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AERD Associated Nasal Polyposis: Efficacy of Postoperative Antileukotriene Therapy in Comparison with Aspirin Desensitization. A Retrospective Study

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Keywords
Aspirin-exacerbated respiratory disease · Nasal polyposis · Asthma · Antileukotriene therapy · Aspirin desensitization

Abstract
Introduction: AERD (aspirin-exacerbated respiratory disease) is a severe form of an inflammatory disease of the upper airway system. Therapy remains challenging due to a complex underlying pathophysiology. ***Objective:*** To evaluate the efficacy of postoperative antileukotriene therapy concerning recurrence of nasal polyposis in patients with AERD and to compare it with AD (aspirin desensitization) over time. ***Methods:*** In this retrospective study we analyzed AERD patients ($N = 61$) after functional endoscopic sinus surgery (FESS). Patients were treated at our institution postoperatively with topical mometasone (control group, $N = 22$), leukotriene-receptor-antagonists (montelukast [MT], $N = 18$) or underwent an aspirin desensitization ($N = 21$). Subjective parameters as assessed by SNOT (sinonasal outcome test) questionnaire and endoscopic endonasal examination (polyposis grading) were evaluated throughout a follow-up period of 6–9 and >12 (long-term) months after surgery. ***Results:*** Endoscopic endonasal examinations 6–9 months after sinus surgery showed a good disease control in all 3 groups with significant reduction in polyp grading in the AD group. After a follow-up period of more than 12 months, MT and AD patients had significantly less polyp recurrences as compared to the topical treatment group. Subjective sinonasal symptoms revealed that hyposmia and nasal obstruction were prominent factors in all 3 groups throughout the follow-up period. MT group showed significant improvement in sinonasal symptoms over time. ***Conclusion:*** Postoperative treatment with leukotriene-receptor-antagonists and aspirin desensitization both significantly reduce nasal polyp recurrence. MT has a positive effect on subjective sinonasal outcomes and patients' quality of life over time.

Introduction

AERD, aspirin-exacerbated respiratory disease, is a severe form of an inflammatory disease of the upper airway system [1]. Patients suffer from asthma, refractory nasal polyposis and aspirin sensitivity. AERD is also known as

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"Samter" [2] or "Widal" triad [3] as well as aspirin triad. Nasal polyposis in AERD patients is aggressive, characterized by an early, recalcitrant recurrence after surgery. This leads to a high rate of functional endoscopic sinus surgeries (FESS) [4] and to a substantial negative impact on patient's quality of life (QoL). Thus, surgical management of nasal polyposis in AERD is, in accordance with the latest scientific understanding, just a temporary symptom relieving strategy. The underlying complex pathomechanism of chronic rhinosinusitis with nasal polyps (CRSwNP), and here in particular AERD, needs to be addressed systemically. This is based on the prerequisite of understanding the immunological and molecular processes of CRS, its endotypes and phenotypes [5].

Chronic rhinosinusitis with nasal polyps (CRSwNP) is generally characterized by a dominant eosinophilic, T_H2 dominated reaction [6–8]. This eosinophilic pro-inflammatory milieu leads to oedematous stroma with subepithelial and perivascular infiltration of inflammatory cells [5]. Beyond that, AERD patients seem to suffer from a dysbalance between pro- and anti-inflammatory mediators derived from arachidonic acid [9, 10]. By pharmacological inhibition of cyclooxygenase COX pathway, lipoxygenase pathway increases and results in an increase of proinflammatory cysteinyl-leukotrienes (CysLT) and decrease of anti-inflammatory and bronchoprotective prostaglandins (e.g., PGE2) [11]. PGE2 is an important inhibitor of 5-lipoxygenase which again leads to an uncontrolled synthesis of leukotrienes [12]. Furthermore, the reduced PGE2-synthesis causes a destabilization of mastcells, which release histamine and PGD2 (recruiting eosinophils and T_H2 cells) [13]. Overall, the excessive increase in leukotrienes together with a decrease of anti-inflammatory prostaglandins leads to the typical symptoms of severe broncho- and vasoconstriction after COX-1 inhibition by aspirin ingestion [14]. Thus, the strict avoidance of trigger substances is mandatory.

Main therapeutic strategies for nasal polyposis in AERD patients besides surgery are topical and/or systemic corticosteroids, aspirin desensitization and antileukotriene therapies [7]. Medication with topical and/or systemic corticosteroids is essential in CRSwNP and AERD, but in most cases not sufficient for control of polyp regrowth in AERD. If eligible, aspirin desensitization (AD) should be discussed with AERD patients. The repeated daily intake of aspirin is aimed to induce a tolerance level and thus a downregulation of the arachidonic acid imbalance. As shown before, AD is proven to be an effective treatment option [15–17] in AERD. However, some patients are not eligible for a repeated ingestion of aspirin: Patients with a history of gastritis, ulcer, gastroesophageal reflux, patients with the repeated need of surgical interventions, female patients with planned pregnancies etc. Leukotriene receptor antagonists (e.g. montelukast) inhibit the pro-inflammatory and pro-fibrotic effect of leukotrienes and lead to a symptom relief in chronic respiratory disease, for example Asthma [18]. Antileukotrienes are well known in asthma therapy and constitute, due to minimal side effects, an important option in its therapy (e.g., for children or adolescents [19]). In addition, they seem to be an effective therapy for AERD [20–22].

In this retrospective study, we evaluated the efficacy of postoperative antileukotriene therapy concerning recurrence of nasal polyposis in patients with AERD. Furthermore, we compared their subjective and objective clinical data with those patients receiving topical mometasone and AD over time.

Material and Methods

Study Population and Treatment Groups

In this retrospective study we analyzed the data of 61 AERD patients with recurrent nasal polyposis, who underwent a functional endoscopic sinus surgery (FESS) at our institution. The definition and inclusion criteria for patients with AERD and nasal polyposis were applied as described in detail in our previous publication by Havel et al. [15]. The patients were followed postoperatively in multiple clinical visits for up to 72 months and classified into 3 treatment groups:

1. Control group: Patients were treated with topical mometasone and nasal lavage ($N = 22$).
2. AD group: Patients underwent an aspirin desensitization with a target oral maintenance dose of 500 mg aspirin a day [15] ($N = 21$).
3. MT group: Patients were treated daily with 10 mg montelukast p. o., a leukotriene receptor antagonist ($N = 18$).

All postoperative treatment options were discussed with patients individually. Depending on patient's medical history as well as patient's preference, a postoperative treatment regime was assigned. All patients were treated with topical mometasone and nasal lavage throughout the follow-up period.

The data collection conformed to the privacy policy as determined by the data security administrator at our clinic and was approved by the Institutional Review Board at the University of Munich.

Follow-Up

All patients were followed postoperatively in our clinic and data was collected in a chart review. Sinonasal symptoms were analyzed using subjective indications and objective data. All patients were asked to fill out a sinus-specific quality-of-life (QoL) questionnaire. The German version of SNOT-22 (Sinonasal Outcome Test, here Sinusitis Symptom Score SSS-20) contains questions including severity of sinonasal symptoms (nasal obstruction, sneez-

Table 1. Polyposis grading system according to G. Rasp

0	No polyps
1	Polyp growth in the roof of the ethmoid
2	Polyp growth in the middle and upper meatus reaching no further than the lower part of middle turbinate
3	Polyps exceeding the middle meatus
4	Complete obstruction of the nasal cavity

ing, rhinorrhea, postnasal drip, thick nasal discharge, hoarse throat, cough, facial pain, ear fullness, ear pain, decrease/loss of sense of smell) and general QoL items (dizziness, difficulty falling asleep, arousal, fatigue, reduced productivity, reduced concentration, frustrated/restless/irritable, sadness, embarrassment). Each item is scored from 0 to 5, with higher scores representing lower QoL.

Clinical assessment with rigid endonasal endoscopy (0°/4 mm, Karl Storz, Tuttlingen, Germany) was conducted on each visit. The extend of recurrence of nasal polyps was assessed according to Rasp polyp grading system [15] as shown in Table 1.

Statistics

Distribution of demographic data was assessed using the χ^2 test. Multiple comparisons of the collectives in respect to subjective and objective measurements were conducted using the Kruskal-Wallis test. Correlations of endonasal findings and patients' symptoms were assessed using the Spearman correlation coefficient. A p value <0.05 was considered statistically significant.

Results

Subject Demographics and Baseline Disease Characteristics

We included 61 patients in our study. There were no significant differences in age and sex in all 3 groups: Mean age in control group was 56 ± 9 years, in AD group 58 ± 14 years and in MT group 56 ± 12 years. We included 6 (27%) males and 16 (73%) females in the control group, 7 (33%) males and 14 (67%) females in AD group and 5 (28%) males and 13 (72%) females in MT group. Regarding the amount of previous FESS, all included patients underwent at least once surgery. Control group had a mean amount of 1.5 surgeries, AD group 2 and MT group 2.5 surgeries (Table 2).

Preoperative data were available for all 61 patients. The preoperative endonasal endoscopic examination revealed a massive polyp growth in all groups. According to Rasp grading system, control group presented a polyposis score of 3.18 ± 0.80, AD group and MT group showed a score of 3.00 ± 0.70 and 2.89 ± 0.58 respectively. All 3 groups were statistically comparable (p = 0.397).

Table 2. Demographic characteristics of AERD patients

	Control (N = 22)		AD (N = 21)		MT (N = 18)	
	n	%	*n*	%	*n*	%
Age						
≤25	0	0	0	0	1	5.6
26–50	8	36.4	6	28.6	7	38.8
≥51	14	63.6	15	71.4	10	55.6
Sex						
Male	6	29.5	7	33.3	5	27.8
Female	16	70.5	14	66.7	13	72.2
Previous FESS						
1–2	19	86.3	13	61.9	9	50
>2	3	13.7	8	38.1	9	50

Sinonasal data as assessed via SNOT 22 revealed a comparable high level of discomfort, with a clear focus on nasal symptoms. Primary nasal symptoms (nasal obstruction, sneezing, rhinorrhea, postnasal drip, thick nasal discharge, decrease/loss of smell) had a mean score of 2.86 ± 1.25 in control group, 3.04 ± 2.50 in AD group and 3.54 ± 1.19 in MT group. Secondary nasal symptoms (hoarse throat, cough, facial pain, ear fullness, ear pain) had a mean score of 1.92 ± 1.07 in control group, 2.29 ± 1.00 in AD group and 2.19 ± 1.29 in MT group. For further details please refer to Table 3.

Follow-Up Parameters

Patients were followed postoperatively from 6 to 72 (mean 35) months. To highlight the temporal dynamic in polyp recurrence, the clinical visits were divided into 2 follow-up periods: 6–9 months after surgery (mid-term follow-up) and >12 months after surgery (long-term follow-up).

Endoscopic Findings

6–9 months after FESS all patients showed a good recovery and a steady control of polyp regrowth. According to Rasp polyposis grading system, controls showed a mean grade of 1.67 ± 1.03, AD group 1.20 ± 0.90 and MT group 1.54 ± 0.89. When compared to baseline, reduction in polyposis grade of AD groups was significant (Fig. 1).

More than 12 months after surgery the control group had an increased mean polyposis grade of 2.34 ± 1.16. The AD group and the MT group showed a steady disease control with a polyposis grade of 1.32 ± 1.06 and 1.18 ±

Table 3. QoL assessment (validated German version of SNOT, SSS-20) for all 3 groups (controls, AD group, and MT group) at baseline, 6–9 months, and >12 months after functional endoscopic sinus surgery (FESS)

SSS-20	Baseline			6–9 months post-OP			>12 months post-OP		
	controls (*N* = 22)	AD (*N* = 21)	MT (*N* = 18)	controls (*N* = 6)	AD (*N* = 20)	MT (*N* = 13)	controls (*N* = 12)	AD (*N* = 19)	MT (*N* = 11)
Nasal obstruction	3.41	3.1	3.67	2.33	1.79	1.62	2.17	1.58	1.18
Sneezing	2.14	2.29	3.41	2.17	1.68	1.85	1.83	1.58	1.27
Rhinorrhea	2.18	2.62	3.5	2	1.8	1.85	1.67	1.74	1.36
Post nasal drip	2.5	2.62	3.33	2	1.95	1.92	1.75	1.89	1.27
Thick nasal discharge	2.5	2.62	3.17	2	1.95	1.46	1.75	1.84	1.27
Decrease/loss of smell	4.09	4.62	3.94	3.5	3.15	2.23	3.83	3.32	2.55
Hoarse throat	3.05	2.81	2.5	2	1.75	1.54	1.83	1.32	0.73**
Cough	1.59	2.15	2.22	1.67	1.68	1.31	1.08	1.68	0.64*
Ear fullness	1.27	1.95	1.44	0.83	1.37	0.54	0.75	1.58	0.45*
Ear pain	1.27	1.95	1.28	0.83	1.37	0.46*	0.75	1.63	0.55*
Dizziness	1	1.05	0.94	1	0.4	0.62	0.25	0.21	0.36
Facial pain	1.82	2.24	2.39	1.33	1.4	1.31	1.17	1.21	0.64
Difficulty falling asleep	1.64	2.2	2.17	1.5	1.5	1	1.58	1.16	0.64**
Arousal	2.68	2.76	2.56	1.83	1.65	1.08	1.83	1.53	0.91
Fatigue	2.68	2.62	2.33	1.83	1.65	1.08	1.92	1.26	0.73**
Reduced productivity	2.86	3.14	2.28	2.17	1.9	0.85*	1.83	1.74	0.73*, **
Reduced concentration	2.95	3.14	2.33	2.17	1.95	0.85*	1.83	1.68	0.73*, **
Frustrated/irritable	2.14	2.1	2.28	1.67	1.25	1	1.08	1.32	0.91
Sadness	1.73	1.75	2.06	1.33	1.05	0.54	0.83	1.05	0.64
Embarrassment	2.09	1.8	2.22	1.33	1.1	0.92	1.25	1.11	1.09

Significant differences ($p < 0.05$) are indicated with asterisk (* compared to AD, ** compared to controls).

0.87 respectively. When analyzing these data in the course of time, AD an MT group showed significantly less polyp growth >12 months after surgery as compared to baseline (Fig. 1).

Furthermore, when comparing the 3 groups >12 months after surgery, MT group as well as AD group had significantly less polyps as compared to controls (*p* value: 0.02 respectively) (Fig. 2).

Sinonasal and QoL Scores

Primary nasal symptoms (nasal obstruction, sneezing, rhinorrhea, post nasal drip, thick nasal discharge, decrease/loss of smell) were still a dominant complaint 6–9 months after FESS in all 3 groups. Controls had a mean primary nasal symptom score of 2.40 ± 0.94, AD group 2.07 ± 0.73 and MT group 1.80 ± 0.90. In particular the decrease/loss of smell (controls 3.5 ± 1.64, AD group 3.15 ± 1.79, MT group 2.23 ± 1.30) and nasal obstruction (controls 2.33 ± 0.52, AD group 1.79 ± 0.79, MT group 1.62 ± 0.77) were rated with a negative impact on QoL. >12 months after surgery MT group decreased in primary nasal symptom score to 1.53 ± 1.44. In comparison, controls and AD group had a score of 2.25 ± 0.88 and 2.01 ± 0.98. This difference to MT group was not significant. Overall, patients in all groups were impaired mainly by the decrease/loss of smell (controls 3.89 ± 1.59, AD group 3.32 ± 1.57, MT group 2.55 ± 1.97).

Secondary nasal symptoms (hoarse throat, cough, ear fullness, ear pain) showed good results for MT group. 6–9 months after surgery MT group indicated significantly less ear pain as compared to AD group (*p* value = 0.04). >12 months after surgery, scores for hoarse throat were significantly better in MT group as compared to controls (*p* value = 0.037). Furthermore, MT groups indicated a significant reduction in cough (*p* value = 0.006), ear fullness (*p* value = 0.001) and ear pain (*p* value = 0.002) as compared to AD group.

General QoL scores (dizziness, facial pain, difficulty falling asleep, arousal, fatigue, reduced productivity, reduced concentration, frustrated/irritable, sadness, embarrassment) showed an overall poor impairment with 1.38 ± 1.05 in controls, 1.23 ± 0.72 in AD group and 0.75

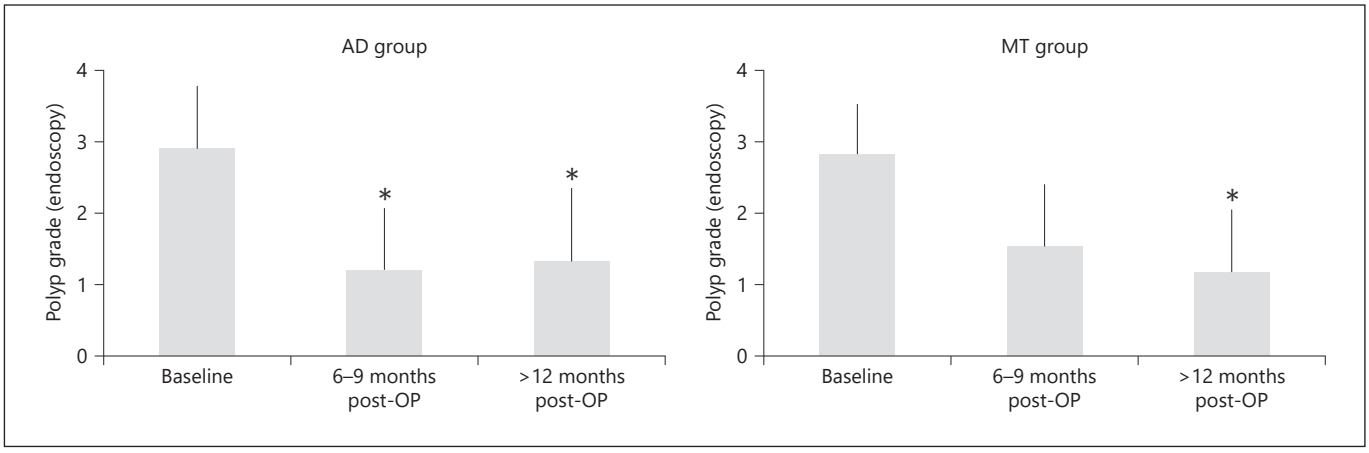

Fig. 1. Endoscopic findings in AERD patients graded according to Rasp polyp grading system at baseline, 6–9 and >12 months after surgery in AD group and MT group. Endoscopic findings in both groups were controlled to baseline over time, significant differences ($p < 0.05$) are indicated with asterisk.

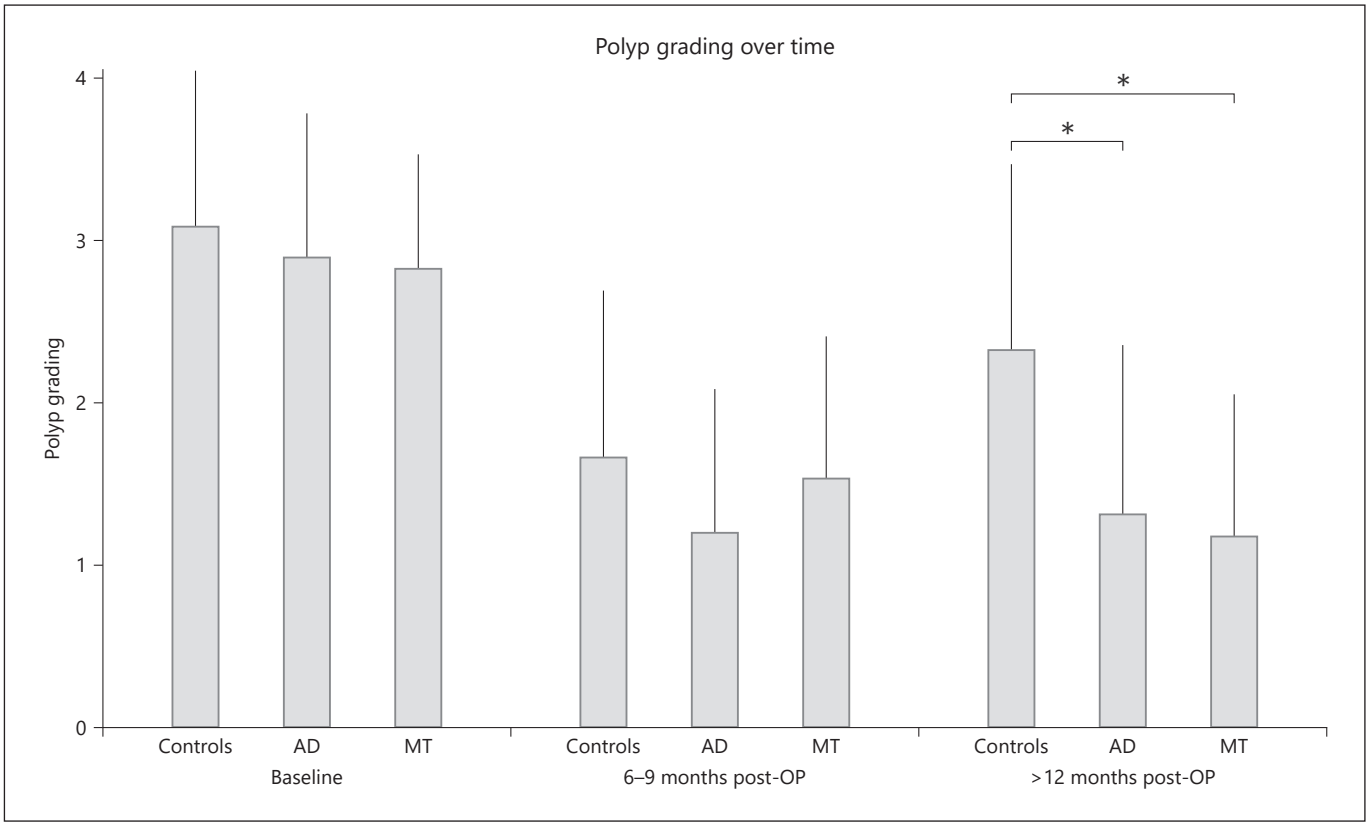

Fig. 2. Endoscopic findings in AERD patients graded according to Rasp polyp grading system at baseline, 6–9 and >12 months after surgery in all 3 groups (mometasone (control), AD and MT). Treatment arms were compared at the different timepoints to controls. At >12 months, significant reduction in polyp grade was found for AD and MT groups.

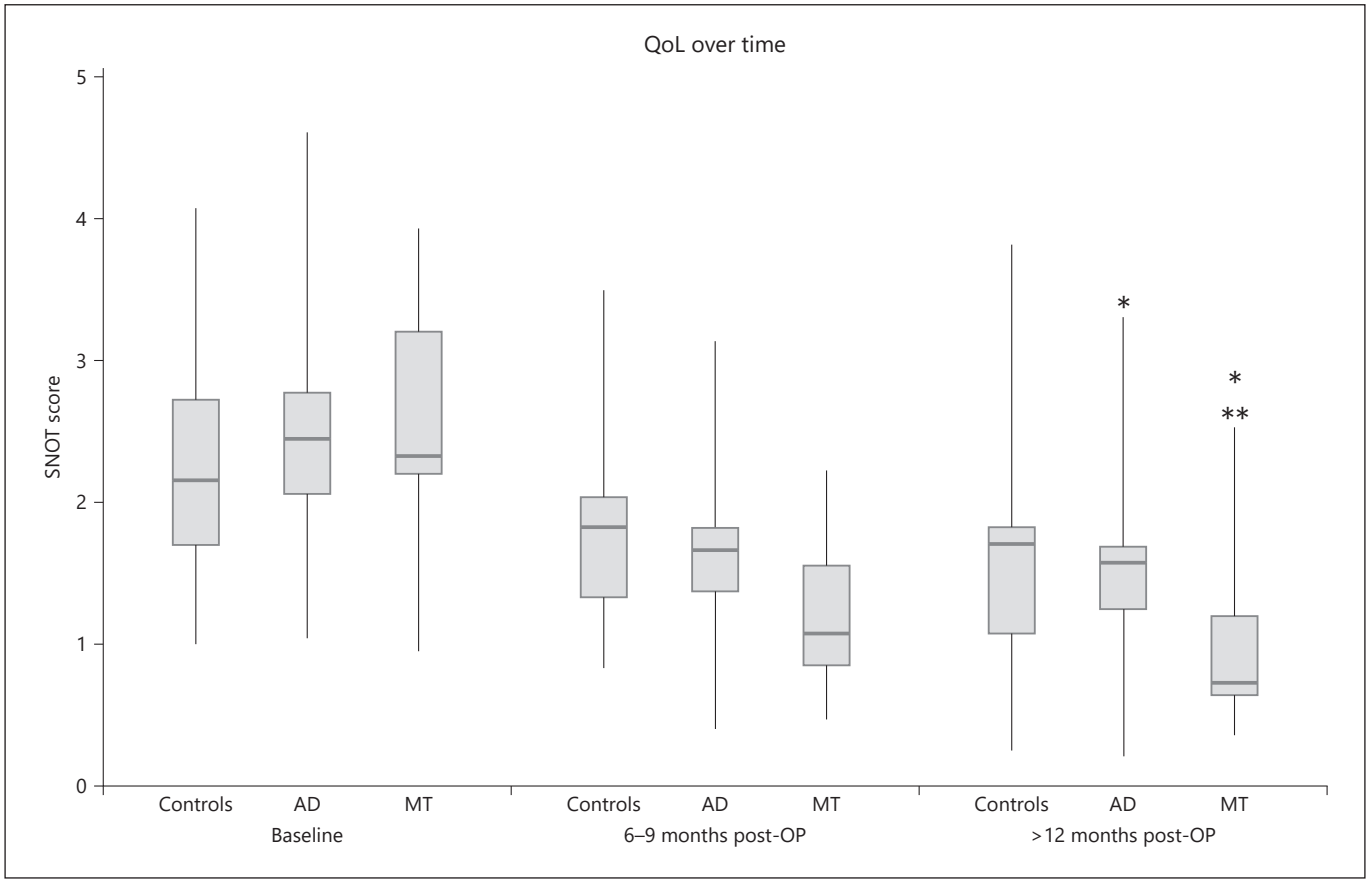

Fig. 3. Assessment of SNOT scores for mometasone (controls), AD and MT groups over the course of time (baseline, 6–9 months and >12 months after surgery). Significant differences ($p < 0.05$) to baseline are indicated with 1 asterisk (*), significant differences in between the groups at 1 timepoint are indicated with 2 asterisks (**).

± 0.97 in MT group. When analyzed separately, 6–9 months after surgery scores for concentration (p value = 0.01) and productivity (p value = 0.08) were significantly better in MT group. >12 months after surgery MT group showed significantly better scores in the items arousal (p value = 0.023) and fatigue (p value = 0.018) as compared to controls as well as for productivity and concentration as compared to controls (p value = 0.017 and 0.02) and AD group (p value = 0.013 and 0.023). For detailed disclosure of all QoL items please refer to Table 3.

When analyzing total SNOT scores over time, significant improvements in QoL are seen at >12 months for AD and MT groups as compared to their baseline (p value = 0.00). Furthermore, MT group showed significantly better QoL results at >12 months as controls (p value = 0.028) or AD (p value = 0.01) groups (Fig. 3).

Discussion

Treatment of nasal polyposis in AERD is often difficult and somehow frustrating – for patients and for doctors. Promising postoperative results tend to deteriorate [23] with a recalcitrant polyp regrowth and repeated sinus surgeries are needed. According to a study conducted by Mendelsohn et al. [24] the overall polyp-free survival rate at 5 years for AERD patients was 10% as compared to controls (CRSwNP) with 84%. Thus, patients with Samter's triad are significantly more likely to suffer from a polyp recurrence. Although the exact pathophysiological mechanism still remains unclear, it is widely accepted that nasal polyps in AERD are just a phenotype of an underlying inflammatory dysbalance with different endotypes [5]. Hence, sinus surgery with polyp extraction has to be considered more as a "debulking" and transient temporary relief for the patient. The postop-

erative application of anti-inflammatory topical glucocorticoids is mandatory, even though mostly insufficient [25].

Thus, postoperative treatment strategies like antileukotriene-therapy, aspirin desensitization or – very recently – therapy with biologicals, have to be discussed with the patient. Our data clearly highlight the benefit of a concomitant postoperative treatment with antileukotrienes and confirm the benefit of AD. Aspirin desensitization has been proven before to be an effective treatment modality, improving patient's QoL and reducing symptoms [15, 26, 27]. However, the daily intake of aspirin is not tolerated by everyone and side effects like prolonged bleeding, ulcer and gastrointestinal bleeding occur. In accordance to that, sinonasal data of our study reveals significantly better subjective patient's condition over time in MT group. In fact, >12 months after surgery MT group showed the significantly lowest functional impairment in QoL in all subgroups. So even if patients undergoing AD have comparable good objective results and a steady disease control, they might still suffer from side effects of an ongoing aspirin therapy – impairing their QoL more than antileukotrienes do.

Antileukotrienes have been proven to be a valuable symptom relieving drug for asthma patients with mild to moderate symptoms [18, 28]. Furthermore, it has been proven, that leukotriene-antagonists reduce aspirin induced bronchospasm and exacerbation rates [28]. As elevated levels of leukotrienes are seen in CRSwNP, the therapy with leukotriene-receptor-inhibitors should be considered as a promising option [29, 30]. In a prospective double blind study Mostafa et al. [31] compared topical therapy with beclometasone alone with the effect of MT therapy in CRSwNP ($N = 40$). One year after surgery, they found comparable results in polyp recurrence rate in both groups. In contrast, Van Gerven et al. [32] compared postoperative monotherapy applying intranasal corticosteroids (INCS) with INCS and montelukast p.o. in a prospective, randomized setting ($N = 72$). In their study, no significant difference in subjective and objective scores of the 2 treatment arms was seen 1 year after surgery, suggesting no further benefit of MT for the treatment of CRSwNP [32]. Here certainly a larger scale study with a significant number of patients is needed to effectively describe the impact of MT in CRSwNP.

AERD is based on an imbalance of arachidonic acid metabolism. The increase of proinflammatory cysteinyl-leukotrienes (CysLT) could be target for an effective antileukotriene therapy. Our data reveal significantly less polyp recurrence over time in patients treated with either AD or MT postoperatively. This is in accordance with other studies focusing on the effect of MT on nasal polyps in AERD [33–35]. Grundmann et al. [36] treated 18 AERD patients postoperatively with MT and followed them for 1 year. They reported no polyp recurrence and a decrease in pulmonary and rhinologic symptoms. Furthermore, reduced levels of eosinophil cationic protein (ECP) and a decreased level of IL-5 were seen in MT group as compared with INCS group.

With ongoing progress in understanding the complex pathophysiology of AERD new treatment modalities, more targeted treatment strategies, are evolving. New insights in the immunological mechanism and pathophysiology of AERD are currently an active field of research. Indeed, nasal polyposis is characterized by a T_H2 dominated milieu, producing IL-4 and IL-5 as well as the ECP and eotaxin [5, 8]. Therapy with biologicals, specifically addressing those immunological processes, show promising results [37–40]. Thus, biologicals might and will significantly enrich therapeutic strategies for patients with AERD. However, personalized treatment options as with biologicals, are a cost intensive therapeutic strategy and currently limited only to a restricted patient collective. Thus, based on our data, a postoperative treatment with MT is a safe and effective treatment option of recalcitrant nasal polyposis for patients with AERD. Certainly, a larger scale, prospective and controlled-randomized study setting is needed to adequately address the indication of antileukotrienes in AERD.

Conclusion

AERD is a severe inflammatory disease of the upper airway. Removal of nasal polyps in AERD by endoscopic sinus surgery provides a temporary symptom relief but does not address the complex underlying pathophysiology. Thus, postoperative treatment is mandatory to reduce polyp recurrence. Our data show, that treatment with INCS is not sufficient. Postoperative AD and MT therapy both show good subjective and objective disease control. However, due to negligible side effects, MT therapy convinces in QoL items.

Statement of Ethics

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee (Ethikkommission der Universität München) and with the 1964 Helsinki declaration and its later

amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Conflict of Interest Statement

The authors declare that they have no conflict of interest.

Author Contributions

All listed authors substantially contributed to the work. Marion San Nicoló was involved in design of the work, data acquisition, analysis and interpretation as well as drafting and critically revising it, Nicole Habermann was involved in data acquisition, drafting and analysis and Miriam Havel was involved in conception and design, analysis and interpretation, revising and final approval for publication.

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