
CME review

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Oral corticosteroid–dependent asthma: a 30-year review

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Objective: To identify novel aspects of the pathogenesis, therapeutic options, and prophylaxis measures of corticosteroid-dependent asthma.

Data Sources: PubMed searches were undertaken of studies published between 1966 and 2006 on the pathogenesis of and corticosteroid-sparing therapies for corticosteroid-dependent asthma. Identified review articles were surveyed for additional and earlier citations. Recent American Academy of Asthma, Allergy, and Immunology meeting abstracts were also searched to identify other recently published and unpublished studies.

Study Selection: Inclusion of studies in the review was decided by simple agreement of both reviewers, who independently read the “Methods” and “Discussion” sections of articles identified using the search strategy. Quality assessment was performed by the 2 reviewers.

Results: High-dose inhaled corticosteroids are the first-line option for corticosteroid-dependent asthmatic patients with clear efficacy. Omalizumab is effective in reducing oral corticosteroid requirements in allergic asthma. Methotrexate, gold, and cyclosporine have corticosteroid-sparing effects clinically that must be weighed against a serious adverse effect profile. Nebulized diuretics and lidocaine, with a low adverse effect profile, offer promising results but require further study. Clarithromycin and telithromycin seem to have an independent mechanism of inflammatory modulation, but their effect on corticosteroid-dependent asthma remains to be seen. Etanercept offers only early clinical evidence of a role in corticosteroid-dependent asthma.

Conclusions: With no clear consensus on corticosteroid-sparing treatment in corticosteroid-dependent asthmatic patients, systemic glucocorticoids remain the foremost therapy, with adverse effects that require monitoring and prophylaxis.

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INTRODUCTION

For more than 50 years glucocorticoids have remained the most effective treatment for asthma. At a cellular level corticosteroids reduce the number of inflammatory cells in the airways, including eosinophils, T lymphocytes, mast cells, and dendritic cells.¹ Inhaled corticosteroids (ICSs) are the current mainstay of asthma therapy. Clinical and experimen-

tal evidence demonstrates a spectrum of clinical response to corticosteroids. This phenomenon has also been observed in systemic corticosteroid therapy in the treatment of rheumatoid arthritis, systemic lupus erythematosus, and transplant rejection.^{2,3}

The Global Initiative on Asthma (GINA) 2006 guidelines confer asthma therapy in 4 steps encompassing most asthmatic patients. However, despite strict patient compliance with ICS, long-acting β -agonist, theophylline, and leukotriene modifier therapies, some asthma is still not controlled. Therefore, step 5 of the GINA guidelines recommends low-dose daily oral corticosteroid (OCS) therapy to achieve clin-

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ical control of asthma. This severe subgroup of asthma warrants the exclusion of other comorbid factors, such as gastroesophageal reflux disease, chronic obstructive pulmonary disease, tobacco dependence, and other pulmonary abnormalities.^{4,5} Once these factors of difficult-to-treat asthma are excluded, these patients typically require OCS administration for long periods and are labeled as having OCS-dependent asthma.

The definitions of oral glucocorticoid therapy in severe asthma represent a spectrum of disease (Table 1). The American Thoracic Society consensus definition of severe/refractory asthma has 2 major criteria, including either continuous or greater than 50% yearly OCS use.⁶ Oral corticosteroid-dependent asthma is defined as the daily requirement for oral glucocorticoid medication.⁷ In this OCS-dependent asthma group is a subgroup termed “corticosteroid-resistant asthma (type I and II).” Type I corticosteroid resistance accounts for most corticosteroid-resistant disease. It is an acquired disorder with the onset of corticosteroid use, and it is reversible with the cessation of corticosteroid consumption. Without a clear mechanism of disease, type I corticosteroid-resistant patients have poor glucocorticoid receptor (GR) function, with variable affinity for corticosteroids. These patients also develop hypothalamic-pituitary-adrenal (HPA) axis suppression from long-term corticosteroid treatment. Conversely, the rare, inherited form of type II corticosteroid-resistant asthma involves a systemic decrease in GR number and is not associated with the development of corticosteroid-induced adverse effects.^{8,9} Overall, corticosteroid-resistant asthma is defined by failure to improve baseline morning prebronchodilator forced expiratory volume in 1 second (FEV₁) by greater than 15% of predicted after 7 to 14 days of using oral prednisone, 20 mg twice daily. Note that most patients do not have absolute resistance but rather glucocorticoid insensitivity, and some patients might respond to higher doses of prednisone or its equivalent given for longer periods.¹⁰ Beyond the scope of definitions, daily OCS treatment for asthma mirrors the prevalence of severe asthma.

Although there are no definitive statistics on the prevalence of corticosteroid-resistant or corticosteroid-dependent asthma, an approximate estimate is that corticosteroid-insensitive asthma occurs in less than 5% of asthmatic patients, and

defined resistance is rare and affects less than 0.1% of patients.¹¹ A similar prevalence is observed in other autoimmune diseases treated with systemic corticosteroids, such as inflammatory bowel disease, autoimmune arthritis, and systemic lupus erythematosus.¹²

The purpose of this review is to describe the current pathogenesis, treatment alternatives, and management perspectives for OCS-dependent asthma. The adverse effects of daily OCS therapy are well known and undesirable. Hence, this clinically challenging type of asthma has led to more than 30 years of research initiative on alternative therapies commonly termed *corticosteroid-sparing agents*. Studies cited in this review were located through a search of the PubMed database (1966–2006) for studies on the pathogenesis of and corticosteroid-sparing therapies for corticosteroid-dependent asthma. A separate search was conducted for each corticosteroid-sparing agent described using the generic name and the terms *corticosteroid sparing* and *asthma*. Review articles identified in this process were surveyed for additional and earlier citations. Recent American Academy of Asthma, Allergy, and Immunology meeting abstracts were also searched to identify more recently published and unpublished studies. Inclusion of studies in the review was decided by simple agreement of both reviewers, who independently read the “Methods” and “Discussion” sections of articles identified using the search strategy.

Several therapies have been reviewed previously, with few or no large, corroborative studies of OCS-dependent asthma treatment. Treatments such as oral and inhaled heparin have been shown to decrease airway responsiveness and display benefits in exercise-induced bronchospasm only.^{13,14} A small 2-year study¹⁵ of dapsone showed 50% discontinuation of OCS use, but the hemolytic anemia adverse effects were significant. A small, open-label hydroxychloroquine study¹⁶ showed a modest corticosteroid-sparing effect in 65% of patients taking OCSs. However, with no new, recent data and no double-blind, placebo-controlled studies in the literature, these agents will not be addressed in this review. On the contrary, this review characterizes corticosteroid-sparing therapies based on randomized, placebo-controlled, blinded (RPCB) studies in addition to recent advances in corticosteroid-sparing agents.

PATHOPHYSIOLOGY REVIEW

The molecular basis of glucocorticoid action has been extensively studied.¹⁷ Figure 1 illustrates a reductionist view of cellular glucocorticoid function. Glucocorticoids diffuse readily into the cell and bind to the inactive cytosolic GR α . Cytoplasmic GRs are restricted to the cytoplasm by bound chaperone proteins, such as heat shock protein 90 and FK binding protein. Glucocorticoid-bound GR α is localized in the nucleus via dissociation of the chaperone proteins. Once in the nucleus, multiple pathways participate in the suppression of inflammation. The corticosteroid-GR complex binds to specific glucocorticoid response elements on nuclear DNA upstream of the promoter region in corticosteroid-responsive

Table 1. Definitions of Oral Glucocorticoid Therapy in Severe Asthma

Severe/refractory asthma: umbrella definition per the American Thoracic Society Workshop, which includes the following classes of asthma:
Corticosteroid-resistant asthma: failure to improve baseline morning prebronchodilator forced expiratory volume in 1 second by >15% of predicted after 7–14 d of using oral prednisone, 20 mg twice daily
Type I: vast majority of corticosteroid resistance
Type II: rare, genetic form of corticosteroid resistance
Corticosteroid-dependent asthma: daily oral corticosteroid treatment required for the control of asthma

Mechanisms of Steroid Resistance

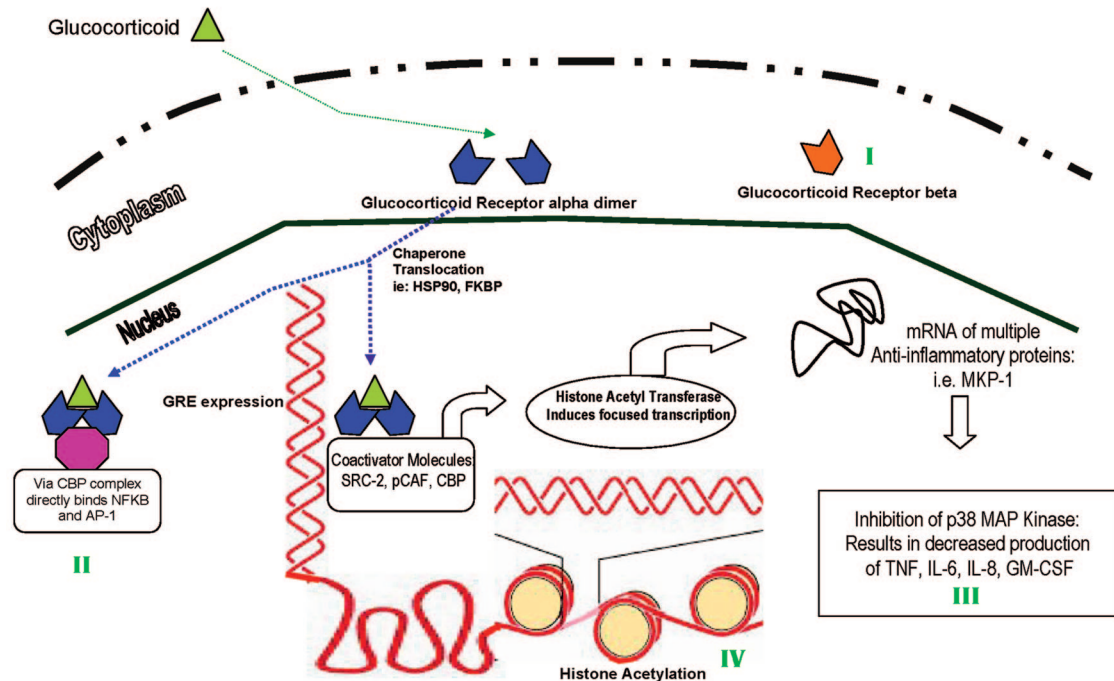


Figure 1. Mechanisms of corticosteroid resistance. AP-1 indicates activated protein 1; CBP, cyclic adenosine monophosphate response element binding protein; FKBP, FK binding protein; GM-CSF, granulocyte-macrophage colony-stimulating factor; GR, glucocorticoid receptor; GRE, glucocorticoid response element; HSP90, heat shock protein 90; IL-6, interleukin 6; MAP, mitogen-activated protein; MKP-1, MAP kinase phosphatase; mRNA, messenger RNA; NFκB, nuclear factor κB; pCAF, p300/CBP-associated factor; SRC-2, corticosteroid receptor coactivator-2; and TNF, tumor necrosis factor.

genes. Binding of the corticosteroid-GR complex to the glucocorticoid response element enhances the transcription of multiple anti-inflammatory proteins, with suppression of proinflammatory gene products. The corticosteroid-GR complex also may increase transcription by interaction with coactivator molecules, thus promoting histone acetylation and subsequent anti-inflammatory targeted gene transcription. These transcription products down-regulate p38 mitogen-activated protein kinase (MAPK) activity, resulting in decreased production of tumor necrosis factor (TNF), interleukin 6 (IL-6), and other proinflammatory molecules. The activated translocated GR may also suppress inflammation via a direct protein-protein interaction with other transcription factors, such as the proinflammatory transcription factors activating protein-1 and nuclear factor κB.¹⁸

The pathogenesis of glucocorticoid insensitivity has been studied in vivo and in vitro at specific cellular pathways involving the GR. Glucocorticoid insensitivity in asthma does not seem to be due to an abnormal interaction between glucocorticoids and the GR. The variable affinity of corticosteroid binding to the GR has been reported in T lymphocytes of patients with corticosteroid-resistant asthma. However, the GR binding characteristics in peripheral blood monocytes and T cells are similar in corticosteroid-resistant asthmatic patients to those reported in healthy individuals.^{19,20} Chemical mutational analysis shows no

evidence of structural differences in GR between sensitive and resistant asthmatic patients.²¹ This evidence has led investigators to focus the research of corticosteroid resistance from the level of nuclear GR translocation to defects in DNA transcriptional effects.

Table 2 outlines 4 possible mechanisms of corticosteroid insensitivity/resistance, with a corresponding illustration in Figure 1. Mechanism 1 involves GRβ dysregulation. Previous studies have shown up-regulation of the GR cytosolic and nuclear β type in corticosteroid insensitivity models. Glucocorticoid receptor β exists intracellularly, with only a 15-amino acid difference to GRα. Unlike GRα, GRβ does not affect gene expression.²² Therefore, GRβ may act as a competitive inhibitor against GRα in the cytoplasm and the nucleus. Goleva et al²³ demonstrated increased cytoplasmic and nuclear GRβ in bronchial macrophages of corticosteroid-insensitive asthmatic patients compared with glucocorticoid-sensitive patients. However, other studies show that corticosteroid-dependent asthmatic patients do not demonstrate up-regulation of GRβ in response to proinflammatory cytokines. In addition, measured levels of GRα outbalance the levels of GRβ in corticosteroid-dependent asthma.^{24,25} Mechanism 2 involves an inefficient direct inactivation binding of nuclear factor κB, and activating protein-1 through coactivator molecules that may be involved in glucocorticoid resis-

Table 2. Four Potential Mechanisms of Corticosteroid Resistance

1. Increased expression of GR β in corticosteroid-resistant patients may compete with GR α . However, no increased expression of GR β is detected in the mononuclear cells in corticosteroid-dependent asthma.
2. As seen in mononuclear cells of corticosteroid-resistant patients, bound GRs may not interact efficiently via coactivator molecules such as CBP to bind inflammatory transcription factors NF κ B and AP-1.
3. Activation of p38 MAPK by asthma-associated cytokines IL-2 and IL-4 result in phosphorylated GR molecules with decreased affinity to corticosteroids in vitro.
4. Defective histone acetylation in corticosteroid-resistant asthma is not yet understood. The balance exists between histone acetylation characterized by activation of the histone complex to an open form of chromatin with eventual transcription and translation of proinflammatory and anti-inflammatory proteins. Histone acetylation is countered by histone deacetylation through transferase subtypes. The GR requires translocation to the nucleus and interaction with coactivator molecules to allow the function of these transferases. Aberrance in multiple upstream paths may explain histone aspects of corticosteroid resistance.

Abbreviations: AP-1, activated protein 1; CBP, cyclic adenosine monophosphate response element binding protein; GR, glucocorticoid receptor; IL-2, interleukin 2; MAPK, mitogen-activated protein kinase; and NF κ B, nuclear factor κ B.

tance.²⁶ Mechanism 3 entails an additional molecule implicated in corticosteroid insensitivity, p38 MAPK, which stabilizes messenger RNA precursors of several proinflammatory cytokines, including TNF, IL-6, and IL-8. In vitro studies²⁷ revealed decreased glucocorticoid-GR affinity secondary to p38 MAPK-induced phosphorylation of the GR. Finally, mechanism 4 of corticosteroid insensitivity/resistance involves the importance of histone acetylation and deacetylation in active transcription of inflammatory gene targets. Histone acetylation is countered by histone deacetylation through transferase subtypes. The GR requires translocation to the nucleus and interaction with coactivator molecules to allow the function of these transferases. Aberrance in multiple upstream paths may explain the histone aspects of corticosteroid resistance.^{28,29} Despite numerous attempts to localize corticosteroid resistance to a single transduction defect, it seems that the phenotype of corticosteroid resistance may have multiple genotypic defects at various molecular stages whose etiology is yet to be clearly defined.

CORTICOSTEROID-SPARING AGENTS

High-Dose ICSs

Inhaled corticosteroids have been the mainstay of asthma therapy since the mid-1980s. Per the GINA guidelines, treatment of mild persistent to severe persistent asthma focuses on ICSs. The TENOR (The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens) study³⁰ ini-

tially has shown that older adults use ICSs more than younger patients. It is well accepted that the toxic effects of ICSs are at most moderate compared with those of oral glucocorticoids. Known adverse effects, especially at high doses, such as glaucoma, cataracts, oral candidiasis, HPA axis suppression, growth retardation, and decrease bone mineral density, are noted.³⁰ The question then arises, "When does the toxicity of high-dose ICSs mimic that of oral prednisone (10 mg/d)?" A recent study by Paton et al³¹ showed a significant impaired response to corticotropin stimulation in children receiving more than 500 μ g of fluticasone propionate daily. Nearly 40% of 217 children displayed impaired adrenal function, and 2.8% had adrenal insufficiency.³¹ Although this HPA axis suppression may be reversible, ICSs retain significant adverse effects when used at higher doses.

High-dose ICSs have been studied in several RPCB studies in the past decade with a clear corticosteroid-sparing profile. In patients with severe asthma, very high doses of fluticasone propionate (2,000 μ g/d) seemed to allow more people receiving OCSs to stop or reduce their OCS use compared with lower doses of fluticasone propionate (1,000–1,500 μ g/g).^{32–34} Similar results were seen with inhaled budesonide.³⁵ Two large studies^{36,37} with mometasone dry powder inhalation at doses of 400 to 800 μ g/d resulted in up to a 46% OCS dose reduction and 40% OCS discontinuation. The OCS reduction noted with the high-dose regimen of ICSs is counterbalanced by the known therapeutic plateau effect of ICSs. Although beneficial in OCS reduction, higher doses of ICSs must be used with caution so as not to mimic the adverse effects of OCSs.³⁸

Ciclesonide is a novel ICS that is inactive in its parent form and is converted to its active metabolite, desisobutyl ciclesonide, by esterases primarily in the lungs. Other benefits of this localized form of therapy include a rapid clearance rate and a high degree of protein binding in the serum. With no clear effect on serum cortisol circadian rhythm, the effect of ciclesonide on the HPA axis may be favorable, although long-term outcomes have not been studied. In a study by Bateman et al,³⁹ a cohort of 141 patients with a near-daily requirement for oral prednisone was found to have significantly higher rates of oral prednisone reduction or cessation with varying doses of ciclesonide compared with the placebo group. However, only 30% of the patients treated with ciclesonide discontinued oral prednisone use altogether compared with 11% of placebo users.³⁹ In addition, ciclesonide has not been compared with other ICSs regarding their ability to reduce oral prednisone use considering that similar results have been seen with fluticasone propionate.

Omalizumab

Omalizumab, a recombinant humanized anti-IgE monoclonal antibody, forms complexes with free IgE, blocking its interaction with mast cells and basophils. Omalizumab has a toxic effect profile that includes risk of anaphylaxis and a 0.5% risk of malignant neoplasm compared with 0.2% in control pa-

tients. The monthly cost of omalizumab varies from \$541 to \$2,706, depending on individual patient requirements.⁴⁰ In 2001, Busse et al⁴¹ showed in an RPCB trial of 525 patients with severe allergic asthma requiring daily ICSs that treatment with omalizumab resulted in significantly fewer asthma exacerbations per patient and in lower percentages of patients experiencing an exacerbation than placebo treatment during the stable corticosteroid phase (0.28 vs 0.54 [$P = .006$] and 14.6% vs 23.3% [$P = .009$], respectively) and during the corticosteroid reduction phase (0.39 vs 0.66 [$P = .003$] and 21.3% vs 32.3% [$P = .004$], respectively). Median beclomethasone dipropionate reduction was significantly greater with omalizumab vs placebo treatment (75% vs 50%; $P < .001$), and beclomethasone dipropionate discontinuation was more likely with omalizumab (39.6% vs 19.1%; $P < .001$). Omalizumab, with the exception of rare anaphylaxis, was well tolerated, with an adverse event profile similar to that of placebo.⁴¹ Humbert et al⁴² studied omalizumab in a large cohort of patients with "difficult-to-control" asthma despite high-dose ICS therapy, inhaled long-acting β -agonist use, and frequent OCS therapy (maximum of 20 mg of prednisone daily). This study⁴² showed a 26% reduction in asthma exacerbation frequency compared with placebo during 28-week follow-up. An earlier study by Milgrom et al⁴³ specifically analyzed OCS-dependent patients. For the 35 patients who required baseline OCS therapy, the median reduction in prednisone use during the 8-week tapering phase was 65% in the low-dose omalizumab group compared with 0% in the placebo group ($P = .11$). Nearly 60% of the patients in this group had a reduction in the dose of OCSs of at least 50% compared with 33% in the placebo group ($P = .23$). Forty-three percent of patients who required baseline OCS therapy stopped taking OCSs altogether vs 17% of those in the placebo group ($P = .15$).⁴³ With a relatively mild adverse effect profile, a larger RPCB trial with omalizumab and OCS-dependent asthmatic patients may corroborate these findings. Although omalizumab is a promising component of GINA step 5 treatment with the few shortcomings of cost and toxicity, it does not address the nonallergic asthmatic patient.

Methotrexate

Low-dose methotrexate, one of the first-used immunosuppressant corticosteroid-sparing agents for asthma, has long been used in the treatment of rheumatoid arthritis and psoriasis. Mullarkey et al⁴⁴ in 1988 published the first RPCB study of 14 patients requiring daily OCSs. The use of low-dose methotrexate, 15 mg/wk, resulted in a 36% reduction in prednisone use compared with the use of placebo (mean daily dose reduction from 26 mg to 17 mg).⁴⁴ A further follow-up, open-label study⁴⁵ of 25 corticosteroid-dependent asthmatic patients showed a mean reduction in daily prednisone use from 27 mg to 6 mg ($P = .001$), with 15 patients tapered off prednisone altogether. In the 1990s, mixed results were seen in various RPCB studies, including that by Taylor et al,⁷ who studied 9 patients in a 24-week crossover trial of methotrex-

ate, 15 mg/wk; no statistically significant difference in oral prednisone taper was noted between the methotrexate group (mean reduction, 14 mg/d) and the placebo group (mean reduction, 13 mg/d). A 1998 meta-analysis of 12 RPCB studies⁴⁶ of the corticosteroid-sparing potential of methotrexate concluded that a pooled 18.2% reduction in OCS use corresponded to a 3.3-mg/d greater reduction in prednisone use compared with placebo use. This benefit was noted with a dose of 15 mg/wk of methotrexate. The overall adverse effect profile of this methotrexate dosage was notable for mild gastrointestinal symptoms in the methotrexate group vs the placebo group (45% vs 31%; $P = .01$). No significant bone marrow suppression or methotrexate pneumonitis was reported, but 2 cases of pneumonia and 1 case of liver dysfunction were noted.⁴⁶ Regardless, this mean reduction in prednisone dose would not negate the adverse effects of daily prednisone dosing. Comet et al⁴⁷ recently reported minimal treatment toxic effects in an RPCB study of 46 corticosteroid-dependent asthmatic patients randomized to receive low-dose methotrexate for 1 year. Using a 10-mg weekly dose of methotrexate, the treatment group decreased daily 6-methylprednisolone doses by 9.5 mg on average compared with 0.5 mg in the control group.⁴⁷ This 2006 study demonstrates the efficacy and safety of a low-dose regimen of methotrexate. However, larger RPCB studies are needed to validate this approach in corticosteroid-dependent asthma.

Intravenous γ -Globulin

Intravenous γ -globulin (IVGG) has been shown to modulate the immune system at variable doses in such diseases as Kawasaki disease, Guillain-Barré syndrome, and immune thrombocytopenic purpura. The exact mechanism remains unclear.⁴⁸ Several open-label studies using IVGG treatment have been completed in patients with hypogammaglobulinemia or IgG subclass deficiency and asthma. After treatment with IVGG, modest improvements in asthma symptom scores, inhaled medication use, hospitalization, and lung function were noted.⁴⁹ However, the study of IVGG in the treatment of immunocompetent, OCS-dependent asthmatic patients has been limited. Salmun et al⁵⁰ completed an RPCB study of 28 immunocompetent corticosteroid-requiring patients with severe asthma. A significant reduction in OCS requirement was observed in IVGG-treated ($n = 16$) and placebo-treated ($n = 12$) patients. It was noted that IVGG, but not placebo, had a significant corticosteroid-sparing effect in patients requiring high doses of OCSs (ie, $>2,000$ mg in the year before the study). In this subgroup, IVGG treatment ($n = 9$) resulted in a significant decrease in OCS requirement, from a median of 16.4 mg/d during the pretreatment period to 3.0 mg/d during the treatment phase ($P = .008$). No significant decrease in OCS requirement was observed in placebo-treated patients ($n = 8$) in this subgroup. Objective and subjective variables of the patients' asthma were unchanged despite the corticosteroid tapering achieved in the group treated with IVGG.⁵⁰ Kishiyama et al⁵¹ completed a multiple-dose 7-month IVGG treatment study in

immunocompetent corticosteroid-dependent asthmatic patients. Patients were randomized to 1 of 3 treatment arms: 2 g/kg of IVGG per month (16 patients), 1 g/kg of IVGG per month (9 patients), or 2 g/kg of intravenous albumin (placebo) per month (15 patients). When adjusted for body weight, the mean dose requirements decreased by 33%, 39%, and 33% in the placebo, IVGG (1 g/kg), and IVGG (2 g/kg) treatment arms, respectively. The differences between therapies were not significantly different ($P = .97$). Other variables of asthma control, such as hospitalizations and emergency department visits, showed no statistically significant difference between treatment arms. In fact, the trial was curtailed owing to 3 patients in the high-dose IVGG arm requiring hospitalization for aseptic meningitis.⁵¹ With a reputation for minimal adverse effects, it seems that IVGG has a limited role in the treatment of immunocompetent, corticosteroid-dependent asthma.

Etanercept

Tumor necrosis factor is an important cytokine that regulates the pathogenetic mechanisms of chronic inflammatory diseases.⁵² Modulation of this cytokine has proven clinical value in the treatment of rheumatoid arthritis, psoriatic arthritis, and plaque psoriasis. Tumor necrosis factor α has been shown to be at increased concentrations in bronchoalveolar lavage fluid from patients with severe asthma. In this same study,⁵³ an open-label treatment course of etanercept, a recombinant soluble TNF- α receptor, markedly improved airway hyperresponsiveness, lung function, and symptom scores in 17 patients with severe asthma. Berry et al⁵⁴ recently reaffirmed the elevated expression of TNF- α and its receptor in peripheral blood monocytes, most notably in the refractory asthma group of 10 patients, of whom 6 were taking daily prednisone. A randomized placebo-controlled trial⁵⁴ of treatment of these patients with etanercept (25 mg twice weekly for 10 weeks) followed, with results showing a significant increase in the concentration of methacholine required to provoke a 20% decrease in FEV₁ (mean difference in doubling concentration changes between etanercept and placebo, 3.5; 95% confidence interval [CI], 0.07–7.0; $P = .05$), an improvement in the asthma-related quality-of-life score (by 0.85 points; 95% CI, 0.16–1.54 points; $P = .02$), and a 0.32-L increase in postbronchodilator FEV₁ (95% CI, 0.08–0.55; $P = .01$). No comment was made on the effect of etanercept on corticosteroid reduction or withdrawal. Although etanercept is a promising new adjunct to asthma therapy, it carries a significant adverse effect profile, including an increased risk of malignancy.⁵⁵ Further studies focusing on the role of etanercept on corticosteroid-dependent asthma are in progress.

Cyclosporine

Cyclosporine is well known for its immune modulation effects in solid organ transplantation. Its inhibition of T-cell activation has been elucidated, and its secondary decrease in immunoglobulin synthesis, including IgE, has led to investi-

gation of cyclosporine in the treatment of asthma.^{56,57} Few RPCB studies have been completed examining the effect of cyclosporine on corticosteroid-dependent asthma. Alexander et al⁵⁸ randomized 33 corticosteroid-dependent asthmatic patients in a 12-week crossover trial of cyclosporine (initial dose, 5 mg/kg per day) or placebo. Although patients taking cyclosporine showed an increase in morning peak expiratory flow rates and an increase in FEV₁, the focus of the study was on adverse effects of cyclosporine and not on reduction in OCS use.⁵⁸ Lock et al⁵⁹ published a study of 16 corticosteroid-dependent asthmatic patients who received cyclosporine for 36 weeks. A reduction in the daily dose of prednisolone compared with placebo (median, 62% vs 25%; $P = .04$) along with improvements in peak expiratory flow rate were noted. The median daily prednisolone dosage change was from 10 mg to 3.5 mg in the cyclosporine group compared with a decrease from 10 mg to 7.5 mg in the placebo group.⁵⁹ However, a study⁶⁰ involving 34 patients with severe asthma and longer follow-up demonstrated no statistically significant effects of cyclosporine using the objective markers of pulmonary function. In addition, there was no significant difference in the final dose reduction of prednisone between the treatment groups.⁶⁰ Despite some benefits, cyclosporine therapy lacks a sustained effect and requires close observation of renal function, blood pressure, electrolyte levels, and serum levels. Inhaled forms of cyclosporine are currently being studied in murine models with the potential for corticosteroid reduction with minimal adverse effects.

Inhaled Diuretics

Furosemide, a well-known loop diuretic that blocks the sodium-potassium-chloride cotransporter in the ascending loop of Henle, seems to diminish several mechanisms of bronchoconstriction when inhaled, including early and late responses to allergen and the effects of exercise.^{61,62} However, inhaled furosemide does not show bronchodilatory effects on histamine and methacholine challenge.^{63,64} The exact mechanism of protective bronchodilatory effects with inhaled diuretics remains unclear. Several RPCB studies on the effect of furosemide on acute asthma exacerbations have produced mixed results. Few clinical trials using furosemide therapy for the treatment of chronic asthma were identified, to our knowledge. In a double-blind, randomized, crossover trial by Bianco et al,⁶⁵ 9 patients with mild-to-moderate asthma who were receiving higher doses of inhaled beclomethasone (2 mg/d) were treated with sequential inhaled doses of lysine acetylsalicylate, 720 mg, and furosemide, 40 mg, or placebo twice daily, with scheduled reductions in ICS therapy. After 2 months, treatment with furosemide-lysine acetylsalicylate resulted in a mean $\pm$ SD dose reduction of $71\% \pm 7\%$ ($250 \pm 72 \mu\text{g/d}$) in the amount of inhaled beclomethasone that was required to maintain asthma control, and 2 patients discontinued therapy with ICSs completely.⁶⁵ Despite an excellent safety profile, no study has examined the benefits of inhaled furosemide on OCS-dependent asthma.

Nebulized Lidocaine

For decades, observations on the effect of nebulized or topical lidocaine on the large and small airways have noted an anti-inflammatory glucocorticoid-like effect. Lidocaine shortens eosinophil survival in the presence of proinflammatory cytokines such as IL-5, IL-3, and granulocyte-macrophage colony-stimulating factor.^{66,67} Four times a day nebulized lidocaine treatment of adults with severe glucocorticoid-dependent asthma reduced the oral glucocorticoid dosage in 17 of 20 patients by 80% to 100%, but 3 patients had no apparent response.⁶⁸ Hunt et al⁶⁹ recently published an RPCB study of nebulized lidocaine use in mild-to-moderate asthmatic patients (specifically excluding corticosteroid-dependent asthmatic patients). Patients were weaned off inhaled glucocorticoids and divided into groups receiving 4% nebulized lidocaine 4 times daily or saline placebo during a 4-week washout period of ICSs. An 8-week follow-up of the groups showed continued benefit for the lidocaine-treated group, with changes in FEV₁ ($P \leq .001$), nighttime awakenings ($P \leq .02$), symptoms ($P \leq .01$), bronchodilator use ($P \leq .01$), and blood eosinophil counts ($P \leq .02$). However, patients in both groups reduced their use of inhaled glucocorticoids comparably. Note that as in previous open-label pediatric studies,^{69,70} no significant adverse effects of inhaled lidocaine were noted. The low toxicity associated with the possible significant benefit of OCS reduction warrants further investigation with larger RPCB studies.

Macrolide and Ketolide Antibiotics

Recent studies involving ketolide and macrolide therapy in acute asthma exacerbations have rekindled interest in their therapeutic potential in treating severe, chronic asthma. Macrolides such as troleandomycin and clarithromycin are believed to have a synergistic effect when administered with OCSs. Clinical studies have shown that troleandomycin alters corticosteroid bioavailability by decreasing hepatic metabolism and excretion. The addition of troleandomycin, 14 mg/kg per day, to the regimen of 10 severe corticosteroid-dependent asthmatic patients resulted in a reduction in clearance of intravenous methylprednisolone by a mean $\pm$ SD of 60% $\pm$ 18.7% ($P < .001$).⁷¹ Aside from corticosteroid-sparing bioavailability effects and bactericidal activity, macrolide antibiotics inhibit lymphocyte proliferation in response to phytohemagglutinin, decrease neutrophil accumulation via a decrease in chemotactic activity, and decrease mucous secretion.⁷² In addition, the "membrane-stabilizing effect" of macrolide antibiotics may, in part, account for their anti-inflammatory actions. The hydrophobic and hydrophilic properties of the macrolides may lead to the formation of drug micelles and promote interaction of the micelles with phospholipids in the plasma and intracellular organellar membranes. The intracellular metabolic and transcriptional pathways involved in the inflammatory cascade require membrane oxidation as seen in myeloperoxidase function in neutrophils, and macrolide micelle interference at this level may explain its anti-inflammatory effect.⁷³

The macrolide antibiotic troleandomycin has been studied in depth in the treatment of corticosteroid-dependent asthma. Spector et al⁷⁴ initially demonstrated an improvement in clinical symptoms or a reduction in corticosteroid dosage with troleandomycin and methylprednisolone treatment. In an RPCB study of troleandomycin in 75 corticosteroid-dependent asthmatic patients with significant dropout, patients taking troleandomycin tolerated lower corticosteroid doses at 1 year ($P < .03$), but the number of hospitalizations and emergency department visits were not changed significantly. Patients taking troleandomycin had more cases of bone loss ($P < .01$) and higher cholesterol levels ($P = .053$) than placebo users.⁷⁵

Several studies⁷⁶⁻⁷⁸ have analyzed the effects of macrolide antibiotics, including clarithromycin and roxithromycin, in asthma. Although observing an improvement in airway hyperresponsiveness among other asthma clinical variables, all of these studies excluded OCS-dependent patients. Although clarithromycin seems to decrease bronchial hyperreactivity in asthmatic patients not receiving corticosteroids, only a small case series of 3 patients demonstrated possible benefit of corticosteroid tapering or discontinuation with the long-term use of low-dose clarithromycin.^{76,79} A recent study by Johnston et al⁸⁰ demonstrated an improvement in short-term asthma exacerbations after acute asthma exacerbation therapy with telithromycin. However, OCS-dependent patients were not studied. In addition, although this class of antibiotics has known adverse effects, broad-scale use of these drugs continues to clarify more serious concerns, such as liver toxicity with telithromycin.⁸¹ The potential exists that macrolides and ketolides can work in balance with OCSs or ICSs for the treatment of corticosteroid-dependent asthma. However, the effective dose of antibiotic and concomitant corticosteroid use must be addressed further in multicenter, randomized, double-blind, placebo-controlled trials.

Gold (Auranofin)

Although clinically falling out of favor owing to adverse effects, gold has been used in the past for the treatment of a variety of inflammatory and autoimmune conditions. Gold has been shown to decrease neutrophil and macrophage phagocytosis and lymphocyte reactivity to antigen stimulation.⁸² Gold inhibits eosinophil survival via IL-5 modulation.⁸³ Gold decreases prostaglandin and leukotriene production in vitro and inhibits IgE-mediated release of histamine from isolated basophils and lung mast cells.⁸⁴⁻⁸⁷ The UCLA West Los Angeles Veterans Affairs Hospital was one of the first in the mid-1980s to examine the use of intravenous auranofin in the treatment of corticosteroid-dependent asthma. In the double-blind, crossover study by Klaustermeyer et al⁸⁸ of 8 patients, 5 reduced their prednisone use minimally but had significant improvement in FEV₁. However, a significant trade-off with proteinuria secondary to gold therapy caused 2 patients to discontinue study participation.⁸⁸ In the Auranofin Multicenter Drug Trial,⁸⁹ the largest RPCB clinical trial of gold

therapy, 275 patients with daily oral prednisone requirements of a minimum of 10 mg were randomized to receive 3 mg of auranofin orally twice daily or placebo for 6 months. The primary efficacy outcome was reduction of daily corticosteroid use by 50% or more. The results were limited by a significant patient dropout rate (auranofin group, 40%; placebo group, 46%) due to adverse effects and voluntary withdrawals. No significant differences were found in symptom scores or measurement of pulmonary function. However, more patients treated with gold (60%) reduced their daily OCS dose by 50% or more compared with those receiving placebo (32%) ($P < .001$).⁸⁹ This trial confirmed the known adverse effects of gold therapy, including dyspepsia, diarrhea, pruritic rash, cytopenias, oral ulcerations, proteinuria, and frank nephrotic syndrome. With up to one third of patients in several prospective trials experiencing these adverse effects and despite the self-limitation of these effects once gold therapy was stopped, the risk of gold therapy must be weighed against the significant risks of adverse effects of long-term oral glucocorticoid use.^{90,91}

DISCUSSION

OCS-Sparing Therapy

Inhaled glucocorticoids are the primary therapy for persistent asthma across all clinical classifications, as illustrated by the

GINA 2006 guidelines. In the classes of asthma known as OCS dependent and corticosteroid resistant, this review of more than 30 years of research reveals no clear conclusion for a corticosteroid-sparing asthma therapy (Table 3). High-dose ICSs are still a first-line option for corticosteroid-dependent asthmatic patients with clear efficacy. However, high-dose ICSs, with the potential exception of ciclesonide, are associated with local adverse effects, such as dysphonia and oropharyngeal candidiasis, in addition to a concerning degree of HPA axis suppression. Despite its high cost and potential toxicity, omalizumab is effective in reducing OCS requirements in allergic asthma. Furthermore, data on sustained efficacy of this effect are still forthcoming. Methotrexate, gold, and cyclosporine have corticosteroid-sparing effects clinically but must be weighed against a serious adverse effect profile. Nebulized diuretics and lidocaine, with a low adverse effect profile, offer promising results in acute and chronic asthma, but further studies are required to address their role in corticosteroid-dependent asthma. Clarithromycin and telithromycin, much like troleandomycin, seem to have an independent mechanism of inflammatory modulation, but their effect on corticosteroid-dependent asthma remains to be seen. Finally, etanercept offers only a mechanism and early clinical evidence of a role in corticosteroid-dependent asthma. Future corticosteroid-sparing therapies will be achieved on a better mechanistic

Table 3. Summary of Corticosteroid-Sparing Asthma Therapy

Corticosteroid-sparing agent	Study	Result summary	Overall recommendation
High-dose ICSs	Fish et al, ³⁶ Schmier et al, ³⁷ Noonan et al, ³³ Westbroek et al, ³⁴ Miyamoto et al ³⁵	Significant reduction in OCS dose and moderate OCS cessation.	Positive
Ciclesonide	Bateman et al ³⁹	Significant reduction in OCS dose and moderate OCS cessation.	Positive
Omalizumab	Busse et al, ⁴¹ Humbert et al, ⁴² Milgrom et al ⁴³	Allergic asthma only. Significant reduction in ICS and OCS doses and significant OCS cessation.	Positive
Methotrexate	Mullarkey et al, ⁴⁴ Taylor et al, ⁷ Aaron et al ⁴⁶	Moderate reduction in OCS dose, with toxic effect concerns.	Equivocal
IVGG	Salmun et al ⁵⁰ and Kishiyama et al ⁵¹	No significant reduction in OCS.	Negative
Etanercept	Berry et al ⁵⁴	No data on OCS reduction.	Inconclusive
Cyclosporine	Lock et al ⁵⁹ and Nizankowska et al ⁶⁰	Conflicting studies on OCS reduction, with toxic effect concerns.	Equivocal
Furosemide (nebulized)	Bianco et al ⁶⁵	No data on OCS reduction.	Inconclusive
Lidocaine (nebulized)	Hunt et al ^{68,69}	Small studies with significant reduction in OCS dose and minimal toxic effects.	Equivocal
Macrolide/ketolide	Spector et al, ⁷⁴ Nelson et al, ⁷⁵ Shoji et al, ⁷⁸ Kostadima et al, ⁷⁷ Johnston et al ⁸⁰	Previous studies with no significant OCS reduction with recent ketolide/macrolide studies without data on OCS reduction.	Inconclusive
Gold (auranofin)	Bernstein et al, ⁸⁹ Muranaka et al, ⁹⁰ Nierop et al ⁹¹	Significant reduction in OCS dose and significant OCS cessation with major toxic effects.	Equivocal

Abbreviations: ICS, inhaled corticosteroid; IVGG, intravenous γ -globulin; OCS, oral corticosteroid.

perception of corticosteroid insensitivity. Similar to omalizumab and interferon therapy, targeted therapy at the genetic and molecular foundation of inflammatory asthma holds promise.⁹²

With no clear consensus on OCS-sparing treatment in OCS-dependent asthmatic patients, the physician must be cognizant of the adverse effects of treatment with oral glucocorticoids. The adverse effects of systemic corticosteroid therapy have been well documented for decades. Prophylactic intervention and treatment of these adverse effects are paramount in the clinical management of corticosteroid-dependent asthmatic patients.

Long-term Use of OCSs in Asthma

Several steps should be taken by the physician treating asthma to confirm the need for long-term oral corticosteroid treatment to control corticosteroid-insensitive asthma. Findings from a thorough history and physical examination should confirm the diagnosis of severe asthma and rule out other aggravating factors, such as occupational exposures, allergic bronchopulmonary aspergillosis, and gastroesophageal reflux disease. Special attention should be given to minimize psychosocial factors and stressors. The physician should ensure that the patient is demonstrating the proper method of medication use and dose (inhaled and oral). The allergic component should be addressed with environmental controls and treatment of the allergic upper and lower airways. An informed decision with the patient should determine the need for high-dose ICSs ($>1,000 \mu\text{g}/\text{d}$), and the associated adverse effects should be discussed. Other considerations include determining whether there is incomplete corticosteroid absorption, failure to convert to an active form, rapid elimination, reduced GR number or binding affinity, or a combination of abnormalities.

Once continuous OCS step 5 therapy of GINA is clinically required, it is important to consider the alternative therapies discussed vs the risk of long-term administration of OCSs. The dose of corticosteroid-sparing agent must be carefully titrated so that the patient receives only the minimum amount required to exert the desired therapeutic effect of OCS dose reduction or cessation. However, if OCS therapy is still conjointly required, a preventive maintenance approach to corticosteroid therapy must be undertaken.

Per the guidelines set forth in the evaluation and treatment of glucocorticoid-induced osteoporosis by Adler and Hochberg⁹³ and the American College of Rheumatology, any asthmatic patient who will be starting glucocorticoid therapy with prednisone at more than 7.5 mg/d for more than 3 months should undergo a baseline dual-energy x-ray absorptiometry (DEXA) scan and be administered concomitant bisphosphonate therapy. If 5 to 7.5 mg/d prednisone is used for more than 3 months, the asthma patient should undergo a DEXA scan to ascertain fracture risk, with appropriate therapy based on the DEXA results. Annual DEXA scans should be performed to monitor the risk of glucocorticoid-induced osteoporosis. In addition, all asthmatic patients receiving OCS

therapy for a sustained length of time should be given calcium with cholecalciferol at a dosage of more than 1,000 mg and 800 IU/d, respectively.⁹³

Corticosteroids inhibit corticotropin and cortisol secretion by means of a negative feedback effect on the pituitary gland. Suppression of the HPA axis depends on dose and usually occurs only when a dose of prednisone greater than 7.5 to 10 mg is used daily. Significant suppression after short courses of corticosteroid therapy is rarely a problem, but prolonged suppression may occur after several months or years. Corticosteroid doses after prolonged oral therapy must, therefore, be reduced slowly. Symptoms of corticosteroid withdrawal include lassitude, musculoskeletal pains, and, occasionally, fever. After withdrawal of long-term corticosteroid therapy, monitoring of defective endogenous corticosteroid production should include clinical symptom evaluation and corticotropin stimulation testing until recovery is noted. Any evidence of significant HPA axis suppression warrants concomitant evaluation by an endocrinologist.⁹⁴

Other important effects of long-term glucocorticoid therapy that require surveillance and intervention include the following organ systems⁹⁴: (1) pancreatitis or gastritis (gastrointestinal), which may require prophylactic treatment with H_2 blockers or proton pump inhibitors; (2) hypertension (cardiovascular), which may require antihypertensive therapy; (3) glaucoma and cataract disease (ophthalmic), which requires scheduled dilated eye examination and intraocular pressure measurement; (4) hyperglycemia (increased risk of type 2 diabetes mellitus), dyslipidemia, and obesity (endocrine); (5) avascular necrosis and myopathy (musculoskeletal); and (6) oral candidiasis and caries (dentition).

All asthmatic patients undergoing long-term corticosteroid therapy should be monitored frequently for the complications discussed, and corticosteroid therapy should be discontinued when asthma control is achieved. Serial evaluation of weight, blood pressure, fasting morning blood sugar, serum electrolytes, and serum lipids and ophthalmologic examinations are appropriate surveillance measures. The future management of corticosteroid-dependent asthmatic patients will build on 30 years of previous research and ultimately yield safe, corticosteroid-sparing therapies. Until then, this subgroup of asthmatic patients will require thorough and comprehensive care using glucocorticoids.

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Objectives: After reading this article, participants should be able to demonstrate an increased understanding of their knowledge of allergy/asthma/immunology clinical treatment and how this new information can be applied to their own practices.

Participants: This program is designed for physicians who are involved in providing patient care and who wish to advance their current knowledge in the field of allergy/asthma/immunology.

Credits: ACAAI designates each Annals CME Review Article for a maximum of 2 category 1 credits toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity. The American College of Allergy, Asthma and Immunology is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians.

CME Examination

1–6, Randhawa I and Klaustermeyer WB. 2007;99:291–303.

CME Test Questions

- What is the clinical definition of steroid-resistant asthma?
 - failure to improve baseline morning prebronchodilator forced expiratory volume in 1 second (FEV₁) by greater than 15% of predicted after 60 days of 20-mg, twice-daily oral prednisone.
 - failure to improve baseline morning prebronchodilator FEV₁ by greater than 15% of predicted after treatment with more than 1,000 μ g of daily inhaled fluticasone.
 - failure to improve baseline morning prebronchodilator FEV₁ by greater than 15% of predicted after 7–14 days of 20-mg, twice-daily oral prednisone.
 - daily oral prednisone requirement of more than 20 mg.
 - failure to improve baseline morning prebronchodilator FEV₁ by greater than 30% of predicted after 7–14 days of 20-mg, twice-daily oral prednisone.
- All of the following molecular mechanisms have been implicated in steroid insensitivity except:
 - glucocorticoid receptor β competitive binding
 - inefficient glucocorticoid receptor binding of co-activator molecules such as cyclic adenosine monophosphate response element binding protein

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- c. preferential histone deacetylation
d. increased expression of glucocorticoid receptor α
e. inhibition of p38 MAP kinase
3. Which of the following oral corticosteroid-sparing agents showed no effect on oral corticosteroid use or cessation?
- a. intravenous gammaglobulin
 - b. omalizumab
 - c. ciclesonide
 - d. methotrexate
 - e. cyclosporine
4. All of the following have been associated with the use of high-dose inhaled corticosteroids except:
- a. adrenal axis suppression
 - b. oral candidiasis
 - c. cataract development
 - d. nephrolithiasis
 - e. glaucoma
5. The Global Initiative on Asthma 2006 guidelines on asthma therapy state that daily oral corticosteroids should be considered in patients with nonatopic asthma after failure of therapy with which of the following?
- a. leukotriene modifier therapy
 - b. inhaled corticosteroids
 - c. long-acting β -agonists
 - d. theophylline
 - e. all of the above.
6. Oral corticosteroid-dependent patients with asthma receiving glucocorticoid therapy at more than 7.5 mg/d of prednisone for more than 3 months should do which of the following?
- a. undergo baseline dual energy x-ray absorptiometry scan
 - b. start bisphosphonate therapy
 - c. begin therapy with calcium with vitamin D supplementation at a dosage of more than 1,000 mg/d and 800 IU/d, respectively,
 - d. attempt to wean prednisone to the lowest effective dose
 - e. all of the above.
- Answers found on page 370.**