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## EVIDENCE-BASED REVIEW

# Immunomodulatory and biologic therapies for severe refractory asthma<sup>☆</sup>

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### Summary

Despite undoubted efficacy of the combination of inhaled corticosteroids and  $\beta_2$ -agonists for most asthmatic patients with moderate-to-severe disease, there remains ~10% of the asthmatic population with serious unremitting symptoms, resulting in considerable impact on quality of life, disproportionate use of health care resources, and adverse effects from regular systemic steroid use. In an ideal world, optimal treatment of severe refractory asthma should achieve the best possible asthma control and quality of life with the least dose of systemic corticosteroids. The choice and formulation of therapeutic agent are dictated by the severity of disease and may include immunological modifiers and biologic therapies. Unfortunately, current asthma guidelines offer little contribution to the management of the challenging patient with severe refractory asthma and none of them have addressed therapeutic alternatives to oral corticosteroids. This article reviews the current evidence for immunomodulating and biologic approaches in severe refractory asthma.

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<sup>☆</sup> The following Cochrane reviews have been cited in this Evidence-Based Review. Davies H, Olson L, Gibson P. Methotrexate as a steroid sparing agent for asthma in adults, Issue 2, 2000; Dean T, et al. Azathioprine as an oral corticosteroid sparing agent for asthma, Issue 1, 2004; Evans DJ, Cullinan P, Geddes DM. Troleandomycin as an oral corticosteroid steroid sparing agent in stable asthma, Issue 2, 2001; Evans DJ, Cullinan P, Geddes DM. Cyclosporin as an oral corticosteroid sparing agent in stable asthma, Issue 2, 2001; Evans DJ, Cullinan P, Geddes DM. Gold as an oral corticosteroid sparing agent in stable asthma, Issue 2, 2001; Sandborn W, et al. Azathioprine or 6-mercaptopurine for inducing remission of Crohn's disease, Issue 2, 2000; Walker S, et al. Anti-IgE for chronic asthma in adults and children, Issue 2, 2006.

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## Introduction

Most patients with asthma have mild-to-moderate disease easily controlled by regular use of inhaled corticosteroids (ICS) combined with short-acting inhaled  $\beta_2$ -agonists for relief of symptoms. However, in a small subset of patients, asthma continues to be poorly controlled in terms of ongoing symptoms, frequent exacerbations, persistent and variable airway obstruction and frequent requirement for  $\beta_2$ -agonists despite aggressive treatment.<sup>1</sup> The accurate prevalence of such cases is unknown, but may fluctuate around 5–8% of the total asthma population, depending on the definition of severe refractory asthma.<sup>2,3</sup> A working definition of severe chronic asthma has been recently developed on the basis of the level of intensity of corticosteroid treatment required to minimize symptoms (Table 1).<sup>4</sup>

Severe refractory asthma (SRA) is 2–3 times more common in women, is characterised by a component of irreversible airflow obstruction and peripheral airways disease, neutrophilic inflammation, ongoing mediator release, and a reduced association with atopy. These observations imply that SRA might be a 'different disease' with features that are distinct from mild-to-moderate asthma.<sup>5</sup> Patients with SRA have the greatest impairment of their lifestyles and account for a disproportionate use of health care resources through hospital admissions, unscheduled doctors' visits, and use of emergency services.<sup>6–8</sup>

In a patient with intractable respiratory symptoms (wheeze, breathlessness, chest tightness, and cough) despite frequent requirement for  $\beta_2$ -agonists and administration of substantial dose of inhaled and/or oral corticosteroids, physicians should consider the possibility of SRA.

**Table 1** American Thoracic Society workshop consensus for definition of severe/refractory asthma<sup>a</sup>

### Major characteristics

- Treatment with continuous or near continuous ( $\geq 50\%$  of year) oral corticosteroids
- Need for treatment with high-dose inhaled corticosteroids

### Minor characteristics

- Need for additional daily treatment with a controller medication (e.g. long-acting  $\beta$ -agonist, theophylline, or leukotriene antagonist)
- Asthma symptoms needing short-acting  $\beta$ -agonist use on a daily or near-daily basis
- Persistent airway obstruction ( $FEV_1 < 80\%$  predicted, diurnal peak expiratory flow variability  $> 20\%$ )
- One or more urgent care visits for asthma per year
- Three or more oral steroid bursts per year
- Prompt deterioration with  $\leq 25\%$  reduction in systemic corticosteroid dose
- Near-fatal asthma event in the past

<sup>a</sup> Definition requires that at least one major criterion and two minor criteria are met, other disorders have been excluded, exacerbating factors have been treated, and patient is generally compliant.

Certain conditions need to be systematically excluded and form part of the differential diagnosis of SRA.<sup>1</sup>

Current asthma guidelines offer little contribution to the management of the challenging patient with SRA and none of them have addressed therapeutic alternatives to high-dose ICS combined with a long-acting inhaled  $\beta_2$ -agonist (LABA) and oral corticosteroids.<sup>9</sup> Moreover, there remain a significant number of patients with severe unremitting disease that require regular systemic corticosteroids in order to minimize symptoms and exhibit a deterioration as soon as the dose of corticosteroids is tapered. Some excellent review articles on this topic have been published,<sup>1,10–12</sup> but very little attention has been paid to complementary therapeutic options.

In this review article, we appraise former and recent findings of immunological modifiers and biologic therapies used in patients with SRA in order to inform physicians about their potential role in this challenging condition.

## Methodology of the review

The overall methodology for this systematic review follows the directives published by the Cochrane Collaboration (see: [www.cochrane.org/resources/handbook/Handbook4.2.6Sep2006.pdf](http://www.cochrane.org/resources/handbook/Handbook4.2.6Sep2006.pdf)).

Full-text papers were identified on the basis of a literature search in the Cochrane Central Register of Controlled Trials and MEDLINE (January 1966 to June 2007). The terms for the electronic search were severe asthma/or/refractory asthma/or/steroid-dependent asthma/AND/therapy/or/azathioprine/or/cyclosporin/or/TNF/or/etanercept/or/inflximab/or/macrolides/or/gold/or/methotrexate/or/omalizumab. We limited our search to titles and abstracts of human studies published in English. All randomised-controlled trials (RCTs) and crossover-controlled trials (CCTs) of immunological modifiers and biologic therapies in steroid-dependent asthmatics were included. The main outcome of interest was the decrease in oral steroid dose. The search also identified a small number of clinical trials of poor quality with hydroxychloroquine and colchicine; their findings were inconclusive and they were not included in this review.

This article examines the respective immunological modifiers and biologic drugs by focusing on key studies to critically appraise effects in terms of key efficacy outcomes and safety. Some commentary is provided in order to help physicians with their clinical decision-making.

## Immunological modifiers for severe refractory asthma (Table 2)

In order to minimize the need for long-term systemic steroids, and to reduce their adverse effects, an exploratory trial with alternative anti-inflammatory and immunologic modifiers such as thiopurines (azathioprine (AZT)), macrolide anti-bacterials, cyclosporin A, gold and methotrexate (MTX), should be considered. If, however, the addition of these drugs does not lead to a substantial reduction in oral corticosteroid requirement within 24–36 weeks, they should be withdrawn. Careful monitoring of patients' symptoms and laboratory tests are mandatory to

**Table 2** Immunological modifiers for severe refractory asthma

| Drug              | Evidence for efficacy                     | No. of patients | Significant reduction in OCS dose | Improvements in other parameters                                                                  | Common side effects for agent                                                                                                                                                             |
|-------------------|-------------------------------------------|-----------------|-----------------------------------|---------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Thiopurines (AZT) | Hodges et al. <sup>17</sup> (CS)          | 10              | No                                | Increase in airway conductance.                                                                   | <ul style="list-style-type: none"> <li>■ GI upsets (diarrhoea, nausea, vomiting)</li> <li>■ Flu-like symptoms</li> </ul>                                                                  |
|                   | Hodges et al. <sup>17</sup> (CS)          | 13              | No                                | —                                                                                                 |                                                                                                                                                                                           |
| Macrolides (TAO)  | Ball et al. <sup>23</sup> (DBPC)          | 15              | Yes                               | Improvement in AHR.                                                                               | <ul style="list-style-type: none"> <li>■ Steroid related side effects (for TAO)</li> </ul>                                                                                                |
|                   | Kamada et al. <sup>24</sup> (DBPC)        | 18              | Yes                               | Improvement in AHR, asthma symptoms.                                                              |                                                                                                                                                                                           |
|                   | Nelson et al. <sup>25</sup> (DBPC)        | 57              | Yes                               | Reduction in hospital admissions, ER attendances and OCS boosts.                                  |                                                                                                                                                                                           |
| Cyclosporin A     | Alexander et al. <sup>38</sup> (CS)       | 30              | Not assessed                      | Improvements in PEF, FEV <sub>1</sub> . Reduction in asthma exacerbations.                        | <ul style="list-style-type: none"> <li>■ Hypertrichosis</li> <li>■ Hypertension</li> <li>■ Paraesthesias</li> <li>■ GI upsets (nausea, diarrhoea)</li> <li>■ Flu-like symptoms</li> </ul> |
|                   | Lock et al. <sup>36</sup> (DBPC)          | 36              | Yes                               | Improvements in morning PEF.                                                                      |                                                                                                                                                                                           |
|                   | Nizankowska et al. <sup>37</sup> (DBPC)   | 32              | No                                | Reduction in symptoms scores and reliever use.                                                    |                                                                                                                                                                                           |
| Gold              | Klaustermeyer et al. <sup>49</sup> (DBPC) | 8               | No                                | —                                                                                                 | <ul style="list-style-type: none"> <li>■ GI upsets (abdominal pain, diarrhoea)</li> <li>■ Pruritic rash</li> </ul>                                                                        |
|                   | Nierop et al. <sup>45</sup> (DBPC)        | 28              | Yes                               | Improvements in symptom scores, FEV <sub>1</sub> . Reductions in OCS boosts.                      |                                                                                                                                                                                           |
| MTX               | Bernstein et al. <sup>46</sup> (DBPC)     | 279             | Yes                               | —                                                                                                 | <ul style="list-style-type: none"> <li>■ LFT abnormalities</li> <li>■ GI upsets (abdominal pain, nausea, diarrhoea)</li> <li>■ Oral ulcers and stomatitis</li> </ul>                      |
|                   | Mullarkey et al. <sup>52</sup> (CS)       | 13              | Yes                               | —                                                                                                 |                                                                                                                                                                                           |
|                   | Dyer et al. <sup>54</sup> (CS)            | 10              | Yes                               | —                                                                                                 |                                                                                                                                                                                           |
|                   | Shiner et al. <sup>53</sup> (DBPC)        | 60              | Yes                               | Reduction in asthma exacerbations.                                                                |                                                                                                                                                                                           |
|                   | Erzurum et al. <sup>55</sup> (DBPC)       | 17              | No <sup>a</sup>                   | —                                                                                                 |                                                                                                                                                                                           |
|                   | Trigg et al. <sup>56</sup> (CS)           | 12              | No                                | —                                                                                                 |                                                                                                                                                                                           |
|                   | Taylor et al. <sup>57</sup> (CS)          | 9               | No                                | —                                                                                                 |                                                                                                                                                                                           |
|                   | Stewart et al. <sup>58</sup> (DBPC)       | 21              | No <sup>a</sup>                   | Improvements in subjective and physician symptom scores.                                          |                                                                                                                                                                                           |
|                   | Coffey et al. <sup>59</sup> (DBPC)        | 11              | Yes                               | —                                                                                                 |                                                                                                                                                                                           |
|                   | Kanzow et al. <sup>60</sup> (DBPC)        | 21              | No <sup>a</sup>                   | —                                                                                                 |                                                                                                                                                                                           |
|                   | Ogirala et al. <sup>61</sup> (DBPC)       | 19              | No                                | Improvements in FEV <sub>1</sub> , PEF, AHR. Reduction in hospital admissions and ER attendances. |                                                                                                                                                                                           |
|                   | Hedman et al. <sup>62</sup> (CS)          | 12              | Yes                               | Reduction in reliever use.                                                                        |                                                                                                                                                                                           |
|                   | Comet et al. <sup>63</sup> (DBPC)         | 46              | Yes                               | —                                                                                                 |                                                                                                                                                                                           |

CS, crossover study; DBPC, double-blind placebo-controlled study; OCS, oral corticosteroids; AZT, azathioprine; TAO, troleandomycin; AHR, airway hyper-responsiveness; ER, emergency room; CSA, cyclosporin A; PEF, peak expiratory flow; FEV<sub>1</sub>, forced expiratory volume in 1 s; QoL, quality of life.

<sup>a</sup> Significant within group improvements in the respective agent group.

prevent serious side effects. In this section we shall discuss these immunologic modifiers to evaluate their efficacy and safety in chronic severe asthmatics. Of note is that a number of trials discussed in this section are similar to those in Cochrane reviews, due the limited number of RCTs and CCTs that have been conducted in the respective agents.

## Thiopurines

Azathioprine (AZT) and its metabolite 6-mercaptopurine (MCP) are known to induce lymphopenia and reduce T-cell numbers.<sup>13</sup> They have been used for more than 30 years as steroid-sparing immunomodulatory agents. Rheumatoid

arthritis (RA), organ transplant recipients, chronic active hepatitis and inflammatory bowel disease are some of conditions in which AZT has been used.<sup>14–16</sup>

### The evidence

Two double-blind placebo-controlled randomised (DBPC) trials, with crossover design, in patients with stable oral corticosteroid (OCS)-dependent asthma meeting our inclusion criteria, will be discussed here.<sup>17</sup> Hodges et al.<sup>17</sup> recruited adult asthmatics with poorly controlled severe chronic asthma with a predicted FEV<sub>1</sub> of 21–48% and an OCS dose of 7–30 mg over a duration of 2–6 years. Ten subjects were randomised by a neutral observer to receive AZT (2 mg/kg) or placebo in addition to normal medication for 3 weeks. No significant reductions in OCS use, arterial oxygen partial pressure, lung function (FEV<sub>1</sub> and FVC) and asthma symptoms (cough, wheeze and climbing stairs) were reported between the 2 groups. There was a small significant difference in favour of AZT in airway conductance. The other study by the same group<sup>17</sup> was carried out in a similar fashion in 13 OCS-dependent adult severe asthmatics. Allocation by subjects to the groups (AZT (5 mg/kg) or placebo) was performed by a neutral observer and the drugs were administered over 4 weeks. Similar to the previous study there were no significant reductions in OCS consumption, improvement in PEF or asthma symptoms between the 2 groups.

### Adverse events

In the latter trial, 3 subjects in the AZT group suffered an asthma exacerbation during the first treatment period and participants were subsequently withdrawn from the study.<sup>17</sup> Mild myelosuppression was reported with a small but significant reduction in white cell count in the AZT group.<sup>17</sup> Occasional dyspepsia and herpes labialis were also reported. No hospitalisations occurred during treatment in either study.

### Implications for practice and research

There are a number of problems with these two studies. Firstly, it is unlikely that AZT administration for such a short period of time (3–4 weeks) could have been playing a significant role. Secondly, neither study formally assessed the effect of AZT on OCS consumption. However, anecdotal reports described 2 patients (1 from each trial) were able to reduce their OCS consumption when they resumed treatment with AZT, but this occurred outside the randomised comparison period. Thirdly, the very low FEV<sub>1</sub>% predicted, the lack of reversibility data and the significant sputum production in patients of both studies appear to suggest that some of them may have had COPD and been incorrectly enrolled. Fourthly, the number of subjects in the studies was small, notwithstanding the dropouts. Given these important methodological problems, the role of AZT in OCS-dependent asthma continues to be uncertain. To elucidate any significant steroid-sparing role for thiopurines in SRA, larger high quality randomised-controlled trials would be required.

### Macrolide anti-bacterials

The initial experience with macrolides in treating chronic asthma dates back almost 40 years and began primarily

with troleandomycin (TAO), a potent steroid-sparing agent with specific inhibitory effects on methylprednisolone (MP) clearance.<sup>18</sup> Improvement in asthma symptoms did not appear to be correlated with a direct anti-microbial effect.<sup>19,20</sup> Important benefits to patients with chronic asthma have been also reported with the newer macrolides<sup>21,22</sup> and they are consistent with the notion that these drugs act as biological modifiers, attenuating respiratory tract inflammation.

### The evidence

There have been 3 randomised DBPC parallel-group trials that have studied the effect of TAO in OCS-dependent asthmatics.<sup>23–25</sup> The dose of 250 mg daily of TAO was used in all studies. Two of these were conducted in a small number of children with OCS-dependent asthma and shared similar protocols.<sup>23,24</sup> Both studies reported substantial reductions in OCS usage in the TAO group (by at least 50% in the study by Ball et al.<sup>23</sup>), but significant reductions in the Kamada et al. study were also observed in the placebo group.<sup>24</sup> An improvement in the airway hyper-responsiveness (AHR) to methacholine after TAO was also observed in both studies. Specifically, for the TAO group of the study by Kamada et al.<sup>24</sup> a significant 50% reduction in asthma symptoms was reported. The third study was a much larger and longer trial in 75 steroid-dependent adult subjects randomised to receive TAO or placebo for 1 year.<sup>25</sup> For some of the study subjects, a single blind phase was added for an additional year. There was no formal tapering of steroids prior to study entry. Steroid tapering was attempted throughout the study if PEF measurements and asthma symptoms remained stable or improved. In the 57 subjects who completed the double-blind phase of the study, it was reported a significant reduction in mean daily steroid dose both in the TAO (from 30.8 to 6.3 mg/day) and in the placebo group (from 32.8 to 10.4 mg/day). Moreover, no differences were observed between the 2 study groups in terms of the number of hospitalisations and emergency room attendances, asthma control, and AHR to methacholine.

The effect of clarithromycin (500 mg twice daily for 6 weeks) has been investigated in a small randomised DBPC pilot study of 21 asthmatic patients with daily OCS requirements of  $\geq 5$  mg/day.<sup>26</sup> In this study, an overall improvement in lung function (FVC, but not FEV<sub>1</sub>) and symptoms was reported together with a concomitant reduction in prednisone usage. Interestingly, in 3 patients who continued clarithromycin therapy for 1 year, 2 of the 3 patients discontinued prednisone and no serious adverse effects, bacterial resistance or immunosuppression were reported.<sup>27</sup>

In the recent study by Simpson et al.<sup>28</sup> 45 subjects with SRA (44% received at least one course of oral prednisone in the past year) were randomised to receive either clarithromycin (500 mg twice daily) or placebo for 8 weeks as add-on therapy. Steroid dose reduction was not included as a study endpoint. Treatment significantly reduced inflammatory outcomes (sputum IL-8, sputum neutrophils), improved asthma-related quality of life (AQLQ) scores, and reduced self-reported wheezing compared with placebo, specifically in the subgroup of patients with non-eosinophilic asthma.

### Adverse events

With reference to safety issues unrelated to steroid side effects, there is an overall shortage of data. Interestingly the important side effect of TAO, namely abnormalities of liver function did not emerge as a major problem. In the TAO group, Nelson et al.<sup>25</sup> reported more cases of bone loss, higher cholesterol levels and reduction in IgG levels. Unlike TAO, no serious adverse events were reported in any of the trials with clarithromycin.

### Implications for practice and research

In a Cochrane systematic review of macrolides in chronic severe asthma, a meta-analysis of 90 patients recruited into the 3 TAO studies,<sup>23–25</sup> demonstrated that there was no treatment effect in terms of steroid dose reduction.<sup>29</sup> Similarly, for measures of lung function, a meta-analysis of the data from the studies by Kamada et al.<sup>24</sup> and Nelson et al.<sup>25</sup> showed no benefit for the addition of TAO. It must be noted that the studies carried out in the paediatric populations not only included a very small number of subjects, but their treatment duration was far too short to appropriately assess TAO efficacy. In the study by Nelson et al.<sup>25</sup> there were a substantial number of dropouts, which impairs interpretation of their findings. Also, in the trials by Ball et al.<sup>23</sup> and Nelson et al.<sup>25</sup> there was no formal OCS tapering protocol. Although preliminary data on the use of clarithromycin in SRA appears to indicate some beneficial effects, future large placebo-controlled studies in OCS-dependent asthma are required to establish the true potential of this drug as a biological modifier.

### Cyclosporin A

Cyclosporin A (CSA) is a fungal metabolite that is commonly known for its inhibitory effect on T-cell activation.<sup>30,31</sup> The use of CSA in asthma was implicated as T-cells have been shown to play a significant role in asthma pathogenesis.<sup>32</sup> CSA has been reported to antagonise the late-phase asthmatic reaction (LAR),<sup>33</sup> inhibit eosinophil-related cytokine production following allergen challenge<sup>34</sup> and attenuating AHR.<sup>35</sup>

### The evidence

Two prospective DBPC studies<sup>36,37</sup> and one placebo-controlled crossover study<sup>38</sup> have examined the efficacy of CSA (5 mg/kg/day) in OCS-dependent asthmatics. Alexander et al.<sup>38</sup> studied 33 asthmatic patients with a mean OCS usage of 8.5 mg/day. After a 4-week run-in period, they received CSA or placebo orally for 12 weeks. CSA therapy showed significant improvements compared to placebo in lung function (mean increase of 12% and 17.6% in morning PEF and FEV<sub>1</sub>, respectively) and exacerbations (48% reduction in the frequency of disease exacerbations) but no differences in symptom scores or rescue medication use. Although no specific OCS reduction was attempted, 11 weeks of run-out demonstrated that the mean morning PEF was significantly higher compared to baseline in the CSA group. In another DBPC parallel-group study by Lock et al.<sup>36</sup> 39 severe adult asthmatics on a mean prednisone dose of 12 mg/day were randomised to receive CSA (*n* = 19) or placebo (*n* = 20) for 36 weeks. After a 4-week run-in

period, patients randomised to receive CSA or placebo, with OCS tapering attempted from week 12 of treatment by a blinded physician if the patients' asthma remained stable or improved on a 2-weekly basis. A significant reduction in the median daily OCS usage from baseline (62%; from 10 to 3.5 mg/day) for the CSA-treated group (*n* = 16; 3 withdrawals) compared to the placebo group (25%; from 10 to 7.5 mg/day) was reported. Besides the significant reduction in OCS, there were marked improvements in morning PEF for the CSA group. In a similarly designed study, Nizankowska et al.<sup>37</sup> studied 34 OCS-dependent adult asthmatics on a mean prednisone dose of 16 mg/day were randomised to receive CSA or placebo for 36 weeks. No run-in period was included, but the lowest dose of steroid maintaining stable state of asthma was predetermined at the beginning of the trial. Significant reductions in OCS dose were observed in both study groups (CSA group: from 15.9 to 9.8 mg/day; placebo group: from 16.5 to 12.2 mg/day), but no significant difference between the groups. Also, it was observed that there was a small but significant difference in symptom scores and rescue medication use in favour of the CSA-treated group, however no improvements between the 2 study groups in terms of lung function.

Of note, CSA in open-labelled studies and case reports in OCS-dependent asthma have been shown to allow OCS dose reduction and improvements in asthma control.<sup>39,40</sup> In fact, there are a small number of subjects who actually are responders when treated over 9 months with CSA<sup>40</sup> and that withdrawal of CSA resulted in a rapid relapse of asthma symptoms and increase in use of OCS to pre-CSA treatment doses.<sup>41</sup>

### Adverse events

CSA toxicity is well described in transplant literature, with dose-dependent nephrotoxicity being the main concern. Mild renal impairment, abnormal liver function tests, increase in blood pressure, increase incidence of hypertrichosis and paraesthesia have been reported.<sup>36–40</sup> These side effects usually reversed upon discontinuation of CSA therapy.

### Implications for practice and research

The trials discussed vary in methodology and have certain limitations that have impact on the interpretation of the results. All 3 trials were small with approximately 30 patients in each and hence a Type 2 statistical error cannot be excluded for the non-significant results. In the crossover study by Alexander et al.<sup>38</sup> admonition should be expressed about the brief washout period between the treatment arms. Meta-analyses were limited by differences in the way data for steroid doses were expressed by the two steroid-sparing trial designs.<sup>36,37</sup> Despite these problems there were statistically significant effects of CSA on steroid doses. For the study by Nizankowska et al.<sup>37</sup> this effect amounted to a mean reduction of 6.1 mg in the CSA treated patients and 4.3 mg in the placebo treated patients. Likewise in the study by Lock et al.<sup>36</sup> there was an even smaller incremental reduction in the daily steroid dose. These minor reductions in OCS reduction may be of uncertain clinical importance. From the safety viewpoint there are definite changes in blood pressure and renal function, hence careful monitoring is important when using CSA. Although further trials with more subjects and longer duration are necessary to

elucidate the efficacy and steroid-sparing role of CSA in SRA, it should be taken into account that long-term use in other chronic inflammatory conditions such as RA and ulcerative colitis is burdened by a substantial failure rate.<sup>42,43</sup> However, novel cyclosporin analogues with much improved safety profiles, such as tacrolimus and pimecrolimus, which are effective for atopic dermatitis that is refractory to corticosteroid treatment, should be tested in SRA.

## Gold

Gold is an immunological modifier that has been used in inflammatory and autoimmune conditions including RA. Gold sodium thiomalate (GST), gold thioglucose and auranofin are examples of gold agents, of which the former 2 are administered parenterally and the latter orally. Not only is the mechanism of action of gold poorly understood, but also the action of oral and parenteral gold is thought to be different.<sup>44</sup>

### The evidence

Three DBPC studies of OCS-dependent asthmatics, 2 with oral gold<sup>45,46</sup> and one with parenteral gold<sup>49</sup> were identified. Klaustermeyer et al.<sup>49</sup> studied 10 asthmatic patients with a mean OCS dose of 21.15 mg/day. They were randomised to receive parenteral gold in the form of aurothioglucose 50 mg ( $n = 6$ ) or matched placebo ( $n = 4$ ) by intramuscular injections weekly for 22 weeks. There were no OCS tapering attempts made prior to enrolment. Two subjects from the treatment group and 1 from the placebo group were withdrawn due to heavy proteinuria (after weeks 4 and 15) and gas transfer abnormalities. Although there were significant improvements in the parenteral gold group compared to placebo, it was reported that 5 out of 8 subjects on parenteral gold improved in terms of reducing OCS requirements while maintaining or improving their lung function.

In the first study using oral gold, Nierop et al.<sup>45</sup> recruited 32 severe asthmatics with a mean OCS dose of 7.9 mg/day. Subjects were randomised to receive either auranofin 3 mg twice daily or matched placebo for 26 weeks, however no prior OCS tapering was attempted during or prior to the 1 week run-in period. The subjects were reviewed on a 2-weekly basis with tapering initiation at 12 weeks if appropriate. One patient was withdrawn from placebo due to non-compliance, and 3 (2 in the gold-treated group and 1 in placebo) due to severe eczema resistant to topical treatment. It was reported that the treated group achieved a significantly greater reduction in steroid use (auranofin group: from 9.3 to 5.3 mg/day; placebo group: from 11 to 10.7 mg/day). Correspondingly, there were significant differences between the 2 groups, in favour of gold, for improvements in symptom scores, FEV<sub>1</sub>, and courses of added prednisone for exacerbations.

In the largest trial, the Auranofin Multicentre Drug Trial,<sup>46</sup> 275 adult subjects with daily OCS requirements of  $\geq 10$  mg/day were randomised to receive either auranofin 3 mg twice daily or placebo for 6 months, where the primary outcome was therapeutic success as defined as at least 50% reduction in OCS from baseline. Efforts to taper the OCS dose were attempted in the 3 months prior to screening, with the majority of subjects being on 10–19 mg/day. Assessments were conducted on a 2-weekly basis with steroid tapering commencing at 12 weeks if

appropriate. Although the results were limited by a significant patient dropout rate in both study groups and no intention-to-treat analyses performed, a significant overall reduction in OCS use of 41% in the gold-treated group was achieved compared to 27% in the placebo group. However, no differences between groups for lung function, symptoms or concomitant medication use were observed.

Of note, in an open-labelled study of auranofin in 18 steroid-dependent asthmatics for 24 weeks, the overall steroid-sparing effect was associated with attenuation in AHR.<sup>47</sup> Interestingly, the study demonstrated a subgroup response, whereby 13 subjects reduced OCS dose by 72%, but 5 increased their OCS slightly.

### Adverse events

Side effects from gold therapy are common but mild. Proteinuria, severe exacerbations of eczema and mucocutaneous reactions to gold may compel withdrawal from gold treatment.<sup>45–49</sup> Other commoner and milder side effects reported include gastrointestinal upset, urticaria and stomatitis. Side effects are normally self-limiting with discontinuation or reduction of therapy.

### Implications for practice and research

Inadequacies of the discussed studies include discrepancies in the ICS use, lack of tapering prior to randomisation, besides the small numbers and short duration of 2 of the studies.<sup>45,49</sup> A meta-analysis of 376 subjects in the studies above<sup>45,46,49</sup> has demonstrated a small but significant improvement in favour of gold as a steroid-sparing agent.<sup>44</sup> Furthermore, given the various possible mechanisms of action and established differences in pharmacological profiles between auranofin and parenteral gold, comparisons of these 2 agents for steroid-sparing effects and efficacy are difficult. It also important to acknowledge that the results of the meta-analysis were driven by the large sample size of the study by Bernstein et al.<sup>46</sup> From the studies discussed, oral gold appears to be a useful steroid-sparing agent with acceptable toxicity. Further larger, adequately powered, DBPC studies are needed to determine long-term efficacy and safety of gold on SRA.

## Methotrexate

Methotrexate (MTX) is a folic acid inhibitor that antagonises the enzyme dihydrofolate reductase, in doing so impeding thymidine synthesis and consequently hampering DNA synthesis and cell division. Whereas at higher doses ( $>50$  mg/week) it is useful as an anti-mitotic agent for leukaemia,<sup>50</sup> at lower doses (5–25 mg/week) MTX possesses immunosuppressive and anti-inflammatory properties,<sup>51</sup> of which the exact mechanisms are poorly understood.

### The evidence

MTX has been the most investigated immunological modifier in asthma. The first trial to elucidate the steroid-sparing effect of MTX was a DBPC crossover study conducted by Mullarkey et al. in 1988.<sup>52</sup> This was soon followed by a DBPC parallel-group study published by Shiner et al.<sup>53</sup> In the study by Mullarkey et al.<sup>52</sup> 22 adult OCS-dependent asthmatics with a mean initial prednisone dose of 24.8 mg/day were recruited to receive oral MTX (15 mg/week) or placebo for 24

weeks (i.e.  $2 \times 12$  week treatment periods). No details of attempts to taper steroid doses before the trial were given. Participants were subjected to dose reduction by 5 mg every 5 days if their symptoms improved. In the 13 subjects who completed the study it was reported that in the MTX group there was a significant (36.5%) reduction in OCS use compared to placebo. A similar DBPC crossover study in 12 adults with OCS-dependent asthma with a mean initial prednisone dose of 13.1 mg/day was conducted with a 3-week run-in OCS taper period, a 12-week randomised period and 4-week washout, followed by a 12-week crossover. A significant (30%) reduction in OCS use was observed with MTX (15 mg/week). In the study by Shiner et al.<sup>53</sup> 69 OCS-dependent asthmatics with a mean initial prednisone dose  $\geq 7.5$  mg/day for at least 1 year before the trial were randomised to receive either MTX (15 mg/week) or placebo. Total duration of the trial was 38 weeks. It had a 4-week run-in, a 24-week treatment and 10-week run-out periods. OCS tapering was attempted every 4 weeks of treatment, if asthma remained stable or improved. In the 60 subjects who completed the study (32 in the MTX arm and 28 in the placebo arm), it was reported that there was a significant 50% reduction in OCS with MTX compared to placebo. The final dose fell to 6.6 mg/day compared to a 14% fall in OCS dose in the placebo group whose final dose was 12.9 mg/day. Of note, the steroid-sparing effect of MTX was not evident until after 12 weeks of treatment, and this effect did not persist when MTX was stopped, with subjects reverting to baseline OCS requirements in their run-out periods.

Since these initial observations, many other well-conducted studies evaluated the use of MTX in SRA.<sup>55–63</sup> Most of the studies recruited subjects who were taking regular OCS ( $>10$  mg/day) and used oral MTX at doses of at least 15 mg/week. The duration of treatment ranged from 12 to 24 weeks with no long-term follow-up, with the exception of the study by Comet et al.<sup>63</sup> where MTX was given for 12 months. For 3 of these studies,<sup>59,62,63</sup> a significant reduction in OCS dose with MTX was reported, whereas in the remaining 6 studies no significant change between MTX and placebo was observed.<sup>55–58,60,61</sup>

An important placebo effect was noted in most studies with significant reductions in OCS use, that could be attributed to the increased multiple follow-ups and patient education. Only a few trials had tapering of OCS in the run-in to maximise treatment prior to enrolment.<sup>56,60,63</sup> Treatment with MTX was noted only to have very minimal and often no significant improvements in FEV<sub>1</sub>,<sup>56,58</sup> subjective assessment of breathing ability,<sup>52</sup> reduction in daily bronchodilator use and asthma symptoms.<sup>62</sup>

In two separate prospective open-labelled extension studies<sup>64,65</sup> of 31 and 21 subjects respectively, treated with 15 mg/week of MTX for up to 28 months, it has been reported that there were statistically significant reductions in baseline OCS dosage with over half being weaned off all OCS. These long-term studies answered previous concerns regarding the possibility of tachyphylaxis or unusual toxicities unique to asthma when MTX is used to treat SRA. Recently, the data from a well-designed, DBPC study of 46 steroid-dependent asthmatic patients treated with MTX (10 mg/week) for 12 months has become available.<sup>63</sup> In this study, a substantial reduction ( $>50\%$ ) in OCS dose was observed in the MTX group compared to the placebo group.

At the end of the study, the OCS dose decreased from 17.3 to 7.8 mg/day in the MTX group, but only from 12.8 to 12.4 mg/day in the placebo group.

### Adverse events

Although low-dose MTX toxicity differs from the high doses used in cancer chemotherapy, side effects at these low doses may manifest in up to 60% of subjects.<sup>51</sup> Frequently reported side effects include abnormal liver function tests, GI symptoms, stomatitis, anorexia, alopecia, headaches, rashes, pneumonia and constitutional symptoms (fatigue and reduced concentration).<sup>52–62</sup> Most of these adverse events reversed on dose reduction or discontinuation of MTX therapy.

### Implications for practice and research

Three meta-analyses have been performed to date on 10–12 studies, some of which are discussed in the review.<sup>51,66,67</sup> A Cochrane meta-analysis of the 10 trials discussed,<sup>52–60,62</sup> demonstrated a reduction in OCS dose favouring MTX in parallel-group trials (WMD  $-4.1$  mg/day; 95% CI  $-6.8$ ,  $-1.3$ ) and also in crossover trials (WMD  $-2.9$  mg/day; 95% CI  $-5.9$ ,  $-0.2$ ).<sup>51</sup> No improvements in FEV<sub>1</sub> were noted and the commonest adverse event was hepatotoxicity. Thus, MTX may have a small steroid-sparing effect in adult OCS-dependent asthmatics. Similar results have been reported by the other 2 meta-analyses.<sup>66,67</sup> The trials discussed had some flaws in terms of the varied methodology and design, small numbers, lack of tapering of OCS and optimisation of ICS doses prior to randomisation, short duration of study, and variable washout periods in the crossover studies. Although there are no predicting factors for 'responders', there have been subgroups who have benefited from MTX. Also, steroid-sparing effects may require prolonged treatment ( $>3$  months) to appreciate benefits, which tend to disappear on therapy discontinuation. Large, adequately powered DBPC parallel-group studies need to be conducted to elucidate the steroid-sparing role, efficacy and safety of MTX in SRA.

## Biologic therapy for severe refractory asthma (Table 3)

Novel biologics have been developed for the treatment of asthma in recent years and some of them might be valuable substitutes to corticosteroid-sparing agents and immunological modifiers. In particular, monoclonal antibodies directed against TNF- $\alpha$  (infliximab, etanercept) and immunoglobulin (Ig)E (omalizumab) have been tested in patients with chronic severe asthma and could be useful in patients who have failed to respond to anti-inflammatory and immunomodulatory agents. Unlike the trials with immunological modifiers considered above, most of the good quality studies with anti-IgE and anti-TNF- $\alpha$  discussed below included only few OCS-dependent asthmatics and only rarely the main outcome of interest was the decrease in oral steroid dose.

### Anti-IgE (omalizumab)

IgE plays a pivotal pathophysiological role in the development of a number of allergic conditions by enhancing allergen uptake by dendritic cells and activating mast cells and basophils for mediator release.<sup>68</sup>

**Table 3** Biologics for severe refractory asthma

| Drug                                       | Evidence for efficacy                     | No. of patients | Significant reduction in OCS dose | Improvements in other parameters                                                                                    | Common side effects for agent                                                                                                               |
|--------------------------------------------|-------------------------------------------|-----------------|-----------------------------------|---------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| Anti-IgE —<br>omalizumab<br>(sc/iv)        | • Milgrom et al. <sup>73</sup><br>(DBPC)  | 317             | Yes <sup>a</sup>                  | Improvements in morning PEF, QoL. Reduction in asthma exacerbations and reliever use.                               | <ul style="list-style-type: none"> <li>■ Injection-site rashes</li> <li>■ Headache</li> <li>■ GI upsets (nausea, abdominal pain)</li> </ul> |
|                                            | • Busse et al. <sup>74</sup><br>(DBPC)    | 525             | Yes                               | Improvements in symptom scores, FEV <sub>1</sub> , morning PEF. Reduction in asthma exacerbations and reliever use. |                                                                                                                                             |
|                                            | • Soler et al. <sup>75</sup><br>(DBPC)    | 546             | Yes                               | Improvements in symptom scores, FEV <sub>1</sub> , morning PEF. Reduction in asthma exacerbations and reliever use. |                                                                                                                                             |
|                                            | • Milgrom et al. <sup>76</sup><br>(DBPC)  | 334             | Yes                               | Reduction in asthma exacerbations and reliever use.                                                                 |                                                                                                                                             |
|                                            | • Holgate et al. <sup>77</sup><br>(DBPC)  | 246             | Yes <sup>a</sup>                  | Reduction in reliever use. Improvements in symptom score and QoL.                                                   |                                                                                                                                             |
|                                            | • Humbert et al. <sup>78</sup><br>(DBPC)  | 482             | Yes                               | Reduction in asthma exacerbations and attendances to ER. Improvement in QoL, morning PEF, asthma symptom scores.    |                                                                                                                                             |
| Anti-TNF- $\alpha$ —<br>etanercept<br>(sc) | • Berry et al. <sup>89</sup><br>(CS)      | 10              | Not assessed                      | Improvement in FEV <sub>1</sub> , FVC, PEF, AHR and QoL.                                                            | <ul style="list-style-type: none"> <li>■ Injection-site reaction</li> <li>■ Headache</li> <li>■ Pharyngitis</li> </ul>                      |
|                                            | • Morjaria et al. <sup>90</sup><br>(DBPC) | 39              | Not assessed                      | Improvement in asthma control. Voluntary cessation of nebulised reliever use.                                       |                                                                                                                                             |

DBPC, double-blind placebo-controlled study; ICS, inhaled corticosteroids; sc, subcutaneous; iv, intravenous; PEF, peak expiratory flow; QoL, quality of life; FEV<sub>1</sub>, forced expiratory volume in 1 s; AHR, airway hyper-responsiveness; CS, crossover study.

<sup>a</sup> Non-significant within group improvements in the respective agent group.

Omalizumab, a humanized IgE-specific non-anaphylactogenic IgG1 that binds to free IgE at the Fc $\epsilon$ RI binding site on the C3 domain of IgE, thereby preventing its interaction with Fc $\epsilon$ RI receptors on effector cells,<sup>69,70</sup> and has been developed for the treatment of allergic asthma. Pharmacodynamic studies have reported the omalizumab attenuates allergen-induced early- and late-phase responses, the acquired AHR and inflammation, and allergen-induced skin prick tests.<sup>71,72</sup>

### The evidence

An early large Phase III trial of omalizumab, administered subcutaneously every 4 weeks at 0.016 mg/kg/IgE (IU/ml) in a heterogeneous population including also a few OCS-dependent asthmatics (35 out of 317, with a median prednisone usage of 10 mg/day), demonstrated modest improvements in asthma symptom scores and reduction in overall corticosteroid usage (inhaled and oral), but larger effects on reduction of asthma exacerbations.<sup>73</sup> These results were subsequently confirmed in at least three Phase III clinical trials in adults, adolescents, and children with poorly controlled allergic asthma, by demonstrating that omalizumab improves symptom control and allows patients to be managed with lower doses of ICS.<sup>74–76</sup>

Two other large DBPC parallel-group multicentre studies have also included patients with OCS-dependent asthma.<sup>77,78</sup> Holgate et al.<sup>77</sup> recruited 246 subjects following a run-in period for optimisation of ICS to receive sc omalizumab or

placebo for 16 weeks as add-on therapy followed by a 12-week of ICS dose-reduction phase at 2-weekly intervals if appropriate. There was a significantly greater reduction in ICS and in rescue medication use with omalizumab together with modest improvements in asthma control scores. Although there was 35–40% reduction in exacerbation rates, in the omalizumab group compared to placebo, this was not statistically significant. Importantly, asthma-related QoL reported a significant 88% improvement in the omalizumab group compared to 39% in the placebo group.

In the study by Humbert et al.<sup>78</sup> 419 subjects with chronic severe asthma including some 22% OCS-dependent asthmatics (with a mean OCS usage of 7.9 mg/day) were randomised to receive either sc omalizumab or placebo for 28 weeks as add-on therapy. There was a significant (26%) reduction in exacerbation rates and a 50% reduction in severe exacerbations in the omalizumab-treated subjects compared to placebo. Modest improvements in favour of omalizumab were reported for morning PEF, FEV<sub>1</sub>% predicted, total symptom and AQLQ scores. The results presented in this study, do not allow us to comment on potential additional effects of omalizumab in the subgroup with OCS-dependent asthma.

### Adverse events

It is worth mentioning that, in the above mentioned trials, omalizumab-associated adverse events did not differ significantly from placebo and most of the reported side

effects were minor (e.g. headaches, cough, GI symptoms, ENT infections, urticaria and injection-site reactions). However, a review of spontaneous post-marketing adverse events reports identified a number of anaphylaxis and anaphylactoid reactions (0.2% of total treated patients).<sup>79</sup> Hence, it is now recommended that patients taking omalizumab should be educated regarding the signs, symptoms and treatment of anaphylaxis and should be kept under observation for at least 2 h after each injection.<sup>80</sup>

### Implications for practice and research

Pooled analyses of omalizumab as add-on therapy have reported significant risk reduction of exacerbations and ER visits in moderate-to-severe asthma.<sup>81,82</sup> Likewise, pooled analyses of QoL outcomes have been reported to be significantly improved with omalizumab in the steroid-stable and reduction phases.<sup>83,84</sup> These findings have been also confirmed by a recent Cochrane review,<sup>85</sup> which also indicated that treatment with omalizumab results in a significant reduction in ICS and rescue medication use. In view of the large placebo effects noted and the presence of variable baseline steroid doses as well as difference in steroid consumption, the true effect of omalizumab remains controversial. Moreover, it is clear that not all subjects benefited from omalizumab treatment indicating the importance of recognizing responders from non-responders. Also, given that the large majority of patients with chronic severe asthma are non-atopic with normal IgE levels, it is likely that anti-IgE therapy with omalizumab will be a limited option. Sub-analyses carried out in the OCS-dependent asthmatics (mean prednisone usage of 10.2 mg/day) randomised to receive either omalizumab ( $n = 50$ ) or placebo ( $n = 45$ ) in the study by Holgate et al.<sup>77</sup> failed to show any significant difference in terms of asthma exacerbations or reduction in daily OCS dose.<sup>85</sup> Therefore, extrapolation of the positive effects of omalizumab in patients on step 2/3 of the guidelines to patients with OCS-dependent asthma is not supported by the data. Additional trials in this severe oral steroid-dependent population are required to determine whether they would benefit from omalizumab therapy.

### Anti-TNF- $\alpha$ (etanercept/infliximab)

TNF- $\alpha$  is a multifunctional pro-inflammatory cytokine (TH1) whose effects are regulated both by local concentrations and cell surface receptor dynamics. TNF- $\alpha$  has been implicated in the initiation and perpetuation of the asthmatic inflammatory process, epithelial damage and remodelling, AHR and mucin hypersecretion<sup>86</sup> and it has been reported to be elevated in subjects with severe asthma.<sup>87</sup> Beneficial antagonism of TNF- $\alpha$  has been shown in a range of chronic inflammatory disorders including rheumatoid arthritis, juvenile arthritis, ankylosing spondylitis, Crohn's disease and psoriasis.<sup>88</sup>

#### The evidence

Efficacy of TNF- $\alpha$  antagonism, using the soluble TNF- $\alpha$  receptor (TNFR) fusion protein, etanercept, has been also reported in 2 small studies of chronic severe asthmatics.<sup>87,89</sup> Objective improvements of lung function (FEV<sub>1</sub>, FVC and PEF) as well as AHR with methacholine were reported.

Significant subjective improvements of asthma control<sup>87</sup> and asthma-related QoL<sup>89</sup> were also noted. All but one subject voluntarily withdrew from using regular nebulised bronchodilators, but the beneficial effects last only 2–4 weeks after termination of treatment, reverting back to pre-treatment levels.<sup>87</sup> In another more recent larger DBPC study by Morjaria et al.<sup>90</sup> the use of etanercept failed to show any significant subjective as well as objective improvements in patients with SRA, with the exception of ACQ scores. Although steroid dose reduction was not included as a study endpoint, it is however worth mentioning that 4 patients randomised in the etanercept arm of the study completely withdrew the use of nebulised salbutamol.

Conversely, a DBPC study in mild-to-moderate asthmatics using the chimeric mouse/human monoclonal anti-TNF- $\alpha$  antibody, infliximab, failed to demonstrate any definite improvements as reported in the more severe studies.<sup>91</sup>

### Adverse events

Safety data on TNF- $\alpha$  antagonists has mostly been gathered from clinical studies of rheumatoid arthritis subjects where they have proven to be safe and well tolerated.<sup>92,93</sup> However, some adverse events have been reported and the long-term safety of these biological agents have not been thoroughly evaluated. Adverse events seen include increase risk of malignancy, opportunistic infections and reactivation of tuberculosis, demyelination and worsening cardiac failure.<sup>86</sup> A recent meta-analysis of the risk of serious infections and development of malignancy has recently been reported.<sup>94</sup> In the conducted asthma trials to-date TNF- $\alpha$  antagonism has shown no major adverse events of note.<sup>86,87,89,91</sup> The minor side effects seen noted include injection-site reactions, skin rashes, respiratory tract infections and headaches.

### Implications for practice and research

Overall, the role of anti-TNF treatment in SRA appears to be rather disappointing. However, additional considerations may explain the essentially negative findings of the above mentioned studies. First, the total symptoms score showed a large improvement over placebo, potentially offsetting any benefit observed within anti-TNF treatment; why patients with chronic severe asthma on placebo manifested such substantial improvements remains to be investigated. Second, the degree of disease severity in some of the trials discussed above may not be adequate to show a significant response; this is particularly pertinent for the study in mild-to-moderate asthmatics<sup>91</sup> where, given the larger role of TNF- $\alpha$  on airway inflammation in the more severe end of the disease spectrum, the observed lack of efficacy in mild-to-moderate asthma patients is not unexpected. Third, it is also possible that the dose was too low and the duration of the trials too short to detect significant changes. Last, the small sample size of these trials did not have enough power to detect changes. Nonetheless, some patients clearly benefited from anti-TNF treatment indicating, once again, the importance of recognizing responders from non-responders. Large clinical trials with etanercept and a variety of anti-TNF- $\alpha$  monoclonal antibodies are now in progress to evaluate the efficacy, safety and possibly steroid-sparing benefits of this subclass of biologics.

## Practice points and research implications

In spite of encouraging developments in asthma management, there is a small subset of patients whose asthma continues to be seriously symptomatic despite aggressive treatment with high-dose ICS and  $\beta_2$ -agonists. In these patients, reasonable symptom control is often achieved by regular systemic corticosteroids at the cost of significant adverse effects. Steroid tapering and reduction of their adverse effects may be achieved in SRA through add-on therapies with anti-inflammatory drugs, immunologic modifiers and biologic therapies.

These agents are infrequently used in patients with SRA. One of the reasons why these agents may have limited acceptance by respiratory physicians is because of concern in term of lack of efficacy and of unacceptable side effects. These safety concerns may be unfounded and need to be weighed against the significant adverse effects of long-term systemic corticosteroids. There is a large and growing experience of using immunologic modifiers to treat chronic inflammatory rheumatic diseases. This experience shows us that immunologic modifiers are effective for some but not for all patients, and that significant benefits may take months to occur. Moreover, most immunologic modifiers at low dose appear to be safe for long-term use, providing careful monitoring of patients' symptoms and laboratory tests is arranged.

Unfortunately, the large majority of the trials presented in this review article fail to support their role in OCS-dependent asthma because of major drawbacks in methodology, small sample size, heterogeneous patient populations, unsatisfactory follow-up period, lack of adequate run-in for stabilization of patients' steroid requirements, poorly defined response criteria for steroid tapering, short treatment duration and under-dosing are probably important causes for the inconclusive results reported in SRA. Apart from these obvious methodological considerations, the large placebo effect observed in some trials and the considerable heterogeneity in the drug response in individual patients requires additional care when designing clinical trials in patients with SRA.

In future, more efforts should be devoted towards determining the best use of anti-inflammatory, immunologic modifiers and biologic therapies in SRA and for the detection of the key characteristics of those who are going to respond to these agents. In an ideal world, SRA subjects might be considered for inclusion in a range of collaborative trials of add-on therapies that better control their asthma. The development of novel and powerful therapies that reduce the need for systemic corticosteroids in patients with severe refractory asthma should be a main priority for the academic world and the pharmaceutical industry.

## Conflict of interest

R.P. has participated as a speaker for CV Therapeutics, Novartis, Merck and Roche. He is also a consultant for CV Therapeutics, Duska Therapeutics and NeuroSearch.

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