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Effects of Six-Week Clarithromycin Therapy in Corticosteroid-Dependent Asthma: A Randomized, Double-Blind, Placebo-Controlled Pilot Study

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ABSTRACT

Background: Although corticosteroids such as prednisone are efficacious for the treatment of severe asthma, chronic administration of oral corticosteroid therapy is associated with significant adverse effects. Previous studies have shown that clarithromycin is effective in reducing bronchial hyperresponsiveness and allergen-induced bronchoconstriction. However, the effect of long-term clarithromycin therapy in patients with prednisone-dependent asthma is uncertain.

Objective: This study was conducted to determine the effects of oral clarithromycin on prednisone daily dosage, pulmonary function, quality of life (QOL), and asthmatic symptoms in patients with corticosteroid-dependent asthma.

Methods: This 14-week, prospective, randomized, double-blind, placebo-controlled pilot study was conducted at Pulmonary Associates (Phoenix, Arizona) and the University of Illinois at Chicago Medical Center (Chicago, Illinois). Patients aged 18 to 75 years with an established diagnosis of asthma and who had been receiving ≥5 mg/d of prednisone for the preceding 6 months were enrolled. After a 4-week data-collection period, patients received clarithromycin 500 mg BID for 6 weeks, followed by a 4-week follow-up period. The effects of clarithromycin therapy on prednisone dosage requirements, pulmonary function (as assessed using spirometry), QOL, and asthmatic symptoms (nocturnal asthma, shortness of breath, chest discomfort, wheezing, and cough) were assessed.

Results: Fourteen patients (9 men, 5 women; mean [SD] age, 62 [13] years) completed the study and were included in the final analysis. One patient withdrew from the study due to clarithromycin-related nausea. After 6 weeks of

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clarithromycin therapy, patients were able to tolerate a significant reduction in mean (SD) prednisone dosage from baseline (30% [18%]; $P = 0.020$). Pulmonary function, QOL, and asthmatic symptoms did not significantly worsen despite reduction in prednisone dose. All patients who completed the study tolerated clarithromycin therapy.

Conclusions: In this pilot study of patients with corticosteroid-dependent asthma, 6-week clarithromycin 500 mg BID was clinically effective in allowing a reduction in prednisone dosage, without worsening pulmonary function, QOL, or asthmatic symptoms. In addition, clarithromycin was well tolerated, with only 1 patient discontinuing therapy due to treatment-related nausea. (*Curr Ther Res Clin Exp.* 2004;65:1–12)

Key words: clarithromycin, corticosteroid-dependent asthma, steroid-sparing effect, prednisone.

INTRODUCTION

Airway inflammation in a majority (>95%) of patients with asthma can be managed with inhaled corticosteroid therapy.[1] However, severely affected individuals (1%–2%) require oral corticosteroids, such as prednisone, to control asthmatic symptoms.[1,2] Although corticosteroids produce significant decreases in asthmatic inflammation, bronchial hyperresponsiveness, and the frequency of acute exacerbations, asthmatic patients experience increased morbidity secondary to adverse effects (AEs) associated with long-term corticosteroid use.[3] Corticosteroid toxicities, such as osteoporosis, diabetes mellitus, hypertension, and neuropsychiatric disorders, have led to an interest in glucocorticoid-sparing agents.

Macrolide antibiotics are widely studied corticosteroid-sparing agents.[4–11] Although macrolides have been shown to significantly improve quality of life (QOL) and asthmatic symptoms in severely asthmatic patients,[4–6] their corticosteroid-sparing effect and subsequent AEs have been attributed to the ability of macrolides to selectively increase the elimination half-life of methylprednisolone sodium succinate.[7–9]

However, some studies[10–15] have indicated that macrolides possess antimicrobial and anti-inflammatory properties that may be beneficial in patients with severe asthma. Macrolides have excellent activity against atypical pathogens, which have been associated with the development and/or poor control of asthma.[10,11] In addition, macrolides have been shown to exert anti-inflammatory effects in patients with diffuse panbronchiolitis,[12] chronic bronchitis,[13] chronic sinusitis,[14] and asthma.[15]

To further explore the corticosteroid-sparing properties of macrolides, we studied the effects of 6-week clarithromycin therapy on daily prednisone dosage, pulmonary function, QOL, and asthmatic symptoms in patients with corticosteroid-dependent asthma. Patients who were on prednisone therapy

were recruited for this study because a significant decrease in methylprednisolone elimination by macrolides is not observed with prednisone.[7,8]

PATIENTS AND METHODS

This study was conducted at Pulmonary Associates (Phoenix, Arizona) and the University of Illinois at Chicago Medical Center (Chicago, Illinois), and the protocol was approved by the institutional review board. All patients provided written informed consent to participate.

Patients

Patients aged 18 to 75 years with an established diagnosis of asthma[2] and who had been receiving ≥5 mg/d of prednisone for the preceding 6 months were enrolled in the study. All patients were required to have stable asthma with a ≤20% change in prednisone or bronchodilator dosage in the previous 4 weeks. Women of childbearing potential were required to have a negative pregnancy test and to use an effective method of contraception throughout the study period.

Exclusion criteria were hypersensitivity to macrolides; a history of myocardial infarction, arrhythmias, angina, uncontrolled hypertension, or uncompensated congestive heart failure; moderate to severe hepatic dysfunction[16]; moderate to severe renal dysfunction[17]; and a respiratory infection requiring antimicrobials (macrolide/azalide and/or fluoroquinolones) within the 6 weeks before the study. Pregnant or breastfeeding women were excluded from the study.

Study Design

This was a 14-week, prospective, randomized, double-blind, placebo-controlled pilot study consisting of 3 phases. Observation periods of 4 weeks preceded and followed the 6-week treatment phase. During the study period, each patient was assessed every 2 weeks.

Phase 1

Phase 1 (the first 4 weeks of the study) was devoted to collecting demographic information and measuring baseline characteristics. In addition, every attempt was made by the study physicians to reduce the prednisone dosage until the lowest effective dosage, in accordance with current guidelines,[2] was found. For patients receiving 5 to 14 mg/d of prednisone, the maximum allowable decrease in the daily dosage was 2.5 mg every 2 weeks. For patients receiving 15 to 29 mg/d of prednisone, the daily dosage could be lowered up to 5 mg every 2 weeks. Finally, for patients receiving ≥30 mg/d of prednisone, the maximum decrease in the daily dosage was 10 mg every 2 weeks. In addition, proper use of a

metered-dose inhaler and a peak flow meter was demonstrated by study physicians or pharmacists.[1]

Phase 2

During phase 2 (the 6-week treatment period), patients were randomized (based on a code developed by a computerized random-number generator) to receive either clarithromycin* 500-mg tablets by mouth BID or identical placebo. During this period, all scheduled antiasthmatic medications were held constant. In patients who were receiving theophylline as part of their antiasthmatic regimen, plasma theophylline concentrations were monitored by the study physicians or pharmacists to avoid adverse interactions with clarithromycin therapy. After 2 weeks of clarithromycin therapy, a study physician reduced the prednisone dosage if a patient remained stable. The corticosteroid taper was based on a patient's daily dosage of prednisone and followed the same taper schedule used in phase 1. No reduction in the prednisone dosage was made after the third visit (week 4) of the treatment phase.

If a patient experienced an asthma exacerbation, the corticosteroid taper was discontinued and the prednisone dose was increased at the treating physician's discretion. After the exacerbation was controlled, the prednisone dosage used before the exacerbation was reintroduced. *Asthma exacerbation* was defined as worsening asthmatic symptoms that resulted in a telephone call to the physician's office, an unscheduled office visit, or a visit to an emergency department accompanied by an increase in prednisone dose or a >50% increase in rescue $beta_2$-agonist use ($\geq$6 extra puffs or 3 extra nebulizer treatments per day).

Phase 3

Phase 3 (the final 4 weeks of the study) was the observational period after treatment was discontinued. Patients were maintained on the tapered prednisone dose after the treatment period, unless they experienced worsening of asthmatic symptoms requiring increases in prednisone dosages.

Measurements

At screening, patients underwent spirometry (forced expiratory volume in 1 second [FEV_1], forced vital capacity [FVC], FEV_1/FVC ratio, and peak expiratory flow [PEF]) and completed a QOL questionnaire.[18] This 20-item, self-administered questionnaire has been validated to measure QOL in adults with asthma. A 5-point scale (0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, 3 = severe symptoms, 4 = very severe symptoms) was used to assess breathlessness, mood disturbance, social disruption, and concerns for health. At all subsequent study visits, spirometry was performed, the QOL questionnaire was administered, and diary cards were reviewed (diary cards

*Trademark: Biaxin® (Abbott Laboratories, Abbott Park, Illinois).

were to be completed each morning and evening and include daytime and nighttime asthmatic symptoms [nocturnal asthma, shortness of breath, chest discomfort, wheezing, and cough] according to a 4-point scale [0 = none, 1 = mild, 2 = moderate, 3 = severe]). PEF rates and use of rescue bronchodilator therapy (short-acting beta$_2$-agonist) also were recorded.

AEs were assessed at each study visit using patients' self-reporting of any unusual symptoms (eg, diarrhea, nausea, vomiting, abdominal pain) since the start of treatment. Drug interactions such as those observed with theophylline were monitored using plasma theophylline concentrations. The potential for clinically relevant selection of bacterial resistance was monitored using observation of occurrences of infections during the 14-week study period.

Statistical Analysis

All statistical analyses were performed using SAS software version 8 (SAS Institute Inc., Cary, North Carolina). The Wilcoxon signed rank test was used for comparison of baseline data with data obtained after clarithromycin treatment and at the end of the study period. $P \leq 0.05$ was considered statistically significant.

RESULTS

Although the study was designed for 40 patients, it was discontinued after the enrollment of 21 patients due to slow enrollment. During the analysis phase, it became clear that the clarithromycin and placebo groups were unequal in size, thereby preventing valid comparisons. Because the clarithromycin group was so much larger than the placebo group (15 patients vs 6 patients), we analyzed only the clarithromycin group by comparing the findings before and after treatment. The data are presented according to this analytic scheme.

Fifteen patients were enrolled in the clarithromycin group, and 1 patient (6.7%) withdrew from the study after visit 4 because of clarithromycin-related nausea. Fourteen patients (9 men, 5 women; mean [SD] age, 62 [13] years) were included in the final efficacy and tolerability analyses (**Table I**). The study patients had been diagnosed with asthma for a mean [SD] duration of 20 [16] years, and the majority of patients (85.7%) had adult-onset asthma. Prednisone had been a part of their treatment regimen for a mean [SD] of 5.8 [5.6] years. In addition to their prednisone and inhaled short-acting beta$_2$-agonist therapy, 8 (57.1%) patients received theophylline; 8 (57.1%), inhaled corticosteroids; 2 (14.3%), cromolyn; 2 (14.3%), ipratropium bromide; and 2 (14.3%), leukotriene modifiers. None of the 8 patients needed adjustment of their theophylline doses during the study. All antiasthmatic drugs were maintained at the same doses throughout the study.

By the end of phase 1, each patient's prednisone dosage had been adjusted to allow good control (based on spirometry results and clinical symptoms) of asthmatic symptoms at the lowest possible dosage.

Table I. Baseline demographic and clinical characteristics of study completers (N = 14).

Patient No.	Sex	Age, y	Duration of Asthma, y*	Prednisone Dosage, mg/kg · d†	Duration of Prednisone Therapy, y‡	FEV_1, L	Predicted FEV_1, %	FVC, L	Predicted FVC, %	FEV_1/FVC Ratio, %
1	M	54	37	0.05	1	1.56	48	3.27	82	48
2	M	48	13	0.14	10	1.76	53	4.07	100	43
3	M	72	5	0.09	4	1.33	46	2.67	73	50
4	M	68	15	0.06	2	2.50	75	4.49	106	55
5	M	62	5	0.09	4	1.34	43	1.92	49	69
6	M	63	12	0.30	10	1.67	68	3.33	109	50
7	M	73	50	0.33	16	0.71	19	0.38	28	53
8	M	64	46	0.24	1	0.92	33	1.98	57	46
9	M	36	17	0.38	15	2.57	73	3.27	76	78
10	F	65	7	0.15	0.7	1.83	81	2.74	97	67
11	F	79	5	0.07	4	1.82	62	2.35	86	77
12	F	73	20	0.07	12	1.51	78	2.33	95	65
13	F	67	5	0.06	1	2.44	92	3.31	99	74
14	F	40	38	0.19	0.7	1.79	60	2.52	70	71

FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity.
*Time from diagnosis of asthma to study entry.
†Prednisone dose at the time of study entry.
‡Duration of prednisone use before study entry.

During phase 2, the prednisone dose was tapered twice (after 2 and 4 weeks of clarithromycin therapy). The doses of prednisone at baseline, after treatment, and at the end of the study are shown in **Table II**. The mean (SD) reductions in the baseline prednisone dosage at the end of 2 and 4 weeks of clarithromycin therapy were 15.1% (10.8%) and 32.8% (16.1%), respectively (both $P < 0.005$).

Results of spirometry are shown in Table II. During clarithromycin therapy and prednisone taper, FVC, FEV_1, FEV_1/FVC ratio, and PEF were not significantly different compared with baseline. At the end of phase 1, mean (SD) FVC and FEV_1 increased by 7.3% (6.5%) and 9.9% (18.4%), respectively, following acute

Table II. Mean (SD) spirometric findings, quality of life (QOL) scores, asthmatic symptoms, and use of rescue medication with clarithromycin therapy (N = 14).

Parameter	Baseline	After Treatment	End of Study
Prednisone dosage, mg/d	12.86 (7.77)	8.54 (5.44)*	10.36 (6.15)†
Spirometry			
FEV_1, L	1.62 (0.55)	1.80 (0.79)	1.66 (0.72)
FEV_1, %	57.22 (20.45)	62.73 (28.09)	61.49 (26.54)
FVC, L	2.73 (0.95)	2.95 (1.22)	2.79 (1.14)
FVC, %	78.61 (25.04)	83.97 (29.86)	80.43 (28.36)
FEV_1/FVC ratio, %	59.86 (12.19)	60.14 (11.86)	58.93 (9.61)
PEF, L/s‡	327.93 (116.96)	331.79 (133.81)	347.36 (134.85)
QOL§	2.82 (1.82)	2.38 (1.66)	2.38 (1.56)
Asthmatic symptoms‖			
Combined asthmatic symptoms	1.47 (1.11)	1.19 (1.16)	0.98 (0.90)
Shortness of breath	0.98 (0.91)	0.88 (0.93)	0.86 (0.90)
Wheezing	0.94 (0.75)	0.76 (0.80)	0.61 (0.62)
Chest discomfort	0.82 (0.82)	0.56 (0.72)¶	0.57 (0.71)
Cough	0.73 (0.74)	0.58 (0.77)	0.48 (0.65)†
Nocturnal asthma	0.63 (0.78)	0.66 (0.89)	0.58 (0.89)
PEF, L/s#	323.49 (80.34)	362.22 (104.30)**	339.88 (91.86)††
Albuterol puffs in 24 hours	7.52 (4.29)	7.07 (4.60)	7.41 (4.79)

FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; PEF = peak expiratory flow.
*$P < 0.001$ versus baseline (Wilcoxon signed rank test).
†$P = 0.020$ versus baseline (Wilcoxon signed rank test).
‡PEF measured as part of pulmonary function test.
§A 5-point scale (0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, 3 = severe symptoms, and 4 = very severe symptoms) was used to assess QOL.
‖Symptoms were recorded mornings and evenings on diary cards. Scale: 0 = none, 1 = mild, 2 = moderate, and 3 = severe.
¶$P = 0.031$ versus baseline (Wilcoxon signed rank test).
#PEF measured by patients.
**$P = 0.021$ versus baseline (Wilcoxon signed rank test).
††$P = 0.010$ versus baseline (Wilcoxon signed rank test).

treatment with a $beta_2$-agonist. At the end of clarithromycin therapy, mean (SD) FVC and FEV_1 increased by 9.6% (15.7%) and 10.5% (11.9%), respectively. At the end of the study, mean (SD) FVC and FEV_1 increased by 10.5% (11.9%) and 12.7% (11.8%), respectively, following treatment with a $beta_2$-agonist.

Mean QOL scores and mean scores of asthmatic symptoms are presented in Table II. The QOL score did not significantly change during clarithromycin therapy and prednisone taper. Diary-reported symptoms such as chest discomfort and cough improved significantly during and after clarithromycin therapy and prednisone taper, respectively ($P = 0.031$ and 0.020, respectively). Patient-reported PEF improved significantly after treatment and at study end ($P = 0.021$ and 0.010, respectively). The number of rescue albuterol puffs used during a 24-hour period did not change significantly throughout the study.

One of the 14 patients (7.1%) did not tolerate the prednisone taper and required an increase in prednisone dose during clarithromycin therapy. In this patient, 5 days of high-dose corticosteroid therapy (methylprednisolone 125 mg q6h) coincided with a 3-day hospitalization for renal angioplasty and biopsy for tumor assessment. The patient improved after discharge from the hospital. The baseline prednisone dose was reinstituted, and pulmonary function test values, QOL score, and daily asthmatic symptom scores returned to baseline values.

After the discontinuation of clarithromycin therapy, 6 patients (42.9%) required an increase in their prednisone dosage to baseline levels. However, 7 patients (50.0%) remained stable on their tapered prednisone doses. All patients were clinically stable at the completion of the study.

Except for 1 patient who withdrew due to treatment-related nausea, none of the 14 patients who completed the study reported AEs associated with clarithromycin therapy.

DISCUSSION

The results of this study suggest that by using clarithromycin as a corticosteroid-sparing agent, prednisone dosage can be decreased in patients with corticosteroid-dependent asthma, with good tolerability. Prednisone dosage reduction in these patients was accompanied by no significant worsening of their pulmonary function test values, QOL, or asthmatic symptoms. This finding is important because long-term corticosteroid therapy has been associated with serious AEs.[3]

Most of the patients (85.7%) in the present study had adult-onset asthma. Although little is known about the differences between childhood- and adult-onset asthma, evidence indicates that the impairments in lung function, requirements for oral glucocorticoid therapy, duration of glucocorticoid therapy, responses to glucocorticoids in vitro, and prednisone pharmacokinetic properties are similar in childhood- and adult-onset asthma.[19] Despite the differences in disease duration, the severity of illness in adults is similar.[19] In adult-

onset asthma, patients display an acute loss in lung function soon after the diagnosis is made, followed by relatively stable lung function thereafter.[19] Because the treatment does not significantly differ between childhood- and adult-onset asthma, we do not believe that clarithromycin will act differently in these 2 groups.

Most patients in the present study tolerated decreases in prednisone dosage, but the decreases may have been greater if the duration of the treatment had been longer. The prednisone taper guidelines designed for the study protocol were the maximum decreases allotted in this study and were based on each patient's corticosteroid dose. The study physicians managed the prednisone dose based on the asthmatic symptoms. In addition, the corticosteroid taper occurred twice during the study (after 2 and 4 weeks of clarithromycin therapy); if the clarithromycin treatment period had been longer, it is possible that the corticosteroid doses may have been decreased further. In fact, 3 of the study patients chose to continue clarithromycin therapy after the study.[20] Two of them were able to discontinue prednisone completely within 6 months, and the other reported improved spirometric findings and better QOL. In all 3 patients, spirometric findings and QOL improved.

The mechanism by which macrolide therapy allows a reduction in prednisone dosage in asthmatic patients is not completely understood. However, the effect of macrolides on corticosteroid metabolism can be eliminated as the cause because, unlike methylprednisolone, clarithromycin does not affect prednisone elimination.[7,8] Numerous studies indicate that the immunomodulatory and anti-inflammatory effects of macrolides are similar to those of glucocorticoids such as prednisone.[21,22] Both agents have been shown to improve airway hyperreactivity and to reduce inflammatory cell (including mast cells, eosinophils, and lymphocytes) infiltration into airways. Macrolides, especially 14- and 15-membered ring compounds, suppress the production of proinflammatory cytokines via inhibition of nuclear factor-κB activation and repress interleukin-8 gene transcription, mainly via the activator protein-1 binding site.[23] Macrolides and glucocorticoids share similar transcriptional targets in exerting anti-inflammatory activity in asthmatic patients.[21–23]

Furthermore, clarithromycin has been shown to act synergistically with glucocorticoids (eg, dexamethasone) in suppressing lymphocyte activation.[24] In a study[24] of patients with asthma, a 10-day course of clarithromycin heightened the sensitivity of lymphocytes to the suppressive effects of dexamethasone, requiring less dexamethasone to suppress phytohemagglutinin activation compared with baseline. In this manner, clarithromycin may have acted synergistically with corticosteroid, allowing the reduction of prednisone, as observed in our study. Also in our study, pulmonary function, QOL, and control of asthmatic symptoms during corticosteroid dosage reductions were maintained with clarithromycin therapy. These results are encouraging in light of the fact that oral corticosteroids are potent immunomodulatory agents.

In addition to the anti-inflammatory effects, macrolides have potent antibacterial activity against *Mycoplasma* and *Chlamydia* spp.[25] Some data[10,11] support *Mycoplasma* and *Chlamydia* respiratory infections as factors contributing to poor control of asthma in selected patients. In the study by Hahn,[26] eradication of *Chlamydia pneumoniae* has been associated with asthma cure in 4 (8.7%) of 46 patients, as determined by resolution of symptoms and results of pulmonary function tests. Even in the 50% of patients who remained seroreactive in that study, 4 weeks of treatment with clarithromycin produced major clinical improvements. The beneficial effects observed in the patients in the present study also may have resulted from the antibacterial effect of clarithromycin therapy. However, optimal therapy for the eradication of these atypical organisms is unknown.[25]

One of the concerns of long-term administration of any antibiotic is the potential for selecting resistant pathogens. Although we did not actively assess susceptibility of colonizers, we did monitor for infections requiring antibiotic therapy. None of the 14 patients in our study developed infections requiring such therapy within the 14-week study period. This concern also was raised, and similar results were reported, by other researchers.[27,28] Kadota et al[27] reported no pulmonary infections with resistant pathogens in 10 patients who received a 4-year course of clarithromycin therapy for diffuse panbronchiolitis. Another study[28] examined respiratory samples before and after treatment with azithromycin or placebo for 3 days a week for 168 days in 185 patients with cystic fibrosis and did not find any significant differences in the eradication or emergence rates of resistant organisms between the 2 groups, except that 10% fewer participants in the azithromycin group had newly detected methicillin-susceptible *Staphylococcus aureus* ($P = 0.01$).

Although this study involved a small number of patients, it provides insights into reducing potential toxicities associated with chronic prednisone therapy by administering clarithromycin concomitantly. Based on the beneficial effects seen in these patients, a larger, prospective, placebo-controlled trial assessing long-term clarithromycin therapy in patients with corticosteroid-dependent asthma is warranted.

CONCLUSIONS

In this pilot study of patients with corticosteroid-dependent asthma, 6-week clarithromycin 500 mg BID was clinically effective in allowing a reduction in prednisone dosage, without worsening pulmonary function, QOL, or asthmatic symptoms. In addition, clarithromycin was well tolerated, with only 1 patient discontinuing therapy due to treatment-related nausea.

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