-onset HPP, asfotase alfa rapidly improved radiographically-assessed rickets severity scores at 24 weeks (primary timepoint) as reflected in improvements in bone mineralization, with these benefits sustained after more than 3 years of treatment. Furthermore, patients typically experienced improvements in respiratory function, gross motor function, fine motor function, cognitive development, muscle strength (normalization) and ability to perform activities of daily living, and catch-up height-gain. In life-threatening perinatal and infantile HPP, asfotase alfa also improved overall survival. Asfotase alfa was generally well tolerated in clinical trials, with relatively few patients discontinuing treatment and most treatment-related adverse events being of mild to moderate intensity. Thus, subcutaneous asfotase alfa is a valuable emerging therapy for the treatment of bone manifestations in patients with paediatric-onset HPP.

Osimertinib: First Global Approval
Sarah L. Greig

Osimertinib (Tagrisso™, AZD9291) is an oral, third-generation epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI) that is being developed by AstraZeneca for the treatment of advanced non-small cell lung cancer (NSCLC). Osimertinib has been designed to target the EGFR T790M mutation that is often present in NSCLC patients with acquired EGFR TKI resistance, while sparing wild-type EGFR. In November 2015, the tablet formulation of osimertinib was granted accelerated approval in the USA for the treatment of patients with metastatic EGFR T790M mutation-positive NSCLC (as detected by an FDA-approved test) who have progressed on or after EGFR TKI therapy. Osimertinib has also been granted accelerated assessment status for this indication in the EU, and is in phase III development for first- and second-line and adjuvant treatment of advanced EGFR mutation-positive NSCLC in several countries. Phase I trials in patients with advanced solid tumours are also being conducted. This article summarizes the milestones in the development of osimertinib leading to this first approval for NSCLC.
Daratumumab: First Global Approval
Kate McKeage

ABSTRACT
Daratumumab (Darzalex™) is a first-in-class, humanized IgG1κ monoclonal antibody that targets the CD38 epitope and was developed by Janssen Biotech and Genmab. Intravenous daratumumab was recently approved via an accelerated approval programme in the USA for patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent. The drug is in preregistration for this indication in the EU and Canada. In a phase II trial in patients with previously treated (as described above) relapsed or refractory multiple myeloma, monotherapy with daratumumab 16 mg/kg achieved an overall response rate of approximately 30%. This article summarizes the milestones in the development of daratumumab leading to this first approval for multiple myeloma.

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Targeted Therapy for Idiopathic Pulmonary Fibrosis: Where to Now
Sunad Rangarajan, Morgan L. Locy, Tracy R. Luckhardt, Victor J. Thannickal

ABSTRACT
Idiopathic pulmonary fibrosis (IPF) is an aging-associated, recalcitrant lung disease with historically limited therapeutic options. The recent approval of two drugs, pirfenidone and nintedanib, by the US Food and Drug Administration in 2014 has heralded a new era in its management. Both drugs have demonstrated efficacy in phase III clinical trials by retarding the rate of progression of IPF; neither drug appears to be able to completely arrest disease progression. Advances in the understanding of IPF pathobiology have led to an unprecedented expansion in the number of potential therapeutic targets. Drugs targeting several of these are under investigation in various stages of clinical development. Here, we provide a brief overview of the drugs that are currently approved and others in phase II clinical trials. Future therapeutic opportunities that target novel pathways, including some that are associated with the biology of aging, are examined. A multi-targeted approach, potentially with combination therapies, and identification of individual patients (or subsets of patients) who may respond more favourably to specific agents are likely to be more effective.
ABSTRACT

Alzheimer’s disease (AD) is characterised by a progressive loss of cognitive functions. Histopathologically, AD is defined by the presence of extracellular amyloid plaques containing Aβ and intracellular neurofibrillary tangles composed of hyperphosphorylated tau proteins. According to the now well-accepted amyloid cascade hypothesis is the Aβ patholgy the primary driving force of AD pathogenesis, which then induces changes in tau protein leading to a neurodegenerative cascade during the progression of disease. Since many earlier drug trials aiming at preventing Aβ pathology failed to demonstrate efficacy, tau and microtubules have come into focus as prominent downstream targets. The article aims to develop the current concept of the involvement of tau in the neurodegenerative triad of synaptic loss, cell death and dendritic simplification. The function of tau as a microtubule-associated protein and versatile interaction partner will then be introduced and the rationale and progress of current tau-directed therapy will be discussed in the biological context.

What to Do, and What Not to Do, When Diagnosing and Treating Breakthrough Cancer Pain (BTcP): Expert Opinion


ABSTRACT

Clinical management of breakthrough cancer pain (BTcP) is still not satisfactory despite the availability of effective pharmacological agents. This is in part linked to the lack of clarity regarding certain essential aspects of BTcP, including terminology, definition, epidemiology and assessment. Other barriers to effective management include a widespread prejudice among doctors and patients concerning the use of opioids, and inadequate assessment of pain severity, resulting in the prescription of ineffective drugs or doses. This review presents an overview of the appropriate and inappropriate actions to take in the diagnosis and treatment of BTcP, as determined by a panel of experts in the field. The ultimate aim is to provide a practical contribution to the unresolved issues in the management of BTcP. Five ‘things to do’ and five ‘things not to do’ in the diagnosis and treatment of BTcP are proposed, and evidence supporting said recommendations are described. It is the duty of all healthcare workers involved in managing cancer patients to be mindful of the possibility of BTcP occurrence and not to underestimate its severity. It is vital that all the necessary steps are carried out to establish an accurate and timely diagnosis, principally by establishing effective communication with the patient, the main information source. It is crucial that BTcP is treated with an effective pharmacological regimen and drug(s), dose and administration route prescribed are designed to suit the particular type of pain and importantly the individual needs of the patient.
Prevention and Treatment of Venous Thromboembolism in Patients with Cancer: Focus on Drug Therapy

Nick van Es, Suzanne M. Bleker, Ineke T. Wilts, Ettore Porreca, Marcello Di Nisio

ABSTRACT

Venous thromboembolism (VTE) is a frequent complication in patients with cancer and is associated with significant morbidity and mortality. The use of anticoagulants for the prevention and treatment of VTE in this population is challenging given the high risk of both recurrent VTE and bleeding complications. Thromboprophylaxis with subcutaneous low-molecular-weight heparin (LMWH) is recommended in cancer patients hospitalized for an acute medical illness and in those undergoing major surgery. In ambulatory cancer patients with or without central venous catheters, routine thromboprophylaxis is not recommended because of the relatively low benefit-to-risk ratio. To identify cancer outpatients at very high risk of VTE who may benefit from thromboprophylaxis, VTE risk stratification tools based on tumour type, clinical parameters, or coagulation biomarkers have been proposed, but their clinical utility needs validation. The mainstay of treatment for cancer-associated VTE is LMWH for at least 6 months or longer in case of active disease. The same initial and long-term treatment for incidental VTE as for symptomatic VTE can be suggested while awaiting additional studies in this area.

Insulin Glargine 300 U/mL: A Review in Diabetes Mellitus

Hannah A. Blair, Gillian M. Keating

ABSTRACT

Insulin glargine 300 U/mL (Toujeo®) is a long-acting basal insulin analogue approved for the treatment of diabetes mellitus. Insulin glargine 300 U/mL has a more stable and prolonged pharmacokinetic/pharmacodynamic profile than insulin glargine 100 U/mL (Lantus®), with a duration of glucose-lowering activity exceeding 24 h. In several 6-month phase III trials, insulin glargine 300 U/mL achieved comparable glycaemic control to that seen with insulin glargine 100 U/mL in patients with type 1 or type 2 diabetes, albeit with consistently higher daily basal insulin requirements. These improvements in glycaemic control were maintained during longer-term (12 months) treatment. Insulin glargine 300 U/mL was generally associated with a lower risk of nocturnal hypoglycaemia than insulin glargine 100 U/mL in insulin-experienced patients with type 2 diabetes, while the risk of nocturnal hypoglycaemia did not significantly differ between treatment groups in insulin-naïve patients with type 2 diabetes or in patients with type 1 diabetes. To conclude, once-daily subcutaneous insulin glargine 300 U/mL is an effective and generally well tolerated basal insulin therapy option for patients with type 1 or type 2 diabetes.
Pembrolizumab: A Review in Advanced Melanoma

Emma D. Deeks

ABSTRACT

Pembrolizumab (Keytruda®) is a humanized monoclonal antibody against programmed death receptor-1 (PD-1), a key immunoinhibitory checkpoint protein implicated in down-regulating anti-tumour immune responses. This intravenous drug is indicated for the treatment of advanced (unresectable or metastatic) melanoma, on the basis of its clinical benefit in this setting in the phase I KEYNOTE 001 trial (expansion cohorts) and the phase II and III trials, KEYNOTE 002 and 006. These studies were conducted in ipilimumab-naïve and/or ipilimumab-experienced patients and assessed varying pembrolizumab regimens administered every 2 or 3 weeks, all of which helped to determine the recommended dosage of 2 mg/kg every 3 weeks. In the trials with active comparator arms, pembrolizumab regimens significantly improved progression-free survival (PFS), overall survival (OS) and overall response rates (ORR) relative to ipilimumab in ipilimumab-naïve patients (KEYNOTE 006), and significantly improved PFS and ORR, but not OS (although OS data are immature), relative to chemotherapy in ipilimumab-refractory patients, who had also received BRAF/MEK inhibitor therapy if BRAF-mutation positive (KEYNOTE 002). Pembrolizumab has an acceptable tolerability profile, with immune-related adverse events that are generally manageable/reversible. Thus, pembrolizumab is a valuable treatment option for patients with advanced melanoma, including those who have progressed on ipilimumab and BRAF/MEK inhibitors.

Sacubitril/valsartan: A Review in Chronic Heart Failure with Reduced Ejection Fraction

Paul L. McCormack

ABSTRACT

Sacubitril/valsartan (Entresto™; LCZ696) is an orally administered supramolecular sodium salt complex of the nepriylisin inhibitor prodrug sacubitril and the angiotensin receptor blocker (ARB) valsartan, which was recently approved in the US and the EU for the treatment of chronic heart failure (NYHA class II–IV) with reduced ejection fraction (HFrEF). In the large, randomized, double-blind, PARADIGM-HF trial, sacubitril/valsartan reduced the incidence of death from cardiovascular causes or first hospitalization for worsening heart failure (composite primary endpoint) significantly more than the angiotensin converting enzyme (ACE) inhibitor enalapril. Sacubitril/valsartan was also superior to enalapril in reducing death from any cause and in limiting the progression of heart failure. Sacubitril/valsartan was generally well tolerated, with no increase in life-threatening adverse events. Symptomatic hypotension was significantly more common with sacubitril/valsartan than with enalapril; the incidence of angio-oedema was low. Therefore, sacubitril/valsartan is a more effective replacement for an ACE inhibitor or an ARB in the treatment of HFrEF, and is likely to influence the basic approach to treatment.
Elotuzumab: First Global Approval

Anthony Markham

ABSTRACT
Elotuzumab (Empliciti™) is a humanised IgG1 monoclonal antibody developed by Bristol-Myers Squibb (BMS) and AbbVie that has been approved as combination therapy with lenalidomide and dexamethasone for relapsed/refractory multiple myeloma in the US. Elotuzumab binds to the cell surface receptor signalling lymphocytic activation molecule F7 (SLAMF7), which is selectively expressed on myeloma cells and natural killer cells, leading to antibody-dependent cellular cytotoxicity and direct natural killer cell activation. In a phase III clinical trial, addition of elotuzumab to lenalidomide and dexamethasone therapy in patients with relapsed/refractory multiple myeloma was associated with a significant improvement in progression-free survival and overall response rate. This article summarizes the milestones in the development of elotuzumab leading to this first approval for relapsed/refractory multiple myeloma.

Ixazomib: First Global Approval

Matt Shirley

ABSTRACT
Ixazomib (Ninlaro®) is an orally bioavailable, reversible proteasome inhibitor developed by Millennium Pharmaceuticals, Inc. (now Takeda Oncology). Ixazomib acts by binding to and inhibiting the β5 subunit of the 20S proteasome. In November 2015, the US FDA approved ixazomib for use in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy. Ixazomib is under regulatory review for this indication in the EU. Phase III development of ixazomib is underway worldwide for newly-diagnosed multiple myeloma (in patients who are not eligible for stem cell transplant, or as maintenance therapy) and for relapsed or refractory systemic light chain (AL) amyloidosis. Ixazomib is also under phase I–II development for the treatment of several other haematological and non-haematological malignancies, graft-versus-host disease and lupus nephritis.

Selexipag: First Global Approval

Lesley J. Scott

ABSTRACT
Selexipag (Uptravi®) is a highly selective, long-acting, nonprostanoid, prostacyclin receptor agonist that is being developed by Actelion Pharmaceuticals Ltd and Nippon Shinyaku. Oral selexipag is approved in the USA for the treatment of pulmonary arterial hypertension (PAH; WHO Group I) to delay disease progression and reduce the risk of hospitalization for PAH. It has subsequently been approved in Canada for the long-term treatment of PAH, and received a positive opinion in the EU for the treatment of PAH in adult patients with WHO functional class II–III. Selexipag received orphan drug designation for the treatment of PAH in Japan in 2014 and is in undergoing regulatory review in several countries for use in this indication. In the large, event-driven, phase III GRIPHON trial, selexipag reduced the risk of the primary composite endpoint of death or a complication related to PAH (whichever occurred first) by 40% compared with placebo in patients with PAH (80% were also receiving stable dosages of an endothelin receptor antagonist and/or a phosphodiesterase 5 inhibitor).

Zafeiris Zafeiriou, Anuradha Jayaram, Adam Sharp, Johann S. de Bono

ABSTRACT

In recent years, the therapeutic options for treating men with metastatic castration-resistant prostate cancer have increased substantially. The hormonal treatments abiraterone acetate and enzalutamide, the chemotherapeutics docetaxel and cabazitaxel, the radiopharmaceutical alpharadin and the immunotherapeutic Sipuleucel-T have entered the field. Additionally, corticosteroids, which are used extensively, have documented activity but no documented survival benefit. Physicians treating patients with metastatic prostate cancer immediately after castration resistance develops currently have at least four different options to choose from for the first treatment. These therapeutic choices and their several possible ways of sequential use have not yet been compared to each other head-to-head and may never be. Therefore, there is an unmet need to inform their use with prospective clinical data. Additionally, the new indications of docetaxel for hormone naïve prostate cancer is changing the landscape of prostate cancer treatment and questions the traditional classifications ‘pre-chemotherapy’ and ‘post-chemotherapy’. In this work we attempt to address these challenges in the treatment of metastatic castration-resistant prostate cancer with the focus mainly on the non-cytotoxic agents. We try to integrate available clinical and preclinical information to suggest optimal ways of treatment.

Pharmacotherapy for Fragile X Syndrome: Progress to Date

Matthew H. Davenport, Tori L. Schaefer, Katherine J. Friedmann

ABSTRACT

To date, no drug is approved for the treatment of Fragile X Syndrome (FXS) although many drugs are used to manage challenging behaviors from a symptomatic perspective in this population. While our understanding of FXS pathophysiology is expanding, efforts to devise targeted FXS-specific treatments have had limited success in placebo-controlled trials. Compounds aimed at rectifying excessive glutamate and deficient gamma-aminobutyric acid (GABA) neurotransmission, as well as other signaling pathways known to be affected by Fragile X Mental Retardation Protein (FMRP) are under various phases of development in FXS. With the failure of several metabotropic glutamate receptor subtype 5 (mGlur5) selective antagonists under clinical investigation, no clear single treatment appears to be greatly effective. These recent challenges call into question various aspects of clinical study design in FXS. More objective outcome measures are under development and validation. Future trials will likely be aimed at correcting multiple pathways known to be disrupted by the loss of FMRP. This review offers a brief summary of the prevalence, phenotypic characteristics, genetic causes and molecular functions of FMRP in the brain (as these have been extensively reviewed elsewhere), discusses the most recent finding in FXS drug development, and summarizes FXS trials utilizing symptomatic treatment.
Severe Cushing’s syndrome presents an acute emergency and is defined by massively elevated random serum cortisol [more than 36 μg/dL (1000 nmol/L)] at any time or a 24-h urinary free cortisol more than fourfold the upper limit of normal and/or severe hypokalaemia (<3.0 mmol/L), along with the recent onset of one or more of the following: sepsis, opportunistic infection, intractable hypokalaemia, uncontrolled hypertension, heart failure, gastrointestinal haemorrhage, glucocorticoid-induced acute psychosis, progressive debilitating myopathy, thromboembolism or uncontrolled hyperglycaemia and ketocidosis. Treatment focuses on the management of the severe metabolic disturbances followed by rapid resolution of the hypercortisolaemia, and subsequent confirmation of the cause. Emergency lowering of the elevated serum cortisol is most rapidly achieved with oral metyrapone and/or ketoconazole; if parenteral therapy is required then intravenous etomidate is rapidly effective in almost all cases, but all measures require careful supervision. The optimal order and combination of drugs to treat severe hypercortisolaemia—mostly in the context of ectopic ACTH-secreting syndrome, adrenocortical carcinoma or an ACTH-secreting pituitary adenoma (mainly macroadenomas)—is not yet established. Combination therapy may be useful not only to rapidly control cortisol excess but also to lower individual drug dosages and consequently the possibility of adverse effects. If medical treatments fail, bilateral adrenalectomy should be performed in the shortest possible time span to prevent the debilitating complications of uncontrolled hypercortisolaemia.

Dichlorphenamide: A Review in Primary Periodic Paralyses
Sarah L. Greig

Oral dichlorphenamide (Keveyis™) is a carbonic anhydrase inhibitor that is approved in the USA for the treatment of primary hyperkalaemic and hypokalaemic periodic paralyses and related variants. The efficacy and safety of dichlorphenamide in patients with primary periodic paralyses have been evaluated in four 9-week, randomized, double-blind, placebo-controlled, phase III trials [two parallel-group trials (HOP and HYP) and two crossover trials]. In two trials in patients with hypokalaemic periodic paralysis, dichlorphenamide was associated with a significantly (eightfold) lower paralytic attack rate and fewer patients with acute intolerable worsening compared with placebo. In two trials in patients with hyperkalaemic periodic paralysis, the attack rate was lower with dichlorphenamide than placebo, with this comparison reaching statistical significance in one trial (crossover) but not the other (HYP), although the attack rate was approximately fivefold lower with dichlorphenamide than placebo in the HYP trial. In 52-week, open-label extensions of the HOP and HYP trials, dichlorphenamide provided sustained efficacy in patients with hypokalaemic or hyperkalaemic periodic paralysis. Dichlorphenamide was generally well tolerated in all four phase III trials and during the extension trials; the most common adverse events were paraesthesia, cognitive disorders and dysgeusia. As the first agent to be approved in the USA for this indication, dichlorphenamide is a valuable treatment option for patients with primary hyperkalaemic or hypokalaemic periodic paralysis.
Neuropsychiatric systemic lupus erythematosus (NPSLE) is a generic definition referring to a series of neurological and psychiatric symptoms directly related to systemic lupus erythematosus (SLE). NPSLE includes heterogeneous and rare neuropsychiatric (NP) manifestations involving both the central and peripheral nervous system. Due to the lack of a gold standard, the attribution of NP symptoms to SLE represents a clinical challenge that obligates the strict exclusion of any other potential cause. In the acute setting, management of these patients does not differ from other non-SLE subjects presenting with the same NP manifestation. Afterwards, an individualized therapeutic strategy, depending on the presenting manifestation and severity of symptoms, must be started. Clinical trials in NPSLE are scarce and most of the data are extracted from case series and case reports. High-dose glucocorticoids and intravenous cyclophosphamide remain the cornerstone for patients with severe symptoms that are thought to reflect inflammation or an underlying autoimmune process. Rituximab, intravenous immunoglobulins, or plasmapheresis may be used if response is not achieved. When patients present with mild to moderate NP manifestations, or when maintenance therapy is warranted, azathioprine and mycophenolate may be considered. When symptoms are thought to reflect a thrombotic underlying process, anticoagulation and antiplatelet agents are the mainstay of therapy, especially if antiphospholipid antibodies or antiphospholipid syndrome are present. Recent trials on SLE using new biologicals, based on newly understood SLE mechanisms, have shown promising results. Based on what we currently know about its pathogenesis, it is tempting to speculate how these new therapies may affect the management of NPSLE patients.

Liposomal Amphotericin B (AmBisome®): A Review of the Pharmacokinetics, Pharmacodynamics, Clinical Experience and Future Directions

Neil R. H. Stone, Tihana Bicanic, Rahuman Salim, William Hope

Liposomal amphotericin B (AmBisome®; LAmB) is a unique lipid formulation of amphotericin B. LAmB is a standard of care for a wide range of medically important opportunistic fungal pathogens. LAmB has a significantly improved toxicity profile compared with conventional amphotericin B deoxycholate (DAmB). Despite nearly 20 years of clinical use, the pharmacokinetics and pharmacodynamics of this agent, which differ considerably from DAmB, remain relatively poorly understood and underutilized in the clinical setting. The molecular pharmacology, preclinical and clinical pharmacokinetics, and clinical experience with LAmB for the most commonly encountered fungal pathogens are reviewed. In vitro, experimental animal models and human clinical trial data are summarized, and novel routes of administration and dosing schedules are discussed. LAmB is a formulation that results in reduced toxicity as compared with DAmB while retaining the antifungal effect of the active agent. Its long terminal half-life and retention in tissues suggest that single or intermittent dosing regimens are feasible, and these should be actively investigated in both preclinical models and in clinical trials. Significant gaps remain in knowledge of pharmacokinetics and pharmacodynamics in special populations such as neonates and children, pregnant women and obese patients.
Lesinurad: First Global Approval
Sheridan M. Hoy

ABSTRACT
Lesinurad (ZURAMPIC®) is an oral urate–anion exchanger transporter 1 (URAT1) inhibitor developed by Ardea Biosciences (a subsidiary of AstraZeneca) for the treatment of hyperuricaemia associated with gout. It reduces serum uric acid (sUA) levels by inhibiting the function of the transporter proteins (URAT1 and organic anion transporter 4) involved in uric acid reabsorption in the kidney. In December 2015, lesinurad was approved in the USA as combination therapy with a xanthine oxidase inhibitor for the treatment of hyperuricaemia associated with gout in patients who have not achieved sUA target levels with a xanthine oxidase inhibitor alone. Lesinurad has also received a positive opinion from the European Medicines Agency’s Committee for Medicinal Products for Human Use for this indication and is in phase III development as a combination therapy in several other countries. This article summarizes the milestones in the development of lesinurad leading to this first approval for hyperuricaemia associated with gout.

Brivaracetam: First Global Approval
Anthony Markham

ABSTRACT
Brivaracetam (Briviact®), a 4-n-propyl analogue of levetiracetam developed by UCB Pharma, has been approved in the EU as an adjunctive therapy for the treatment of partial-onset seizures. Brivaracetam binds to synaptic vesicle glycoprotein 2a (SV2A) in the brain with greater selectivity and 15- to 30-fold higher affinity than levetiracetam, as demonstrated in preclinical models, and has demonstrated efficacy in reducing the frequency of partial onset seizures in clinical trials. This article summarizes the milestones in the development of brivaracetam leading to this first approval for use as adjunctive therapy for uncontrolled partial-onset seizures in adults with epilepsy.

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Two-Drug Treatment Approaches in HIV: Finally Getting Somewhere?
Sean G. Kelly, Amesika N. Nyaku, Babafemi O. Taiwo

ABSTRACT
The advent of combination antiretroviral therapy (ART) has significantly decreased AIDS-related morbidity and mortality. Nevertheless, the benefits of ART are only realized through adherence to lifelong treatment. Though contemporary antiretroviral (ARV) drugs have fewer adverse effects in comparison to older ARV drugs, many agents are associated with negative or unknown long-term effects. There is increasing evidence that two-drug (dual-therapy) regimens may be an effective alternative to the currently recommended three-drug (triple-therapy) regimens. In this review, we provide a comprehensive and critical review of recently completed and ongoing trials of dual-therapy regimens in treatment-naïve and treatment-experienced HIV-1-infected patients. We also review current HIV/AIDS society recommendations regarding dual therapy as well as future therapeutic possibilities.
Serious Non-AIDS Events: Therapeutic Targets of Immune Activation and Chronic Inflammation in HIV Infection

Denise C. Hsu, Irini Sereti

ABSTRACT

In the antiretroviral therapy (ART) era, serious non-AIDS events (SNAEs) have become the major causes of morbidity and mortality in HIV-infected persons. Early ART initiation has the strongest evidence for reducing SNAEs and mortality. Biomarkers of immune activation, inflammation and coagulopathy do not fully normalize despite virologic suppression and persistent immune activation is an important contributor to SNAEs. A number of strategies aimed to reduce persistent immune activation including ART intensification to reduce residual viremia; treatment of co-infections to reduce chronic antigen stimulation; the use of anti-inflammatory agents, reducing microbial translocation as well as interventions to improve immune recovery through cytokine administration and reducing lymphoid tissue fibrosis, have been investigated. To date, there is little conclusive evidence on which strategies beyond treatment of hepatitis B and C co-infections and reducing cardiovascular risk factors will result in clinical benefits in patients already on ART with viral suppression. The use of statins seems to show early promise and larger clinical trials are underway to confirm their efficacy. At this stage, clinical care of HIV-infected patients should therefore focus on early diagnosis and prompt ART initiation, treatment of active co-infections and the aggressive management of co-morbidities until further data are available.

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The Role of mTOR Inhibitors in the Treatment of Patients with Tuberous Sclerosis Complex: Evidence-based and Expert Opinions

Paolo Curatolo, Marit Bjørnvold, Patricia E. Dill, José Carlos Ferreira

ABSTRACT

Tuberous sclerosis complex (TSC) is a genetic disorder arising from mutations in the TSC1 or TSC2 genes. The resulting over-activation of the mammalian target of rapamycin (mTOR) signalling pathway leaves patients with TSC susceptible to the growth of non-malignant tumours in multiple organs. Previously, surgery was the main therapeutic option for TSC. However, pharmacological therapy with mTOR inhibitors such as everolimus and sirolimus is now emerging as an alternate approach. Everolimus and sirolimus have already been shown to be effective in treating subependymal giant cell astrocytoma (SEGA) and renal angiomyolipoma (AML), and everolimus is currently being evaluated in treating TSC-related epilepsy. In November 2013 a group of European experts convened to discuss the current options and practical considerations for treating various manifestations of TSC. This article provides evidence-based recommendations for the treatment of SEGA, TSC-related epilepsy and renal AML, with a focus on where mTOR inhibitor therapy may be considered alongside other treatment options. Safety considerations regarding mTOR inhibitor therapy are also reviewed. With evidence of beneficial effects in neurological and non-neurological TSC manifestations, mTOR inhibitors may represent a systemic treatment for TSC.
ABSTRACT

Eravacycline is an investigational, synthetic fluorocycline antibacterial agent that is structurally similar to tigecycline with two modifications to the D-ring of its tetracycline core: a fluorine atom replaces the dimethylenine moiety at C-7 and a pyrrolidinoaceatamido group replaces the 2-tertiary-butyl glycylamido at C-9. Like other tetracyclines, eravacycline inhibits bacterial protein synthesis through binding to the 30S ribosomal subunit. Eravacycline demonstrates broad-spectrum antimicrobial activity against Gram-positive, Gram-negative, and anaerobic bacteria with the exception of Pseudomonas aeruginosa. Eravacycline is two- to fourfold more potent than tigecycline versus Gram-positive cocci and two- to eightfold more potent than tigecycline versus Gram-negative bacilli. Intravenous eravacycline demonstrates linear pharmacokinetics that have been described by a four-compartment model. Oral bioavailability of eravacycline is estimated at 28% (range 26–32%) and a single oral dose of 200 mg achieves a maximum plasma concentration (Cmax) and area under the plasma concentration-time curve from 0 to infinity (AUC0–∞) of 0.23 ± 0.04 mg/L and 3.34 ± 1.11 mg·h/L, respectively. A population pharmacokinetic study of intravenous (IV) eravacycline demonstrated a mean steady-state volume of distribution (Vss) of 320 L or 4.2 L/kg, a mean terminal elimination half-life (t½) of 48 h, and a mean total clearance (CL) of 13.5 L/h. In a neutropenic murine thigh infection model, the pharmacodynamic parameter that demonstrated the best correlation with antibacterial response was the ratio of area under the plasma concentration-time curve over 24 h to the minimum inhibitory concentration (AUC0–24h/MIC). Several animal model studies including mouse systemic infection, thigh infection, lung infection, and pyelonephritis models have been published and demonstrated the in vivo efficacy of eravacycline. A phase II clinical trial evaluating the efficacy and safety of eravacycline in the treatment of community-acquired complicated intra-abdominal infection (cIAI) has been published as well, and phase III clinical trials in cIAI and complicated urinary tract infection (cUTI) have been completed. The eravacycline phase III program, known as IGNITE (Investigating Gram-Negative Infections Treated with Eravacycline), investigated its safety and efficacy in cIAI (IGNITE 1) and cUTI (IGNITE 2). Eravacycline met the primary endpoint in IGNITE 1, while data analysis for IGNITE 2 is currently ongoing. Common adverse events reported in phase I–III studies included gastrointestinal effects such as nausea and vomiting. Eravacycline is a promising intravenous and oral fluorocycline that may offer an alternative treatment option for patients with serious infections, particularly those caused by multidrug-resistant Gram-negative pathogens.
Antipsychotic Management of Schizoaffective Disorder: A Review

Jean-Pierre Lindenmayer, Amandeep Kaur

ABSTRACT

Schizoaffective disorder (SAD) is an incapacitating illness that presents clinicians with challenges in terms of both its diagnosis and its psychopharmacological management. Most studies conducted on the psychopharmacological treatment of SAD also include patients with schizophrenia or other psychotic illnesses, thereby providing an unspecific view to the clinician as to the best way of treating patients with SAD. The objective of this article is to review studies on evidence-based treatment of patients with SAD. We conducted a systematic literature search in MEDLINE/PubMed for full-text studies in the English language using the terms ‘Schizoaffective and treatment’ or ‘antipsychotic schizoaffective’. Our review found relatively few studies with either an active comparator or placebo that examined the efficacy of antipsychotics for patients with SAD without an admixture of patients with schizophrenia. Only oral paliperidone extended release (ER), paliperidone long-acting injection (LAI), and risperidone have been shown to be effective and safe in reducing psychotic as well as affective components in acutely ill SAD patients in controlled studies. Paliperidone ER and LAI have also been shown to be efficacious in the maintenance treatment phase of SAD patients. While no supportive data exist, it is possible that other atypical antipsychotics may have similar efficacy to the two mentioned above. We conclude with a number of research recommendations for the study of treatment options for patients with SAD. First, there is a need for studies with patients specifically diagnosed with SAD for both the acute and the maintenance phase. The sample size needs to be adequate to allow a primary analysis of efficacy and to allow for analysis of the SAD subtypes: depressed and bipolar. Another recommendation is the need for studies of patients with SAD stratified into patients with and without mood stabilizers or antidepressants to allow the examination of the adjunctive role of these psychotrophic medications. A third recommendation is to focus on specific co-morbid aspects of patients with SAD, such as suicidality and substance use disorders. Data from such studies will fill the gap of evidence-based treatment approaches and help clinicians in making important treatment decisions for patients with this complex condition.

Cobimetinib Plus Vemurafenib: A Review in BRAF V600 Mutation-Positive Unresectable or Metastatic Melanoma

Gillian M. Keating

ABSTRACT

The MEK inhibitor cobimetinib (Cotellic®) is indicated for the treatment of patients with BRAFV600 mutation-positive unresectable or metastatic melanoma, in combination with the BRAF inhibitor vemurafenib (Zelboraf®). In the pivotal coBRIM trial, previously untreated patients with BRAFV600 mutation-positive unresectable, stage IIIC or stage IV melanoma received cobimetinib 60 mg once daily for the first 21 days of each 28-day cycle plus vemurafenib 960 mg twice daily or vemurafenib alone. Compared with vemurafenib alone, cobimetinib plus vemurafenib significantly prolonged progression-free survival (primary endpoint) and was associated with a significantly higher overall response rate and significantly prolonged overall survival. Cobimetinib plus vemurafenib had a manageable tolerability profile. In conclusion, cobimetinib plus vemurafenib is a valuable option for use in BRAFV600 mutation-positive unresectable or metastatic melanoma.
Elbasvir/Grazoprevir: First Global Approval
Gillian M. Keating

ABSTRACT
A fixed-dose combination tablet of the hepatitis C virus (HCV) NS5A inhibitor elbasvir and the HCV NS3/4A protease inhibitor grazoprevir (elbasvir/grazoprevir; Zepatier™) is under development by Merck. Oral elbasvir/grazoprevir 50/100 mg once daily has been approved in the USA for the treatment of adults with chronic HCV genotype 1 or 4 infection. This article summarizes the milestones in the development of elbasvir/grazoprevir leading to this first global approval for chronic HCV genotype 1 or 4 infections.

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Biosimilar DMARDs: What Does the Future Hold?
Filipe Araújo, João Gonçalves, João Eurico Fonseca

ABSTRACT
Biological medicinal products, albeit fundamental in unresponsive inflammatory rheumatic diseases, represent a significant economic burden to healthcare systems worldwide. A new landmark in the treatment of these conditions was achieved with the European Medicines Agency’s endorsement of CT-P13, the first biosimilar of a monoclonal antibody, infliximab. The main driving force behind biosimilar development is to improve accessibility at lower costs, provided the quality, efficacy and safety of the biosimilar is similar to that of the reference drug. Many other biosimilar candidates are currently under development and will probably be approved in the near future, posing complex prescribing decisions for rheumatologists. In this article, biosimilar disease-modifying anti-rheumatic drugs (DMARDs) are put into perspective: what they are, the stepwise manufacturing process and the available mechanisms that regulate the thorough comparability exercise. Non-clinical and clinical data leading to CT-P13 approval are briefly reviewed, and current clinical data on upcoming biosimilars are also addressed. Other matters covered include extrapolation of clinical indications, interchangeability and automatic substitution. As cumulative evidence on the use of biosimilars grows, controversies abate and patients and physicians become reassured. However, adequate answers to the uncertainties still surrounding biosimilar agents are necessary to ensure the trust of rheumatologists and, on a larger scale, to guarantee their widespread use and success.

The Emerging Role of PI3K Inhibitors in the Treatment of Hematological Malignancies: Preclinical Data and Clinical Progress to Date
Till Seiler, Grit Hutter, Martin Dreyling

ABSTRACT
The phosphoinositide 3-kinase (PI3K)/Akt/mTOR pathway is implicated in the pathogenesis of lymphoma. Deeper understanding of the diversity and biological impact of this pathway has led to the development of specific inhibitors to this pathway. Preclinical data in cell lines, patient samples and disease models have broadened our understanding of PI3K inhibition. Several PI3K inhibitors are currently in advanced stages of clinical development. Idelalisib is the first agent of this new substance class to be approved in chronic lymphocytic leukemia and follicular lymphoma. Other agents specifically target different PI3K isoforms and show promising clinical efficacy.
Pharmacotherapy for Neonatal Seizures: Current Knowledge and Future Perspectives
Maria D. Donovan, Brendan T. Griffin, Liudmila Kharoshankaya, John F. Cryan

**ABSTRACT**

Seizures are the most common neurological emergencies in the neonatal period and are associated with poor neurodevelopmental outcomes. Seizures affect up to five per 1000 term births and population-based studies suggest that they occur even more frequently in premature infants. Seizures are a sign of an underlying cerebral pathology, the most common of which is hypoxic-ischaemic encephalopathy in term infants. Due to a growing body of evidence that seizures exacerbate cerebral injury, effective diagnosis and treatment of neonatal seizures is of paramount importance to reduce long-term adverse outcomes. Electroencephalography is essential for the diagnosis of seizures in neonates due to their subtle clinical expression, non-specific neurological presentation and a high frequency of electro-clinical uncoupling in the neonatal period. Hypoxic-ischaemic encephalopathy may require neuroprotective therapeutic hypothermia, accompanying sedation with opioids, anticonvulsant drugs or a combination of all of these. The efficacy, safety, tolerability and pharmacokinetics of seven anticonvulsant drugs (phenobarbital, phenytoin, levetiracetam, lidocaine, midazolam, topiramate and bumetanide) are reviewed. This review is focused only on studies reporting electrographically confirmed seizures and highlights the knowledge gaps that exist in optimal treatment regimens for neonatal seizures. Randomised controlled trials are needed to establish a safe and effective treatment protocol for neonatal seizures.

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**Beyond TNF Inhibitors: New Pathways and Emerging Treatments for Psoriatic Arthritis**
Ennio Lubrano, Fabio Massimo Perrotta

**ABSTRACT**

Psoriatic arthritis (PsA) is a chronic inflammatory disease characterized by psoriasis, synovitis, enthesitis, spondylitis and association with other extra-articular manifestations. Chronic inflammation of involved tissues possibly leads to structural damage and to a reduction in function and quality of life. The treatment of PsA dramatically changed with the introduction of anti-tumor necrosis factor (TNF)-α drugs, which have been shown to reduce the symptoms and signs of the disease, and slow radiographic progression. However, some patients do not respond to anti-TNFα or have a loss of response. Recently, the discovery of new pathogenic mechanisms have made possible the development of new drugs that target pro-inflammatory cytokines, such as interleukin (IL)-12, IL-23 and IL-17, or interfere with cellular pathways involved in skin, joint and entheseal inflammation. New molecules, namely ustekinumab, secukinumab, and apremilast have shown efficacy and safety over the various components of the disease in randomized clinical trials. These drugs have been recently approved for the treatment of PsA and included in new treatment recommendations. Other molecules are currently being tested in phase III clinical trials and are potential new treatment options for PsA. The aim of this review is to update the new pathways involved in the development of the disease and the emerging treatments for PsA beyond TNFα inhibition.
Nail Psoriasis: A Review of Treatment Options
Marcel C. Pasch

ABSTRACT
Nail involvement affects 80–90% of patients with plaque psoriasis, and is even more prevalent in patients with psoriatic arthritis. This review is the result of a systemic approach to the literature and covers topical, intralesional, conventional systemic, and biologic systemic treatments, as well as non-pharmacological treatment options for nail psoriasis. The available evidence suggests that all anti-tumor necrosis factor-α, anti-interleukin (IL)-17, and anti-IL-12/23 antibodies which are available for plaque psoriasis and psoriatic arthritis are highly effective treatments for nail psoriasis. Conventional systemic treatments, including methotrexate, cyclosporine, acitretin, and apremilast, as well as intralesional corticosteroids, can also be effective treatments for nail psoriasis. Topical treatments, including corticosteroids, calcipotriol, tacrolimus, and tazarotene, have also been shown to have a position in the treatment of nail psoriasis, particularly in mild cases. Finally, non-pharmacological treatment options, including phototherapy, photodynamic therapy, laser therapy, and several radiotherapeutic options, are also reviewed but cannot be advised as first-line treatment options. Another conclusion of this review is that the lack of a reliable core set of outcomes measures for trials in nail psoriasis hinders the interpretation of results, and is urgently needed.

Eslicarbazepine Acetate Monotherapy: A Review in Partial-Onset Seizures
Matt Shirley, Sohita Dhillon

ABSTRACT
Eslicarbazepine acetate (Aptiom®) is a once-daily, orally administered antiepileptic drug (AED) approved previously in the EU, USA and several other countries for use as adjunctive therapy for the treatment of partial-onset seizures. Based on the findings of two randomized, dose-blinded, conversion-to-monotherapy phase III trials in patients with uncontrolled partial epilepsy, the US license for eslicarbazepine acetate has recently been expanded to include use as monotherapy for partial-onset seizures. The pivotal trials demonstrated that seizure control following conversion from other AEDs was superior for eslicarbazepine acetate monotherapy (1200 or 1600 mg once daily) compared with a pseudo-placebo historical control. Other efficacy outcomes appeared to support the benefit of treatment, with up to 10% of patients remaining seizure free and up to 46% of patients experiencing a ≥50% reduction from baseline in standardized seizure frequency during the monotherapy periods of the trials. Eslicarbazepine acetate monotherapy was generally well tolerated, with most treatment-emergent adverse events being mild to moderate in severity. Its tolerability profile was generally consistent with the established profile of the drug based on its use as adjunctive therapy. Thus, once-daily eslicarbazepine acetate, either as monotherapy or adjunctive therapy, represents a useful option for the treatment of patients with partial-onset seizures. The recent licensing of the drug in the USA as monotherapy expands the range of treatment options for patients with partial-onset seizures and increases the opportunity to tailor therapy to the individual patient.
Sublingual Sufentanil: A Review in Acute Postoperative Pain
James E. Frampton

ABSTRACT

The sufentanil sublingual tablet system (SSTS; Zalviso®) is a novel patient-controlled analgesia (PCA) device intended to overcome some of the drawbacks of opioid-based intravenous PCA (IV-PCA). Based on the results of three phase III studies, the SSTS has been approved in the EU for the management of acute moderate to severe postoperative pain in adults in a hospital setting. In a head-to-head comparison with morphine, the gold standard for opioid-based IV-PCA, the SSTS was associated with a more rapid onset of analgesia and higher rates of success, based on patient and healthcare professional global assessments of the method of pain control. Patients and healthcare professionals also rated the SSTS as being easier to use and expressed a greater level of overall satisfaction with this device. The SSTS was generally well tolerated, with an adverse event profile typical of that of other opioids and generally similar to that of placebo. By virtue of its preprogrammed, noninvasive design, the SSTS avoids the risk of pump programming errors and other complications (e.g. infections and analgesic gaps) that can occur with IV-PCA technology; it also imposes less restriction on postoperative mobility. As such, the SSTS provides an effective alternative to opioid-based IV-PCA for the management of acute moderate to severe postoperative pain. Future studies should ideally focus on evaluating the relative cost effectiveness of the SSTS and comparing it with other available needle-free PCA modalities.

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Ivabradine: Cardioprotection By and Beyond Heart Rate Reduction
Gerd Heusch, Petra Kleinbongard

ABSTRACT

Ivabradine inhibits hyperpolarization-activated cyclic nucleotide-gated channels in the sinus node, thereby reducing heart rate, and heart rate reduction improves regional myocardial blood flow and contractile function in ischemic myocardium. Accordingly, ivabradine reduces anginal symptoms in patients with stable coronary artery disease but does not improve their clinical outcome. Heart rate reduction with ivabradine in patients with symptomatic heart failure reduces symptoms, attenuates remodeling, and improves clinical outcome. In pigs and mice, ivabradine reduces infarct size from myocardial ischemia/reperfusion, even when heart rate reduction is abrogated by atrial pacing. Improved viability is also observed in isolated ventricular cardiomyocytes subjected to simulated ischemia/reperfusion. These beneficial effects are attributed to reduced reactive oxygen species formation from the mitochondria. There is also evidence for a heart rate-independent benefit from ivabradine in the vasculature of mice and humans, and in left ventricular contractile function of pigs. Finally, in mice, ivabradine also has anti-aging potential.
ABSTRACT

Iron overload used to be considered rare in hemodialysis patients but its clinical frequency is now increasingly realized. The liver is the main site of iron storage and the liver iron concentration (LIC) is closely correlated with total iron stores in patients with secondary hemosideroses and genetic hemochromatosis. Magnetic resonance imaging is now the gold standard method for LIC estimation and monitoring in non-renal patients. Studies of LIC in hemodialysis patients by quantitative magnetic resonance imaging and magnetic susceptometry have demonstrated a strong relation between the risk of iron overload and the use of intravenous (IV) iron products prescribed at doses determined by the iron biomarker cutoffs contained in current anemia management guidelines. These findings have challenged the validity of both iron biomarker cutoffs and current clinical guidelines, especially with respect to recommended IV iron doses. Three long-term observational studies have recently suggested that excessive IV iron doses may be associated with an increased risk of cardiovascular events and death in hemodialysis patients. We postulate that iatrogenic iron overload in the era of erythropoiesis-stimulating agents may silently increase complications in dialysis patients without creating frank clinical signs and symptoms. High hepcidin-25 levels were recently linked to fatal and nonfatal cardiovascular events in dialysis patients. It is therefore tempting to postulate that the main pathophysiological pathway leading to these events may involve the pleiotropic master hormone hepcidin (synergized by fibroblast growth factor 23), which regulates iron metabolism. Oxidative stress as a result of IV iron infusions and iron overload, by releasing labile non-transferrin-bound iron, might represent a ‘second hit’ on the vascular bed. Finally, iron deposition in the myocardium of patients with severe iron overload might also play a role in the pathogenesis of sudden death in some patients.

Drug-Induced Dyskinesia, Part 1: Treatment of Levodopa-Induced Dyskinesia

Dhanya Vijayakumar, Joseph Jankovic

ABSTRACT

Dyskinesias encompass a variety of different hyperkinetic phenomenologies, particularly chorea, dystonia, stereotypies, and akathisia. Levodopa-induced dyskinesia (LID) is one of the main types of drug-induced dyskinesia, occurring in patients with Parkinson’s disease (PD) who have been treated with levodopa for long time, but this side effect may be encountered even within a few weeks or months after initiation of levodopa therapy. Based on the temporal pattern in relationship to levodopa dosing, LIDs are divided into “peak-dose dyskinesia,” “diphasic dyskinesia,” and “wearing off” or “off-period” dyskinesia, of which peak-dose dyskinesia is the most common, followed by off-period, and then diphasic dyskinesia. Treatment strategy includes identifying the kind of dyskinesia and tailoring treatment accordingly. Peak-dose dyskinesia is treated mainly by reducing individual doses of levodopa and adding amantadine and dopamine agonists, whereas off-period dystonia often responds to baclofen and botulinum toxin injections. Diphasic dyskinesias, occurring particularly in patients with young-onset PD, are the most difficult to treat. While fractionation of levodopa dosage is the most frequently utilized strategy, many patients require deep brain stimulation to control their troublesome motor fluctuations and LIDs. A variety of emerging (experimental) drugs currently in development promise to provide better control of LIDs and other levodopa-related complications in the near future.
Dyskinesias encompass a variety of different hyperkinetic phenomenologies, particularly chorea, dystonia, stereotypies, and akathisia. The main types of drug-induced dyskinesias include levodopa-induced dyskinesia (LID) in patients with Parkinson’s disease and tardive syndrome (TS), typically present in patients with psychiatric or gastrointestinal disorders treated with dopamine receptor blocking drugs, also referred to as neuroleptics. Besides preventive measures (i.e., avoiding the use of the offending drugs), general treatment strategies include slow taper of the offending agent and use of dopamine-depleting agents like tetrabenazine. Botulinum toxin may be helpful for wearing off focal dystonia and some forms of tardive dystonia. Deep brain stimulation is usually reserved for patients with disabling motor fluctuations, LID, and for severe TS that cannot be managed medically.

Naphthoquine: An Emerging Candidate for Artemisinin Combination Therapy
Brioni R. Moore, Moses Laman, Sam Salman, Kevin T. Batty, Madhu Page-Sharp

Naphthoquine is a 4-aminoquinoline antimalarial drug first synthesised in China in 1986 but which was not developed for clinical use until the late 1990s. Early in vitro parasite sensitivity and in vivo efficacy data, together with a long terminal elimination half-life (up to 23 days), suggested that it could be used as monotherapy for uncomplicated falciparum and vivax malaria, but is now marketed as a single-dose, fixed co-formulation with artemisinin in a milligram per kilogram ratio of 1:2.5. This form of artemisinin combination therapy (ACT) has also shown high cure rates, especially in two randomised trials in which, consistent with World Health Organization recommendations for all ACTs, it was administered daily for 3 days rather than as single dose for Plasmodium falciparum and P. vivax infections (28-day adequate clinical and parasitological response ≥98.4 %). Although detailed safety monitoring has been performed in a minority of subjects, >4000 healthy volunteers and patients with malaria have been exposed to naphthoquine without any documented significant toxicity. As with other 4-aminoquinolines, naphthoquine is associated with prolongation of the electrocardiographic QT interval but not with cardiac or neurological events. It has been administered to children as young as 4 months of age but, due to a lack of pharmacokinetic, efficacy and toxicity data in young infants and in pregnant/lactating women, it should not be used in these vulnerable patient groups. With the emergence of parasite resistance to other ACTs, naphthoquine partnered with a potent artemisinin derivative may prove a viable alternative treatment for uncomplicated malaria.
Idebenone: A Review in Leber’s Hereditary Optic Neuropathy
Katherine A. Lyseng-Williamson

ABSTRACT

Idebenone (Raxone®), a short-chain benzoquinone, is the only disease-specific drug approved to treat visual impairment in adolescents and adults with Leber’s hereditary optic neuropathy (LHON), a rare genetic mitochondrial disease that causes rapid and progressive bilateral vision loss. The mechanism of action of idebenone involves its antioxidant properties and ability to act as a mitochondrial electron carrier. Idebenone overcomes mitochondrial complex I respiratory chain deficiency in patients with LHON by transferring electrons directly to mitochondrial complex III (by-passing complex I), thereby restoring cellular energy (ATP) production and re-activating inactive-but-viable retinal ganglion cells, which ultimately prevents further vision loss and promotes vision recovery. The approval of idebenone in the treatment of LHON was based on the overall data from a randomized clinical trial, a follow-up study and real-world data. Taken together, these studies provide convincing evidence that oral idebenone 900 mg/day for 24 weeks has persistent beneficial effects in preventing further vision impairment and promoting vision recovery in patients with LHON relative to the natural course of the disease. Therefore, idebenone is a valuable agent to treat visual impairment in adolescents and adults with LHON.

Susoctocog Alfa: A Review in Acquired Haemophilia A
Celeste B. Burness, Lesley J. Scott

ABSTRACT

Intravenous susoctocog alfa (Obizur®) is a recombinant, B-domain deleted, porcine sequence antihaemophilic factor VIII (FVIII) product that has recently been approved for the treatment of bleeding episodes in adults with acquired haemophilia A (AHA). Intravenous susoctocog alfa was an effective and generally well tolerated treatment for serious bleeding episodes in adult patients with AHA in a multinational, phase II/III trial (n = 28 evaluable). Patients received an initial dose of susoctocog alfa 200 U/kg, with subsequent dosages based on target FVIII trough levels and clinical assessments. All patients had a positive haemostatic response (based on predefined criteria) of the primary bleed 24 h after the first infusion of susoctocog alfa, with the bleed successfully controlled at the time of final dosing in 86 % of patients. The most frequently reported adverse reaction (incidence >5 %) was the development of inhibitory antibodies against susoctocog alfa (porcine FVIII). Overall, 25 % of antibody naive patients developed anti-susoctocog alfa antibodies during the study. No serious treatment-related adverse events, thrombotic events or allergic reactions were reported during the trial. In conclusion, intravenous susoctocog alfa is a useful addition to the limited treatment options available for the management of acute bleeding episodes in adults with AHA.
Obiltoxaximab: First Global Approval
Sarah L. Greig

ABSTRACT
Obiltoxaximab (Anthim®, ETI-204) is a monoclonal antibody that is being developed by Elusys Therapeutics and the US Department of Health and Human Services’ Biomedical Advanced Research and Development Authority for the prevention and treatment of inhalational anthrax due to Bacillus anthracis. Obiltoxaximab has been designed to neutralize the free protective antigen of B. anthracis, thereby inhibiting the lethal effects of anthrax toxins. In March 2016, intravenous obiltoxaximab was approved in the USA for the treatment (in combination with appropriate antibacterial drugs) and prophylaxis of inhalational anthrax. Obiltoxaximab is being developed under the US FDA Animal Rule, in which marketing approval is based on its efficacy in relevant animal models and safety in phase I studies in healthy human volunteers. An intramuscular formulation of obiltoxaximab has also been evaluated in animal studies and a phase I study in healthy human volunteers. This article summarizes the milestones in the development of obiltoxaximab leading to this first approval for the treatment and prevention of inhalation anthrax.

Management of NSCLC Disease Progression After First-Line EGFR Tyrosine Kinase Inhibitors: What Are the Issues and Potential Therapies?
Raffaele Califano, Ourania Romanidou, Giannis Mountzios, Lorenza Landi

ABSTRACT
Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) represent the standard of care for advanced non-small cell lung cancer (NSCLC) patients whose tumor harbors an activating EGFR mutation. The vast majority of patients will experience disease control with an EGFR-TKI but inevitably all patients will progress, often within a year of treatment. There is no current standard of care for this scenario but, in clinical practice, most of the patients will be offered platinum-based doublet chemotherapy. In some situations, continuation of the EGFR-TKI beyond radiological progression, with or without use of local treatments in case of oligo-progressive disease, represents a reasonable therapeutic option. The aim of this review is to describe the different treatment strategies that have been developed to tackle progression on EGFR-TKIs, including specific clinical scenarios and novel agents designed to tackle the common T790M resistance mutation.
Pharmacological Management of Secondary Hyperparathyroidism in Patients with Chronic Kidney Disease

S. N. Salam, A. Khwaja, M. E. Wilkie

ABSTRACT

Secondary hyperparathyroidism (SHPT) is a common complication of chronic kidney disease (CKD) and is part of the CKD-mineral bone disorder (CKD-MBD). SHPT is associated with increased risk of fracture and mortality; thus, SHPT control is recommended as kidney function declines. Effective SHPT management becomes more difficult once skeletal and cardiovascular adverse effects associated with severe SHPT have become established. However, interventional studies to lower parathyroid hormone (PTH) have so far shown inconsistent results in improving patient-centred outcomes such as mortality, cardiovascular events and fracture. Pharmacological treatment effect on PTH level is also inconsistent between pre-dialysis a CKD and dialysis patient, which adds to the complexity of SHPT management. This review aims to give an overview on the pathophysiology, pharmacological and non-pharmacological treatment for SHPT in CKD including some of the limitations of current therapeutic options.

Practical Considerations for the Use of Daratumumab, a Novel CD38 Monoclonal Antibody, in Myeloma

Philippe Moreau, Niels W. C. J. van de Donk, Jesus San Miguel, Henk Lokhorst

ABSTRACT

Monoclonal antibodies (mAbs) are a recent addition to multiple myeloma (MM) therapies and a number of mAbs directed at myeloma cell surface molecules are in development. Daratumumab is a CD38 mAb that has demonstrated substantial activity and good tolerability in four phase I, phase I/II and phase II studies as monotherapy, as well as in combination with current standard treatments in MM. The positive results obtained in the relapsed/refractory setting in patients with advanced-stage disease and in a small number of patients with newly diagnosed disease provide the rationale for the investigation of the agent in a number of ongoing phase III trials. mAbs are generally better tolerated than conventional chemotherapy; however, their use requires other special considerations. Such factors include those common to all mAbs, namely infusion-related reactions, but also factors that are observed with mAbs used in myeloma, such as interference with response assessment, or factors that are related to CD38 mAbs such as daratumumab, for instance blood typing interference. Our review provides an overview of the results from the daratumumab clinical trials conducted to date, as well as practical management considerations for the use of daratumumab based on our experience with the agent.
Eltrombopag: A Review in Paediatric Chronic Immune Thrombocytopenia

Celeste B. Burness, Gillian M. Keating, Karly P. Garnock-Jones

ABSTRACT

Eltrombopag (Promacta®; Revolade®) is an orally active thrombopoietin receptor agonist recently approved in the USA and the EU for use in paediatric patients aged ≥1 year with chronic immune thrombocytopenia (ITP) who have had an insufficient response or are refractory to other ITP treatments (e.g. corticosteroids, immunoglobulins or splenectomy). The efficacy of 7 or 13 weeks’ therapy with oral eltrombopag (up to 75 mg/day) was compared with that of placebo in patients aged 1–17 years with previously treated chronic ITP in randomized, double-blind, multicentre phase II and III trials (PETIT and PETIT-2). In these trials, the platelet response rate (primary endpoint of PETIT) and the sustained platelet response rate (primary endpoint of PETIT-2) were significantly higher with eltrombopag than with placebo. A clinical benefit was shown by a reduction in the need for rescue therapy with eltrombopag versus placebo in both trials and a reduction of clinically significant bleeding in PETIT. During longer-term therapy (open-label treatment period for ≥24 weeks), eltrombopag maintained platelet counts above 50 × 109/L in the majority of patients and approximately one-half of patients were able to reduce or discontinue concurrent ITP drugs. Eltrombopag was generally well tolerated. Current evidence suggests that eltrombopag is a valuable addition to the limited treatment options available for the management of chronic ITP in paediatric patients with an inadequate response to first-line therapies.

Gabapentin Enacarbil: A Review in Restless Legs Syndrome

Esther S. Kim, Emma D. Deeks

ABSTRACT

Gabapentin enacarbil is an extended-release prodrug of gabapentin that is approved in the USA (Horizant®) and Japan (Regnite®) for the treatment of moderate to severe primary restless legs syndrome (RLS) in adults [featured indication]. This article summarizes pharmacological, efficacy and tolerability data relevant to the use of oral gabapentin enacarbil in this indication. In double-blind, multicentre trials, treatment with gabapentin enacarbil 600 mg/day for 12 weeks significantly improved the symptoms of moderate to severe primary RLS in adults. Gabapentin enacarbil also significantly improved RLS pain scores and generally improved sleep and mood outcomes. These data are supported by retrospective pooled analyses of three of these trials (XP081, PIVOT RLS I and PIVOT RLS II), with gabapentin enacarbil generally improving symptoms irrespective of disease severity, associated sleep disturbance or prior dopamine agonist use. Responses to gabapentin enacarbil were sustained in longer-term trials, with lower relapse rates in gabapentin enacarbil than placebo recipients in a longer-term maintenance study. Overall, in short and longer-term trials, relatively few patients discontinued treatment, adverse events were mostly mild to moderate in severity, and somnolence/sedation and dizziness were the most commonly reported adverse events. Notably, there were no reports of augmentation or QT-interval prolongation. Gabapentin enacarbil is an important agent for the treatment of adults with moderate to severe primary RLS.
Azacitidine: A Review in Myelodysplastic Syndromes and Acute Myeloid Leukaemia

Lesley J. Scott

ABSTRACT

Azacitidine (Vidaza®) is a pyrimidine nucleoside analogue of cytidine and is approved in the EU for use in patients with higher-risk myelodysplastic syndromes (MDS) and acute myeloid leukaemia (AML), including older patients (aged ≥65 years) with AML with >30 % bone marrow blasts (BMB) who are ineligible for haematopoietic stem cell transplant. This article reviews the clinical efficacy and tolerability of azacitidine in the treatment of these patient populations, as well as summarizing its pharmacological properties. In pivotal, international, phase 3 trials, subcutaneous azacitidine was an effective and well tolerated treatment in patients with higher-risk MDS or AML, including older patients with AML with >30 % BMB, with extensive evidence from the real-world setting confirming its efficacy and safety in these patient populations. Azacitidine is the only approved hypomethylating agent that has been shown to prolong overall survival compared with conventional care regimens and thus, it is recommended as the first-line hypomethylating agent for most patients with higher-risk MDS. Hence, azacitidine remains and important agent for use in the treatment of higher-risk MDS and AML, including in older patients with AML with >30 % BMB.

Ixekizumab: First Global Approval

Anthony Markham

ABSTRACT

Ixekizumab (Taltz®) is a humanised monoclonal immunoglobulin G antibody developed by Eli Lilly and Company that has been approved in the USA as a treatment for plaque psoriasis. Ixekizumab is a specific inhibitor of interleukin-17A (IL-17A), a pro-inflammatory cytokine that has a role in the development of several inflammatory conditions. This article summarizes the milestones in the development of ixekizumab leading to this first approval for plaque psoriasis.

Reslizumab: First Global Approval

Anthony Markham

ABSTRACT

Reslizumab (Cinqair®) is a humanised monoclonal interleukin-5 (IL-5) antibody developed by Teva that has been approved in the USA for patients aged ≥18 years as add-on maintenance treatment for severe asthma with an eosinophilic phenotype. IL-5 stimulates the production, activation and maturation of eosinophils and is therefore thought to play a role in the development of bronchial hyper-responsiveness. This article summarizes the milestones in the development of reslizumab leading to this first approval for add-on maintenance treatment of severe asthma with an eosinophilic phenotype.
ONGOING PHARMACOLOGICAL MANAGEMENT OF CHRONIC PAIN IN PREGNANCY

Bengt Källén, Margareta Reis

ABSTRACT
The article discusses possible effects of the use of analgesics during pregnancy. It summarizes the pertinent literature and reports some previously unpublished data from the Swedish Medical Birth Register. Most likely the use of analgesics does not cause spontaneous abortion. Only small malformation risk increases are seen after the use of opioids and perhaps non-steroid anti-inflammatory drug (NSAID) use. If possible, the latter should be avoided during the first trimester. If exposure has occurred there is no reason to consider an interruption of the pregnancy. Continued use of analgesics may increase the risk of preeclampsia and of preterm birth, especially valid for opioids. Use of acetylsalicylic acid (ASA) in late pregnancy should be avoided because of the risk of bleeding and (valid also for NSAIDs) premature closure of the ductus arteriosus. A small risk for neonatal abstinence syndrome may exist after the use of opioids for chronic pain, notably during the third trimester and long-lasting effects on child development can possibly occur. For a woman with chronic pain, adequate use of pain killers during pregnancy is needed. It is prudent to avoid ASA and NSAIDs towards the end of the pregnancy, while acetaminophen is an acceptable option all through pregnancy. If continued use of opioids is necessary, the associated risks are low. Triptans can be used for migraine during pregnancy.

Cancer Treatment with Anti-PD-1/PD-L1 Agents: Is PD-L1 Expression a Biomarker for Patient Selection?

Lucia Festino, Gerardo Botti, Paul Lorigan, Giuseppe V. Masucci, Jason D. Hipp

ABSTRACT
Strategies to help improve the efficacy of the immune system against cancer represent an important innovation, with recent attention having focused on anti-programmed death (PD)-1/PD-ligand 1 (L1) monoclonal antibodies. Clinical trials have shown objective clinical activity of these agents (e.g., nivolumab, pembrolizumab) in several malignancies, including melanoma, non-small-cell lung cancer, bladder cancer, squamous head and neck cancer, renal cell cancer, ovarian cancer, microsatellite-unstable colorectal cancer, and Hodgkin’s lymphoma. Expression of PD-L1 in the tumor microenvironment appears to be crucial for therapeutic activity, and initial trials suggested positive PD-L1 tumor expression was associated with higher response rates. However, subsequent observations have questioned the prospect of using PD-L1 expression as a biomarker for selecting patients for therapy, especially since many patients considered PD-L1-negative experience a benefit from treatment. Importantly, there is not yet a definitive test for determination of PD-L1 and a cut-off reference for PD-L1-positive status has not been established. Immunohistochemistry with different antibodies and different thresholds has been used to define PD-L1 positivity (1–50 %), with no clear superiority of one threshold over another for identifying which patients respond. Moreover, the type of cells on which PD-L1 expression is most relevant is not yet clear, with immune infiltrate cells and tumor cells both being used. In conclusion, while PD-L1 expression is often a predictive factor for treatment response, it must be complemented by other biomarkers or histopathologic features, such as the composition and amount of inflammatory cells in the tumor microenvironment and their functional status.
Impact of Statin Therapy on Plasma Uric Acid Concentrations: A Systematic Review and Meta-Analysis

Giuseppe Derosa, Pamela Maffioli, Željko Reiner, Luis E. Simental-Mendía

ABSTRACT

Purpose: The aim of this study was to ascertain the effect size of statins in modulating plasma uric acid concentrations.

Data Sources: A search was undertaken of the MEDLINE, SCOPUS, Web of Science and Google Scholar electronic databases.

Study Selection: Studies meeting the following criteria were included: (i) randomized controlled trials with either a parallel or crossover design; (ii) investigated the impact of statin therapy on plasma uric acid concentrations; and (iii) presentation of sufficient information on uric acid values at baseline and at the end of follow-up in each group, or presenting the net change.

Data Synthesis: The present meta-analysis suggested a significant reduction in plasma uric acid levels following statin therapy; however, this does not seem to be a class effect as subgroup analysis revealed a significant reduction with atorvastatin and simvastatin only, and not with pravastatin and rosuvastatin.

Conclusions: Atorvastatin and simvastatin, but not the other statins, can reduce serum uric acid levels.

Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide: A Review in HIV-1 Infection

Sarah L. Greig, Emma D. Deeks

ABSTRACT

Tenofovir alafenamide (tenofovir AF) is a novel oral prodrug of the nucleos(t)ide reverse transcriptase inhibitor (NRTI) tenofovir that has several pharmacological advantages over tenofovir disoproxil fumarate (tenofovir DF), including increased plasma stability and reduced tenofovir systemic exposure. Tenofovir AF has been coformulated with elvitegravir, cobicistat and emtricitabine as a once-daily, single-tablet regimen (elvitegravir/cobicistat/emtricitabine/tenofovir AF; Genvoya®) for the treatment of adults and adolescents with HIV-1 infection. With regard to establishing and/or maintaining virological suppression over 48 weeks in randomized, phase III trials, elvitegravir/cobicistat/emtricitabine/tenofovir AF was noninferior to elvitegravir/cobicistat/emtricitabine/tenofovir DF in antiretroviral therapy (ART)-naive adults, and statistically superior (subsequent to established noninferiority) to ongoing treatment with tenofovir DF-containing regimens in ART-experienced adults with virological suppression. In single-arm, phase III trials, elvitegravir/cobicistat/emtricitabine/tenofovir AF also provided high rates of virological suppression among ART-naive adolescents and ART-experienced adults with stable renal impairment. In general, elvitegravir/cobicistat/emtricitabine/tenofovir AF was well tolerated and associated with more favourable renal and bone parameters, but a less favourable lipid profile, than tenofovir DF-containing regimens. Thus, elvitegravir/cobicistat/emtricitabine/tenofovir AF is an alternative single-tablet regimen for adults and adolescents with HIV-1 infection, particularly those with an estimated creatinine clearance of ≥30 to <50 mL/min or an increased risk of tenofovir DF-related bone toxicity.
Nivolumab: A Review in Advanced Nonsquamous Non-Small Cell Lung Cancer
Gillian M. Keating

ABSTRACT
The programmed death (PD)-1 immune checkpoint inhibitor nivolumab (Opdivo®) is approved in the USA for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) who have progression on or after platinum-based chemotherapy and in the EU for the treatment of adults with locally advanced or metastatic NSCLC after prior chemotherapy. In previously-treated patients with advanced nonsquamous NSCLC, overall survival was significantly prolonged and the overall response rate was significantly higher in patients who received intravenous nivolumab 3 mg/kg every 2 weeks versus intravenous docetaxel in the pivotal CheckMate 057 trial. Progression-free survival did not significantly differ between patients receiving nivolumab and those receiving docetaxel. Intravenous nivolumab had a manageable adverse event profile (including immune-mediated adverse events) and was better tolerated than docetaxel in the CheckMate 057 trial. Thus, nivolumab is an important new option for use in previously-treated patients with advanced nonsquamous NSCLC.

Venetoclax: First Global Approval
Emma D. Deeks

ABSTRACT
Venetoclax (Venclexta™) is an oral selective inhibitor of the prosurvival protein BCL-2 and therefore restores the apoptotic ability of malignant cells. The drug arose from research by Abbott Laboratories (now AbbVie) during a collaboration with Genentech and is being co-developed by AbbVie and Genentech/Roche primarily for the treatment of haematological malignancies. Venetoclax is approved in the USA for use as monotherapy in patients with chronic lymphocytic leukaemia (CLL) with the 17p deletion (as detected by an approved FDA test) who have received at least one prior therapy, and is awaiting approval for similar indications in the EU and Canada. Venetoclax is also in phase I-III development as combination therapy for CLL, phase I/II development as monotherapy and/or combination therapy for non-Hodgkin lymphomas (including diffuse large B-cell lymphoma, mantle cell lymphoma, follicular lymphoma) and acute myeloid leukaemia, and phase I development for multiple myeloma, systemic lupus erythematosus and breast cancer. This article summarizes the milestones in the development of venetoclax leading to this first approval for CLL.

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Pain Relief for Acute Urolithiasis: The Case for Non-Steroidal Anti-Inflammatory Drugs
Peter L. Steinberg, Steven L. Chang

ABSTRACT
Pain from renal colic is often severe and incapacitating. Many patients require emergent hospitalization and aggressive analgesia to relieve such discomfort. For many years, the optimal analgesic strategy has been sought to manage such severe pain. One of the mainstays of therapy for acute renal colic is with non-steroidal anti-inflammatory drugs (NSAIDs). This paper reviews the mechanism by which NSAIDs allow pain relief in renal colic, the evidence for their use in this condition, and the use of NSAIDs combined with other agents in renal colic.
Long-Acting Muscarinic Antagonists for Difficult-to-Treat Asthma: Emerging Evidence and Future Directions
Adeeb Bulkhi, Farnaz Tabatabaian, Thomas B. Casale

ABSTRACT
Asthma is a complex disease where many patients remain symptomatic despite guideline-directed therapy. This suggests an unmet need for alternative treatment approaches. Understanding the physiological role of muscarinic receptors and the parasympathetic nervous system in the respiratory tract will provide a foundation of alternative therapeutics in asthma. Currently, several long-acting muscarinic antagonists (LAMAs) are on the market for the treatment of respiratory diseases. Many studies have shown the effectiveness of tiotropium, a LAMA, as add-on therapy in uncontrolled asthma. These studies led to FDA approval for tiotropium use in asthma. In this review, we discuss how the neurotransmitter acetylcholine itself contributes to inflammation, bronchoconstriction, and remodeling in asthma. We further describe the current clinical studies evaluating LAMAs in adult and adolescent patients with asthma, providing a comprehensive review of the current known physiological benefits of LAMAs in respiratory disease.

Fimasartan: A New Angiotensin Receptor Blocker
Hae-Young Lee, Byung-Hee Oh

ABSTRACT
Fimasartan is the ninth, and most recent, angiotensin II receptor antagonist approved as an antihypertensive agent. Fimasartan, a pyrimidin-4(3H)-one derivative of losartan with the imidazole ring replaced, which enables higher potency and longer duration than losartan. Fecal elimination and biliary excretion are the predominant elimination pathways of fimasartan and the urinary excretion was found to be less than 3 % 24 h after administration. Fimasartan is primarily catabolized by cytochrome P450 isoform 3A and no significant drug interaction was observed when used in combination with hydrochlorothiazide, amlodipine, warfarin, or digoxin. Fimasartan at a dosage range of 60–120 mg once daily showed an antihypertensive effect over 24 h. In a large, population-based observational study, fimasartan showed an excellent safety profile. Anti-inflammatory and organ-protecting effects of fimasartan have been shown in various preclinical studies, including aortic balloon injury, myocardial infarct ischemia/reperfusion, doxorubicin cardiotoxicity, and ischemic stroke models.

Pimavanserin: First Global Approval
Anthony Markham

ABSTRACT
Pimavanserin (Nuplazid™) is a selective and potent serotonin 2A (5-HT2A) receptor inverse agonist and antagonist developed by ACADIA Pharmaceuticals that has been approved in the US as a treatment for patients with hallucinations and delusions associated with Parkinson’s disease psychosis. Up to 60 % of patients with Parkinson’s disease may develop Parkinson’s disease psychosis, which is associated with increased morbidity and mortality and has few treatment options. This article summarizes the milestones in the development of pimavanserin leading to this first approval for the treatment of hallucinations and delusions in patients with Parkinson’s disease psychosis.
Secukinumab: A Review in Ankylosing Spondylitis
Hannah A. Blair, Sohita Dhillon

ABSTRACT
Secukinumab (Cosentyx®) is a fully human monoclonal antibody against the proinflammatory cytokine interleukin-17A. It is the first drug in its class to be approved for use in patients with active ankylosing spondylitis (AS). This article reviews the efficacy and tolerability of secukinumab in this indication and briefly summarizes its pharmacology. In ongoing phase III trials, 16 weeks’ treatment with subcutaneous secukinumab 150 mg was effective in terms of improving the clinical signs and symptoms of disease and health-related quality of life in patients with AS, with these improvements maintained during longer-term (up to 2 years) treatment. In subgroup analyses, secukinumab was effective both in tumour necrosis factor (TNF) inhibitor-naïve patients and in patients intolerant of or refractory to TNF inhibitors. Secukinumab was generally well tolerated, with a tolerability profile consistent with that seen previously in patients with plaque psoriasis. In the absence of head-to-head trials, the position of secukinumab with respect to TNF inhibitors remains to be fully determined. Nevertheless, secukinumab is an effective and generally well tolerated treatment option for patients with AS.

Rotigotine Transdermal Patch: A Review in Restless Legs Syndrome
Karly P. Garnock-Jones

ABSTRACT
Rotigotine transdermal patch (Leganto®, Neupro®) is indicated for the treatment of restless legs syndrome (RLS); this article reviews the pharmacological properties of rotigotine transdermal patch and its clinical efficacy and tolerability in patients with RLS. The transdermal patch allows for a continuous, stable release of rotigotine (avoiding first-pass metabolism), which in turn leads to continuous receptor stimulation, believed to closely mimic physiological striatal dopamine receptor function. In short-term and 6-month studies, especially at the higher dosages of 2 and 3 mg/24 h, rotigotine transdermal patch was generally associated with a significantly greater improvement in IRLS total score and CGI-S total score than placebo, and rotigotine recipients were generally more likely to respond to treatment and enter remission. In noncomparative extension studies, efficacy was sustained for ≤5 years. Rotigotine transdermal patch is generally well tolerated, and appears to have a tolerability profile that is similar to that of other non-ergolinic dopamine-receptor agonists. The most common adverse events in clinical trials included application-site reactions, nausea, headache and asthenic conditions. The drug has a relatively low risk of clinically significant augmentation of restless legs syndrome symptoms. In conclusion, rotigotine transdermal patch offers continuous administration of the drug in a daily treatment, and is a useful treatment option in patients with RLS.
Sugammadex: A Review of Neuromuscular Blockade Reversal

Gillian M. Keating

ABSTRACT

Sugammadex (Bridion®) is a modified γ-cyclodextrin that reverses the effect of the steroidal nondepolarizing neuromuscular blocking agents rocuronium and vecuronium. Intravenous sugammadex resulted in rapid, predictable recovery from moderate and deep neuromuscular blockade in patients undergoing surgery who received rocuronium or vecuronium. Recovery from moderate neuromuscular blockade was significantly faster with sugammadex 2 mg/kg than with neostigmine, and recovery from deep neuromuscular blockade was significantly faster with sugammadex 4 mg/kg than with neostigmine or spontaneous recovery. In addition, recovery from neuromuscular blockade was significantly faster when sugammadex 16 mg/kg was administered 3 min after rocuronium than when patients spontaneously recovered from succinylcholine. Sugammadex also demonstrated efficacy in various special patient populations, including patients with pulmonary disease, cardiac disease, hepatic dysfunction or myasthenia gravis and morbidly obese patients. Intravenous sugammadex was generally well tolerated. In conclusion, sugammadex is an important option for the rapid reversal of rocuronium- or vecuronium-induced neuromuscular blockade.

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Sphingosine-1-Phosphate (S1P) and S1P Signaling Pathway: Therapeutic Targets in Autoimmunity and Inflammation

Hsing-Chuan Tsai, May H. Han

ABSTRACT

Sphingosine-1-phosphate (S1P) and S1P receptors (S1PR) are ubiquitously expressed. S1P-S1PR signaling has been well characterized in immune trafficking and activation in innate and adaptive immune systems. However, the full extent of its involvement in the pathogenesis of autoimmune diseases is not well understood. FTY720 (fingolimod), a non-selective S1PR modulator, significantly decreased annualized relapse rates in relapsing–remitting multiple sclerosis (MS). FTY720, which primarily targets S1P receptor 1 as a functional antagonist, arrests lymphocyte egress from secondary lymphoid tissues and reduces neuroinflammation in the central nervous system (CNS). Recent studies suggest that FTY720 also decreases astrogliosis and promotes oligodendrocyte differentiation within the CNS and may have therapeutic benefit to prevent brain atrophy. Since S1P signaling is involved in multiple immune functions, therapies targeting S1P axis may be applicable to treat autoimmune diseases other than MS. Currently, over a dozen selective S1PR and S1P pathway modulators with potentially superior therapeutic efficacy and better side-effect profiles are in the pipeline of drug development. Furthermore, newly characterized molecules such as apolipoprotein M (ApoM) (S1P chaperon) and SPNS2 (S1P transporter) are also potential targets for treatment of autoimmune diseases. Finally, the application of therapies targeting S1P and S1P signaling pathways may be expanded to treat several other immune-mediated disorders (such as post-infectious diseases, post-stroke and post-stroke dementia) and inflammatory conditions beyond their application in primary autoimmune diseases.
Targeting Select Cellular Stress Pathways to Prevent Hyperglycemia-Related Complications: Shifting the Paradigm
Arshag D. Mooradian

ABSTRACT

Despite the advances made in preventing complications of diabetes, there is still substantial residual risk. Hence the need for developing new therapeutic agents that target the various facets of the pathogenesis of complications in people with diabetes. Traditionally four general biochemical pathways had been recognized as major contributors to glucotoxicity. These include the polyol pathway, the protein kinase C (PKC) pathway, glycosylation pathway, and oxidative stress. The latter has been proposed as a common impetus of the other pathways of glucotoxicity. More recently, the cross talk between oxidative stress and other recognized cellular stresses such as endoplasmic reticulum (ER), inflammatory, and mitochondrial stresses has emerged as an important additional mechanism of glucotoxicity. The observation that targeting oxidative stress with antioxidants has been associated with unfavorable clinical outcomes and the recognition that in cell cultures antioxidants may aggravate ER stress, suggests that selective targeting of individual cellular stresses may not be sufficient for preventing glucotoxicity. Future efforts should focus on developing therapeutic agents that can ameliorate cellular stress globally by simultaneously targeting the oxidative, ER, mitochondrial, and inflammatory stresses.

Psychosis in Parkinson’s disease: Epidemiology, Pathophysiology, and Management
Anna Chang, Susan H. Fox

ABSTRACT

Psychotic symptoms are common in Parkinson’s disease (PD) and are associated with poorer quality of life and increased caregiver burden. PD psychosis is correlated with several factors, such as more advanced disease, cognitive impairment, depression, and sleep disorders. The underlying causes of psychosis in PD thus involve a complex interplay between exogenous (e.g., drugs, intercurrent illnesses) and endogenous (e.g., PD disease pathology) factors. Current theories of the pathophysiology of PD psychosis have come from several neuropathological and neuroimaging studies that implicate pathways involving visual processing and executive function, including temporo-limbic structures and neocortical gray matter with altered neurotransmitter functioning (e.g., dopamine, serotonin, and acetylcholine). Treatment of PD psychosis requires a step-wise process, including initial careful investigation of treatable triggering conditions and a comprehensive evaluation with adjustment of PD medications and/or initiation of specific antipsychotic therapies. Clozapine remains the only recommended drug for the treatment of PD psychosis; however, because of regular blood monitoring, quetiapine is usually first-line therapy, although less efficacious. Emerging studies have focused on agents involving other neurotransmitters, including the serotonin 5-HT2A receptor inverse agonist pimavanserin, cholinesterase inhibitors, and antidepressants and anxiolytics.
Management of Myopic Choroidal Neovascularization: Focus on Anti-VEGF Therapy
Kelvin Yi Chong Teo, Wei Yan Ng, Shu Yen Lee, Chui Ming Gemmy Cheung

ABSTRACT

Myopic choroidal neovascularization (mCNV) is the second most common form of CNV after age-related macular degeneration (AMD). It is a sight-threatening complication of pathologic myopia (PM) and often affects patients in their working years causing significant impact on quality of life. Previous therapies such as photodynamic therapy with verteporfin have shown limited success. Due to the similarities in pathogenesis of mCNV and AMD CNV, anti-vascular endothelial growth factor therapy (anti-VEGF), which has so far been the mainstay of treatment for AMD CNV, has been shown to be effective in the treatment of mCNV and has become the first-line treatment of choice. This article aims to examine briefly the epidemiology and pathophysiology of mCNV, as well as review the evidence for efficacy, safety, and clinical use of anti-VEGF treatment for mCNV.

Secukinumab: A Review in Psoriatic Arthritis
Matt Shirley, Lesley J. Scott

ABSTRACT

Secukinumab (Cosentyx®) is a high affinity, human monoclonal antibody targeted against interleukin (IL)-17A. It is the first-in-class anti-IL-17 agent, initially approved for the treatment of plaque psoriasis, and more recently for the treatment of ankylosing spondylitis and psoriatic arthritis. This article reviews the therapeutic efficacy of subcutaneous secukinumab in the treatment of psoriatic arthritis, as well as discussing the tolerability and pharmacological properties of the drug. Phase III clinical trial data demonstrated that, compared with placebo, subcutaneous secukinumab was efficacious in improving the signs and symptoms of psoriatic arthritis in patients with active disease despite previous treatment with non-steroidal anti-inflammatory drugs (NSAIDs) or disease-modifying anti-rheumatic drugs (DMARDs). In addition, secukinumab treatment was associated with significant improvements in patient-reported measures of physical functioning and health-related quality of life. Secukinumab is generally well tolerated, with the most common adverse events being mild to moderate, non-serious infections, such as upper respiratory tract infections and nasopharyngitis. In conclusion, although longer-term and comparative data are lacking, current clinical data indicate that secukinumab is efficacious and well tolerated in the treatment of psoriatic arthritis, and it thus provides a useful treatment alternative to tumour necrosis factor inhibitors and other targeted DMARDs.

Migalastat: First Global Approval
Anthony Markham

ABSTRACT

Migalastat (Galafold™)—a small molecule drug developed by Amicus Therapeutics that restores the activity of specific mutant forms of α-galactosidase—has been approved for the treatment of Fabry disease in the EU in patients with amenable mutations. Fabry disease is a rare disorder that results in a deficiency or absence of α-galactosidase, leading to accumulation of globotriaosylceramide in the lysosomes of various cells. This article summarizes the milestones in the development of migalastat leading to this first approval in the EU for the long-term treatment of adults and adolescents aged ≥16 years with a confirmed diagnosis of Fabry disease.
Olmutinib: First Global Approval
Esther S. Kim

ABSTRACT

Olmutinib (OlitaTM) is an oral, third-generation epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI) that is being developed by Boehringer Ingelheim and Hanmi Pharmaceutical Co. Ltd for the treatment of non-small cell lung cancer (NSCLC). Third-generation EGFR TKIs with covalent binding to the receptors demonstrate irreversible enzymatic inhibition of activating EGFR mutations and T790M mutation (a common reason for acquired EGFR TKI resistance), while sparing wild-type EGFR. In December 2015, olmutinib was granted breakthrough therapy designation in NSCLC by the US FDA. In May 2016, olmutinib received its first global approval in South Korea for the treatment of patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC. This article summarizes the milestones in the development of olmutinib leading to this first approval.

Daptomycin Pharmacokinetics and Pharmacodynamics in Septic and Critically Ill Patients
Antonio D’Avolio, Debora Pensi, Lorena Baietto, Giovanni Pacini, Giovanni Di Perri

ABSTRACT

Infections, including sepsis, are associated with high mortality rates in critically ill patients in the intensive care unit (ICU). Appropriate antibiotic selection and adequate dosing are important for improving patient outcomes. Daptomycin is bactericidal in bloodstream infections caused by Staphylococcus aureus and other Gram-positive pathogens cultured in ICU patients. The drug has concentration-dependent activity, and the area under the curve/minimum inhibitory concentration ratio is the pharmacokinetic/pharmacodynamic (PK/PD) index that best correlates with daptomycin activity, whereas toxicity correlates well with daptomycin plasma trough concentrations (or minimum concentration [Cmin]). Adequate daptomycin exposure can be difficult to achieve in ICU patients; multiple PK alterations can result in highly variable plasma concentrations, which are difficult to predict. For this reason, therapeutic drug monitoring could help clinicians optimize daptomycin dosing, thus improving efficacy while decreasing the likelihood of serious adverse events. This paper reviews the literature on daptomycin in ICU patients with sepsis, focusing on dosing and PK and PD parameters.
Unmet Needs in LDL-C Lowering: When Statins Won’t Do!
Stephan Krähenbühl, Ivana Pavik-Mezzour, Arnold von Eckardstein

ABSTRACT

The use of low-density lipoprotein cholesterol (LDL-C)-lowering medications has led to a significant reduction of cardiovascular risk in both primary and secondary prevention. Statin therapy, one of the cornerstones for the prevention and treatment of cardiovascular disease (CVD), has been demonstrated to be effective in lowering LDL-C levels and in reducing the risk for CVD and is generally well-tolerated. However, compliance with statins remains suboptimal. One of the main reasons is limitations by adverse events, notably myopathies, which can lead to non-compliance with the prescribed statin regimen. Reducing the burden of elevated LDL-C levels is critical in patients with CVD as well as in patients with very high baseline levels of LDL-C (e.g. patients with familial hypercholesterolaemia), as statin therapy is insufficient for optimally reducing LDL-C below target values. In this review, we discuss alternative treatment options after maximally tolerated doses of statin therapy, including ezetimibe, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, and cholesteryl ester transfer protein (CEPT) inhibitors. Difficult-to-treat patients may benefit from combination therapy with ezetimibe or a PCSK9 inhibitor (evolocumab or alirocumab, which are now available). Updates of treatment guidelines are needed to guide the management of patients who will best benefit from these new treatments.

Lumacaftor/Ivacaftor: A Review in Cystic Fibrosis
Emma D. Deeks

ABSTRACT

Lumacaftor/ivacaftor (Orkambi™) is a fixed-dose tablet containing a corrector (lumacaftor) and potentiator (ivacaftor) of the cystic fibrosis transmembrane conductance regulator (CFTR) and is the first therapy approved to treat the underlying cause of cystic fibrosis in patients (aged ≥12 years) homozygous for the most common CFTR mutation, F508del. Lumacaftor improves the processing of F508del CFTR and its transport to the cell surface, while ivacaftor increases the channel’s open probability and transport of chloride. In two 24-week trials in the approved patient population (TRAFFIC and TRANSPORT), lumacaftor 400 mg plus ivacaftor 250 mg, administered every 12 h in combination with standard therapy, was associated with an ≈3 % statistically significant improvement in lung function relative to placebo (as measured by the percent predicted forced expiratory volume in 1 s). Lumacaftor plus ivacaftor did not significantly improve respiratory symptoms, although reduced pulmonary exacerbations to a clinically meaningful extent and, in one trial (TRANSPORT), significantly improved body mass index (BMI). In an ongoing extension of these studies (PROGRESS), lumacaftor plus ivacaftor provided clinical benefit over a further 72 weeks of treatment. Lumacaftor plus ivacaftor had an acceptable tolerability profile, with the most common adverse events being respiratory or gastrointestinal in nature. Thus, lumacaftor/ivacaftor expands the treatment options available for patients with cystic fibrosis homozygous for the F508del-CFTR mutation, although its precise place in clinical practice remains to be determined.
Ombitasvir/Paritaprevir/Ritonavir: A Review in Chronic HCV Genotype 4 Infection
Gillian M. Keating

ABSTRACT
A fixed-dose tablet comprising the NS5A inhibitor ombitasvir, the NS3/4A inhibitor paritaprevir and ritonavir (ombitasvir/paritaprevir/ritonavir) (Technivie®, Viekirax®) is available for use, in combination with ribavirin, for the treatment of chronic hepatitis C virus (HCV) genotype 4 infection. High sustained virological response rates at 12 weeks post-treatment (SVR12) were achieved in treatment-naive or -experienced patients with chronic HCV genotype 4 infection, including patients without cirrhosis who received ombitasvir plus paritaprevir and ritonavir in combination with ribavirin for 12 weeks (SVR12 100 %) (PEARL-I trial), patients with compensated cirrhosis who received ombitasvir/paritaprevir/ritonavir plus ribavirin for 12 or 16 weeks (SVR12 97 and 98 %) (AGATE-I trial), or Egyptian patients without cirrhosis who received ombitasvir/paritaprevir/ritonavir plus ribavirin for 12 weeks (SVR12 94 %) or with compensated cirrhosis who received ombitasvir/paritaprevir/ritonavir plus ribavirin for 12 or 24 weeks (SVR12 97 and 93 %) (AGATE-II trial). Ombitasvir/paritaprevir/ritonavir was generally well tolerated in patients with chronic HCV genotype 4 infection without cirrhosis or with compensated cirrhosis in clinical trials. There have been postmarketing reports of hepatic decompensation and hepatic failure, which mainly occurred in patients with advanced cirrhosis who received regimens containing ombitasvir/paritaprevir/ritonavir. In conclusion, ombitasvir/paritaprevir/ritonavir is a valuable option for use in patients with chronic HCV genotype 4 infection without cirrhosis or with compensated cirrhosis.

Diclofenac Sodium Bolus Injection (DylojectTM): A Review in Acute Pain Management
Sheridan M. Hoy

ABSTRACT
An intravenous bolus formulation of the non-steroidal anti-inflammatory drug diclofenac sodium has been developed using hydroxypropyl-β-cyclodextrin (HPβCD) as a solubility enhancer. HPβCD diclofenac (DylojectTM) is available for use in adults in the USA for the management of mild to moderate pain, and as monotherapy or in combination with opioid analgesics for the management of moderate to severe pain. In two multicentre, phase III studies in adults with acute moderate to severe postoperative pain, HPβCD diclofenac significantly reduced pain intensity and the need for rescue medication compared with placebo. In these studies, the tolerability profile of HPβCD diclofenac was generally similar to that of placebo and adverse events were mostly mild to moderate in severity. Constipation, infusion-site pain and dizziness were the most frequently reported adverse reactions occurring numerically more frequently with HPβCD diclofenac than placebo. Therapy with HPβCD diclofenac does not appear to be associated with an increased risk of cardiovascular, renal or bleeding-related adverse events versus placebo. Thus, HPβCD diclofenac extends the treatment options currently available for the management of moderate to severe postoperative pain in adults.
Obeticholic Acid: First Global Approval
A. Markham, Susan J. Keam

ABSTRACT
Obeticholic acid (OcalivaTM) is a farnesoid-X receptor (FXR) agonist that is being developed by Intercept Pharmaceuticals for the treatment of various liver diseases, and has recently been granted accelerated approval in the USA for the treatment of primary biliary cholangitis in combination with ursodeoxycholic acid in adults with an inadequate response to ursodeoxycholic acid, or as monotherapy in adults unable to tolerate ursodeoxycholic acid. The drug is in preregistration for this indication in the EU. This article summarizes the milestones in the development of obeticholic acid leading to this first approval for primary biliary cholangitis.

Atezolizumab: First Global Approval
Anthony Markham

ABSTRACT
Atezolizumab (Tecentriq™)—a monoclonal antibody targeting programmed death ligand 1 (PD-L1 or CD274 antigen)—is being developed by Genentech as treatment for a variety of haematological malignancies and solid tumours. It has been approved in the US as a second-line therapy for urothelial carcinoma and is awaiting approval as a second-line therapy for non-small cell lung cancer. This article summarizes the milestones in the development of atezolizumab leading to this first approval for urothelial carcinoma.

Vol. 76, Issue 13, September 2016

Management of Hyperglycemia in Patients With Acromegaly Treated With Pasireotide LAR
Susan L. Samson

ABSTRACT
Pasireotide (Signifor®) long-acting release (LAR) is a next-generation somatostatin receptor ligand (SRL) approved for treatment of patients with acromegaly who have had an inadequate response to surgery or for whom surgery is not an option. Pasireotide LAR has been shown to be more effective than other SRLs in providing biochemical control in patients with acromegaly. However, hyperglycemia-related adverse events were more frequent in patients treated with pasireotide LAR than in those treated with other SRLs. Given the effectiveness of pasireotide LAR, it is important to understand whether these hyperglycemia-related events are manageable and, if so, the appropriate steps to take to manage them. In patients treated with pasireotide LAR, levels of fasting plasma glucose (FPG) and glycated hemoglobin (HbA1c) increased in the first 1–3 months and stabilized for as long as 26 months thereafter. In phase III trials of patients with acromegaly, only 3.4–3.8 % discontinued pasireotide LAR because of hyperglycemia-related adverse events. In cases in which pasireotide LAR was discontinued, FPG and HbA1c levels returned to baseline. Frequent monitoring of glucose levels is recommended, especially immediately after initiating and discontinuing pasireotide LAR. The treatment strategies suggested herein are made on the basis of available clinical data from healthy volunteers and post hoc analyses of phase III trials. Data from several clinical trials indicate a predictable and possibly reversible hyperglycemic effect that is manageable with proactive monitoring and available antidiabetic medications.
Molecular and Pharmacologic Properties of the Anticancer Quinolone Derivative Vosaroxin: A New Therapeutic Agent for Acute Myeloid Leukemia

Gene C. Jamieson, Judith A. Fox, Ming Poi, Stephen A. Strickland

ABSTRACT

Vosaroxin is a first-in-class anticancer quinolone derivative that targets topoisomerase II and induces site-selective double-strand breaks in DNA, leading to tumor cell apoptosis. Vosaroxin has chemical and pharmacologic characteristics distinct from other topoisomerase II inhibitors due to its quinolone scaffold. The efficacy and safety of vosaroxin in combination with cytarabine were evaluated in patients with relapsed/refractory acute myeloid leukemia (AML) in a phase III, randomized, multicenter, double-blind, placebo-controlled study (VALOR). In this study, the addition of vosaroxin produced a 1.4-month improvement in median overall survival (OS; 7.5 months with vosaroxin/cytarabine vs. 6.1 months with placebo/cytarabine; hazard ratio [HR] 0.87, 95% confidence interval [CI] 0.73–1.02; unstratified log-rank p = 0.061; stratified log-rank p = 0.024), with the greatest OS benefit observed in patients ≥60 years of age (7.1 vs. 5.0 months; HR 0.75, 95% CI 0.62–0.92; p = 0.003) and patients with early relapse (6.7 vs. 5.2 months; HR 0.77, 95% CI 0.59–1.00; p = 0.039), two AML patient groups that typically have poor prognosis. Here we review the chemical and pharmacologic properties of vosaroxin, how these properties are distinct from those of currently available topoisomerase II inhibitors, how they may contribute to the efficacy and safety profile observed in the VALOR trial, and the status of clinical development of vosaroxin for treatment of AML.

Therapeutic Monoclonal Antibodies for the Treatment of Chronic Obstructive Pulmonary Disease

Maria Gabriella Matera, Clive Page, Paola Rogliani, Luigino Calzetta

ABSTRACT

Chronic obstructive pulmonary disease (COPD) is a disorder characterized by a complex chronic inflammatory response that is largely poorly responsive to treatment with corticosteroids. Consequently, there is a huge need to find effective anti-inflammatory agents for the treatment of patients with this disease. Inhibition of cytokines and chemokines or their receptors using monoclonal antibodies (mAbs) could be a potential strategy to treat the inflammatory component of COPD. In this article, we review the therapeutic potential of some of these mAbs; however, to date there has been little or no therapeutic effect of any mAb directed against cytokines or chemokines in patients with COPD. This may reflect the complexity of COPD in which there is no dominant role for any single cytokine or chemokine. It is also likely that since the umbrella term COPD covers many endotypes having different underlying mechanisms, mAbs directed towards specific cytokines or chemokines should be tested in restricted and focused populations.
ABSTRACT

Chronic hand eczema is a common but frequently disabling skin condition which poses a significant social and economic burden. Although skin protection measures and topical therapies are fundamental in its management, some patients are refractory to first-line therapy with topical corticosteroids and require systemic treatment. Alitretinoin (9-cis-retinoic acid; Toctino®) is an endogenous vitamin A derivative with high binding affinity for both retinoic acid receptors and retinoid X receptors. Alitretinoin is the first systemic treatment to be approved in the EU for use in patients with severe chronic hand eczema unresponsive to potent topical corticosteroids. This article updates an earlier review of alitretinoin in this indication, focusing on recently published data. In clinical trials, treatment with alitretinoin 10 or 30 mg once daily for up to 24 weeks improved the severity and extent of severe chronic hand eczema in adults, with significantly more alitretinoin than placebo recipients achieving ratings of ‘clear’ or ‘almost clear’ hands on the Physician Global Impression of Change scale. For the most part, data obtained in real-world studies were consistent with those observed in clinical trials. Alitretinoin was generally well tolerated, with most adverse events being reversible, dose-dependent and of mild or moderate severity. Thus, oral alitretinoin is a useful treatment option for patients with severe chronic hand eczema unresponsive to potent topical corticosteroids.

Efmorococog Alfa: A Review in Haemophilia A

James E. Frampton

ABSTRACT

Efmorococog alfa (Elocta®, Eloctate®, Eloctate™), a first-in-class recombinant factor VIII-Fc fusion protein (rFVIIIIFc), has an extended half-life compared with conventional factor VIII (FVIII) preparations, including recombinant FVIII (rFVIII) products. It is approved for the treatment and prophylaxis of bleeding in patients with haemophilia A in multiple countries worldwide. Data accumulated from pivotal phase III studies (A-LONG in adults and adolescents aged ≥12 years; Kids A-LONG in children aged <12 years) and their ongoing extension study (ASPIRE) have demonstrated the long-term effectiveness of efmorococog alfa for the treatment of acute bleeding episodes, perioperative management and routine prophylaxis in previously treated males with severe haemophilia A. Among patients on individualized efmorococog alfa prophylaxis who had previously received FVIII prophylaxis, all but one of those aged ≥12 years and three-quarters of those aged <12 years reduced their injection frequency compared with their pre-study regimen. FVIII replacement therapy with efmorococog alfa was generally well tolerated in previously treated patients, with no evidence of increased immunogenicity. The safety and efficacy of FVIII replacement therapy with efmorococog alfa in previously untreated males aged <6 years with severe haemophilia A are currently being evaluated. Although there are no direct, head-to-head studies, the available clinical trial evidence indicates that efmorococog alfa provides an effective alternative to conventional FVIII preparations (including rFVIIIs) for the management of haemophilia A. Moreover, by reducing the frequency of injections required, it has the potential to reduce treatment burden, and hence improve adherence to prophylaxis.
Opicapone: A Review in Parkinson’s disease
Lesley J. Scott

ABSTRACT
Oral opicapone (Ongentys®), a potent, third-generation, long-acting, peripheral catechol-O-methyltransferase (COMT) inhibitor, is approved as adjunctive treatment to levodopa (L-Dopa)/dopa-decarboxylase inhibitor (DDCI) therapy in adults with Parkinson’s disease (PD) and end-of-dose motor fluctuations who cannot be stabilized on those combinations. In 14- to 15-week, double-blind, multinational trials and in 1-year, open-label extension studies in this patient population, opicapone was an effective and generally well tolerated adjunctive therapy to L-Dopa plus a DDCI and other PD therapy. During the double-blind phase, adjunctive opicapone 50 mg once daily provided significantly greater improvements in motor fluctuations than placebo, with these improvements noninferior to those with entacapone. These beneficial improvements in motor fluctuations with opicapone were maintained in patients who continued adjunctive opicapone during the extension studies, with patients who switched from placebo or entacapone to opicapone experiencing significant improvements in motor fluctuations during this year. No new unexpected safety concerns were identified after ≈1.4 years’ treatment with opicapone, with no serious cases of hepatotoxicity reported in clinical trials. With its convenient once-daily regimen, oral opicapone is an emerging COMT inhibitor option for use as adjunctive therapy to L-Dopa/DDCI therapy in adults with PD and end-of dose motor fluctuations who cannot be stabilized on those combinations.

Tetravalent Dengue Vaccine: A Review in the Prevention of Dengue Disease
Lesley J. Scott

ABSTRACT
Tetravalent, live-attenuated, dengue vaccine (Dengvaxia®; CYD-TDV) is the first vaccine approved for the prevention of dengue disease caused by dengue virus (DENV) serotypes 1–4 in individuals aged 9–45 or 9–60 years living in high dengue endemic areas. This narrative review discusses the immunogenicity, protective efficacy, reactogenicity and safety of CYD-TDV in the prevention of dengue disease. In Latin American and Asian phase 3 trials in children and adolescents (n > 30,000), the recommended three-dose CYD-TDV regimen was efficacious in preventing virologically-confirmed dengue (VCD) during the period from 28 days after the last dose (month 13) to month 25, meeting the primary endpoint criteria. Protective efficacy against VCD in the respective individual trials was 60.8 and 56.5 % (primary analysis). During the 25-month active surveillance phase, CYD-TDV also provided protective efficacy against VCD, severe dengue, any grade of dengue haemorrhagic fever and VCD-related hospitalization in children aged 9 years and older. CYD-TDV was generally well tolerated, with no safety concerns identified after up to 4 years’ follow-up (i.e. from post dose 1) in ongoing long-term studies. Based on evidence from the dengue clinical trial program, the WHO SAGE recommended that countries with high dengue endemicity consider introducing CYD-TDV as part of an integrated disease prevention strategy to lower disease burden. Pharmacoeconomic considerations will be pivotal to implementing dengue vaccination prevention strategies in these countries. The availability of a dengue vaccine is considered essential if the 2012 WHO global strategy targets for reducing the burden of dengue disease by 2020 are to be attained. Hence, CYD-TDV represents a major advance for the prevention of dengue disease in high dengue endemic regions.
Pitolisant: First Global Approval
Yahiya Y. Syed

ABSTRACT

Pitolisant (Wakix™) is an inverse agonist of the histamine H3 receptor that is being developed by Bioproject. Oral pitolisant is approved in the EU for the treatment of narcolepsy with or without cataplexy in adults. Pitolisant has received a Temporary Authorization of Use in France for this indication in case of treatment failure, intolerance or contraindication to currently available treatment. Pitolisant has orphan drug designation in the EU and the USA. In the pivotal HARMONY I trial, pitolisant significantly decreased excessive daytime sleepiness versus placebo in adults with narcolepsy with or without cataplexy (primary endpoint). Pitolisant also significantly decreased cataplexy rate versus placebo in these patients. This article summarizes the milestones in the development of pitolisant leading to this first approval for narcolepsy.

Vol. 76, Issue 14, September 2016

Second-Line Treatment of Non-Small Cell Lung Cancer: New Developments for Tumours Not Harbouring Targetable Oncogenic Driver Mutations
Paul C. Barnfield, Peter M. Ellis

ABSTRACT

Platinum-based doublet chemotherapy with or without bevacizumab is the standard of care for the initial management of advanced and metastatic non-small cell lung cancer (NSCLC) without a targetable molecular abnormality. However, the majority of patients with NSCLC will ultimately develop resistance to initial platinum-based chemotherapy, and many remain candidates for subsequent lines of therapy. Randomised trials over the past 10–15 years have established pemetrexed (non-squamous histology), docetaxel, erlotinib and gefitinib as approved second-line agents in NSCLC without targetable driver mutations or rearrangements. Trials comparing these agents with other chemotherapy, evaluating the addition of an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) to chemotherapy or the addition of another targeted agent to erlotinib or gefitinib have all failed to demonstrate an improvement in overall survival for patients with NSCLC. In contrast, recent data comparing therapy with novel monoclonal antibodies against programmed cell death 1 (PD-1) or PD ligand (PD-L1) pathway versus standard chemotherapy following platinum failure have demonstrated significant improvements in overall survival. Therapy with nivolumab or pembrolizumab would now be considered standard second-line therapy in patients without contraindication to immune checkpoint inhibitors. Atezolizumab also appears promising in this setting.
Therapeutic Potential of Nitroxyl (HNO) Donors in the Management of Acute 
Degenerated Heart Failure 
Barbara K. Kemp-Harper, John D. Horowitz, Rebecca H. Ritchie 

ABSTRACT 
Heart failure (HF) is a major cause of hospital admission in the Western world, yet there 
remains a paucity of effective pharmacological management options. With the recent 
development of synthetic, next-generation nitroxyl (HNO) donors and their progress into 
clinical trials, it is timely to now provide an update on the therapeutic potential of HNO 
donors in the management of acute decompensated heart failure. In this article, we summarize 
current understanding of the pharmacology of HNO (in comparison with its redox sibling, 
nitric oxide), its spectrum of cardioprotective actions, and efforts to translate these into the 
clinic. Future research directions for this exciting new class of HF drugs are also considered. 

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Androgenetic Alopecia: An Update of Treatment Options 
Yanna Kelly, Aline Blanco, Antonella Tosti 

ABSTRACT 
Androgenetic alopecia (AGA) is characterized by a non-scarring progressive miniaturization 
of the hair follicle in predisposed men and women with a pattern distribution. Although AGA 
is a very prevalent condition, approved therapeutic options are limited. This article discusses 
the current treatment alternatives including their efficacy, safety profile, and quality of 
evidence. Finasteride and minoxidil for male androgenetic alopecia and minoxidil for female 
androgenetic alopecia still are the therapeutic options with the highest level evidence. The 
role of antiandrogens for female patients, the importance of adjuvant therapies, as well as new 
drugs and procedures are also addressed. 

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Fosaprepitant Dimeglumine: A Review in the Prevention of Nausea and Vomiting Associated 
with Chemotherapy 
Karly P. Garnock-Jones 

ABSTRACT 
Intravenous fosaprepitant dimeglumine (Emend® for injection, IVEmend®; henceforth 
referred to as fosaprepitant) is a prodrug of and is rapidly converted to the antiemetic 
aprepitant, and is approved in several countries worldwide (as part of an antiemetic regimen) 
for the prevention of nausea and vomiting associated with highly and moderately emetogenic 
chemotherapy (HEC and MEC). This narrative review discusses the pharmacological 
properties of intravenous fosaprepitant and its clinical efficacy and tolerability in the 
prevention of nausea and vomiting associated with HEC and MEC. In large, randomized 
phase III clinical trials, a single intravenous dose of fosaprepitant 150 mg was an effective 
and generally well tolerated addition to an antiemetic regimen that included dexamethasone 
and a serotonin 5-HT3 receptor antagonist in adult cancer patients undergoing treatment with 
HEC or MEC. It was also noninferior to an oral aprepitant-based regimen in adult cancer 
patients undergoing HEC treatment. The tolerability profile of a fosaprepitant-based regimen 
was typical of that in patients receiving emetogenic chemotherapy, and adverse events were 
generally consistent with those observed with an aprepitant-based regimen. Fosaprepitant 
provides a useful addition to antiemetic therapy regimens.
IncobotulinumtoxinA: A Review in Upper Limb Spasticity

Yvette N. Lamb, Lesley J. Scott

ABSTRACT

Intramuscular incobotulinumtoxinA (Xeomin®) is indicated for the treatment or improvement of adult patients with upper limb spasticity (featured indication), cervical dystonia, blepharospasm and glabellar lines. It is a highly purified formulation of botulinum toxin type A that inhibits acetylcholine signalling at neuromuscular junctions, reducing muscle hypertonia. This narrative review discusses the clinical use of incobotulinumtoxinA in adults with upper limb spasticity and summarizes its pharmacological properties. In single-treatment phase 3 trials, compared with placebo, incobotulinumtoxinA treatment improved muscle tone, global spasticity, functional spasticity-related disability and some aspects of carer burden in adults with upper limb spasticity. These beneficial effects of incobotulinumtoxinA on muscle tone were generally maintained in extension studies, in which up to five additional incobotulinumtoxinA treatments were administered. Functional spasticity-related disability and carer burden were also reduced during longer-term incobotulinumtoxinA treatment. IncobotulinumtoxinA was generally well tolerated in clinical trials, with relatively few patients experiencing treatment-related adverse events, most of which were of mild to moderate intensity. No neutralizing antibodies that would potentially cause secondary nonresponse against incobotulinumtoxinA were detected after single and multiple treatments in these trials or in phase 3 and 4 trials of incobotulinumtoxinA in other indications, which may be an advantage of this purified formulation. Further research would help to more fully determine the impact of neurotoxin purification in terms of reducing the potential risk of immunogenic responses during long-term treatment. Hence, incobotulinumtoxinA is a useful treatment option for upper limb spasticity in adult patients.

Daclatasvir: A Review in Chronic Hepatitis C

Gillian M. Keating

ABSTRACT

The hepatitis C virus (HCV) NS5A replication complex inhibitor daclatasvir (Daklinza®) is indicated for use in combination with sofosbuvir, with or without ribavirin, in a pangenotypic all-oral regimen. In patients with chronic HCV genotype 1 or 3 infection without cirrhosis, a 12-week regimen of daclatasvir plus sofosbuvir achieved high sustained virological response rates 12 weeks’ post-treatment (SVR12), regardless of prior treatment experience, according to the results of the AI444040 and ALLY-3 trials. In the ALLY-3+ trial, high SVR12 rates were achieved with a 12- or 16-week regimen of daclatasvir plus sofosbuvir and ribavirin in patients with chronic HCV genotype 3 infection and advanced fibrosis or compensated cirrhosis. A daclatasvir plus sofosbuvir-based regimen demonstrated efficacy in patients with chronic HCV genotype 1, 3 or 4 infection and advanced cirrhosis or post-transplant recurrence in the ALLY-1 trial, and in patients co-infected with HCV genotype 1, 3 or 4 and HIV-1 in the ALLY-2 trial. Results of clinical trials were supported by real-world data from early-access programmes that included high numbers of patients who would have been excluded from phase 3 trials because of advanced disease and/or concomitant medical conditions. Daclatasvir plus sofosbuvir with or without ribavirin was generally well tolerated. In conclusion, an all-oral regimen comprising daclatasvir plus sofosbuvir with or without ribavirin is an important option for use in treatment-naive or treatment-experienced patients with chronic HCV genotype 1, 3 or 4 infection, including in patients with advanced liver disease, post-transplant recurrence and HIV-1 co-infection.
Trifluridine/Tipiracil: A Review in Metastatic Colorectal Cancer
Celeste B. Burness, Sean T. Duggan

ABSTRACT
Trifluridine/tipiracil (Lonsurf®) is a novel, orally active, antimetabolite agent comprised of trifluridine, a thymidine-based nucleoside analogue, and tipiracil, a potent thymidine phosphorylase inhibitor. Trifluridine is incorporated into DNA via phosphorylation, ultimately inhibiting cell proliferation. Tipiracil increases systemic exposure of trifluridine when coadministered. Trifluridine/tipiracil has recently been approved for the treatment of adult patients with metastatic colorectal cancer (mCRC) who are refractory to or are not considered candidates for, current standard chemotherapy and biological therapy in the EU and USA and in unresectable advanced or recurrent CRC in Japan. The approved regimen of oral twice-daily trifluridine/tipiracil (35 mg/m² twice daily on days 1–5 and 8–12 of each 28-day cycle) significantly improved overall survival and progression-free survival and was associated with a significantly higher disease control rate than placebo when added to best supportive care in the multinational, pivotal phase III trial (RECOURSE) and a phase II Japanese trial. Trifluridine/tipiracil was associated with an acceptable tolerability profile, with adverse events generally being managed with dose reductions, temporary interruptions in treatment or administration of granulocyte-colony stimulating factor. The most common grade 3–4 adverse events (≥10 %) were anaemia, neutropenia, thrombocytopenia and leukopenia. In conclusion, trifluridine/tipiracil is a useful additional treatment option for the management of mCRC in patients who are refractory to, or are not considered candidates for, currently available therapies.

Brodalumab: First Global Approval
Sarah L. Greig

ABSTRACT
Brodalumab (Lumicef®) is a human monoclonal immunoglobulin G antibody that is being developed by Kyowa Hakko Kirin in Japan, where it has been approved for the treatment of psoriasis vulgaris, psoriatic arthritis, pustular psoriasis and psoriatic erythroderma. Brodalumab binds with high affinity to interleukin (IL)-17 receptor A, thereby inhibiting several pro-inflammatory cytokines from the IL-17 family. Regulatory applications for brodalumab in plaque psoriasis are also under review in the USA, EU and Canada. This article summarizes the milestones in the development of brodalumab leading to this first approval for the treatment of psoriasis.
Biosimilar Monoclonal Antibodies for Inflammatory Bowel Disease: Current Comfort and Future Prospects
Krisztina B. Gecse, Péter L. Lakatos

ABSTRACT
Biosimilars are biologic medicines that enter the market after a patent for an original reference product expires. The European Medicines Agency (EMA) developed a stringent legislation process for biosimilar monoclonal antibodies, whereby similarity to the reference medicinal product in terms of quality characteristics, biological activity, clinical safety and efficacy must be demonstrated. Biosimilar infliximab CT-P13 was the first biosimilar monoclonal antibody to receive EMA marketing authorization, and further biosimilar molecules are being developed. The phase I and III clinical trials were conducted in ankylosing spondylitis and rheumatoid arthritis, and the use of CT-P13 in inflammatory bowel disease (IBD) was extrapolated on the results of these trials. Medical professionals were initially concerned about the reversed engineering process, the novel legal framework and the lack of clinical data in IBD. Emerging real-world data have confirmed the similarities between CT-P13 and the reference product in terms of efficacy, safety and immunogenicity in IBD. The cost reduction represented by biosimilars promotes industry competition and improves treatment access with sustained quality of care. This article reviews the existing and emerging clinical data for CT-P13 and a future perspective on biosimilar use in IBD.

Predictors of Response to Multiple Sclerosis Therapeutics in Individual Patients
Harald Hegen, Michael Auer, Florian Deisenhammer

ABSTRACT
Multiple sclerosis (MS) is a chronic inflammatory disorder of the central nervous system. Several disease-modifying therapies have been shown to ameliorate the disease course; however, the individual treatment response and the occurrence of adverse events remain highly unpredictable. In the last 2 decades, a multitude of studies have aimed to identify biomarkers that enable treatment allocation in the individual patient or subgroup of patients with regard to treatment efficacy and safety profile. Following a PubMed database search, we provide an overview on what is presently known about body fluid markers for the prediction of response to the currently approved MS therapeutics. We also discuss the potential use of biomarkers with regard to drug-induced adverse events. To date, only a few molecules have been introduced in clinical routine: anti-drug antibodies against interferon (IFN)-β and natalizumab that are associated with abolished drug levels and treatment failure; anti-JC virus (JCV) antibody index that allows risk stratification for the development of progressive multifocal leukoencephalopathy (PML), a rare but severe adverse event during natalizumab treatment; and serostatus of varicella zoster virus as screening examination prior to fingolimod therapy to prevent the infection. A few candidate biomarkers still need closer examination, such as type I IFN signature and T-helper cell (Th)-17 reactivity for prediction of IFN-β treatment response, L-selectin expression for prediction of natalizumab-associated PML, interleukin (IL)-21 levels for prediction of secondary autoimmunity after exposure to alemtuzumab, lymphocyte count with regard to PML risk while receiving dimethyl fumarate or N-terminal-pro-B-type natriuretic peptide (NT-proBNP) for monitoring of cardiac side effects during mitoxantrone therapy.
Patient-Centered Interventions to Improve Adherence to Statins: A Narrative Synthesis of Systematically Identified Studies

Magnus Jörntén-Karlsson, Stéphane Pintat, Michael Molloy-Bland, Staffan Berg

ABSTRACT

Poor adherence to statins increases cardiovascular disease risk. We systematically identified 32 controlled studies that assessed patient-centered interventions designed to improve statin adherence. The limited number of studies and variation in study characteristics precluded strict quality criteria or meta-analysis. Cognitive education or behavioural counselling delivered face-to-face multiple times consistently improved statin adherence compared with control groups (7/8 and 3/3 studies, respectively). None of four studies using medication reminders and/or adherence feedback alone reported significantly improved statin adherence. Single interventions that improved statin adherence but were not conducted face-to-face included cognitive education in the form of genetic test results (two studies) and cognitive education via a website (one study). Similar mean adherence measures were reported for 17 intervention arms and were thus compared in a sub-analysis: 8 showed significantly improved statin adherence, but effect sizes were modest (+7 to +22 % points). In three of these studies, statin adherence improved despite already being high in the control group (82–89 vs. 57–69 % in the other studies). These three studies were the only studies in this sub-analysis to include cognitive education delivered face-to-face multiple times (plus other interventions). In summary, the most consistently effective interventions for improving adherence to statins have modest effects and are resource-intensive. Research is needed to determine whether modern communications, particularly mobile health platforms (recently shown to improve medication adherence in other chronic diseases), can replicate or even enhance the successful elements of these interventions while using less time and fewer resources.

Intravenous Minocycline: A Review in Acinetobacter Infections

Sarah L. Greig, Lesley J. Scott

ABSTRACT

Intravenous minocycline (Minocin®) is approved in the USA for use in patients with infections due to susceptible strains of Gram-positive and Gram-negative pathogens, including infections due to Acinetobacter spp. Minocycline is a synthetic tetracycline derivative that was originally introduced in the 1960s. A new intravenous formulation of minocycline was recently approved and introduced to address the increasing prevalence of multidrug-resistant (MDR) pathogens. Minocycline shows antibacterial activity against A. baumannii clinical isolates worldwide, and exhibits synergistic bactericidal activity against MDR and extensively drug-resistant (XDR) A. baumannii isolates when combined with other antibacterial agents. In retrospective studies, intravenous minocycline provided high rates of clinical success or improvement and was generally well tolerated among patients with MDR or carbapenem-resistant A. baumannii infections. While randomized clinical trial data would be useful to fully establish the place of minocycline in the management of these infections for which there are currently very few available options, clinical trials in patients with infections due to Acinetobacter spp. are difficult to perform. Nevertheless, current data indicate a potential role for intravenous minocycline in the treatment of patients MDR A. baumannii infections, particularly when combined with a second antibacterial agent (e.g. colistin).
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Apixaban: A Review in Venous Thromboembolism
Sarah L. Greig, Karly P. Garnock-Jones

ABSTRACT
Apixaban (Eliquis®) is an oral, direct factor Xa inhibitor that is available for use in the treatment and secondary prevention of venous thromboembolism (VTE). Like other direct oral anticoagulants (DOACs), apixaban has generally predictable pharmacological properties and does not require routine anticoagulation monitoring. In large phase III trials, oral apixaban was noninferior to subcutaneous enoxaparin sodium overlapped with and followed by oral warfarin (enoxaparin/warfarin) in the treatment of adults with acute VTE over 6 months with regard to the incidence of recurrent VTE or VTE-related death (AMPLIFY), and was significantly more effective than placebo in the prevention of recurrent VTE or all-cause mortality over 12 months in patients who had completed 6–12 months’ anticoagulation treatment for VTE (AMPLIFY-EXT). Apixaban was generally well tolerated in these trials; the risks of major bleeding and the composite endpoint of major or clinically relevant nonmajor (CRNM) bleeding with apixaban were significantly lower than enoxaparin/warfarin in AMPLIFY and not significantly different from that of placebo in AMPLIFY-EXT. Similarly, in Japanese adults with acute VTE (AMPLIFY-J), apixaban was associated with a significantly lower risk of major or CRNM bleeding than unfractionated heparin plus warfarin, and no cases of recurrent VTE or VTE-related death over 24 weeks. Thus, apixaban is useful therapeutic alternative for the management of adults with VTE.

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Chronotherapy: Intuitive, Sound, Founded…But Not Broadly Applied
Julia M. Selfridge, Tetsuya Gotoh, Samuel Schiffhauer, JingJing Liu

ABSTRACT
Circadian rhythms are a collection of endogenously driven biochemical, physiological, and behavioral processes that oscillate in a 24-h cycle and can be entrained by external cues. Circadian clock molecules are responsible for the expression of regulatory components that modulate, among others, the cell’s metabolism and energy consumption. In clinical practice, the regulation of clock mechanisms is relevant to biotransformation of therapeutics. Accordingly, xenobiotic metabolism and detoxification, the two processes that directly influence drug effectiveness and toxicity, are direct manifestations of the daily oscillations of the cellular and biochemical processes taking place within the gastrointestinal, hepatic/biliary, and renal/urologic systems. Consequently, the impact of circadian timing should be factored in when developing therapeutic regimens aimed at achieving maximum efficacy, minimum toxicity, and decreased adverse effects in a patient. However, and despite a strong mechanistic foundation, only 0.16% of ongoing clinical trials worldwide exploit the concept of ‘time-of-day’ administration to develop safer and more effective therapies. In this article, we (1) emphasize points of control at which circadian biology intersects critical processes governing treatment interventions; (2) explore the extent to which chronotherapeutics are incorporated into clinical trials; (3) recognize roadblocks; and (4) recommend approaches to precipitate the integration of chronobiological concepts into clinical practice.
Collagenase *Clostridium Histolyticum* for the Treatment of Peyronie’s Disease: A ‘Real World’ Clinical Perspective

James Anaissie, Wayne J. G. Hellstrom, Faysal A. Yafi

**ABSTRACT**

The introduction of collagenase Clostridium histolyticum (CCH) as a treatment option for Peyronie’s disease (PD), defined as the abnormal formation of collagen on the tunica albuginea of the penis, has provided patients with a promising new conservative therapy. Studies have shown that CCH improves curvature by an average of 17°, and although patient and sexual partner satisfaction is high, the improvement has arguable clinical implications. Similarly, the efficacy and cost of CCH contrasts strongly with more invasive surgical management, and is further limited by rare, but serious, complications and several contraindications. The future of CCH involves well-designed trials analyzing the effects of CCH on patients who are currently not indicated for therapy, and the optimal amount of treatment for the most efficient treatment possible. CCH provides a promising treatment option for patients who do not desire invasive management, but need further trials to fully elucidate its treatment implications.

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**Drug Treatment of Hypertension: Focus on Vascular Health**

Alan C. Cameron, Ninian N. Lang, Rhian M. Touyz

**ABSTRACT**

Hypertension, the most common preventable risk factor for cardiovascular disease and death, is a growing health burden. Serious cardiovascular complications result from target organ damage including cerebrovascular disease, heart failure, ischaemic heart disease and renal failure. While many systems contribute to blood pressure (BP) elevation, the vascular system is particularly important because vascular dysfunction is a cause and consequence of hypertension. Hypertension is characterised by a vascular phenotype of endothelial dysfunction, arterial remodelling, vascular inflammation and increased stiffness. Antihypertensive drugs that influence vascular changes associated with high BP have greater efficacy for reducing cardiovascular risk than drugs that reduce BP, but have little or no effect on the adverse vascular phenotype. Angiotensin converting enzyme ACE inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) improve endothelial function and prevent vascular remodelling. Calcium channel blockers also improve endothelial function, although to a lesser extent than ACEIs and ARBs. Mineralocorticoid receptor blockers improve endothelial function and reduce arterial stiffness, and have recently become more established as antihypertensive drugs. Lifestyle factors are essential in preventing the adverse vascular changes associated with high BP and reducing associated cardiovascular risk. Clinicians and scientists should incorporate these factors into treatment decisions for patients with high BP, as well as in the development of new antihypertensive drugs that promote vascular health.
The Impact of Shortages on Medication Prices: Implications for Shortage Prevention
Michail Alevizakos, Marios Detsis, Christos A. Grigoras, Jason T. Machan

ABSTRACT

Background: Medication shortages are frequent and have clinical and financial ramifications; however, their effect on drug prices remains unknown.

Objective: To examine price progression of medications affected by a shortage.

Methods: We collected prices of medications covered under Medicare Part B, reflective of general market prices, and data on clinically relevant shortages for the period 2005–16. We used linear mixed-effects models to examine the price growth of affected medications.

Results: Shortage medications demonstrated a quarterly price growth of \(-0.5\%\) (95% confidence interval [CI] \(-1.6, 0.6\)) in the period preceding a shortage, 4.3% (95% CI 3.6, 4.5) during a shortage, and 4.1% (95% CI 2.6, 5.5) in the post-shortage period. Medications not affected by a shortage had a quarterly price growth of 0.2% (95% CI \(-0.3, 0.6\)).

Conclusions: Medication shortages are associated with price increases, and these increases are likely reactive to the low profitability of the affected medications and thus, proactive collaboration between the US Food and Drug Administration and industry can serve to identify low-profit drugs and evaluate measures to ensure continued production.

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Paliperidone Palmitate Intramuscular 3-Monthly Formulation: A Review in Schizophrenia
Yvette N. Lamb, Gillian M. Keating

ABSTRACT

A 3-monthly formulation of intramuscular paliperidone palmitate (3-monthly paliperidone palmitate) has recently been approved for the maintenance treatment of schizophrenia in adult patients in the EU (Trevicta®), following earlier approval in the USA (Invega Trinza®). This narrative review discusses the clinical use of 3-monthly paliperidone palmitate in the maintenance treatment of schizophrenia in adult patients and summarizes its pharmacological properties. The efficacy of the 3-monthly paliperidone palmitate formulation as a maintenance treatment for schizophrenia has been demonstrated in well designed, phase III trials. Three-monthly paliperidone palmitate was more effective than placebo in delaying time to relapse and reducing relapse rates, and was noninferior to 1-monthly paliperidone palmitate in the proportion of patients that remained relapse-free. The 3-monthly formulation was also more effective than placebo in controlling the symptoms of schizophrenia, whilst not differing significantly from the 1-monthly formulation in terms of symptomatic control. Three-monthly paliperidone palmitate was generally well tolerated in clinical trials, with a tolerability profile consistent with that of the 1-monthly formulation. In conclusion, 3-monthly paliperidone palmitate is a useful treatment option for adult patients with schizophrenia who are adequately treated with the 1-monthly formulation, particularly for those who would prefer, or may benefit from, longer dosing intervals.
Sofosbuvir/Velpatasvir: A Review in Chronic Hepatitis C
Sarah L. Greig

ABSTRACT
A once-daily, single-tablet, pangenotypic regimen comprising the hepatitis C virus (HCV) NS5B polymerase inhibitor sofosbuvir and the HCV NS5A inhibitor velpatasvir (sofosbuvir/velpatasvir; Epclusa®) was recently approved for the treatment of adults with chronic HCV genotype 1, 2, 3, 4, 5 or 6 infection in the USA, EU and Canada. In the phase III ASTRAL trials, once-daily oral sofosbuvir/velpatasvir for 12 weeks provided very high rates of sustained virological response at 12 weeks post treatment (SVR12) in treatment-naive and -experienced patients with chronic HCV genotype 1–6 infection, including those with compensated cirrhosis or HIV-1 co-infection. High SVR12 rates were also observed with sofosbuvir/velpatasvir plus ribavirin for 12 weeks in patients with chronic HCV genotype 1–6 infection and decompensated cirrhosis. Sofosbuvir/velpatasvir was generally well tolerated, with low rates of adverse events. Thus, sofosbuvir/velpatasvir represents a valuable treatment option in adults with chronic HCV genotype 1–6 infection, including those with compensated or decompensated cirrhosis, previous treatment experience or HIV-1 co-infection.

Pixantrone: A Review in Relapsed or Refractory Aggressive Non-Hodgkin’s Lymphoma
Gillian M. Keating

ABSTRACT
Pixantrone (Pixuvri®) is an aza-anthracenedione with a novel mode of action that is conditionally approved in the EU for use as monotherapy in adult patients with multiply relapsed or refractory aggressive B-cell non-Hodgkin’s lymphoma (NHL). In the randomized, open-label, multinational, phase 3 PIX301 trial in patients with multiply relapsed or refractory aggressive NHL, the complete response (CR) plus unconfirmed CR (uCR) rate at the end of treatment (primary endpoint) was significantly higher with intravenous pixantrone monotherapy than with a single-agent comparator (vinorelbine, oxaliplatin, ifosfamide, etoposide, mitoxantrone or gemcitabine). Post hoc analysis also demonstrated a significantly higher CR/uCR rate in the subgroup of patients with centrally confirmed aggressive B-cell NHL who were receiving pixantrone versus a comparator agent as third- or fourth-line therapy. Pixantrone was generally well tolerated in PIX301, with a manageable adverse event profile. In conclusion, pixantrone is a useful option in patients with multiply relapsed or refractory aggressive B-cell NHL. Further results examining the use of pixantrone in combination with rituximab in patients previously treated with rituximab-containing regimens are awaited with interest.

Florence Herr, Melanie Brunel, Nathalie Roders, Antoine Durrbach

ABSTRACT

Long-term survival of solid allografts depends on both immunosuppressive efficacy and reducing the side effects associated with these therapies. Immunotherapies developed over the past 15 years to prevent organ rejection have greatly improved cardiovascular and renal function compared with classical therapies, such as calcineurin inhibitors and corticosteroids. Immunotherapies that target T cells through the co-stimulation blockade (CTLA-4-Ig) improve renal function and the survival of grafts and patients, but are associated with higher rates of T-cell-mediated acute rejection. Improvements to safe and efficacious therapeutic options could combine a co-stimulation blockade with a depleting immunotherapy. Herein, we describe the clinical outcomes and the likely causes of defects in the co-stimulation blockade, and comment on new therapeutic strategies to overcome these. Great progress has been made to optimize immunotherapy using the co-stimulation blockade, but the therapeutic combinations should be assessed further.

Treating the Underlying Pathophysiology of Primary Sjögren Syndrome: Recent Advances and Future Prospects

Pilar Brito-Zerón, Soledad Retamozo, Hoda Gheitasi, Manuel Ramos-Casals

ABSTRACT

Sjögren Syndrome (SS) is a systemic autoimmune disease with a wide clinical spectrum that extends from sicca symptoms of the mucosal surfaces to extra-glandular systemic manifestations. Understanding of the pathophysiology of primary SS has advanced over recent years, and this, in turn, has presented new targeted treatment options. We provide a brief, up-to-date description of the pathophysiology of SS and the main etiopathogenic pathways implicated in the disease process and review clinical evidence in support of new treatment options targeting these pathways, highlighting successes and failures, and concluding with a summary of gaps in knowledge and where future research should be focused. Direct and indirect B-cell targeted therapies are currently the most promising biological agents in primary SS, especially for systemic involvement, but other pathways (T-cell co-stimulation, cytokine-based therapies, intracellular pathways and gene therapies) are under development. The next 10 years may witness a disruptive therapeutic scenario in primary SS.
ABSTRACT

Congenital human cytomegalovirus (HCMV) infection can result in severe and permanent neurological injury in newborns, and vaccine development is accordingly a major public health priority. HCMV can also cause disease in solid organ transplant (SOT) and hematopoietic stem-cell transplant (HSCT) recipients, and a vaccine would be valuable in prevention of viremia and end-organ disease in these populations. Currently there is no licensed HCMV vaccine, but progress toward this goal has been made in recent clinical trials. A recombinant HCMV glycoprotein B (gB) vaccine has been shown to have some efficacy in prevention of infection in young women and adolescents, and has provided benefit to HCMV-seronegative SOT recipients. Similarly, DNA vaccines based on gB and the immunodominant T-cell target, pp65 (ppUL83), have been shown to reduce viremia in HSCT patients. This review provides an overview of HCMV vaccine candidates in various stages of development, as well as an update on the current status of ongoing clinical trials. Protective correlates of vaccine-induced immunity may be different for pregnant woman and transplant patients. As more knowledge emerges about correlates of protection, the ultimate licensure of HCMV vaccines may reflect the uniqueness of the target populations being immunized.

Isavuconazole: A Review in Invasive Aspergillosis and Mucormycosis

Matt Shirley, Lesley J. Scott

ABSTRACT

Isavuconazole is a second-generation triazole with activity against a broad spectrum of clinically important fungi. Its water-soluble prodrug, isavuconazonium sulfate (Cresemba®), available in interchangeable intravenous and oral formulations, is approved in the USA and EU for the treatment of adults with invasive aspergillosis and mucormycosis. In international phase III clinical trials, isavuconazole was efficacious and generally well tolerated in the treatment of these life-threatening diseases. In the phase III SECURE trial, isavuconazole was non-inferior to voriconazole for the primary treatment of invasive mould disease (primarily aspergillosis) and was associated with fewer drug-related treatment-emergent adverse events (TEAEs) than voriconazole. In addition, the single-arm, phase III VITAL trial and a matched case–control analysis of isavuconazole- versus amphotericin B-treated patients provided evidence of the efficacy of isavuconazole in the treatment of mucormycosis. The most commonly reported TEAEs among isavuconazole recipients were gastrointestinal disorders such as nausea, vomiting and diarrhea. Isavuconazole has several other attributes that make it a useful new treatment option for these invasive mould diseases, including predictable pharmacokinetics, excellent bioavailability, no food effect with the oral formulation, and its potential utility in renally impaired patients given the absence of cyclodextrin in the intravenous formulation.
Vortioxetine: A Review in Cognitive Dysfunction in Depression

James E. Frampton

ABSTRACT

Vortioxetine (Brintellix®; Trintellix®), a generally efficacious and well tolerated antidepressant agent, is approved in the EU and USA for the treatment of major depressive disorder (MDD) in adults. The drug has a distinctive pharmacological profile (combining inhibition of the serotonin transporter with modulation of multiple serotonin receptors) and has been shown to enhance cognitive performance in various animal models and clinical trials. Across three large, placebo-controlled studies in adults with recurrent MDD, short-term treatment with vortioxetine almost always resulted in statistically significant and clinically meaningful improvements in performance on two objective measures (the Digit Symbol Substitution Test and Rey Auditory Verbal Learning Test) that together cover a broad range of cognitive domains, including executive function, attention, processing speed, learning and memory. Vortioxetine also significantly improved a subjective measure of cognitive function (the Perceived Deficits Questionnaire) and an objective measure of functional capacity (the University of San Diego performance-based skills assessment). In general, the beneficial effects of vortioxetine on these measures were largely independent of its effect on improving depressive symptoms. Based on the available data, therefore, vortioxetine is a useful treatment option in patients with MDD where impaired cognitive function is apparent.
Zoledronic Acid (Reclast®, Aclasta®): A Review in Osteoporosis
Sohita Dhillon

ABSTRACT
Zoledronic acid (Reclast®, Aclasta®) is an intravenous, highly potent aminobisphosphonate approved worldwide, including in the USA, EU and Japan for use in patients with primary or secondary osteoporosis or low bone mass (approved indications vary between countries). Its high affinity to and long half-life in bone, and long duration of action, allow for once-yearly administration, which has the potential to improve adherence to therapy. Zoledronic acid once yearly for up to 3 years improved bone mineral density (BMD) at several skeletal sites, reduced fracture risk and bone turnover, and/or preserved bone structure and mass relative to placebo in clinical studies in patients with primary or secondary osteoporosis. While additional benefits were seen when treatment was continued for up to 6 years, as evidenced by a reduced risk of vertebral fractures and higher BMD relative to 3 years’ therapy, there was minimal advantage of treatment beyond 6 years. Therefore, in patients with low fracture risk, treatment discontinuation should be considered after approximately 5 years’ therapy. Zoledronic acid administered annually or once in 2 years was also effective in preventing bone loss in patients with low bone mass. Zoledronic acid was generally well tolerated, with the most common adverse events (AEs) being transient, mild-to-moderate post-infusion symptoms, which decreased with subsequent infusions. To conclude, zoledronic acid once yearly is an effective and generally well tolerated treatment option for patients with osteoporosis.

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Management of Post-Liver Transplant Recurrence of Hepatitis C
Justin Taylor, Paula Cox-North, Charles S. Landis

ABSTRACT
Cirrhosis due to chronic hepatitis C (HCV) is the leading indication for liver transplantation in North America and Europe. HCV re-infection post-transplant is nearly universal and if left untreated negatively affects patient and graft survival. Until recently, treatment options for HCV were limited to interferon (IFN)-based therapies which had low sustained viral response (SVR) rates and were poorly tolerated in the post-transplant setting. In the last 3 years, the promise of the directly acting antivirals (DAAs) for the treatment of HCV has been fulfilled with high sustained viral response (SVR) rates and a low side effect profile demonstrated in both registration trials and real-world studies. This innovation has allowed post-liver transplant patients with HCV recurrence access to interferon-free therapies with extraordinary efficacy, safety, tolerability, and fewer drug–drug interactions.

Etelcalcetide: First Global Approval
Hannah A. Blair

ABSTRACT
Etelcalcetide (Parsabiv™) is a novel second generation calcimimetic agent developed by Amgen for the treatment of secondary hyperparathyroidism (SHPT), a complication of chronic kidney disease (CKD). Etelcalcetide reduces circulating levels of parathyroid hormone and calcium by binding directly to the calcium-sensing receptor. Intravenous etelcalcetide has been approved in the EU for the treatment of SHPT in adult patients with CKD on haemodialysis therapy. Regulatory applications for etelcalcetide in SHPT are also under review in the USA and Japan. This article summarizes the milestones in the development of etelcalcetide leading to this first global approval for the treatment of SHPT.
Comparative Pharmacology and Guide to the Use of the Serotonin 5-HT₃Receptor Antagonists for Postoperative Nausea and Vomiting

Anthony L. Kovac

ABSTRACT

Since the introduction of the serotonin 5-hydroxy tryptamine 3 (5-HT₃) receptor antagonists in the early 1990s, the incidence of postoperative nausea and vomiting (PONV) and post-discharge nausea and vomiting (PDNV) has decreased, yet continues to be a problem for the surgical patient. The clinical application of the 5-HT₃ receptor antagonists has helped define the approach and role of these antiemetics in the prevention and treatment of PONV and PDNV. Pharmacological and clinical differences exist among these medications resulting in corresponding differences in effectiveness, safety, optimal dosage, time of administration, and use as combination and rescue antiemetic therapy. The clinical application of the 5-HT₃ receptor antagonist antiemetics has improved the prevention and treatment of PONV and PDNV. The most recent consensus guidelines for PONV published in 2014 outline the use of these antiemetics. The 5-HT₃ receptor antagonists play an important role to help prevent PONV and PDNV in perioperative care pathways such as Enhanced Recovery After Surgery (ERAS). Comparisons and guidelines for use of the 5-HT₃ receptor antagonists in relation to the risk for PONV and PDNV are reviewed.

Oxycodone DETERx® ER Capsules: A Review in Severe, Chronic Pain

Yvette N. Lamb, Karly P. Garnock-Jones, Susan J. Keam

ABSTRACT

Oxycodone DETERx® extended-release (ER) capsules (Xtampza® ER), an abuse-deterrent formulation of oxycodone as the myristate salt, are approved in the USA for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. This narrative review discusses the clinical efficacy and tolerability of the oxycodone DETERx® ER capsule formulation in the management of severe pain, and provides an overview of pharmacokinetics, abuse-deterrent properties and alternative administration options. The microsphere-in-capsule DETERx® drug delivery platform allows administration via sprinkle-dosing or enteral tubes. The physicochemical properties of the formulation make it difficult to manipulate and its ER pharmacokinetic profile is retained after crushing or chewing. Clinical abuse-potential studies suggest these properties may translate to reduced intranasal abuse, with implications for abuse via the oral route less certain. The efficacy of oxycodone DETERx® ER in the management of moderate to severe, chronic pain was demonstrated in a well designed, phase III trial, in which it was more effective than placebo at reducing pain intensity. The formulation was generally well tolerated in this trial; the most common treatment-emergent adverse events were nausea and constipation. As an opioid, oxycodone DETERx® ER carries risks of addiction, abuse and misuse. Post-marketing epidemiological studies will be necessary in determining the impact of oxycodone DETERx® on oxycodone abuse liability. Nevertheless, oxycodone DETERx® ER is a useful treatment option for patients with severe, chronic pain, particularly when comorbid dysphagia or difficulty swallowing is a concern.
Solithromycin: A Novel Fluoroketolide for the Treatment of Community-Acquired Bacterial Pneumonia

George G. Zhanel, Erika Hartel, Heather Adam, Sheryl Zelenitsky, Michael A. Zhanel

ABSTRACT

Solithromycin is a novel fluoroketolide developed in both oral and intravenous formulations to address increasing macrolide resistance in pathogens causing community-acquired bacterial pneumonia (CABP). When compared with its macrolide and ketolide predecessors, solithromycin has several structural modifications which increase its ribosomal binding and reduce its propensity to known macrolide resistance mechanisms. Solithromycin, like telithromycin, affects 50S ribosomal subunit formation and function, as well as causing frame-shift errors during translation. However, unlike telithromycin, which binds to two sites on the ribosome, solithromycin has three distinct ribosomal binding sites. Its desosamine sugar interacts at the A2058/A2059 clef in domain V (as all macrolides do), an extended alkyl-aryl side chain interacts with base pair A752-U2609 in domain II (similar to telithromycin), and a fluorine at C-2 of solithromycin provides additional binding to the ribosome. Studies describing solithromycin activity against Streptococcus pneumoniae have reported that it does not induce erm-mediated resistance because it lacks a cladinose moiety, and that it is less susceptible than other macrolides to mef-mediated efflux due to its increased ribosomal binding and greater intrinsic activity. Solithromycin has demonstrated potent in vitro activity against the most common CABP pathogens, including macrolide-, penicillin-, and fluoroquinolone-resistant isolates of S. pneumoniae, as well as Haemophilus influenzae and atypical bacterial pathogens. Solithromycin displays multi-compartment pharmacokinetics, a large volume of distribution (>500 L), approximately 67% bioavailability when given orally, and serum protein binding of 81%. Its major metabolic pathway appears to follow cytochrome P450 (CYP) 3A4, with metabolites of solithromycin undergoing biliary excretion. Its serum half-life is approximately 6–9 h, which is sufficient for once-daily administration. Pharmacodynamic activity is best described as fAUC0–24/MIC (the ratio of the area under the free drug concentration–time curve from 0 to 24 h to the minimum inhibitory concentration of the isolate). Solithromycin has completed one phase II and two phase III clinical trials in patients with CABP. In the phase II trial, oral solithromycin was compared with oral levofloxacin and demonstrated similar clinical success rates in the intention-to-treat (ITT) population (84.6 vs 86.6%). Clinical success in the clinically evaluable patients group was 83.6% of patients receiving solithromycin compared with 93.1% for patients receiving levofloxacin. In SOLITAIRE-ORAL, a phase III trial which assessed patients receiving oral solithromycin or oral moxifloxacin for CABP, an equivalent (non-inferior) early clinical response in the ITT population was demonstrated for patients receiving either solithromycin (78.2%) or moxifloxacin (77.9%). In a separate phase III trial, SOLITAIRE-IV, patients receiving intravenous-to-oral solithromycin (79.3%) demonstrated non-inferiority as the primary outcome of early clinical response in the ITT population compared with patients receiving intravenous-to-oral moxifloxacin (79.7%). Overall, solithromycin has been well tolerated in clinical trials, with gastrointestinal adverse events being most common, occurring in approximately 10% of patients. Transaminase elevation occurred in 5–10% of patients and generally resolved following cessation of therapy. None of the rare serious adverse events that occurred with telithromycin (i.e., hepatotoxicity) have been noted with solithromycin, possibly due to the fact that solithromycin (unlike telithromycin) does not possess a pyridine moiety in its chemical structure, which has been implicated in inhibiting nicotinic acetylcholine receptors.
ABSTRACT

The multiple tyrosine kinase inhibitors (TKI) cabozantinib (Cabometyx™) is approved in the USA for the treatment of patients with advanced renal cell carcinoma (RCC) who have received prior antiangiogenic therapy. In the EU, cabozantinib is indicated for the treatment of advanced RCC in adults following prior vascular endothelial growth factor (VEGF)-targeted therapy. In adults with advanced or metastatic clear-cell RCC who had previously received VEGF receptor (VEGFR) TKIs, progression-free survival (PFS) and overall survival (OS) were significantly prolonged in patients who received oral cabozantinib versus oral everolimus in the pivotal METEOR trial. Objective response was achieved in a significantly higher proportion of patients receiving cabozantinib than those receiving everolimus. Cabozantinib had a manageable adverse events profile in patients with advanced RCC. Thus, cabozantinib is an important new option for use in patients with advanced RCC who have previously received antiangiogenic therapy.

Granisetron Extended-Release Injection: A Review in Chemotherapy-Induced Nausea and Vomiting

Emma D. Deeks

ABSTRACT

An extended-release (ER) subcutaneously injectable formulation of the first-generation 5-HT3 receptor antagonist granisetron is now available in the USA (Sustol®), where it is indicated for the prevention of acute and delayed chemotherapy-induced nausea and vomiting (CINV) following moderately emetogenic chemotherapy (MEC) or anthracycline and cyclophosphamide combination chemotherapy regimens in adults. Granisetron ER is administered as a single subcutaneous injection and uses an erosion-controlled drug-delivery system to allow prolonged granisetron release. Primary endpoint data from phase III studies after an initial cycle of chemotherapy indicate that, when used as part of an antiemetic regimen, granisetron ER injection is more effective than intravenous ondansetron in preventing delayed CINV following highly emetogenic chemotherapy (HEC); is noninferior to intravenous palonosetron in preventing both acute CINV following MEC or HEC and delayed CINV following MEC; and is similar, but not superior, to palonosetron in preventing delayed CINV following HEC. The benefits of granisetron ER were seen in various patient subgroups, including those receiving anthracycline plus cyclophosphamide-based HEC, and (in an extension of one of the studies) over multiple MEC or HEC cycles. Granisetron ER injection is generally well tolerated, with an adverse event profile similar to that of ondansetron or palonosetron. Thus, granisetron ER injection expands the options for preventing both acute and delayed CINV in adults with cancer receiving MEC or anthracycline plus cyclophosphamide-based HEC.

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