Appropriate use of oral corticosteroids for severe asthma

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Asthma remains one of the most common chronic respiratory conditions worldwide, affecting about 300 million people. The prevalence is particularly high in most resource-rich nations, and is on the rise.[1] The global burden of asthma affects a large segment of the population and represents a substantial economic burden to many countries. In Europe alone, it is estimated that €17 billion in costs are associated with both the direct and indirect consequences of asthma, more than half due to lost productivity.[1] In addition, up to 10% of the population with asthma has disease that can be defined as severe.[2] At present, the most widely accepted definition of severe asthma, outlined in a joint statement from the European Respiratory Society and the American Thoracic Society (ERS/ATS), is "asthma which requires treatment with guidelines suggested medications for [Global Initiative for Asthma] steps 4–5 asthma (high dose [inhaled corticosteroids and long-acting β-agonists] or leukotriene modifier/theophylline) for the previous year or systemic [corticosteroids] for ≥ 50% of the previous year to prevent it from becoming 'uncontrolled', or which remains 'uncontrolled' despite this therapy".[2]

While patients with severe asthma may represent less than 10% of all individuals with asthma, they are responsible for generating half the health care costs associated with the disease.[3] Meanwhile, the development of new therapies has been slow, and although there have been major improvements in asthma-related morbidity and mortality for the majority of patients with asthma, in those with severe disease this has not been the case.[4] In the face of a large body of evidence about the side effects and complications related to systemic corticosteroid use, and with the influx of novel biological therapies that target specific disease pathways, the role of oral corticosteroids (OCS) has narrowed. However, OCS still remain critical in the maintenance of severe asthma and in the management of acute exacerbations.

Summary

- Severe asthma represents a significant burden of disease, particularly in high income nations; oral corticosteroids (OCS) remain an important part of the management toolkit for these patients.
- Corticosteroids are effective at targeting numerous elements of the type 2/eosinophilic inflammatory pathway and lead to both rapid reduction in eosinophilic inflammation and longer term reduction in airway hyper-responsiveness.
- Resistance or insensitivity to corticosteroids is a feature of severe asthma, with persistent type 2 inflammation often occurring despite regular use of OCS.
- OCS remain the only accepted, effective treatment for acute asthma, and also continue to play an important role in the long term management of severe asthma, in spite of their significant side effect profile.
- Even with the availability of the new biological therapies against IgE and interleukin-5, it is likely that a large proportion of patients will continue to require OCS to control their asthma.
- Future work should focus on optimising the balance between OCS efficacy and safety, and continued development of agents that allow reduction, or ideally discontinuation of their use, is needed.

History of oral corticosteroids use in asthma

Before the 1950s, the treatment for asthma was restricted to those compounds that were either plant-derived or adrenaline derivatives. This treatment consisted primarily of bronchodilator agents.[4] With the development of steroid and adrenocorticotropic hormone extracts, a 1952 seminal study by McCombs noted the marked improvement that could be derived with respect to asthma symptoms and control using either corticosteroids or adrenocorticotropic hormone.[5] It has since been determined that oral and parenteral corticosteroids have no significant difference in bioavailability, and thus oral corticosteroids are by far the most common formulation of systemic corticosteroid used in the treatment of asthma today. It was not until 1958 that the association between successful treatment with OCS and a reduction in eosinophils in the sputum was noted.[6] This revelation opened the door to widespread treatment with OCS, both on a chronic and acute basis,[4] but with this came increasing recognition of the side effects of systemic corticosteroids. The subsequent development of inhaled corticosteroids and the recognition that these can be equally as effective in the majority of patients with asthma, therefore, led to a decline in the use of OCS, except in the population with severe asthma.[7]

Pathophysiology and mechanisms of action of oral corticosteroids in asthma

The anti-inflammatory nature of OCS is the key to their efficacy in asthma. At present, it is suspected that at least half of all patients with asthma have predominantly eosinophilic inflammation, including the majority with early onset disease associated with allergy.[8] It is this population with eosinophilic inflammation that are the best understood and studied, especially with respect to the efficacy of corticosteroids. In these individuals, a complex interaction between genetics, airway damage and a maladaptive immune response within the airways leads to the development of asthma.[9] Meanwhile, re-exposure to allergen, infection or other irritants initiates an inflammatory pathway mediated by cell signalling molecules, namely interleukins (IL)-4, 5 and 13. The term "type 2 inflammation" has been used to describe this eosinophilic pathway for inflammation in the patient with asthma, which is differentiated from non-type 2 inflammation, thought to be predominantly associated with neutrophilic or paucigranulocytic sputum phenotypes, and with potentially different pathobiological mechanisms. The inciting irritants and subsequent type 2 inflammatory cascade lead to recruitment of mast cells, eosinophils and CD4+ T lymphocytes and further

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release of their associated type 2 cytokines. The presence of this inflammation is associated with increased thickness of the smooth muscle layer, excessive and variable airway narrowing (airway hyper-responsiveness) and increased secretion of mucus.[10]

Corticosteroids are effective at targeting numerous elements of this pathway. Eosinophils, especially, respond quite rapidly to corticosteroids and undergo apoptosis due to down-regulation of the roles of IL-5 and granulocyte-macrophage colony-stimulating factor in promoting eosinophil survival.[11,12] Corticosteroids also inhibit transcription at the genomic level of IL-4 and IL-5, thereby inhibiting this portion of the type 2 inflammatory cascade responsible for the maturation, chemotaxis and survival of eosinophils.[12] Increased secretion of mucus is thought to be reduced by direct effects of corticosteroids on the submucosal glands as well as a reduction in the inflammatory milieu of the airway wall. Reductions in airway hyper-responsiveness are seen over many months,[13] a much longer timeframe than that seen for inflammation.[14] During this period, the patient is likely to remain at risk of symptomatic recurrence. Although corticosteroids reduce the thickness of the reticular basement membrane in asthma, their effect on the increased airway smooth muscle seen in asthma is not known.[14]

The pathology of severe asthma is similar in nature but more marked in terms of inflammatory cell infiltration and remodelling than that of milder asthma cases; however, an additional inherent feature of severe asthma seems to be a resistance, or at least insensitivity, to the effect of corticosteroids.[15] Resistance has been defined previously as "failure of the peak expiratory flow measured on waking to improve after treatment for 10 to 14 days with OCS given in high doses".[16] This is contrasted with insensitivity, where patients can only be controlled on large doses of corticosteroids but may still improve with dose escalation.[16,17] In those with severe asthma, persistent type 2 inflammation occurs despite regular use of OCS. Interestingly, eosinophilia in treated severe asthma has not been linked with increases in cytokines from the type 2 inflammatory pathway, and these are found in lower concentrations than in steroid-naive patients with milder asthma. Meanwhile, mild asthma has been reported to have an equivocal tendency to airway neutrophilia, with up to 50% of severe cases showing no eosinophilic inflammation.[18] It is unclear how much of this population with neutrophilic airway inflammation reflects the effects of treatment with corticosteroids. In a recent study of 80 individuals with severe asthma, asthma onset before 12 years of age was associated with atopy (98% *v* 76%), higher serum IgE and increased eosinophils, lymphocytes and mast cells in the airway wall, compared with onset after 12 years of age.[19] In those with later onset asthma, half had no airway eosinophilia and tended to have poorer lung function and a history of near-fatal attacks.[19]

These findings were recently replicated in the larger Severe Asthma Research Program (SARP) — a severe asthma cohort in which about half of the patients had persistent type 2 inflammation.[20] It has been proposed that those with non-eosinophilic asthma are more refractory to the effects of corticosteroids, perhaps a consequence of different disease mechanisms, and this appears to be the case with inhaled corticosteroids.[21] However, OCS are widely used in non-eosinophilic asthma, although their relative efficacy compared with those with refractory type 2 eosinophilic inflammation is unclear. At least one small study of children with difficult asthma showed that OCS resulted in a similar improvement in lung function irrespective of whether the children had elevated sputum eosinophils or not.[22]

Thus, OCS remain a key therapeutic option for patients with severe asthma, particularly in the setting of active type 2 inflammation, due to their efficacy at multiple levels of the inflammatory cascade. Treatment with OCS has demonstrable biological plausibility and is effective, although at higher doses, in the settings of steroid insensitivity.[17]

Long term use of oral corticosteroids for asthma

Current asthma guidelines recommend advancing asthma treatment in a step-wise fashion to reach disease control, for both improvement in symptoms and prevention of exacerbations.[23] This step-wise progression begins with low dose inhaled corticosteroids, then, if necessary, it progresses to inhaled corticosteroids combined with long-acting β-agonists, which will control most cases of asthma. Until recently, regular use of OCS was often the only effective option for those with severe disease that could not be controlled with the previous steps. Contemporary research has therefore focused on optimal dosing, and a Cochrane review has confirmed that OCS treatment that is titrated based on sputum eosinophil counts results in reductions in exacerbation rates compared with dosing based on clinical markers alone.[24] The options have recently expanded and now include inhaled long-acting anticholinergic therapies and biological agents that directly target IgE and IL-5. Currently, the latter only have a role in patients who have severe allergic or eosinophilic asthma refractory to treatment with inhaled corticosteroids or long-acting β-agonists, and can only be prescribed by specialists. When used appropriately, these biological agents are effective at reducing exacerbations and improving symptoms and control.[25] In view of their more acceptable side effect profiles, they are often preferentially selected, when available, over the initiation or dose escalation of long term OCS.[26]

To date, even with the introduction of the new biological agents, there remains a prominent role for OCS in the management of severe asthma. In the setting of the anti-IgE agent omalizumab for severe allergic asthma, in one review omalizumab has not been shown to allow a dose reduction in OCS.[27] In a separate study, in patients treated with omalizumab for over a year, they still required a baseline, although lower, dose of OCS, particularly if they were intolerant of withdrawal of their biological agent, which may suggest an ongoing need for anti-inflammatory therapy.[28] For patients treated with omalizumab, however, a treatment duration ≥ 60 months is better associated with the ability to step down treatment (including lowering OCS dose) compared with a shorter duration.[29]

The withdrawal of OCS has been more successful in the setting of treatment with the anti-IL-5 agent, mepolizumab; while only 14% of patients with severe eosinophilic asthma were able to discontinue their OCS entirely, a substantial dose reduction was possible, with 54% of participants decreasing maintenance OCS to or below 5 mg per day.[30] The, anti-IL-5 receptor antibody benralizumab (recently approved by the Therapeutic Goods Administration, though not currently listed by the Pharmaceutical Benefits Scheme in Australia) has shown even greater promise as a steroid-sparing agent in patients with severe eosinophilic asthma, with up to 56% of patients studied being able to completely discontinue OCS. The remaining patients

continued to use OCS, although at lower doses than at the onset of the study.[31]

Therefore, the experience, at least so far, with the biological agents has been that continued use of OCS is likely to remain important in a large proportion of patients with severe asthma, and even in the setting of these novel biological therapies, there is still a role for long term treatment with OCS as adjunctive therapy. Further study is required to determine why this may be the case, but it may be due to the multiple pathways through which corticosteroids have an anti-inflammatory effect in asthma. Nevertheless, given the potential adverse effects with OCS, it is hoped that this role will be reduced in the presence of biological agents.

Despite the long history of OCS use in severe asthma, there are no studies that have determined the optimal duration or dose to control the disease.[2] There are two studies currently underway that aim to clarify how OCS could be used long term, combined with monitoring of biomarkers of inflammation, such as exhaled nitric oxide, peripheral blood eosinophil counts and serum periostin to titrate OCS dose.[32,33] A previous case series of patients with overlap of asthma and chronic obstructive pulmonary disease showed marked improvements in symptoms and exacerbation rates through titrating OCS to suppress markers of type 2 inflammation, at least in those individuals with poor disease control and severe refractory eosinophilic inflammation.[34] Given that these existing markers have been variably described to predict the presence of type 2 inflammation and that their use has been linked with reduced exacerbation rates in populations of patients with asthma, it is postulated that this method may help to achieve the delicate balance between using the required dose of OCS to control asthma, while minimising side effects. Although titrating OCS to target normalisation of biomarker values has shown promise in a pilot study,[32] the optimal way to use these markers will require more definitive evidence.

The population with severe asthma is the last major cohort of patients with asthma who continue to be treated with long term maintenance OCS, and no discussion of the role of OCS would be complete without acknowledging the significant long term side effects of treatment which have been recognised since their early initial use in the 1950s. The most common serious complications include: bone density loss and risk of fracture, weight gain and metabolic syndrome, adrenal suppression and relative immunosuppression. In addition, patients variably experience neuropsychiatric symptoms such as insomnia, mania and anxiety, peptic ulcer disease, hypertension, dyslipidaemia, cataracts, glaucoma, bruising, fat redistribution (giving rise to "moon faces" and "buffalo humps"), skin striae, change in appetite, and worsening congestive heart failure or fluid retention.[35] These side effects are most commonly described with doses above 10 mg per day of systemic corticosteroid, but there is evidence of a dose-dependent relationship with increased side effects from 6 mg per day upward.[36] To mitigate some of these long term effects, monitoring of bone mineral density, blood pressure, blood lipids and glucose levels and assessment for adrenal insufficiency are suggested. In particular, the use of bisphosphonates to prevent osteoporosis is recommended, and gastric ulcer prophylaxis should be considered for those patients at risk.[37] While many of these side effects are dependent on cumulative dosage, it is hopeful that, in the future, the further development of targeted therapies will reduce or avoid altogether the need for long term prednisone, and thus the development of these side effects.

Oral corticosteroids in the management of acute exacerbation of asthma

The most well defined and frequent use of OCS in the management of severe asthma is during an asthma exacerbation. The current Global Initiative for Asthma guidelines suggest that an asthma exacerbation is a progressive increase in symptoms sufficient to require a change of treatment.[23] In the setting of severe exacerbations, this change in treatment usually entails the addition of a short course of OCS, which has been shown to be useful to prevent the need for visits to the emergency department (ED) and hospital, and prevent relapse of exacerbation in the subsequent weeks.[38] Treatment with OCS forms the backbone of management of all severe asthma exacerbations. For patients capable of asthma self-management, self-treatment with a short course of OCS (about 1 mg/kg per day up to a maximum of 50 mg) is clearly effective at reducing relapse, need for additional care and required dose of β-agonists.[39] Similarly, in those patients treated in primary care or in hospital who can tolerate oral therapy, OCS in the same dose range are effective for the treatment of asthma exacerbations.[23] As long as patients are able to tolerate oral therapy, there is no proven benefit of intravenous therapy.[38] The standard duration of OCS therapy that is effective is 5–10 days.[40] In the acute care setting, it is suggested that OCS should be initiated within the first hour of presentation to the ED for patients presenting with acute exacerbation of asthma.[41] It is not clear whether OCS are as effective in individuals with non-eosinophilic asthma. In one study in patients with moderate to severe asthma, the frequency of eosinophilic exacerbations was reduced by OCS, whereas non-eosinophilic exacerbations, which were the most common type, were not reduced.[42] Further exploration is needed; however, there is no alternative treatment currently available.

Conclusion

In summary, OCS continue to play an important role in the management of severe asthma. In spite of their well known and significant side effects, they remain a crucial element in the management of this disease. Even with the availability of the novel biological therapies targeting IgE and IL-5, a large proportion of patients will continue to require OCS to control their asthma. It is estimated that up to 30% of patients with severe asthma still require the use of long term OCS, and they remain the only effective treatment to improve exacerbation frequency. This situation is unlikely to change in the near future.[43] It is anticipated that their role will diminish with the advent of newer biological agents and more targeted therapy; however, although their use is often maligned or regretted, they cannot be replaced — at least for now. Further work should explore ways to optimise the balance between their efficacy and their safety.

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