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BIOLOGICAL THERAPY IN CHRONIC RHINOSINUSITIS WITH NASAL POLYPS: A LITERATURE REVIEW OF TREATMENT METHODS INCLUDING DUPILUMAB AND MEPOLIZUMAB

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ABSTRACT

Introduction and purpose: Nasal polyps occur in chronic mucosal inflammation of the nasal cavity. Overgrown mucosa forms pale colored, smooth, lobular, poorly vascularized structures which expand into nasal cavity causing obstruction, nasal congestion and hyposmia. Corticosteroids used topically or systemically significantly improve patients' quality of life by reducing the size of the polyps, however long-term steroid use is associated with systemic side effects. Sinus surgeries alleviate breathing problems, however sinonasal symptoms can reoccur even 3 years after the surgery. Recently introduced biological treatment such as mepolizumab or dupilumab, showed itself effective and safe. Studies show that patients treated with dupilumab or mepolizumab have lower risk of sinonasal symptoms reoccurrence.
The aim of this review is to investigate the treatment methods in chronic rhinosinusitis with nasal polyps and the potential of the new biological therapy.
Materials and methods: A literature review was conducted using databases including PubMed, Scopus and Google Scholar. Additionally, European position paper on rhinosinusitis and nasal polyps (2020) was used. Search terms included "chronic rhinosinusitis with nasal polyps", "nasal polyposis", "endoscopic sinus surgery", "mepolizumab", "dupilumab".
Summary and Conclusions: Steroid therapy and endoscopic sinus surgery as a well-known form of therapies alleviate symptoms of chronic rhinosinusitis with nasal polyps although often do not offer sustain outcomes. New studies concerning biological therapy including dupilumab and mepolizumab suggest a potential breakthrough for patients. Reoccurrence rate was significantly lower, and symptom control enhanced due to biological therapeutics. Dupilumab and mepolizumab should be considered in CRSwNP treatment.

KEYWORDS

Chronic Rhinosinusitis, Chronic Rhinosinusitis With Nasal Polyps, Dupilumab, Mepolizumab, Asthma, Eosinophils

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1. Introduction

Chronic rhinosinusitis with nasal polyps (CRSwNP) occurs in about 4 % of European population. This chronic disease is associated with high symptom burden and elevated rates of reoccurrence after invasive surgical treatment (Bachert et al., 2019). In addition, poor health-related quality of life is observed in patients with nasal polyps (Hoehle et al., 2016).

Typical therapeutic approach includes corticosteroids as a first-line therapy and Endoscopic Sinus Surgery (ESS) as a subsequent step. Regrettably ESS may not provide long term remission, and the recurrence rate of polyposis is 25-40% (DeConde et al., 2017; Smith et al., 2019). New targeted therapy includes monoclonal humanized antibodies (mepolizumab and dupilumab) and opens a new perspective for patients with CRSwNP.

2. Chronic rhinosinusitis

Chronic rhinosinusitis (CRS) is a clinical syndrome characterized by inflammation of the sinal and nasal mucosa lasting over 12 weeks. Patients with CRS present with nasal discharge, nasal congestion, hyposmia, facial pain and impaired quality of life (Stevens et al., 2016). Imaging diagnostic studies such as nasal endoscopy or CT scan confirm the diagnosis. There are 2 types of CRS classified by the presence or absence of polyps. Polyps occur in 25-30% patients with CRS, are more frequent in men and prevalence tends to increase with age. CRS has greater occurrence in population <40 years old whereas chronic rhinosinusitis with nasal polyps in population > 40 years old (Fokkens et al., 2020).

3. Nasal Polyps

Nasal polyp is an overgrown inflamed nasal mucosa. It can be classified based on size and location - diffused or localized. While localized type could have neoplasm or inflammatory origin, the diffused one is often found in patients with CRSwNP (Fokkens et al., 2020).

The most common localization of nasal polyp is the middle meatus and ethmoidal region (Hellquist, 1996a).

The exact pathogenesis of CRSwNP is not fully investigated and elucidated. Mucosal chronic inflammatory reaction involves infiltration of eosinophils, local IgE production, and cytokine secretion. Type 2 inflammation is linked to the CRSwNP but this type of immune response is not exclusive for this condition. Atopic dermatitis, asthma and eosinophilic esophagitis (Hellquist, 1996a) are just a few examples of diseases with type 2 inflammation pattern (Mullol et al., 2022). Histologically the most frequent nasal polyp with 85-90% (Hellquist, 1996b) type is called "allergic" or edematous due to a big concertation of eosinophils and mast cells in the stroma (Hellquist, 1996a).

4. Risk Factors

The most studied risk factors of CRSwNP are asthma, nonsteroidal anti-inflammatory drug–exacerbated respiratory disease (NSAID-ERD), cystic fibrosis, tobacco use and exposure to secondhand smoke, obesity, metabolic syndrome and contact with air pollutants. The association of CRS with asthma is significant. Around 25% patients suffering from CRS also are diagnosed with asthma when prevalence of asthma in general population reaches 5% (Fokkens et al., 2020). Patients with non-allergic asthma are found to have the prevalence of NP of 13% whereas with allergic asthma 5% (Settipane, 1996). Furthermore, 40% to 67% of patients with CRSwNP have asthma (Laidlaw et al., 2021). Inflammation pattern remains similar in asthma and CRSwNP. Eosinophils and T helper type 2 cells plays a major role in both diseases. Nonsteroidal anti-inflammatory drug–exacerbated respiratory disease, also known as aspirin-exacerbating respiratory disease (AERD) is a syndrome including asthma, chronic rhinosinusitis with nasal polyps and hypersensitivity to nonsteroidal anti-inflammatory drug (NSAIDs). This triad of symptoms is called as a Samter's triad. Nasal polyps occur in 5-10% patients with NSAID-ERD (Drake-Lee, 2004).

In children with CRwNP, cystic fibrosis should be suspected since 50% children with CF experience nasal polyposis in comparison to non-CF patients (Mainz & Koitschev, 2012).

Tabacco smoke and inhalation of air pollution can impair mucosal barrier of nasal cavity and sinuses causing oxidative stress and inflammation. The study by Montaño-Velázquez et al. (2017) showed that teenagers with perennial allergic rhinitis exposed to cigarette smoke showed higher eosinophils and eotaxin-1 count in nasal mucosa than children with no exposure (Montaño-Velázquez et al., 2017). Significant correlation between nasal polyps and dust exposure was pointed out in Portuguese publication that showed higher prevalence of CRSwNP in textile workers than in retail workers as a control group (Veloso-Teles et al., 2018).

Obesity and metabolic syndrome, associated with high triglyceride level, lowered HDL level, and elevated blood pressure, are a pro-inflammatory condition due to endocrine-active adipose tissue secreting inflammatory cytokines (Richard et al., 2000). CRS occurs more often in patients with metabolic sequelae than without (Lee et al., 2017).

5. Quality of life in patients with nasal polyps

Quality of life in patients with nasal polyps is impaired due to inconvenient symptoms such as facial pain, postnasal drainage, nasal congestion or anosmia. Hoehle et al. (2016) demonstrated that symptoms of chronic rhinosinusitis significantly impaired quality of life of patients with CRS. Ailments listed in the publication were divided into 4 categories – sleep quality, sinonasal symptoms, otologic and facial pain, and emotional function. Predominant and most troublesome symptom reported by patients was a "lack of good night's sleep" (Hoehle et al., 2016) .

The American publication showed that female patients with CRS had notable lower PSQI (Pittsburg Sleep Quality Index) scores compared to men. Moreover, smokers and patient diagnosed with depression received lower PSQI scores than nonsmokers and non-depressed participants. Curiously, severity of CRS assessed in imaging studies did not correlate with PSQI score (Alt et al., 2013).

Patients with chronic rhinosinusitis with nasal polyps often suffer from comorbidities that diminish their quality of life. Nasal polyps are associated with allergic rhinitis and asthma with 40-67% chance of having asthma in nasal polyposis (Laidlaw et al., 2021). When these 2 conditions coexist, symptoms of asthma and chronic rhinosinusitis deteriorate, and ESS is more often performed. Moreover, patients with comorbid

diseases have a higher prevalence of polyp regrowth after surgery and are more corticosteroid-dependent than with asthma alone (Mullol et al., 2022).

CRSwNS has an impact on psychological health. Patients are more prone to experience reduced concentration, frustration, sadness, depression, anxiety, phobia, hopelessness and embarrassment (Kim et al., 2020). Patients suffering anosmia, one of the main symptoms of CRSwNS, are more prone to suffer from depression, anxiety and phobias (Chung et al., 2015). In addition, long term treatments, recurrence of symptoms and repeated surgeries have detrimental effects on patients' life. Reoperation is needed even in 25-40% of patients with CRSwNS in 10 years duration (DeConde et al., 2017; Smith et al., 2019).

6. Treatment approach

6.1 Corticosteroids

First line therapy includes topical nasal corticosteroids such as fluticasone, mometasone, budesonide. It ameliorates patients' symptomatology in crs and crswnp (Rudmik et al., 2012). Moreover, it has a greater impact on reduction of the symptoms in crswnp than without. Nasal corticosteroids enhance quality of life and mitigate disease manifestation in patients with CRS (Fokkens et al., 2020). In addition, corticotheraphy reduces polyp size. Furthermore, patients who underwent sinus surgery had experienced significantly greater reduction of polyp size compared to placebo, moreover when nasal corticosteroids were applied after ESS the prevention of polyp regrowth was significantly better than placebo (Fokkens et al., 2020).

Corticosteroids such as prednisolone can be administered systemically in therapy of nasal polyps. Publications show that short term systemic corticotheraphy (1-3 weeks) can improve the quality of life by improvement of nasal airflow, smell and polyp size (Kirtsreesakul et al., 2012). Administered independently as well as with local corticosteroid have a significant impact on the reduction of symptoms. Systemic corticotheraphy should be no longer than 3 months due to the increasing risk of adverse effects and lack of increasing the treatment results after this time (Fokkens et al., 2020). Short term systemic corticotheraphy is associated with gastric problems and insomnia while long term adverse effects are more severe including weight gain, hyperglycemia, type 2 diabetes, cataract and hypertension (Rice et al., 2017).

Another form of administering corticosteroid is an eluting implant. Implant could be positioned in ethmoid sinus after ESS. It was proven that patients with steroid implant demonstrated greater alleviation of symptoms than in placebo group. In addition, requirement of sinus surgery was lowered in corticosteroid group by 61% (Kern et al., 2018). However, the safety of implantations remains uninvestigated and is a discussion in the otolaryngological community (Fokkens et al., 2020).

6.2 Anti-leukotrienes

Anti-leukotrienes were also a target for finding the new ways of treatment, nevertheless due to a low quality of evidence EPOS2020 steering group does not recommend Montelukast application nor independently nor with corticosteroids (Fokkens et al., 2020).

6.3 Decongestants

Oxymetazoline and xylometazoline as an example of decongestants cause airway clearing by decreasing the oedema. These vasoconstrictors are not recommended for a permanent therapy with nasal polyposis since they don't reduce polyp size. Long term usage can lead to rhinitis medicamentosa and rebound swelling. In case of severe nasal blockage, a short-term co-administration of a nasal decongestant and corticosteroid could be warranted (Fokkens et al., 2020).

6.4 Surgical treatment

When pharmacotherapy fails and does not provide satisfactory outcome, surgery is recommended (Fokkens et al., 2020).

CT scan without contrast is obligatory before every ESS to assess the size and location of polyps. Since the operators work on delicate structures like mucosa, which is highly vascularized and swollen from inflammation, corticosteroids are used. This drug is administered before, during and after the surgery to reduce bleeding. Surgical field is more apparent, therefore duration of the procedure decreases (Albu et al., 2010). Intranasal corticosteroid therapy is recommended by EPOS steering group in peri-operating time (Fokkens et al., 2020).

Early ESS is crucial for the results of the treatment. A patient who underwent ESS 12 months after CRSwNP diagnosis had significant superior outcomes of therapy and lower reoccurrence rate than patients with longer medical history (Benninger et al., 2015).

EES, since it's a minimally invasive procedure, is a gold standard in treating CRS.

This type of surgery lowers the symptoms and improves the quality of life in CRS (Hopkins et al., 2006). However, reoperation is needed in 4% of patients which 88% have CRSwNP (Miglani et al., 2018). Another study also showed that patients with nasal polyposis are more likely to have reoccurrence of the disease. Veloso-Teles Et al. (2018) reported that after 1 year of surgery 3,5% patients wih CRSwNP required revision ESS while only 1,6% in CRS group (Veloso-Teles et al., 2018).

It is essential to remember that ESS complications during operation, may occur. Most mentioned are epistaxis, injury of the lamina papyracea and periorbital ecchymosis (Fokkens et al., 2020).

6.5 Anti IgE

Omalizumab, an anti-IgE monoclonal antibody. This drug binds IgE and thus prevents mast cells, basophils and dendritic cells activation. Since the most frequent type of nasal polyp is infiltrated with eosinophils and there is a strong connection between nasal polyposis and asthma, omalizumab provides perspective for an effective therapeutic approach. While Pinto et. Al (2010) demonstrated no significant differences in alleviating symptoms between omalizumab and placebo group (Pinto et al., 2010). Gevaert et al. (2013) associated omalizumab therapy with improvement of the quality of life and decreasing of nasal polyp size (Gevaert et al., 2013). Mixed results of those insufficient number of studies makes it difficult to draw a conclusion and safely apply this treatment to the clinical practice.

7. Biological therapeutics

7.1 Dupilumab

Therapy with dupilumab was the first biological therapy approved in CRSwNP (Patel et al., 2020). Dupilumab is a humanized monoclonal antibody targeting IL-4Rα that prevents binding of interleukin 4 (IL4) and interleukin 13 (IL13). IL4 and IL13 share the same receptor component (Howard et al., 2002). IL4 pathway is responsible for type 2 inflammatory response since it induces differentiation of T helper type 2 cells (TH2) and production of IgE. Dupilumab downregulates inflammation in allergic disorders in example atopic dermatitis and asthma (Harb & Chatila, 2020). CRSwNP mostly presents type 2 inflammation pattern and is comorbid with asthma.

Bachert et al. (2019) demonstrated that dupilumab treatment significantly reduces symptoms, size of the polyps, reoccurrence after the surgery, shortens the course of steroid use and limits the need for surgery. Peak nasal inspiratory flow and improvement of nasal congestion was observed after 1-2 months following the start of the therapy. Moreover, patients with nasal polyps and asthma have improved lung function and asthma control. Patient well tolerated dupilumab and it had acceptable safety profile. Conclusion of this trial was "the results support the benefits of adding dupilumab to daily standard of care for patients with CRSwNP" (Bachert et al., 2019). Additionally, Lane et al. (2025) showed significant smell improvement in 24 weeks dupilumab therapy in patients with CRSwNP resulting in enhancement of quality of life (Lane et al., 2025).

7.2 Mepolizumab

Mepolizumab is an anti-IL-5 antibody which blocks the pathway of eosinophil activation. It is used in treatment for eosinophilic asthma and eosinophilic granulomatosis with polyangiitis. The most common nasal polyp type is infiltrated with eosinophils and is often comorbid with asthma. Chronic inflammation of nasal mucosa and polyp formation id driven cytokines released by eosinophil. By inhibiting eosinophils' activation local inflammation is reduced.

In a new study from 2023 in a placebo-controlled clinical study - Phase III SYNAPSE (Desrosiers et al., 2024) 100 mg of mepolizumab or placebo was administered subcutaneously (SC) every 4 weeks for 52 weeks in patients with nasal polyps and the outcome of the therapy was compared to the placebo treatment. The aim of the study was to assess the durability of mepolizumab treatment after cessation, therefore a 24-week follow-up was made. At 52- and 76-week mepolizumab group patients had significant smaller polyps, and probability of surgery (week 52: 23% mepolizumab group vs 50% in placebo control; week 76: 30% vs 50% respectively). Although greater improvement of quality of life and reduction overall of sinonasal symptoms was observed in mepolizumab group in comparison to placebo control, the follow up examinations showed that these improvements did not remain on the same level after treatment cessation (Desrosiers et al., 2024).

A MERIT trial showed a positive befit -risk profile for mepolizumab in patients with CRSwNP from Japan, China and Russia (Fujieda et al., 2024).

8. Conclusions

CRSwNP is a burdensome disease with symptoms including hyposmia, nasal congestion and lowered quality of life. While well-known forms of therapy like steroid therapy and endoscopic sinus surgery are a gold standard for the treatment, it frequently does not provide long term alleviation of the symptoms. Reoccurrence of nasal polyposis and symptoms are common in patients undergoing operation and steroid therapy therefore new treatment approaches have been studied. New biological therapy showed significant improvement of symptoms and lower reoccurrence rate of the disease in comparison to the gold standard treatment. Biological therapy explicitly targets type 2 inflammation pattern. In addition, biologic therapy mitigates symptoms of comorbid diseases such as asthma.

It is considered safe, moreover it is less invasive than surgery. Dupilumab and mepolizumab should be considered in CRSwNP patients because it could improve patients' lives and provide long-term efficacy.

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