

Oral Steroid Dosing in Acute-Stage Allergic Bronchopulmonary Aspergillosis

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Practice Options from Beyond Our Pages focuses on identifying, critiquing, and placing into context research studies published in other journals that have the potential to change our clinical practices. It is written by Allergy-Immunology Fellows partnered with faculty members, and does not require an invitation for submission. This feature is coordinated by Editorial Board members Matthew Rank, MD and Julie Wang, MD.

REFERENCE

Agarwal R, Aggarwal AN, Dhooira S, Sehgal IS, Garg M, Saikia B, et al. A randomized trial of glucocorticoids in acute-stage allergic bronchopulmonary aspergillosis complication asthma. *Eur Respir J* 2016;47:385-7.

BACKGROUND

Allergic bronchopulmonary aspergillosis (ABPA) occurs secondary to an exaggerated immunologic response against the antigens of *Aspergillus* species, typically *Aspergillus fumigatus*. This disorder causes significant respiratory distress and poor quality of life in patients and if untreated, it can progress to end-stage lung disease.¹ Oral steroids are the first-line treatment during the acute stage of ABPA; however, because of a paucity of literature, there is no single consensus treatment strategy.¹ Two commonly employed and suggested strategies exist, which can be called the medium-dose and high-dose regimen. In the medium-dose regimen, the patient is administered prednisone 0.5 mg/kg/day, or an equivalent, for 1-2 weeks, then on alternate days for 6-8 weeks, followed by tapering of 5-10 mg every 2 weeks, until discontinuation.² In the high-dose regimen, a prednisone dose, or equivalent, of 0.75 mg/kg/day is given for 6 weeks, then 0.5 mg/kg/day for 6 weeks, followed by a tapering of 5 mg every 6 weeks to complete a total duration of 6-12 months.³ Before this study, there had not been any study directly comparing the efficacy and safety of the above 2 protocols.

METHODS

This was a prospective, open-label, randomized controlled trial conducted at a single site in India. Subjects were enrolled if they met inclusion criteria for ABPA as follows: (1) asthma, (2) skin prick

positivity to *Aspergillus* or *A. fumigatus* specific IgE levels > 0.35 kUA/L, (3) elevated total IgE levels >1000 IU/mL, and 2 of the following features: (1) presence of precipitating antibodies against *A. fumigatus* in serum, (2) fixed or transient radiographic pulmonary opacities, (3) total eosinophil count >1000/ μ L, and (4) bronchiectasis on high-resolution chest computed tomography. Subjects who required antifungal treatment before randomization were excluded from the study. The use of asthma medications was allowed.

Patients who met the above criteria were randomized to either the medium-dose or high-dose protocol. Participants were followed every 6 weeks (physical exam, chest radiograph, and serum IgE level). Spirometry was repeated at the first 6-week follow-up.

The study's primary outcomes were (1) the exacerbation rate after 12 months of therapy and (2) the number of subjects who progressed to glucocorticoid-dependent ABPA after 24 months of treatment. Secondary outcomes included (1) proportion of subjects with a composite response (a combination of clinical improvement score, improvement in radiograph, and decline in IgE levels) after 6 weeks of treatment, (2) percentage decline in IgE after 6 weeks, (3) improvement in lung function after 6 weeks, (4) time to first exacerbation after stopping treatment, (5) cumulative dose of oral glucocorticoid received, and (6) steroid-related adverse effects.

RESULTS

A total of 110 subjects with ABPA were screened and 92 subjects were randomized to either the high-dose ($n = 44$) or medium-dose steroid group ($n = 48$). The average FEV1 percentage amongst participants was 69.4% despite being on inhaled corticosteroids. The median total IgE level was 8900 IU/mL and total eosinophil count 670 cells/ μ L. Both groups had similar withdrawal rate at 1 year and 2 years. The number of patients with exacerbations after 1 year of treatment was similar in both groups (high dose 18, medium dose 24; $P = .592$). Overall, 45.7% ($n = 42$) of subjects experienced an exacerbation after completion of treatment. These exacerbations were treated with glucocorticoids and itraconazole and most responded well. Only 12 of the 42 subjects had glucocorticoid-dependent ABPA. The number of glucocorticoid-dependent ABPA did not differ between the 2 groups (high dose 5, medium dose 7; $P = .882$).

When analyzing the secondary outcomes, those treated with the high-dose steroids had a higher composite response compared with the medium-dose at 6 weeks after treatment (high dose: 100% of patients had improvement, medium dose: 87.5% of

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patients had improvement; $P = .045$). Those treated with the high-dose regimen also had a higher percentage decline in IgE at 6 weeks after treatment (high dose 43.8%, medium dose 11.8%; $P = .025$). However, the improvement in lung function at 6 weeks and time to first exacerbation was similar in the 2 groups. The total dose of corticosteroid consumed in the high-dose arm was 40% higher (4911 mg vs 1694 mg) and similarly, those in the high-dose arm had more glucocorticoid-related adverse reactions (cushingoid habitus and weight gain).

Of note, there were 6 subjects in the medium-dose arm who did not respond at 6 weeks. All 6 were treated with high-dose steroids and showed clinical and/or radiological and immunological response. There were no differences in characteristics of these 6 nonresponders compared with those who responded.

CRITICAL APPRAISAL

This is, to our knowledge, the first and largest randomized control trial evaluating the dose of corticosteroids in the setting of acute ABPA. Although this study does show significant advantages of using a medium-steroid dose regimen compared with a higher steroid dose protocol, there are some noteworthy limitations. First, the authors did note that the study might have been underpowered, as a 30% difference between the 2 arms was not seen. However, a total sample of 502 participants in each arm would have been needed to detect a significant difference, which would be difficult to acquire. Second, this study only looked at the treatment for the acute stage of ABPA. It is unclear if findings from this study can be extrapolated to treatment during the latter stages of ABPA. Third, this study included only patients with asthma. Patients with cystic fibrosis are also at a higher risk of ABPA and management may be different in this

population compared with those with asthma. Although the study did record some glucocorticoid-related adverse reactions in both arms, they did not gather information regarding more concerning adverse reactions such as adrenal suppression and bone mineral density. If these were not different between the 2 groups, the argument for the medium-dose regimen would lose some ground.

Finally, one cannot overlook the fact that 100% of subjects in the high-dose arm responded at 6 weeks, whereas 12.5% of those in the medium-dose arm did not respond at 6 weeks of therapy. In addition, based on the Kaplan-Meier curve in the article, it appears that approximately 25% of those in the medium-dose arm exacerbated within the first 2-3 weeks. Thus, although not justifying the use of the high-dose regimen, this points to the fact that there are patients who will not respond to the medium-dose regimen, and that this will be evident early. These patients will need to be identified and their therapy adjusted.

RECOMMENDATION

The medium-dose oral steroid regimen appears to be a safer option, and may be as effective when compared with the high-dose steroid regimen when treating acute ABPA in asthmatics.

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