Perioperative adjuvant therapy with short course of dupilumab with ESS for recurrent CRSwNP

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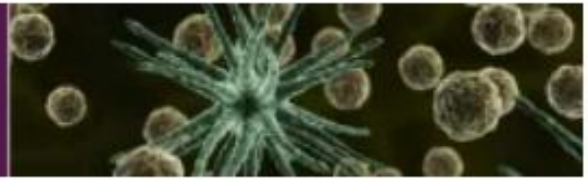
International Forum of IFAR: Allergy & Rhinology



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Perioperative adjuvant therapy with short course of dupilumab with ESS for recurrent CRSwNP

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Introduction

- **Chronic rhinosinusitis with nasal polyposis (CRSwNP)**: an inflammatory disease of the upper respiratorytract and paranasal sinuses
- Sufferings: nasal obstruction, reduced sense of smell(olfaction), sleep disturbances
- Characterized by a **Type 2 inflammation** profile, which includes elevated levels of tissue or blood eosinophils or total IgE
- Modulating Type 2 inflammation during the early stages of post-ESS healing may enhance epithelial repair and strengthen pathogen defense, potentially leading to improved long-term outcomes.

Aim

- To investigate this hypothesis, design a placebo-controlled, prospective trial evaluating the impact of short-term dupilumab treatment during the peri-operative period of ESS.
- measured by objective endoscopic endpoints such as **edema**, **nasal polyp (NP) recurrence**, and **improvements in sense of smell**

Materials and methods

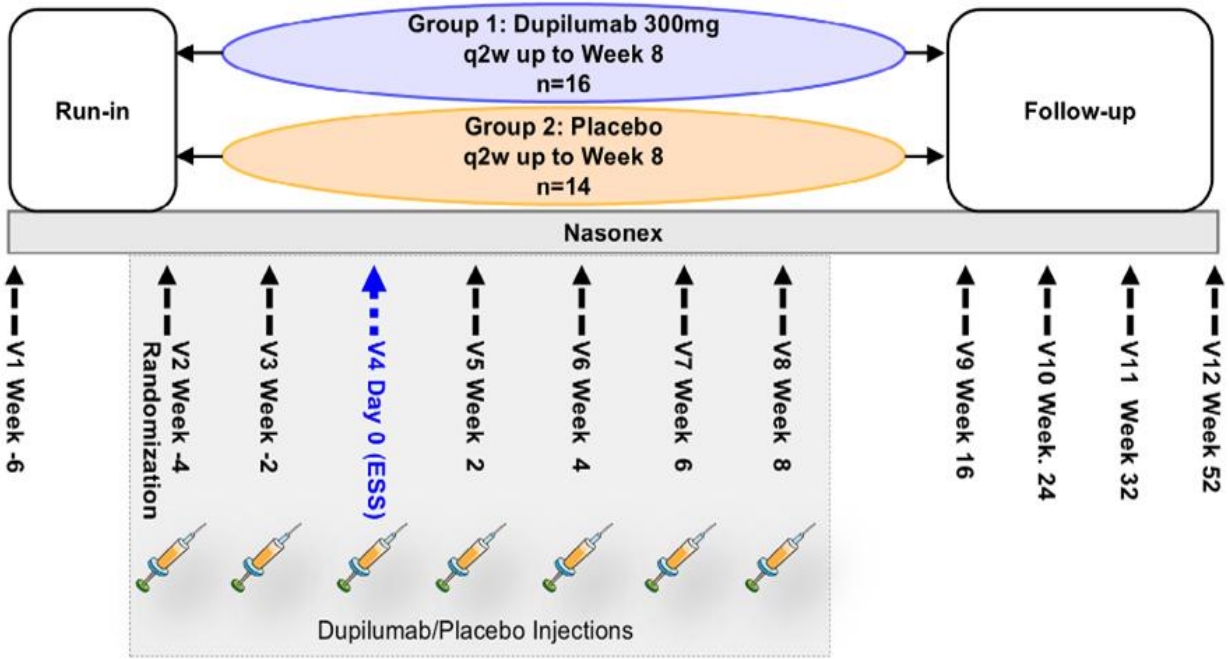
Approved and supervised by the institutional review board of the Centre de Recherche du Centre Hospitalier de l’Université de Mon-tréal (CRCHUM)

Population

- Recruited
  - CRSwNP undergoing revision surgery for recurrence
  - at least one previous ESS
  - both with or without asthma
- Exclusion criteria:
  - local complications such as mucoceles and tumors
  - underlying systemic disorders, including sarcoidosis, eosinophilic granulomatosis with polyangiitis, immune deficiency, cystic fibrosis
  - a history of neoplasia (excluding basocellular carcinoma) within the past 2 years

Study design

- Prospective, randomized, double-blinded,and controlled by placebo
- The recruitment period was from May 2021 to March 2023

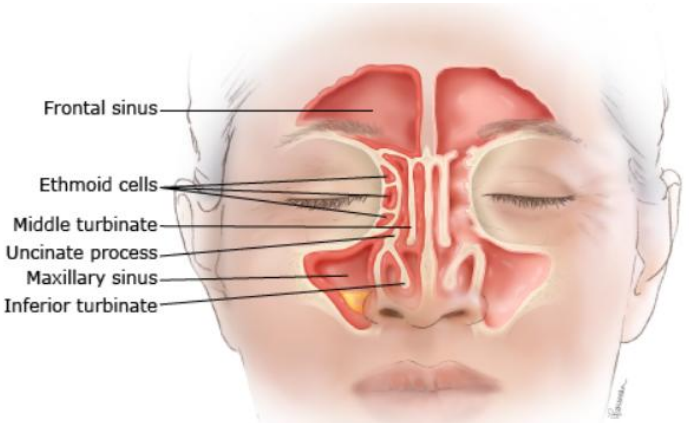


Study treatments

- Dupilumab (300 mg):
  - subcutaneous injections
  - every 2 weeks for 12 weeks
- All patients took mometasone furoate nasal spray 200 mcg intranasally twice daily throughout the study
- If unable to tolerate 200µg twice a day due to adverse events, could reduce to 200 µg once per day

Study treatments

- Surgery was performed by a single surgeon, who was also responsible for pre- and post-operative assessments.
- Surgery consisted of complete clearance of tissue in maxillary, ethmoid, sphenoid, and frontal sinuses
- using a “small hole” surgery approach, without drilling of the frontal recess.



Schematic diagram from Uptodate

Study treatments

- All patients received a standardized post-operative course
  - 875 mg amoxicillin/125 mg clavulanic acid oral antibiotic therapy for 14 days
  - prednisone orally 30 mg/day for 5 days followed by 15 mg/day for 5 days
  - encouraged to hydrate their nose with sterile pressurized nasal spray until the first post-operative visit

Data analysis

- Primary outcome: degree of success in controlling the return of sinus mucosal oedema as an early sign of polyp recurrence at 52 weeks as assessed by endo-scopic mucosal score
- “Success”
  - the percentage of patients with no endoscopic signs of recurrence after ESS as defined by the absence of polyps and no more than mild (one out of a score of 2) oedema as assessed per the modified Lund–Kennedy scoring system

Modified Lund-Kennedy scoring system[§]

Polyps	0 = no polyps
	1 = polyps in middle meatus only
	2 = beyond middle meatus
Edema	0 = absent
	1 = mild
	2 = severe
Discharge	0 = no discharge
	1 = clear, thin discharge
	2 = thick, purulent discharge

- Secondary outcome:
  - sinonasal symptoms: Visual Analogue Scale assessing total sinus symptoms, VAS CRS symptoms; 0–10
  - Individual symptoms of obstruction, pain, and secretions: three-point grading scale in the Total Nasal Symptom Score, TNSS
  - Disease-specific QoL: Sino-Nasal Outcome 22-item (SNOT-22) questionnaire
  - SNOT-22 domains were also assessed separately using the following classification; nasal (items1–8), ear/facial (items 9–12), sleep (items 13–16), function(items 17–19), and emotion (items 20–22)

- Secondary outcome:
  - Olfaction: VAS of decreased smell, and the 40-item University of Pennsylvania Smell Identification Test(UPSIT)
  - Computed tomography (CT) scan: obtained in our institution and was graded using the Lund–McKay grading scale

- One subject in the dupilumab group withdrew before its last visit, the missing follow-up values were replaced by that subject's previously observed value
- Subgroup analysis could not be performed for the aspirin-exacerbated respiratory disease (AERD) population given the small group sizes
- (in the licensing trial for dupilumab, AERD did not have significantly greater magnitude of response than conventional patients.)

Statistical analyses

- R version 4.3.2
- To assess within-group changes over time, a repeated measures analysis of variance (ANOVA) was conducted
- A mixed-effects ANOVA was employed to determine whether there were significant differences in the outcome variable between the Treatment and Placebo groups, and how these differences changed over time
- All statistical tests were conducted with a significance threshold of $\alpha = 0.05$

RESULTS

Demographics

- Due to recruitment challenges, the study enrolled 30 patients instead of the initially planned 36
- 16 in the dupilumab group
- 14 in the placebo group

TABLE 1 Demographics of the study cohort.

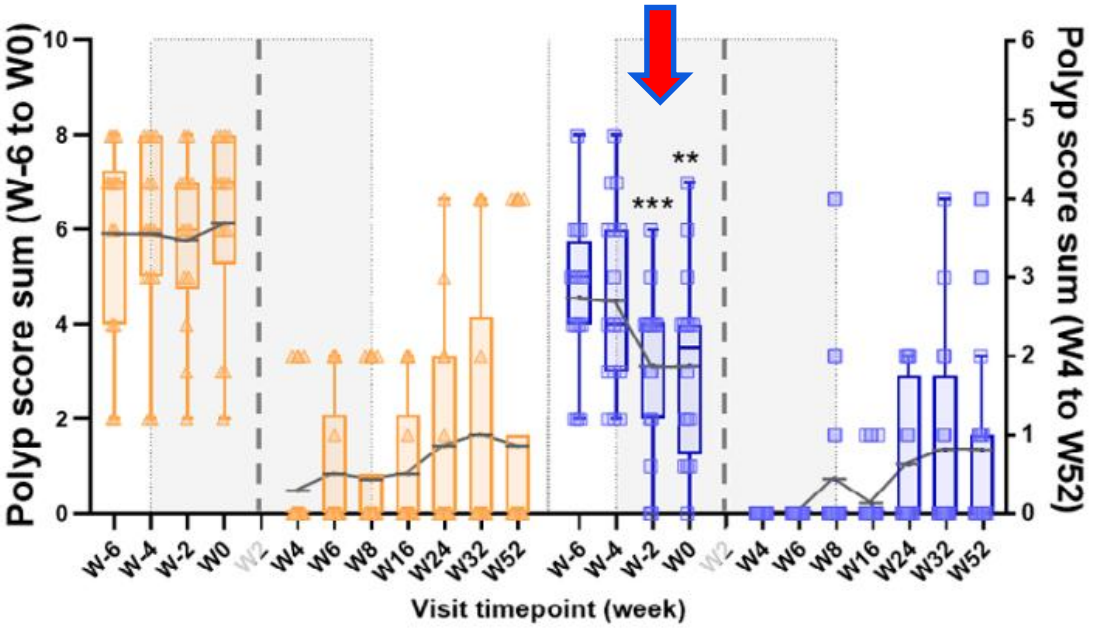
Characteristic	Placebo (N = 14)	Dupilumab (N = 16)	p-value[d]	q-value[e]
Age[a]	54.85 (137.38)	53.70 (74.71)	0.8	>0.9
Gender[b]			>0.9	>0.9
Male	11/14 (79%)	13/16 (81%)		
Female	3/14 (21%)	3/16 (19%)		
Asthma[b]			0.7	0.8
Yes	11/14 (79%)	11/16 (69%)		
No	3/14 (21%)	5/16 (31%)		
Number of prior nasal polyp surgery[c]	(14) 2.7 ± 3.4	(16) 2.4 ± 1.3		
Smoking[a]	4/14 (29%)	3/16 (19%)	0.7	>0.9
Weight[a]	94.5 (84.6–101.9)	93.0 (80.3–102.9)		
Height[c]	170.7 ± 7.5	173.0 ± 7.4		
Atopy[b]				
Yes	7/14 (50%)	12/16 (75%)		
No	6/14 (43%)	4/16 (25%)		
ASA sensitivity (AERD)	3 / 14 (21%)	3/16 (19%)		
IgE blood[a] (kIU/L)	122.00 (39,682.47)	106.30 (42,304.30)	>0.9	>0.9
Eosinophil blood[a] (10^{*9}/L)	0.30 (0.09)	0.30 (0.07)	0.9	>0.9
Neutrophil blood[a] (10^{*9}/L)	4.20 (2.21)	4.60 (3.05)	>0.9	>0.9
Lymphocyte blood[a] (10^{*9}/L)	1.60 (0.55)	1.90 (0.50)	0.2	0.7
Monocyte blood[a] (10^{*9}/L)	0.50 (0.02)	0.60 (0.03)	0.082	0.6
Initial polyp score sum[a] (W-4)	6.00 (4.07)	4.00 (3.63)	0.067	0.4
Initial CT scan Lund–Mackay (LM) score sum[a] (W-4)	21.50 (12.29)	15.50 (19.18)	0.015	0.2
Initial SNOT-22 score[a] (W-4)	42.00 (321.23)	45.00 (480.60)	0.7	>0.9
Initial UPSIT score[a] (W-4)	10.00 (71.21)	12.50 (52.93)	0.4	0.7
Type 2 inflammation[b] (W-4) (EOS > 300 cells/μL or IgE > 100 KIU/L)	11/14 (78.6%)	13/16 (81.1%)		

[a]Median (variance), median (first quartile –third quartile).
[b]n/N (%).
[c]Mean ± standard deviation.
[d]Fisher's exact test for categorical variables; Wilcoxon rank sum test, and Wilcoxon rank sum exact test for continuous variables.
[e]False discovery rate correction for multiple testing.

- Males (80%)
- Asthma (70%)
- ASA intolerance (20%)
- Type 2 disease (75%): serum eosinophilia >300 cells/μL and/or serum IgE ≧100 KIU/μL
- Symptom severity was high

Effect of dupilumab pre-surgery

- significant reduction in endoscopic scores for NP

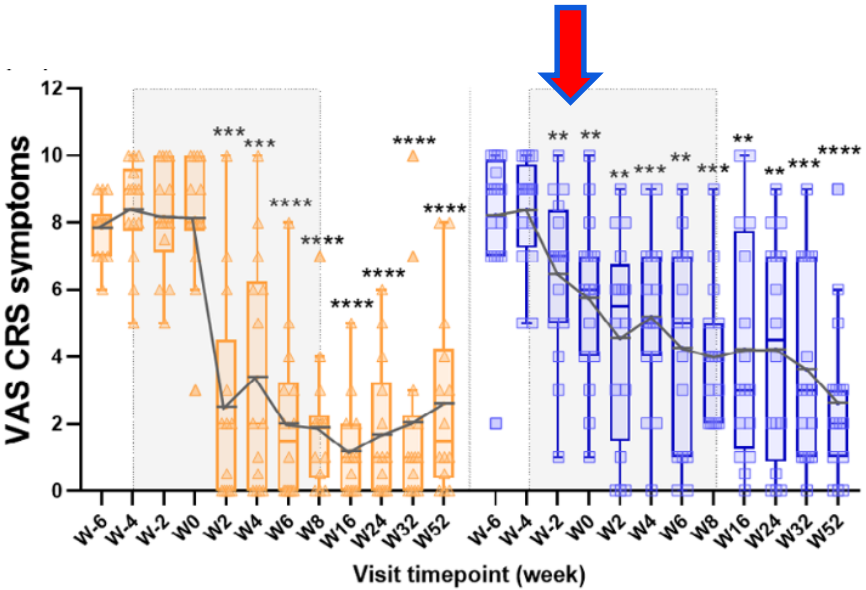


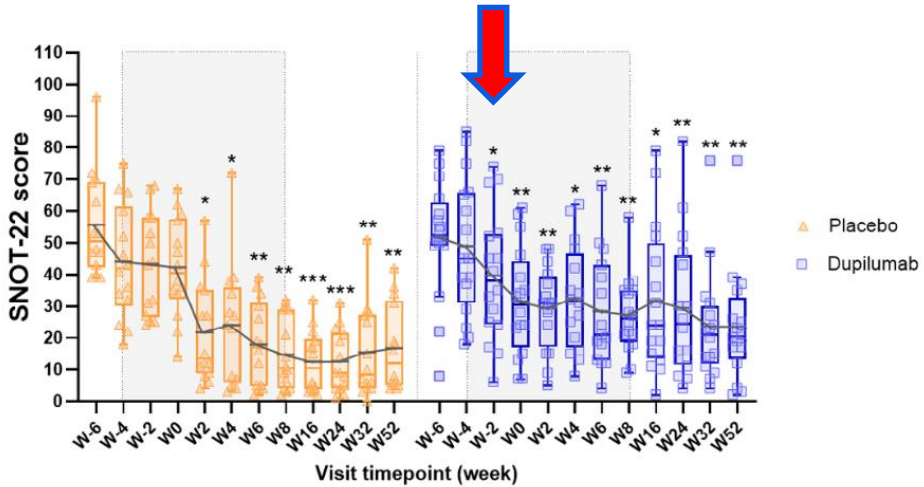
*p ≤ 0.05
**p ≤ 0.01
***p ≤ 0.001
****p ≤ 0.0001)
for the comparison to the pre-treatment at week −4

or for (A) polyp size post-endoscopic sinus surgery (post-ESS) for the comparison to week 4

Effect of dupilumab pre-surgery

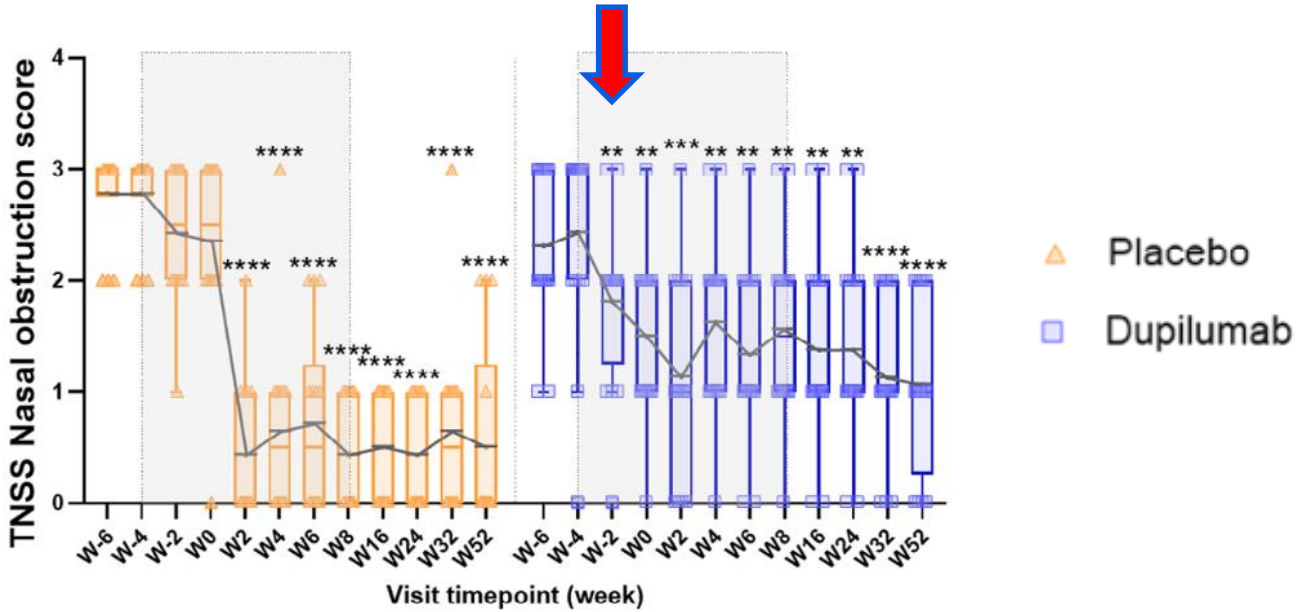
- significant improvements in sinonasal symptoms (VAS CRS symptoms) and QoL (SNOT-22)





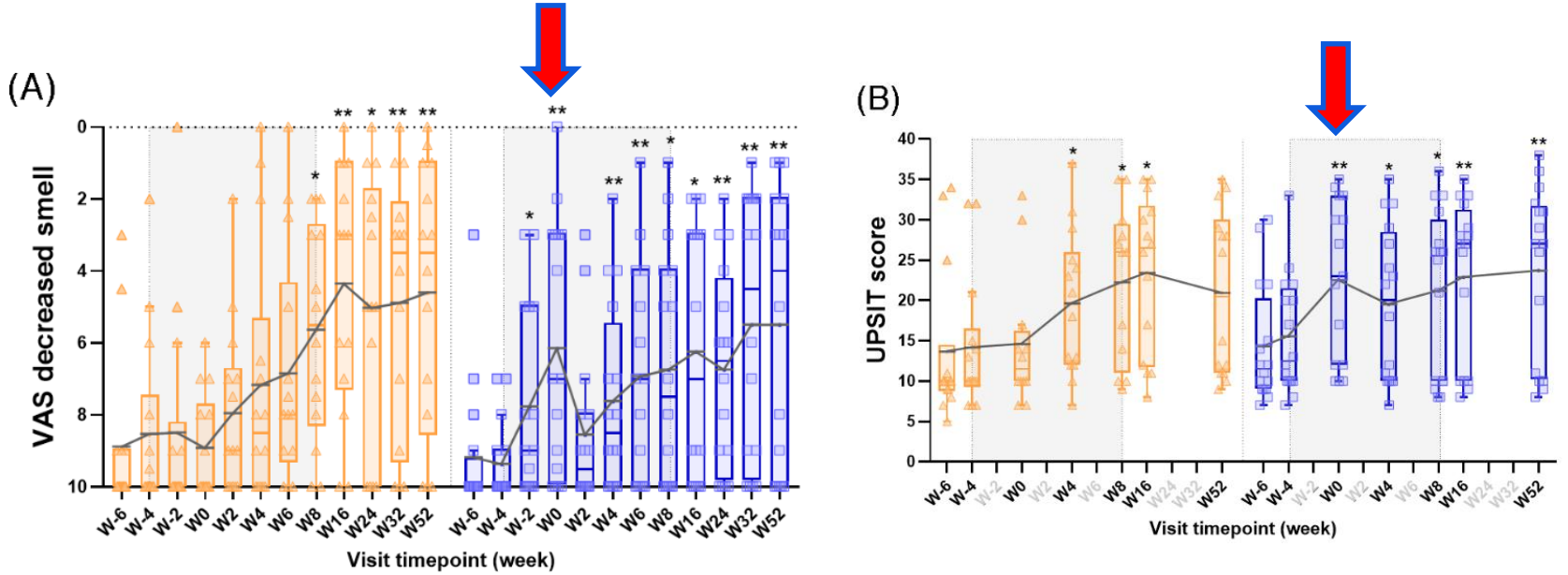
Effect of dupilumab pre-surgery

- Improvement in the nasal obstruction from the TNSS questionnaire



Effect of dupilumab pre-surgery

- improvement in the VAS of sense of smell and UPSIT scores



Effect of dupilumab pre-surgery

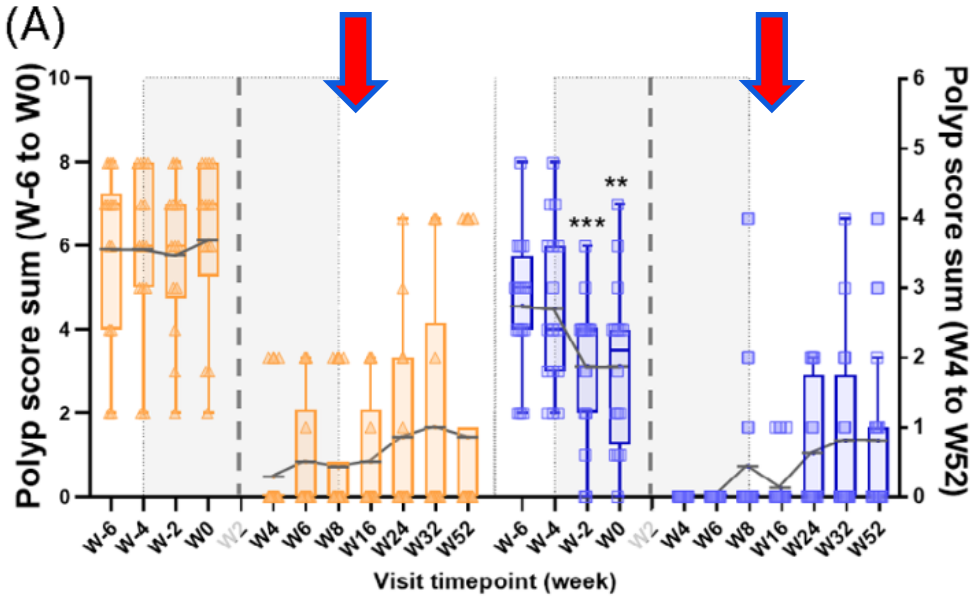
- Regarding adverse effects, no infections or exacerbations were recorded during the pre-ESS period.
- Bleeding, surgical difficulty, and surgery duration were comparable between the groups.

Evolution post-surgery: Time course to week 52

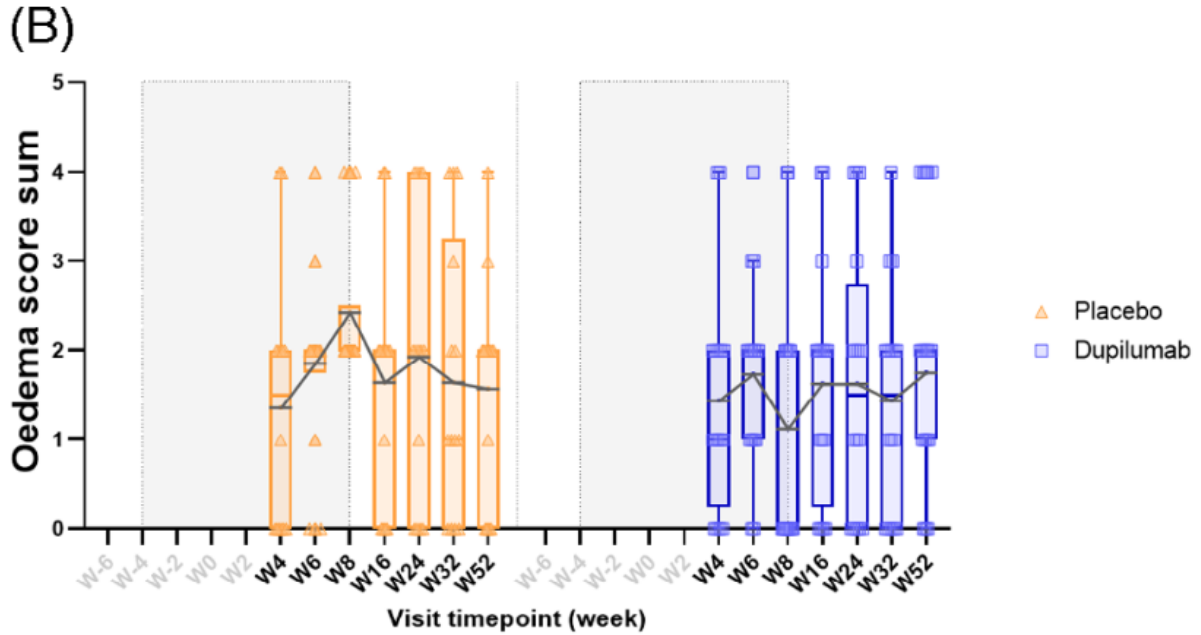
Evolution post-surgery: Time course to week 52

- Following surgery, symptoms and objective measures of nasal obstruction, secretions, sense of smell, and QoL indices all improved and were confirmed by CT imaging.

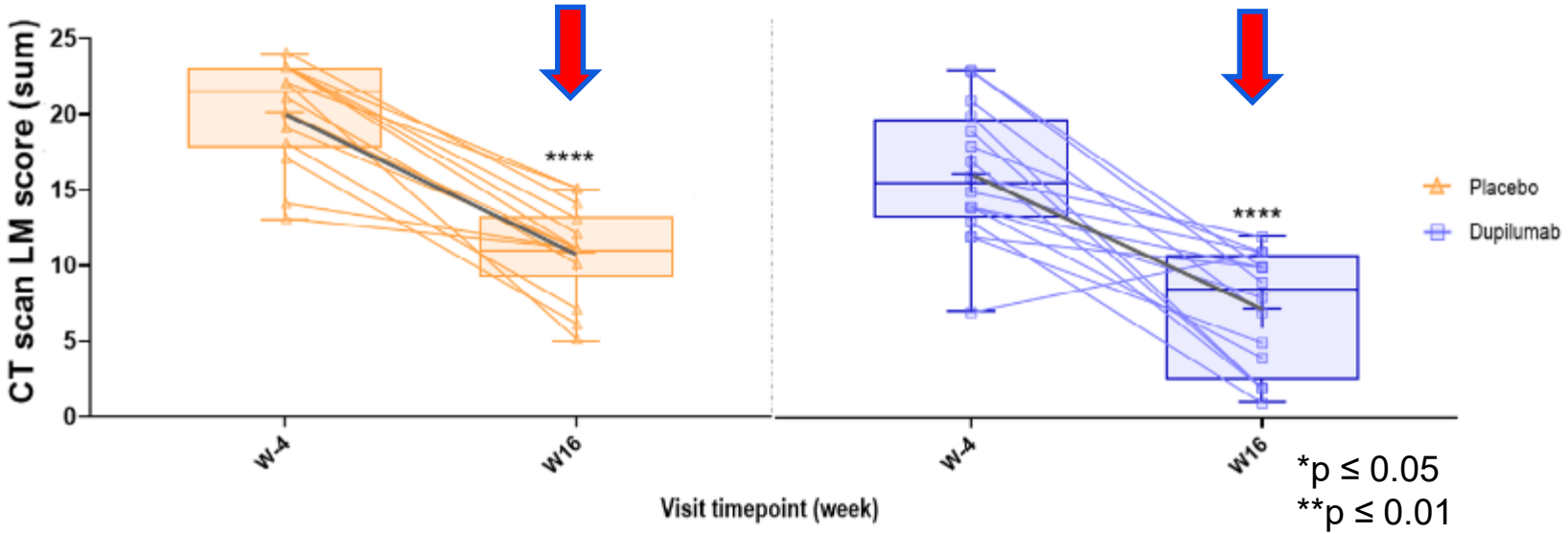
- The polyp burden was reduced to near zero following surgery
- Until 4 months post-ESS, at which point a limited number of polypoid recurrences began to be noted in both groups.



- Oedema persisted at most time points after ESS, showing minimal variation and no significant differences between groups



- CT scan scores showed similar improvement in both groups at16 weeks



*p ≤ 0.05
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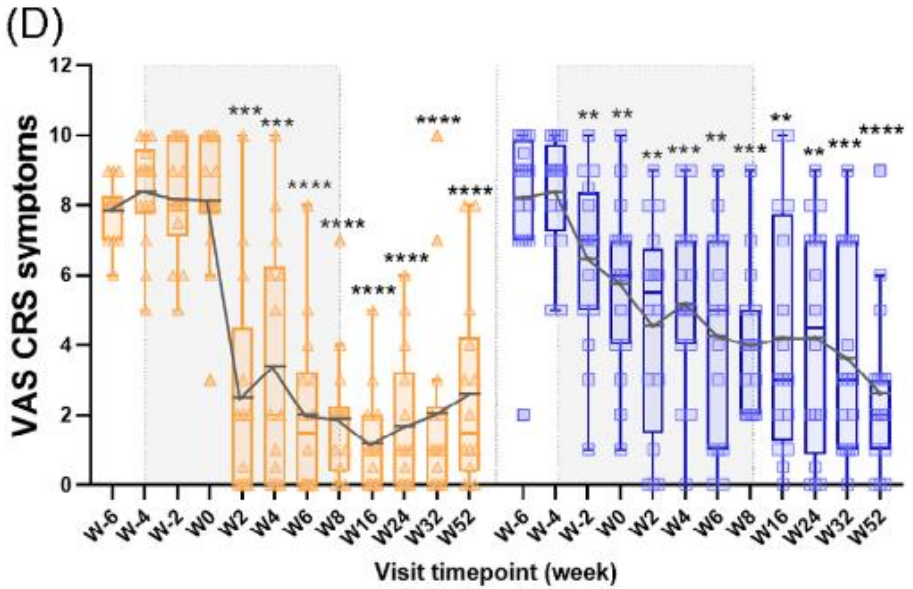
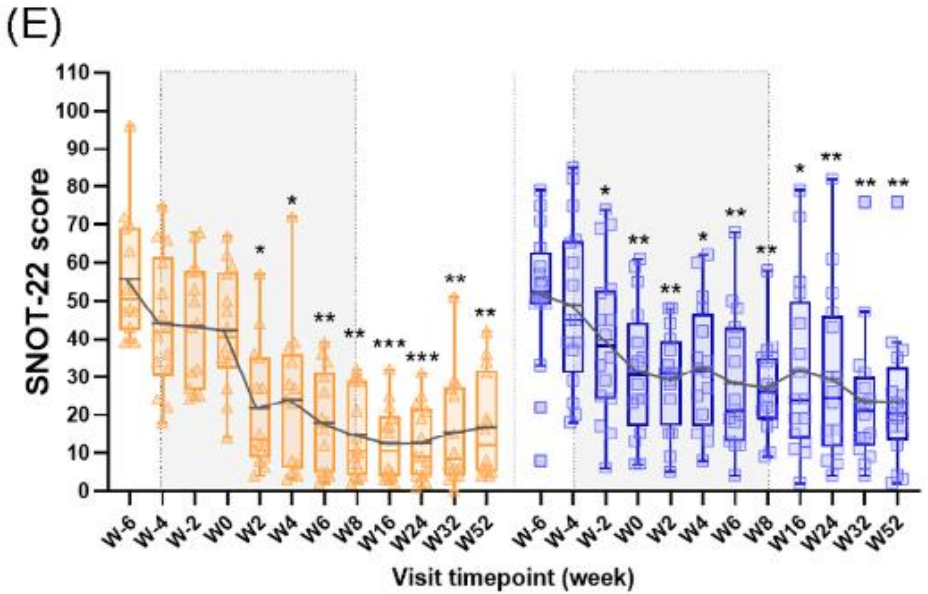
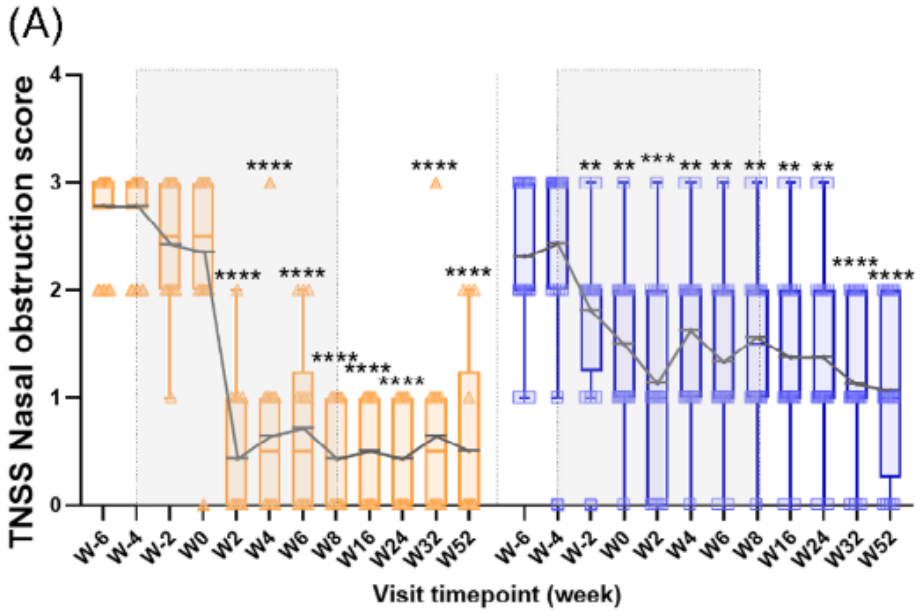
****p ≤ 0.0001)
for the comparison to the pre-treatment at week −4

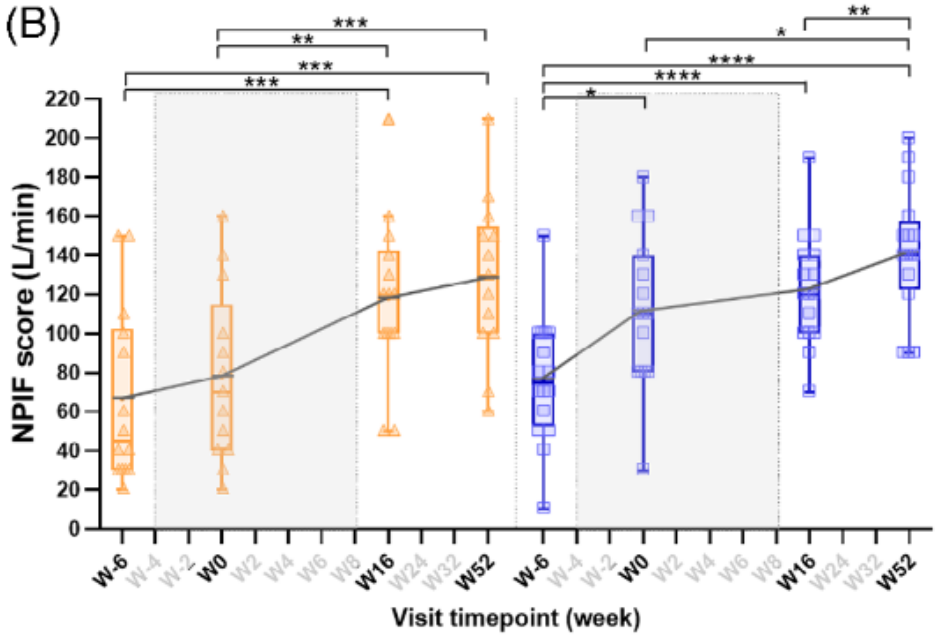
- Subjective symptoms of CRS significantly improved in both the placebo and dupilumab groups at every post-surgery timepoints



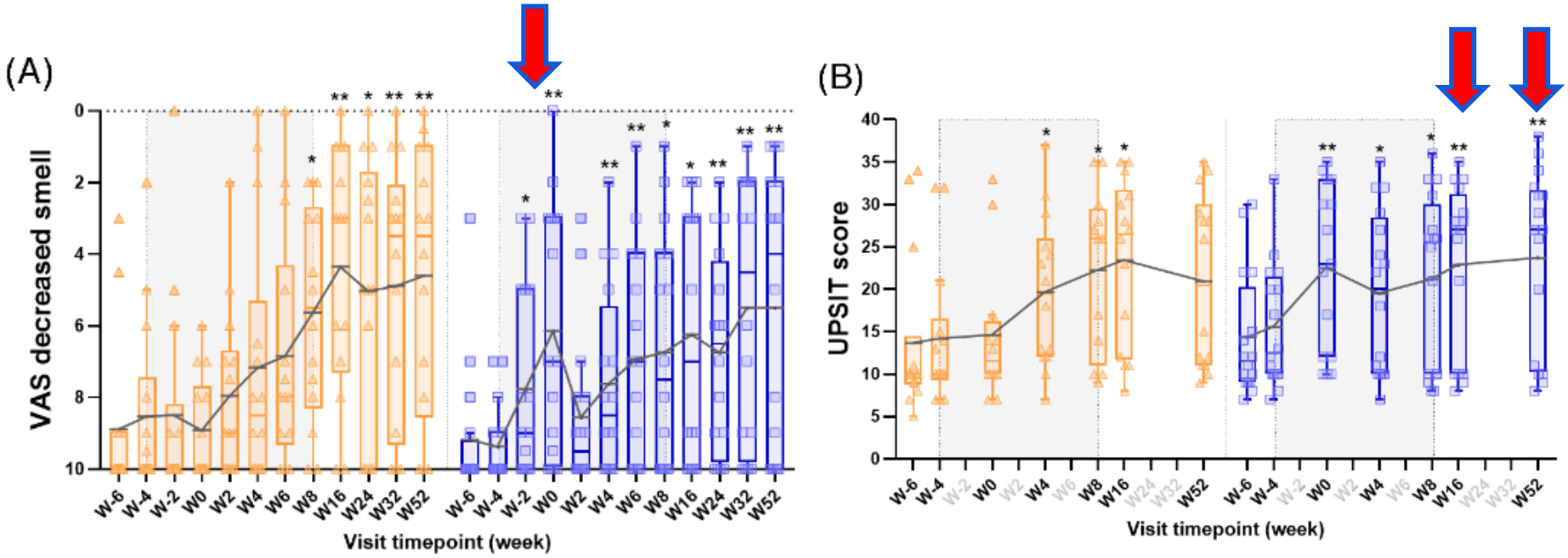


- A trend toward greater symptoms of nasal obstruction in the dupilumab group over the recovery period
- Objective measures of nasal obstruction, assessed by NPIF, showed similar improvements in both groups

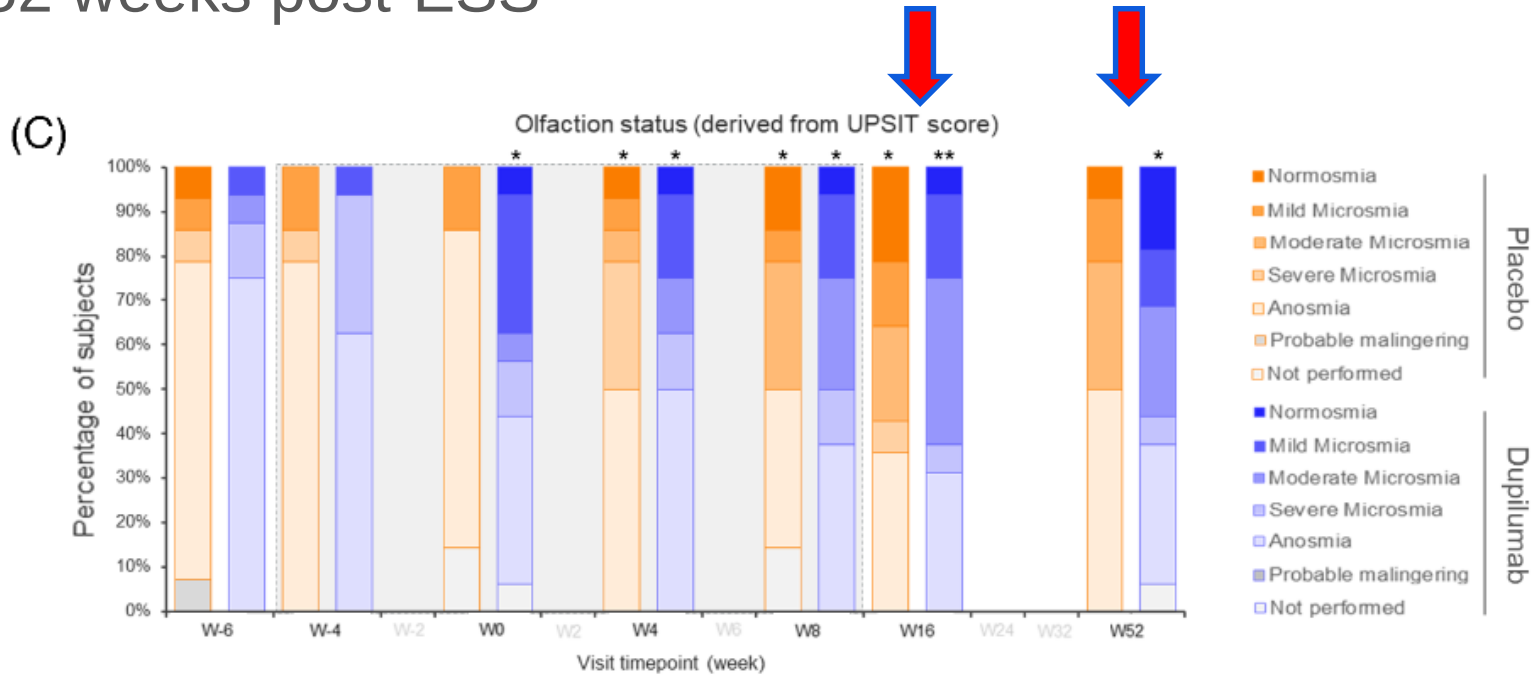




- Olfaction showed changes following surgery, with differences in response between placebo and dupilumab-treated groups



- Overall, a smaller proportion of subjects in the dupilumab group was classified as having anosmia (defined as UPSIT score < 19) compared to the placebo group at both 16 and 52 weeks post-ESS



Outcomes at the end of the study

TABLE 2 Outcome at week 52.

	Placebo ($N = 14$)	Dupilumab ($N = 16$)	p-value[c]	q-value[d]
Endoscopy				
Polyp score sum[a]	0.93 ± 1.62	0.75 ± 1.20	0.9	>0.9
Oedema sum[a]	1.57 ± 1.18	1.69 ± 1.36	0.9	>0.9
Success (polyp < 2 and oedema < 2)[b]	11/14 (79%)	12/16 (75%)		
Sense of smell				
Mild microsmia or normosmia[b]	3/14 (21%)	5/16 (31%)		
Severe or moderate microsmia[b]	4/14 (29%)	5/16 (31%)		
Anosmia[b]	7/14 (50%)	5/16 (31%)		

[a]Mean ± standard deviation.
[b]n/N (%).
[c]Wilcoxon rank sum test, and Wilcoxon rank sum exact test.
[d]False discovery rate correction for multiple testing.

The rate of recurrence was low, and similar in both groups (dupilumab: 4/16 [25%], placebo: 3/14[21.4%])

TABLE 2 Outcome at week 52.

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NP scores remained consistently low and showed no differences between the groups

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Oedema in the ethmoid cavity was moderate across both groups

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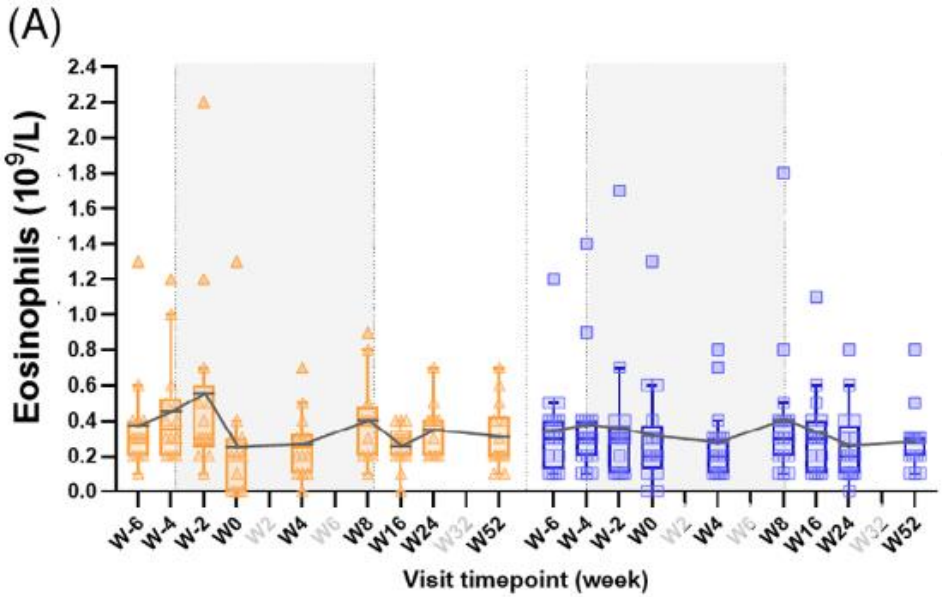
[d]False discovery rate correction for multiple testing.

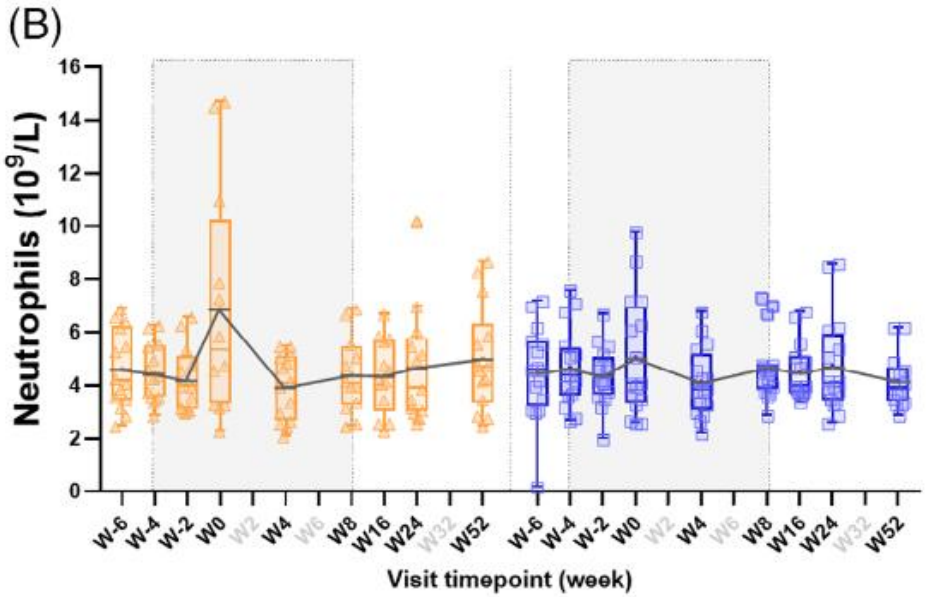
Anosmia was present in 50.0% of placebo-treated patients and 31.3% in the dupilumab group, but this trend was not significant.

- Nasal obstruction, SNOT-22 scores, QoL: no notable difference between both groups.

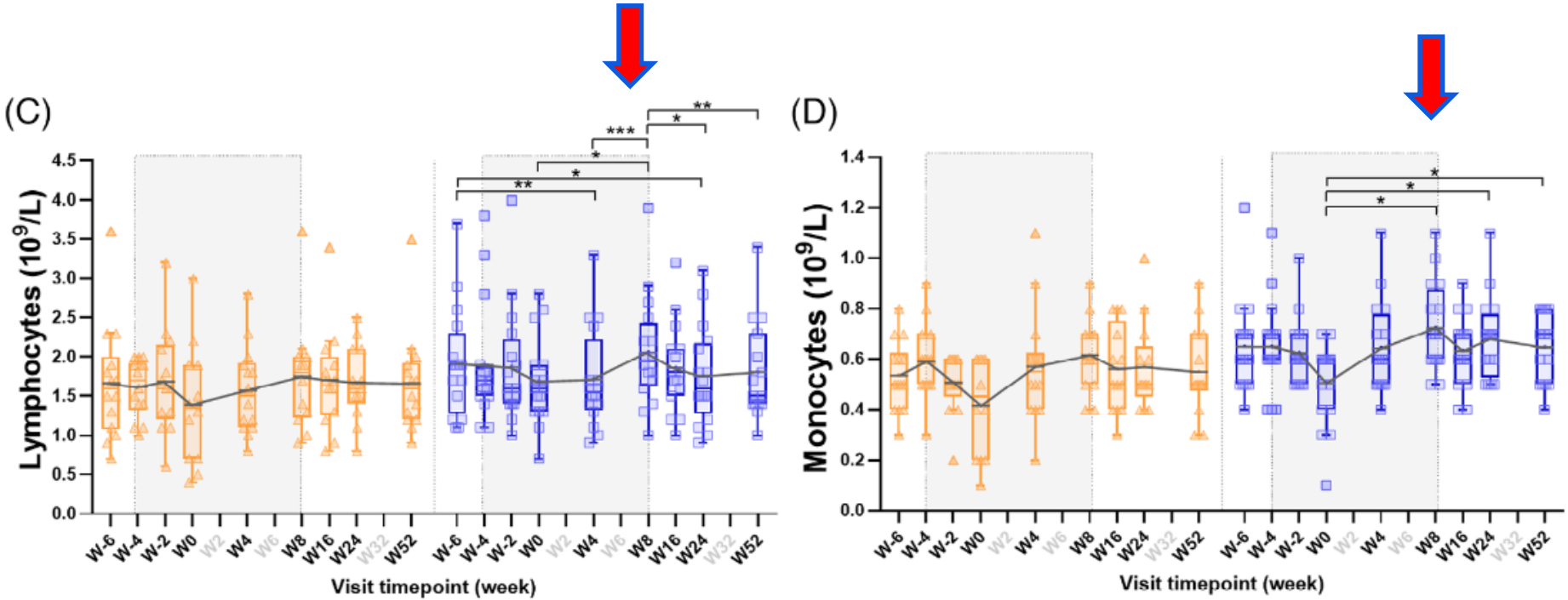
Blood parameters and bacteriology

- Isolated incidences of increased eosinophilia occurred in both placebo and dupilumab-treated groups and required no attention
- neutrophil counts were relatively stable for all subjects,

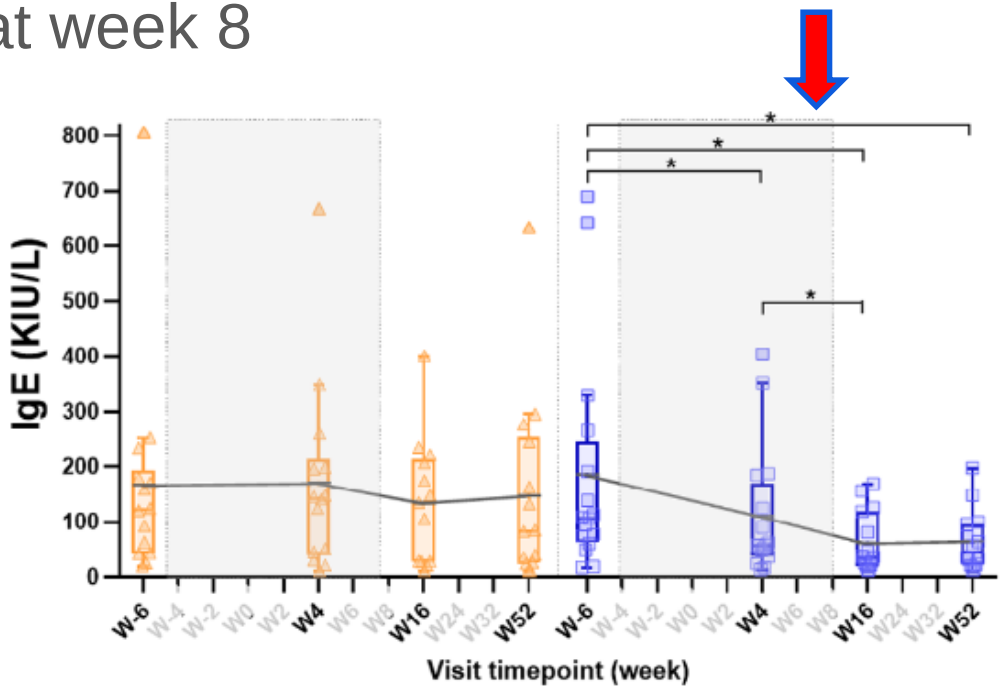




- lymphocytes and monocytes showed variations in the dupilumab groups while remaining within normal ranges



- Reduction in serum IgE below baseline but within normal ranges was noted as of week 4 post-ESS and persisted through weeks 16 and 52, despite the dupilumab treatment cessation at week 8



Adverse effects

- Adverse events occurred at an equal rate in both groups.
- No incidences of conjunctivitis were reported.
- Musculoskeletal pain was reported by two of 16 patients in the dupilumab group and two of 14 patients in the placebo group

DISCUSSION

- A prospective, placebo-controlled trial assessing whether dupilumab administered during the peri-operative period in a population at high risk prevents recurrences of CRSwNP after ESS

- Injections of dupilumab treatment had a rapid and objectively demonstrable effect.

- sinus cavity oedema and NP scores were not good monitors of disease recurrence, as the number of patients with recurrences were lower than originally anticipated.

- This suggests that the study period may have been insufficient to detect recurrences

- Significant differences were seen in objective and subjective measures of olfaction and the timing of improvements was different in treated and untreated groups.

- Despite objective improvements as seen in UPSIT scores, VAS assessments of olfactory impairment remained high throughout the study period, suggesting that this metric did not reflect olfactory ability as assessed by the UPSIT test.

- The sustained improvement in olfaction, despite NP size and oedema, suggests that olfactory restoration and NP reduction follow distinct pathways.

- This discordance between subjective and objective assessments was also noted for measures of nasal obstruction.

- Why these subjective differences occur may reflect a different evolution in regeneration and repair at the level of the specialized olfactory epithelium or may reflect an improved perception of disease in the dupilumab-treated group

- Serum IgE was reduced with dupilumab and persisted following the cessation of dupilumab treatment.

- High circulating levels of IgE and local IgE production in nasal tissue are characteristic of Type 2 CRSwNP

- post-treatment reduction in serum IgE seen in this study suggesting a modification in the biology of the disease.

- Despite concerns that dupilumab might induce a Type 2 to Type 1 shift, potentially increasing bleeding and surgical complexity, the performance of surgery and perioperative blood loss were comparable between both groups

- The results of this study should not be directly extrapolated to the general population.

- The cohort primarily consists of severely ill, multi-operated asthmatic males, many of whom have irreversible anosmia from previous surgeries and are afflicted by a mix of Type 2 and non-Type 2 disease.

- Nevertheless, this study provides a valuable initial exploration of the effects of short-course biologic therapy combined with ESS and lays the groundwork for the design of longer duration,

Conclusion

- The addition of a short course of adjuvant treatment with dupilumab prior to ESS yielded rapid improvements in subjective and objective measures of nasal obstruction, QoL, olfaction, and NP size

- Medication had no impact on the performance of surgery

- Adjuvant biologic therapy at ESS had no effect on the polyp recurrence rate

- Improvements in objective olfaction testing using UPSIT persisted throughout the study in the dupilumab group, whereas such improvements did not persist in the placebo group

- may be related to the sustained reduction of IgE in the dupilumab group, possibly via a modification of underlying biology

- These preliminary findings warrant further validation in larger studies with varied treatment durations and extended follow-up periods

Thank you for listening