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Low frequency of acetyl salicylic acid hypersensitivity in mastocytosis: The results of a double-blind, placebo-controlled challenge study

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Abstract

Background: Patients with mastocytosis are at increased risk of anaphylaxis. The use of nonsteroidal anti-inflammatory drugs (NSAIDs) is often discouraged because of this reason. However, the actual prevalence and severity of NSAID-related hypersensitivity among patients with mastocytosis is unknown.

Methods: A double-blind, placebo-controlled acetylsalicylic acid (ASA) challenge up to a cumulative dose of 520 mg was performed among adult patients with mastocytosis. In addition, a retrospective search of the entire outpatient cohort was performed to obtain "real-life" data on NSAID hypersensitivity.

Results: Fifty patients underwent an ASA challenge. Seventy percent had indolent systemic mastocytosis, 18% had mastocytosis in the skin, and 12% had advanced mastocytosis. The ASA challenge was positive in 1 patient who developed urticaria. The additional retrospective chart review revealed that 8 of 191 patients had a history of NSAID-related hypersensitivity reaction(s), of whom 3 reported severe systemic reactions. All 8 patients had already experienced NSAID-related hypersensitivity reactions before mastocytosis was diagnosed.

Conclusions: The frequency of ASA hypersensitivity was 2% in a prospective challenge study and 4.1% in a retrospective chart review of 191 patients with mastocytosis. NSAIDs can be administered safely to most patients with mastocytosis. Extra caution should be taken in patients with a history of hypersensitivity reactions to other drugs, or traditional risk factors for NSAID hypersensitivity.

KEYWORDS

drug challenge, epidemiology, hypersensitivity, mastocytosis, nonsteroidal anti-inflammatory drugs

Trial registration: This trial was registered in the EudraCT database, Number 2015-004604-37.

1 | INTRODUCTION

Mastocytosis is a disease in which aberrant mast cells accumulate. The WHO recognizes different subtypes of SM.[1,2] The prevalence of anaphylaxis is higher in patients with mastocytosis compared to healthy persons.[3,4] A wide variety of stimuli can trigger mast cell degranulation and thereby lead to anaphylaxis.[5] Historically, the use of certain medications that could theoretically trigger mast cell degranulation is discouraged in patients with mastocytosis. Among these are radiocontrast media, general anesthetics, opioid analgesics, and nonsteroidal anti-inflammatory drugs (NSAIDs).[3] For general anesthetics and radiocontrast media, case reports on severe (and sometimes lethal) anaphylaxis in patients with mastocytosis are available, although the absolute risk still appears low.[6-8]

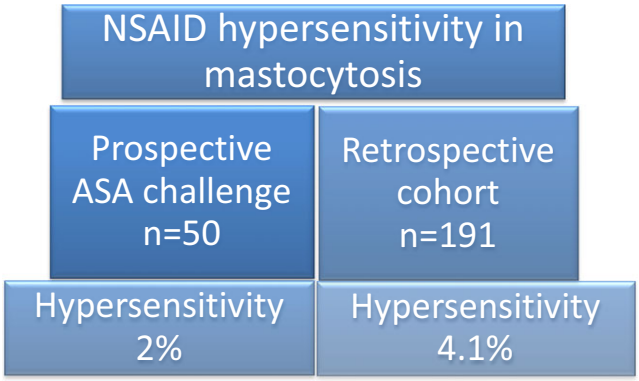
The prevalence and severity of anaphylaxis due to NSAIDs in patients with mastocytosis is actually not known. Anxiety for NSAID-related hypersensitivity reactions leads to confusion among both physicians and patients, and different advices between practices. The use of NSAIDs is therefore often avoided, resulting in the risk of mistreatment of patients with mastocytosis for several reasons. Firstly, these patients are at increased risk of cardiovascular morbidity, which often necessitates acetylsalicylic acid (ASA) for secondary prevention.[4,9] Secondly, ASA is a well-known treatment for flushing in mastocytosis.[10,11] Thirdly, patients with mastocytosis relatively often suffer from various types of pain for which analgesics might be necessary.[12,13] Currently, they are often advised to only take acetaminophen which is not always sufficient.

In our practice, we noted that many patients used NSAIDs uneventfully, until they received were diagnosed to have mastocytosis. Furthermore, previously performed NSAID challenges were always negative. We therefore hypothesized that the frequency and severity of NSAID-related hypersensitivity is overestimated in patients with mastocytosis. For drug hypersensitivity in general, drug challenge tests are the gold standard diagnostic procedure.[14] ASA is often used to test for general NSAID hypersensitivity because of its strong COX-1-inhibiting properties.[15] Therefore, we designed a study using standardized drug challenge tests with ASA to investigate the exact prevalence and severity of NSAID hypersensitivity reactions in patients with mastocytosis.

2 | METHODS

2.1 | Patient eligibility

Patients were recruited from the Mastocytosis Outpatient Clinic of the Erasmus University Medical center. All adult patients with biopsy-proven cutaneous or systemic mastocytosis were eligible. Patients were excluded if they had a history of a prior NSAID-related hypersensitivity reaction(s), uncontrolled asthma, rhinosinusitis, nasal polyps, active pregnancy, and high dosage of beta-blocking drugs (equivalent to ≥100 mg of metoprolol), when they were not able to stop antihistamines or prednisolone, or were not deemed capable of handling possible delayed anaphylactic reactions at home.



GRAPHICAL ABSTRACT

The frequency of ASA hypersensitivity among patients with mastocytosis was 2% in a prospective study and 4.1% in a retrospective cohort. NSAIDs can probably be safely administered to most patients with mastocytosis. A history of hypersensitivity reactions to other drugs might increase the risk of NSAID hypersensitivity among patients with mastocytosis.

Preexistent mast cell mediator-related symptoms such as pruritus or flushing were not considered to be exclusion criteria in order to represent the real-life situation at an outpatient clinic. Moreover, flushing can be an indication for ASA.

2.2 | Study protocol

All patients underwent a double-blind, placebo-controlled ASA challenge in a randomized order. The minimum interval between the two test days was 14 days. The study medication was provided in a blinded fashion by the pharmacy of the Erasmus MC. Patients had to stop H1-antagonists and leukotriene antagonists for 3 days prior to the drug challenge. The challenge took place at the Allergy Outpatient Clinic. Patients received three incremental doses of ASA of 40, 80, and 400 mg (or matched placebo tablets), leading to a cumulative dose of 520 mg. The interval between each dose was 1 hour, and patients were observed for an additional 2 hours after the administration of the third dose.

Mast cell mediator-related symptoms were systematically scored before the start of each drug challenge and after 1, 2, and 4 hours. We used an adapted form of the scoring system for food challenges as proposed by Grabenhenrich et al.[16] This form scores symptoms according to organ system and severity and is in our practice routinely used for both food and drug challenges. In addition, numeric rating scale (NRS) score was obtained for mast cell mediator-related symptoms such as pruritus and headache. An increase of 3 points in this scale during the challenge was considered significant. All challenges were conducted and assessed by MH and/or SdV. In cases of doubt, a second investigator (RGvW or PvD) was consulted to assess the symptoms. Deblinding of the investigators and patients took place 24 hours after all 50 patients completed both challenge days.

2.3 | Outcomes and definitions

The ASA challenge was considered positive when a patient developed objective mast cell mediator-related symptoms within 12 hours after the administration of the third dose on the day they received the verum, and had no symptoms on the placebo day. The challenge was considered negative when a patient developed no symptoms on the verum day, regardless of any symptoms on the placebo day.

The WHO criteria were used to define the subtype of mastocytosis.[1] Patients with maculopapular cutaneous mastocytosis (MPCM) who never underwent bone marrow biopsy, or had negative bone marrow investigation, were categorized as mastocytosis in the skin (MIS). An atopic background was defined as a history of atopic dermatitis, asthma, rhinoconjunctivitis, and/or positive specific IgE for inhalation or food allergens. Next to atopy, other traditional risk factors for NSAID hypersensitivy were defined as the presence of asthma, nasal polyps, and chronic rhinosinusitis. Eosinophilia was defined as an absolute eosinophil count of $>500 \times 10^6$ in peripheral blood.

2.4 | Additional retrospective cohort study

Next to the prospective challenge study, we retrospectively searched the electronic patient records of all adult patients who visited the mastocytosis center from January 2009 until January 2017 and who fulfilled the criteria for mastocytosis in the skin (MIS), cutaneous or systemic mastocytosis (SM). Patients who already participated in the challenge study were excluded from the retrospective cohort. Patients with a history of NSAID-related hypersensitivity reactions, or patients who had proven NSAID tolerance prior to the start of this study, were subsequently contacted to obtain further clinical details. NSAID tolerance was considered as proven when a drug challenge was negative or when (accidental) NSAID ingestion was uneventful after the diagnosis of mastocytosis was made. The characteristics of the patients with and without NSAID tolerance from this retrospective cohort were compared to identify possible differences.

2.5 | Ethical considerations

This trial was performed according to the latest Helsinki guidelines. The study was approved by the local medical ethics committee. All participants provided written informed consent. The trial was registered in the EudraCT database, Number 2015-004604-37.

2.6 | Statistical analysis

We used IBM SPSS 21 for all analyses. Patient characteristics were noted as median with interquartile range (IQR) for continuous variables and as the number with percentage for dichotomous variables. To calculate potential differences between the groups with and without NSAID hypersensitivity, the Mann-Whitney *U* test was used for continuous variables and the chi-square test for dichotomous variables.

2.7 | Power calculation

The prevalence of NSAID-related hypersensitivity reactions in the general population is <1%. We hypothesized that the risk in patients

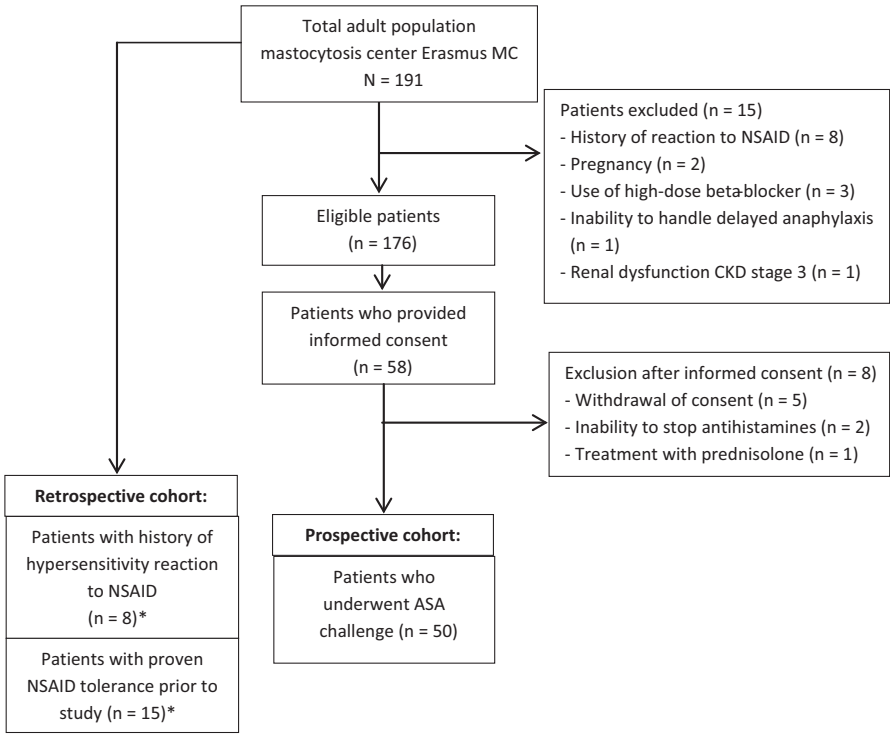


FIGURE 1 Flow diagram of the inclusion process. The total patient cohort in April 2017 consisted of 191 patients with mastocytosis. After the inclusion process, 50 patients underwent acetylsalicylic acid (ASA) challenge, of whom one had a reaction to ASA. Next to these challenges, the entire patient cohort was researched retrospectively. Patients with a reliable history of nonsteroidal anti-inflammatory drug (NSAID) hypersensitivity reactions, and patients with proven NSAID tolerance, were identified. This resulted in a pooled population of 73 patients (50 + 8 + 15), of whom 64 had proven NSAID tolerance (49 from the current study and 15 from the retrospective data set) and 9 had proven NSAID hypersensitivity (1 from the current study and 8 from the retrospective data). *These patients did not participate in the prospective challenge study [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Baseline characteristics study population (n = 50)

Age in years, median (IQR)	55 (16)
Male, n (%)	16 (32)
Subtype according to WHO criteria (1,2), n (%)	
MIS	9 (18)[a]
ISM	
With skin lesions	26 (52)
Without skin lesions	9 (18)
SSM	3 (6)
SM-AHN	2 (4)
ASM	1 (2)
Serum tryptase level at diagnosis in μg/L, median (IQR)	25.0 (17.8)
Atopic background, n (%)	13 (26)
Eosinophilia, n (%)	2 (4)
Previous hypersensitivity reaction to any drug, n (%)	5 (10)
Previous anaphylaxis due to any trigger, n (%)	23 (46)
Wasp	7 (30)
Unknown	7 (30)
Physical stimuli	4 (17)
Other drugs[b]	5 (22)
Miscellaneous[c]	6 (26)

ASM, aggressive systemic mastocytosis; IQR, interquartile range; ISM, indolent systemic mastocytosis; MIS, mastocytosis in the skin; SSM, smoldering systemic mastocytosis; SM-AHN, systemic mastocytosis with associated hematological neoplasm.

[a]One patient underwent incomplete bone marrow investigation, and 8 patients declined bone marrow punction.

[b]Other drugs: proton pump inhibitor (1×), morphine (2×), penicillin (1×), and codeine (1×).

[c]Miscellaneous triggers: horsefly (n = 2), jellyfish sting (n = 1), fire ant (n = 1), anesthesia (n = 1), codeine (n = 1).

with systemic mastocytosis is only marginally higher than in the general population. With an estimated frequency of allergic reactions of 4% in our study population, inclusion of 50 subjects in total will lead to a 95% confidence interval of 1%-13%. The estimated frequency was based on self-reported reactions by patients in the Erasmus MC cohort combined with circumstantial data of other cohort studies on mastocytosis (see Discussion section for references).

3 | RESULTS

3.1 | Study population

At the moment of inclusion in April 2017, 173 patients were considered eligible to participate in the trial (Figure 1), and 58 patients signed the informed consent. After inclusion, 8 patients dropped out before the ASA challenge was performed completely. One of these patients was excluded after the first challenge day because she started to use prednisolone for arthritis which was not related to the trial. Two patients experienced anaphylactoid reactions related to their mastocytosis within days after cessation of the antihistamines. The other patients withdrew consent. The inclusion process was stopped after 50 subjects completed both days of the challenge. The final study population thus consisted of 50 patients. The median age was 55 years, and most participants had indolent SM (Table 1).

3.2 | Results of ASA challenge

The challenge was positive in one patient (2%), who developed an urticarial rash 4 hours after ingestion of the third dose of ASA, which corresponds with a cumulative dose of 520 mg. The rash subsided after she took 10 mg of hydroxyzine. This patient had smoldering SM based on a serum tryptase level of ≥200 μg/L and hepatosplenomegaly. She had never used NSAIDs before. She had previously developed a rash after the administration of radiocontrast media and reported an increase in mast cell mediator-related symptoms after the consumption of alcoholic beverages and histamine-rich food.

Three other patients reported subjective symptoms on the day of the verum but not on the day they received placebo. These symptoms consisted of mild flushing in 1 patient, generalized pruritus in 1 patient, and lightheadedness in 1 patient. The flushing was not considered as a positive challenge because it occurred after the second dose of 80 mg and subsided spontaneously despite the fact that the next increasing dose of ASA was administered according to protocol. Moreover, this patient has spontaneous flushes multiple times a week. Similarly, the patient with pruritus already had pruritus before the start of the challenge and the NRS score increased by 2 points throughout the day of the challenge which was below the prespecified threshold of 3 points (see Methods section). The last patient experienced lightheadedness 15 minutes after the ingestion of the third dose of ASA, but had no other mast cell mediator-related symptoms and stable vital parameters. The serum tryptase level did not increase as compared to a baseline measurement. Seven patients had a reaction on the placebo day, of whom 1 had objective macular erythema on the arms and trunk and the other 6 patients had subjective symptoms. Four patients who had a reaction to placebo already had mast cell mediator-related symptoms at the start of the challenge, consisting of pruritus and/or flushing.

3.3 | Patients with a history of NSAID-related reactions

In addition to the challenge study, we retrospectively searched the electronic records of all adult patients with mastocytosis that visited the Erasmus MC from 2009 until 2017. Of a total of 191 patients, 8 patients had an annotation of "NSAID allergy" in their medical record. This results in a prevalence of self-reported NSAID-related hypersensitivity of 4.1% in our entire cohort. Fifteen patients had proven NSAID tolerance prior to this study. Table 2 summarizes the clinical characteristics of these patients.

All patients had experienced NSAID-related reactions before they received the diagnosis of mastocytosis. The most frequent symptoms were angioedema, erythema, and hypotension. Three patients required treatment in an emergency department. Of the patients

TABLE 2 Characteristics of patients with self-reported hypersensitivity reaction(s) to NSAIDs

	Age at diagnosis (years)	Sex	Subtype	Skin involvement	Serum tryptase at diagnosis (μg/L)	Atopy	Type of NSAID	Timing of reaction	Symptoms of reaction	MC mediator-related reaction to other stimuli
1	41	F	CM[a]	MPCM	8.6	Yes	ASA[b] 80 mg	2 h	Angioedema	Penicillin, lidocaine
2	72	M	ISM	No	20.0	No	Ibuprofen Diclofenac[c]	Unknown	Generalized pruritus, blurry vision	–
3	51	F	ISM	MPCM	125.0	Yes	Ibuprofen Diclofenac[c]	5 min	Angioedema, palpitations, collapse[d]	Heat
4	62	F	ISM	MPCM	118.0	No	Diclofenac	Unknown	Angioedema	Alcohol consumption
5	42	M	ISM	MPCM	31.4	No	Naproxen	10 min	Erythema, stridor, hypotension[d]	Alcohol consumption, wasp sting, temperature changes (cold)
6	40	M	ISM	No	24.7	Yes	Acetaminophen 1000 mg	5 min	Diffuse erythema	Morphine, strong odors
7	48	F	ISM	MPCM	43.5		Naproxen	5 min	Diffuse erythema	–
8	68	F	ISM	MPCM	17.8	No	Diclofenac	20 min	Hypotension, collapse[d]	Iodated contrast media

ASA, acetylsalicylic acid; CM, cutaneous mastocytosis; MPCM, maculopapular cutaneous mastocytosis; NSAID, nonsteroidal anti-inflammatory drug.
[a]Complete workup with bone marrow investigation was negative for mastocytosis.
[b]Hymenoptera sensitization could not be confirmed by specific IgE nor intradermal tests.
[c]Two separate reactions at different occurrences.
[d]Treatment at emergency department required.

who could reliably recall their reaction at the time of questioning, everyone experienced a reaction within 2 hours after the ingestion of the NSAID. Patient number 5 developed a reaction after the combination of naproxen and a wasp sting. Hymenoptera sensitization could not be confirmed. Although it is likely that Hymenoptera was the main culprit and naproxen acted as a cofactor, the patient was labeled as "NSAID intolerant" because of the severity of the reaction and the risk of aggravation of future reactions with the use of NSAIDs. Patient number 3 later had a drug challenge with celecoxib which was negative. Patient numbers 6 and 8 both later had a negative drug challenge with naproxen, which excludes a general nonspecific NSAID hypersensitivity. Notably, seven patients (87.5%) reported mast cell mediator-related reactions to physical stimuli. These reactions ranged from flushing or gastrointestinal symptoms to anaphylaxis.

3.4 | Characteristics associated with NSAID hypersensitivity

As only one patient had a positive ASA challenge, the data from the prospective study could not be used to reliably identify any potential clinical characteristics that are associated with NSAID hypersensitivity. Therefore, the data from the retrospective cohort were analyzed for this purpose (Table 3).

Overall, patients with NSAID tolerance appear to have more daily mast cell mediator-related symptoms such as flushing, cognitive problems, fatigue, and pruritus. Only the latter was statistically significant ($P = .021$, chi-square test), probably due to the small numbers of patients. Patients with NSAID hypersensitivity reported more reactions to other drugs, although this difference did not reach statistical significance ($P = .063$). The same accounted for peripheral blood eosinophilia ($P = .181$), osteoporosis ($P = .186$), and alcohol intolerance ($P = .308$). Strikingly, traditional risk factors for NSAID hypersensitivity in the general population such as atopy, asthma, or rhinitis were not more frequent in the NSAID hypersensitivity group of our cohort. Neither were there any relevant differences in age, sex, serum tryptase levels, or skin involvement of mastocytosis.

4 | DISCUSSION

This is the first double-blind, placebo-controlled challenge study to investigate the prevalence and severity of ASA hypersensitivity among patients with mastocytosis. Only 1 of 50 participants (2%) had a positive ASA challenge, consisting of an urticarial rash. Three other patients had subjective symptoms to ASA. The characteristics of the study population were overall representative of a patient cohort in a tertiary center for mastocytosis, except for a relatively low number of male participants.[13,17,18]

However, the exclusion of patients with known risk factors for NSAID hypersensitivity might have led to a selection bias. Therefore, we performed an additional retrospective analysis of our entire cohort of 191 patients. This resulted in a prevalence of self-reported

TABLE 3 Comparison of clinical characteristics of patients with and without NSAID hypersensitivity of retrospective cohort mastocytosis center EMC

	No NSAID hypersensitivity (n = 15)	NSAID hypersensitivity (n = 8)	*P*-value
Age, median (IQR)	51 (20)	49 (25)	>.10
Male sex, n (%)	6 (40)	3 (33.3)	>.10
Subtype, n (%)			
MIS	5[a] (33.3)	1[b] (12.5)	>.10
ISM	10 (66.7)	7 (87.5)	
SSM	0	0	
SM-AHN	0	0	
ASM	0	0	
Presence of skin mastocytosis, n (%)	11 (73.3)	5 (62.5)	>.10
Serum tryptase at diagnosis, median (IQR)	28.2 (10.9)[c] Range: 2.2-72.0	28 (53)[c] Range: 8.6-125.0	>.10
History of anaphylaxis, n (%)	5 (33.3)	4 (50)	>.10
Pruritus, n (%)[d]	7 (46.7)	0	.021
Flushing, n (%)[d]	5 (33.3)	1 (12.5)	>.10
Dyspepsia, n (%)[d]	3 (10.3)	1 (12.5)	>.10
Diarrhea, n (%)[d]	3 (20)	0	>.10
Fatigue, n (%)[d]	6 (42.9)	1 (12.5)	>.10
Subjective cognitive problems, n (%)	4 (40)	0	.074
Osteoporosis, n (%)	1 (7.1)	2 (28.6)	>.10
Eosinophilia, n (%)	2 (13.3)	3 (37.5)	>.10
Atopy, n (%)	4 (26.7)	3 (37.5)	>.10
History of hypersensitivity reaction to other drugs, n (%)[e]	1 (6.7)	3 (37.5)	.063
Alcohol intolerance, n (%)[f]	4/5 (44.4)	4/5 (80)	>.10
MC mediator-related reaction to physical triggers, n (%)[c]	5/8 (62.5)	4/5 (80)	>.10

[a]Bone marrow investigation was incomplete in 1 patient and not performed in the other patients.
[b]Bone marrow investigation negative, classifying this patient as cutaneous mastocytosis.
[c]Physical triggers: heat, cold, stress, exercise.
[d]Symptom present ≥3 d per week.
[e]The culprit drug was amoxicillin in the NSAID-tolerant patient. See Table 2 for the culprit drugs in the NSAID hypersensitivity group.
[f]Not known for all patients because some patients never consume alcohol.

NSAID-related hypersensitivity of 4.1%. Importantly, all patients with NSAID hypersensitivity experienced one or more reactions before the diagnosis of mastocytosis was established. Although interpretation of any differences between the patients with and without NSAID hypersensitivity is difficult due to the small patient numbers, it appears from the retrospective cohort that patients with NSAID hypersensitivity more often experienced hypersensitivity reactions to other drugs and/or alcohol. It must be noted that three patients reported a hypersensitivity reaction to amoxicillin, which is the third most reported culprit for drug-related reactions in the Netherlands. We cannot exclude that the relationship between amoxicillin and the reported reactions was based on coincidence. Another notable difference is the higher prevalence of mast cell mediator-related symptoms among NSAID-tolerant patients. Possibly, this difference represents the clinical practice, because patients with symptoms such as flushing are more often in need for ASA and therefore were more likely to undergo an NSAID challenge out of medical necessity. A causal explanation seems unlikely.

Interestingly, 2 of 8 patients with a history of NSAID-related hypersensitivity reactions later had negative unblinded challenges with another NSAID. This can be explained in multiple ways: They might have a specific, IgE-mediated allergy to the culprit NSAID. Another, more likely, explanation is the fact that NSAIDs can be a cofactor to augment anaphylaxis.[19,20] The current trial does not provide prospective data on the role of NSAIDs as a cofactor in patients with mastocytosis. Also, although the use of ASA as a model for general NSAID hypersensitivity is widely accepted, a specific allergy for one type of NSAID is potentially missed with this approach. Moreover, the currently presented data cannot be extrapolated to patients with traditional risk factors for NSAID hypersensitivity, such as asthma, nasal polyposis, or atopic constitution. However, most patients with mastocytosis do not have such risk factors[21]; thus,

most patients would fulfill the currently used inclusion criteria. Lastly, a possible caveat of drug challenges in patients with mastocytosis is the fact that many of them already have mast cell mediator-related symptoms on a daily basis, especially as anti-mediator medications need to be interrupted prior to a challenge. Using NRS scores, we tried to score these symptoms as objectively as possible; however, some degree of bias in the assessment of challenge studies cannot be excluded in this patient category.

The prevalence of NSAID hypersensitivity in our cohort of patients with mastocytosis is only slightly higher compared to the prevalence of 1%-2% of self-reported NSAID-related hypersensitivity in a general population.[22] There are few comprehensive data on NSAID hypersensitivity among patients with mastocytosis published to date. One retrospective study described 20 patients who received ASA in varying dosages and schedules. Two patients (10%) reported a mild reaction: either delayed urticaria or immediate flushing.[10] Other descriptive population studies reported a prevalence ranging between 2.3% and 6%, of mostly mild immediate-type reactions.[20,23,24] We could not find published proof of fatal anaphylaxis due to NSAIDs in patients with mastocytosis. Conversely, in a population of 137 persons with drug- or food-related anaphylaxis, mastocytosis was found in only 2 patients.[25] Moreover, there was no association between NSAID hypersensitivity and serum tryptase levels in a general cohort.[26]

An EAACI position paper advises that patients with mastocytosis and known NSAID tolerance can safely keep taking NSAIDs, but all others should undergo workup.[27] However, that workup is not further specified in this study. Based on our current results, we suggest that everyone with mastocytosis who has never experienced a hypersensitivity reaction to NSAIDs, or other drugs, can safely start taking NSAIDs at home. Given the fact that patients who have experienced a hypersensitivity reaction to another drug appear to be at a higher risk of NSAID hypersensitivity reactions, it seems appropriate to administer the first dose in a clinical setting, preferably with an incremental challenge protocol. As mentioned before, the interpretation of such challenges is very delicate and requires experience in this area. Despite the placebo-controlled approach, some patients will have only subjective symptoms to an NSAID, and although this is likely to be a "placebo reaction," it cannot be excluded that these minor symptoms reflect some reaction to the NSAID. The risk of developing more serious reactions in the future is unclear for these patients, and careful counseling is of paramount importance.

Possibly, patients with a history of NSAID-related hypersensitivity reactions can also be challenged with another NSAID. Depending on the type and severity of the previous reaction(s), it can be safer to challenge with a selective COX-2 inhibitor in these cases. Unfortunately, our study cannot corroborate this suggestion. Prospective placebo-controlled studies on these topics would be highly interesting, although are hindered by potential safety issues. On a final note, although the possible benefits of ASA and NSAIDs in general for patients with mastocytosis are clear, the indication must be weighed against possible adverse effects. For instance, patients with mastocytosis already are at risk of peptic ulcer disease,[28] which might be increased by the use of NSAIDs. Moreover, it is well-known that NSAIDs can act as a cofactor in anaphylaxis. Ultimately, a careful consideration of risks and benefits needs to be made for each individual, and patients should be consulted on the possible risks.

5 | CONCLUSIONS

In summary, the frequency of NSAID hypersensitivity among patients with mastocytosis was 2%, as determined by a prospective double-blind ASA challenge. The frequency of self-reported NSAID hypersensitivity in a retrospective cohort was 4.1%. Based on the mild reactions we saw in our study, combined with the real-life experience that all patients with severe NSAID hypersensitivity experienced these reactions prior to their diagnosis of mastocytosis, we conclude that it is safe to administer NSAIDs to most patients with mastocytosis if they do not have a history of prior NSAID hypersensitivity reactions. Extra caution might be taken in patients with previous hypersensitivity reactions to other drugs, or with traditional risk factors for NSAID hypersensitivity.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

AUTHORS' CONTRIBUTIONS

MH and PvD are responsible for the concept and design of the study. MH and SdV performed the inclusion and drug challenges and collected and analyzed the data. PvH and RGvW gave advice about the design of the trial and interpretation of the data. All authors revised the manuscript on multiple occasions.

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