Anti-immunoglobulin E therapy: is it a valid option for the management of chronic rhinosinusitis with nasal polyposis?
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Received 1 March 2019
Accepted 1 July 2019

The Egyptian Journal of Otolaryngology 2019, 35:269–277

Objectives
To evaluate the efficacy of omalizumab (OMA) therapy for patients with chronic rhinosinusitis with nasal polyposis as a sole therapeutic line versus traditional therapy.

Patients and methods
Eighty-six patients were randomly divided into two equal groups: study patients received OMA [0.016 mg/kg/immunoglobulin E (IgE) (IU/ml)] therapy only and control patients received conventional therapy. All patients completed a questionnaire to determine the total subjective score (TSS), who underwent rigid nasal endoscopy for endoscopic scoring according to the Lund-Kennedy scoring system, had paranasal sinuses computed tomographic (CT) imaging for scoring according to the Lund-Mackay scale, and estimation of pretreatment serum IgE levels. Study outcomes included the therapeutic effect determined as more than 50% decrease of TSS with improvement on endoscopic findings, recurrence rate, and frequency of decision; shift to surgery or repeat the trial of OMA therapy.

Results
Serum IgE level positively correlated with TSS and endoscopic and CT scores. Seventeen patients had successful response without recurrence with significantly lower TSS in the study versus control patients. Twenty-seven patients had recurrence after primary successful outcome with significantly lower TSS in study than control patients and significantly longer duration till recurrence with OMA than conventional therapy. Forty-two patients showed no response to the first session of therapy. Nineteen study patients with recurrent manifestations received a second session of OMA therapy; 11 had successful response, five patients had recurrence, and three patients failed to respond. Surgery-sparing effect is significantly higher with OMA than conventional therapy (46.5 vs. 18.6%). Endoscopic and CT scores of total patients, at the end of follow-up, were nonsignificantly lower in control while they were significantly lower in the study group.

Conclusion
OMA significantly superiorly improved the outcome of conservative treatment of chronic rhinosinusitis with nasal polyposis than conventional with higher surgery-sparing rate. The second session of OMA minimized the recurrence rate of manifestations.

Keywords:
chronic rhinosinusitis with nasal polyposis, omalizumab, recurrence rate, surgery-sparing effect

Egypt J Otolaryngol 35:269–277
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1012-5574

Introduction
Chronic rhinosinusitis (CRS) is one of the most frequent chronic diseases [1] with an overall prevalence ranging between more than 10% [2] and 28.4% based on the European Position Paper on Rhinosinusitis and Nasal Polyps [3]. CRS was associated with multiple environmental factors especially pollutants, tobacco smoke, occupational toxins, and adulthood age [4] but its major causes are allergic rhinitis [1] and asthma [3].

CRS comprises a spectrum of different diseases with distinct clinical presentations and pathogenic mechanisms, thus defining the distinct phenotypes and endotypes of CRS affects prognosis and is the basis for making therapeutic decisions [5]. chronic rhinosinusitis with nasal polyposis (CRSwNP) is characterized by eosinophilic inflammation and polyposis at the nose and paranasal sinus with high concentrations of immunoglobulin E (IgE) in NP, but the causative antigen for CRSwNP and its pathogenesis is still unknown [6].

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Prevention of chronicity of rhinosinusitis and/or minimizing its impact on the quality of life constitutes the cornerstone for CRS management [7] and involves avoidance of exposure to environmental factors, detecting the disease in its earliest stages, minimizing the impact of an ongoing illness or injury and lastly amelioration of disease-induced anxiety and depression [5].

Basophils, which are the rarest granulocytes, play crucial roles in protective immunity against the development of allergic disorders [8]. Basophils and mast cells, to initiate its secretion, depend on aggregation of the high-affinity IgE receptor, FceRI, which is characterized by variable densities by up to 100-fold among participants’ basophils and these high densities are responsible for sensitivity to certain monomeric IgE antibodies or spontaneous release [9].

The availability of targeted biotherapeutic agents such as anti-IgE and anti-cytokine antibodies could benefit patients in whom the targeted mediator is expressed and is a central mechanism in CRS patients [5]. Omalizumab (OMA) is a humanized clinically approved therapeutic anti-IgE antibody [10] that inhibits the interaction between IgE and Fc epsilon RI, thus preventing mast cell and basophil activation [11] and blocks IgE binding to CD23 on B cells and antigen-presenting cells, thus blocking the release of inflammatory cytokines from these cells [10]. Moreover, OMA may accelerate dissociation of receptor-bound IgE from Fc epsilon RI [12], thus blocking the IgE-mediated release of inflammatory mediators [10].

Objectives
The study tried to evaluate the efficacy of OMA (Xolair) therapy for patients with CRSwNP as a sole therapeutic line versus traditional CRS treatment (ttt) as evaluated by subjective and objective CRS severity parameters.

Design
Prospective comparative, double-blinded, two-arm study.

Setting
Yanbu National Hospital, KSA.

Patients and methods
The study was conducted since January 2015 till May 2018 including a 12-month follow-up period for the last case enrolled in the study. The study protocol was approved by the local ethics committee and the enrolled patients signed a fully informed consent to participate in the study and to receive the study drug.

Patients presenting to the outpatient clinic of otorhinolaryngology with symptoms suggestive of CRS were eligible for evaluation for inclusion and exclusion criteria. CRS was diagnosed according to the criteria defined by the rhinosinusitis task force [13] and patients fulfilling the inclusion criteria were enrolled in the study. The inclusion criteria included CRSwNP having more than or equal to two major or one major and more than or equal to two minor factors (Table 1) for more than or equal to 12 weeks despite the antibiotic therapy for 4 weeks, assigned for functional endoscopic sinus surgery (FESS), age range of 18–65 years and having pre-ttt serum IgE level less than 700 IU/ml. Exclusion criteria included pregnancy, lactation, body weight more than 150 kg, presence of associated allergic disorders, autoimmune disease, hepatic and renal diseases, diabetes mellitus, maintenance on immunosuppressive therapy, or other forms of anti-allergic therapies.

All patients were asked to complete a questionnaire to determine the total subjective score (TSS) [14]. The questionnaire included eight symptoms namely: blocked nose, nasal discharge, postnasal drip, sneezing, headache, cough, decreased sense of smell, and facial swelling. Each symptom was scored concerning intensity and frequency on a scale ranging between 0 and 3 for a TSS ranging between 0 and 48 [15]. Then, patients and controls underwent full otorhinolaryngological examination to assure the inclusion and exclusion criteria.

Only patients fulfilling the inclusion and exclusion criteria were included in the study and underwent rigid nasal endoscopy; and endoscopic findings were graded bilaterally according to the Lund-Kennedy

| Major factors                          | Minor factors                  |
|---------------------------------------|--------------------------------|
| Facial pain/pressure                  | Headache                       |
| Nasal obstruction/blockage            | Fever (all nonacute rhinosinusitis) |
| Nasal discharge/purulence/discolored postnatal drainage | Halitosis                      |
| Hyposmia/anosmia                      | Fatigue                        |
| Purulence in nasal cavity on examination | Dental pain                   |
| Fever (acute rhinosinusitis only)    | Ear pain/pressure/ fullness    |
scoring system with a score range of 0–12 and diagnostic cutoff point score of more than 2 [16]. Thereafter, the patients had paranasal sinuses computed tomography (CT) imaging that was evaluated according to the Lund-Mackay scale [17] with a score range of 0–24 points, and the higher the score, the greater the severity of the disease.

Randomization and grouping
Patients fulfilling the inclusion criteria were randomly allocated into two equal groups according to the applied therapeutic line: the study group (group S) included patients assigned to receive OMA therapy without any supplemental conventional therapy and the control group (group C) included patients assigned to receive conventional therapy consisting of antibiotic and corticosteroid therapy according to severity [18].

Omalizumab dosing, preparation, and administration
According to the instructions of the manufacturer (Genentech Inc., South San Francisco, California, USA) the dose of OMA (XOLAIR; Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA) was dependent on body weight and serum IgE levels and was given as 0.016 mg/kg/IgE (IU/ml). If the calculated dose was more than 150 mg, it was divided among more than one injection site to limit injections to not more than 150 mg per site. If the calculated dose was more than 300 mg, half the total dose was administered every 2 weeks. The calculated dose was prepared according to the manufacturer’s instructions and was injected subcutaneously.

Study outcome
The therapeutic effect of the applied therapy as judged by amelioration of clinical symptoms manifested by more than 50% decrease of TSS with concomitant improvement on nasoendoscopic findings.

The frequency of responders for whom surgical decision was postponed secondary to relieve disease manifestations.

The recurrence rate of disease severity manifestations during follow-up and the frequency of decision shift to surgery or to repeat the trial of medical therapy.

Statistical analysis
The obtained data were presented as mean±SD, ranges, numbers, and ratios. The results were analyzed using paired t test and one-way analysis of variance test. Possible relationships were investigated using Pearson’s linear regression analysis. Statistical analysis was conducted using the SPSS (version 15, 2006, SPSS Inc., Chicago, IL, USA) for Windows Statistical Package. P value less than 0.05 was considered statistically significant.

Results
The study included 98 patients eligible for evaluation; 12 patients were excluded and 86 patients were randomly divided into two equal groups (Fig. 1).

Demographic and clinical data of patients of both groups showed nonsignificant (P>0.05) difference. Also, the mean pre-ttt serum IgE levels showed nonsignificant (P>0.05) difference between patients of both groups (Table 2).

Collectively, mean serum IgE level was 187±121 IU/ml; range: 75–610 IU/ml and showed positive nonsignificant (P>0.05) correlation with endoscopic (r=0.135, P=0.216) and CT scores (r=0.112, P=0.306), while it showed positive significant (r=0.282, P=0.009) correlation with TSS (Fig. 2).

Nine patients received OMA single dose of less than 150 mg, 24 patients received 150–299 mg that was divided into two injection sites on the same session and only 10 patients received more than 300 mg divided into two doses given on two sessions 2-week apart.

Concerning the therapeutic effect as the primary outcome, for the first session, 17 (19.8%) patients had successful response with significantly (P=0.007 and P<0.00001) lower TSS in the control and study groups, respectively, compared with their pre-ttt score, and significantly (P=0.0037) lower TSS was reported in patients of study versus control groups. At the end of 12-month follow-up, TSS was nonsignificantly (P>0.05) higher in both groups compared with their post-ttt score, but with significantly (P=0.0148) lower TSS in the study versus control patients (Table 3, Figs 1 and 3).

Another 27 (31.4%) patients showed a primary successful outcome with significantly (P=0.047 and P<0.0001) lower post-ttt TSS compared with prettt score in the control and study groups, respectively, and significantly (P<0.0001) lower TSS in patients of the study versus control groups. Unfortunately, these 27 patients had recurrent manifestations with reincreasing TSS after a mean duration till recurrence of 2.8±0.7 m; range: 2–4 m in control and 5.6±1.1 m; range: 4–7 m in study patients. Anti-IgE
therapy allowed significantly ($P<0.0001$) longer duration till recurrence than conventional therapy. Moreover, at the time of recurrence, TSS was nonsignificantly ($P=0.318$) lower in control but was still significantly ($P<0.0001$) lower in study patients in comparison to their respective pre-ttt scores with significantly ($P=0.013$) lower scores in study versus control patients (Table 3, Figs 1 and 3).

Unfortunately, 42 showed no response with nonsignificantly lower post-ttt TSS compared with pre-ttt TSS and nonsignificant difference between both groups, despite being in favor of the study group. Collectively, for total patients both therapies did favorably with significantly lower post-ttt TSS score in control ($P=0.004$) and study ($P<0.0001$) groups compared to their pre-ttt scores and significantly lower post-ttt score in the study ($P=0.0005$) versus the control group (Table 3, Figs 1 and 3).

All of the 19 study patients with recurrent manifestations accepted to receive another session of OMA therapy, but three patients failed to respond and were shifted to FESS, while 16 patients gave successful response with significantly ($P=0.010$) lower post-ttt-2
TSS (9.3±2.1) compared with pre-ttt-2 (11.5±2.5). Five patients had recurrence after a mean duration of 4.8±1.3 m; range: 3–6 m with a mean post-ttt-2 TSS of 7.2±0.4, which is significantly lower ($P=0.005$) compared with pre-ttt-2 (9.2±1.1) (Figs 1 and 4).

Regarding the frequency of FESS, 35 control patients were shifted to FESS, 27 nonresponders and eight had recurrent manifestations for a surgery-sparing rate of 18.6%. On the other hand, 23 study patients underwent surgery: 15 had failed the first session, three had failed the second session, and five had recurrence after the second session for a surgery-sparing rate of 46.5% with significantly ($P=0.0058$) higher surgery-sparing rate with OMA therapy.

Endoscopic and CT scores of total patients, irrespective of the outcome, both scores determined at the end of follow-up were nonsignificantly ($P=0.313$ and 0.463, respectively) lower in control patients while were significantly ($P=0.013$ and 0.027, respectively) lower in patients of the study group in comparison to their respective pre-ttt scores. Moreover, at the end of follow-up, both endoscopic and CT scores were significantly ($P=0.046$ and 0.022, respectively) lower in patients of the study versus control groups. For study group
responders, at the end of follow-up, mean endoscopic scores were significantly lower compared with pre-ttt scores \((P=0.015)\) and scores of nonresponders at the time of shift to FESS \((P=0.035)\). CT scores of study group responders were significantly lower than pre-ttt scores \((P=0.045)\), while in comparison to CT scores of nonresponders the difference was nonsignificantly \((P=0.098)\) lower (Table 4).
Discussion

Patients’ selection for inclusion relied on the estimation of serum IgE, in support of such reliance, the estimated serum IgE showed a positive significant correlation with TSS, a score for patients’ complaints and presenting symptoms. Similarly, Zhang et al. [15] detected a certain correlation between allergic rhinitis and allergic factors with chronic sinusitis with or without NP and recommended avoiding allergen exposure and ttt of allergic rhinitis to effectively control recurrence of CRS and NP. Also, Bakhshaee et al. [19] reported that allergic reactions were found to be much higher in CRS patients with or without polyposis than the general population and at least one allergen was noted in 64% of the CRS patients. Moreover, Xiu et al. [20] detected higher scores of facial pressure, nasal discharge, and loss of smell in CRS patients with positive skin prick and specific IgE.

Anti-IgE therapy, OMA did better than conventional therapy for CRSwNP as manifested by multiple outcomes; first, the significant improvement of patients’ symptoms as evidenced by the significant decrease of TSS in all patients who received OMA, even the nonresponders, in comparison to their pre-ttt score. Similarly, Bachert et al. [21] reported significant improvement in all individual symptom scores and sino-nasal outcome test patient-reported outcome score with anti-IgE, mepolizumab, compared with placebo. Recently, in 2018, Bidder et al. [22] using the sino-nasal outcome test-22 score detected rapid improvement on using OMA at 4 and 16 weeks of ttt in both CRSwNP and asthma and this improvement was similar to that reported in patients who received surgery for CRSwNP.

Moreover, the responders who developed recurrence after the first session of OMA therapy accepted to receive another session and 68.8% of patients who had a second session responded without recurrence, which is an indirect proof for effectiveness of OMA therapy despite the recurrence and indicated a need for a second or prolonged course of OMA therapy to get the desired effect. In support of this assumption, Ledford et al. [23] found a continuation of OMA therapy after long-term ttt results in continued benefit, as evidenced by improved symptom control and reduced exacerbation risk. Second, endoscopic scoring also showed improvement especially in responders, a finding indicating a role of allergy in aggravation of the endoscopic findings and use of anti-IgE allowed amelioration of these aggravations of endoscopic findings. These findings go hand in hand with Bachert et al. [21] who reported significant improvements in NP severity score and endoscopic NP score with mepolizumab compared with placebo. Also, Rivero and Liang [24] through meta-analysis of the literature documented that anti-

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Table 4: Endoscopic and computed tomography scorings of patients of both groups

| Score          | Patients   | Time        | Control | Study | P1 |
|----------------|------------|-------------|---------|-------|----|
| **Endoscopic score** |            |             |         |       |    |
| Nonresponders  | Pre-ttt    | 8.1±3       | 8.1±2   | 0.906 |    |
|                | Time of shift to surgery | 7.8±2 | 7.5±1.8 | 0.539 |    |
| Responders     | Pre-ttt    | 8.1±3       | 8±2.4   | 0.874 |    |
|                | End of follow-up | 7±1.5 | 6.3±1.7 | 0.325 |    |
| Total          | Pre-ttt    | 8.2±2.7     | 8±2.2   | 0.827 |    |
|                | Post-ttt   | 7.7±2       | 6.9±1.3 | 0.046 |    |
| **CT score**   |            |             |         |       |    |
| Nonresponders  | Pre-ttt    | 14.5±5.3    | 13.2±6.1| 0.653 |    |
|                | Time of shift to surgery | 13.9±4.2 | 12.2±3.1 | 0.729 |    |
| Responders     | Pre-ttt    | 14±6        | 14.1±5.4| 0.871 |    |
|                | End of follow-up | 12.5±4.7 | 11.4±2.3 | 0.658 |    |
| Total          | Pre-ttt    | 14.4±5.3    | 14±5.7  | 0.725 |    |
|                | Post-ttt   | 13.7±4.3    | 11.8±2.7| 0.022 |    |

Data are shown as mean±SD. ttt, treatment. P1: indicates significance of difference between scores of both groups. P2: indicates significance of difference between pre-ttt and post-ttt scores. P3: indicates significance of difference between pre-ttt and post-ttt at 12-month scores.
IgE therapy, OMA, reduces NP score in patients with recalcitrant NP especially those who had severe comorbid asthma.

Third, the surgery-sparing effect is significantly higher with OMA therapy than conventional therapy (46.5 vs. 18.6%) as surgery was postponed for 20 patients, who responded to anti-IgE without recurrence, thus allowing avoidance of surgery and saving of resources. In line with these findings, Bachert et al. [21] reported that significantly greater proportion of patients who received mepolizumab no longer required surgery at week 25 (30 vs. 10%) compared with placebo. In support of the efficacy of OMA as a sole line of ttt for CRS, Chandra et al. [25] found that the OMA therapy is associated with a decrease in overall antibiotic use for CRS with significant reduction in steroid dependence. Also, Clavenna et al. [26] observed better improvement of pulmonary function tests with OMA in asthma patients with CRS than in asthma patients without CRS. Recently, Cavaliere et al. [27] compared asthma patients who underwent nasal surgical polypectomy and received postoperative OMA or not and reported polyp recurrence more frequently in patients who did not receive postoperative OMA, while none of the patients received OMA developed this complication.

Furthermore, Tsetsos et al. [28] through a literature search found that biologic therapy was proved to be effective in reducing total nasal endoscopic polyp score versus placebo with improvement in other outcomes such as opacification in CT, quality of life measures, nasal airflow and olfaction, and concluded that the use of biologic agents was safe, effective, and well tolerated as a line of management for CRS patients with or without NP.

In trial to explore the effectiveness and mechanism of action De Schryver et al. [29] evaluated the effect of doxycycline, methylprednisolone, and OMA separately on nasal and systemic expression of periostin, a biomarker for eosinophilic inflammation, in patients with CRSwNP and found methylprednisolone and OMA significantly reduced serum periostin levels at 4 and 8 weeks of ttt, but the effect of methylprednisolone was transient and concluded that the reported influence on periostin expression reflects the interference with the local or systemic eosinophilic inflammatory cascade.

**Conclusion**

CRSwNP is a deleterious disease state that badly impacted patients’ well-being and quality of life. Allergy aggravates the manifestations of CRSwNP and worsens its diagnostic scorings. Anti-IgE therapy significantly improves the outcome of conservative ttt of CRSwNP with superior outcome than conventional therapy and higher surgery-sparing rate. The use of a second session of anti-IgE therapy minimized the recurrence rate of manifestations. However, wider scale studies are required to compare the effect of interrupted courses versus prolonged course of anti-IgE therapy on the outcome of CRSwNP.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

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