Volume 2 • Number 4 • 2006

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The fourth issue of volume two of *Therapeutics and Clinical Risk Management* contains twelve review articles from international authors that address a broad range of current and apposite topics within the remit of the journal.

Glaucoma is a multifactorial optic neuropathy that results in progressive vision loss secondary to optic nerve atrophy and a reduction in retinal ganglion cells (RCGs). Raised intraocular pressure (IOP) has been identified as a major risk factor in both the development and progression of the condition. Hence, a primary aim of glaucoma therapy is to effect a reduction in IOP to attenuate the risk of disease progression and loss of vision; a strategy whose effectiveness has been demonstrated through recent randomized, controlled clinical trials (RCTs). Brimonidine is the only selective alpha-adrenergic receptor agonist currently approved for chronic use in glaucoma and has established efficacy as mono-, adjunct, and replacement therapy in the treatment of ocular hypertension and open-angle glaucoma. Louis Cantor opens this issue with a consideration of the pharmacology, pharmacokinetics, and mechanism of action of topical brimonidine. Cantor's review continues with an assessment of clinical trials of brimonidine in neuroprotection, the primary goal of which is the attenuation of neuronal death and preservation of physiological function; a strategy that enables treatment even in cases of unknown etiology. In addition, the author discusses the different drug formulations available, brimonidine's clinical efficacy in IOP reduction, and addresses issues of safety and tolerability and patient acceptability and compliance.

Asthma is a complex syndrome, characterized by a variable degree of airway obstruction, with many clinical phenotypes in both adults and children. Despite improvements in asthma treatment and increased understanding of the underlying pathogenic mechanisms, the incidence and prevalence of asthma have been rising worldwide. Asthma is now the most common disease in westernized countries. Although the cause of the increase is unknown, it is clear that environmental triggers play an important role. The majority of allergic asthmatic children are sensitive to indoor allergens of which the house dust mite (HDM) appears to be the most important environmental agent associated with asthma. There have been many attempts to lessen the impact of asthma by reducing infestation with HDM. However, several meta-analysis and review studies have suggested that simple interventions do little to reduce HDM allergen levels. Vallance and colleagues have reviewed whether HDM avoidance is efficacious in the treatment of asthma. In addition to a comprehensive and critical review of the literature they also present findings of their own experience with the association between HDM levels and asthma in Scotland, which has the highest incidence of adolescent asthma in the world. Modern building regulations in the UK have resulted in a warmer and more humid domestic environment, which is the perfect microclimate for the proliferation of HDM. The authors point out that the many studies designed to reduce the impact of asthma by reducing indoor allergens, primarily HDM, have proved to be difficult and costly and their efficacy has been unconvincing. They recommend an intervention strategy that uses the best evidence-base from the most promising published methods, and to use this to impact on building regulations to encourage change in the design, construction, and use patterns of domestic buildings in the UK. Overall, the challenge appears to be to further refine

the interventions to reduce HDM levels so that positive clinical outcomes may be more easily demonstrated.

Over the past thirty years, an outstanding combination of innovative clinical achievement coupled with technological advancement and refinement has enabled the fields of fertility medicine and research to experience significant leaps forward in both basic knowledge and translational activity. In that time, assisted reproductive technologies (ART) have resulted in the birth of over 2 million children worldwide and in vitro fertilization (IVF) techniques have developed to the level of a routine procedure can be performed in 10 to 15 minutes in a physician's consulting room without the need for hospitalization or general anesthesia. Wang and Sauer review the rapid and exciting developments in the field since the pioneering birth of Louise Brown in 1978 under the guidance of Patrick Steptoe and Robert Edwards at Oldham General Hospital and offer an intriguing insight into the evolution of modern techniques for addressing the needs of infertile couples. The authors present an overview of the initial work on IVF during the 1970s that focused on women who presented with tubal disease. They then move on to discuss the advancements of the mid-1980s amongst women with natural or premature ovarian failure and a discussion of the increasing emphasis on women of advanced reproductive age and the evolving role of embryo cryopreservation. The developments of gamete intrafallopian transfer (GIFT) and zygote intrafallopian transfer (ZIFT) are considered and compared, together with the ooctye retrieval technique of transvaginal ultrasound-guided transvaginal follicle aspiration that rapidly became the procedure of choice following its introduction in 1987. Until the late-1980s, male infertility remained a rate-limiting factor in the overall success rate of fertility treatment. The authors highlight the role of a number of techniques that were developed to address this situation, including partial zona dissection (PZD) and subzonal insemination (SUZI). They then discuss the later combined techniques of microepididymal sperm aspiration and intracytoplasmic sperm injection (MESA-ICSI) and include an assessment of the relative developmental outcomes of children born via ICSI and standard IVF procedures. An examination of the evolving role of pre-implantation genetic diagnosis (PGD) includes the transition from polymerase chain reaction (PCR) techniques to fluorescence in-situ hybridization (FISH) and a consideration of expanding the role of PGD to disorders other than infertility, including HLA-typing for stem cell donation and preservation of fertility amongst cancer patients. The authors conclude with the observation that, in spite of the significant technological advances of the past three decades, continuing intense enquiry is required in order to assess the long-term effects of a technique whose eldest beneficiary is only 27 years old.

Rheumatoid arthritis (RA) is a prevalent condition whose clinical sequelae can result in significant reductions in functional capacity and quality of life with considerable attendant debilitating impact upon psychological health. Although there have been recent therapeutic advances, a number of challenges remain: only a percentage of patients will respond to the disease-modifying anti-rheumatic drugs (DMARDs); toxicity and/or resistance dictate that another sub-group requires combinations of DMARDs and the anti-tumor necrosis factor-α (TNF-α) agents; and further sub-groups gain no worthwhile benefit from any of the existing therapies. There is a growing body of evidence to support the role of T-cell activation in the development and progression of RA. Abatacept is a soluble fusion protein that comprises the extracellular domain of human CTLA4 and a fragment of the Fc portion of human immunoglobulin G1 (IgG1) that targets T-cell activation. Edward Vital and Paul Emery review abatacept's mechanism of action and studies examining its efficacy and safety. The authors present an overview of the rationale for co-stimulation blockade in RA, pharmacokinetic data from in vitro studies and a Phase I dose-finding clinical trial, and immunological activity and immunogenicity. A review of efficacy studies includes a discussion of relevant outcome measures including the American College of Rheumatology response rates, the Disease Activity Score 28 (DAS28), and the Modified Stanford Health Assessment Questionnaire (mHAQ). They further discuss studies in patients who do not respond to DMARDs, analyse findings relating to disease activity and structural change, and functional capacity and quality of life. In considering studies in patients who did not respond to anti-TNF-α agents, the authors discuss the Phase III ATTAIN trial including primary and secondary end-points for disease activity and function and their correlations with patients' own perceived improvements. Considerable data from Phase III trials indicate that abatacept is both safe and effective and support its use in the management of RA, in particular amongst patients who do not respond to DMARDs and TNF-α agents. There is a brief discussion of abatacept's safety either as monotherapy or when administered in combination with other RA therapies (the ASSURE trial)

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