

Precision Medicine for Treatment of Rhinosinusitis: Biologics

Sinüzit Tedavisinde Hedefe Yönelik İlaçlar: Biyolojik Ürünler

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ABSTRACT The term chronic rhinosinusitis (CRS) is an umbrella term that covers different conditions related with the paranasal sinus system. In recent years, effort was made to understand the underlying pathophysiology in terms of detecting its phenotypes and endotypes. These efforts resulted with the identification of biomarkers that have an important role in pathophysiology of CRS. CRS is mainly divided into two phenotypes: CRS without (sine) nasal polyps (CRSsNP) and CRS with nasal polyps (CRSwNP). CRS with nasal polyposis share the same mechanisms with allergic rhinitis and asthma in which type 2 inflammation is predominant. Biological monoclonal antibodies have a long use for treatment of uncontrolled asthma. Based on previous experience with asthma and allergic diseases, biological treatments started to gain place in management of uncontrolled CRS which is difficult to treat against maximal treatment effort. Recently; European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS 2020) was released at the beginning of 2020. For the first time, EPOS 2020 reported the indications of biological products in treatment of CRS. It is predictable that targeted biological treatments are going to take place in standard treatment of CRS in ongoing years. Biological monoclonal antibodies offer "precision treatment" for various diseases for decades. They offer a new targeted therapy, however their use in new areas are still under investigation. This review is focused on available literature related with the use of biologics in treatment of CRS.

ÖZET Kronik rinosinüzit (KRS) terimi, paranasal sinüs sistemi ile ilgili farklı hastalıkları kapsayan bir şemsiye terimidir. Son yıllarda KRS fizyopatolojisi, KRS fenotip ve endotiplerini saptamak üzerine yapılan çalışmalar artmıştır. Çalışmalar KRS fizyopatolojisi önemli rol oynayan biyobelirteçlerin tanımlanması ile sonuçlanmıştır. KRS temel olarak iki fenotipe ayrılır. Bunlar burun poliplerinin eşlik etmediği KRS ve burun poliplerinin eşlik ettiği KRS'lerdir. Nazal poliplerin eşlik ettiği KRS, tip 2 inflamasyonun baskın olduğu alerjik rinit ve astım ile aynı mekanizmaları paylaşır. Biyolojik monoklonal antikolar, kontrolsüz astım tedavisi için uzun süredir kullanım alanına sahiptir. Astım ve alerjik hastalıklarla ilgili önceki deneyimlere dayanarak, maksimum tedavi çabalarına karşı tedavisi zor olan kontrolsüz KRS'lerde biyolojik tedaviler yer almaya başlamıştır. En güncel olarak; European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS 2020) 2020'nin başında yayınlandı. EPOS 2020 ilk kez KRS tedavisinde biyolojik ürünlerin endikasyonlarını bildirdi. Hedefli biyolojik tedavilerin, KRS'in standart tedavisinde devam eden yıllarda olacağı öngörülebilmektedir. Biyolojik monoklonal antikolar, onlarca yıldır çeşitli hastalıklar için "hassas tedavi" olanağı sunmaktadır. Yeni bir hedefe yönelik tedavi seçeneği sunan bu ajanların, yeni alanlarda kullanımları halen araştırılmaktadır. Bu derleme, KRS tedavisinde biyolojik ürünlerin kullanımı ile ilgili mevcut literatürü derlemeyi amaçlamıştır.

Keywords: Omalizumab; mepolizumab; dupilumab; reslizumab; phenotype; monoclonal antibody

Anahtar Kelimeler: Omalizumab; mepolizumab; dupilumab; reslizumab; fenotip; monoklonal antikor

Chronic rhinosinusitis (CRS) is an umbrella term that covers different paranasal sinus pathologies. It is estimated that CRS can effect up to 12.5% of the population around globe.¹ However all subtypes of rhinosinusitis are completely different; which single

treatment modality cannot reach a definite treatment goal.²

The CRS covers CRS without (sine) nasal polyps (CRSsNP), CRS with nasal polyps (CRSwNP), allergic fungal rhinosinusitis (AFRS), CRS

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Peer review under responsibility of Türkiye Klinikleri Journal of Medical Sciences.

Received: 26 Mar 2020 **Accepted:** 01 Apr 2020 **Available online:** 12 Apr 2020

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related with aspirin exacerbated respirator disease (AERD).³ Phenotypes differ according to type of inflammation, need of surgery and recurrence after appropriate treatment.⁴ These different clinical phenotypes have different mechanisms (e.g type 2 inflammation is predominant for CRSwNP, AFRS, and AERD) and even in same phenotype; subtypes may have different pathophysiology (e.g. nasal polyps in CRSwNP vs nasal polyps in cystic fibrosis). In recent years effort was made to understand the underlying pathophysiology among these different phenotypes and endotypes of CRS.⁵ These efforts resulted with the identification of biomarkers that have important role in pathophysiology of CRS.

The main treatment of CRS consists of the use of antibiotics, local/systemic steroids, saline irrigation and functional endoscopic sinus surgery (ESS).⁶ Despite all treatment modalities there is a group of “*difficult to treat subjects*” in which symptom control cannot be achieved despite appropriate/maximal use of current treatment modalities. Defined CRS phenotypes and endotypes and targeted biological treatment allow to plan a more tailored therapy.⁵

Chronic rhinosinusitis is mainly divided into CRSsNP and CRSwNP.⁷ The CRSwNP has a strong association with asthma and both asthma and CRSwNP share some similar characteristics according to pathophysiology of the disease. The biological treatment modalities has a long use in treatment of asthma (15 years). Shared inflammatory pathways started to guide the biological treatment modalities if they are useful in rhinosinusitis.⁴

Targeted biological treatment is the state of art of the treatment of CRSwNP. This review tended to define biological treatment, monoclonal antibody production, present the potential agents, in the light of literature to discuss the current situation and potential future applications.

PHENOTYPES AND ENDOTYPES OF RHINOSINUSITIS

According to literature, there are 3 inflammatory pathways.¹ These are T-helper 1 (Th-1) driven, T-

helper 2 (Th2) driven and T-helper 17 (Th17) driven pathways. In CRSsNP, inflammation process is mainly driven by Th1 cells. There are increased number of myeloperoxidase-related neutrophils. Levels of interferon (IFN)- γ , interleukin (IL)-2, and tumor necrosis factor (TNF α) were increased in CRSsNP.

Chronic rhinosinusitis with nasal polyps, AERD and AFRS share same inflammatory pathway that is mainly driven by Th2 cells (Th2). T-helper 2 predominant inflammation often related with increased level of eosinophils. Type 2 inflammation's biomarkers are eosinophilic cationic protein, IL-4, IL-5, IL-10 and IL-13 of which some are all targets of biological treatment. In sino-nasal epithelial cells healthy epithelial barrier function is lost. Ig-E which is the inducer for eosinophilia are also present in local polyp tissue and blood in Th2 driven inflammation.⁷

T-helper 17 driven pathway is another pathway that is not extensively studied. Previous data demonstrated that in Asian patients Th17 driven inflammatory pathway is mainly driven from IL-6, IL-17, IL-22, and TNF- α .⁸

MONOCLONAL ANTIBODY PRODUCTION

Monoclonal antibodies are large molecules (normal size between 150-200,000 Daltons) that have a specific epitope or antigen target. They are the important part of host defense system that evolved over the past 400 million years among all kind of vertebrates.⁹ Monoclonal antibodies are highly specific and they are the future treatment of various diseases.

All monoclonal antibodies have a different common-**mab** (Omelizumab) suffix which was given them to differentiate from other therapeutic agents. Next nomenclature of the monoclonal antibodies was made according to their origin as follows:¹⁰

- *Mouse antibody (-omab)*
- *Chimeric antibody (-ximab)*
- *Humanized antibody (-zumab)*
- *Fully human antibody (-umab)*

Further nomenclature was made according to target as following:¹¹

- *Tumor (-tu-(m))*
- *Immune system (-li(m)-)*
- *Circulation system (-ci/c(ir)-)*
- *Anti-angiogenic (-anibi-)*
- *Anti-viral (-vi-)*
- *Interleukin (-ki(n)-)*
- *Bone (-os-)*

First creation and production of monoclonal antibodies were made in mouse (murine). Although this is a useful method for experimental studies; these monoclonal antibodies include some degree of foreign mouse proteins. When used in humans as therapeutic agents; these proteins lead to undesired common immune reactions due to foreign mouse protein so called human anti-mouse antibody (HAMA). Current mouse (murine) originated antibody examples are catumaxomab and ibritumomab tiuxetan which targeted tumor tissue.

A further humanizing of monoclonal antibodies was achieved with chimeric mousses. This problem was partly solved with recombinant DNA technology. Chimerisation is the replacement of most mouse Fc sequences with human Fc.⁹ By chimerisation 30-35% mouse/65-70% human derived antibodies can be achieved.¹¹ However new reactions occurred due to Human anti-chimeric antibody (HACA) that less than reactions with HAMA. Example of chimeric antibodies is Cetuximab which targeted tumor. Chimeric antibodies have more common use than mouse antibodies and they are in current use for tumor and diseases effecting the immune and circulation system.¹¹

Since the reaction in human body is against mouse (murine) based proteins; attempts were given to maximize the humanized part of MA (humanization). Humanized monoclonal antibodies contains 5-10% mouse (murine) proteins. For creation of humanized MA, complementarity determining regions (CDR) of the mouse are incorporated human antibody.¹² This process is called CDR grafting. By humanization the immunologic reactions are much

lower however it can be still expected. Humanized antibodies now have a use in oncology, immune system, circulation system, anti-angiogenic purposes and as anti-viral. Omelizumab is an example for humanized antibodies that further presented in this report.

Final solution comes from genetic engineering that allowed the creation of fully human monoclonal antibodies. Two methods were used for this purpose.¹³ Bacteriophage displayed antibody is the most common form. For this purpose a bacteriophage was infected to an Escheria Coli (EC). The phages are enlarged and selected. After various steps desired gene locus was obtained and cloned to a plasmid. By inoculating the plasmid to bacteria (e.g E.coli), yeast (e.g. Pichia pastoris) or mammal (e.g Chinese Hamster Ovary Cell) antibodies can be produced.^{9,13} Second approach is transgenic mice approach in which mouse native antibody genes were replaced with their human counterparts. This approach is the combination of recombinant DNA and genetic transfer technology. The production of antibodies in fully human structure is the most common and desired way. They have a current use in all aspects of biological treatment. Dupilumab and mepolizumab are the examples of fully human monoclonal antibodies that are further presented in this report.

Future techniques for antibody production are immortal β -Lymphocyte cell line, immortal myeloma cell line, single type reverse transcription polymerase chain reaction (RT-PCR), heterohybridoma etc.¹¹ Since this part is written to give a brief explanation of monoclonal antibody production process to the audience; details of these processes are beyond the topic of this article.

ANTI-IGE

Omalizumab is the first anti Ig-E monoclonal antibody that used both in allergic rhinitis (AR), asthma and CRSwNP.² Omalizumab acts by binding IgE's Fc receptor. It blocks the Ig-E mediated inflammation and decreases the Ig-E concentrations. Omalizumab also downregulate the Fc receptors in various cells and reduce inflammatory mediator release.¹⁴

Omalizumab have an FDA approval since 2003 for asthmatic subjects whose symptoms cannot be controlled with inhaled corticosteroids. Recent meta-analysis from Rivero et al. demonstrated beneficial effect of anti IgE therapy on poly size reduction in subjects with severe asthma.¹⁵

Omalizumab can be administered to subjects over the age of 12. The only contraindication of the treatment is anaphylactic reaction to agent (0.2% of the treated subjects). The administration route of omalizumab is subcutaneous injection for every 2 to 4 weeks with weight based dosing. In general, 16 weeks is required to achieve clinical response. When the omalizumab therapy is ceased; the beneficial effects ended in a few months.¹⁴ There was concern related with the malignancy, cardiovascular events and reported side effects are increased upper respiratory tract infections including pharyngitis sinusitis and injection site reactions.

In most recent Cochrane database review; 3 studies, that evaluated omalizumab in the management of CRS WNP, were included. These 3 studies included 65 subjects and final comment of the Cochrane review cannot reach to a certainty on use of omalizumab in CRSwNP.³ This is why the study results are in limited number and conflicting. In 14 subjects Pinto et al. could not find a significant difference between omalizumab and placebo in terms of endoscopic nasal polyp score.¹⁶ Gaveart et al. compared omalizumab with placebo in 24 subjects.¹⁷ Subcutaneous 4 to 8 doses of omalizumab (n=16) was used in subjects with nasal polyposis. Endoscopic polyp scores as well as Lund Mackay scores, symptom/quality of life scores were improved with omalizumab therapy.

Ig-E targeted therapy is also found to be effective in subjects with subjects with AFRS, eosinophilic granulomatosis with polyangiitis (EGPA) and AERD.¹⁴ A recent meta-analysis by Rivero et al. included 5 studies in which omalizumab was evaluated for treatment of nasal polyposis.¹⁵ Overall, no significant reduction was observed in nasal polyp size but a tendency for improvement is observed. But in post hoc analysis in subjects with concomitant asthma a significant reduction was ob-

served in nasal polyp size. Authors support the use of omalizumab in CRSwNP with concomitant asthma. Ligelizumab and Quilizumab are the other anti Ig-E drugs that are under investigation.⁸

ANTI-IL-5

Mepolizumab and reslizumab have an FDA approval since 2015/2016 in asthmatic subjects that have concomitant eosinophilia.¹⁵ Mepolizumab blocks IL-5 /IL-5 receptor (IL-5R α) complex binding and neutralize IL-5 signaling. Primary effect is based on the reduction of eosinophils and previous studies indicated the agent as a potential biologic in treatment of eosinophilic diseases including CRSwNP.² Bachert et al. conducted a prospective study in 105 subjects (4 subjects received 750 mg of intravenous (IV) mepolizumab for every 4 weeks for 6 times-51 subjects received placebo). Mepolizumab significantly reduced the need for sinus surgery and treatment improved endoscopic nasal polyp score, Visual analog scales and symptom scores.¹⁸

Gavaert et al. evaluated 30 subjects with either grade 3/4 nasal polyps or recurrent nasal polyposis (20 subjects received 750 mg of IV mepolizumab for every 28 days for two times-10 subjects received placebo). In 12 subjects, nasal polyp score and CT appearance of nasal polyps improved in mepolizumab group vs 1 subject in placebo group.¹⁹

Most recent Cochrane review analysis includes two studies. Authors commented that they have low certainty about the beneficial effect of mepolizumab therapy in means of symptom severity, risk of surgery, extent of disease, quality of life and serious side effects.³ Reslizumab (target molecule IL-5R) is also a new drug that is currently under investigation.⁴ Other biologics that are related with IL-5 pathway are benralizumab (target molecule IL-5R α), TPI ASM8 (target molecule IL-5R β).⁸ Benralizumab has a different mechanism that leads to a depletion of eosinophils. Hyper sensitivity to drug and anaphylaxis is the common adverse events of biologics. Increased risk of malignancy is one of the main concerns. Opportunistic infections also serves a risk of biological treatment.¹⁵

ANTI-IL-4/IL-13

Alpha (α) chain of IL-4R α is a common receptor for IL-4 and IL-13 which has an important effect on nasal polyp formation. Dupilumab acts as anti-IL-4 mAb.² Dupilumab is the only approved drug by Food and Drug Administration (FDA) for treatment of patients with CRSwNP. Literary data about the use of dupilumab have strongest evidence level for now in subjects with CRSwNP. Most recent Cochrane review includes 784 subjects from different studies.³ The results are almost clear that dupilumab show a superiority in extent of disease, need for surgery, disease severity quality of life and side effect profile.³ In the setting of 8.9 points clinically important difference subjects receiving dupilumab have a 19.6 points better values than placebo. The VAS scores lowered 3.0. A large effect size (7.0) was observed for Lund Mackay scores. Pitakinra and AMG 317 is another IL-4R α antagonist that is under investigation.²⁰ IL-4 antagonists that are currently under investigation are Quilizumab, Pascolizumab and Altrakincept.²⁰

Although mentioned biomarkers were reviewed extensively, we need to note that there are other biologics that are currently investigated. Targeted biomarkers (biological treatment) for IL-13 are Lebrikizumab and Tralokinumab Anrukinzumab and GSK679586. Other biomarkers that are currently investigated are IL-9 (MEDI-528), IL-17a (Secukinumab) Siglec-8 (AK001) IL-4/IL-13 (SAR156597) TSLP (Tezepeluma) OX40LG (Oxelumab).²⁰

INDICATIONS FOR BIOLOGICAL TREATMENT FOR SINUSITIS

In EPOS 2020, the indications for biological treatment in rhinosinusitis took place for the first time.⁶ The indication is limited to CRSwNP with bilateral nasal polyps who had endoscopic sinus surgery. Three out of 5 indications are needed to start biological treatment. These indications are

- Presence of comorbid asthma that requires regular inhaled corticosteroids
- Presence of anosmia on smell test

- Significant impairment of quality of life scores (Sinonasal outcome test-22 score (SNOT-22) over 40)

- Contraindication for systemic steroid use or need for systemic steroid use ≥ 2 courses/year or need of low dose need for systemic steroid use for more than 3 months.

- Presence of biochemical evidence of type 2 inflammation (total IgE ≥ 100 or blood eosinophilia ≥ 250 or tissue eosinophilia ≥ 10 /high power field (x400)

EPOS 2020 also reported the evaluation process after biological treatment. First evaluation needs to be done 16 weeks after therapy. Response was evaluated also with 5 parameters according to nasal polyp size, need for systemic steroids, quality of life, smell quality and reduction in comorbid diseases. Response needs to be categorized as excellent (5 criteria), moderate (3-4 criteria), poor (1-2 criteria) and no response, and the treatment ceased if no response was detected. If any response was detected after 16 weeks, the subject is evaluated after 1 year therapy.

DISCUSSION

Chronic rhinosinusitis is an important health problem that has direct and indirect consequences. CRS covers different diseases as CRSsNP, CRSwNP, AFRS, CRSwNP with asthma and AERD. Subjects with CRSwNP almost all needed a long term therapy no single modality exists to eliminate the disease.²⁰ General success rate of available medical treatments are around 50%.¹⁴ and sinus surgery revision rates will be up to 15%.² In contrast with the optimal use if available therapeutic options a degree of subjects disease cannot be controlled. Difficult to treat subjects are candidates for second line treatment modalities including macrolides, leukotriene receptor antagonists, topical antibiotics and biological treatment.²⁰

One disease one airway concept accepted that all airway system is a single unit that shares same properties.¹⁵ There is a well demonstrated clinical connection with the allergic rhinitis, rhinosinusitis and

asthma. The comorbidity and overlapping situation with AR and asthma is widely seen in CRSwNP and presence of one condition complicate the overall control of disease. The Ig-E is the key inflammatory marker which has been widely implicated in the pathogenesis of airway related diseases. The number of eosinophils as well as IL-5 is widely shown in nasal polyp pathogenesis. In asthma and atopic dermatitis, Ig-E and TH2 targeted biological treatments improve clinical success rates.

The available options mostly include medical treatment that includes severe systemic steroid treatment and endoscopic sinus surgery.³ Glucocorticoid receptor-b expression and neutrophil accumulation in nasal polyp tissue are related with steroid insensitivity.⁷ Main treatment failure is possible and observed in certain group of subjects. Presence of nasal polyposis, presence of diffuse high endoscopic scored nasal polyps, comorbid disease like asthma and AERD/AFRS are the main failure-related factors.¹⁴ In 36 subjects, Van Zele et al. reported that Ig-E levels, presence of *Staphylococcus aureus* enterotoxin specific IgE (SE-Ig-E), eosinophilic cationic protein (ECP), and high IL-5 levels were significantly high in recurrent cases.²¹ In the same study, asthma and aspirin intolerance were also associated with recurrence.

Biological products are monoclonal antibodies that target specific part of any diseases pathophysiology. Their production in years significantly improved and now they are the mainstay treatment of various diseases. Their advantages are offering a more biologic, precise treatment by eliminating the possible side effects of conventional therapies. In any disease treatment as oncologic, immunologic ones there are always a number of difficult to treat subjects and these therapies also offered a new way for such diseases.²² In general 69 biologic agents are under investigation for Th1, Th2 and Th-17 mediated inflammation and the number is increasing.²⁰ A limited number of these agents are also suggested for treatment of CRS. The initial indication of biological treatments are on CRSwNP because of its close relation to asthma but it seems to expand to the subjects with eosinophilic CRS.

On the basis of previous experience with asthma, atopic dermatitis etc. CRSwNP a new a potential CRS subgroup in which biologics are indicated. There are a few number of studies in which the dupilimab seems effective biological agent.³ However the studies will increase in number and quality in ongoing years. Besides a continuous work was done to better identify endotypes and phenotypes and new biomarkers continuously identifies and defining as a potential for targeted biological treatment.

The main points related to a biological product use is cost effectiveness and especially long term side effects. The direct annual cost of biological product use can be between 10000 and 40000 dollars.⁴ Most of the biological products are in markets for a few years. Specific contraindications as well as ideal dosage, ideal timing are missing. A major concern is the interaction with human immune system in means of decreasing resistance to infections and may be resulted with long term cancer development.

CRS is mainly divided into two phenotypes as CRSsNP and CRSwNP as mentioned. These two forms are completely different from another since the biomarker type of inflammation treatment modality and effectiveness differ. Besides defined phenotypes, there also different cluster subjects even in the CRS subjects. Liao et al. evaluated 246 subjects with CRS with at least 1 year follow up. Subjects were evaluated according to 28 clinical and 39 molecular/cellular variables. In summary, these results indicated 7 different clusters in CRS. Previous studies found 5 to 10 clusters according to number of parameters.²³

Targeted biological treatment currently takes position in European Position Paper on Rhinosinusitis and Nasal Polyps 2020.⁶ The EPOS 2020 now presents an indication scale for biological treatment modalities and showed how the treatment will be evaluated.

CONCLUSION

Biological agents are state of art treatment options for controlling airway diseases. Recent studies on

endotypes and phenotypes of rhinosinusitis resulted with detection of useful biomarkers which lead to develop targeted biological treatment. Now these treatments come into clinical applications with the suggestion of EPOS 2020 and faster use of biological products will be expected for forthcoming years. Research for new biomarkers and new target molecules are the future of precision treatment. Upon use of each product, future clinical studies will clarify their efficiency.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: İbrahim Sayın, Nurcan Orhan, Neşe Sevgili, Zahide Mine Yazıcı; **Design:** İbrahim Sayın, Nurcan Orhan, Neşe Sevgili, Zahide Mine Yazıcı; **Control/Supervision:** İbrahim Sayın, Nurcan Orhan, Neşe Sevgili, Zahide Mine Yazıcı; **Data Collection and/or Processing:** İbrahim Sayın, Nurcan Orhan, Neşe Sevgili, Zahide Mine Yazıcı; **Analysis and/or Interpretation:** İbrahim Sayın, Nurcan Orhan, Neşe Sevgili, Zahide Mine Yazıcı; **Literature Review:** İbrahim Sayın, Neşe Sevgili; **Writing the Article:** İbrahim Sayın, Nurcan Orhan, Neşe Sevgili, Zahide Mine Yazıcı; **Critical Review:** İbrahim Sayın, Nurcan Orhan, Neşe Sevgili, Zahide Mine Yazıcı.

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