

The role of anti-IgE immunoglobulin therapy in nasal polyposis: A pilot study

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ABSTRACT

Background: Although the etiology of nasal polyposis (NP) remains unknown, emerging evidence showing elevated local IgE levels and eosinophilic infiltration suggests an allergic etiology. Given this evidence, this pilot study examined whether anti-IgE therapy is efficacious in the treatment of NP.

Methods: Data were retrospectively collected on two groups of patients with atopic asthma and NP who underwent endoscopic sinus surgery (ESS), including a control group ($n = 4$) and an anti-IgE treatment group ($n = 4$), who received the anti-IgE agent, omalizumab, postoperatively. Both groups were evaluated by sinus computed tomography (CT) and nasal endoscopic examination, and comparisons were made between the groups with respect to differences in the recurrence of NP after ESS.

Results: Collectively, the subjects showed a direct relationship between NP severity and pretreatment total serum IgE levels. Preoperatively, there were no differences between the groups with regard to their total serum IgE levels, sinus CT scores, and endoscopically determined NP scores. Relative to corresponding preoperative values, there was no significant improvement in the sinus CT scores in either treatment group postoperatively. In contrast, relative to preoperative values, the nasal polyp scores significantly improved in the anti-IgE group, whereas the control group showed no significant improvement.

Conclusion: This pilot study provides new evidence establishing that (1) endoscopic NP severity directly correlates to total serum IgE levels and (2) inclusion of anti-IgE therapy in the postpolypectomy management of atopic asthmatic individuals may reduce the severity of NP recurrence.

(Am J Rhinol 21, 428–432, 2007; doi: 10.2500/ajr.2007.21.3060)

Key words: Allergic rhinosinusitis, allergy, asthma, atopic asthma, atopy, IgE, nasal polyps, omalizumab, perennial allergies, Xolair

Nasal polyposis (NP) is a chronic inflammatory disease of the mucous membranes in the nose and paranasal sinuses. Edematous masses of inflamed mucosa balloon from nasal epithelium and prolapse into the nose, leading to nasal obstruction, secretion, anosmia, headache, and a reduced quality of life. Although the etiology of NP remains largely unknown and is assumed to be multifactorial in nature, the reported association of NP with atopic asthma and aspirin sensitivity suggests an allergic etiology, at least in a subpopulation of patients. In support of this concept, recent studies have established the presence of both elevated local (mucosal) IgE levels and eosinophilic inflammation in biopsy specimens of nasal polyps from asthmatic individuals.^{1,2} In this context, a potential etiologic role for elevated local IgE production has been implicated in the proinflammatory mechanism underlying the development of NP in allergic asthmatic patients.^{1,2} The present pilot study was conducted to evaluate the efficacy of anti-IgE therapy in preventing the postsurgical recurrence of NP in patients with atopic asthma and allergic rhinosinusitis (ARS). Currently, anti-IgE therapy is available as omalizumab (Xolair; Genentech/Novartis, South San Francisco, CA, and East Hanover, NJ). Omalizumab is a humanized anti-IgE monoclonal antibody that binds to the Fc region of free circulating IgE and has been approved for the treatment

of atopic asthma.³ In addition, it has been shown to clinically improve ARS.^{4,5}

METHODS

A retrospective review of patients treated for NP between November 2003 and August 2005 was conducted. Patient outcome was compared between subjects undergoing anti-IgE treatment (the anti-IgE group) and a control group. While both groups were studied retrospectively, the control group was studied as historical matched controls. This study received approval by the Georgetown University Hospital (GUH) Institutional Review Board in July 2005.

A similar number of four patients, including three women and one man were studied in each group. Their age ranges were 31–69 years (median age, 39.5 years) in the control group and 23–80 years (median age, 28.0 years) in the anti-IgE group. Inclusion criteria required that all enrolled patients are ≥ 18 years of age and have the diagnoses of NP, atopic asthma, and ARS. All subjects were required to have a positive RAST test to at least one common perennial allergen, and all included patients had been placed on similar medical treatments, including: antihistamines, leukotriene inhibitors, nasal steroids, and at least one documented use of oral steroids. Finally, all enrolled subjects had undergone endoscopic sinus surgery (ESS). In the anti-IgE group of subjects, omalizumab was added to their postoperative medical management. The drug was administered by subcutaneous injection every 2 or 4 weeks, with dosing based on both the patients' weight and the patients' respective pretreatment serum IgE levels, as indicated for the treatment of allergic asthma³ (range of dosing, 150–375 mg in either 2- or 4-week intervals).

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Exclusion criteria for enrollment in the study included having the diagnosis of medical conditions with established association with NP, such as cystic fibrosis, Churg-Strauss syndrome, Kartagener's syndrome, and ciliary dyskinesia (Table 1). The treatment group consisted of four patients who met the aforementioned criteria and who wished to start on anti-IgE therapy after ESS between November 2003 and November 2004. The therapy was maintained in the anti-IgE group for an average of 5.5 months, although the duration of subsequent omalizumab therapy varied among these subjects (range, 3–8 months). The control group consisted of four patients who similarly met the foregoing criteria and who had undergone ESS for NP between November 2003 and February 2005. The control group subjects were ascertained by enrolling four consecutive patients who presented to our Otolaryngology Outpatient Clinic for routine follow-up, who met the foregoing criteria and had undergone ESS within the previous 18 months. Differences in the postoperative medical management are shown in Table 2. Aside from the surgery associated with this study, several patients in both the anti-IgE group and the control group had undergone prior ESS. In the anti-IgE group, patients had undergone between one and four previous surgeries (median, one surgery) before surgery at GUH and initiation of anti-IgE therapy. In contrast, the control group included only one patient who had undergone prior ESS before surgery at GUH. In addition, there were differences with respect to immunotherapy treatments before the initiation of the study. Two out four patients in the anti-IgE group had prior immunotherapy treatments, but combined only had four treatments administered. This contrasts the control group in which one of four patients had undergone prior immunotherapy, but 15 treatments were administered for this particular patient.

Presurgical and posttreatment outcome measurements were obtained in the control and anti-IgE treatment groups at similar average intervals of 9.0 (median, 8; range, 7–13 months) and 10.5 months (median, 11; range, 4–16 months), respectively. NP severity was assessed in both groups before and after treatment by nasal endoscopy using the Nasal Polyp Grade system developed by Lund and Mackay (Table 3).⁶

Subjects also were assessed radiographically *via* sinus computed tomography (CT) scans obtained before and after treat-

Table 1 Study criteria

Inclusion Criteria	Exclusion Criteria
>18 years	Cystic Fibrosis
NP	Churg-Strauss syndrome
Atopic asthma	Kartagener's syndrome
ARS	Ciliary Dyskinesia
RAST + to perennial allergen	
Medical treatments	
Anti-histamines	
Leukotriene inhibitors	
Nasal steroids	
Oral steroids	
ESS	

Table 2 Post-operative medical regimens

Control Group		Anti-IgE Group	
Subjects	Medications	Subjects	Medications
1	ah, ns, Li	1	ah, ns, Li
2	ah, os, Li	2	ah, ns
3	ah, os, Li	3	ah, ns, Li
4	ah, os	4	ah, ns, Li

**ah = anti-histamine, ns = nasal steroid, os = oral steroid, Li = leukotriene inhibitor.*

Table 3 Endoscopic polyp grade

Grade*	
0	No polyps
1	Restricted to middle meatus
2	Below inferior border of middle turbinate
3	Diffuse polyposis; complete involvement of ipsilateral nasal cavity

**Applied to unilateral side with worse disease.*

Source: Ref. 6.

ment. The CT scans were evaluated using the Mackay and Lund CT grading system for bilateral quantification of rhinosinusitis (Table 4).⁷ In contrast, endoscopic polyp grade scores were characterized bilaterally and, although bilateral involvement was typically detected, the score pertaining to the worse affected side was applied for the data analysis described later. Both the polyp grade and the CT scores were determined by a single, unblinded examiner. Finally, baseline pretreatment total serum IgE levels were determined in both study groups, and posttreatment IgE levels were obtained also in the anti-IgE study group.

All results were analyzed by means of nonparametric testing using the Mann-Whitney test (two-tailed) and applying Spearman correlation analyses. The analyses were performed using the Prism statistical software package (GraphPad Software, San Diego, CA). Values of $p \leq 0.05$ were considered statistically significant. No direct funding or involvement by either Genentech, Inc., or Novartis Pharmaceuticals Corp. was provided for this study.

Table 4 Sinus CT grading system for rhinosinusitis

Maxillary	0–2
Anterior ethmoid	0–2
Posterior ethmoid	0–2
Sphenoid	0–2
Frontal	0–2
Osteo-meatal complex	0–2
Total:	/24*

**Total score reflects scoring from right and left sides.*

Source: Ref. 7.

RESULTS

In accordance with earlier reports showing an association between IgE and NP in atopic asthmatic individuals,¹ pretreatment total serum IgE levels of all subjects were found directly correlated to presurgical endoscopic polyp scores (Spearman correlation, $r = 0.73$; $p < 0.05$; Fig. 1). Contrasting this observation, no correlation was found between the subjects' total serum IgE levels and their respective sinus CT scores (Spearman correlation, $r = 0.42$; $p = 0.30$).

When comparing the control and anti-IgE treatment groups before receiving their respective therapies, there was no significant difference between the study groups with regard to their mean ($\pm$ SD) total serum IgE levels, CT scores, and nasal polyp grades (Fig. 2). The pretreatment mean total serum IgE levels for the control and anti-IgE group averaged 533.3 ± 686.8 IU/mL and 684.5 ± 903.8 IU/mL, respectively (Fig. 2A). There was no significant difference between these mean values. Before therapy, the mean sinus CT score was greater in the anti-IgE group at 18.00 ± 9.52 versus 12.75 ± 8.38 in the control group (Fig. 2 B); however, this difference was not statistically significant ($p = 0.49$). Relative to these values, after treatment there was little change in the mean sinus CT score for the control group, because their posttreatment CT score averaged 10.00 ± 3.56 compared with their pretreatment mean CT score of 12.75 ± 8.38 ($p = 0.69$). Compared with the control group, the mean sinus CT score decreased to a relatively greater extent in the anti-IgE treatment group from a pretreatment value of 18.00 ± 9.52 to 9.75 ± 9.14 posttreatment; however, this change did not achieve statistical significance (Fig. 3). Although the average CT score in the anti-IgE group decreased to a greater degree than in the control group, comparing the posttreatment CT scores in both treatment groups revealed no significant difference ($p = 0.49$).

In evaluating the pretreatment endoscopic polyp grades, the mean polyp grade was relatively greater in the anti-IgE group at 2.00 ± 0.82 versus 1.25 ± 0.50 in the control group (Fig. 2 C); however, this difference was not statistically significant

($p = 0.20$). In the control group, the mean polyp grade decreased to 0.50 ± 0.58 after treatment (Fig. 4 A); however, this reduction did not achieve statistical significance ($p = 0.20$). Contrasting this observation, the mean polyp grade markedly decreased to 0.25 ± 0.50 after treatment in the anti-IgE group (Fig. 4 B). This improvement in the mean polyp grade in the anti-IgE group was found to be statistically significant ($p = 0.03$). However, the posttreatment mean polyp grade scores of the control and anti-IgE groups were not found to be significantly different from one another ($p = 0.69$).

To better assess the uniformity of the surgical effect on the posttreatment groups, polyp grade score was evaluated in all of the subjects at 1 month after surgery. This evaluation was part of a standard postoperative care assessment. CT scans, however, were not routinely ordered at this time. All subjects in both the control and the anti-IgE groups were found to have no residual polyps (all polyp grade scores = 0) at 1 month after surgical intervention. One individual in the anti-IgE-treated group had mucosal polypoid changes but no frank polyp growth was appreciated (Fig. 4).

Pretreatment total serum IgE levels were evaluated for potential correlation with observed changes in either the CT scores or the polyp grades. The total serum IgE levels did not show a statistically significant correlation either with the changes in the CT scores (Spearman correlation, $r = 0.8000$) or with the changes in the polyp grades ($r = 0.9487$).

When examining the effect of anti-IgE therapy on total serum IgE levels, we found that the anti-IgE treatment group exhibited relatively higher total serum IgE levels after omalizumab therapy. Accordingly, the mean total serum IgE averaged 905.3 ± 869.4 after treatment compared with the pretreatment mean value of 684.5 ± 903.8 . Clearance of IgE complexed with omalizumab is believed to be slower than that of free IgE alone, thereby resulting in an elevated total serum IgE concentration,⁸ whereas free serum IgE has been found consistently to decrease significantly with omalizumab therapy.⁸⁻¹⁰

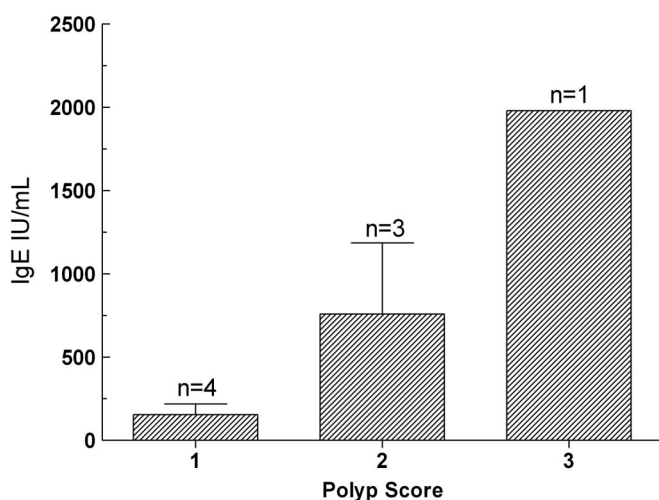


Figure 1. Relationship between total serum IgE levels and endoscopic scores of nasal polyp severity determined in all the subjects studied before therapeutic intervention. Data represent mean $\pm$ SD values.

DISCUSSION

IgE is well known to play a critical causal role in atopic asthma. Accordingly, omalizumab, an anti-IgE therapy, was approved for treatment of atopic asthma. NP in atopic individuals possibly is associated with local (nasal mucosal) IgE production.^{1,2} However, an etiologic role of IgE in nasal polyp formation still has to be identified. This pilot study evaluated the recurrence of NP after polypectomy in atopic asthmatic patients in the absence and presence of anti-IgE therapy. The results provide new evidence demonstrating (1) endoscopic evidence of NP severity directly correlates with total serum IgE levels in atopic asthmatics and (2) that inclusion of anti-IgE therapy in the postpolypectomy medical management of atopic asthmatic individuals significantly reduces the severity of NP recurrence. Taken together, these findings implicate a mechanistic association between IgE and nasal polyp formation.

In a recent study by Hirschberg *et al.*, nasal polyp tissue IgE concentrations were found to correlate with corresponding total serum IgE levels in atopic individuals.¹¹ Given this evidence, together with our present observations, the need is

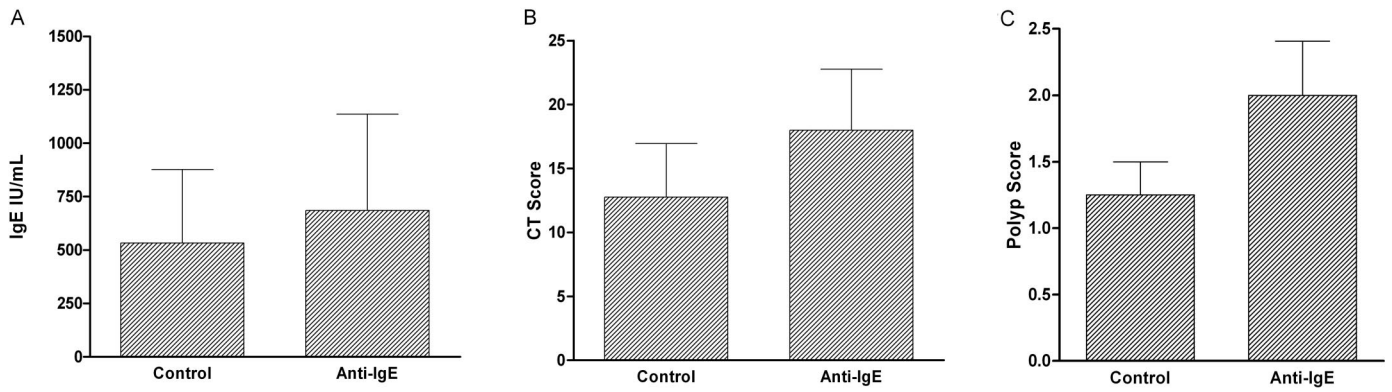


Figure 2. Comparison of levels of total serum IgE (A), sinus CT scores (B), and nasal polyp scores (C) between control and anti-IgE groups before treatment. Data represent mean $\pm$ SD values.

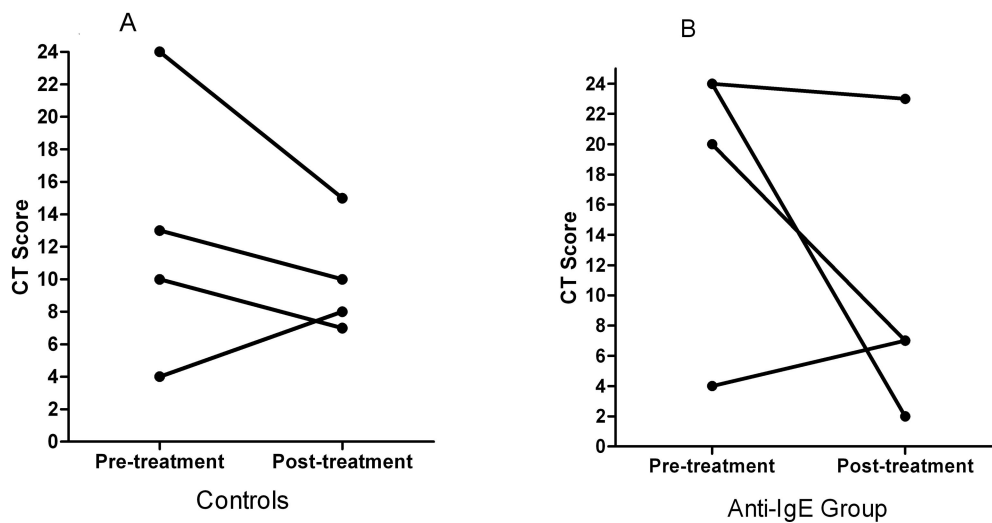


Figure 3. Comparison of changes in the sinus CT scores before and after therapeutic intervention in the control (A) and anti-IgE (B) treatment groups.

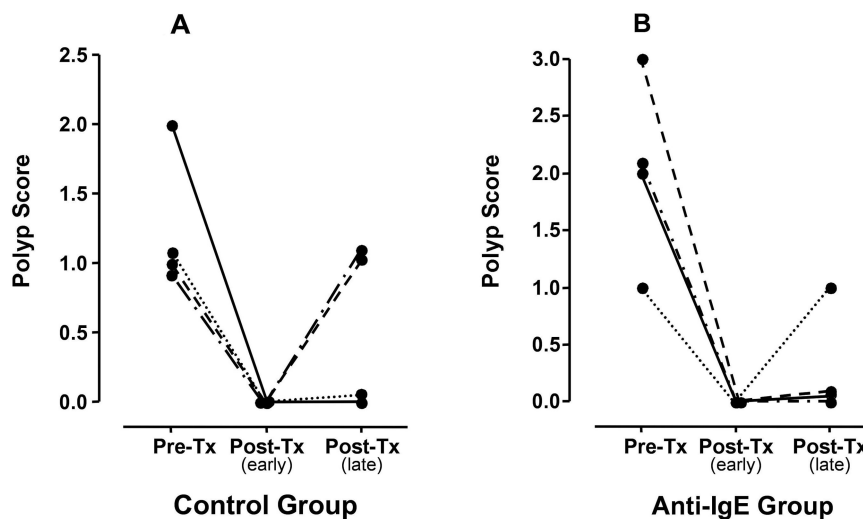


Figure 4. Comparison of changes in the endoscopic polyp scores before, at early post-operative follow up (~1 month) and at later post-operative follow up (mean 9.0 months in the control group (A); and mean 10.5 months in the anti-IgE group (B)).

emphasized for future studies aimed at investigating potential mechanisms underlying the mechanism of action of IgE in the formation of nasal polyps. Such studies should include a systematic examination of the effects of IgE on the proliferation of nasal epithelial cells and identification of the potential roles of specific growth factors and proinflammatory mediators (e.g., cytokines and chemokines) in regulating this process.

In evaluating our present observations, it is relevant to note that there were no significant pretreatment differences between the study groups with respect to total serum IgE levels, sinus CT scores, or nasal polyp scores. However, endoscopic assessment revealed relatively greater nasal polyp severity in the anti-IgE group before therapy (Fig. 2 C). After treatment, both subject groups showed improvement in their nasal polyp grades. This improvement was not found to be statistically different between the two groups; however, unlike the controls, the subjects comprising the anti-IgE group, which exhibited more pronounced pretreatment NP severity, displayed a significant decrease in NP severity by endoscopic exam when compared with their pretreatment assessment (Fig. 4). Interestingly, in concert with this enhanced improvement in the polyp grades, the sinus CT scores also tended to improve to a relatively greater extent after therapy in the anti-IgE treatment group when compared with controls, although the magnitude of this effect did not attain statistical significance (Fig. 3).

It appears that, in addition to attenuating the postsurgical recurrence of NP as appreciated by nasal endoscopy examination, anti-IgE therapy also tended to improve CT evaluation as used to assess rhinosinusitis. However, using CT in the evaluation of NP is problematic because sinus CT opacification may represent an air-fluid level, debris within the sinuses, mucosal thickening secondary to inflammation due to varied causes, or NP. Furthermore, the CT scoring in those individuals who had undergone surgery before this study is likely to be inaccurate. A grossly patent maxillary meatus may minimize adjacent mucosal disease that would otherwise appear significant with unaltered anatomy. As such, CT scores most likely do not accurately represent NP as a lone entity.

Regarding this study, certain relevant issues must be taken into consideration, most notably including that this study represents a pilot investigation comprising relatively few subjects in each study group, thereby limiting its statistical power. Moreover, the study lacks prospective, blinded randomization of its subjects into the different treatment groups. A selection bias exists, because patients were able to choose whether they received anti-IgE therapy, and it is possible that the number of prior surgeries and prior immunotherapy treatments influenced this decision. Furthermore, notable differences in postoperative medical therapies other than omalizumab must be accounted for in comparing the control and anti-IgE groups (Table 2). Notwithstanding these notable limitations, the present results are sufficiently compelling in providing new insight into the potential role of IgE in the pathogenesis of NP, as well as the potential efficacy of anti-IgE therapy in the management of this process.

The present findings provide provocative new evidence that incorporation of anti-IgE therapy may be therapeutically beneficial in reducing the postsurgical recurrence of NP in

patients with allergic asthma. Clearly, the need exists for future studies to substantiate the use of anti-IgE therapy in the management of NP in several respects. Anti-IgE immunoglobulin therapy may provide a role in nasal polyp regression in the absence of surgery. Although NP ultimately may remain a condition that requires surgical intervention, it is conceivable that medical management incorporating anti-IgE therapy may prove beneficial to nonsurgical candidates, as well as in lengthening intervals between recurrences that necessitate surgery. Symptoms such as anosmia and obstruction, which typically afflict those suffering from NP, also may show improvement in the presence of anti-IgE therapy. We anticipate that these findings will spur future studies that address these issues.

CONCLUSION

In conclusion, this pilot study evaluated the recurrence of NP after polypectomy in atopic asthmatic patients in the absence and presence of anti-IgE therapy. The findings implicate a mechanistic association between IgE and nasal polyp formation and support the rationale for future studies to further examine the efficacy of anti-IgE therapy in the management of NP.

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