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A rare case of refractory asthma managed with azathioprine

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ABSTRACT

Introduction: Azathioprine is an immune-modulating agent used in the management of autoimmune diseases and in preventing graft rejection. Its role in the management of refractory asthma is not very well-established.

Case study: A 47-year-old female with an underlying severe refractory asthma, managed with high dose steroids, was seen as an outpatient. Her course was complicated by frequent asthma exacerbation and severe adverse effects of chronic steroid use. Her symptoms did not respond to standard asthma management per Guidelines for the Diagnosis and Management of Asthma 1. She was tried on other management which included methotrexate and omalizumab injections without success. Azathioprine was started as a steroid-sparing agent following which her symptoms showed dramatic improvement with fewer exacerbations, higher peak flow measurements, and she was able to wean down her daily prednisone dose from 60 mg/day to 5 mg/day.

Conclusion: Azathioprine is still an investigational agent for the management of asthma and more research needs to be done to evaluate its role. To our knowledge, this is the second case report which details the therapeutic role of Azathioprine in the management of asthma.

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Introduction

Asthma is a chronic inflammatory disorder of the airways characterized by reversible airflow obstruction (1). It is one of the most common respiratory problems encountered by clinicians with a current prevalence of 8.7% in adults and 8.5% in children (2). Although the management of asthma is centered at avoiding the trigger for an exacerbation, most patients require some form of maintenance therapy for their asthma.

Inhaled long and short-acting beta-adrenergic receptor agonists, inhaled anticholinergics and inhaled corticosteroids are commonly employed agents for maintenance therapy and intravenous or oral corticosteroids are typically used at the time of an asthma exacerbation. However, many patients are known as “steroid resistant” asthmatics that require additional agents to control their symptoms.

Azathioprine is an immunomodulatory agent used frequently for autoimmune diseases and renal transplant but very limited data exist on its utilization in asthma.

In this report, we describe a case of a severe persistent, steroid-dependent asthmatic that showed dramatic improvement in her symptoms with azathioprine.

Case

A 47-year-old non-Hispanic, nonsmoker female with a past medical history of hypertension and controlled acid reflux disease was seen in the office for poorly controlled, steroid dependent, severe persistent bronchial asthma. She was being managed with montelukast 10 mg daily, mometasone-formoterol 200 mcg/5 mcg 2 puffs twice a day, aclidinium bromide 1 puff twice a day, prednisone 10 mg daily, and albuterol-ipratropium nebulizers as needed.

Work up of her Asthma is shown in Table 1.

Her asthma was complicated by frequent exacerbation {defined by a drop in her peak expiratory flow(PEF) from a baseline of 300 L/min to early 200's L/min, expected baseline for her age and height is 415 L/min} requiring hospitalization and 40–60 mg

Table 1. Work up of her asthma.

Complete blood count	Normal
Complete metabolic profile	Normal
IgE levels	Normal 36.5 kU/L Ref range: <114 kU/L
Anti-nuclear antibodies	Normal <0.3 Ref range : <1.5 OD
Rheumatoid factor	Normal <10 Ref range: <20 IU/ml
c,p -Anti-neutrophil cytoplasmic antibody	Negative
Aspergillus antibody	Negative
Direct laryngoscopy	No vocal cord dysfunction
Esophagogastroduodenoscopy	Normal, no signs of reflux disease
Echocardiogram	Normal , negative bubble study
Skin allergy testing	Negative
CT chest without contrast	Normal lung parenchyma and airways
Bronchoscopy with broncho-alveolar lavage	Normal cytology with no bacterial or fungal growth
Bronchial biopsy	Bronchial mucosa with changes compatible with reactive airway disease
Pulmonary function test	Forced expiratory volume, Forced vital capacity - 98%, 91% of predicted respectively, with no bronchodilator response. Diffuse lung capacity for carbon monoxide 69% of predicted.

*On high dose prednisone.

prednisone/day. After 6 months of “high-intensity treatment” (use of > 1000 mcg/day of fluticasone equivalent and/or daily oral corticosteroids combined with long-acting β_2 agonists or any other controller medication) (3,4) and failure to taper down the prednisone, omalizumab was initiated. Her first dose was complicated by a deep vein thrombosis and a second dose complicated by a pulmonary embolism requiring her to be on lifelong anticoagulation, making her ineligible for bronchial thermoplasty. Omalizumab was discontinued and Methotrexate was initiated. She had minimal improvement with low dose methotrexate and developed transaminitis with a higher dose and was discontinued. She was then started on Azathioprine at a dose of 50 mg/day and showed a significant improvement in her symptoms after 6–8 weeks. Over one year, her dose was slowly increased to the current dose of 175 mg/day and her prednisone tapered to current dose of 5 mg/day, with good control of her asthma symptoms, increased exercise tolerance (walking actively from being wheelchair bound), improved PEF (from a baseline of approx. 300 L/min to 400 L/min) and substantially fewer exacerbations (Figure 1).

Discussion

Steroid-resistant asthma is defined as a failure to increase FEV1 by 15% following a 7-day course of oral steroid therapy at a dose of 20 mg of prednisolone daily or equivalent (5). These patients require additional immunosuppressants such as methotrexate, cyclosporine or biological agents such as omalizumab and mepolizumab.

Azathioprine is an immune-modulating drug that works by interfering with DNA replication and T lymphocytes activation 5. It is a commonly employed agent in the management of autoimmune diseases

such as inflammatory bowel disease, lupus nephritis, and multiple sclerosis (6–8).

Several studies have evaluated its role in managing refractory, steroid-dependent asthma. Hodges et al. conducted a double-blind controlled crossover trial using 2 doses of azathioprine (2 mg/kg/day and 5 mg/kg/day for 3 and 4 weeks respectively) in 20 chronic severe asthmatics and reported mild short term improvement in 4 patients and significant sputum reduction in two of them (9). However, no significant improvement in FEV1 or a reduced number of asthma exacerbations was reported in the study. This study was a prospective trial and the long-term effects of azathioprine and dose reduction of prednisone were not reported. In our case study, we demonstrated a clear effect of azathioprine on FEV1 and a reduction in the number of exacerbations over a course of 1 year.

Rudyk et al. published a clinical trial using azathioprine alone and in conjunction with either prednisolone or chloroquine, and reported partial effectiveness of azathioprine in short term but worse outcomes in 8 years follow up (10).

Saaddeh et al. published the first case report demonstrating the effectiveness of azathioprine in a steroid-dependent, severe persistent asthma. Azathioprine was dosed at 1.5 mg/kg/day for 16 weeks and a significant increase in exercise tolerance and FEV1 and substantial reduction of prednisone from 80 mg/day to 7.5 mg/day was reported (11).

In our case, alternative diagnoses such as chronic obstructive pulmonary disease, churg strauss syndrome, vocal cord dysfunction, allergic bronchopulmonary aspergillosis, etc. were carefully ruled. She demonstrated proper inhaler technique and had good compliance with her medications.

Besides the conventional therapy for severe asthma, omalizumab and methotrexate provided minimal

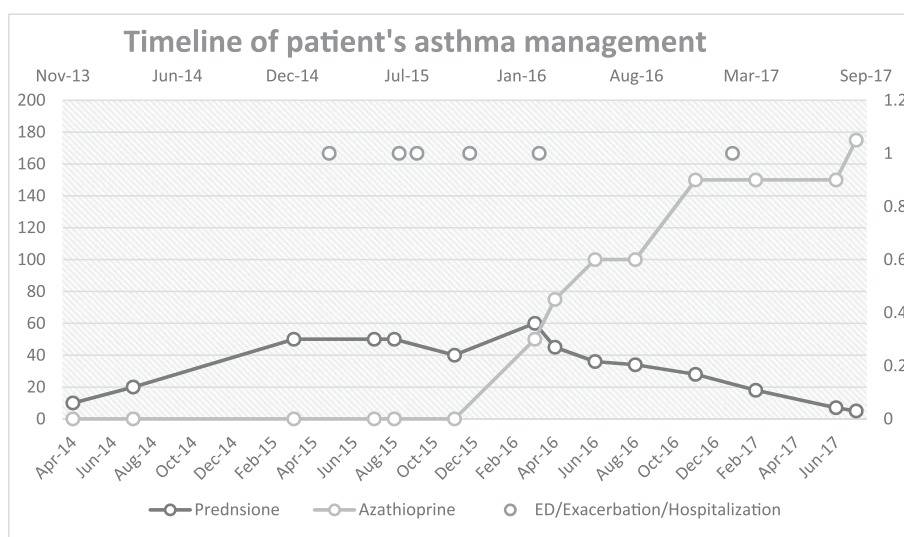


Figure. 1 Timeline of patient's asthma management.

relief. Meanwhile, she had been on high dose steroids and suffered complications. Azathioprine was started at 50 mg daily dose and gradually increased with an improvement in symptoms in 8 weeks which corresponded to the initial and peak response period of azathioprine. Her improvement in symptoms and PEF were attributed to azathioprine since no other medications were started during this period and a clear temporal relation of symptomatic relief and initiation of therapy was seen.

Conclusion

To our knowledge, this is the second case report highlighting the beneficial effects for azathioprine in asthma as a steroid-sparing agent. Although there is plenty of evidence of the use of other immunosuppressant agents in asthma, azathioprine is still considered as an investigational agent and more research needs to be done to look into its role in severe refractory asthma.

Declaration of interest

The authors report no conflict of interest.

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