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This issue of *Therapeutics and Clinical Risk Management* contains interesting reviews on rheumatoid arthritis (RA), ulcerative colitis (UC) and steroid-resistant asthma all of which are distressing chronic inflammatory conditions of unclear etiology. 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. Despite recent therapeutic advances, a number of challenges remain: only a percentage of patients will respond to the disease-modifying antirheumatic drugs (DMARDs); toxicity and/or resistance dictate that another sub-group requires combinations of DMARDs and the antitumor necrosis factor-α (TNF-α) agents. Poor disease control in RA leads to joint pain and deformity with consequent functional impairment and loss of independence, patients may also experience significant systemic illness including nodules, vasculitis, pulmonary fibrosis and nerve entrapment. Among the new and more powerful DMARDs that have recently become available infliximab (IFX), a chimeric TNF-α monoclonal antibody (mAb), has shown great promise. Levels of TNF-α, a potent pro-inflammatory cytokine, are elevated in the sites of inflammation associated with RA, for example in the synovial fluid and sera of patients with active disease. TNF-α acts as a potent osteogenic cytokine and is thought to be the central mediator of joint destruction in rheumatoid arthritis. However, as Sophie Martin Du Pan and colleagues (2007) point out in the current issue of TCRM, the use of the more expensive biologic agents such as IFX tend to be limited to patients who have failed one or more traditional approaches to treatment on cost grounds. As this effectively eliminates these agents from the management of early RA, these authors have examined the evidence in support of the use of IFX in early RA as this approach may be more effective than treatment later in the course of the disease. They therefore conducted a systematic review of the literature and performed a meta-analysis of the RA bone erosion score (vdH Sharp Score) and RA functional disability score in randomized clinical trials that compared treatment with methotrexate-IFX (MTX-IFX) with methotrexate-placebo (MTX-placebo). The authors report that there is no evidence to support the superiority of MTX-IFX over MTX in combination with traditional disease-modifying antirheumatic drugs but they recommend that IFX should be used in those early RA patients demonstrating signs of aggressive disease, such as a limited response to MTX alone or the presence of rapidly progressing erosions.

Ulcerative colitis is a chronic inflammatory condition of the large bowel leading to abdominal pain, diarrhea and in some cases other systemic features such as fever and weight loss. The underlying cause of UC remains elusive although current thinking favours defects in the mucosal immune system and/or epithelial integrity resulting in an abnormal inflammatory response to normal intestinal microflora. Raffi Karagozian and Robert Burakoff (2007) have provided an excellent review on the eitiology, pathogenesis and clinical course of UC. They detail current treatment modalities for UC with an emphasis on mesalamine a 5-aminosalicylate; these are newer formulations of salicylates-based drugs with fewer side-effects. The authors rate mesalamine as an excellent first-line therapy for treatment of mild to moderate UC and also for the maintenance of remission. They further emphasise the importance of maximization of local mucosal concentration of mesalamine by utilizing the most appropriate delivery

formulation. Furthermore, newer formulations have been developed which will require less frequent dosing and this should aid compliance. However, as UC is a chronic remitting active inflammatory condition, the majority of patients are likely to require life-long therapy.

Asthma is another chronic inflammatory condition requiring life-long therapy for the majority of patients. Antiinflammatory therapy in asthma is largely reliant on glucocorticoids (GC) – particularly in their inhaled form – with or without the addition of short- or long-acting bronchodilators. The symptoms of most asthmatics are satisfactorily controlled by regular use of inhaled GC. However, their use often raises concerns with respect to compliance. There is also increasing evidence that long-term use of inhaled GC, especially in high doses, can cause systemic adverse effects, including adrenal suppression, reduced growth and reduced bone-mineral density, as well as local side effects such as dysphonia. Moreover, a sub-group of asthmatic patients responds poorly or not at all to high-dose inhaled or systemic GC treatment. Although the numbers of these patients are small they do require a disproportionate amount of scarce resources to treat their condition. As there are few alternative treatments, these patients can be difficult to treat and may require frequent hospitalisation. Their quality of like is also severely impaired by both symptoms and the toxic effects of high-dose systemic GC. Thus a timely review from Christopher Corrigan (2007) comprehensively addresses the current status of our understanding of the key clinical issues surrounding this important condition. In particular the difficulties of reliably identifying these patients is emphasised in addition to the thorny problem of non-compliance by patients in relation to inhaled GC therapy. The molecular mechanisms by which for GC exert their actions are described together with potential defects in these complex processes thought to be responsible for steroid resistance in asthma. A number of alternatives to GC therapy are discussed but the majority of these are far from satisfactory. The author concludes that the identification of reliable biomarkers for airway inflammation in asthma are required to permit GC responsiveness to be assessed accurately and objectively in the short and long term.

The cysteinyl leukotrienes (LTC^4, LTD^4, LTE^4) induce bronchoconstriction and are highly potent mediators of airway inflammation in asthma. The cysteinyl leukotriene receptor antagonists were the first new class of antiasthma drugs to be introduced in the last 30 years and are now an established part of the treatment of adult asthma. Overall, they are less effective than inhaled corticosteroids but some patients show a striking improvement and a corticosteroid-sparing effect has been demonstrated. Three drugs of this class are in use at present: zafirlukast, pranlukast, and montelukast. All three are specifically active against the cysteinyl leuko-trienes by blocking their receptor, CysLT1. Thus, to continue with the asthma theme in the current issue, Koray Harmanci (2007) has provided a detailed review of the use of montelukast in childhood asthma. Overall, it appears that montelukast is not suitable as monotherapy in mild and moderate-severe persistent asthma in children being inferior to inhaled corticosteroids. However, montelukast appears to be effective in exercise-induced and aspirin intolerant asthma in children and has the advantage of being administered orally rather than as inhaled therapy.

References

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