

## Azoles in Allergic Bronchopulmonary Aspergillosis

Allergic bronchopulmonary aspergillosis (ABPA) is a hypersensitivity pulmonary disorder caused by *Aspergillus fumigatus* (Af), manifesting with poorly-controlled asthma, recurrent pulmonary infiltrates and central bronchiectasis. There are over 4 million patients worldwide suffering from ABPA.<sup>1</sup> The ABPA occurs most commonly in patients with asthma or occasionally, cystic fibrosis (CF). The precise prevalence of ABPA in asthma and CF in the population is not known, but approximately 2% of patients with asthma and 1% to 15% of patients with CF have been reported to develop ABPA. The prevalence of ABPA in asthma clinics may be as high as 13%.<sup>1</sup>

The ABPA is variably responsive to treatment with corticosteroids and early diagnosis and treatment may prevent progression to end-stage lung disease. However, if the condition is not diagnosed and treated appropriately, extensive bronchiectasis and pulmonary fibrosis can develop leading to type 2 respiratory failure and cor-pulmonale.

The management of ABPA includes two important modalities, namely institution of anti-inflammatory therapy with oral glucocorticoids and use of antifungal agents to attenuate the fungal burden secondary to fungal colonisation in the airways.<sup>2</sup> Oral steroids are considered as the treatment of first choice and are usually effective in the management of ABPA. However, once the steroids are tapered, almost 50% of patients relapse and 20% to 45% remain steroid dependent.<sup>3</sup>

The long term use of systemic steroids is not recommended as there is no proof that this treatment prevents the progression of bronchial destruction and damage of lung lesion.<sup>4</sup> Patients also likely to develop adverse effects due to chronic steroid therapy. These issues have lead clinicians to look for alternative treatment approaches including anti-fungal agents.

The currently available anti-fungal agents with known efficacy against Af are amphotericin-B and the azoles. Treatment of *Aspergillus* infection with amphotericin is effective, but its use has been limited by its toxicity and cost. Azoles are effective, easy to administer and have a favourable side effect and cost profile. These inhibit ergosterol synthesis in the fungal cell membrane, and thereby, inhibit fungal growth.<sup>5</sup>

In the past, anti-fungal therapies, such as nystatin, natamycin, haymycin, miconazole, clotrimazole etc were used but discarded because of lack of efficacy or adverse effects. Ketoconazole has also been tried in the past but its use has been limited by its inconsistent results and side effects including severe hepatic impairment and sexual dysfunction.

Itraconazole has fewer side effects and a better spectrum of activity than ketoconazole. A systematic review identified only two randomised controlled studies, which have evaluated the role of itraconazole in ABPA.<sup>6,7</sup> Pooled analysis showed that itraconazole could significantly decrease the immunoglobulin (Ig) E levels by  $\geq 25\%$  when compared to placebo but did not cause significant improvement in lung function. The evidence from both these trials demonstrates that itraconazole reduces the inflammation associated with ABPA and improves clinical outcomes. As both the intensity of the inflammatory response and acute exacerbations of the disease are felt to lead to progressive lung disease, the ability of itraconazole to modify both these factors in the short-term results may have important implications for the chronic management of the disease. Both these trials had a small number of patients, and long-term follow-up was not available. Hence, larger and long-term trials are required before a firm recommendation can be made on its use as adjunct treatment in patients with ABPA.

Nearly 40% do not respond to itraconazole<sup>2</sup> and it may cause significant adverse effects like nausea, vomiting, diarrhoea, elevated liver enzymes, rash, headache, fatigue and decreased libido etc. It can also inhibit the metabolism of methylprednisolone (but not prednisolone), and thus, lead to increased frequency of steroid side effects including adrenal insufficiency. It is not settled whether it is the anti-fungal action of azoles or the coexistent anti-inflammatory property of the drug that leads to improvement in patients with ABPA.

Voriconazole (300-600 mg/day) and posaconazole (800 mg/day) for atleast six months are newer azoles under evaluation in patients with ABPA<sup>8</sup>. Evidence on efficacy is lacking. Few adverse events, such as sleep disturbances, photosensitivity, peripheral neuropathy, depression and gastro-intestinal disturbances, etc have been reported with these newer azoles. Presently, itraconazole is the first choice among azoles in doses of 200 mg twice daily for atleast 16 weeks, whereas newer agents may be reserved for patients not responding to itraconazole or for those who have adverse reactions with itraconazole.

What is the present status of azoles in the management of ABPA? The use of azoles in ABPA seems rational with some studies demonstrating short-term efficacy with the use of the drug. By decreasing the fungal burden, itraconazole seems to modify the immune activation seen in ABPA and improves the symptoms. However, long-term trials are required to assess the impact of azoles on the lung function and the disease course in ABPA, before a consensus can be

evolved. Itraconazole may be used after the first relapse of ABPA despite steroid therapy and in patients with steroid-dependent ABPA.<sup>9</sup> It may also be recommended in patients in whom oral steroids are absolutely contraindicated or are ineffective. Azoles are not the first-line therapy in patients of ABPA.<sup>9</sup> Questions also remain about the right dose and the duration of treatment and when these should be commenced. These issues await further studies.

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