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# Comparison of the Safety Profiles of 3 Different Hymenoptera Venom Immunotherapy Protocols: A Retrospective 2-Center Study of 143 Patients

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**Keywords**

Cluster protocol · Hymenoptera venom allergy · Rush protocol · Side effects · Ultra-rush protocol · Venom immunotherapy

**Abstract**

***Introduction:*** Venom immunotherapy (VIT) is highly effective and the treatment of choice for patients with a history of systemic anaphylactic reactions to a Hymenoptera sting. It has been assumed that VIT protocols with a rapid dose increase during the induction phase are associated with a higher frequency of systemic reactions (SR); however, study data addressing this issue are conflicting. ***Objective:*** The aim of this study was to compare the safety of 3 different Hymenoptera VIT protocols (half-day ultra-rush, 3-day rush, 3-week cluster). ***Methods:*** This retrospective 2-center study included 143 Hymenoptera venom-allergic patients, who underwent 147 VIT procedures during the years 2015–2018. Twenty cluster, 75 rush, and 52 ultra-rush VIT protocols were performed with honeybee (54 protocols) and wasp (93 protocols) venom. All documented side effects were classified into large local and SR (Ring and Messmer classification). ***Results:*** SR were observed during 11 (7.5%) VIT procedures and did not exceed severity grade II. SR occurred more frequently in cluster compared to accelerated protocols. This result was observed for both honeybee (cluster: 25%, rush: 8.7%, and ultra-rush: 15.8%) and wasp VIT (cluster: 12.5%, rush: 0%, and ultra-rush: 6.1%), though the differences were statistically significant only in the wasp VIT subgroup. Honeybee venom elicited more SR than wasp venom (14.8 and 3.2%, respectively, $p = 0.01$). The risk for SR did not depend on age, sex, concomitant antihypertensive medication, hypertryptasemia, or severity of the index sting reaction. ***Conclusion:*** Accelerated VIT protocols, namely, rush and ultra-rush protocols are safe therapeutic options for Hymenoptera venom-allergic patients and displayed fewer SR than cluster VIT protocols in our study.

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## Introduction

Hymenoptera stings, besides drugs and food, represent one of the most relevant elicitors of systemic allergic reactions in Europe and are associated with hospitalization, quality of life impairment, and potential fatality [1, 2]. In central Europe, honeybees (*Apis mellifera*) and wasps (*Vespula vulgaris* and *Vespula germanica*) are considered as major culprit insects [3]. The majority of the population exhibits only minor local reactions in response to an insect sting. However, up to 25% of general population develop large local reactions (LLR), defined as swelling exceeding the diameter of 10 cm with persistence for more than 24 h [2]. IgE-mediated systemic anaphylactic sting reactions are a less frequent, yet potentially life-threatening clinical presentation. They are estimated to occur in up to 7.5% of the European adults and to cause approximately 0.1 fatalities per million population per year [2, 4].

Venom immunotherapy (VIT) is highly effective as it offers long-term protection against further systemic anaphylactic reactions in 77–84 and 91–96% of honeybee and wasp venom-allergic subjects, respectively [5, 6]. Therefore, Hymenoptera VIT is considered as treatment of choice in insect-allergic patients with previous severe systemic sting reactions.

Different schedules for VIT have been established in the past. They mainly differ concerning the duration of the induction phase (synonyms: up-dosing/build-up phase), in which venom dose is increased stepwise until reaching the usual maintenance dose of 100 μg venom: (i) conventional protocols of several weeks (weekly single injections) [7], (ii) cluster protocols of approximately 3 weeks (up to 5 injections per day on a weekly basis) [8, 9], and (iii) ultra-rush and rush protocols of 1 to 3 consecutive days (up to 7 injections per day) [10, 11]. Nowadays, accelerated regimens (rush/ultra-rush) are widely used given the advantage of achieving protection very rapidly and increasing patient comfort and compliance compared to slower protocols, which demand more frequent consultations over a longer period of time.

Hymenoptera VIT in general is considered as safe, although on rare occasions potentially life-threatening systemic reactions (SR) can occur. Reported frequency of SR during VIT is highly variable in different studies, ranging from 0–67% [9, 12]. It has been assumed that accelerating dose increase during induction phase by using rush/ultra-rush protocols may result in a higher rate of side effects, especially SR, compared to cluster and conventional protocols with a slower up-dosing schedule. However, the study data addressing this issue are conflicting. Therefore, we aimed to compare the frequency and severity of side effects during the induction phase of 3 different VIT protocols, namely, a half-day ultra-rush, a 3-day rush, and a 3-week cluster protocol.

## Materials and Methods

*Study Design and Population*

Records of 143 patients, who underwent VIT for Hymenoptera allergy at the Department of Dermatology, Kepler University Hospital, Linz, Austria, in the years 2015–2017 and at the Clinic for Dermatology, Venerology, and Allergology, Kantonsspital St. Gallen, Switzerland, in the years 2016–2018 were analyzed in this retrospective 2-center study. The only inclusion criterion was a VIT start in the above stated years and performance according to one of the chosen protocols (cluster, rush, or ultra-rush). Repeated VIT build-up courses were excluded if a previous discontinued VIT course in the same patient with the same Hymenoptera venom had already been included in the study. Analysis was confined to the induction phase of VIT, as it has been shown that side effects accumulate in this first part of VIT rather than in the maintenance phase [13–15]. The study protocol was approved by the Ethics Committees of the Federal State Upper Austria (ethics committee number 1083/2019) and the Greater Region of East Switzerland (EKOS 19/110).

*VIT Procedure*

Diagnosis and indication for VIT was made based on the recommendations of the European Academy of Allergy and Clinical Immunology. If applicable, patients were instructed to continue their antihypertensive medication. Detailed documentation, including time, dosage, and location of injections, occurrence of side effects (local/systemic), as well as required therapeutic interventions, was made during VIT by the administering medical staff in the patient's records.

Two different VIT schedules were used at the Department of Dermatology, Kepler University Hospital Linz, namely, an outpatient 3-week cluster protocol (9 injections, cumulative venom dose 255 μg) and an inpatient 3-day rush protocol (10 injections, cumulative venom dose 316.11 μg). Patients could freely choose between these protocols according to their preferences. At the Department of Dermatology, Kantonsspital St. Gallen, an outpatient half-day ultra-rush protocol (6 injections, cumulative venom dose 111.1 μg) was applied. Detailed up-dosing schedules can be found in the online suppl. Table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000509187).

Cluster and rush VIT was predominantly performed using the purified aqueous extract Aquagen SQ® for *A. mellifera* and/or *Vespula* spp. (ALK-Abelló, Hørsholm, Denmark). Only during 2 rush VIT courses, Venomenhal® wasp vaccine (Hal Allergy, Leiden, Netherlands) was applied. Ultra-rush VIT was mainly conducted with the aqueous preparation Pharmalgen® for *A. mellifera* and/or *Vespula* spp. (ALK-Abelló, Hørsholm, Denmark). Because of a delivery bottleneck of Pharmalgen®, the aqueous preparation Venomil® (Bencard Allergy, Munich, Germany) was used for 20 ultra-rush VIT courses (8 honeybee and 12 wasp VIT procedures).



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**Table 1.** Patient characteristics of the total study population and the VIT protocol subgroups

| | Total | Cluster VIT | Rush VIT | Ultra-rush VIT | *p* value |
|---|---|---|---|---|---|
| Protocols, *n* | 147 | 20 | 75 | 52 | |
| Sex, *n* (%) | | | | | |
| Male | 86 (58.5) | 12 (60.0) | 46 (61.3) | 28 (53.8) | 0.694 |
| Female | 61 (41.5) | 8 (40.0) | 29 (38.7) | 24 (46.2) | |
| Age, years | | | | | |
| Mean (SD) | 46.3 (14.6) | 44.8 (13.2) | 50.3 (14.7) | 41.1 (13.2) | 0.001[a] |
| Range | 15–74 | 19–73 | 16–74 | 15–57 | |
| Hymenoptera venom, *n* (%) | | | | | |
| Honeybee | 54 (36.7) | 12 (60.0) | 23 (30.7) | 19 (36.5) | 0.054 |
| Wasp | 93 (63.3) | 8 (40.0) | 52 (69.3) | 33 (63.5) | |
| Severity of index sting reaction (local) (I) (II) (III) (IV)[b] | (5) (7) (62) (46) (27) | (2) (2) (12) (4) (0) | (3) (3) (48) (17) (4) | (0) (2) (2) (25) (23) | <0.001[a] |
| Hypertryptasemia, *n* (%) | 8 (5.4) | 0 | 5 (6.7) | 3 (5.8) | 0.502 |
| Medication with at least one antihypertensive agent, *n* (%) | 21 (14.3) | 2 (10) | 15 (20) | 4 (7.7) | 0.126 |
| BB | 12 | 2 | 9 | 1 | |
| ARB | 12 | 1 | 8 | 3 | |
| ACEI | 4 | 0 | 4 | 0 | |

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BB, β-blocker; SD, standard deviation; VIT, venom immunotherapy. [a] Indicates significant *p* values. [b] According to Ring and Messmer classification.

During cluster and rush VIT at the Kepler University Hospital Linz, pre- and concurrent medication with antihistamines (desloratadine) was administered only on demand if allergic symptoms appeared. By contrast, all patients who underwent ultra-rush VIT in the Kantonsspital St. Gallen received antihistamines (levocetirizine) as a premedication before VIT.

*Data Acquisition*

Data were collected by thoroughly investigating the medical records of the included patients in April 2018 (Kepler University Hospital Linz) and August 2019 (Kantonsspital St. Gallen). Following main points were obtained and transferred to a pseudonymized excel table: demographic data, detailed medical history, including long-term medication, severity of the index sting reaction, baseline tryptase concentration, type and severity of documented side effects, and required therapeutic interventions. SR were graded in accordance to the 4-step severity classification of Ring and Messmer, which starts from grade I (isolated skin symptoms) and increases with progressive organ involvement (gastrointestinal and/or cardiorespiratory system) to the most severe grade IV (circulatory and/or respiratory arrest) [16]. LLR were defined as swelling exceeding the diameter of 10 cm, which persisted for more than 24 h [2]. Concerning concomitant antihypertensive medication, we focused analysis on angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers and β-blockers as these drug classes were assumed to aggravate allergic reactions during VIT in the past.

*Statistical Analysis*

Due to the explorative study design, we did not use power calculation to determine needed sample size. Descriptive statistics were performed to characterize study population. Furthermore, it was tested if baseline patient characteristics were distributed equally among the protocol subgroups. Afterward, we analyzed if there was a difference in the frequency of side effects between the 3 protocol subgroups (primary outcome). Secondary outcome was the effect of type of Hymenoptera venom, sex, age, and severity of the index sting reaction and of concomitant antihypertensive medication on the occurrence of side effects. For these purposes, we used the $\chi^2$ test for nominal data, the Mann-Whitney U test for ordinal data, and the independent samples *t* test (2 groups)/one-way ANOVA (more than 2 groups) for continuous variables. If required, testing for normal distribution was done by the Kolmogorov-Smirnov test. A $p$ value < 0.05 was considered statistically significant. All statistical analyses were carried out using SPSS Statistics© Version 24.

## Results

A total of 143 patients underwent 147 VIT procedures in the years between 2015 and 2018. Four patients had clinical double allergy to honeybee and wasp venom and underwent both VIT procedures non-simultaneously. The patient characteristics of the study population are demonstrated in Table 1.

In the whole study population, SR were observed during 11 (7.5%) VIT procedures. Objective symptoms were present in 7 (4.8%) and emergency allergy medications (antihistamines and/or corticosteroids) were required during 8 (5.4%) of these VIT courses. SR did not exceed severity grade II (grade I $n = 8$, grade II $n = 3$), and epinephrine administration was never required (online suppl. Table 2). A total of 146 VIT induction treatments



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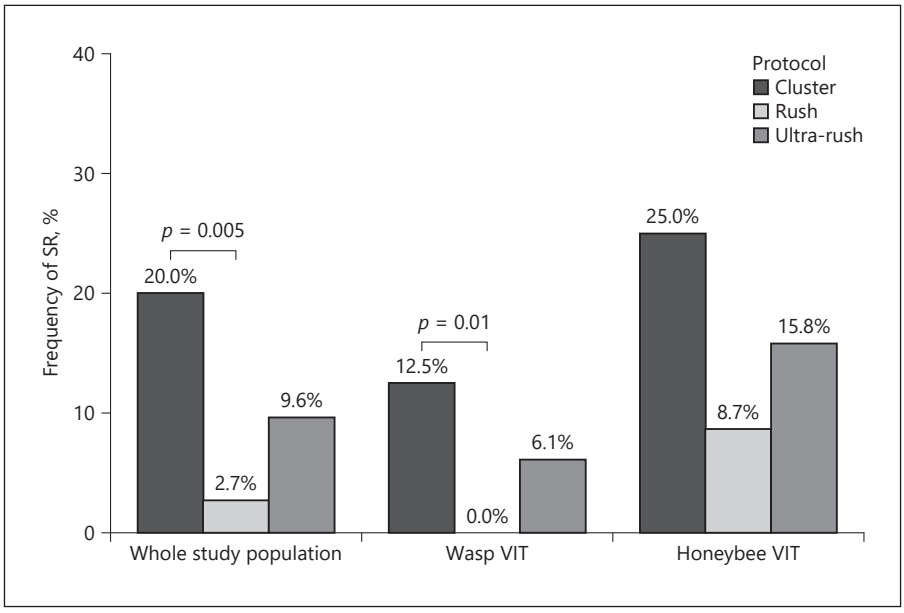


**Fig. 1.** Comparison of the frequency of SR (% of conducted protocols) between the 3 protocols during VIT induction phase. Significant results are marked with square brackets and respective *p* values. SR, systemic reactions; VIT, venom immunotherapy.

(99.3%) were successfully completed. VIT was discontinued in 1 patient (no. 2 in the online suppl. Table 2) because of another SR grade I in his second cluster up-dosing procedure. Inpatient VIT and pretreatment with omalizumab was planned, but the patient did not keep his appointment and was not available for further treatment by the responsible allergy center.

Honeybee VIT was associated with a significant higher rate of SR, which were observed during 8 (14.8%) honeybee compared to 3 (3.2%) wasp VIT courses in the total study population ($p = 0.01$, 2-sided $\chi^2$ test). A higher prevalence of SR with honeybee venom was shown with all 3 VIT protocols (Fig. 1).

SR in the overall study population were distributed unequally among the protocols (cluster protocol 20%, rush protocol 2.7%, and ultra-rush protocol 9.6%). However, in the pairwise comparisons of protocols, only the cluster protocol statistically significantly elicited more SR compared to the rush protocol (cluster vs. rush $p = 0.005$, 2-sided $\chi^2$ test), whereas level of significance was not reached in other comparisons (rush vs. ultra-rush $p = 0.092$, cluster vs. ultra-rush $p = 0.233$, 2-sided $\chi^2$ test; Fig. 1).

To rule out confounding of the results by the unequal Hymenoptera distribution, we compared the 3 protocols separately for honeybee and wasp VIT. As shown in Figure 1, in both Hymenoptera subgroups, most SR occurred with the cluster, followed by the ultra-rush and rush protocol. In the wasp VIT subgroup ($n = 93$), a trend toward less SR with rush VIT compared to both other protocols was found (cluster protocol 12.5%, rush protocol 0%, and ultra-rush protocol 6.1%). However, only the pairwise comparison of the rush and cluster protocol was statistically significant (rush vs. cluster $p = 0.01$, rush vs. ultra-rush $p = 0.072$, and cluster vs. ultra-rush $p = 0.53$; 2-sided $\chi^2$ test). A similar distribution of SR among the 3 protocols was found with honeybee venom ($n = 54$), although significance was not reached (cluster protocol 25%, rush protocol 8.7%, and ultra-rush protocol 15.8%, $p = 0.431$, 2-sided $\chi^2$ test).

LLR occurred during 6.8% of all 147 VIT courses with no difference between the type of Hymenoptera venom (honeybee 7.4% and wasp 6.5%, $p = 0.824$, 2-sided $\chi^2$ test). Furthermore, no statistical difference concerning the distribution of LLR among the 3 VIT protocols was observed (whole study population: cluster protocol 0%, rush protocol 6.7%, and ultra-rush protocol 9.6%, $p = 0.348$; wasp VIT: cluster protocol 0%, rush protocol 3.8%, and ultra-rush protocol 12.1%, $p = 0.341$; honeybee VIT: cluster protocol 0%, rush protocol 13%, and ultra-rush protocol 5.3%, $p = 0.235$; further pairwise comparison of all protocols in each Hymenoptera group did not show any significant results [*p* values not shown]; 2-sided $\chi^2$ test was used for each comparison; online suppl. Fig. 1).

Frequency of SR was not associated with sex ($p = 0.361$, 2-sided $\chi^2$ test) or age ($p = 0.810$, 2-sided independent-samples *t* test). Furthermore, medication with at least one antihypertensive agent (angiotensin-converting enzyme



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inhibitor, angiotensin II receptor blocker and/or β-blocker) did not increase the risk for SR during VIT ($p = 0.159$, 2-sided $\chi^2$ test): None of the 21 patients with an antihypertensive medication experienced SR. Patients in the ultra-rush protocol subgroup showed higher severity grades of the index sting reaction (country-specific stricter indication for VIT in Switzerland). However, statistical analysis did not reveal a significantly higher prevalence of SR with increasing severity of index sting reaction ($p = 0.078$, 2-sided Mann-Whitney U test) in the overall study population.

Baseline tryptase concentration was elevated in 8 included subjects (2 honeybee- and 6 wasp-allergic patients). Two of them were diagnosed with cutaneous mastocytosis and 2 with indolent systemic mastocytosis prior to VIT, whereas in the others pre-existing mastocytosis was not known. Elevated baseline tryptase concentration did not increase the risk for SR in our study ($p = 0.584$, 2-sided $\chi^2$ test). Only 1 patient with slightly elevated baseline tryptase concentration (12.4 μg/L) without previous diagnosis of mastocytosis, who underwent ultra-rush honeybee VIT, experienced grade II SR. Side effects in the other 7 patients did not exceed mild local reactions.

## Discussion

In this study, we retrospectively analyzed the safety of 3 different Hymenoptera VIT protocols, namely, a cluster, a rush, and an ultra-rush regime. We showed that (i) VIT in general is safe and well tolerated and (ii) rapid dose increase with rush and ultra-rush protocols does not elicit more SR than a more time-consuming up-dosing using a cluster protocol.

In line with previous reports, we confirmed the overall safety of VIT as SR in our study did not exceed severity grade II (Ring and Messmer classification), and epinephrine administration was never required. In large multicenter studies, the reported incidence rates for SR were 8.4–20% [13, 14, 17]. SR in our study, therefore, occurred within the lower range of previous studies, namely, during 7.5% of VIT procedures. We documented more SR with honeybee than wasp venom (14.8 and 3.2%, respectively), which is in accordance with a Cochrane Review (reported SR: honeybee VIT 14.2% and wasp VIT 2.8%) [18] and multiple previous studies with various treatment schedules [5, 13–15, 19–21].

Our results indicate that VIT protocols with an accelerated venom up-dosing are safe therapeutic options. We even found fewer SR with rush and ultra-rush regimes than a cluster VIT protocol. Furthermore, although fewest SR occurred with the rush protocol, no statistical significant difference between the rush and ultra-rush protocol was detected. These observations were independent from the type of Hymenoptera venom extract. Therefore, unequal Hymenoptera distribution cannot solely explain the divergent distribution of SR among the protocols. The applied protocol per se presumably contributed to a significant extent to these results.

Existing study data investigating whether certain treatment schedules are associated with a higher frequency of SR are highly conflicting [11, 13, 14, 22–24]. Large-scale studies ascribed accelerated protocols to a higher incidence of SR [13, 14]. By contrast, a considerable number of other, though smaller, studies reported lower rates of SR when the VIT induction phase was shortened [11, 22–24]. In general, cluster protocols for Hymenoptera VIT were less studied and rarely compared to other VIT protocols in the past. In most reports, rapid protocols (ultra-rush/rush) were compared to a conventional protocol [23–26]. The only larger study which comprised rush, ultra-rush, as well as cluster VIT protocols was the European Academy of Allergy and Clinical Immunology multicenter study of Mosbech and Müller [14]. In this study, a similar percentage of patients experienced SR with rapid (diverse rush and ultra-rush protocols subsumed, 24%) and cluster protocols (22%) during the induction and maintenance phase. Lowest frequency of SR was found with a conventional treatment schedule (12%). Regarding the comparison of accelerated protocols, some studies reported equal or lower SR with ultra-rush than rush protocols [11, 25]. By contrast, Ruëff et al. [13], similarly to our results, reported slightly less SR with a rush (7.2%) compared to an ultra-rush protocol (11.4%).

Interestingly, the rush protocol, which comprised the highest number of injections and highest cumulative venom dose, showed to be the safest in our study. This is in contrast to some studies, which suggested that occurrence of SR can be diminished by reducing the number of injections and cumulative venom dose in protocols with a rapid build-up phase [7, 11, 22]. According to the current guidelines, a starting dose of 0.001–0.1 μg is recommended, although also 1 μg seems to be safe [27, 28]. Therefore, the starting dose of 5 μg in our cluster protocol appears quite high and unequal distribution of SR between the protocols might be explained by the more cautious dose increase at the beginning of the build-up phase with the rush compared to other protocols (cumulative venom dose of 30 μg was exceeded after 3 [cluster], 4 [ultra-rush], or 6 [rush] injections; see up-dosing schedules



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in the online supp. Table 1). High starting dose might have also contributed to the comparatively high rate of SR, namely, 20%, with our cluster protocol, which is at the upper range of previously published study data (0–22%) [9, 14, 29].

LLR were reported in 6.8% of patients without statistical difference between the VIT protocols or Hymenoptera species. Similarly, Roll et al. [19] reported LLR in 5% of patients during an ultra-rush protocol, whereas other studies reported a marked higher rate of LLR [7, 25, 30]. Notably, no LLR was observed in the cluster protocol group. Similarly, Čerpes et al. [31] reported a very low incidence rate of LLR with a cluster protocol (honeybee 3.6% and wasp 5.5%) compared to other protocols (rush/conventional). However, given the outpatient approach with intervals of 1 and 2 weeks between the up-dosing days (day 1, 8, and 22), LLR might have been missed in this patient cohort.

Major limitations of our study are the retrospective character and the relatively small sample size, which especially applies to the cluster protocol. Subjects were not distributed equally among the 3 protocols regarding number as well as the type of Hymenoptera allergy, owing to the retrospective study character and the predominance of accelerated protocols in clinical practice. Furthermore, each VIT protocol was performed only in 1 clinic; therefore, center-specific influences (i.e., documentation standards, different Hymenoptera venom brands, and specific patient characteristics) cannot be ruled out.

Despite the abovementioned limitations, our results expand the currently still sparse and conflicting study data on VIT protocol comparison and, therefore, might contribute to the improvement of VIT procedure. In conclusion, we showed that accelerated rush and ultra-rush protocols exhibit a comparable safety profile and elicit fewer SR than a 3-week cluster protocol. Therefore, accelerated VIT protocols generate rapid protection in Hymenoptera venom-allergic patients without concurrently increasing the risk for systemic side effects.


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## Statement of Ethics

This study was performed in adherence to the guidelines of the Declaration of Helsinki, the guidelines for Good Clinical Practice of the International Council for Harmonization, and applicable local law and regulations. The study protocol was approved by the competent Ethics Committees of the Federal State Upper Austria (ethics committee number 1083/2019) and the Greater Region of East Switzerland (EKOS 19/110).

## Conflict of Interest Statement

The authors declare that they have no conflict of interest with regard to this study.


## Funding Source

There is no funding to declare.


## Author Contributions

W.H. and B.B.W. conceived and supervised the study. I.P. contributed to data collection and analyzed study data. M.K. collected the data from the Kantonsspital St. Gallen as a part of her master thesis. A.C. and I.A.F. were mainly involved in patient examination and treatment. E.G. contributed to the interpretation of the results. W.H. and I.P. wrote the manuscript in close collaboration with all co-authors. All authors provided critical feedback and contributed to the final manuscript.

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