

## Occasional review

## Corticosteroid sparing agents in asthma

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Chest physicians are all too aware of the serious side effects associated with the long term use of systemic corticosteroids, particularly weight gain, indigestion, impairment of glucose tolerance, and osteoporosis. The introduction of potent and topical inhaled corticosteroids allowed most patients on regular oral corticosteroids to reduce or stop these, but there are still patients with chronic severe asthma whose symptoms are inadequately controlled by high doses of inhaled corticosteroids and maximal bronchodilator therapy. Such patients receive increasingly frequent courses of oral corticosteroids, often culminating in their long term use. Side effects may not be a problem with a regular low dose of oral corticosteroid, but they become increasingly troublesome as higher doses are required. The management of these patients is extremely difficult and the treatment of their asthma and the side effects of corticosteroid therapy consumes much time and money.

Before discussing corticosteroid sparing agents three points need to be made. Firstly, in our experience it is relatively unusual for patients with asthma who are taking inhaled treatment correctly to require more than 5-7.5 mg prednisolone per day for asthma; patients taking more than this should be investigated very carefully. Preventable factors that need to be considered include non-compliance, occupational factors, gastro-oesophageal reflux, specific antigens, and dietary factors. Anxiety about asthma deaths has led to the overuse of corticosteroids by some patients and psychosocial factors and concomitant hyperventilation syndrome can be particularly difficult to disentangle. The second point is that some patients are truly corticosteroid resistant, showing a response to bronchodilators but none to corticosteroids.<sup>1,2</sup> These patients should not be prescribed corticosteroids. More commonly, patients on oral corticosteroids with severe asthma have some response to corticosteroids although this is relatively small. These are better described as having severe asthma rather than corticosteroid resistance. Lastly, any drug that is effective in asthma – whatever its mechanism of action – will, by definition, have a corticosteroid sparing effect in that less oral corticosteroid will be required to achieve a given improvement in asthma control. This review will not discuss recognised asthma therapies in this category.

**Corticosteroid sparing agents**

Several agents that have been shown to have corticosteroid sparing properties in other conditions have been studied in chronic severe asthma. For this reason we have described them as corticosteroid sparing agents, although some of the studies have looked at the effect of adding, rather than substituting, these agents to existing therapy which has usually, though not always, included corticosteroids (table). Many of the trials have involved small numbers of patients and patients have not necessarily been receiving optimal doses of inhaled corticosteroids and bronchodilators. In this review we describe the agents, their presumed mode of action, and the evidence for their efficacy in corticosteroid dependent asthma.

**GOLD**

Gold has anti-inflammatory properties; it has been shown to inhibit the IgE-mediated release of histamine and LTC<sub>4</sub> from basophils and mast cells,<sup>3</sup> and guinea pig tracheal smooth muscle incubated in the presence of gold is less responsive to histamine and specific antigen.<sup>4</sup> Intramuscular gold is prescribed worldwide for severe rheumatoid arthritis. There have been two studies of intramuscular gold and three of oral gold in asthma.

The first placebo controlled trial of intramuscular gold was carried out by Muranaka *et al* in 79 asthmatic patients.<sup>5</sup> After 30 weeks the gold treated group had fewer symptoms and required less medication; lung function was not measured. Seven patients receiving gold withdrew from the study because of dermatitis, stomatitis, or proteinuria. The same authors subsequently reported that, of 14 subjects studied for five years, five had discontinued all asthma medications whereas six had withdrawn because of dermatitis or stomatitis.<sup>6</sup>

The first study specifically to address the corticosteroid sparing qualities of intramuscular gold involved 10 corticosteroid dependent asthmatic patients treated with intramuscular gold or placebo for 22 weeks.<sup>7</sup> Five of the patients required lower doses of prednisolone whilst receiving gold without deterioration in their lung function. Gold had to be stopped in two patients who developed severe proteinuria.

In the first trial of oral gold 20 corticosteroid dependent asthma patients treated for 20 weeks

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## Summary of trials of corticosteroid sparing agents in asthma

Drug and dose	Trial design (duration of active treatment in weeks)	No. in trial	Type of trial	Prednisolone daily dose on entry	Significant findings with active drug compared with placebo
Hydroxychloroquine 400 mg/day oral (ref 37)	Double blind crossover (8)	9	SRT	For 12 months ?dose	None
	Open (28)	11	SRT if on steroids	7/11 steroid dependent	Improved symptoms, lung function and reduced steroid dose
Colchicine 0.5 mg/day oral (ref 44)	Double blind crossover (4)	10	Add on. No prednisolone	None (all on theophylline)	Reduced symptoms and bronchodilator use
Troleandomycin 250–500 mg/day oral (ref 52)	Double blind crossover (4)	74	SRT	High dose in previous 1 month	Reduced steroid dose and symptoms. Increased FEV <sub>1</sub>
	Double blind (104)	75	SRT	15 mg prednisolone or equivalent steroid	None
	Open (52)	14	SRT	At least 6 months ?dose	Reduced asthma attacks. Increased FEV <sub>1</sub> and PEF compared with baseline*
Azathioprine 2 or 5 mg/kg/day oral (ref 56)	Double blind crossover (3/4)	20	Add on	At least 10 mg	None
Cyclosporin A 5 mg/kg/day oral (ref 21)	Double blind crossover (12)	33	Add on	5–20 mg	Reduced asthma attacks. Increased PEF and FEV <sub>1</sub>
	Double blind (36)	39	SRT	Mean dose 11.3 mg/day + max inhaled steroid	Reduced steroid dose; improved morning PEF
Gold 12–100 mg every 4 weeks im (ref 5)	Double blind (30)	79	Add on. No prednisolone	None	Reduced bronchodilator use and steroid requirements
	Double blind (22)	10	SRT	10 mg for 12 months or 20 mg for 4 months	None
	Open (20)	20	SRT	Over 5 mg	Reduced symptoms and steroid requirement compared with baseline*
	Double blind (26)	32	SRT	5 mg or 2.5 mg + inhaled steroid	Reduced symptoms, steroid dose; increased FEV <sub>1</sub>
	Double blind (12)	19	Add on. No prednisolone	None	Small decrease in FEV <sub>1</sub> and in bronchial reactivity
Methotrexate 15 mg/week oral (ref 27)	Double blind crossover (12)	14	SRT	10 mg	Reduced steroid dose and symptoms
	Double blind (24)	69	SRT	7.5 mg + inhaled steroid	Reduced asthma attacks and steroid requirement
	Double blind (13)	19	SRT	12 months or 15 mg for 3 months	None
	Double blind crossover (12)	24	SRT	23.8 mg/day	Reduced steroid dose and symptom scores
	Double blind crossover (12)	10	SRT	7.5 mg or 20 mg alternate days	Reduced steroid requirement
	Double blind crossover (24)	18	SRT	10 mg for 6 months + inhaled steroid	None
	Double blind crossover (12)	11	SRT	Steroid dependent	None

SRT = steroid reducing trial; add on = agent added to steroid treatment; im = intramuscular; FEV<sub>1</sub> = forced expiratory volume in one second; PEF = peak expiratory flow. \* No placebo control.

with oral gold showed an improvement in symptoms and the frequency of asthma attacks, reduced bronchial reactivity to methacholine, and a 34% reduction in corticosteroid requirement.<sup>8</sup> There was, however, no control group and, since virtually all studies attempting corticosteroid reduction in the presence of placebo have reported improvement, the results are difficult to interpret. A subsequent controlled trial in 32 corticosteroid dependent asthma patients given oral gold (3 mg twice daily) or placebo for 26 weeks suggested some benefit.<sup>9</sup> Although there was no difference in the peak expiratory flow (PEF) or the number of asthma exacerbations between the two groups, the group given gold showed a greater reduction in oral corticosteroid use and the number of exacerbations requiring increased corticosteroid dose, and an improvement in forced expiratory volume in one second (FEV<sub>1</sub>) and symptoms of wheeze and cough compared with the placebo group. A recent double blind study of the effect of oral gold (3 mg twice daily) or placebo over 12 weeks in 19 mild non-corticosteroid dependent asthma patients showed a greater reduction in bronchial re-

sponsiveness to methacholine in those treated with gold.<sup>10</sup>

## CYCLOSPORIN A

Cyclosporin A is a cyclic polypeptide produced by the fungus *Tolypocladium inflatum*. It inhibits the activation of T lymphocytes<sup>11</sup> and the production and release of lymphokines such as IL-2, IL-3, IL-4, IL-5, and tumour necrosis factor.<sup>12–18</sup> It also inhibits histamine and LTC<sub>4</sub> release from mast cells and basophils<sup>19</sup> and neutrophil chemotaxis.<sup>20</sup> It is used to protect against allograft rejection and has been used to treat severe psoriasis, atopic dermatitis, oral lichen planus, nephrotic syndrome, primary biliary cirrhosis, and Crohn's disease. A recent controlled crossover trial assessed the effects of adding cyclosporin A for 12 weeks to 33 patients with corticosteroid dependent asthma on a constant dose of oral prednisolone.<sup>21</sup> Cyclosporin therapy resulted in an improvement in morning PEF (12%) and FEV<sub>1</sub> (18%) and a reduction in diurnal variation of peak flow (28%) and the number of asthma exacerbations requiring extra prednisolone (48%); there was

no improvement in symptom scores or bronchodilator requirement. One third of patients treated with cyclosporin noted significant hypertrichosis, one in eight developed hypertension, and there was a non-significant deterioration in renal function. A more recent parallel group placebo controlled study compared the effect of oral cyclosporin A (5 mg/kg/day) or placebo for 36 weeks in 39 corticosteroid dependent asthmatic patients taking high doses of inhaled corticosteroids. There was a greater reduction in prednisolone dose and a greater increase in morning PEF in the cyclosporin treated group. Three patients withdrew from the cyclosporin group because of hirsutism, a non-asthma related death, and a need for high dose prednisolone.<sup>22</sup>

It has been suggested that the ability of cyclosporin A to modify T cell proliferation and cytokine production might make it a useful drug for patients with corticosteroid resistant asthma,<sup>23</sup> since T cell abnormalities may underlie corticosteroid resistance. This group of patients has not been studied specifically.

#### METHOTREXATE

Methotrexate, an antimetabolite that acts by causing acute folate coenzyme deficiency, has anti-inflammatory and immunosuppressive properties. It has been shown to diminish neutrophil chemotaxis<sup>24</sup> and IL-1 production from activated peritoneal macrophages from animals,<sup>25</sup> and to inhibit basophil histamine release in man.<sup>26</sup> It is used to treat several neoplastic disorders and has been used in patients with severe psoriasis and rheumatoid arthritis. Four positive controlled trials with oral methotrexate have been reported, and three negative trials, two with oral and one with intramuscular methotrexate.

The first trial of methotrexate by Mullarkey *et al*<sup>27</sup> was a randomised, double blind crossover trial in which 22 corticosteroid dependent asthmatic patients requiring at least 10 mg prednisolone a day to keep their FEV<sub>1</sub> within 70% of predicted received oral methotrexate (15 mg/week) or placebo for 12 weeks. The 14 patients who completed the study showed a 36% reduction in oral corticosteroid requirement during methotrexate treatment compared with placebo, and subjective improvement in shortness of breath and wheeze without significant deterioration in lung function; the reason for the dropouts in the study is not, however, clear and doses of inhaled steroids were not reported.

In the largest study of methotrexate Shiner *et al* compared the reduction in oral prednisolone in 69 corticosteroid dependent asthmatic patients randomised to receive oral methotrexate (15 mg/week) or placebo for 24 weeks.<sup>28</sup> At the end of the study there was a greater reduction in prednisolone dose in the methotrexate group than in the placebo group (50% versus 14%); this reduction was not sustained 10 weeks after cessation of treatment. There were fewer exacerbations requiring increased corticosteroid dose during methotrexate treatment and symptom scores and lung function remained stable throughout the study.

Five of the 38 patients on methotrexate had substantially deranged liver function tests.

The findings were similar in a small crossover study of 10 patients with corticosteroid dependent asthma given oral methotrexate (15 mg/week) or placebo for 12 weeks.<sup>29</sup> Corticosteroid requirement fell by 30% with methotrexate compared with placebo, with no change in lung function in either group. Side effects included nausea and anorexia and a 2–3 fold increase in serum aspartate transaminase levels in four of the 10 patients which returned to normal after methotrexate was stopped. A recent placebo controlled crossover study compared the effect of oral methotrexate 15 mg weekly or placebo for 12 weeks in 24 corticosteroid dependent asthmatic patients.<sup>30</sup> During treatment with methotrexate there was a greater reduction in corticosteroid dose and symptoms scores. The only three patients to withdraw from the study were taking placebo. Adverse effects were mild; twice as many patients reported nausea, anorexia, and diarrhoea during treatment with methotrexate which did not necessitate stopping treatment.

Not all studies, however, have shown methotrexate to be efficacious in asthma. When 19 corticosteroid dependent asthmatic subjects were randomised to receive placebo or intramuscular methotrexate (15 mg/week) for 13 weeks both groups were able to reduce their oral corticosteroid requirement by approximately 40%; there was no difference in asthma exacerbations, symptom scores, or lung function between the two groups.<sup>31</sup> In a further 12 week crossover study oral methotrexate (30 mg/week) did not alter corticosteroid requirements or symptom score in 18 corticosteroid dependent asthmatics.<sup>32</sup> Infective complications were higher in the methotrexate treated group. Finally, in a recent crossover trial comparing oral methotrexate (15 mg/week) and placebo for 12 weeks in 11 corticosteroid dependent asthmatic patients there was improvement in lung function and reduction in prednisolone requirement within both treatment arms but no significant difference between placebo and methotrexate.<sup>33</sup>

#### HYDROXYCHLOROQUINE

Hydroxychloroquine is an inhibitor of phospholipase A<sub>2</sub>,<sup>34</sup> an enzyme involved in the synthesis of arachidonic acid from membrane phospholipids.<sup>35</sup> It would therefore be expected to reduce the production of leukotrienes and prostaglandins in the airways, many of which are bronchoconstrictor or proinflammatory. It is used as an antimalarial agent, as a second line agent in rheumatoid arthritis and systemic and discoid lupus erythematosus, and it has been used in sarcoidosis. After a case report in 1983 suggested that hydroxychloroquine had a corticosteroid sparing effect in asthma,<sup>36</sup> a crossover trial compared oral hydroxychloroquine and placebo over eight weeks in nine asthmatic patients.<sup>37</sup> There was no significant difference in symptom scores,  $\beta$  agonist requirement, PEF, FEV<sub>1</sub>, or corticosteroid requirement between the two treat-

ment groups. A recent open study of oral hydroxychloroquine (300–400 mg daily) for 28 weeks in 11 asthmatic patients reported an improvement in symptom scores and lung function and a reduction in steroid dose in the seven steroid dependent patients.<sup>38</sup>

#### COLCHICINE

The mechanism underlying the anti-inflammatory activity of colchicine has not been fully clarified although it has been shown to inhibit various neutrophil functions both in vivo and in vitro.<sup>39</sup> It also inhibits the release of  $LTB_4$ <sup>40</sup> and  $IL-1$ <sup>41</sup> from lymphocytes, and it partly corrected the impaired suppressor T cell function seen in patients with asthma.<sup>42,43</sup> Its anti-inflammatory activity has long been used in the treatment of gout, although benefit has also been seen in patients with psoriasis, primary biliary cirrhosis, familial Mediterranean fever, and Behcet's syndrome. Ten asthmatic patients were treated with colchicine or placebo for four weeks in a crossover study in 1990.<sup>44</sup> All were taking theophylline and none was taking any corticosteroid. Although PEF and  $FEV_1$  measurements were unchanged, symptom scores improved and bronchodilator requirements were lower whilst patients were on colchicine. The significance of this rather equivocal outcome in only 10 non-corticosteroid dependent asthmatic patients is uncertain.

#### TROLEANDOMYCIN

The beneficial effects in asthma of troleandomycin, a macrolide antibiotic, have been recognised since 1958<sup>45</sup> and were initially attributed to its antimicrobial activity.<sup>46</sup> However, pharmacokinetic studies by Szeffler *et al* showed that troleandomycin slows the elimination of methylprednisolone, effectively doubling its half life,<sup>47,48</sup> an effect not seen with prednisolone.<sup>48</sup> Troleandomycin is associated with hepatic dysfunction and the reduced metabolism of methylprednisolone may be due to reduced hepatic microsomal enzyme function. Recent work suggests that troleandomycin may also have anti-inflammatory properties since it inhibited peripheral blood mononuclear cell proliferation in vitro,<sup>49</sup> and, when given intravenously to rabbits, it inhibited the pulmonary accumulation of neutrophils<sup>50</sup> in bronchoalveolar lavage fluid.

After a small open study suggested that troleandomycin had corticosteroid sparing effects in patients with asthma<sup>51</sup> Spector *et al*<sup>52</sup> found a significant reduction in corticosteroid requirement and an improvement in  $FEV_1$  and symptom scores when troleandomycin was added to methylprednisolone in a placebo controlled study of 74 corticosteroid dependent asthmatic patients. More recently 75 corticosteroid dependent asthmatic patients were changed to an equivalent dose of methylprednisolone and randomised to receive troleandomycin or placebo for two years.<sup>53</sup> The ability to reduce methylprednisolone did not differ significantly between the two treatment

groups; the main differences in outcome were that patients on troleandomycin fared less well in that they had lower serum IgG levels, higher fasting blood sugar and serum cholesterol levels, and a greater reduction in bone mineral density. This study supports the suggestion that any beneficial effects of troleandomycin in corticosteroid dependent asthma relate to reduced metabolism of methylprednisolone. Similar findings were reported in a recent open clinical trial of 14 asthmatic patients who had been on oral corticosteroids for at least six months. When treated with troleandomycin and methylprednisolone for 13 months there was some evidence of benefit in asthma control but this was associated with a reduction in bone mineral density and an increase in plasma glucose concentration.<sup>54</sup> In all the troleandomycin studies patients have been taking methylprednisolone and it is still not clear whether all the effects of troleandomycin are due to inhibition of methylprednisolone metabolism.

#### AZATHIOPRINE

Azathioprine, an antimetabolite, is incorporated into intracellular DNA to prevent cell division. The exact mechanism of its immunosuppressive action is not certain but it is known to suppress the cell-mediated immune response.<sup>55</sup> It is used to prevent rejection following organ transplantation and is prescribed for patients with severe rheumatoid arthritis and several other autoimmune disorders. Surprisingly, it has only been studied in asthma in one short and fairly small crossover trial.<sup>56</sup> Twenty patients with corticosteroid dependent asthma were randomised to receive placebo or azathioprine, 2 mg/kg or 5 mg/kg/day for three and four weeks respectively, whilst corticosteroid dose was held constant. There was no improvement in symptoms or lung function with azathioprine despite the high doses. Mild dyspepsia was experienced by a few patients and there was a fall in circulating neutrophil count on the higher dose of azathioprine.

#### INTRAVENOUSLY ADMINISTERED IMMUNOGLOBULIN

Intravenously administered immunoglobulin has immunomodulatory activity and has been shown to inhibit antigen presentation and T and B cell interactions in the immune response. It is efficacious in various immunodeficiency disorders such as idiopathic thrombocytopenic purpura, and has been used to reduce the inflammatory response in systemic juvenile rheumatoid arthritis, Kawasaki disease, and myasthenia gravis. Its side effects include anaphylactoid reactions and symptoms of headache, nausea, and pyrexia. As yet there are only case reports and open studies of intravenous immunoglobulin in asthma. Mazer *et al* reported a reduction in corticosteroid requirement and symptoms and improvement in PEF in an open trial of eight corticosteroid dependent children with asthma treated with

2 g/kg intravenous immunoglobulin per month for six months.<sup>57</sup>

### Conclusions

Oral corticosteroids have a large number of side effects although these are often not unduly troublesome until a patient has been taking prednisolone in doses of 5 mg or more for several years (or the equivalent dose of another corticosteroid). Whether corticosteroids can be successfully replaced by another drug depends on the extent to which the new drug can replace oral prednisolone (corticosteroid sparing effect) and the side effects of the new drug compared with those of the dose of prednisolone that it replaces.

At present there is no evidence of any corticosteroid sparing effect of hydroxychloroquine in asthma. The only study in the literature of the use of azathioprine in asthma did not show any improvement in lung function or symptom scores although its corticosteroid sparing effect was not assessed. Colchicine showed some efficacy in one study in patients with mild non-corticosteroid dependent asthma but has not been assessed as a corticosteroid sparing agent. There is evidence of a corticosteroid sparing effect of troleandomycin in asthmatic patients taking methylprednisolone, but most of the evidence suggests that this is due to a reduction in the metabolism of methylprednisolone and is equivalent therefore to increasing the dose of oral corticosteroid. One study showed an increase in side effects with no improvement in asthma control. Troleandomycin has not been studied with prednisolone in asthma but at present there are insufficient data to support its use.

There is more convincing evidence of benefit from cyclosporin A, gold, and methotrexate. Cyclosporin A showed efficacy in corticosteroid dependent asthma and its corticosteroid sparing effect has recently been assessed. The trials involving intramuscular and oral gold are encouraging although some are small and of short duration. Methotrexate showed benefit in four of seven studies including the larger and one of the longer studies in asthma. There is some evidence that the benefit of low dose methotrexate therapy in patients with rheumatoid arthritis wanes after 4–6 months, though this was not the case in the positive study of 24 weeks which showed benefit.<sup>28</sup>

If cyclosporin A, gold, and methotrexate have corticosteroid sparing activity, how effective are they? When corticosteroid sparing studies have been carried out the reduction in mean prednisolone dose in the short term has been fairly low, with a range of 0–9.5 mg/day for methotrexate and 0–5 mg/day for gold. The important question is whether this improvement is maintained and, if so, how the side effects of the new drugs over many years compare with the reduction in side effects expected from this reduction in prednisolone dose (0–10 mg) over the same period. Side effects of gold (stomatitis, dermatitis, and proteinuria) have necessitated treatment being stopped in up to 20% of patients.<sup>7</sup> Side effects of metho-

trexate include hepatic dysfunction (up to 40% in one study<sup>29</sup>), opportunistic infections such as *Pneumocystis carinii*,<sup>58–62</sup> pulmonary cryptococcosis,<sup>63</sup> and nocardiosis,<sup>64</sup> and, rarely, pulmonary fibrosis. The latter two are of particular concern in patients with asthma since the symptoms may be confused with deteriorating asthma. Treatment with cyclosporin A causes hypertrichosis, hypertension, and renal damage in a proportion of patients. Equating benefit and side effects is further complicated by the fact that both are likely to be a function of log dose rather than dose and the effect of reducing the dose of prednisolone from 25 to 20 mg may be considerably less than the effect of reducing the dose from 10 to 5 mg per day.

Side effects clearly vary between patients and, for an individual patient, a corticosteroid sparing drug is worthwhile if it is effective and has no important side effects. For others the reverse will be true. Some of the potential side effects can be monitored (blood pressure, white cell count) but others such as opportunistic infections can occur rapidly and may on occasions be fatal. If gold, methotrexate, and cyclosporin A are given to patients with asthma they need appropriate monitoring. The drugs should only be continued if they are beneficial with no important side effects.

A further point that emerges from these studies is that pharmacokinetic data on interactions between some of the agents under investigation and concomitant medications that may also be prescribed are very limited. It is possible that some of the agents are acting by affecting the metabolism of other drugs such as theophylline.

Many of the studies discussed in this review include small numbers of patients and are of relatively short duration. If corticosteroid sparing drugs have a role in the treatment of asthma they need to be effective long term and more information is needed about their side effects over years rather than months. Large multi-centre trials are probably needed since the number of patients for whom such a study is appropriate is fairly small. Current management of these patients is unsatisfactory and finding a safer alternative to oral prednisolone should be an important priority.

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