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Pharmacological Management of Nasal Polyposis

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Abstract

Nasal polyposis affects nearly 4% of the total population in Western countries, and presents a real challenge to the physician because of its severity, chronicity and recurrence rate. Characteristic histomorphological features of polyps are an eosinophilic inflammation and the destruction of connective tissue; recent research has focused on cytokines, chemokines, growth factors and metalloproteinases to explain these features, as the aetiology of nasal polyposis remains largely unclear. Currently, topical and systemic corticosteroids are first-choice drug therapy approaches, and good evidence from controlled trials is available for topical, but not for systemic, corticosteroid therapy. Surgery is indicated if adequate drug treatment fails, which often needs to be maintained after surgery. There is limited experience for other drugs, such as antihistamines, leukotriene antagonists and frusemide (furosemide), which may be added to corticosteroid therapy in selected patients. Aspirin (acetylsalicylic acid) desensitisation may be a therapeutic option for patients who do not respond to corticosteroids or surgery. Recently, antibiotics such as macrolides have been suggested to have therapeutic activity based on their anti-inflammatory properties but large-scale controlled trials are lacking. New approaches are currently evolving, specifically targeting

eosinophilic recruitment (chemokine receptor 3, eotaxin) and inflammation (interleukin-4, -5, -13), immunoglobulin-E, or tissue remodeling by reducing the activity of metalloproteinases.

This review summarises current knowledge on pathogenesis as well as established and future approaches in the pharmacological management of bilateral eosinophilic nasal polyposis.

Nasal polyps represent oedematous semi-translucent masses in the nasal and paranasal cavities, mostly originating from the mucosal linings of the middle nasal meatus, the middle turbinate and the sinuses, and prolapsing into the nasal cavities.[1] They cause long-term symptoms such as prominent nasal obstruction, post-nasal drip, loss of smell and a feeling of a 'full head', and may have a severe impact on the quality of life of the patient. Furthermore, in the case of secondary sinus infection, patients experience headache and facial pain, and may develop severe bony, orbital or cerebral complications. Bilateral nasal polyps are often linked to comorbidities such as asthma and aspirin (acetylsalicylic acid) sensitivity, or may represent part of an inherited systemic disease such as cystic fibrosis.

The prevalence of nasal polyps in the general population is considered to be low. A postal questionnaire survey of a population-based random sample of 4300 adult women and men aged 18–65 years recently performed in Finland[2] demonstrated a prevalence of nasal polyposis of 4.3%. However, this figure may be an underestimation, as a significantly higher prevalence has been reported in autopsy studies.[3] The incidence is higher in men than in women and significantly increases after the age of 40 years. However, nasal polyps occur more frequently in subgroups of patients with asthma and aspirin sensitivity.[4] About 40–80% of patients with aspirin sensitivity have polyposis[5,6] and about 15% of patients with polyps are hypersensitive to aspirin. In studies involving large series of patients with nasal polyposis, asthma was found in 20–70%,[5,7] and non-allergic asthma was significantly more frequently linked to polyps than was allergic asthma.

A hallmark of bilateral nasal polyposis in adults, on which this review focuses, is the abundant number of eosinophils within the tissue,[8] which can be found in about 70–90% of patients in Western countries. Consequently, oral and topical corticosteroids represent the major treatment strategies, followed by surgical interventions; however, recurrences are frequent regardless of treatment, especially in a subgroup of patients with systemic disease manifestations, making a combination of repeated surgical interventions and a long-term drug treatment necessary. Furthermore, surgical interventions may lead to unsatisfactory healing and may cause complications secondary to scar formation, and oral corticosteroid therapy has its limitations because of systemic adverse effects. Thus, new therapeutic approaches are clearly needed.

Recently, an increasing body of knowledge on the role of cytokines, chemokines and adhesion receptors has emerged from studies in different models of eosinophilic airway inflammation and in nasal polyposis.[9] Furthermore, very recent findings point to bacterial or fungal organisms involved in the initiation or modification of the disease.[10-13] Another new aspect being studied is remodelling, involving the system of metalloproteinases and transforming growth factor (TGF)-β.[14,15] This review summarises established and new approaches to the pathophysiology and pharmacological management of bilateral eosinophilic nasal polyposis.

1. Histomorphology and Pathomechanisms

Mature nasal polyps are characterised mainly by their oedematous nature, appearing as central 'empty' pseudocyst formations and a subepithelial accumulation of inflammatory cells, amongst which EG2+ (activated) eosinophils are a prominent feature in about 80%.[16] Albumin and other plasma

proteins are deposited within the pseudocysts, adjacent to the eosinophilic infiltration. Histomorphological characterisation of polyp tissue reveals frequent epithelial damage, a thickened basement membrane and oedematous to sometimes fibrotic stromal tissue, with a reduced number of vessels and glands, but virtually no neural structure.[17] In small polyps, not larger than 5mm, growing on normal mucosa of the middle turbinate in patients with bilateral polyposis, numerous subepithelial EG2+ eosinophils were present in the luminal compartment of the early stage polyp, forming a cap over the central pseudocyst area.[16] These observations suggest a central deposition of plasma proteins, regulated by the subepithelial, mainly eosinophilic, inflammation as a principle of the pathogenesis of polyp formation and growth.

Subsequently, a large body of studies have focused on the recruitment and survival of eosinophils in nasal polyp tissue, and the cytokines and chemokines mediating these processes. There is evidence that interleukin (IL)-5 plays a major role in the recruitment, activation and inhibition of apoptosis of eosinophils,[18] but other related cytokines may also contribute to a network of factors.[19-23] IL-5, a key cytokine for the maturation and activation of mature eosinophils, was found to be significantly increased in nasal polyps, compared with healthy controls and in patients with other forms of rhinosinusitis, independent of the atopic status of the patient.[1,18,24] Among eosinophil-related cytokines, IL-5 correlates best with eosinophil cationic protein (ECP), indicating its close relationship with the degree of eosinophilic inflammation. High levels of IL-5 were found in patients with non-allergic asthma and aspirin sensitivity (conditions that are linked to severe tissue eosinophilia), and eosinophils themselves could possibly contribute to IL-5 release, as documented by immunohistochemistry. The key role of IL-5 was supported by the finding that treatment of eosinophil-infiltrated polyp tissue with neutralising anti-IL-5 monoclonal antibody (mAb), but not anti-IL-3 or anti-granulocyte-macrophage colony-stimulating factor (GM-CSF) mAbs *in vitro*, resulted in eosinophil apoptosis and decreased tissue eosinophilia *in vitro*.[25]

IL-5 transduces a signal to the nucleus of the target cell via the IL-5 receptor (IL-5R) expressed on eosinophils and basophils, which shares a common β-chain with IL-3 and GM-CSF receptors. Regulated alternative splicing of the IL-5Rα subunit leads to the generation of a signalling, membrane-anchored isoform or a secreted, antagonistic variant. Secreted receptor (SOL) and membrane-anchored receptor (TM) IL-5Rα messenger RNA (mRNA) and protein expression are significantly increased in nasal polyps versus control tissues (inferior turbinates).[26] In polyp tissue, SOL IL-5Rα expression correlates with disease severity and eosinophil percentages, whereas TM IL-5Rα levels inversely correlate with eosinophils and SOL IL-5Rα expression (unpublished data). This demonstrates a differential expression of SOL and TM IL-5Rα in eosinophilic inflammation, which may be decisive for approaches to target IL-5 or its receptor. As TM IL-5Rα is downregulated and SOL IL-5Rα (antagonistic?) is upregulated in polyp tissue, but eosinophils still show prolonged survival, strategies to antagonise IL-5 have faced unexpected difficulties.

TGF-β_1, a cytokine with IL-5 counteracting activities, is only produced in low quantities and is bound to the extracellular matrix in its latent, inactive form.[16] TGF-β_1 is a potent fibrogenic cytokine that stimulates extracellular matrix formation, thus, it is involved in fibrosis and acts as a chemoattractant for fibroblasts, but inhibits the synthesis of IL-5 and abrogates the survival-prolonging effect of haematopoietins (IL-5 and GM-CSF) on eosinophils.[27] The expression of TGF-β_1 was recently analysed in nasal tissue from controls and from patients with chronic rhinosinusitis or polyps.[28] Tissue from patients with chronic rhinosinusitis exhibited significantly higher concentrations of TGF-β_1 at protein and mRNA level than polyp tissue, and TGFβ_1-positive staining of the ECM was abundant and related to fibrosis. In contrast, no TGF-β_1 staining was found in the pseudocyst areas in polyp tissue, which also showed a lower expression of TGF-β_1 compared with tissue from chronic rhinosi-

nusitis. Thus, the overproduction of IL-5 and the lack of TGF-β_1 would favour eosinophil survival and facilitate degradation of tissue matrix – both characteristics of polyp formation.

The eosinophilic inflammation in polyps is orchestrated by T cells, which have been characterised as activated.[29] They represent a mixed population, consisting of CD4+ and CD8+ cells, and show a mixed T-helper (T_h)1/T_h2 profile. However, inflammatory cells such as eosinophils, macrophages or mast cells may also contribute to the release of cytokines, as was especially shown for eosinophils, contributing IL-4 and IL-5 in an autocrine manner.[18,30]

Recent studies have shown that nasal polyps also express high levels of RANTES (regulated upon activation normal T cells expressed and secreted) and eotaxin, the predominantly recognised eosinophil chemoattractants.[31,32] According to our data, it appears that eotaxin, rather than RANTES, in cooperation with IL-5, plays a key role in chemoattraction and activation of eosinophils in polyp tissue.[16] However, RANTES may be involved in the localisation of the eosinophils near the epithelium. Both chemokines act on eosinophils via a common receptor, CCR3, and could thus be targeted in parallel.

Early studies by Symon and colleagues[33] demonstrated that intercellular adhesion molecule (ICAM)-1, E-selectin and P-selectin were expressed by nasal polyp endothelium, and contribute to eosinophil recruitment. However, Jahnsen et al.,[32] employing three-colour immunofluorescence staining, have demonstrated that both the number of eosinophils and the proportion of vessels positive for vascular cell adhesion molecule (VCAM)-1 were significantly increased in nasal polyps compared with the turbinate mucosa of the same patients. Moreover, treatment with topical corticosteroids decreases the density of eosinophils and the expression of VCAM-1 in polyps.[34] The ligand of VCAM-1 on the peripheral blood eosinophil is very late antigen (VLA)-4 and both adhesion molecules could serve as therapeutic targets. The interaction between VLA-4 on eosinophils and VCAM-1 on endothelial cells may not only be of particular importance for the transendothelial migration of eosinophils, but also may modify their activation and effector functions

So far, the initial trigger causing the eosinophilic inflammation in nasal polyps is not known. Different hypotheses have been suggested, including allergy, and bacterial, fungal, mycoplasma or viral infections,[17] but none has been confirmed. Recently, a potential role for fungi was proposed in chronic rhinosinusitis with or without polyps.[12,13] However, fungi can be detected in diseased and control tissue,[35] without differences between groups. Thus, it remains unclear whether fungi play a role in disease and, if so, whether this is a primary cause or a secondary phenomenon. Furthermore, no placebo-controlled treatment studies have been performed as proof of concept yet and no profound pathophysiological explanation has been provided so far. Recently, we proposed a model in which bacterial colonisation could at least modify disease severity. We investigated nasal tissue from patients with bilateral nasal polyps, which are characterised by a severe eosinophilic inflammation and often coexist with asthma, for a possible impact of *Staphylococcus aureus* enterotoxins.[10,11] We demonstrated increased levels of total IgE and *S. aureus* enterotoxin-specific IgE antibodies as well as a polyclonal IgE response – including IgE antibodies to fungal allergens – related to the severity of the eosinophilic inflammation in nasal polyps, suggesting that these enterotoxins may act as superantigens in polyp tissue. Coagulase-positive *S. aureus* is one of the most common bacteria in nasal airways – up to 25% of the population are permanent carriers of *S. aureus* in the vestibulum nasi, and about 70% of these strains would be able to produce enterotoxins under appropriate conditions – and bacterial triggering by classical enterotoxins, *S. aureus* enterotoxin (SAE)-A to SAE-E or toxic shock syndrome toxin-1 (TSST-1), may represent a disease-modifying mechanism leading to chronic sinonasal inflammation and, in particular, to nasal polyp formation in individuals colonised with enterotoxin-producing bacteria. Studies in mice have shown that enterotoxins trigger

airway recruitment of inflammatory cell types (including T cells, eosinophils, neutrophils and macrophages) and the release of cytokines (including IL-5, IL-4 and tumour necrosis factor [TNF]-α), which are associated with increased airway responsiveness in these animals. Moreover, more recent findings have suggested that staphylococcal superantigens may lead to poor disease control, as they can induce corticosteroid insensitivity in peripheral blood mononuclear cells. These findings suggest that eradication of *S. aureus* colonisation in the nose may provide an effective means for the management of polyps at least in a subgroup of patients.

Further understanding of remodelling has recently evolved from the investigation of metalloproteinases, which are able to degrade extracellular matrix proteins.[15,36] Concentrations of matrix metalloproteinase (MMP)-9 and MMP-7 protein were found to be significantly increased in polyps compared with control tissue, whereas their natural antagonist tissue inhibitor of metalloproteinase (TIMP)-1 was not. Furthermore, MMP-9-positive inflammatory cells could be detected in increased numbers in the pseudocyst formations, indicating that these metalloproteinases are probably involved in the tissue degradation. Thus, antagonising MMPs could also form a new therapeutic target.

2. Classical Treatment Approaches

The management of nasal polyps has so far involved drug treatment approaches – mainly based on the use of topical or systemic corticosteroids – and surgical procedures, from the extraction of polyps within the nasal lumen to radical sphenoethmoidectomy, trying to eradicate all polyp tissue. However, as nasal polyposis is a chronic disease with a high rate of recurrences in about one-third of the patients, surgical over-treatment and its sequelae should be avoided. In a 20-year follow-up study of 41 patients with nasal polyps, 85% of patients still had the disease, with anosmia present in 61%.[37] Eight patients, including seven with aspirin sensitivity, had undergone 11 or more surgical operations during the 20-year period. This study as well as others showing the high recurrence rate of nasal polyps clearly indicate the chronicity of the disease, especially in this subgroup of patients, and suggest a reserved surgical approach. Instead, a combined treatment strategy involving surgical and medical treatment approaches is recommended for long-term control of the disease.[38]

The primary goal of treatment is the relief of patient symptoms, the primary symptoms being nasal blockage, congestion, hyposmia or anosmia, and hypersecretion. Other symptoms include post-nasal drainage, facial pain, headache, sleep disturbance and diminished quality of life. Secondary goals of treatment include a decrease in the frequency of infections and disease recurrences, an improvement in associated lower airway symptoms, and the prevention of complications such as mucocoeles or orbital involvement.

2.1 Topical and Systemic Corticosteroids

As nasal polyposis represents an eosinophilic inflammation with consecutive tissue changes, topical and systemic corticosteroids are the first-choice treatment approaches. Systemic application affects all polyp tissue within the nose and sinuses, but has the disadvantage of systemic adverse effects, when used for long-term treatment. Topical application of corticosteroids significantly reduces adverse effects but does not impact polyps within the sinuses. In fact, the distribution of the drug within the nasal cavity, partially or completely obstructed by polyp tissue, already presents a notable problem to treatment success.

Lipophilic corticosteroids easily enter the cytoplasm of target cells, where they bind to a single glucocorticoid receptor, which is expressed in high density in airway mucosa.[39] After binding of the corticosteroid, the complex moves to the nuclear compartment, where corticosteroids pro-duce their effect on inflammatory cells by increasing or inhibiting gene transcription through processes known as transactivation and transrepression, respectively. Transactivation is mediated by binding of the hormone-activated glucocorticoid receptor to a DNA sequence called glucocorticoid response element.[40] For example, corticosteroids can stimulate the syn-

thesis of anti-inflammatory molecules such as IL-10 or IL-1Rα. Transrepression is mediated by inhibitory protein-protein interactions between the hormone-activated glucocorticoid receptor and transcription factors such as AP-1 and nuclear factor (NF)-κB.[41] By binding to these factors, corticosteroids block the transcription of cytokines, chemokines and enzymes.

Corticosteroids can suppress many phases of the inflammatory process,[42,43] which may explain their strong effect on inflammation. They inhibit the liberation of vasoactive mediators reducing vasodilatation, fluid extravasation and local deposition of mediators. Corticosteroids reduce the amplification of the inflammatory reaction by reducing recruitment of inflammatory cells, and also diminish fibroblast proliferation and synthesis of extracellular matrix proteins. However, the extent to which cells and cytokines are reduced differs. T cells are highly sensitive to treatment with corticosteroids, reducing the number of T cells dose-dependently, and the expression of mRNA and protein for IL-3, IL-4, IL-5 and IL-13 and their receptors.[44] The secretion of numerous other cytokines and chemokines is also reduced, among them IL-1β, IL-2, IL-4, IL-6, IL-8, TNFα, interferon (IFN)-γ, GM-CSF, RANTES and eotaxin.[45] This affects recruitment, localisation, activation, protein synthesis and survival of inflammatory cells such as eosinophils. The recruitment of inflammatory cells is also diminished by the inhibition of expression of adhesion molecules such as ICAM-1 and VCAM-1, which affects the influx of basophils and mast cells in the epithelial layers of the nasal mucosa. Corticosteroids may also reduce the release of preformed and newly generated mediators, such as histamine, prostanoids and leukotrienes. However, this action may be partly due to the reduction of the number inflammatory cells in the mucosa. It has been established that corticosteroids act as negative modulators of MMP-9 overexpression by alveolar macrophages in idiopathic pulmonary fibrosis.[46] Corticosteroids normalise the total cell influx, MMP-9 at protein and mRNA level, and the TIMP-1 production by alveolar macrophages. Finally, corticosteroids can also act on IgE production[47] and may affect plasma protein retention. However, macrophages and neutrophils do not seem to be influenced,[48] which might explain why topical corticosteroids do not have a negative effect on the immunity to bacterial infections.

Systemic oral corticosteroids are indicated to initiate or enforce conservative local treatment, mainly as a 2- to 3-week course with decreasing dosage, taken in the morning (i.e. methylprednisolone 32mg once daily, halved every 5 days until reaching 8mg). Such a regimen may be given up to four times a year, if no contraindications are present in the individual patient. So far, to our knowledge, not a single placebo-controlled, randomised trial with oral corticosteroids in patients with nasal polyps has been published. However, oral corticosteroid treatment has been investigated in an uncontrolled study, showing a significant effect for some months with an improvement of symptoms in 72% of the patients, and a reduction of polyp size and sinus opacification in the CT scan in 52%.[49] In those individuals responding, recurrences happened mostly within 5 months. Thus, oral corticosteroids may be indicated to delay surgery or to facilitate surgery. However, there is no evidence so far that the natural course of the disease may be influenced by short- or long-term low-dose treatment regimens.

Although clinically ill-defined, corticosteroid insensitivity of inflammatory cells may interfere with the efficacy of topical or systemic corticosteroids. Different mechanisms have been proposed to significantly inhibit glucocorticoid signalling, including downregulation of the α-receptor, the inhibition by the β-isoform of the receptor, and repression by transcription factor NF-κB.[50] Of interest, stimulation of normal peripheral blood mononuclear cells (PBMCs) with the *Staphylococcus* superantigen SEB can induce a significant increase of glucocorticoid receptor-β, which is paralleled by corticosteroid insensitivity compared with unstimulated cells.[14] The percentage of inflammatory cells expressing the β-isoform was found to be increased in nasal polyps, and expressed by T cells, eosinophils and macrophages.[51] An inverse correlation was observed between the baseline inflammatory cell

glucocorticoid receptor-β expression and the reduction after corticosteroid treatment in EG2-positive eosinophils, CD4+ T cells, endothelial VCAM-1 expression, and IL-4 mRNA+ cells.

The symptomatic efficacy of intranasal corticosteroids in patients with nasal polyps is well documented.[52,53] Symptoms such as nasal blockage, rhinorrhoea and occasionally hyposmia are reduced during the period of treatment, especially in obstructive polyposis.[54,55] The effects on nasal obstruction and polyp masses could also be documented by objective methods such as peak nasal inspiratory flow, rhinomanometry, rhinometry, MRI and smell tests.[56-58] However, recurrence of symptoms or polyp growth, monitored by symptoms, endoscopy or rhinomanometry, occurs within weeks to months.[59,60] After surgery, topical corticosteroids may also reduce the incidence of polyp recurrences or prolong the symptom-free time interval.[61,62] The dosage of the topical corticosteroids used in these studies is often higher than the dosage recommended for allergic rhinitis. However, topical corticosteroids may be insufficient in severe bilateral polyps,[63] and polyp growth may be observed despite treatment in these patients. Adverse effects with topical corticosteroids are rare, but may consist of dry nose, crusting and eventually mild bleeding. Because of long-term treatment with high dosages, modern drugs with low bioavailability are preferred.

In summary, the use of topical corticosteroids, administered on a daily basis for several months to years, is considered first-line therapy in patients with small to medium sized nasal polyps to reduce symptoms, and to avoid surgery and relapse. Topical treatment may be boosted with oral corticosteroids, for which controlled studies are clearly needed, or combined with other treatment approaches. However, surgery needs to be considered in cases of failure, adverse effects or unwillingness of the patient to comply with drug treatment, as well as in patients with complications. Delivery of topical drugs may be improved by formulations other than spray, and the adverse effects of corticosteroids may be further reduced by different approaches to the glucocorticosteroid receptor. Furthermore, postoperative topical corticosteroid treatment also seems to improve wound healing; controlled studies of wound healing after sinus surgery are desirable.

2.2 Antimicrobials

The nasal cavity is normally colonised with non-pathogenic bacteria: cultures are positive in about 80% of healthy individuals, with corynebacteria, coagulase-negative staphylococci, propionibacteria and peptostreptococci representing the main commensal organisms.[64] Microbiological studies of 265 adult patients with chronic rhinosinusitis demonstrated the presence of Gram-negative bacilli, coagulase-negative staphylococci and *S. aureus* as the most common micro-organisms in the paranasal sinuses, compared with a healthy control population.[65] In patients with nasal polyp disease, we recently showed that coagulase-positive *S. aureus* are the most frequent bacteria and can be found in the middle meatus in nearly 70% of patients (unpublished data), with the potential to produce enterotoxins in about 70%. Antibacterials are indicated for superimposed bacterial infection and their potential benefit in bilateral polyps has been discussed by Bachert and Van Cauwenberge.[1] It was recently suggested that macrolide antibiotics not only decrease the virulence of colonising bacteria but also to possess anti-inflammatory activities, leading to a significant reduction of polyp size paralleled by a decrease in local IL-8.[66,67]

Other effects of macrolides include inhibition of fibroblast proliferation[68] and downregulation of expression of human leukocyte antigen (HLA)-DR and co-stimulatory molecules on antigen-presenting cells in nasal polyps.[69] In a clinical study, an improvement in 52% of 20 patients with nasal polyps associated with chronic rhinosinusitis was observed with roxithromycin 150 mg/day administered for at least 8 weeks. The combination of roxithromycin with azelastine (1mg twice a day), an antihistamine also inhibiting the release of leukotrienes, was examined in another 20 patients with polyps, with an improvement seen in 68%.[70] However, in a placebo-controlled study to determine the effects of clarithromycin (500mg twice daily for 6 weeks) in

patients with asthma, sinus CT scan revealed no relevant changes related to the treatment.[71] Large-scale placebo-controlled studies with macrolides in nasal polyps are clearly needed before final conclusions on the role of macrolides in the management of this disease can be drawn. Low-dose, long-term treatment with macrolides may also induce bacterial resistance, which may limit this approach.

However, the recent finding of a possible role of *S. aureus* enterotoxins in the aetiology/pathomechanism of nasal polyps calls for a placebo-controlled study to eventually confirm the long-term use of antibacterials effective for this pathogen.[10,11] A multicentre trial is currently ongoing.

2.3 Antihistamines

Antihistamines may be indicated in patients with nasal polyposis and allergic rhinitis, however, their use in patients with only polyps has not been extensively studied. Furthermore, even patients with ragweed positive skin tests did not show enhanced symptoms or an increase in markers of eosinophilic inflammation (eosinophil percentage or eosinophil cationic protein concentrations in nasal secretions) due to seasonal exposure.[72] Thus, the role of allergic immune reactions in nasal polyposis remains unclear.

However, several antihistamines have been shown *in vitro* to significantly inhibit, in a dose-dependent manner, the release of leukotriene (LT) C4/D4, LTB4, prostaglandin (PG)D2, TNFα and GM-CSF in enzymatically dispersed cells obtained from nasal polyps.[73-76] Histamine, which may be released from mast cells in polyp tissue, significantly increased the number of epithelial cells expressing ICAM-1 and HLA-DR, and this effect was blocked by antihistamines.[77] Thus, at least theoretically, there is a pathophysiological basis for antihistamine therapy.

In a clinical study of 45 patients with residual or recurrent nasal polyposis after ethmoidectomy, treatment with either cetirizine at twice the daily recommended dose (20mg) or placebo for 3 months was investigated.[78] Although the number and size of polyps remained unchanged during the study period, the active treatment reduced sneezing and rhinorrhoea effectively, and also had a late effect on nasal obstruction.

2.4 Leukotriene Antagonists

Changes in the arachidonic acid metabolism have been suggested to be involved in the pathogenesis of nasal polyposis, especially in aspirin-sensitive individuals, and cys-LTs have been found in increased levels in nasal tissue from those patients,[79] whereas concentrations of PGE2 were decreased.[80] Furthermore, the LTC4 synthase was found to be upregulated in nasal polyps,[81] as well as the number of leucocytes expressing the CysLT1 receptor as compared with their non-aspirin-sensitive counterparts.[82] Thus, the use of leukotrienes antagonists, especially in aspirin-sensitive nasal polyp patients, seems appropriate.[83] However, large-scale controlled trials in clearly characterised patients – with or without aspirin sensitivity – are lacking so far.

Parnes and Chuma[84] treated 40 patients diagnosed with sinonasal polyposis and rhinosinusitis with either zileuton or zafirlukast in addition to the classical treatment. Outcome measures included subjective interviews and questionnaire responses, as well as office endoscopic examinations and chart reviews. Overall, 26 patients experienced subjective improvement of symptoms after starting the medication, and four patients discontinued the medication because of adverse effects. In a retrospective clinical trial including 15 patients with aspirin sensitivity, symptom scores indicated an improvement in nine patients with leukotriene antagonists; three other patients reported some overall benefit from therapy, despite no improvement in their symptom scores. Endoscopic nasal examination findings were consistent with the reports of overall benefit.[85] In another non-randomised clinical trial including a control group receiving topical corticosteroid and antihistamine treatment, 40 patients with aspirin sensitivity and nasal polyps were recruited after surgery and treated with montelukast, a LTD4 receptor antagonist, 10 mg/day for 6 months.[86] The montelukast recipients reported a reduction in the use of corticosteroids and bronchodilator inhalants during the

course of the study compared with the control group. However, both groups showed analogous results, with total absence of local recurrence, good nasal patency and lack of nasal symptoms, possibly due to an observation period of insufficient length.

Finally, montelukast was studied as an add-on therapy to topical and inhaled corticosteroids in patients with or without aspirin sensitivity, both with nasal polyposis and asthma.[87] In this study, aspirin sensitivity was assessed by history together with intranasal lysine aspirin challenge; objective methods such as nasal endoscopy, acoustic rhinometry and nasal inspiratory peak flow were used. Asthma was monitored using symptom scores and peak expiratory flow measurements. Upper and lower airway nitric oxide measurements were made before and during treatment. Clinical subjective improvement in nasal polyposis occurred in 64% tolerant and 50% of sensitive patients, and asthma improvement in 87% and 61%, respectively. However, acoustic rhinometry, nasal inspiratory peak flow and nitric oxide levels did not change significantly in any group, and improvement on montelukast therapy was not associated with aspirin sensitivity. The findings are consistent with a subgroup of nasal polyps/asthma patients in whom leukotriene receptor antagonists may be effective, however, unrelated to aspirin sensitivity. Again, this study was not placebo-controlled.

2.5 Aspirin Desensitisation

In aspirin-sensitive patients with polyps, conservative treatment possibilities consist of: (i) avoidance of aspirin and other NSAIDs, which does prevent exacerbations but does not prevent progression of disease; (ii) oral and/or topical corticosteroids, as specified in section 2.1; (iii) eventually leukotriene receptor antagonists or synthesis inhibitors; and (iv) in selected patients, aspirin desensitisation. To prevent exacerbations, the ingestion of aspirin and cyclo-oxygenase (COX)-inhibiting NSAIDs has to be avoided, while paracetamol (acetaminophen), nimesulide (dose-dependently) and selective COX-2 inhibitors (celecoxib, rofecoxib) may be tolerated.[6] Aspirin desensitisation consists of administering incremental oral doses, to reach a maintenance dose of >650mg daily, inducing a refractory period of a few days. Continuous treatment over years may lead to a significant reduction in numbers of sinus infections per year, hospitalisations for treatment of asthma per year, improvement in olfaction and reduction in use of systemic corticosteroids.[88] Furthermore, numbers of sinus operations per year were significantly reduced in one study.[88]

As a rather high dosage of aspirin has to be ingested every day, gastrointestinal adverse effects and hives are frequent, and relapses occur with noncompliance.[89] In one study, however, smaller dosages of aspirin were also successfully used.[90] Furthermore, aspirin desensitisation does not seem to change the long-term course of the disease. Treatment with daily aspirin may be a therapeutic option for patients who do not respond to topical and systemic corticosteroids.

2.6 Frusemide (Furosemide)

Frusemide, an inhibitor of the sodium chloride co-transporter channel at the basolateral surface of the respiratory epithelial cell, has also been shown to reduce arachidonic acid-stimulated production of prostaglandins in human epithelial cell cultures from nasal polyps *in vitro*.[91] These mechanisms make nasal frusemide a candidate for treatment of oedema formation in nasal polyps.

In one trial, patients with polyps were either treated with topical frusemide or did not receive treatment after surgery. Six years after surgery, more patients in the control group demonstrated recurrence of disease.[92] The same authors also performed a prospective controlled study of frusemide versus topical corticosteroids versus no treatment, and found more severe relapses after surgery in the no-treatment group compared with active treatments.[93] However, no data are available in patients without prior surgery.

3. Possible Future Treatment Modalities

Consistent with the current knowledge on the pathophysiology of nasal polyposis, new therapeutic approaches could focus on eosinophilic inflamma-

tion, eosinophil recruitment, the T cell as the orchestrating cell and IgE antibodies, as well as on tissue destruction and remodelling processes. In particular, the introduction of humanised antibodies has created new possibilities; however, tissue distribution, the concept of a single 'key mediator' to approach and natural antagonistic systems in place could make these approaches hazardous. Thus, small molecule approaches circumventing these hazards could offer solutions, if they demonstrate more effectiveness and better tolerability than corticosteroids.

3.1 Interleukin (IL)-5 Antagonists

IL-5 is an eosinophil differentiation factor, which increases the sensitivity of eosinophils towards other stimuli and delays their cell death. High-affinity IL-5 receptors are exclusively expressed by eosinophils and basophils, but no other human cells. Therefore, neutralisation of IL-5 appeared to be an obvious approach for treating eosinophilic disorders, since no major side effects, due to effects on other cells, are expected.[94] Anti-IL-5 mAb strongly reduced both bronchoalveolar lavage (BAL) and bone marrow eosinophilia in ovalbumin-sensitised and exposed Balb/c mice.[95] In contrast, anti-IL-3 mAb and anti-GM-CSF mAb alone had little and no inhibitory effect on these responses, respectively. Results from animal experiments suggested that anti-IL-5 mAb may have anti-asthmatic activities,[96] and similar effects could also be expected in human eosinophilic diseases. As IL-5 was increased in polyp tissue and related to eosinophilic inflammation,[18] and anti-IL-5 mAb treatment *in vitro* induced eosinophil apoptosis,[25] this cytokine was a reasonable target for antibody therapy in nasal polyps. Different humanised anti-IL-5 mAb have been developed and studied in asthma, and a pilot study in nasal polyposis is currently being evaluated.

However, major concern developed in recent years about the efficacy of such a treatment. Given the key role of IL-5 in eosinophil function, we investigated SOL IL-5Rα expression pattern in nasal polyposis.[26] Analysis of nasal tissue samples revealed that SOL IL-5Rα protein concentrations were significantly increased in polyp versus control tissue. Furthermore, we recently also demonstrated the downregulation of the TM IL-5 receptor in polyp tissue in severe eosinophilic inflammation (unpublished data). As SOL IL-5Rα expression is increased, demonstrating antagonistic properties *in vitro*, and TM IL-5 receptor expression is decreased, these studies shed new light on the mechanisms of specific immunomodulatory therapies, such as anti-IL-5 mAb. Similar findings were described following airway antigen challenge, with a striking reduction in TM IL-5Rα on airway eosinophils compared with circulating cells, and an elevation of SOL IL-5Rα concentrations in BAL fluid.[97] Studies examining the cross-regulation and functional consequences of modulation of eosinophil cytokine receptor expression by IL-3, IL-5 and GM-CSF suggest a dynamic and differential regulation of eosinophil receptors for these cytokines.[98] Incubation of eosinophils with IL-3, IL-5 or GM-CSF led to reduced expression of TM IL-5Rα, possibly making tissue eosinophils relatively insensitive to anti-IL-5 mAb treatment.

Nevertheless, eosinophils in the bone marrow and peripheral blood seem to respond greatly to anti-IL-5 mAb treatment. Mepolizumab decreased mature eosinophil numbers in the bone marrow and numbers of eosinophil myelocytes and metamyelocytes in the blood of asthmatic patients treated with this monoclonal antibody.[99] However, mepolizumab had no effect on numbers of blood or bone marrow CD34+/IL-5Rα+ cells, or eosinophil/basophil colony-forming units. There was a significant decrease in bronchial mucosal CD34+/IL-5Rα mRNA+ cell numbers in the mepolizumab treated group. These data suggest that anti-IL-5 mAb therapy might induce partial maturational arrest of the eosinophil lineage in the bone marrow and only long-term treatment would sufficiently suppress eosinophil numbers in the tissue to possibly achieve clinical efficacy. Data on anti-IL-5 mAb treatment in human and animal models are so far confounded by the failure of this approach to completely resolve tissue eosinophilia and the belief that IL-5 alone is the critical molecular switch for eosinophil develop-

ment and migration.[100] However, small molecule approaches to inhibit IL-5 synthesis or action may overcome some of these problems.

3.2 Chemokine Receptor 3 and Eotaxin Antagonists

Chemokine receptor 3 (CCR3)-stimulating chemokines are likely to have important *in vivo* roles in the regulation of eosinophil, basophil, and potentially T_h2 and mast cell recruitment. Several CCR chemokines including eotaxin (CCL-11), eotaxin-2 (CCL-24), RANTES (CCL-5), and monocyte chemotactic protein-3 (MCP-3, CCL-7) and -4 (MCP-4, CCL-13) are potent eosinophil chemotactic and activating peptides acting through CCR3. CCR3 binds to at least seven different CCR chemokines required for tissue eosinophilia in atopic dermatitis and asthma.[101,102] As eosinophils have also been implicated in the pathogenesis of nasal polyposis, and RANTES and eotaxin have been identified as eosinophil chemoattractants in polyp tissue,[16,30,31] antagonism of CCR3 could have a therapeutic role in this disease. This receptor is also expressed by airway epithelial cells and recent studies suggest that CCR3 ligands may influence epithelial cell functions.[103]

Using an *in vitro* migration system mimicking the airway mucosa, pretreatment of eosinophils with anti-CCR3 antibodies as shown to inhibit their transmigration.[104] Furthermore, these antibodies inhibited the expression of eotaxin mRNA by cultured human bronchial epithelial cells.[105] Recently, the anti-eotaxin mAb bertilimumab (CAT-213) was administered intranasally to grass pollen-sensitive individuals. After nasal challenge, pretreatment with bertilimumab reduced nasal obstruction, eosinophil influx and mast cells compared with placebo pretreatment.[106] The development of small non-peptide molecule CCR3 antagonists[107] currently offers advantages over anti-chemokine (i.e. eotaxin) antibodies in terms of a broader approach, affecting several chemokines and effector cells, and a favourable pharmacokinetic profile, targeting the receptors on peripheral blood cell surfaces and being independent from tissue penetration. Studies in nasal polyps have not been reported yet.

3.3 IL-4 and IL-13 Antagonists

The closely related T_h2 cytokines, IL-4 and IL-13, share biological functions that are considered important in the development of airway inflammation, including induction of the IgE isotype switch, increased expression of VCAM-1, promotion of eosinophil transmigration across the endothelium, stimulation of mucus production and T_h2 cell differentiation, leading to release of IL-4, IL-5, IL-9, IL-13 and eotaxin. Furthermore, elevated levels of IL-4 at a site of injury could result in the development of fibrosis by enhancing fibroblast subset proliferation and collagen synthesis.[108] The overlap of their functions results from the IL-4Rα chain forming an important functional signalling component of both the IL-4 and IL-13 receptors. IL-4 and IL-13 mRNA+ cells have been described in polyps,[109] and the number of cells expressing IL-4 mRNA was shown to be increased compared with in healthy mucosa independent of the atopic status.[110] It can be expected that strategies to antagonise IL-4/IL-13 would also reduce inflammation in nasal polyps, although no specific studies have been performed.

Early studies with inhaled recombinant human soluble IL-4R in adult asthmatics have shown promising results,[111] and further progress may be expected from combined IL-4/IL-13 antagonists, based on recent data from murine asthma models.[112,113]

3.4 IgE Antagonism

Considering the marked local production of IgE antibodies in nasal polyps and its relation to severity of disease,[10] it appears that local IgE is functional and involved in the regulation of chronic inflammation. Thus, strategies to antagonise IgE could be relevant. Treatment of allergic asthma and rhinitis with omalizumab, a humanised anti-IgE mAb, causes a marked reduction in circulating free IgE levels.[114-119] Treatment has been shown to reduce symptoms and exacerbations, and decrease the need

for other medication in patients with these allergic diseases. No studies in nasal polyposis have been performed to investigate whether high concentrations of IgE antibodies within the polyp tissue can be targeted with success.

3.5 Immunosuppression

The disease management of severe and corticosteroid-resistant eosinophilic airway inflammation remains a real challenge, including severe asthma and nasal polyposis. Ciclosporin (cyclosporin) has been a mainstay of immunosuppression therapy in organ transplantation for many years. While its application clearly is efficacious in the inhibition of T-cell proliferation and results in the decrease of inflammatory processes, the adverse effects associated with its long-term use manifested most prominently through nephrotoxicity have been a serious concern. Several new strategies are currently being pursued to address ciclosporin toxicity, leading to the development of novel ciclosporin analogues,[120] and other molecules that inhibit T cell proliferation and IL-5 production in PBMCs from asthmatic individuals at physiological concentrations.[121] A small but significant treatment effect for ciclosporin in terms of corticosteroid dose reduction has been shown in patients with stable asthma, but possible adverse effects have so far prevented routine use.[122] Ciclosporin significantly inhibited the release of histamine, LTC4/D4, and thromboxane B_2 in a concentration-dependent manner in enzymatically dispersed cells from nasal polyps.[123] Clinical studies with immunosuppressive agents are lacking in nasal polyposis.

3.6 Matrix Metalloproteinase Inhibitors

A new target for possible intervention evolves from recent knowledge on tissue remodelling processes, focusing on matrix metalloproteinases, especially MMP-9.[36,124] Besides the natural tissue inhibitors of metalloproteinases, TIMP-1 and TIMP-2, synthetic broad spectrum inhibitors of MMPs and antibodies to MMP-9 and MMP-2 were developed. *In vitro*, anti-MMP-9 antibodies, TIMP-1, the synthetic MMP inhibitor batimastat (BB-94), and the protein kinase (PK) C inhibitor calphostin-C, all reduced MMP-9 activity.[125] However, none of these agents are being investigated further. Doxycycline and chemically modified tetracyclines not only inhibited MMP-9 (gelatinase B) activity, but also the synthesis of MMPs in human endothelial cells *in vitro*; however, they did not affect the MMP inhibitors TIMP-1 and TIMP-2.[126] Inhibition of MMPs by doxycycline has been studied in patients with abdominal aortic aneurysms, decreasing elevated serum concentrations at baseline gradually over a 6-month treatment period.[127] A placebo-controlled randomised study of doxycycline in nasal polyposis is currently in progress.

4. Conclusions

Nasal polyposis may present as a severe, chronic and disabling disease of the sinuses and nasal cavity, which frequently recurs after medical and surgical treatment. First-choice drug treatment comprises topical and systemic corticosteroids, with other compounds used in selected patients. During the last decade, added fascinating knowledge on the pathogenesis of nasal polyps offers new strategies, targeting both the inflammation and consecutive remodelling processes. Currently, studies are ongoing using specific approaches to downregulate the eosinophilic inflammation characteristic of nasal polyposis, as well as metalloproteinases involved in tissue destruction. Further approaches are to be expected, mostly based on the comparability of inflammatory processes seen in nasal polyposis and asthma.

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