Long-term Clarithromycin Decreases Prednisone Requirements in Elderly Patients With Prednisone-Dependent Asthma

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Prolonged use of prednisone is associated with serious side effects, such as osteoporosis, particularly among elderly individuals. Macrolide antibiotics exhibit anti-inflammatory effects that are distinct from their antimicrobial properties. Thus, the purpose of this case report is to describe the effects of prolonged treatment with clarithromycin, 500 mg bid, in reducing prednisone requirements in three elderly patients with prednisone-dependent asthma. Three patients (one woman and two men) aged 63 to 69 years, who had been treated with 5 to 10 mg prednisone daily for at least the last 12 months, were given clarithromycin, 500 mg bid. They were followed regularly for changes in daily prednisone dose, spirometry, quality of life, and adverse events. The prednisone dose was tapered in a stepwise fashion at each clinic visit. Within 3 to 6 months of initiation of treatment with clarithromycin, and throughout the 12-month follow-up, two of three patients discontinued prednisone therapy, while the third patient displayed increased spirometry readings and noted an increasingly better quality of life. Pulmonary function tests were stable or improved over this time period, with no reported adverse events, including increased rate of infections. One patient relapsed upon discontinuation of clarithromycin therapy but has since responded to re-initiation of treatment. Long-term oral clarithromycin may have a role in reducing prednisone requirements in elderly patients with prednisone-dependent asthma.

Key words: anti-inflammatory; clarithromycin; macrolides; prednisone-dependent asthma

Several studies have suggested that macrolide antibiotics have salutary effects in patients with asthma, including a corticosteroid-sparing effect.1–3 The mechanisms underlying this response are thought to be related, in part, to anti-inflammatory effects of the drugs, which are distinct from their antimicrobial effects.4 Elderly patients with prednisone-dependent asthma are at high risk for developing devastating side effects from prolonged use of the drug, particularly osteoporosis.5 Hence, the use of macrolides in these patients in an attempt to reduce prednisone dependency would be advantageous.

Case Report

This case report begins to address the issue by describing three elderly patients with prednisone-dependent asthma who reduced or discontinued oral prednisone therapy after long-term treatment with clarithromycin, a 14-membered ring macrolide.

Patient 1

A 63-year-old white woman received a diagnosis of severe asthma in 1995 and had been prednisone-dependent since that time. She had received a diagnosis of asthma as a child, and that condition had resolved as she reached the age of 18 years. He had quit smoking approximately 20 years before this study (14 pack-year history). Skin allergy tests were positive for mold dust. Physical examination was significant for a cushingoid appearance. Baseline FVC and FEV1 were 1.72 L and 1.12 L/s, respectively (44% and 36% predicted, respectively). His current asthma treatment consisted of inhaled triamcinolone, 1,600 mcg daily; inhaled albuterol, 810 mcg daily; oral theophylline, 400 mg daily; and prednisone, 10 mg daily. His symptoms were aggravated by attempts to taper his prednisone dose. In August 1998, he was given clarithromycin, 500 mg bid. Five months later, he discontinued prednisone entirely with no significant change in spirometry. Due to unexplained ecchymoses while receiving clarithromycin alone for 2 months, the drug was discontinued. The patient experienced an acute exacerbation of asthma 1 month later and was given oral prednisone and clarithromycin, 500 mg bid. Within 2 months, the patient discontinued prednisone. He has remained on clarithromycin through 12 months of follow-up. No other changes were made to his medications. Clarithromycin was well tolerated, and he has remained asymptomatic.

Patient 2

A 65-year-old white woman received a diagnosis of severe asthma in 1996. Her symptoms were frequently exacerbated by attempts to taper her prednisone dose. Her medical history was significant for a 22-year history of allergic rhinitis and infrequent symptoms of gastroesophageal reflux. The patient had quit...
smoking at the age of 27 years (5 pack-year history). Baseline FVC and FEV\textsubscript{1} were 3.25 L and 2.26 L/s, respectively (115% and 100% predicted, respectively). Current asthma treatment regimens consisted of inhaled triamcinolone, 1,000 μg qd; inhaled metaproterenol, 7.5 mg qd; inhaled cromolyn sodium, 6,400 μg qd; and prednisone, 10 mg qd.

In February 1997, the patient was given clarithromycin, 500 mg bid. Within 3 months, she tapered her prednisone to 5 mg qd, with a concomitant increase in FVC and FEV\textsubscript{1} to 3.54 L and 2.69 L/s, respectively (127% and 120% predicted, respectively). Three months later, she discontinued prednisone entirely. No changes in spirometry or adverse events were noted through 12 months of follow-up.

**Patient 3**

A 67-year-old white man had received a diagnosis of asthma in 1984 and had been dependent on prednisone for the past 1.5 years. He experienced four to five acute exacerbations of asthma per year. His medical history was significant for gastroesophageal reflux. He had no smoking history. Baseline FVC and FEV\textsubscript{1} were 3.25 L and 2.26 L/s, respectively (115% and 100% predicted, respectively). He was treated with ipratropium, 144 μg qd; salmeterol, 24 μg qd; flunisolide, 2,000 μg qd; beclomethasone, 168 μg qd; theophylline, 600 mg qd; and prednisone, 5 mg qd.

He was given clarithromycin, 500 mg bid, and within 3 months, FVC increased to 5.3 L (125% predicted) with no change in FEV\textsubscript{1}. Plasma theophylline concentrations were unchanged throughout the observation period. The patient noted a significant improvement in quality of life, manifested by increased energy levels and enthusiasm. Several attempts to taper oral prednisone to 5 mg qd failed. Nonetheless, the patient did not experience an acute exacerbation of asthma throughout the 12 months of clarithromycin therapy. No adverse events were noted.

**DISCUSSION**

The new finding from these case reports is that long-term (12 months) treatment with oral clarithromycin, 500 mg bid, is associated with a significant reduction in prednisone dependency in elderly patients with prednisone-dependent asthma. Importantly, this phenomenon was associated with a significant improvement in asthma coupled with significant improvement in quality of life, manifested by increased energy levels and enthusiasm. Several attempts to taper oral prednisone to 5 mg qd failed. Nonetheless, the patient did not experience an acute exacerbation of asthma throughout the 12 months of clarithromycin therapy. No adverse events were noted.

Previous studies from Japan have shown that relatively short-term (<3 months) therapy with oral erythromycin and roxithromycin, two macrolide antibiotics, was associated with significant improvement in bronchial hyperreactivity in patients with asthma. However, the mechanisms underlying this response were not determined. Moreover, these patients were either children or adults. The results of our case studies support and extend these observations by showing that long-term treatment with clarithromycin may be beneficial in elderly patients with prednisone-dependent asthma. Whether the corticosteroid-sparing effects of this drug are related, in part, to downregulation of the inflammatory cascade in the airway of patients with asthma remains to be determined.

Prolonged use of prednisone in patients with asthma, particularly elderly patients, is associated with devastating side effects, including osteoporosis. Hence, therapeutic measures to reduce or eliminate prednisone dependency in these patients are desirable. The results of this case report suggest that long-term administration of oral clarithromycin may be a useful approach to accomplish this goal. However, the mechanisms underlying the corticosteroid-sparing effect of clarithromycin were not elucidated in this study. Earlier studies had suggested possible interactions between macrolides and corticosteroids, causing increased concentrations of the steroid. This is unlikely in the cases reported here, as two patients were able to discontinue prednisone entirely for a sustained period while remaining in remission. Also, Fost et al. recently demonstrated that clarithromycin did not affect the pharmacokinetics of prednisone. Clearly, additional prospective studies are indicated to investigate the role of long-term clarithromycin therapy in elderly patients with prednisone-dependent asthma.

In summary, long-term oral clarithromycin therapy may have a role in the treatment of elderly patients with prednisone-dependent asthma. Future research will be necessary to further elucidate their effects.

**REFERENCES**