

Introduction: leukotriene receptor antagonists — exciting new approach to the management of childhood asthma

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The advent of leukotriene receptor antagonists has heralded the start of a new era in childhood asthma management. It might seem rather a long time since the slow-reacting substance of anaphylaxis was characterized as being a combination of the cysteinyl leukotrienes, LTC₄, D₄ and E₄ (1). However, while these mediators were clearly shown to have potent broncho-constrictor and subsequently also proinflammatory effects, the sceptical medical world merely added them to the long list of factors contributing to the asthma mediator soup. Confidence in single mediator antagonists as therapeutic modalities for asthma diminished rapidly, as it was clear that there was considerable redundancy among many of the factors identified. However, increasing evidence pointed to the cysteinyl leukotrienes as being important mediators in asthma because they were not only broncho-constrictors but also promoted eosinophilic inflammation which is so characteristic of asthma (2). However, proof of concept had to await the development of appropriate effective antagonists. The demonstration that they were highly efficacious in asthma has now proved beyond doubt that the cysteinyl leukotrienes are indeed pivotal mediators of asthma. Furthermore, for the very first time, successful drug development has evolved from the identification of the target through to the development of an appropriate antagonist. There is no doubt that this will herald a new era in targeted asthma pharmacotherapy.

Management of childhood asthma has over the previous 30 years become entrenched in the use of inhaled beta-agonist and corticosteroids, with the prejudice that oral therapy will not offer any significant additional benefits, other than with the use of oral corticosteroids for acute exacerbation. This approach left a number of unmet issues for childhood asthma sufferers. Poor compliance with regular inhaled therapy compromised abilities to achieve effective control.

Many patients required relatively high doses of inhaled corticosteroids, which has engendered inevitable concern about long-term adverse effects and exercise-induced symptoms have often not been adequately prevented without the use of frequent doses of short-acting beta-agonists. The degree to which this produces beta receptor sub-sensitization remains contentious and this issue is a similar concern for the long acting beta-agonists. Furthermore, since this symposium actually occurred, the publication of the Childhood Asthma Management Program (CAMP) results has highlighted a further problem. The primary outcome measure in CAMP was an improvement in post-bronchodilator lung function (forced expiratory volume in 1 second). The continuous use of either nedocromil sodium or inhaled corticosteroids for 5 years had no effect on this variable by comparison with placebo. While there were clear therapeutic benefits, particularly for inhaled corticosteroids, it has highlighted the need for additional modalities of therapy (3). To what extent leukotriene receptor antagonists will contribute to improving long term outcome remains to be established. However, their addition to the therapeutic armoury has clearly provided considerable short- to medium-term benefits.

Of the leukotriene receptor antagonists available, namely montelukast, zafirlukast and pranlukast, the former has had the most extensive trials performed in children. Being orally active and only required once daily, montelukast has considerable advantages over all other therapies hitherto available for asthma in aiding compliance. Montelukast has proved particularly valuable as add-on therapy to regular inhaled corticosteroid and evidence is beginning to accrue that would suggest it will also have a role as primary prophylaxis in frequent episodic and mild chronic persistent asthma at step 2 of the therapeutic algorithm. However in this area, further trials are required. Furthermore, there is a

strong suspicion that montelukast will have benefits not only for asthma but also for allergic rhinitis and may be even atopic dermatitis which are such common associated problems in asthmatic children. It also provides considerable benefit in reducing exercise-induced bronchospasm, thus facilitating more normal participation in physical exercise which is so important to children, and highlighted very clearly in the activity

component of the quality of life assessments which showed considerable improvements on montelukast compared with placebo (4).

The papers presented in this supplement, which are the outcome of a very successful symposium, present the state of the art in relation to leukotrienes and childhood asthma, and will hopefully stimulate further research and interest in this topic.

References

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