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Management of chronic rhinosinusitis with nasal polyps in Samter triad by low-dose ASA desensitization or dupilumab

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Abstract

Samter triad is a chronic condition where patients suffer from intolerance to aspirin, recurring nasal polyposis and bronchial asthma. Causative treatment is often hard. Potential approaches are the daily intake of acetylsalicylic acid (ASA), shunting arachidonic acid into the lipoxygenase pathway, and a subsequent habituation to this constant inflammatory stimulus. Alternatively, the paramount interleukins 4 and 13 may be antagonized by the monoclonal antibody dupilumab. Hence, we evaluated the daily intake of 100 mg ASA and systemic dupilumab (300 mg s.c. every 2 weeks) therapy in refractory patients for its efficacy and compliance.

We conducted a retrospective chart review for the efficacy and compliance of both continuous ASA desensitization and systemic dupilumab therapy for refractory patients.

Thirty-one patients were included in this retrospective chart review, mean follow-up was 20.4 ± 15.7 months. All patients underwent ASA desensitization. Twenty-one patients had eventually discontinued therapy after 5.8 ± 4.5 months; 11 for its side effects, 12 for its inefficacy. Twenty patients developed sinunasal complaints soon thereafter. Ten patients were still undergoing desensitization (mean duration 15.3 ± 15.7 months). These patients had a higher prevalence of concomitant anti-asthmatic medication. Seventeen refractory patients underwent systemic dupilumab therapy. After 6.4 ± 2.7 months of treatment, sinunasal outcome test (68.1 ± 13.9 vs 20.1 ± 13.9) and visual analogue scales of overall complaints (8.7 ± 0.9 vs 2.2 ± 1.5) as well as endoscopic findings and olfactory function (brief smell identification test; 3.5 ± 2.6 vs 8.6 ± 2.4) all improved significantly.

A considerable number of patients with Samter triad discontinued ASA desensitization, equally for ineffectiveness or side effects. If desensitization is to be effective, special care needs to be taken in respect to concomitant anti-asthmatic medication. Dupilumab is highly effective and safe in treating refractory patients.

Abbreviations: ASA = acetylsalicylic acid/aspirin, FESS = functional endoscopic sinus surgery, NSAID = non-steroidal anti-inflammatory drugs, SNOT-22 = sinunasal outcome test, VAS = visual analogue scale.

Keywords: ASA desensitization, dupilumab, nasal polyps, Samter triad

1. Introduction

The term Samter triad (also called Morbus Widal or Non-steroidal-Drug Exacerbated Respiratory Disease, NERD) describes an entity that often initially manifests with nasal symptoms like nasal obstruction, hyposmia, rhinorrhea, and recurring nasal polyps.[1] These are caused by chronic sinusitis with nasal polyps. During the later course of the disease, patients regularly develop bronchial asthma and an intolerance to

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The study was registered with the Ethics committee of the Ludwig-Maximilians University (file no. 20-842).

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non-steroidal anti-inflammatory drugs (NSAID), reacting with asthmatic attacks and an increase in above mentioned nasal symptoms. Some patients may also develop a cutaneous form with angioedema and urticaria,[2] while another fraction may exhibit a mixture of all these symptoms.

The general prevalence of Samter triad is believed to range between 0.5% and 5% of the overall population,[3,4] with up to 20% of patients with asthma suffering from Samter triad. Even though the likelihood of Samter triad increases when relatives are affected by the disease, no single gene or distinct hereditary pattern has been linked to the disease. However, it is generally believed that the symptoms of Samter triad are caused by a dysfunction in the metabolism of arachidonic acid.[5,6]

Due to the chronic nature of the disease with numerous and often fast relapses after therapy, treatment is often difficult and enervating for patients. The nasal polyps have a strong tendency to relapse shortly even after functional endoscopic sinus surgery (FESS). Moreover, the polyps regularly only insufficiently respond to topical steroids. Systemic steroids may provide temporary relief. However, compared to topical steroids, systemic steroids are considerably more likely to cause side effects.

The concept of aspirin (or acetylsalicylic acid [ASA]) desensitization is based on the observation that after oral application of aspirin (ASA), there is a short refractory period during which repeated application of aspirin will not cause the same symptoms to arise again.[7] It is believed that the constant and irreversible inhibition of both subtypes of the cyclo-oxygenases by application of aspirin causes a constant shunting of arachidonic acid into the 5-lipoxygenase pathway, causing a constant overflow in inflammatory leukotrienes and a subsequent habituation to this state.

However, there is to this date considerable debate not only about the efficacy, but also about the appropriate dosing of ASA. Consequently, clinical approaches may differ from institution to institution. At our institution, patients that exhibited clinical symptoms of Samter triad and suffered short-term relapses after FESS were offered ASA desensitization with daily doses of 100 mg ASA. As we noticed during clinical practice that a proportion of patients still did not experience sufficient symptom relief, those patients were offered dupilumab therapy. Dupilumab as a monoclonal antibody that is directed against the receptors of interleukins 4 and 13, a main driver of inflammation in Samter triad. We therefore conducted a retrospective chart review to analyze the success of this approach.

2. Materials and methods

2.1. Ethics

The study at hand was registered with the appropriate authorities under the file number 20-842. The need for informed consent was waived since the entire nature of the study was in its entirety retrospective.

2.2. Clinical approach

Patients were considered to suffer from Samter triad if they fulfilled all 3 criteria (recurrent nasal polyposis, bronchial asthma, and sensitivity to ASA, either by patient's anamnesis or documented reaction to ASA challenge). Patients that suffered from Samter triad, had recently underwent FESS at our institution and a history of rapid recurrence of nasal polyps were offered desensitization as an additional treatment to prevent recurrence after surgery. Initial desensitization was performed in an inpatient setting. A carrier without active ingredients as well as 500 mg of paracetamol were orally administered on the first day. After each individual dose, spirometry was performed. The following days, ASA doses of 50, 75, 100 and 500 mg were applied daily, with subsequent spirometric controls. After a dose of 500 mg was well tolerated, patients were discharged with the recommendation of a constant ASA intake of 100 mg daily. Follow-up visits were then met at a special rhinology consultation desk at our institution, during which nasal endoscopy was performed. Whenever there was a relevant relapse of polyposis and/or sinunasal complaints became too severe, patients were counted as a relapse of polyposis under desensitization therapy. Patient that had undergone unsuccessful desensitization due to relapse or side effects were evaluated for a therapy with Dupilumab. If internal criteria for dupilumab treatment were met (sinunasal outcome test [SNOT-22] >50, rapid recurrence of nasal polyps after surgery or ASA desensitization, objective hyposmia and/or impaired quality of life, indicated on a visual analogue scale [VAS] of $\geq 7/10$), treatment with dupilumab (300 mg applied subcutaneously, every 2 weeks) was commenced. Patients under treatment with dupilumab were checked upon every 3 months in the specialized consultation desks. Patients that had not completed at least 1 follow-up visit after dupilumab treatment was initiated were excluded from the further study.

2.3. Data collection

All patients that were registered with the ICD-10 code J33.8 (Polyposis nasii et sinuum) were screened for this study. Only patients that suffered from Samter triad and that underwent ASA desensitization were included in the study. Exclusion criteria were an age of under 18 years or insufficient documentation. Electronic patient files were then used to collect information on age, sex, previous surgeries, follow up after ASA desensitization, concomitant medication, measures of olfaction (brief smell identification test) subjective and objective measurements of discomfort (VAS, SNOT-22) and endoscopic findings.

2.4. Statistics

Statistics were carried out using Project R for Mac (Build 3.4.1 for El Capitan, The R Project for Statistical Computing, http://www.r-project.org/). To detect significant differences between the groups, Pearson χ^2-test and Student t test, as appropriate, was used. Statistical differences of <0.05 were considered to be significant.

3. Results

Overall, 31 patients were included in the study at hand. Average age was 45.9 ± 15.4 years; out of the patients included, 14 were male and 17 female. On average, each patient had undergone 3.1 ± 1.3 previous FESSs. Mean follow up of all patients was 20.4 ± 15.7 months. Out of the 31 patients, 21 had discontinued oral desensitization. Average age of these patients was 47.0 ± 13.7 years, with a male to female ratio of 11 to 10. On average, oral desensitization was tolerated for 5.8 ± 4.5 months, ranging from 0.5 to 15 months (Fig. 1). The main reasons to discontinue oral desensitization were recurrence of nasal polyps (12 patients), and

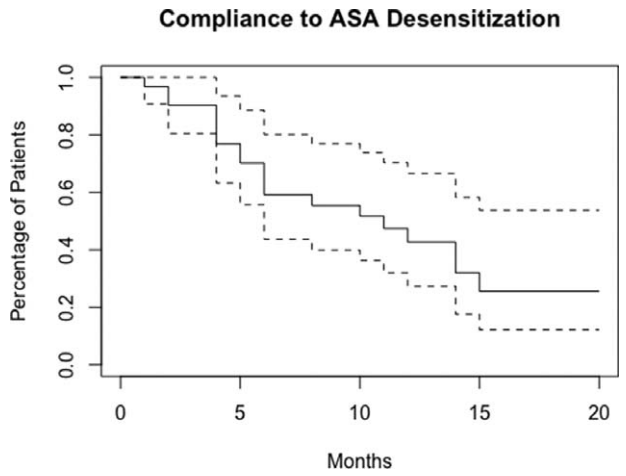

Figure 1. Compliance to oral ASA desensitization. n = 31, - - - = confidence interval. ASA = acetylsalicylic acid.

side effects (11 patients), where 5 patients suffered from increased asthma, 2 patients suffered from urticarious skin reactions and gastrointestinal discomfort, respectively, and 1 patient suffered from renal side effects and bleeding, respectively. Out of the patients where ASA desensitization was unsuccessful, 20 eventually developed nasal symptoms again that caused them to seek medical attention. Average time from beginning of desensitization until the recurrence of symptoms was 7.6 ± 4.6 months, ranging from 1 to 17 months (Fig. 2). The 10 patients that still underwent oral desensitization were on average 43.5 ± 18.1 years, with a male to female ratio of 5:5. Average duration of oral desensitization was 15.3 ± 15.7 months, ranging from 2 to 60 months (Table 1).

Generally speaking, both groups received considerable additional medication. Every patient in both groups received nasal spray containing cortisol. Eight out of the patients with ongoing desensitization and 8 patients with unsuccessful treatment were treated with daily PARI-Sinus (PARI GmbH, Starnberg, Federal Republic of Germany) corticosteroid inhalations. Five and 6 patients, respectively, took anti-leukotrienes during the therapy and 8 and 10 patients, respectively, used inhalative anti-asthmatics during desensitization. Four and 5 patients, respectively, used systemic steroids regularly. The differences between the groups were not statistically significant (Table 2).

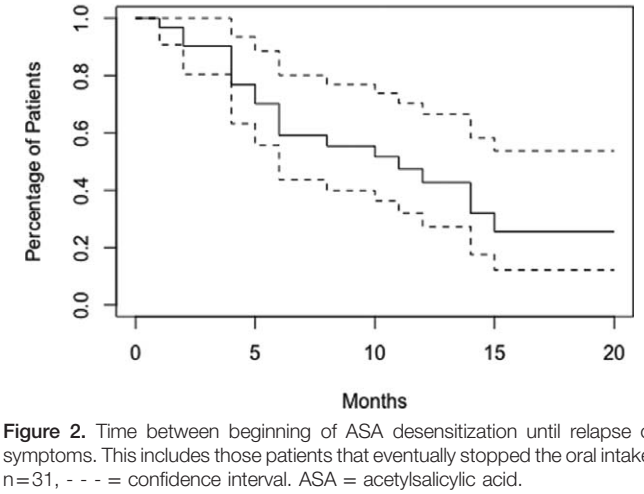

Figure 2. Time between beginning of ASA desensitization until relapse of symptoms. This includes those patients that eventually stopped the oral intake. n = 31, - - - = confidence interval. ASA = acetylsalicylic acid.

Table 1

Overall patient characteristics, ± standard deviation, ( ) = relative proportions, [ ] = range.

Overall patients	
No. of patients	31
Average age (years)	45.9 ± 15.4 [19.8–83.4]
Sex (M/F)	14/17
Follow up period (mos)	20.4 ± 15.7 [2–60]
No. of previous surgeries	3.1 ± 1.3 [1–6]
Unsuccessful desensitization	
No. of patients	21
Average age (yrs)	47.0 ± 13.7 [19.8–68.0]
Sex (M/F)	11 / 10
Average duration of desensitization (mos)	5.8 ± 4.5 [0.5–15.0]
Average duration until recurrence of symptoms (mos, n = 20)	7.6 ± 4.6 [1.0–17.0]
Reasons for discontinuation	
Recurrence of nasal polyps	12 (57.1%)
Side effects – asthmatic	5 (33.3%)
Side effects – urticaria	2 (9.5%)
Side effects – gastrointestinal	2 (9.5%)
Side effects – hemorrhage	1 (4.7%)
Side effects – renal	1 (4.7%)
Patients undergoing desensitization	
No. of patients	10
Average age (yrs)	43.5 ± 18.1 [20.9–83.4]
Sex (M/F)	5/5
Average duration of desensitization (mos)	15.3 ± 15.7 [2.0–60.0]

Out of the 21 patients that discontinued oral desensitization, 17 were interested in consecutive therapy with dupilumab. In these patients, average time between discontinuation of desensitization and commencing of dupilumab therapy was 33.9 ± 33.0 months. Patient scores on the brief smell identification test, SNOT-22, and VAS were 3.5 ± 2.6, 68.1 ± 13.9, and 8.7 ± 0.9, respectively, before treatment was commenced. After at least 3 months (average 6.4 ± 2.7 months, range 3–12 months) of treatment, the scores were 8.6 ± 2.4, 20.1 ± 13.9, and 2.2 ± 1.5, respectively. The differences in all these measurements were significantly lower compared to before the commencement of dupilumab treatment. Degrees of polyposis as described by Rasp et al[8] before and after treatment can be found in Table 3. The

Table 2

Concomitant anti-inflammatory therapy during oral ASA desensitization, ( ) = relative proportions, # = Pearson χ^2-test.

Therapy	Desensitization ongoing (n = 10)	Unsuccessful desensitization (n = 21)	*P*
Cortisol nasal spray	10 (100%)	21 (100%)	.784#
PariSINUS inhalative corticosteroids	8 (80.0%)	8 (38.1%)	
Anti-leukotrienes	5 (50.0%)	6 (28.6%)	
Inhalative anti-asthmatics	8 (80.0%)	10 (47.6%)	
Oral carticosteroids	4 (40.0%)	5 (23.8%)	

ASA = acetylsalicylic acid.

Table 3

Sinunasal characteristics before and after initiation of dupilumab therapy, [ ] = range, n = 17, # = Pearson χ^2-test, † = Student *t* test.

	Before dupilumab therapy	>3 months after initiation of dupilumab therapy	*P*
Time between discontinuation of desensitization and beginning of dupilumab therapy (mos)		33.9 ± 33.0 [1–116]	n/a
B-SIT	3.5 ± 2.6 [0–8]	8.6 ± 2.4 [4–12]	<.001†
SNOT-22	68.1 ± 13.9 [50–86]	20.1 ± 13.9 [11 - 60]	<.001†
VAS	8.7 ± 0.9 [7–10]	2.2 ± 1.5 [1–6]	<.001†
Polyposis°			
0	/	10	<.001#
I	1	3	
II	3	2	
III	9	2	
IV	4	/	

B-SIT = brief smell identification test, SNOT-22 = sinunasal outcome test, VAS = visual analogue scale.
A *P* value of smaller than 0.05 was conisdered to be significant.

differences before and after 3 months of treatment were significantly different. In terms of side effects, 2 patients reported conjunctivitis and 2 patients reported increased frequency of migraine attacks.

4. Discussion

Overall, we found that oral ASA desensitization with daily doses of 100 mg resulted in a relatively low compliance in patients. This was in the majority of cases due to side effects or due to ineffectiveness. Generally speaking, side effects that limit ASA desensitization have been reported in almost every study that addressed this topic (Table 4). Interestingly, even low doses such as 350 or even 100 mg per day seem to yield relevant side effects as has been reported in other studies.[9] In that respect, our findings are in line with the relevant literature. However, the fact that almost one third of patients developed recurrence of nasal polyps while undergoing desensitization is considerable and even beyond the findings of Rozsasi et al.[10] Still, there is some evidence in the literature[9,11] and at hand that low dose ASA desensitization may still be effective in controlling nasal polyposis and its subsequent complaints in a considerable proportion of patients.

Table 4

Overview of studies addressing oral ASA desensitization.

Author	Year	Dose	Study type	Key findings
Stevenson et al	1984	325 mg/die	Prospective 38 patients	Compared to placebo, desensitization showed significant decrease in nasal obstruction and pain, increase in smell and decrease in doses of corticosteroids. Thirteen patients discontinued desensitization.
Sweet et al	1990	325 mg/die	Retrospective, 65 patients + 42 control	Continuous application significantly decreased hospital/ER visits, steroid use, nasal symptoms, sinus operations and significantly increased sense of smell compared to controls. 30/65 patients discontinued desensitization.
Stevenson et al	1996	1300 mg/die	Retrospective, 65 patients	Significant decrease in use of systemic steroids, no. of FESSs, sinus infections and significantly improved olfaction, 10/65 discontinuation due to gastric symptoms.
Gosepath et al	2002	100 mg/die	Prospective 30 patients	Relevant decrease in nasal polyps, number of acute infection of the paranasal sinuses, improvement of in-vitro parameters. 5/30 patients discontinued desensitization.
Berges-Gimeno et al	2003	1300 mg/die	Retrospective 172 patients	One hundred fifteen patients showed positive response to desensitization: Significant increase in sense of smell, decrease of acute sinus infections, amount of oral steroids used and asthmatics symptoms. Twenty-four patients discontinued desensitization due to side effects.
Lee et al	2007	650 mg/die + 1300mg/die	Prospective 137 patients	Both doses showed significant improvement in number of sinus infections, sinus operations, hospitalizations for asthma, need of systemic corticosteroids, anosmia, nasal/sinus symptoms and asthma symptoms. Some patients needed to change from 650 mg/die to 1300 mg/die. Twenty-three patients discontinued therapy due to adverse effects.
Rozsasi et al	2008	100 mg/die + 300 mg/die	Prospective 14 patients	100 mg/die failed to show any significant effect, 300 mg/die showed improvement in terms of recurrence of nasal polyps, olfaction and amount of asthma medication.
Forer et al	2011	1300 mg / die	Prospective 27 patients	Significant decrease in subjective nasal symptoms, only mild improvement of endoscopic findings within 12 months. 12/27 patients dropped out of the study.
Fruth et al	2013	100 mg/die	Prospective 70 patients	Considerable, albeit non-significant decrease of nasal polyposis. Significant decrease of nasal symptoms and increase in quality of life. 39/70 patients dropped out of study.

ASA = acetylsalicylic acid, FESS = functional endoscopic sinus surgery.

Shortly after discontinuation of ASA desensitization for any reason, most people's complaints relapse. This is in accordance with previous literature addressing this aspect of ASA desensitization.[12] Bearing this in mind, we find it logical that studies that have tested considerably higher ASA doses found significant effects on almost every aspect of the disease.[13–16] However, taking into account the fact that all studies that assessed daily doses of 300 mg[10,12,17] and most studies that assessed daily doses of 100 mg[9,11] still found significant effects, one would always recommend using these relatively low doses. Table 4 gives an overview of the relevant studies addressing oral ASA desensitization.

A central aspect we found in the study at hand is that the amount of concomitant medication was considerably higher in those patients that were still successfully undergoing desensitization. Bearing this in mind, together with the fact that a major proportion of patients that discontinued the therapy did so relatively early and that half the patients claimed this discontinuation due to asthmatic side effects, we believe that adequate concomitant medication is paramount in successful desensitization. Fittingly, there are several studies that show beneficial effects of anti-leukotrienes in chronic rhinosinusitis with nasal polyps.[18,19] Moreover, we believe that the relatively high prescription rate of PariSINUS, an inhalation device that has specifically been designed for the paranasal sinuses, may play a pivotal role in upkeeping the efficacy of ASA desensitization with doses as low as in the study at hand.

If ASA desensitization fails, we found dupilumab to be very effective in reducing all aspects of the nasal symptoms of nasal polyposis in Samter triad. While the observation of its considerable efficacy is in line with large prospective studies addressing this topic,[20] we believe this is – to the best of our knowledge – the first time this has been reported for this specific subgroup of patients.

Nonetheless, while there is sufficient evidence at hand and in the literature that systemic treatment with dupilumab is highly effective in treating nasal polyps – particularly in patients with Samter triad – we believe that ASA desensitization – in low doses – may have its place in multimodal treatment of Samter triad. Firstly, there are considerable costs[21,22] that are associated with long term dupilumab therapy. Moreover, ASA desensitization allows the administration of oral NSAID. While NSAID not only play a pivotal role in modern day-to-day analgetic therapy, many patients with coronary artery disease rely on the intake of ASA to prevent myocardial infarction or stroke.[23,24] Patients undergoing systemic dupilumab therapy will have to rely on more expensive COX-2 inhibitors for non-opioid analgesia.[25,26]

Finally, the strengths and limitations of this study should be outlined. While there is little debate about side effects in high-dose ASA desensitization, the amount of data, particularly side effects, in low-dose ASA desensitization is very limited. In that respect, the study at hand offers novel insights – if low-dose ASA desensitization is to be successful, concomitant medication (particularly anti-leukotrienes and inhalative corticosteroids) needs to be selected carefully.

Still, the retrospective nature as well as the limited number of patients need to be taken into account: This study is most likely subject to systematic lack of data and various kinds of bias. Moreover, there might have been factors that influenced clinical decision making that could not be deducted from the patient files.

5. Conclusion

We found that compliance to low-dose ASA desensitization is relatively low. This is partially due to ineffectiveness and partially due to side effects. However, there is still a proportion of patients that benefit from desensitization. If low-dose ASA desensitization is attempted, we recommend that concomitant anti-asthmatic medication, in particular anti-leukotrienes and inhalative corticosteroids, is optimized. Patients that do not benefit from ASA desensitization will most likely benefit greatly from systemic dupilumab therapy, as this was able to significantly decrease the burden of disease and increase quality of life as indicated by the sinunasal parameters.

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