REVIEW

Current and Emerging Pharmacotherapies in Children with Moderate to Severe Chronic Asthma

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Abstract: Moderate to severe chronic asthma in children provides challenges in both diagnosis and treatment for paediatricians. The clinician treating difficult to control asthma meets a number of challenges such as non-adherence and paucity of strong clinical evidence. Understanding different asthma phenotypes, pathophysiology and the inflammatory process that underpins asthma is essential in order to appreciate the action of the pharmacotherapies available for use beyond the British Thoracic Society Guidelines. Many of the newer drugs used today are inspired by other inflammatory diseases. Through this review we have summarised these issues for the reader and outlined the emerging therapies that may be available in the future.

Keywords: asthma, children, severe, treatment, pharmacology

1. Introduction

Asthma is estimated to affect at least 300 million people worldwide and the prevalence of asthma has risen in many industrialised countries over recent decades.[1] The prevalence of asthma in the paediatric population has followed the same trajectory, although overlap with viral wheeze and difficulties in establishing airway reversibility in young children makes the true numbers difficult to establish. In contrast to acute severe asthma it is difficult to define chronic moderate or severe asthma using physiological or other objective criteria.[2] Asthma UK describes severe, difficult to treat asthma as having "almost continual asthma symptoms despite being prescribed high levels of asthma medicines" and frequent severe asthma attacks.[3] Bush and Saglani[4] have defined those children referred for asthma specialist management as severe. It is difficult to agree an easily applied threshold over which asthma would be defined as moderate or severe.

The problems in defining severe asthma may reflect growing recognition that this represents a heterogeneous group of patients.[4] Approaches to defining phenotypes of severe asthma include variation in exacerbation pattern[5] those based on variability of responses of the glucocorticoid receptor[6] (steroid resistance has been described and defined in adults[7,8] and is also reported in children) and inflammatory mechanisms, such as predominance or paucity of eosinophils in bronchial biopsies.[9] Treatments tailored to distinct phenotypes have been reported to improve clinical outcomes compared with treatments guided by lung function and symptoms alone.[10,11] It is possible that the initial assessment of children with severe asthma will move towards more precise classification of phenotype based on clinical and pathological features and individually-tailored treatment.[4]

In the following review we will describe the pathological processes and thus the pharmacological targets involved in asthma and discuss some of the difficulties involved in treating childhood asthma, such as paucity of clinical evidence and non-adherence to treatment. We will outline the pharmacological management of moderate to severe asthma in children under three broad headings; i) the unconventional application of conventional asthma medications, ii) the use of medications that were developed for the treatment of diseases other than asthma, and iii) new and emerging medications for the treatment of asthma.

Pathophysiology of Severe Asthma

Asthma is characterised by spontaneously variable airflow obstruction, reversibility with beta-2-agonists and airway hyper-responsiveness to a variety of chemical and physiological stimuli. Histology of the lungs in post-mortem specimens of patients who have died of severe acute asthma demonstrate an intense inflammatory process in the large conducting airways with bronchial mucosal cells shed into the lumen, trans-mucosal oedema, bronchial smooth muscle hypertrophy, sub-mucosal capillary dilatation, hyperplasia of the mucosal cells, sub-epithelial fibrosis and inflammatory cells in the bronchial wall.[12] In chronic asthma the airways may show no histological changes between attacks or may display changes as above.[13]

The small, peripheral airways in asthma also show evidence of airway inflammation.[14,15] Recognition of the involvement of small airways in asthma inflammatory processes has therapeutic implications. The distal airways make up a substantial proportion of the lung surface area and inhaled drugs are not distributed equally throughout the bronchial tree, being preferentially deposited in the proximal airways.[16] Additionally, inflammation may not be uniform throughout the airways. There is some evidence of differences in the distribution of CD45 positive (common leucocyte antigen) inflammatory cells in the small and large airways in asthma, which may represent different inflammatory processes. However, there have been no convincing, sufficiently powered studies that have shown a differential effect of inhaled treatment on the small and large airways.[17]

Recruitment of eosinophils and T cells to the airway epithelium is characteristic of the allergic airway response to inhaled stimuli in asthma.[15] The airways demonstrate up-regulation of pro-inflammatory T helper type 2 (Th2) cytokines, interleukin-4 (IL-4), IL-5, IL-9 and IL−13. In the presence of antigen, IL-4 promotes naïve T-helper cells to differentiate into Th2 cells which drive B-cell class switching to produce IgE.[18] Eosinophil differentiation is stimulated by IL-5 before migration under the influence of IL-4 and IL-13. There is good evidence of distal airway

eosinophilia being temporally related to poor lung function in symptomatic asthmatics, supporting their role in the acute response in the small airways.[19]

The glucocorticoid receptor has an important role in the pathophysiology of asthma control.[20] Glucocorticoids bound to the cytoplasmic receptor are transferred to the cell nucleus where they act to promote the development of intrinsic anti-inflammatory proteins, up-regulate beta-2 receptors and also suppress pro-inflammatory mechanisms. A corticosteroid resistant phenotype of asthma has been described for over 30 years.[7] Patients showing poor clinical responses to glucocorticoids may have their dose escalated in an effort to bring symptoms under control but are likely to experience increased adverse events without evidence of increased clinical efficacy.

Other processes which promote recruitment of inflammatory cell infiltration are suppressed by the natural anti-inflammatory cyclic adenosine monophosphate. The inhibition of this protein by phosophodiesterase-4 makes phosphodiesterase another target for asthma therapies.[21]

Evidence for Treatment in Children
The evidence base for therapeutic interventions in children with moderate to severe asthma is limited and this must be appreciated when reading this review. The relative lack of invasive studies of asthma inflammation in children and the tendency in the past to extrapolate results of therapeutic trials of asthma treatment in adults to the paediatric age group has limited progress in developing new treatments for severe asthma in children. It is still estimated that over two thirds of medications used in the paediatric population are off-label or unlicensed.[22]

The use of many medications in children is extrapolated from adult use. Although this may allow the more rapid introduction of some drugs into the paediatric pharmacopeia, it assumes the physiology of children is the same as adults, or the models used to infer responses in children from adult data are always reliable. This is clearly an untenable assumption in a proportion of cases. Changes in regulation by bodies such as the Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK[23] that are designed to ensure drugs are adequately tested in children are likely to influence the development of new medicines intended primarily or exclusively for children.

Adherence to Treatment
Adherence to medications is a significant problem in asthma therapy and one which needs to be addressed before considering add-on treatments. Much of the evidence on treatment adherence in asthma comes from therapeutic trial data, which might be expected to represent optimal circumstances for adherence. In one study 27% of potential participants were excluded because of poor adherence.[24] Jones and others have shown that physician assessed poor compliance is significantly associated with poor control of mild, moderate and severe asthma.[25] Even patients with poorly controlled asthma are resistant to taking treatment.[26,27] Further barriers to adherence include patient and parental expectations, concerns about drug safety and complicated treatment regimens.[28] Therefore, Gamble and colleagues[26] advocate the use of multiple measures of adherence to address this aspect prior to prescribing additional medications.

2. Current Pharmacological Interventions Used in Moderate to Severe Asthma in Children
Where do we start?
The current management of children with asthma in the UK is based on an evidence-based guideline developed by the British Thoracic Society (BTS) and Scottish Intercollegiate Guideline Network (SIGN).[2] This advises treatment with inhaled corticosteroids (ICS) at doses up to 800 mcg/day (beclomethasone equivalent), often in combination with a long-acting beta-2 agonist (LABA) and/or leukotriene receptor antagonist. In patients who remain uncontrolled on this regimen, the use of regular oral steroids would usually be considered and referral to a respiratory paediatrician made. Respiratory specialists may then use additional medications with which they are familiar and which are licensed, before using off license or experimental approaches.[4] For the purposes of this review we will be discussing what is available to the respiratory specialist 'beyond the BTS Guideline'. Although outside the realms of this review it is also important to consider non-pharmacological aspects, co-morbidities such as psychological factors and

the optimisation of conventional treatment, before considering therapeutic options beyond the BTS guidelines.

Standard Asthma Medications Used in Different Ways in Difficult Asthma

Some commonly used asthma medications are used in different ways in difficult asthma. Newer versions of older drugs have also been developed. These include the use of combined LABA and ICS inhalers as reliever medications (SMART), the use of continuous subcutaneous infusion of terbutaline (CSIT), intra-muscular triamcinolone, methylxanthines and new inhaled steroids.

Single Maintenance and Reliever Therapy (SMART)

Long acting beta 2 agonists (LABAs) primarily act to provide prolonged broncho-dilatation. Evidence has emerged that LABAs also influence inflammatory processes through suppression of histamine release from mast cells in vitro and in vivo and reduced plasma exudation and inhibition of endothelial cell adhesion.[29] Although long-term exposure to beta-2 agonists causes a down-regulation of airway receptors, this can be countered by an increase in beta-2 receptor transcription in response to steroids and there is evidence in vitro of interactions between beta-2 agonists and corticosteroids suggesting synergism.[29,30] There is evidence that LABAs alone are associated with increased asthma morbidity and mortality[31,32] but the combination of LABA with inhaled corticosteroid has been shown in adult patients to improve symptom control compared with ICS alone.[33]

There is evidence that adding a LABA to ICS treatment is more effective for managing difficult to control asthma than substantial increases in ICS alone.[34] The use of a single maintenance and reliever therapy (SMART); a combined ICS and LABA used form both preventative therapy and for relief of breakthrough symptoms of asthma has been used in both adults and children. This is generally based on the use of budesonide/formoterol combinations due to the more rapid onset of action of the latter. There is evidence that SMART reduces the number of asthma exacerbations requiring oral corticosteroids in adults[35–37] and in children, the use of combination therapy as a reliever reduced the need for increasing

ICS dose, in comparison with use of regular inhaled corticosteroid.[36] The use of SMART has by no means been accepted by all respiratory specialists and critics remain concerned about lack of blinding and recruitment bias in previous studies. They are also concerned about the finding of increased eosinophilia in airways one year in to treatment.[38] Further research may be needed to resolve these issues.

Continuous Subcutaneous Infusion of Terbutaline (CSIT)

Although CSIT has been suggested as an effective treatment for difficult to control asthma in children, no large studies have been performed to assess its efficacy. Bush and Saglani[4] recommend commencing treatment with CSIT in hospital using an n-of-1, double-blinded trial. This is not an approach we use with our own practice but eliminates the possibility of bias when assessing efficacy. This treatment has, in adults, been shown to reduce variability in peak expiratory flow (PEF) and symptoms by 50%[39] and in small case series in children to reduce oral steroid use.[40] Side effects mainly include local administration site problems such as bruising, skin infection, inflammatory nodules at injection sites and even abscess formation.[40,41] The role of an experienced respiratory nurse is crucial for affective organisation, monitoring and liaison with distributors.

Intramuscular triamcinolone acetonide

Triamcinolone acetonide is a potent, synthetic gluco-corticoid that when given intra-muscularly is absorbed slowly with biologically detectable activity for weeks or months. Immunosuppression is a potentially serious side effect of parenteral steroid use. As with patients on high-dose oral steroids, patients receiving triamcinolone who are not chicken pox immune would need varicella immunoglobulin if in contact with an infectious person. Ideally patients should be vaccinated against chicken pox and measles prior to commencing treatment. They should not receive live vaccines such as BCG. Patients should also carry a steroid card due to the potential risk of adrenal suppression. Treatment is usually given in children over 6 years old and consists of one intra-muscular injection every four to six weeks for a limited period (eg, 3–6 months). Triamcinolone has not been sub-jected to a large randomised trial in children. However,

case series have shown it to be beneficial in terms of reducing exacerbations, hospital admissions and a reduction in exhaled nitric oxide (a marker of airway inflammation).[42,43]

As we have discussed adherence is a complex problem when treating childhood difficult asthma. It is possible that supervised and reliable administration of these last two drugs rather more than the pharmacokinetics that may be more attributable to their success.

New inhaled steroids

Ciclesonide is a novel inhaled steroid that was originally developed as a topically active corticosteroid for dermatological use. The inactive ciclesonide compound is metabolised at the pulmonary epithelium into its active form, desisobutyryl-ciclesonide.[44] Ciclesonide is thought to hold a pharmacological advantage over other inhaled steroids as it has low oral bioavailability, is cleared rapidly and has a high level of serum protein binding which thus minimises systemic adverse effects.[44] Reviews of the effectiveness of ciclesonide compared to placebo or with existing ICS (budesonide, beclomethasone, fluticasone) have combined the results of clinical trials in both adults and children. Ciclesonide compared favourably with placebo but longer, larger trials are required and dose ranges are not firmly established.[45] When compared with other ICS, ciclesonide was associated in children with improved quality of life score and a decreased incidence of oral candidiasis.[46] Differences in lung function and symptoms were not found to be clinically significant. Concerns regarding the impact on growth in children were addressed by Skoner et al[47] who found no detrimental effects when compared with placebo. They also however, reported no improvement in forced expiratory volume in one second (FEV_1) in a cohort of children with mild asthma.

Methylxanthines

Theophylline and **aminophylline** are both bronchodilators that act primarily through the mechanism of phosphodiesterase (PDE) inhibition but also act as adenosine receptor antagonists. Inhibition of PDE prevents downstream inactivation of cyclic adenosine monophosphate, thus PDE inhibitors bring about airway smooth muscle relaxation. Theophyllines also have anti-inflammatory actions by increasing the release of the anti-inflammatory IL-10 possibly via PDE inhibition and inhibiting prostaglandin and TNF-α.[48] Long acting slow release preparations are available. These drugs have a narrow therapeutic index, over which the side effects of nausea, vomiting, abdominal pain, tachyarrhythmias and metabolic acidosis may arise. They are comparable with short acting beta-agonists (SABAs) in terms of need for rescue medication and effects on spirometry[49] but the beta-2 agonist medications have a more favourable side effect profile and have largely superceded theophylline's use, leaving it as a second or third line agent. Studies comparing theophylline with LABAs have reported salmeterol in particular to show a greater improvement in peak expiratory flow (PEF) and a reduced need for rescue medication. Fewer side effects were also experienced.[50] When compared with standard dose ICS, theophyllines were inferior with regard to frequency of exacerbations[49] although other studies have found standard dose ICS plus add-on theophylline to be superior to high dose ICS alone in patients uncontrolled at lower dose[51] thus promoting theophylline as a steroid sparing drug. Aminophylline still has a well-established role in the treatment of acute asthma.

Drugs Having Found a New Role in the Treatment of Asthma

Asthma has much in common with many other inflammatory and atopic conditions and thus some treatments used in asthma have originated in treatment of other medical conditions. Here we will discuss the use of immune-modulators, immune-suppressants and the macrolide antibiotics.

Immune-Modulators
Anti-IgE therapy

Since the discovery of mono-clonal antibodies in 1975, their use in medical diagnostic and therapeutic applications has increased. They have been utilised in the treatment of inflammatory conditions in recent years, including asthma.

Omalizumab is a treatment used increasingly in children with severe/difficult to control asthma. It is a murine mono-clonal antibody that inhibits the binding of IgE to the high-affinity IgE receptor (FcεRI) on the surface of mast cells and basophils. This in

turn blocks mediators of the allergic inflammatory response. Treatment is given once every 2–4 weeks by sub-cutaneous injection. The dosing regimen is based on body weight and serum IgE concentration. Omalizumab results in a raised IgE for some time after cessation and thus changes in IgE concentration cannot be used to monitor the success of treatment once it has been started. Clinical trials have shown omalizumab to enable inhaled steroid doses to be reduced and a decrease in exacerbations as supported by a Cochrane meta-analysis.[52] There are significant side effects and thus the treatment is reserved for severely affected, atopic children and is currently only licensed and recommended by National Institute for Clinical Effectiveness (NICE) in the UK and the US Food and Drug Administration (FDA), for use in children over 12 years.[53,54] Due to the limited experience of this drug and potential complications, it is usually reserved for use by tertiary specialists. Commonly seen adverse effects in children include abdominal pain, fever and headache.[54] Clinical trials found an incidence of anaphylaxis of 0.1% with varying times of onset after administration.[53] Clinical trials had found a higher incidence of malignancy in patients treated with omalizumab compared with control subjects but data on long-term follow-up is not yet available and subsequent studies have not confirmed this.

Immunotherapy

The pathological process of allergic inflammation in asthma overlaps with the other atopic diseases, such as eczema and allergic rhinoconjunctivitis and a substantial proportion of children have co-existence of these conditions. A number of children with asthma will have identifiable allergens that clinically trigger asthma exacerbations. Common allergens include the house dust mite, tree and grass pollens, animal dander and moulds. Immunotherapy involves administering an increasing amount of a specific allergen over a prolonged period of time. It is also known as "hyposensitisation" or "desensitisation". Over the years, several routes of immunotherapy have been used but currently only the subcutaneous (SCIT) and sublingual (SLIT) routes are in clinical use. Immunotherapy is not new. SCIT has a good evidence base in adults for the treatment of insect venom anaphylaxis, perennial and seasonal allergic rhinitis. SCIT has been found to be useful in the treatment of asthma where a known allergic trigger exists.[54,55] The use of SCIT does not come without risk. A Cochrane Review of the use of SCIT in asthma found a decreased risk of bronchial hyper-reactivity with an improvement in symptoms and decrease in maintenance medications. However, 1 in 9 patients were found to have a systemic reaction which may range from mild urticaria to fatal anaphylaxis.[54] SLIT remains an evolving therapy in the paediatric population and the efficacy continues to be debated. Meta-analysis investigating a total of 441 patients with allergic asthma concluded a modest reduction in symptoms and reliever medications in children (between the ages of 3 and 18) following SLIT.[56] Few studies have been performed comparing SCIT and SLIT directly though studies that have been done have not found a great difference between the two and found SLIT to be at least as safe,[57] if not safer.[58] Sublingual therapy has an obvious benefit over subcutaneous, particularly in the paediatric population in terms of acceptability of route of administration and possible decrease in adverse effects.

Anti-Inflammatories and Immunosuppressants

Steroid sparing drugs are popular in children, particularly due to the potential adverse effects of corticosteroids on growth. Whilst looking for new treatments for difficult to control asthma we have often looked to the treatment of other inflammatory conditions for inspiration. There are a number of drugs that have been used in non-asthma inflammatory conditions, such as inflammatory arthritis, inflammatory bowel disease, chronic active hepatitis and many of these have been tried in asthma over the years. However, there is little convincing clinical evidence for the efficacy of any one of these drugs in asthma other than anecdotal case reports. These steroid sparing agents may be considered in patients where omalizumab has not been successful or if the patient is not eligible.

Cyclosporin

This is the most commonly used alternative to high dose systemic corticosteroids. Cyclosporin is an immunosuppressant that is used to treat a number of inflammatory disorders. It has a number of actions that are likely to be helpful in asthma.

1. Inhibition of eosinophil function
2. Reduction in production of histamine, platelet activating factor and leukotriene C4 via the inhibition of basophils and mast cells
3. Reduction in IL4 mediated IgE production
4. Inhibition of numerous inflammatory cytokines including interleukins and granulocyte macrophage colony-stimulating factor (GM-CSF).

There is evidence for its use in adult asthma as it has been shown to improve lung function and act as an oral corticosteroid sparing agent in patients with severe asthma[59] but even this body of evidence is small. A Cochrane Review (last updated in September 2010) focused on the use in adults and concluded that given the side effects evidence does not support the routine use of cyclosporin.[60] That said some patients clearly do find benefit. The evidence for use in paediatrics is restricted to a single case series.[61] Side-effects of cyclosporin include raised liver enzymes, neuropathy and gastro-intestinal disturbance. Treatment is relatively contraindicated in the presence of renal impairment and hypertension. Patients on treatment should be monitored with drug levels and liver function tests.

Azathioprine ia an anti-inflammatory and immunosuppressant that has been used in the treatment of asthma though is not used frequently. It has been subject to small clinical trials and there remains some interest in its use in asthma with a possible 're-emergence' in use. Azathioprine affects T and B cells by interfering with purine synthesis essential for DNA production. A Cochrane review, last updated in 2010 identified only two very small randomised control trials with equivocal results.[63] The authors found no new evidence that succeeds this review.

Macrolide Antibiotics

There is a reasonable body of evidence supporting the use of macrolide antibiotics in other lung conditions associated with neutrophilic airway inflammation, such as cystic fibrosis. Trolandeomycin is of historical interest in the treatment of asthma but its use was limited by severe adverse effects. The potential benefits of newer macrolide antibiotics in asthma are two-fold: their antimicrobial actions and anti-neutrophil properties. Macrolides are active against atypical organisms. Chlamydia pneumoniae and

Mycoplasma pneumoniae have both been implicated in acute exacerbations of asthma and increased disease severity and chronicity.[63] Chlamydia pneumonia has been shown to be associated with an increase in IL-8 and neutrophilia on broncho-alveolar lavage in paediatric patients with asthma.[64] A Cochrane review concluded that, due to the small numbers of patients identified, the efficacy of macrolide antibiotics in asthma could neither be confirmed nor refuted.[65] However, some small studies support their use and further research is required, particularly in patients with a neutrophil-predominant asthma phenotype.

3. Emerging Therapies and Drugs on the Horizon

There are many new pharmacotherapies for asthma under development. There is interest in both improving and refining the drugs already in clinical use and also in the birth of novel therapies directed towards specific aspects of the inflammatory process.

New Cytokine Blockers

The inflammatory process in asthma implicates more than 100 mediators.[66] The possibility of blocking all these mediators concurrently is unlikely. Knowledge of the inflammatory cascade however reveals clues as to where new treatments may be useful. Leukotriene receptor antagonists (eg, montelukast) are the only mediator blockers in current use. Interest lies in the development of new therapies that either directly block mediators or act on their receptors.

Tissue Necrosis Factor Alpha (TNF-α)

This is an inflammatory cytokine that has been focused on as a potential target for therapeutic intervention. TNF-α has been shown to be raised in patients with asthma and not reduced by corticosteroid therapy. **Etanercept** is a monoclonal antibody and soluble TNF-α fusion protein. There is supportive evidence for its use in other inflammatory conditions such as rheumatoid arthritis but experience in asthma is limited to small studies and case series in adults. A randomised double-blinded, placebo-controlled trial of etanercept looked at a total of 39 adult patients with half treated with etanercept once a week for 12 weeks. This demonstrated a significant improvement in asthma control and biochemical markers of inflammation.[67] Unlike some other small

studies[68,69] it failed to demonstrate an improvement in quality of life scores, lung function or airway hyperresponsiveness. There were no major adverse effects but an increase in skin rashes and injection site pain in the etanercept treated group. Larger trials are required before etanercept is an accepted treatment for difficult asthma in children. Other TNF-α blockers are under investigation for their use in asthma. These include **infliximab** and **golimumab**. So far studies have failed to convincingly display benefits of these drugs to outweigh potential risks and costs of treatment but further research is required.[70,71]

There are other mono-clonal antibodies emerging such as **mepolizumab** and **daclizumab**. These drugs have action against IL-5 and the IL-2Rα chain respectively. Studies are currently restricted to work in adults. IL-5 has a key role in eosinophil production and mepolizumab has been shown to reduce eosinophil counts in blood and sputum in patients with a variety of inflammatory conditions.[72,73] These studies have shown mepolizumab to result in a decrease in asthma exacerbations but no improvement in lung function. Daclizumab has been subject to a randomised controlled trial of 115 adult patients with asthma. It was found to significantly improve FEV_1, reduce symptoms, exacerbations and use of rescue medications.[74] Neither of these drugs has been trialled in children to date.

Pitrakinra (Aerovant) is a recombinant human IL-4 variant that competitively inhibits the IL-4Rα receptor complex to interfere with the actions of both IL-4 and IL-13.[75] Phase II trials thus far have been encouraging and investigated both nebulised and subcutaneous preparations.[76] The results of phase III trials are awaited.

There are a number of other cytokine blockers that are being studied in the context of asthma (IL-9, IL-17, IL-25, IL-33, GM-CSF and thymic stromal lymphopoietin—TSLP).[66] None of these drugs are yet at the stage of clinical trials.

Ultra LABAs

Adherence to treatment remains a key problem in the management of difficult asthma. Therefore, drugs with low frequency of administration may be beneficial. A number of inhaled beta-2 agonists with clinical action of up to 24 hours, known as 'ultra LABAs' are under-development with indacaterol, carmoterol and GSK-642444 being the most advanced in development.[77] Dosing trials have taken place in adults but the transition into paediatric practice will inevitably take longer. The obvious next step is the development of a combination inhaler. This may include a LABA or ultra-LABA in combination with a current or new inhaled corticosteroids, for example, formoterol and mometasone (MFF258), indacaterol and mometasone (QMF-149) or GSK-642444 and fluticasone furoate.[77]

Long-Acting Anti-Muscarinics (LAMAs)

Anti-muscarinics have an established role in the treatment of acute asthma.[2] However, a Cochrane Review considering the evidence for the use of anti-muscarinic, anti-cholinergics (such as ipatropium bromide) in chronic asthma in the over 2 years age group concluded that there was no evidence to support their use either as an alternative to salbutamol or as add-on therapy.[78] Work has been done predominantly in chronic obstructive pulmonary disease (COPD) to assess the effectiveness of the newer long acting anti-cholinergic, tiotropium bromide. It is possible that LAMAs may have role in the minority of patients that possess beta-2 receptor polymorphisms but this awaits further clinical research.

New Phosphodiesterase Inhibitors

As described above, theophylline belongs to a class of non-specific phosphodiesterase inhibitors. Different subtypes of the enzyme phosphodiesterase have been described[79] and drugs selectively targeting these enzymes are now provoking considerable interest for the treatment of asthma. The selective inhibition of the PDE-4 subtype with **Roflumilast** has been shown to be comparable to low dose inhaled corticosteroids in terms of improved lung function and symptom scores in adults and children >12 years with asthma.[80] The side effect profile of selective PDE-4 inhibitors appears to be similar to that encountered with theophylline. Future interest is likely to be directed to inhaled preparations with less systemic absorption and to more specifically targeted drugs.

Other Pathways

The inflammatory process holds the key to the creation of other new drugs focused on different mediators

along the pathway. Work at various levels is underway looking at kinase inhibitors (eg, Masitinib),[81] new cytokine blockers, blocking adhesion molecules (eg, inhaled bimosiamose)[82] and lipid mediators. New anti-inflammatories and corticosteroids are also an interesting prospect. Non-steroidal selective glucocorticoid receptor activators (SEGRA) are under development with the aim of reducing the adverse effects experienced from traditional corticosteroids.[66]

4. Summary

The diagnosis and management of moderate to severe asthma in children is by no means straight forward. Adherence remains a key issue and is difficult to both identify and manage. The evidence for pharmacotherapies in severe childhood asthma is often sparse and extrapolated from adult data, other inflammatory conditions or children with milder disease. Through this review we have outlined the current medications used in moderate to severe asthma. We have also discussed the emerging therapies in specialist use. The pathological process involved in asthma is complex which provides numerous targets for new medications. However, most of these drugs remain at experimental level and the face of asthma therapy is therefore unlikely to change greatly in the next few years.

Disclosure

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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