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SERIES "HOT TOPICS IN PAEDIATRIC ASTHMA"
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Pharmacological treatment of severe, therapy-resistant asthma in children: what can we learn from where?

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ABSTRACT: There is a lack of high-quality evidence on what treatment should be used in children with properly characterised severe, therapy-resistant asthma. Data have to be largely extrapolated from trials in children with mild asthma, and adults with severe asthma. Therapeutic options can be divided into medications used in lower doses for children with less severe asthma, and those used in other paediatric diseases but not for asthma (for example, methotrexate). In the first category are high-dose inhaled corticosteroids (ICS) ($\leqslant$2,000 $\mu g \cdot day^{-1}$ fluticasone equivalent), oral prednisolone, the anti-immunoglobulin (Ig)E antibody omalizumab, high-dose long-acting β_2-agonists, low-dose oral theophylline and intramuscular triamcinolone. If peripheral airway inflammation is thought to be a problem, the use of fine-particle ICS or low-dose oral corticosteroids may be considered. More experimental therapies include oral macrolides, cyclosporin, cytotoxic drugs such as methotrexate and azathioprine, gold salts, intravenous infusions of Ig, subcutaneous β_2-agonist treatment and, in those sensitised to fungi, oral antifungal therapy with itraconazole or voriconazole. Those with recurrent severe exacerbations, particularly in the context of good baseline asthma control, are particularly difficult to treat; baseline control and lung function must be optimised with the lowest possible dose of ICS, and allergen triggers and exposures minimised. The use of high-dose ICS, leukotriene receptor antagonists or both at the time of exacerbations can be considered. There is no evidence regarding which therapeutic option to recommend. Better evidence is required for all these treatment options, underscoring the need for the international and co-ordinated approach which we have previously advocated.

KEYWORDS: Cyclosporin, long-acting β-agonist, methotrexate, omalizumab, prednisolone, steroid sparing

Two previous reviews in this Series [1, 2] described the approach to the child with problematic severe asthma, and the processes by which the truly severe, therapy-resistant asthmatic children are identified. This review addresses the treatment options to be considered. Almost without exception, the level of evidence is poor and, except for omalizumab, there are no good quality randomised controlled trials. Given the paucity of information in paediatric severe asthma, we have to extrapolate from data in adults with severe asthma, and any data in children with mild-to-moderate asthma not controlled on low-dose inhaled corticosteroids (ICS). Studies in adults will only be mentioned very briefly to give context. Unless otherwise stated, all

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PubMed searches are limited to human studies in children of all ages and to articles written in English. Therapeutic options can be divided into those used in lower doses for children with less severe asthma and those used in other paediatric diseases (for example, methotrexate), but not usually for asthma. It is assumed for the purposes of this review that the child has already undergone a detailed evaluation process [1, 2] and is already taking ICS, and has trialled at least two add-on therapies (long-acting β-agonists (LABA) and leukotriene receptor antagonists (LTRA)). We review what is known about the treatment of distal airway inflammation, and also the vexed problem of the child with apparently well-controlled asthma who has severe exacerbations. Finally, we will discuss what is known about monitoring treatment.

CONVENTIONAL ASTHMA MEDICATIONS

The first step is always to ensure that standard therapies are optimised. It is important to realise that, whereas prolonged poor baseline control may be a risk factor for exacerbations [3], good baseline control does not prevent the child having exacerbations, and no study has succeeded in completely abolishing exacerbations by any strategy. Treatment of exacerbations and the exacerbating phenotype are discussed in a separate section. A summary flow chart of recommendations for treatment is given in figure 1.

High-dose conventional ICS

The level of the plateau of the dose–response curve to ICS in children is a matter of debate. There is marked variation across Europe in the definition of high-dose ICS. Here, we arbitrarily define high-dose ICS as either 500 μg·day^{-1} fluticasone propionate (FP) equivalent, or 800 μg·day^{-1} beclomethasone (BDP), and low dose as ⩽100 μg·day^{-1} FP or 200 μg·day^{-1} BDP. In the majority of children, it may be as low as 200 μg day^{-1} FP [4]. High doses (>500 μg·day^{-1}) of mainly FP have been associated with severe hypoglycaemia secondary to adrenal failure [5, 6]. However, there is reason to believe that in some children, higher than conventional doses of ICS (>800 μg·day^{-1} BDP equivalent) may be beneficial and (perhaps) safe. First, steroid resistance is a spectrum, rather than an all-or-nothing phenomenon. *In vitro*, incubation of peripheral blood mononuclear cells with interleukin (IL)-2 and IL-4 leads to relative steroid insensitivity, which can be overcome by higher doses of dexamethasone [7, 8]. Secondly, high doses may be less well absorbed from the airway, at least in adults with asthma [9, 10]. An intravenous dose of FP was cleared equally rapidly by asthmatics and volunteers, but after both groups inhaled 1,000 μg of FP, the area under the curve for blood levels was significantly lower in the asthmatics, implying a lesser absorption from the airway than in the controls. This implies, but does not prove, that appropriate high doses of ICS, in proportion to the degree of airway inflammation, may be safer than is thought, and that it is only doses disproportionately high compared with the level of severity which are dangerous. A Cochrane review found few studies of high-dose ICS relevant to really severe asthma in children [11]. However, there was some evidence that those on oral prednisolone were able to reduce their prednisolone dosage if they used higher than conventional ICS doses. A clear need for more data was identified. Given the lack of evidence, it is difficult to make firm recommendations. In an asthmatic child dependent on oral corticosteroids (OCS), it would seem reasonable to try to reduce oral intake by increasing ICS, perhaps to as high as 2,000 μg day^{-1}, but reduce the ICS dose if oral steroid reduction is not possible. The use of these high doses of ICS should only occur under the very careful supervision of a specialist paediatric pulmonologist. Although careful surveillance is mandatory, how best and how frequently to monitor adrenal function, cataract formation and bone mineral density cannot be determined at the present time (this monitoring is unnecessary at or below daily ICS doses of 400 μg·day^{-1} FP).

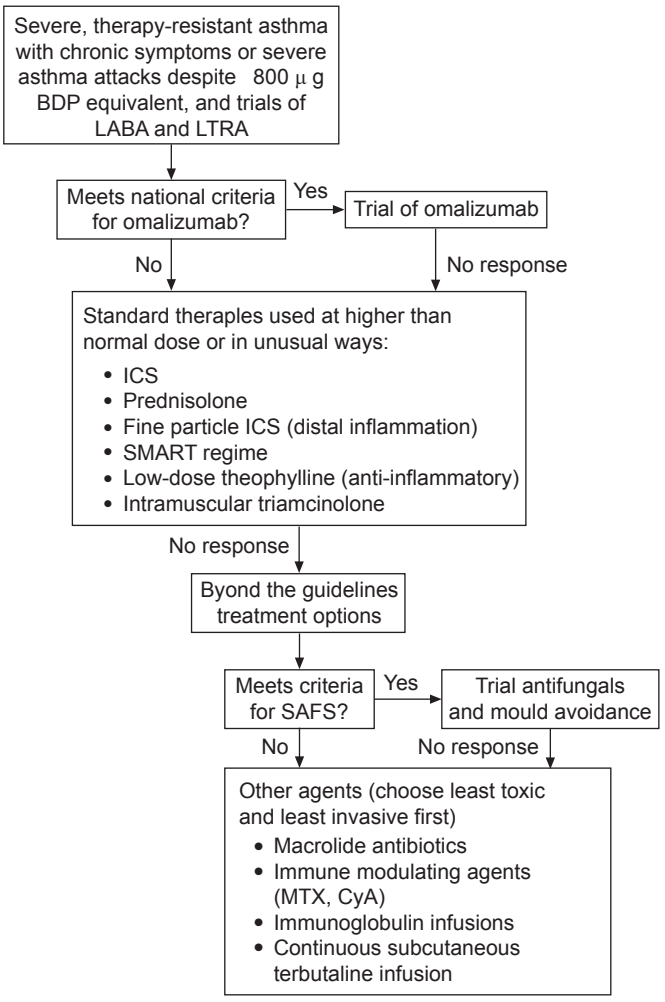

FIGURE 1. Suggested sequence for consideration of therapy for severe steroid-resistant asthma. BDP: beclomethasone dipropionate; LABA: long-acting β_2-agonist; LTRA: leukotriene receptor antagonist; ICS: inhaled corticosteroids; SMART: symbicort maintenance and reliever therapy; SAFS: severe asthma with fungal sensitisation; MTX: methotrexate; CyA: cyclosporine A.

Recommendations

Given the lack of evidence, it is difficult to make firm recommendations and more studies are needed. There are very few children who benefit from ICS doses higher than FP 500 μg·day^{-1}. Increasing doses of ICS (up to ~2,000 μg·day^{-1} FP) can be tried, in particular in parallel with an attempt to taper oral prednisolone. If significant clinical benefits are seen, the dose should be gradually tapered to the lowest dose which will maintain these benefits. If no benefits are seen the dose

should be reduced to the daily dose used prior to the increase. There is no need to routinely monitor for adverse systemic effects at ICS daily doses of $\leqslant$400 μg. It is not known whether and how routine monitoring for adverse systemic effects should be carried out at higher doses. At a minimum, height should be measured at each visit and plotted on a growth chart.

Oral corticosteroids

As for most other drugs the clinical benefits of OCS in children with asthma uncontrolled by ICS, LABA and LTRA are not well studied, but this therapy is often considered the next step in treatment recommendations. There is insufficient evidence in the literature to recommend a starting dose, or how quickly to taper OCS once control has been achieved. There is no evidence suggesting that, in the child with repeated exacerbations mandating oral prednisolone bursts, the prescription of daily or alternate day low-dose OCS will prevent these exacerbations. If regular OCS are contemplated, perhaps a reasonable starting dose might be 0.5 $mg \cdot kg^{-1}$ daily of prednisolone, tapering as symptoms permit, but there is no evidence base for this figure. There is no evidence base to recommend trial duration, but most would use 14 days, stopping the medication if there is no significant benefit. If there is a response, the dose should be minimised, but adequate to control symptoms; a recommendation for an upper dose limit cannot be given. OCS (continuous or intermittent) is associated with an increased risk of fracture and cataracts in children [12] and continuous treatment also with increased risk of adrenal insufficiency and growth retardation [13, 14].

Recommendations

Given the lack of evidence, it is difficult to make firm recommendations and more studies are needed. A therapeutic trial of prednisolone at an initial daily dose of ~0.5 $mg \cdot kg^{-1}$ alternate days should be tried. If significant clinical benefits are seen, the dose should be gradually tapered to the lowest dose which will maintain these benefits. This could involve alternate day dosing. If the therapy is given long term, the most common side-effects should be monitored, but exactly how is not known. However, measurement of height, urinalysis for sugar, and blood pressure measurement should be mandatory at every clinic visit.

Anti-immunoglobulin E antibody

This expensive therapy has become popular despite the inconvenience of administration and the need for observation after each injection. It is a logical option in children with true severe, therapy-resistant asthma who have been through the detailed assessments described previously [1, 2, 15] and who meet the following criteria: 1) ongoing chronic symptoms or severe exacerbations despite high-dose medication, or adequate control of asthma only at the cost of unacceptable side-effects; 2) known immunoglobulin (Ig)E-mediated sensitisation to one or more aero-allergens; and 3) every reasonable effort has been made to reduce the environmental allergen burden. Thus, the child allergic to cats who continues to own pet cats should not be considered for treatment in our view, even despite proven efficacy in cat allergic patients [16]. The upper limit of IgE recommended for therapy has just been raised to 1,300 IU. However, despite this, substantial numbers of children will have higher levels [17]; whether they will still benefit from therapy is controversial.

Omalizumab has proven to be safe and beneficial in children in trials of 1-yr duration. The long-term safety and efficacy has not yet been validated. Two randomised, placebo-controlled studies in children aged 6–12 yrs (n=961 in total) with moderate-to-severe asthma, showed in summary a significant reduction in ICS dose and number of exacerbations and improvement in asthma-related quality of life [18, 19]. Omalizumab was safe and well tolerated in children when used for $\leqslant$1 yr [20]. There were no serious treatment-related events [18, 19, 21]. Many studies of older children also included adults, making the purely paediatric number effects difficult to separate out [22, 23]. Nonetheless, there is sufficient evidence of efficacy in terms of reduction in exacerbations and medication use, and improvement in quality of life [19, 24, 25] for this therapy to be recommended in children with atopic allergic asthma aged $\geqslant$6 yrs if they meet clinical criteria and have an appropriate level of IgE. However, long-term safety and efficacy of omalizumab has not been determined. In a small sub-study, a fall in the exhaled nitric oxide fraction (F_{ENO}), comparable to that achieved with ICS, was observed [26], in keeping with the known effect on airway eosinophilia in adults [27]. There are no tests which can currently be recommended in order to predict who will respond to omalizumab [28]. Cost–benefit analysis suggests a fiscal saving if it is given to children with five or more admissions, cumulatively 20 days or more in hospital [29].

Recommendations

Omalizumab should be tried in children with poor asthma control and/or exacerbations in spite of daily or alternate day OCS treatment or treatment with high doses of ICS or ICS plus LABA or LTRA. Such trials should precede other steroid-sparing agents in children fulfilling the criteria for omalizumab treatment.

Treatment of distal inflammation

The distal airways are difficult to study, both pathologically and physiologically. Early studies using transbronchial biopsy (TBB) [30–32] suggested that distal inflammation was a feature, in particular, of nocturnal asthma and could be much more severe than proximal inflammation, although this is controversial [33]. The risks of TBB [34] make it an unattractive routine investigative modality in children. However, distal inflammation may be studied by partitioning exhaled nitric oxide (NO) into proximal (J_{NO}) and distal (C_{ALV}) fractions by measuring NO production at multiple flow rates [35, 36]. The relationship between NO and eosinophilic inflammation is particularly loose in patients using high-dose ICS or OCS [37, 38]. It is not clear whether distal inflammation is an intrinsic part of severe, therapy-resistant asthma or reflects poor distal airway deposition of conventional ICS. There are two possible approaches to targeting the distal airways, either using OCS and relying on airway perfusion or the use of small particle ICS such as Q_{VAR}^{TM} or ciclesonide [39, 40], which may have enhanced distal airway deposition. In an adult study poorly controlled asthmatics had elevated C_{ALV} which correlated with bronchoalveolar lavage eosinophil count and was reduced by oral prednisolone [41]. In a paediatric study, C_{ALV} was also elevated in poorly controlled asthma [42]. However, the role of distal inflammation in severe asthma is still contentious.

Recommendations

In a child with uncontrolled severe, therapy-resistant asthma and who has evidence of distal airway disease (elevated C_{ALV},

air trapping on a high-resolution computed tomography scan or abnormal lung clearance index), a trial of fine particle ICS or oral prednisolone should be considered. The optimal trial duration is not known, but should probably be at least 3 months.

The symbicort maintenance and reliever therapy regime

This relies on the use of a single inhaler (budesonide and formoterol) as regular therapy and for exacerbation of symptoms. In the original trials, the dose used was budesonide 100 μg and formoterol 6 μg once daily, with extra doses as needed, and there was a reduction in exacerbation rates with no increase in ICS dose, compared with conventional regimes. This regime has mainly been studied in adults with markedly uncontrolled asthma in spite of regular ICS or ICS/LABA combination treatment and a certain number of exacerbations have always been one of the inclusion criteria [43]. The study population was highly selected, and exhibited an average forced expired volume in 1 s (FEV_1) reversibility of >20%. The studies have consistently found that the strategy significantly reduced the risk of severe exacerbations, whereas the effects on asthma control have generally been small. Thus, only a mean of 18% of over 16,000 patients studied were well controlled after 1 yr of treatment. The same seems to be the case for adolescents where the symbicort maintenance and reliever therapy (SMART) regime had no significant effects on hospitalisations, asthma control days, need for rescue treatment and symptom-free days [44]. The optimal SMART daily dose for children with severe asthma has not been studied. It must be said that the SMART regime is still controversial, and data proving efficacy compared with conventional regimes are lacking [45–50]. Overdosing with LABA, both in the population as a whole and in those carrying particular β_2-receptor polymorphisms has been raised as a concern and it is recommended that LABA should never be given without ICS [51]. A recent meta-analysis of more than 100,000 patients did not detect any general adverse effects [52], although the authors stated that more data were needed. Therefore, it seems rather unlikely that treatment with ICS/LABA combinations in a single inhaler is associated with any clinically important adverse effects. The evidence in children with the Arg16/Arg16 polymorphism is less reassuring [53] than in adults [54], with some evidence of an increased risk of exacerbation on LABA.

Recommendations

More studies are needed in children. A trial of the SMART regime, probably using the budesonide 200 μg/formoterol 6 μg turbohaler, is worth considering in children with severe, therapy-resistant asthma in whom severe exacerbations are still a problem.

Low-dose theophylline

Theophylline has been rediscovered as a potentially beneficial agent in asthma. It had largely fallen into disrepute because of side-effects, drug interactions (for example, with erythromycin) and the need to monitor blood levels. However, low-dose theophylline, aiming at blood levels below the conventional therapeutic range (5–10 instead of 10–20 $mol \cdot L^{-1}$) has a number of immunomodulatory properties which might make it attractive. In adult studies, it inhibits the late-phase response to aeroallergen challenge [55]. It accelerates neutrophil apoptosis, making it of particular interest in neutrophilic asthma [56, 57]. Theophylline withdrawal leads to a rise in peripheral blood monocytes (CD14+, activated CD4+ T-lymphocytes (CD4+/CD25+) and activated CD8+ T-cells (CD8+/HLA-DR+)), with a rise in these cells in the bronchial mucosa [58]. Theophylline may downregulate inflammatory gene expression *via* effects on histone acetylases (HATs) and histone deacetylases (HDACs) [59]. HATs are increased and HDACs reduced in asthma, and this is reversed by glucocorticoids as well as theophylline, leading to a nuclear factor-κB dependent reduction in IL-8, tumour necrosis factor (TNF)-α and granulocyte-macrophage colony-stimulating factor in response to lipopolysaccharide. Furthermore, theophyllines may prevent downregulation of the β-receptor by β_2-agonists [60]. It is thus suggestive that at least some forms of acquired steroid resistance may be reversed by low-dose theophylline. However, the molecular mechanisms of steroid resistance in children with severe, therapy-resistant asthma are not known and may be different to adults, and generally the clinical effects of adding theophylline to ICS have been small [61, 62].

Recommendations

More studies are needed before firm recommendations can be made. In the meantime, a therapeutic trial with low-dose theophylline could be tried in individual patients with severe, therapy-resistant asthma. The duration of such a trial is not known, but it should probably be of some months.

Intramuscular triamcinolone

We have discussed elsewhere the use of a single dose of triamcinolone as a therapeutic trial of steroid resistance [63]. Since acquired steroid resistance is a spectrum, not an all-or-nothing phenomenon like congenital resistance [64], it could be argued that multiple injections may be more appropriate, although the dose and time interval is unknown. There has been a suggestion from an adult trial that depot triamcinolone may be better than OCS in the control of asthma, with fewer side-effects [65]. Comparisons of the two strategies are probably dogged by differences in adherence. Depot triamcinolone has the same class effects as prednisolone, with the additional risk of subcutaneous atrophy at the injection site [66]. Two small paediatric studies suggest that triamcinolone may improve symptoms and reduce airway inflammation in children with severe asthma [67, 68].

Recommendations

The exact place of depot triamcinolone as a treatment of severe, therapy-resistant asthma is not clear. It would seem reasonable to offer a trial for a finite period, in particular to those in whom poor adherence to prednisolone is suspected, which may perhaps demonstrate that the child is truly steroid sensitive if the steroids are actually administered.

EXPERIMENTAL THERAPIES

There are no agreed guidelines on the selection of suitable patients or the order in which these therapies should be tried. The use of any of these should be preceded by very careful discussions with the child and family, and rigorous safety monitoring should be in place.

Macrolide antibiotics

Macrolides have an array of immunomodulatory activities, in addition to their antibacterial effects [69–71]. They have

principally found a role in neutrophilic airway diseases, such as diffuse panbronchiolitis (in which their effects have been most dramatic) [72–74], cystic fibrosis [75–78], and non-cystic fibrosis bronchiectasis [79–81]. There is much less evidence in asthma and very little evidence in true severe, therapy-resistant asthma, despite a long standing interest in the role of macrolides in severe asthma, starting with the early studies of troleandomycin. This macrolide was initially popular as a steroid-sparing agent, although liver function abnormalities were a worry [82–85]. However, in a placebo-controlled study of troleandomycin in steroid-dependent asthma, there was no benefit in terms of steroid reduction, with if anything a more adverse profile of steroid side-effects in the active group [86]. This led to the suggestion that troleandomycin only exerted a ''steroid-sparing'' effect by reducing the catabolism of steroids, merely increasing half-life and exposure to toxicity in the face of an apparently reassuring dose reduction. The increase in steroid side-effects was confirmed in other studies, again using methyl prednisolone [87, 88]. A pharmacokinetic study showed that troleandoycin, even in low doses, reduced methyl prednisolone clearance by 60%, but had no effect on prednisolone pharmacokinetics [89]. Troleandomycin is no longer recommended for asthma treatment, although the dataset was small (90 analysable patients) [90]. Clarithromycin also had no effect on prednisolone clearance or drug levels, but decreased methyl prednisolone clearance by 65%, with an increase in blood levels [91]. This suggests that any macrolides may increase the half-life of methyl prednisolone.

The possible role of atypical respiratory infections in asthma led to exploration of the possible benefits of the antibiotic effects of macrolides. There is some evidence in adults that infection with *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* may be important, although this is still controversial. A randomised placebo-controlled, double-blind trial of clarithromycin in 55 adult asthmatic patients showed that only those given clarithromycin and with PCR positivity to *Mycoplasma* or *Chlamydia* had improvements in spirometry; all those treated with clarithromycin showed a reduction in pro-inflammatory cytokines [92]. Conversely, a trial of roxithromycin in adult asthmatics with serological evidence of *C. pneumoniae* infection showed only a transient beneficial effect on asthma control [93]. The macrolide telithromycin was shown be beneficial in acute asthma in a large randomised controlled trial, and the effect was independent of *Mycoplasma* or *Chlamydia* status [94]. With the realisation that there were neutrophilic asthma phenotypes [95], a number of mechanistic studies were performed in adult asthmatics. Macrolides have been shown to reduce neutrophilic inflammation [96], bronchial responsiveness [97–99] and airway oedema [100], and increase the steroid responsiveness of peripheral blood lymphocytes [101].

Mechanistic data in children are confined to small studies, which have shown that macrolides reduce induced sputum neutrophilia, reduce cytokine production by epithelial cells and improve bronchial hyperresponsiveness [102–104]. There is one large clinical study in children, which compared azithromycin with montelukast in children with asthma uncontrolled on ICS and LABAs [105]. The study was futile and underpowered, as recognised by the investigators, because most of those screened either did not have asthma or were not compliant with standard medications. However, the authors considered that even if the recruitment targets had been met, a benefit would have been unlikely.

Recommendations

Macrolides, such as azithromycin and clarithromycin, have immunomodulatory properties which make them attractive agents to explore in children with severe, therapy-resistant asthma. There is a paucity of efficacy data in asthma, but macrolides are safer than the cytotoxic agents. Whether their antibiotic properties could be important is an open question, but the recent finding of a rich bacterial flora in the lower airways using 16s rRNA methodology, and its alteration in children with asthma [106] suggests that these could be even more important than the immunological effects. It is reasonable to give a trial of macrolides, particularly in children with neutrophilic asthma. More data are needed to establish whether other groups may also benefit.

Cyclosporin

A Cochrane review [107] identified three adequate trials of cyclosporin in 106 adults with steroid-dependent asthma (98 patients analysable). There was a very small effect on steroid reduction, of questionable significance. There have been no new randomised trials since the review. One paediatric case series reported benefit in terms of OCS reduction in three out of five children [108]. Whether in the future nebulised cyclosporin may be beneficial with fewer side-effects is an important unanswered question [109, 110].

Recommendations

Paediatric data are very scanty, but a trial of cyclosporin could be considered in children with persistent eosinophilic airway inflammation despite OCS therapy, or requirement of unacceptably high levels of OCS to control their asthma.

Cytotoxics

Methotrexate and azathioprine have been used in severe corticosteroid-dependent asthma. If their use is contemplated in children, careful monitoring along standard lines is essential. There are no special monitoring requirements in the asthmatic child.

Methotrexate

In adults, the Cochrane review of 10 trials in 185 subjects suggested that there was overall a small benefit (reduction of OCS dose by <5 mg·day^{-1}), with risk of hepatotoxicity such that risks probably out-weighed benefits [111]. It is probable that within the group data there were individuals who did well. We identified three open-label trials including 20 children with steroid-dependent asthma aged 3–16 yrs treated with methotrexate. Significant side-effects are uncommon [112–114].

Recommendations

A trial of methotrexate can be considered in children with steroid-resistant airway inflammation and those requiring high-dose OCS to maintain control of asthma.

Azathioprine

A PubMed search using the terms ''Asthma'' and ''Azathioprine'' yielded no papers. The Cochrane review [115] found

only two studies of 23 adult patients which did not give enough evidence to recommend treatment.

Recommendations

Azathioprine cannot be recommended in children with asthma.

Gold salts

There are limited randomised controlled study data showing a steroid-sparing effect of auranofin in adult asthmatics [116–119]. There are no published paediatric data.

Recommendations

Given the need for detailed monitoring, the low chance of benefit, and the risk of adverse events, auranofin cannot be recommended in children with severe, therapy-resistant asthma.

Ig infusions

Adult studies are conflicting. One randomised controlled study, which included adults and children, demonstrated reduction in OCS requirements with no loss of control [120], whereas a second (also spanning the age range) was terminated prematurely because of adverse events, and showed no benefits [121]. There are four purely paediatric series, in which ~40 children received Ig infusions [122–125]. One open-label study reported that six out of 14 children could reduce their OCS, but two of the original 20 were withdrawn because of severe side-effects [122]. An open-label study of eight children documented reduction in steroid dosage and, interestingly, skin test reactivity [123]. By contrast, a randomised controlled trial in 31 children showed no benefits in asthma-related end-points, but did show in the treated group an attenuation of the severity but not the number of upper respiratory tract infections [124]. In a methodological study, analysis of bronchial biopsies before and after treatment showed reduction of all cell types, especially mucosal CD3, CD4 and CD25 positive T-cells, with reduced peripheral blood T-cell activation [125].

Recommendations

There is no adequately powered paediatric trial to support the use of infusion of *i.v.* Ig in asthma. Consideration of its use should probably be confined to asthmatic children who are OCS dependent. Side-effects, including aseptic meningitis are not rare. A trial of *i.v.* infusion of Ig may be justified in some children.

Anti-fungal therapy

In adult practice, and to a lesser extent in paediatrics, the concept of severe asthma with fungal sensitisation (SAFS) is becoming established. There is considerable evidence that fungal sensitisation and exposure are associated with increased morbidity and severity of asthma, including really severe exacerbations [126–130]. If a diagnosis of SAFS is being considered, sensitisation should be tested both with skin prick tests (SPT) and specific radioallergen absorbent tests (RAST) since concordance between the two varies from 70 to 80% [130, 131]. SAFS is diagnosed in a patient of any age with evidence of sensitisation on either SPT or RAST to at least one fungus (table 1) [130]. A randomised, double-blind, placebo-controlled clinical trial in adults showed some benefit in terms of improved quality of life and a reduction in IgE with itraconazole therapy [130]. This was more a proof of concept trial, with small numbers (<60 in total) rather than a study which showed major clinical benefit. The evidence in children is limited to isolated case reports [132]. The approach seems relatively safe.

Recommendations

Children with possible SAFS, who are not controlled after eliminating as far as possible any moulds in the environment, may be candidates for a trial of oral itraconazole or even voriconazole if symptoms persist, although the cost and side-effect profile of the latter mandate caution. The interaction between ICS and itraconazole leading to Cushing's syndrome should not be forgotten [133].

Subcutaneous terbutaline infusion

There is limited literature (n=41) on adults using subcutaneous infusion of terbutaline [134, 135] or salbutamol [136]. In children, fewer than 20 cases have been reported [137, 138]. Only one was a double-blind study [136]. There is obviously a strong placebo effect, and also concern about β-receptor down-regulation with this approach. One group suggested that this could be ameliorated by concomitant oral theophylline treatment [60]. Additional problems include local reactions [134], risk of hypokalaemia [139, 140] and a skeletal myositis with elevation of creatine kinase [141].

Recommendations

There is little evidence to recommend treatment with continuous subcutaneous terbutaline. It might be reasonable to trial it in selected children in whom airway inflammation has been clearly demonstrated to have been controlled by ICS or OCS, and in whom there is marked documented peak flow variability, despite appropriate use of inhaled LABA, especially including the SMART regime. We recommend commencing this treatment in hospital, using a double-blinded protocol. The child has four treatment periods, separated by wash-out periods, with detailed monitoring of peak flow in particular. The child and family know that only the ward pharmacist will know which the active treatment period is. All too often, the child gets better in hospital irrespective of treatment, as medication is given regularly and the influence of adverse home environmental influences wanes. In a few highly selected children, the benefits of continuous subcutaneous infusion of terbutaline may outweigh the considerable inconvenience of treatment.

TREATMENT OF THE EXACERBATING PHENOTYPE

Increasingly, guidelines have separated baseline asthma control from exacerbations. For example, persistently poor baseline control and reduction in lung function are associated

TABLE 1 Fungi implicated in severe asthma with fungal sensitisation

Aspergillus fumigatus
Alternaria alternate
Cladosporium herbarum
Penicillium chrysogenum
Candida albicans
Trichophyton mentagrophytes
Botrytis cinerea

with increased risk of exacerbations [142–146]. However, it is possible to have apparently perfect baseline control with severe viral exacerbations, and increasing conventional medications to the limit does not abolish all exacerbations. A previous very severe exacerbation is a risk factor for future exacerbations, making these children a high-risk group. There is clearly overlap, but children with excellent baseline control still exacerbate, and there is no evidence that increasing ICS dose between exacerbations in a well-controlled child is an effective strategy. There is also physiological evidence that the two are not the same [147]. Poor baseline control is characterised by symptoms and marked diurnal variability in peak flow, and responds well to usually low doses of ICS. Exacerbations are usually virally mediated [148], and characterised by an abrupt drop in peak flow, with little diurnal variability. Acute exacerbations may also be the result of overwhelming allergen exposure, as in the Barcelona soya bean epidemic [149] or thunderstorm asthma [150]. Although management should include every effort to optimise asthma control and lung function, and reduce airway inflammation in between exacerbations, virus-induced exacerbations cannot always be prevented, and can cause acute drops in lung function even on the background of apparent excellent baseline control (but much less frequently in controlled than uncontrolled patients).

Although in pre-school children with purely episodic, viral wheeze there is no evidence of an interaction between viral infection and allergens [151], the interaction is clearly present in school age children. One study showed that the combination of viral upper respiratory tract infection, allergen sensitisation, and high level of allergen exposure in the child's home was strongly predictive of an exacerbation severe enough to merit admission to hospital [152]. Although no study has convincingly shown that reducing allergen burden reduces exacerbations in children with severe, therapy-resistant asthma, such an approach, described in more detail elsewhere [2, 15], would seem sensible. This and other work has shown that low-dose ICS reduce the risk of exacerbations in children with mild-to-moderate asthma [142, 152]. There is some evidence that the use of oral LTRA [153], or very high dose ICS [154, 155], at the time of exacerbation may reduce the need for OCS in exacerbations. There is no study exploring the effects of high-dose ICS and LTRA together, but the combination could be considered if appropriate.

In adult practice, the exacerbating phenotype has been characterised as having few symptoms but discordantly marked ongoing eosinophilic airway inflammation between exacerbations [156]. It is this highly selected group that seem to respond to anti-IL5 therapy [157, 158]. The extent to which this phenotype exists in children and, if it does, whether it will respond to anti-IL5 therapy, remains to be researched.

Finally, the rare child who has catastrophic drops in lung function over a few minutes on the background of apparent excellent control (type 2 brittle asthma) may on an anecdotal basis benefit from being given injectable adrenaline (Epipen™) for emergency treatment of these deteriorations, enabling very rapid administration of a sympathomimetic (α and β) intramuscularly while more selective inhaled treatment is being prepared. Food allergy is common in this group and should actively be sought as part of the treatment programme [159, 160].

Recommendations

Children who have had previous severe exacerbations are at high risk for a future severe exacerbation and should be closely monitored. Every effort should be made to optimise baseline control and lung function; to identify allergic triggers and minimise allergen exposure; and to ensure low-dose ICS are being taken. The use of ever-increasing doses of ICS between exacerbations in children with good baseline control and lung function is not recommended. There is not enough evidence in children to recommend monitoring sputum eosinophils in these children. A trial of high-dose ICS with or without LTRAs at the first sign of an exacerbation may be considered.

MONITORING THERAPY

In the context of adult and less severe paediatric asthma, the use of *F*eNO has not been shown to improve daily asthma control or reduce the daily dose of ICS [161] (two studies found no change, two found an increase and one a reduction in the daily dose of ICS, all of them used different algorithms which made pooling of the data impossible [162–167]). However, some trials using tools such as *F*eNO, induced sputum or bronchial responsiveness to monitor asthma suggested that using inflammometry may lead to better control without the need for bigger ICS doses [164, 168, 169]. From adult data, it would appear that the greatest benefit of inflammometry is in those with more severe disease [170]. In children, exhaled NO has been used to predict successful reduction in ICS dose [171] and relapse after stopping ICS altogether [172]. The only study which has tested this in children with severe, therapy-resistant asthma showed only trends in benefit for inflammometry [173]. Reasons may have included the need to use NO in children who could not produce a sputum sample, despite the poor relationship between them in this population [174]; the much greater instability of sputum cellular phenotypes in children compared with adults [175]; and possibly, the need to make monthly rather than three monthly measurements (*post hoc* there was a benefit for inflammometry, but only in the month immediately after the measurements were made).

Recommendations

More work is needed to determine how best to monitor treatment to minimise side-effects and maximise benefits in this challenging group of patients.

SUMMARY AND CONCLUSIONS

We have reviewed the limited evidence for the various treatment options for children with severe, therapy-resistant asthma. It cannot be over-stressed that before employing any of them, every effort must be made to determine that the child truly has therapy-resistant asthma and that all the basic aspects of management have been correct [1, 2, 15]. A summary of our recommendations is given in figure 1. Therapeutic options can be divided into medications used in lower doses for children with less severe asthma, and those used in other paediatric diseases but not for asthma (for example, methotrexate). In the first category are high-dose ICS ($\leqslant$2,000 $\mu g \cdot day^{-1}$ fluticasone equivalent), oral prednisolone, the anti-IgE antibody omalizumab, high-dose LABAs, low-dose oral theophylline, and intramuscular triamcinolone. If peripheral airway inflammation is thought to be a problem, the use of fine particle ICS or

low-dose OCS may be considered. More experimental therapies include oral macrolides, cyclosporin, cytotoxic drugs such as methotrexate and azathioprine, gold salts, Ig, subcutaneous β_2-agonist treatment and, in those sensitised to fungi, oral antifungal therapy with itraconazole or voriconazole. Those with recurrent severe exacerbations, particularly in the context of good baseline asthma control, are particularly difficult to treat; baseline control and lung function must be optimised with the lowest possible dose of ICS, and allergen triggers and exposures minimised. The use of high-dose ICS, LTRAs or both at the time of exacerbations can be considered. There is no evidence on which therapeutic option to recommend.

In the future, it will be important to ensure that children are part of clinical trials in severe, therapy-resistant asthma. Recent developments in Europe will hopefully increase the likelihood of this [176].There is clearly a tension here, for example, anti-TNF-α strategies looked promising initially in severe therapy-resistant asthma [177], but subsequent studies have largely shown that the risk outweighs the benefit [178]. It is thus good that they were never formally trialled in children, although of course there is a nagging doubt, as children and adults are different, and a useful paediatric treatment may have been discarded. However, it is important that more promising therapies, such as anti-IL5 [157, 158] and bronchial thermoplasty [179, 180] are trialled in suitable children. Since it is highly unlikely that one centre will see enough patients to do a single-centre trial, the need for international collaboration with standard assessments of the children across Europe, is underlined [1, 2, 181, 182].

STATEMENT OF INTEREST

Statements of interest for S. Pedersen, E. Baraldi, F. de Benedictis and K.C. Lødrup Carlsen can be found at www.erj.ersjournals.com/site/misc/statements.xhtml

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