Study protocol; april 2022

Omalizumab Efficacy in Chronic Rhinosinusitis Patients with Refractory Nasal Polyps:

Nasal polyps are benign edematous masses in the nasal cavities, paranasal cavities, or both with a probable overall prevalence of approximately 2% to 4% that can cause nasal obstruction, rhinorrhea, postnasal drip, and loss of smell . Treatment options for these patients include topical corticosteroids, systemic corticosteroids, and functional sinus endoscopic surgery. Especially in patients with chronic rhinosinusitis with nasal polyps and concomitant asthma, they have a poor therapeutic response and a higher recurrence rate, and treatment in these patients often fails. Both diseases have a great impact on the financial burden on society and the quality of life of the patient .

Chronic rhinosinusitis with nasal polyps (CRSwNP) and asthma are both complex airway inflammatory disorders that have become a serious medical and health system issues, nowadays. Among patients with CRSwNP, approximately 15% have aspirin intolerance and 30% have asthma . Asthma, whose symptoms include recurrent episodes of wheezing, shortness of breath, chest tightness, and cough, is a chronic inflammatory disorder of the airways characterized by airway obstruction, chronic inflammation, and airway overreaction. This is a common disease in various societies, with one in 20 people in the United States having asthma which eventually leading to a chronic relapse, Although there are effective treatments for mild asthma, treating severe asthma is still difficult and expensive .

Pathophysiology of 80% of white patients with CRSwNP are characterized by localized eosinophilic inflammation associated with high production of tissue cationic protein eosinophils, interleukin-5, and tissue immunoglobulin E . Also, soluble IL-2 receptor α subunit, soluble IL-5 receptor α subunit and tryptase are important factors in causing inflammation, which ultimately leads to polyp . The presence of asthma in patients with CRSwNP increases local IgE levels. However, independent of the presence of allergy, tissue inflammation and the formation of localized IgE are sometimes seen in patients with CRSwNP . Recent evidence has been shown that Staphylococcus aureus enterotoxins (SEs) act as superantigens by inducing local polyclonal IgE formation associated with severe eosinophilic inflammation . In addition, the formation of IgE against these enterotoxins in the patients with CRSwNP is strongly associated with asthma . Regarding mentioned issues, one of the effective treatment strategies in patients with CRSwNP could be IgE antibody treatment regimens. Omalizumab is a human anti-IgE antioxidant that has previously been approved in the United States for patients with moderate to severe asthma and in Europe for patients with severe asthma. This drug is used if these patients do not respond to high-dose inhaled corticosteroids plus long-acting active β-agonists .

In 2013, in a double blinded randomized study entitled “Omalizumab is effective in allergic and nonallergic patients with nasal polyps and asthma” investigated whether could Omalizumab be a treatment option for patients with nasal polyps and asthma or not. They discovered a significant decrease in total nasal endoscopic polyp scores after 16 weeks in the omalizumab-treated group, which was confirmed by means of computed tomographic scanning. Omalizumab had also a beneficial effect on airway symptoms (nasal congestion, wheezing, anterior rhinorrhea, loss of sense of smell, and dyspnea) and on quality-of-life scores, irrespective of the presence of allergy.

In a newly published paper, Gevaert et al. designed 2 randomized phase 3 trials to find out efficacy and safety of omalizumab in nasal polyposis. They concluded that the global, replicate, phase 3 studies, POLYP 1 nd POLYP 2, met both coprimary end points, demonstrating statistically significant improvements in nasal polyp score (NPS) and mean daily nasal congestion score (NCS) as well as patient-reported assessments of severity of symptoms in response to omalizumab versus placebo, on a background of intranasal mometasone, at week 24. Multiple secondary outcomes were also met. The improvements in Sino-Nasal Outcome Test (SNOT)-22 score illustrate the impact on patient quality of life and place the results into an important context relative to other therapies such as systemic corticosteroid (SCS) and surgery. In these two similar trials, Omalizumab was well tolerated, and adverse effects (AEs) were consistent with those previously reported. They finally represents Omalizumab as a

new promising treatment option for patients with refractory CRSwNP, for whom there is a substantial unmet need for effective therapies.
In another study, used SNOT-22 and asthma control questionnaire (ACQ-7) to evaluate whether treatment with the monoclonal antibody against IgE Omalizumab for severe allergic asthma also effectively treats co-existent CRSwNP or not. They reached rapid improvement at 4 weeks and 16 weeks of treatment in both CRSwNP and asthma control. The improvement in CRSwNP with Omalizumab was similar to that seen in a group of patients who received upper airway surgery. They introduced Omalizumab for severe allergic asthma also co-existent with CRSwNP. They suggested further clinical studies of current and emerging biological agents for severe asthma which include upper airway outcomes.
So, investigators conducted this study in april 2022 to survey the efficacy of Omalizumab on patients with refractory nasal polyp to confirm its efficacy entering to treatment guidelines.

OBJECTIVES & HYPOTHESIS:
Goal:
Determination of Omalizumab Efficacy in Chronic Rhinosinusitis Patients with Recurrent and Refractory Nasal Polyps, a Double Blinded Randomized Clinical Trial
Objectives:

1• Determination of Sino-nasal symptoms in chronic rhinosinusitis patients with recurrent and refractory nasal polyps who received Omalizumab by age.

2• Determination of Sino-nasal symptoms in chronic rhinosinusitis patients with recurrent and refractory nasal polyps who received placebo by age.

3• Determination of Sino-nasal symptoms in chronic rhinosinusitis patients with recurrent and refractory nasal polyps who received Omalizumab by gender.

4• Determination of Sino-nasal symptoms in chronic rhinosinusitis patients with recurrent and refractory nasal polyps who received placebo by gender.

5• Comparison of Sino-nasal symptoms in chronic rhinosinusitis patients with recurrent and refractory nasal polyps who receive Omalizumab with those received placebo regarding age

6• Comparison of Sino-nasal symptoms in chronic rhinosinusitis patients with recurrent and refractory nasal polyps who receive Omalizumab with those received placebo regarding gender

-PURPOSE :
Due to importance of inflammation and the role of IgE in pathogenesis of chronic rhinosinusitis patients with recurrent nasal polyp, the usage of anti-inflammatory drug such as Omalizumab is useful in the treatment of these patients

-HYPOTHESIS:
1. How is the Sino-nasal symptoms in chronic rhinosinusitis patients with recurrent and refractory nasal polyps who received Omalizumab by age?

2• How is the Sino-nasal symptoms in chronic rhinosinusitis patients with recurrent and refractory nasal polyps who received placebo by age?

3• How is the Sino-nasal symptoms in chronic rhinosinusitis patients with recurrent and refractory nasal polyps who received Omalizumab by gender?

4• How is the Sino-nasal symptoms in chronic rhinosinusitis patients with recurrent and refractory nasal polyps who received placebo by gender?

5• Is Sino-nasal symptoms in chronic rhinosinusitis patients with recurrent and refractory nasal polyps who receive Omalizumab is as the same as those received placebo regarding age?

6• Is Sino-nasal symptoms in chronic rhinosinusitis patients with recurrent and refractory nasal polyps who receive Omalizumab is as the same as those received placebo regarding gender

-TYPE OF STUDY;
This study is a double blinded placebo-control clinical trial.

-SAMPLING:
Investigators will conduct a double blinded clinical trial study involving 30 patients who have 18-75 years old with history of 2 years rhinosinusitis with recurrent and refractory nasal polyp referred to Nemazee hospital immune-allergy clinic affiliated with Shiraz University of Medical Sciences since april 2022 during 24 weeks.. Prick test will be done for all patients.

-INCLUSIONS CRITERIA :
1.The patients which have been investigated in Nemazee hospital immune-allergy clinic
2. Patients who completed the informed consent form
3. The Patients aged 18-75 years with a history of sinus surgery at least once and usage of intranasal corticosteroid for at least 4 weeks
4. The patients having a total nasal polyp score (NPS) 5 or more (NPS >2 for each nostril)
5.The patients having a nasal congestion score (NCS) of 2 or higher (with additional symptoms of postnasal drip, runny nose, and/or loss of sense of smell
6. The patients having a SNOT-22 score of 20 or higher on arrival

-EXCLUSIONS CRITERIA:
1. The patients with other sinonasal or pulmonary disorders (except asthma), including current upper respiratory tract infection, cystic fibrosis, or other dyskinetic ciliary syndrome
2. History of past or current malignancy
3. History of a cardiac condition, hepatitis or liver cirrhosis
4. History of recent or current infection requiring hospitalization (<4 weeks, antibiotic (<2 weeks) or antifungal treatment, or parasitic infection (<6 months)
5.History of recent use of systemic corticosteroid (SCS) (<2 months), immunosuppressant, biologic, or leukotriene antagonist or modifier
6. History of recent nasal surgery (<6 months); known allergy to omalizumab; or those who were immunocompromised.

Investigators will randomly (the method of randomization will be explained in greater detail) divide the patients into two groups (1:1) either receive Omalizumab or placebo. The protocol specified study dosing of 75 to 600 mg by subcutaneous injection every 2 or 4 weeks, depending on the pretreatment serum total IgE level and body weight (Table 1). According to low prevalence of the disease, drug expensiveness and absence of similar study investigators forced to choose 15 patients in each group based on retrospectively review the number of patients referring to the hospital during one year. Indeed, in this study patients enter hard and leave easily because of inclusion and exclusion criteria. Sampling method is easy based on purpose. In this way, the investigator will be present at the time of the study and will begin sampling from accessible referral patients to obtain the total sample size.

-RANDOMIZATION METHOD:
One method of randomization is to use the RANDBETWEEN function in Excel. This function allows to investigators generate random numbers. To generate a random number in this study with a sample size of 30, between the two numbers 1 and 31, the function = Randbetween (1,31) is used. This function creates a column of random numbers between 1 and 31. The rand () function selects numbers with equal probability in this interval, so the chance of selecting any number in this interval is equal to the other numbers. This means that each patient is assigned to enter one of two treatments, respectively. These data are 30 people who are randomly assigned to 2 treatments 1 and 2 (15 people in each group). The sample numbers in the first group and the second are as follows:
A: 15,7,6,29,23,13,10,25,12,1,4,17,26,20,11
B: 28,14,21,3,8,22,2,5,16,30,27,19,18,9,24
A or B could be contributed to both control and Omalizumab group.

The researcher who reviews the results is not aware of the group allocation.
All patients provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki (20) and all applicable laws and regulations.
Demographic data and medical history will collect at the first visit during screening. Blood samples will collect at screening and at weeks 16, 24, and 28 for routine analyses. Serum IgE levels will determine at baseline. NPS (point range, 0-8) will determine for each nasal passage at screening and at weeks 4, 8, 16, and 24. Endoscopic videos will score at a central reading center by 2 blinded independent trained otolaryngologists. Discrepancies will adjudicated by a third blinded otolaryngologist. Nasal symptoms will recorde daily with the use of an e Diary (with nasal congestion, sense of smell, postnasal drip, and runny nose each assigned a score ranging from 0 [not at all] to 3 [severe]) ; each component will analyze separately and in a combined summed total nasal symptom score (TNSS) (point range, 0-12)
The nasal congestion question forms the NCS. The University of Pennsylvania Smell Identification Test (UPSIT) will perform at day 1 and at weeks 8, 16, and 24 (point range, 0-40, with higher scores indicating better smell). SNOT-22 (Table 2) score will measure at screening; on day 1; and at weeks 24 (point range, 0-110, with lower scores indicating better disease control and quality of life [OoL]). In patients with comorbid asthma, the Asthma Quality of Life Questionnaire (AQLQ) will administere at day 1 and at weeks 16 and 24 (point range, 1-7, with higher scores indicating better QoL). Adverse events (AEs) and concomitant medications will monitor throughout treatment and safety follow-up.
SNOT-22 questionnaire which is available in Table 2, is our tool. Validity and reliability of this questionnaire has been confirmed by Naghdi et al.in an Iranian population. During the study, researcher will gather information of patients` symptoms by a checklist. This checklist is available at the bottom of this document.

For data analysis from april 2022, the statistical package for social sciences (spss) version 23 software will use through about one year. Descriptive statistics including mean and standard deviation for quantitative variables and number (%) for qualitative variables will use to describe the data. Data analysis will performe using independent sample T-test and Chi-square test. The average of the parameters before and after, as well as the difference between the changes can be made with independent T test. The t-test is used to compare the mean of parameters in each of the two groups. The Chi-square test will use to compare the qualitative variables and qualities between the two groups. The within-group means and between-group differences in absolute change from baseline to week 24 will be the estimated least squares means (LSMs) obtained by using a mixedeffect model with repeated measures with unstructured covariance matrix, adjusted for comorbid asthma/aspirin sensitivity, time point per schedule of assessments, baseline outcome score, treatment by time point interaction, and

baseline outcome score by time point interaction for NCS, UPSIT score, SNOT-22 score, and TNSS. P values will be derived from a t test of difference in LSMs.
P value below 0.05 will be considered as significant.

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