Anti-inflammatory effect of itraconazole in stable allergic bronchopulmonary aspergillosis: A randomized controlled trial

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Background: Allergic bronchopulmonary aspergillosis (ABPA) complicates chronic asthma and results from hypersensitivity to the fungus *Aspergillus fumigatus*, causing an intense systemic immune response and progressive lung damage.
Objective: We sought to determine whether treatment with the antifungal agent itraconazole reduced eosinophilic airway inflammation in subjects with ABPA.
Methods: A randomized, double-blind, placebo-controlled trial was performed in stable subjects with ABPA (n = 29). Subjects received 400 mg of itraconazole per day (n = 15) or placebo (n = 14) for 16 weeks. All subjects were reviewed monthly with history, spirometry, and sputum induction to measure airway inflammation, serum total IgE and IgG levels to *A fumigatus*, and blood eosinophil counts.
Results: By using regression analysis in a random-effects model, subjects receiving itraconazole had a decrease in sputum eosinophils of 35% per week, with no decrease seen in the placebo arm ($P < .01$). Sputum eosinophil cationic protein levels decreased with itraconazole treatment by 42% per week compared with 23% in the placebo group ($P < .01$). Itraconazole reduced systemic immune activation, leading to a decrease in serum IgE levels (310 IU/mL) compared with levels seen in the placebo group (increase of 18 IU/mL, $P < .01$) and a decrease in IgG levels to *A fumigatus* (15.4 IU/mL) compared with levels seen in the placebo group (increase of 3.7 IU/mL, $P = .03$). There were fewer exacerbations requiring oral corticosteroids in those treated with itraconazole compared with in the placebo group ($P = .03$).
Conclusion: Itraconazole treatment of subjects with stable ABPA reduces eosinophilic airway inflammation, systemic immune activation, and exacerbations. These results imply that itraconazole is a potential adjunctive treatment for ABPA. (J Allergy Clin Immunol 2003;111:952-7.)

Key words: *Itraconazole, allergic bronchopulmonary aspergillosis, airway inflammation, induced sputum, asthma*

In allergic bronchopulmonary aspergillosis (ABPA) hypersensitivity to the fungus *Aspergillus fumigatus* triggers chronic asthma, recurrent pulmonary infiltrates, and systemic immune activation.[1] In contrast to many other allergens causing asthma, *A fumigatus* is a viable organism found within airway mucus plugs that causes an intense and local immune reaction, together with marked remodeling of the airway, leading to fixed airflow obstruction with bronchiectasis.[2] The intensity of the inflammatory infiltrate in sputum correlates with the extent of disease on high-resolution computed tomography (HRCT) of the chest.[3]

Treatment of ABPA has focused on suppression of the immune response with corticosteroids.[4] The oral antifungal agent itraconazole[5] is active against *A fumigatus* and provides a novel approach to treatment in ABPA, together with an opportunity to examine the effect of allergen reduction by means of antifungal therapy on airway inflammation. Our aim in this study was to determine whether itraconazole treatment of subjects with clinically stable ABPA would reduce airway inflammation.

METHODS

Subjects

Eligible subjects with clinically stable ABPA were recruited from the Department of Respiratory and Sleep Medicine at John Hunter Hospital. The diagnosis of ABPA was based on the criteria of Patterson and Greenberger,[1,6] with a pre-existing diagnosis of asthma, positive immediate skin prick test response to *A fumigatus* (wheal >2 mm), increased serum total IgE level (>1000 IU/mL), and increased serum IgG and IgE antibody levels specific to *A fumigatus*. Subjects were further divided into those with central bronchiectasis (CB) on HRCT scan (ABPA-CB) and those without CB but with serologic criteria for ABPA. Asthma was defined as per

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Abbreviations used
ABPA: Allergic bronchopulmonary aspergillosis
BDP: Beclomethasone dipropionate
CB: Central bronchiectasis
ECP: Eosinophil cationic protein
HRCT: High-resolution computed tomography
PEF: Peak expiratory flow

American Thoracic Society guidelines,[7] with either a 15% increase in FEV_1 after bronchodilator administration or bronchial hyperresponsiveness with PD_{15} hypertonic saline administration of less than 15 mL. Subjects were excluded if they had cystic fibrosis or had used systemic antifungal agents in the last 6 months. Clinically stable disease was defined as no deterioration in symptoms and no increase in the use of asthma medications or antibiotics for chest disease. All the patients were reviewed by 3 respiratory physicians and only included in the study if a consensus was reached. Subjects provided written informed consent for this study, which was approved by the Hunter Area Health Service and The University of Newcastle Research Ethics Committees.

Study design

Subjects with ABPA were allocated to receive 400 mg of itraconazole daily or identical placebo for 16 weeks by means of double-blind concealed random allocation with random number charts assigned by the pharmacy department and with randomization stratified on the basis of diagnosis of ABPA-CB or ABPA without CB but with serologic criteria.

Subjects attended for 6 visits. At the initial screening visit, diagnosis and clinical stability were reviewed. Subjects then entered a 2-week run-in phase recording daily peak expiratory flow (PEF). At visit 2, clinical stability was reassessed, and stable subjects were randomized to treatment. Subjects then attended for 4 visits on a monthly basis. At each visit, subjects underwent clinical assessment, hypertonic saline challenge, sputum induction, quality-of-life score determination, and blood draw for immune markers. Subjects kept a daily diary recording PEF, medication use, and compliance.

The primary outcome measure was induced sputum eosinophil count. Sputum was induced during the hypertonic saline challenge, as previously described.[3] Sputum was selected from saliva and processed as previously described[8] by using 0.1% dithiothreitol (Sputolysin 10%; Calbiochem Corp, La Jolla, Calif). A total cell count of nonsquamous cells and viability was determined. Cytocentrifuge slides were prepared (Shandon Cytospin II, Sewickey, Pa), and a differential count was obtained from 400 cells counted on May-Grunwald-Giemsa–stained slides. Eosinophils were enumerated from slides stained with Chromotrope 2R in the same fashion. Sputum supernatant eosinophil cationic protein (ECP) was assessed by means of RIA (Kabi Pharmacia Diagnostics AB, Uppsala, Sweden).

Secondary outcome measures included systemic immune activation to *A fumigatus* assessed by means of peripheral blood eosinophil counts (Coulter Gen-S; Beckman-Coulter, Pty Ltd, Sydney, Australia), total serum IgE levels (Unicap system; Pharmacia-Upjohn Diagnostics, AB, Uppsala, Sweden), and serum IgE antibodies to *A fumigatus* (Pharmacia CAP immunoassay, Kabi Pharmacia Diagnostics). The presence of specific IgG antibodies to *A fumigatus* was measured by using a serologic double-gel diffusion assay for the detection of precipitating antibodies to *A fumigatus* (Microgen Bioproducts, Camberley, United Kingdom) and by means of a rapid ELISA for specific IgG antibodies (Genesis Diagnostics, Littleport, United Kingdom). Blood was drawn for safety analysis and was assayed for full blood counts and differentials, liver function tests, electrolytes, and serum creatinine levels.

Clinical details were elicited, including medication history, frequency and severity of asthma symptoms, allergy history, age since the diagnosis of asthma, and frequency of exacerbations. In a daily diary subjects recorded symptoms and the best of 3 PEF values each morning before the use of bronchodilators (Mini-Wright peak expiratory flowmeter; Clement Clarke, Harlow, Essex, United Kingdom). Spirometry was performed with a Minato Autospiro AS-600 (Minato Medical Science Co Ltd, Osaka, Japan). Oral corticosteroids were used for severe exacerbations of lung disease. A severe exacerbation was defined as a worsening of asthma symptoms with increased night waking and β-agonist use, a decrease in FEV_1 of 10% or greater, and failure to improve with doubling of inhaled corticosteroids.

Bronchial provocation testing with hypertonic saline was performed as previously described by using 4.5% saline.[9]

Statistical analysis

Statistical analysis was carried out with STATA software (Stata Corporation, College Station, Tex). We planned to recruit 28 subjects to provide 90% power (2-sided $\alpha = .05$) to detect a clinically significant decrease in sputum eosinophils of 10%. An intention-to-treat analysis was performed on log-transformed data, and differences were detected with a 2-tailed *t* test, or when data were not normally distributed after log transformation, nonparametric tests were used to detect differences on nontransformed data. Univariate relationships between continuous variables were analyzed by using the Spearman rank correlation coefficient. A regression analysis was performed with a random-effects model on the log-transformed data to determine the change in sputum measures over the study period. For sputum eosinophils, where the value was zero, we imputed values from a uniform distribution in the range of 0 to 400 cells $\times 10^6$/mL. *P* values of less than .05 were regarded as statistically significant.

RESULTS

Subject characteristics at baseline

Thirty-four subjects were screened, and 29 eligible subjects were randomized to receive either itraconazole (n = 15) or placebo (n = 14). There were 2 withdrawals from the itraconazole arm. One subject had nausea that developed within 2 weeks of starting treatment, and the subject's symptoms resolved 48 hours after ceasing the medication. The other subject was involved in a motor vehicle accident and withdrew because of injuries. In the placebo arm the subject who withdrew fell and broke her ankle. Serious adverse events leading to hospital admission occurred in 4 subjects in the placebo group: 1 had a supraventricular tachycardia, another had 2 admissions with cardiac failure and atrial fibrillation, and 2 were admitted with exacerbations of ABPA. In the itraconazole group one subject was admitted with a lumbar disc prolapse. None of the subjects had a change in serum potassium or liver transaminase levels.

The subjects in both groups were balanced in terms of clinical disease severity, medication use, and systemic immunologic markers (Table I). The inflammatory indices measured in induced sputum at baseline were similar between the groups, except for a greater proportion of sputum neutrophils and a lower proportion of macrophages in the placebo arm. Overall, subjects in both groups had an increased mean sputum total cell count of 7.4 $\times 10^6$/mL (SD 2.5), mean sputum

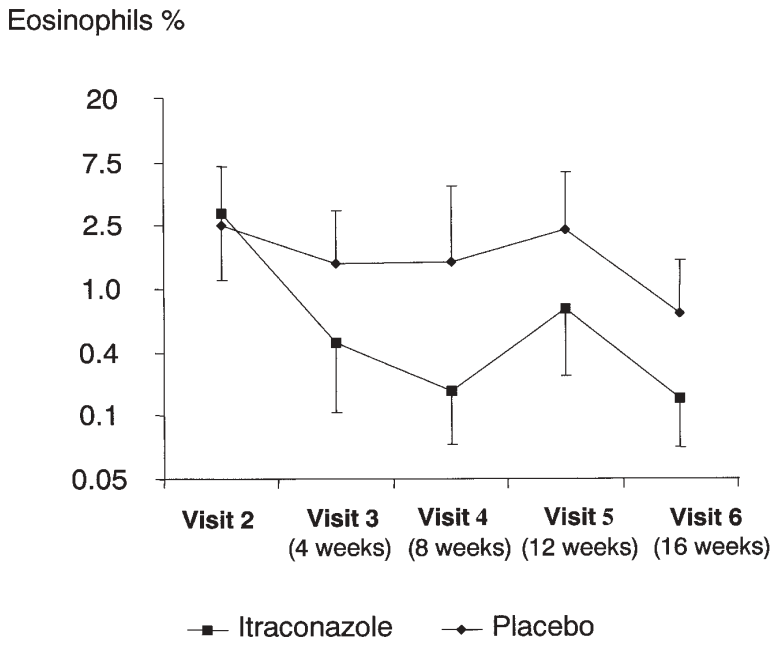

FIG 1. Sputum eosinophils (percentage) at each treatment period in subjects treated with itraconazole or placebo. All values are expressed as the mean and 95% CI. The data were log transformed, and the mean reported is the mean of the log value. The antilog of this value has been recorded to provide meaningful results.

eosinophils of 3.5% (SD 5.0%), and mean sputum ECP levels of 4915 ng/mL (SD 4.5; Table II).

Effect of treatment on airway inflammation in sputum

Subjects in the itraconazole group had a significant decrease in sputum eosinophils from visit 2 to visit 6 ($P < .01$, Fig 1). Sputum eosinophils were reduced to within the normal range,[10] and they remained suppressed at visit 6. Most of the decrease occurred during the first month of treatment, with a 35% reduction in sputum eosinophils per week (95% CI, 20%-48%) in the itraconazole-treated group. The placebo group showed no change (95% CI, 19% reduction to 12% increase).

Subjects treated with itraconazole had a significant decrease in mean sputum ECP levels from baseline at visit 2 (4742 ng/mL) compared with at visit 3 (2966 ng/mL, $P < .001$), which persisted to the completion of the trial (2471 ng/mL, $P < .001$). The decrease seen in the itraconazole group occurred mostly in the first 4 weeks of treatment, with a 42% reduction per week in ECP levels (95% CI, 19%-58% reduction); this had slowed to a 7.7% reduction by the end of 16 weeks. In comparison, the placebo group showed a nonsignificant reduction of 23% (95% CI, 66% reduction to 30% increase; Fig 2). There were no differences in the rate of decrease in sputum eosinophils, ECP levels, or other cells in subjects receiving prednisone and itraconazole (n = 5) compared with those receiving itraconazole alone (data not shown). Among subjects who received itraconazole and were not receiving regular prednisone, all but one was taking inhaled corticosteroids, and all but 4 received 2000 □g of beclomethasone dipropionate (BDP) or more daily. In view of these small numbers, an analysis of the effects of itraconazole in subjects taking low-dose inhaled corticosteroids was not possible.

Effect of treatment on serologic markers of disease activity

Subjects treated with itraconazole demonstrated a significant decrease in total serum IgE levels over time, with a 6% reduction per week (95% CI, 1%-11% reduction). In comparison, the placebo group demonstrated a nonsignificant 9.7% increase (95% CI, 9.9% reduction to 9.2% increase). This is equivalent to a median decrease in serum total IgE levels from visit 2 to visit 6 in the itraconazole group of 310 IU/mL compared with an increase in the placebo group of 18 IU/mL ($P < .01$).

Subjects treated with itraconazole demonstrated a significant decrease in specific IgG antibodies to *A fumigatus* (IgG *A fumigatus*), with an 8% reduction per week (95% CI, 1%-14% reduction). The placebo group demonstrated a nonsignificant 5.5% increase in IgG *A fumigatus* (95% CI, 1% reduction to increase of 12%). There was a median decrease of 15.4 IU/mL in the itraconazole group compared with a small increase in the placebo group of 3.7 IU/mL ($P = .03$) between baseline and the completion of the study.

Effect of treatment on clinical markers

Subjects who received itraconazole had fewer severe exacerbations of lung disease requiring prednisone, with a median number of exacerbations per person of 0 compared with a median number of exacerbations in subjects

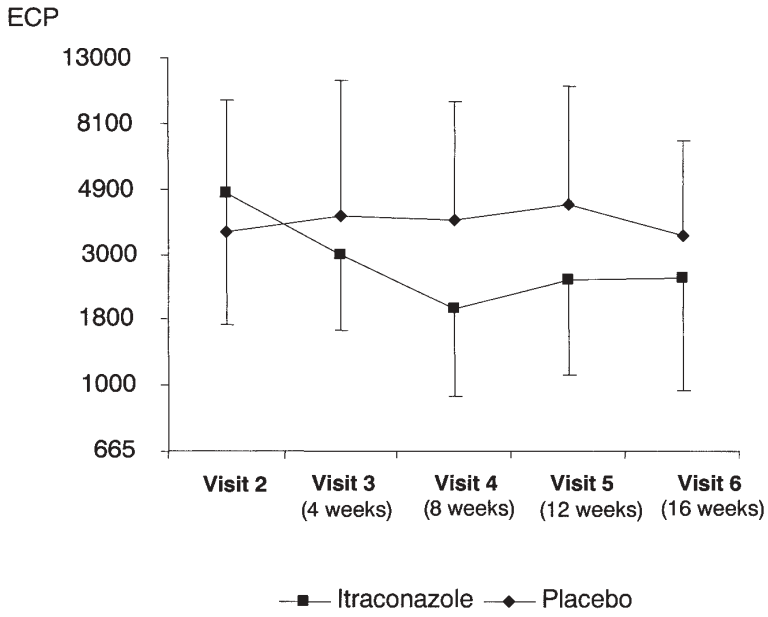

FIG 2. Sputum ECP levels (in nanograms per milliliter) in subjects treated with itraconazole or placebo. All values are expressed as the mean and 95% CI. The data were log transformed, and the mean reported is the mean of the log value. The antilog of this value has been recorded to show meaningful results.

receiving placebo of 1.5 ($P = .03$). There were no significant differences between the 2 groups in terms of percentage change in FEV_1 from baseline, with an increase of 7.9% with itraconazole and a decrease of 1.9% with placebo ($P = .5$), nor was a difference seen in PEF, with those receiving itraconazole having an increase of 20.9 mL compared with an increase of 12.5 mL in those receiving placebo ($P = .5$).

DISCUSSION

In this randomized, double-blind, placebo-controlled study we have shown that in subjects with clinically stable ABPA, the addition of 400 mg of itraconazole daily reduces airway inflammation, with a reduction in sputum eosinophils and a significant decrease in sputum ECP levels. In addition, there was evidence of a reduction in systemic immune activation in those treated with itraconazole, with significant decreases in total serum IgE and IgG antibodies to *A fumigatus*, together with fewer severe exacerbations requiring treatment with prednisone. This is the first controlled study to document a modification of airway inflammation in ABPA with the use of itraconazole, and given the relationship between airway inflammation and disease severity on computed tomographic scanning,[3] this indicates the potential to modify prognosis with long-term use, an issue that requires further study.

Subjects were stratified at randomization on the basis of the presence or absence of bronchiectasis on HRCT of the chest. This was done because we had previously shown that subjects with ABPA-CB had more intense airway inflammation.[3] Because airway inflammation was our primary outcome measure, we did not want the groups to be unbalanced and confound the results. At baseline, both groups were well matched clinically and in terms of sputum eosinophils, which was the primary outcome measure of the study.

A fumigatus triggers an eosinophilic inflammatory response by releasing allergenic peptides, but it also has the ability to directly damage the airway epithelium and matrix by releasing proteases[11] and avoiding phagocytosis by lung macrophages.[12] Fungal hyphae are frequently found within the mucus plugs, and there is an intense immune response with eosinophils, lymphocytes, and plasma cells. As we have recently described using induced sputum,[3] subjects with clinically stable ABPA have increased sputum eosinophil counts, despite the use of high-dose inhaled corticosteroids and, in some cases, oral prednisone. In this study those treated with itraconazole had a substantial reduction in sputum eosinophils by the end of the first month, back to within the normal range,[10] and this was sustained throughout the trial. This is an important effect and implies that itraconazole is active on airway inflammation that has only been partially suppressed with corticosteroid therapy. It also suggests that itraconazole can be used together with corticosteroids in ABPA, as recently observed.[13]

Sputum ECP levels were also significantly reduced, although these remained increased above the normal range. There is evidence that other inflammatory cells, such as neutrophils, might contribute to the release of ECP.[11] We saw no effect of treatment on sputum neutrophils, suggesting this component of airway inflamma-

TABLE I. Subject characteristics at baseline

	Itraconazole	Placebo	Analysis
n 15	14	NA	
Age, y	55.7 (12.1)	57.3 (11.2)	$P = .7$
Male sex, n	8 (53%)	6 (43%)	$P = .6$
Years since asthma first diagnosed	34.2 (18.9)	39.3 (18.3)	$P = .5$
Smoking status			
Never	10	8	
Ex-smoker	4	6	
Current	0	1	$P = .4$
FEV_1, % predicted	55 (20.5)	51.7 (24.8)	$P = .7$
Daily prednisone use, n	5 (36%)	5 (33%)	$P = .9$
Courses of prednisone in last 12 mo	3.5 (4.1)	2 (3.2)	$P = .8$
Inhaled corticosteroids, □g of BDP/d	2829 (1371)	1917 (892)	$P = .6$
LABA use, n	8 (53%)	7 (50%)	$P = .9$
Serum total IgE, IU/mL	1480 (2.7)	1097 (892)	$P = .6$
Blood eosinophils, □10^9/L	0.3 (2.3)	0.4 (2.2)	$P = .8$
Serum IgE *A fumigatus*, IU/mL	3.4 (1.6)	3.6 (1.5)	$P = .7$
Serum IgG *A fumigatus*, IU/mL	52.3 (33.5)	60.3 (34.5)	$P = .5$
A fumigatus precipitins, % positive	8 (53%)	6 (43%)	$P = .6$
Skin prick test reaction to *A fumigatus*, mm	5 (1.4)	4.5 (1.5)	$P = .4$

Values are presented as the mean and SD or n (%).
LABA, Long-acting □-agonist.

TABLE II. Sputum measures at baseline

	Itraconazole	Placebo	Analysis
Nebulizer time, min	9.8 (1.6)	9.2 (1.5)	$P = .8$
TCC, □10^6/mL	6.7 (2.5)	8.2 (2.5)	$P = .8$
Eosinophils, %	3.8 (6)	3.0 (4.1)	$P = .8$
Neutrophils, %	44.5 (24.7)	66.8 (22.9)	$P = .03$
Macrophages, %	37.5 (19)	21.1 (16.2)	$P = .02$
Lymphocytes, %	0.9 (2.2)	1.04 (2.5)	$P = .7$
Epithelial cells, %	2.5 (4.1)	3 (4.1)	$P = .9$
Squamous cells, %	2.5 (4.1)	3.3 (5.0)	$P = .6$
ECP, ng/mL	4743 (6.9)	5484 (2.7)	$P = .8$

Values are presented as the mean and SD. The data were log transformed, and the mean reported is the mean of the log value. The antilog of this value has been recorded to provide meaningful results.
TCC, Total cell count.

tion was unaffected by treatment. Either there was incomplete suppression of eosinophil activation, the increased ECP level was contributed to by means of neutrophilic airway inflammation, or both. The mainstay of treatment for ABPA has been to suppress the immune response with corticosteroids. Although studies of corticosteroid use in ABPA have been uncontrolled, there seems little doubt they are effective in controlling associated asthma and acute exacerbations of ABPA.[4] The efficacy of corticosteroids is less clear in the chronic management of ABPA because exacerbations still occur despite treatment with oral corticosteroids.[4,12]

The treatment of ABPA with itraconazole targets the offending *A fumigatus* and not the immune response that develops as a consequence of it. The assumption is that itraconazole will either eradicate or at least reduce the burden of *A fumigatus* present within the airways, and therefore there will be less immune activation. Alternatively, itraconazole might act to enhance the effect of corticosteroids by inhibiting their hepatic metabolism. This has been shown to occur with methylprednisone,[14] but a similar effect has not been demonstrated with prednisolone.[15] Although recently it has been shown that combination treatment with inhaled budesonide leads to suppression of the adrenocorticotrophic hormone response in 44% of subjects with cystic fibrosis,[16] we did not see any evidence to support this mechanism because the 5 subjects who received itraconazole were also taking oral prednisone and experienced a similar decrease in sputum eosinophil counts as those not receiving oral corticosteroids. All but 5 subjects received 2000 □g of BDP daily or greater, and 4 of the remaining 5 received between 400 and 1800 □g BDP daily. It was thus not possible to examine the effect of itraconazole independent of inhaled corticosteroid use, and we cannot rule out an interaction between itraconazole and inhaled corticosteroids.

Several uncontrolled or retrospective reports of itraconazole in ABPA have suggested it might be effective in the treatment of ABPA.[17-25] One other prospective, randomized, and blinded controlled trial of itraconazole has been reported by Stevens et al[13] in subjects with ABPA who were using oral corticosteroids regularly. They demonstrated that 46% of subjects in the itraconazole group had either a reduction in corticosteroid dose or serum total IgE levels, together with an improvement in either exercise tolerance or pulmonary function. In comparison with this, our study had a smaller sample size but used a comparable dose of itraconazole and shared similar secondary end points. We did not set out to power our study to detect clinical differences. We did demonstrate fewer severe exacerbations requiring prednisone in the itraconazole group, even though the duration of the trial was only 16 weeks. The difference in FEV_1 between the groups at the end of the study was 9.8% of predicted value, which is clinically important but failed to reach statistical significance. The demonstration that treatment of ABPA with itraconazole reduces airway inflammation along with systemic immune activation to *A fumigatus* and reduces severe exacerbations is important in both its demonstration of the mechanisms of disease and in supporting the clinical response established by Stevens et al.[13]

In conclusion, this study has shown that treatment of subjects with clinically stable ABPA with 400 mg of itraconazole daily is effective in normalizing eosinophilic airway inflammation, reducing systemic immune activation, and reducing severe exacerbations. The results suggest that itraconazole is a useful adjunctive treatment of subjects with ABPA and has the potential to modify the disease process. These results certainly justify further investigations in larger studies of longer-term clinical efficacy.

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