De-escalation of dupilumab for chronic rhinosinusitis with nasal polyps: analysis of outcomes after modified dosing regimen*

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Rhinology 63: 6, 765 - 767, 2025
https://doi.org/10.4193/Rhin25.151

***Received for publication:**
March 18, 2025
Accepted: May 23, 2025

Associate Editor:
Sietze Reitsma

Dear Editor:

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a persistent inflammatory condition with severe impacts on quality of life and substantial economic costs [1,2]. Dupilumab targeting the underlying T2 inflammation in CRSwNP showed promising results; however, it is unknown if intensive regimens must be maintained in responders to prevent relapse [3,4]. In 2019, FDA and the European Commission approved Dupilumab 300 mg administered subcutaneously every two weeks for CRSwNP. We hypothesized that disease control might be maintained by reducing the frequency of administration in patients who initially well answered to the standard treatment [3,4]. To date the benefit of de-escalation was only analyzed in short time [5]. We wanted to understand if a de-escalation regimen could be introduced without compromising disease control in long follow-up; to this aim we de-escalated Dupilumab at 300 mg every four weeks following a year of conventional bi-weekly administration.

A single-center, observational study was conducted in a tertiary referral hospital, recruiting forty-three patients with CRSwNP from March 2021 to December 2022. All patients were evaluated by nasal endoscopy, Nasal Polyps Score (NPS) [6] and SNOT-22, at baseline (T0), after 12 months (T12), 18 months (T18), and two years of therapy (T24). All patients were treated with Dupilumab 300 mg subcutaneous dose each 14 days for 12 months [7]. Then at T12 the patients were classified based on their response to therapy in Good-to-Excellent Responders (GERs) and Poor-to-Moderate Responders (PMRs). GERs were advised to decrease the frequency of treatment to once every 4 weeks (de-escalation regimen) - De-escalation treatment group (DTG) - ; PMRs were suggested to continue with the standard treatment regimen once each two weeks (standard treatment group (STG) or to undergo FESS (salvage surgery). All patients were re-evaluated as previously described at T18 and T24. Within and between one-way ANOVA was performed (Supplementary material). Patients who used steroids (oral or nasal) during the observation time were excluded.

One of 43 patients initially included (Table S1) left the study. After 1 year of treatment, of the 42 patients we identified 30 (71.4%) GERs and 12 (28%) PMRs. 27 GERs accepted de-escalation therapy (DTG) regimen (once every 4 weeks), while 3 patients opted for standard treatment (STG). Among PMR, 8 (66.7%) patients continued standard treatment (STG) and 4 underwent endoscopic sinus surgery. Within group analysis showed a statistically significant improvement of the NPS (ANOVA: $p < 0.0001$) comparing T0 with T12, T18 and T24 both in the DGT and STG group (Figure 1A); same results were observed for SNOT-22 (Figure 1B) (supplementary for details). The comparison of NPS and SNOT between DGT and STG at 18- and 24-months follow-ups showed not statistically significant differences between the two groups (details in supplementary) (Figure 1C and D).

This study presents some major limitations i) a very limited statistical power to find any differences between groups and time points in this Bonferroni-corrected multiple testing model, ii) small sample size and iii) decision-process to de-escalate influenced by treatment response profile and patient preference,

Our results confirm previous studies [7-9] and suggest that a modified treatment regimen [9]—transitioning to monthly dosing—sustains symptomatic relief and objective disease control, providing preliminary evidence to support the feasibility of de-escalation in well-selected patients.

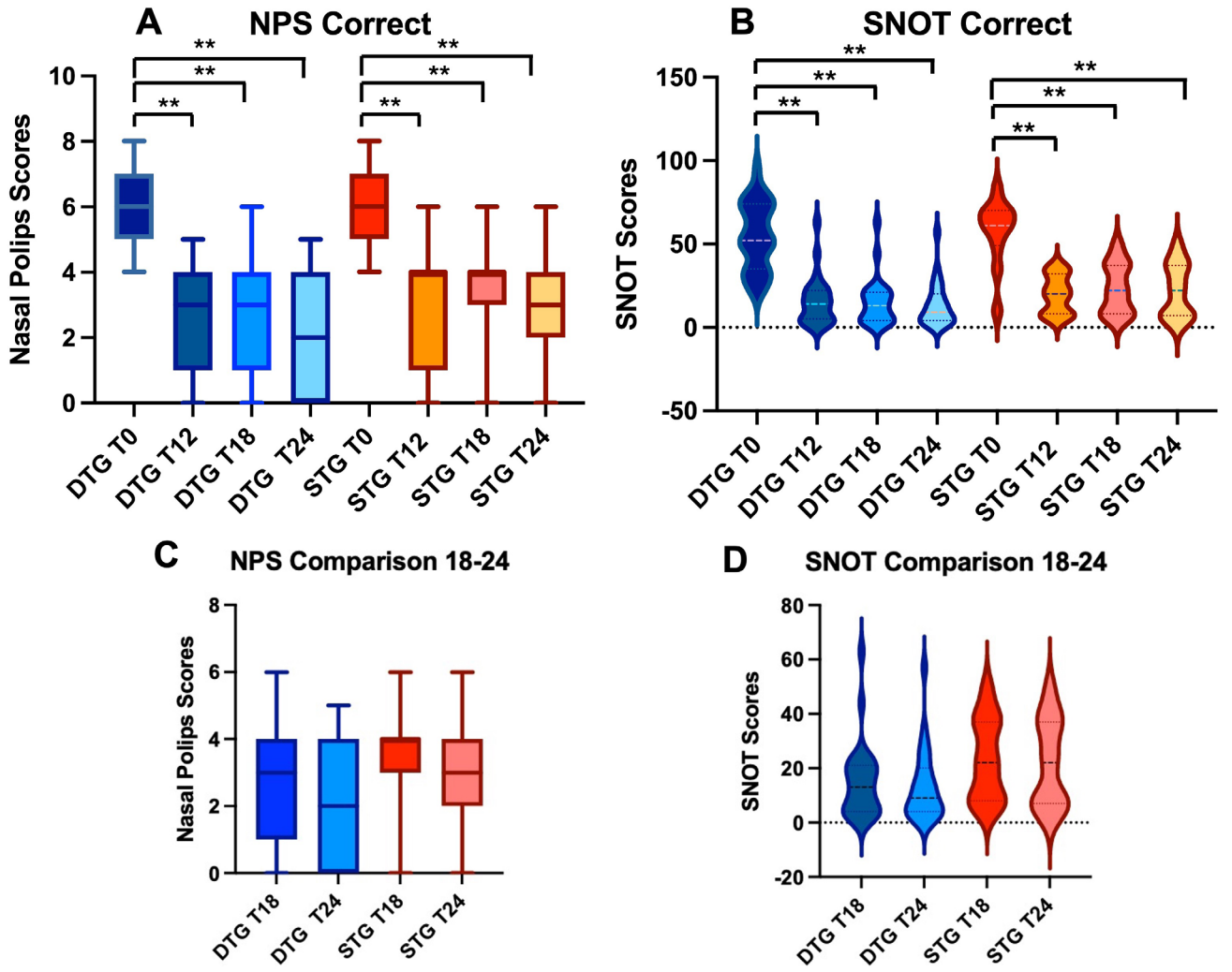

Figure 1. A) comparison of Nasal Polyps Score and SNOT (B) at the different observation points. To note standard treatment was performed in both groups for the first 12 months. "**" indicates p <0.01. C) Comparison of Nasal Polyps Score (NPS) and SNOT (D) between the two groups at follow-up T18 and T24. No statically significant differences were observed between the two groups.

The absence of differences among the two groups at 18 and 24 months suggests that for GERs, reducing the frequency of Dupilumab administration does not compromise clinical outcomes (Full discussion in supplementary). The potential benefits of de-escalation include improved patient adherence, reduced adverse effects, and cost savings, which could enhance accessibility and sustainability of biologic therapy in CRSwNP management.

Authorship contribution

Study design: LDA, PG and ADS; writing first draft: ADS, PG, LDA, LP; data collection: LDA, PG, LP; Literature search: LP, GM; Analyses of data: ADS; Validation: ADS, PG, LDA, NYB, MJB; review and editing: NYB, MJB; supervision: LDA, ADS

Conflict of interest

None of the authors declare conflict of interest.

Funding

No private or public funds supported this study.

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This manuscript contains online supplementary material

SUPPLEMENTARY MATERIAL

Materials and methods

A single-center, observational study was conducted in a tertiary referral hospital. Forty-three patients in the department of otolaryngology were recruited from March 2021 to December 2022 and treated for CRSwNP. All patients signed a written consent to participate in the study and authorized the use of their data for scientific purposes. The study was approved by the Internal Review Board (IRB) of the hospital with number 013/2021. The research was conducted following the Helsinki rules for human rights. The patients were evaluated by two experienced otolaryngologists (LDA and PG). All patients underwent nasal endoscopy and completed a SNOT-22 questionnaire at each follow-up. The endoscopic findings were classified using the NPS.

Scheduled clinical evaluation were performed at the baseline before starting the therapy (T0), and at 12 months (T12), 18 months (T18), and two years of therapy (T24). The patients were asked about intranasal corticosteroids use at each follow-up. Patients who opted to continue intranasal corticosteroid therapy at enrollment were excluded to avoid confounding effects from topical steroids.

All patients included in the study were treated with Dupilumab 300 mg subcutaneous dose each 14 days for 12 months. Side effects and treatment compliance were assessed at each visit. We used Dupilumab for two reasons, the first was that it was the only available drug for the treatment of CRSwNP in our country at the starting of the study, then, although other biologics became available in the following months, we did not change Dupilumab because it is the suggested treatment for CRSwNP without associated asthma.

At the end of 1 year of treatment (T12) the patients were classified based on their response to therapy using EPOS 2020 criteria, revised by EPOS/EUPHOREA in 2023 as Good-to-Excellent Responders (GERs) and Poor-to-Moderate Responders (PMRs). Patients who were among GERs were advised to decrease the frequency of treatment to once every 4 weeks (de-escalation regimen); patients who were among PMRs were counseled to continue with the standard treatment regimen of once every two weeks or were advised to undergo FESS (salvage surgery). All patients were re-evaluated on the previously described at T18 and T24. Patients who agreed to be included in the modified regimen were labelled as De-escalation treatment group (DTG), while patients who continued the traditional dosage were labelled as standard treatment group (STG).
Additional data about age, gender, previous endoscopic surgery and comorbidities were collected.

Statistical analyses

Percentage, average and standard deviation were calculated. Within and between group analyses were done. Within group analyses was done by one-way ANOVA and ad hoc Bonferroni-Holmes (BH) evaluating the changes between T0, T12, T18 and T24 of NPS and SNOT 22 scores. Then the same test was used to compare the scores of NPS at T0, T12, T18 and T24 of the three groups and similar comparison was done for SNOT 22. P was considered significant at <0.05. All tests were performed using Stata ®.

Results

Forty-two of the 43 patients included in the study completed the entire follow-ups at 24 months; 1 subject was excluded because they did not complete the SNOT-22 questionnaire (2% drop-off). Of the 42 patients, 23 (55.8%) were men and 19 (44.2%) were women, with an average age of 60.97 years (CI95%: 30-90). Thirty-seven (88%) of the 42 patients have already undergone FEES at least once. Thirty-one (73.8%) of the 42 patients had medically controlled asthma. Of the 11 remaining patients, two were diagnosed with inhalant allergy, one with allergy to acari, and one with allergy to gadolinium.
After the 12 months treatment by standard therapy none of the patients presented severe adverse events to the medication or had to stop the treatment. After one year of treatment, we identified 30 (71.4%) patients as GERs and 12 (28%) as PMRs. Twenty-seven among the GERs group accepted to change the therapy (DTG) regimen to once every 4 weeks, while 3 patients opted to continue the standard treatment (STG) as they were afraid to lose the reached therapeutic benefits. Among the PMRs group, 8 (66.7%) patients were continued on the standard treatment (STG) and 4 underwent endoscopic sinus surgery.
At the conclusion of the 24-month follow-up period, 27 patients were categorized as belonging to the DTG group, while 11 patients were categorized as being part of the STG group.

WITHIN Group

De-escalation therapy group (DTG)

The patients improved their NPS from T0 at T12, T18 and T24 with statistically significant value (ANOVA: p <0.0001), respectively BH p values were <0.01 (T0 and T12), <0.01(T0 and T18) and <0.01 (T0 and T24). Average NPS at T0 were 6.2 ±1,4 (CI 95%:4-8), 2.8 ± 1.6 (CI 95%: 0-5) at T12, 2.6 ±1.8 (CI 95%:0-6) at T18 and 2.1± 1.7(CI 95%:0-5) at T24. Despite the improvement from T0 at each follow-up no statistically significant variances in the NPS were observed between T12 and T18 (BH: p>0.05), T12 and T24 (BH: p>0.05) and T18 and T24 (BH: p>0.05).

Similar statistically significant differences were observed in SNOT score at T0, T12, T 18 and T24 with an improvement from T0 at each following follow-ups, (ANOVA: p <0.0001), respectively BH p values were <0.01 (T0 and T12), <0.01 (T0 and T18) and <0.01 (T0 and T24).
Average SNOT scores were at T0 54.6 ± 20.4 (CI 95%:21-95), 15.5 ± 14.2 (CI 95%:0-63) at T12, 14.9 ± 13 .8 (CI 95%:2- 63) at T18 and 13 ± 12.7(CI 95%:0-57) at T24. Despite the improvement from T0 at each follow-us no statistically significant variances in the NPS were observed between T12 and T18 (BH: p>0.05), T12 and T24 (BH: p>0.05) and T18 and T24 (BH: p> 0.05).
Above analysis reflects standard treatment up to 12 months for all patients, with transitioning of individuals with good-to-excellent response to the de-escalation regimen at 12 months.

Standard therapy group
The patients improved their NPS from T0 at T12, T18 and T24 with statistically significant value (ANOVA: p=0.0004), respectively BH p values were <0.01 (T0 and T12), <0.01(T0 and T18) and <0.01 (T0 and T24). Average NPS at T0 were 6.1 ±1.2 (CI 95%:4-8), 3.2 ±1.9 (CI 95%: 0-4) at T12, 3.4 ±1.7 (CI 95%:0-5) at T18 and 3 ±1.9 (CI 95%:0-5) at T24. Despite the improvement from T0 at each follow-up no statistically significant variances in the NPS were observed between T12 and T18 (BH: p>0.05), T12 and T24 (BH: p>0.05) and T18 and T24 (BH: p>0.05).
Similar statistically significant differences were observed in SNOT score at T0, T12, T 18 and T24 with an improvement from T0 at each following follow-ups, (ANOVA: p <0.0001), respectively BH p values were <0.01 (T0 and T12), <0.01 (T0 and T18) and <0.01 (T0 and T24).
Average SNOT scores were at T0 57.5 ± 20.1 (CI 95%:10-83), 19.7 ± 11.3 (CI 95%:6-35) at T12, 22.3 ± 25.3 (CI95%: 6-49) at T18 and at 17.3 ± 11.7 (CI95%:2-35) T24. Despite the improvement from T0 at each follow-us no statistically significant variances in the NPS were observed between T12 and T18 (BH: p>0.05), T12 and T24 (BH: p>0.05) and T18 and T24 (BH: p> 0.05).

BETWEEN Groups
DTG and STG groups did not present statistically significant differences none at T0 nor at T12 in NPS, respectively 6.2 ±1,4 (CI 95%:4-8) and 2.8 ± 1.6 (CI 95%: 0-5) for DTG and 6.1 ±1.2 (CI 95%:4-8) and 3.2 ±1.9 (CI 95%: 0-4) for STG (ANOVA: BH: p=4 at T0 and 2.4 at T12). Similarly, the two groups did not statistically differ in SNOT score at T0 and T12, respectively 54.6 ± 20.4 (CI 95%:21-95) and 15.5 ± 14.2 (CI 95%:0-63) for DTG and 57.5 ± 20.1 (CI 95%:10-83) and 19.7 ±11.3 (CI 95%:6-35) for STG (ANOVA:BH: p=3.8 at T0 and 2.9 at T12).
The comparison of NPS scores between DTG and STG at T18 and T24 was not statistically significant (ANOVA: p=0.2). DTG NPS at T18 was 2.6 ± 1.8 (CI 95%:0-6) and 2.1 ± 1.7(CI 95%:0-5) at T24; STG showed NPS 3.4 ±1.7 (CI 95%:0-5) at T18 and 3 ± 1.9 (CI 95%:0-5) at T24.
The comparison of SNOT scores between DTG and STG at T18 and T24 was not statistically significant (ANOVA: p=0.2). DTG SNOT at T18 was 14.9 ±13 .8 (CI 95%:2- 63) and 13 ± 12.7(CI 95%:0-57) at T24; STG showed SNOT 22.3 ±25.3 (CI95%: 6-49) at T18 and at 17.3 ±11.7 (CI95%:2-35) T24.

Discussion

Our data demonstrate that both STG and DTG exhibited sustained improvements in NPS and SNOT-22 scores over 24 months. The absence of significant differences between the two groups at 18 and 24 months suggests that for GERs, reducing the frequency of Dupilumab administration does not compromise clinical outcomes. Although the two groups differed in initial treatment response on conventional therapy, they were homogeneous in comorbidities, gender distribution, and ages. Moreover, even after division of the patients at 12 months into groups STG and DTG, the NPS and SNOT scores were similar. The follow-ups were performed by a consistent team of physicians with more than 30 years of experience, and serial follow was performed through 24 months with good patient retention. These considerations strengthen the study despite limitation of small sample.
The LIBERTY NP SINUS trials showed the efficacy of Dupilumab administered every 4 weeks although the results were considered somewhat poorer if compared with the 2 weeks regime suggesting a benefit for intensive regimens in the initial year of treatment. Our study builds upon this foundation by providing real-world data on tapering treatment frequency. The ability to safely extend dosing intervals without compromising outcomes could have significant implications for patient adherence, healthcare resource allocation, and overall treatment costs. The financial burden of biologics remains a key concern in chronic disease management, and our findings suggest that a structured de-escalation strategy may provide both clinical and economic benefits.

Our results overlap the finding observed by Van der Lans et al in their first real world prospective observational cohort, where the authors evaluated patients treated with off-label Dupilumab scheme every 4 weeks The same authors had an encouraging experience tapering Dupilumab every 6 weeks and 8 weeks Van der Lans hypothesized that the benefit observed by extending the time between doses might be related to pharmacokinetic factors such as i) persistent saturation of IL-4Rα receptor due to high concentration of Dupilumab in blood, ii) high availability of receptor target and iii) possible redundancy of full IL-4Rα saturation for sufficient and/or maximum clinical effectiveness

Study limitations
However, this study has limitations. First, the sample size is rela-

tively small, and while our results align with prior studies, larger prospective trials are needed to confirm these findings. Second, because this was not a randomized controlled trial (RCT), the decision to de-escalate was influenced by treatment response profile and patient preference, introducing potential bias. While this lack of random assignment or blinding is less likely to affect objective measures such as NPS, subjective assessments like SNOT-22 could be influenced by patient perception, warranting further blinded studies. Additionally, longer-term follow-up is necessary to determine whether extended dosing intervals continue to provide durable disease control beyond 24 months.

Table S1. Demographics.

	Number of patients	Age	Gender	Asthma	Allergy	Comorbidities
De-escalation treatment	27	60.7 ± 9.3	16 men, 10 women	12	7	Hypertension: 4
						Parkinson: 1
						Dermatitis: 1
Standard treatment	11	57.4 ± 12	6 men, 5 women	7	4	Hypertension: 2
						Dermatitis: 1
Surgery	4	56.5 ± 3.8	3 men, 1 woman	3	1	Hypertension:1