Topical corticosteroids adherence in chronic rhinosinusitis with nasal polyps patients on dupilumab*

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Dear Editor:

Biologics like dupilumab have revolutionized the management of patients with severe chronic rhinosinusitis with nasal polyps (CRSwNP) and asthma [1-3]. However, topical corticosteroids, such as intranasal (INCS) and inhaled (ICS) corticosteroids still play a fundamental role in the management of these conditions [4, 5]. To this day, limited data is available on topical corticosteroids medication adherence combined with dupilumab in achieving CRSwNP and asthma symptom control. Considering the generally poor medication-adherence among chronic patients and the remarkable efficacy of dupilumab, we suspected low adherence to INCS and ICS [6-8].

We conducted a retrospective single-center cohort study from March to June 2023 with CRSwNP patients on dupilumab treatment at the ENT department of the University Hospital of Zurich, Switzerland. Eligible patients were subjected to a systematic interview protocol regarding their symptoms and current INCS and ICS therapy, categorized as adherent (taken as prescribed), partly adherent (taken at a reduced dosage and/or frequency) and nonadherent (not taken). Symptom control was classified according to EPOS and GINA guidelines as controlled, partly controlled, or uncontrolled [4, 5]. Additionally, we assessed total nasal polyp score (TNPS), Sino-Nasal Outcome Test-22 (SNOT-22), and fractional exhaled nitric oxide (FeNO). All patients received dupilumab treatment. Additional methodological details are provided in the online supplement.

We included 77 patients in our study, with an average age of 52 years. Most patients had a concurrent diagnosis of asthma. Out of all patients, 52 (67.5%) reported reduced adherence to INCS and/or ICS. Distribution of patients' CRSwNP and asthma symptom control and medication adherence are displayed in Table 1. Symptom scores in our cohort were generally low, with mild SNOT-22, TNPS, and FeNO values. No significant association was found between INCS use and the degree of symptom control of CRSwNP ($p = 0.88$), SNOT-22 score ($p = 0.81$), or TNPS ($p = 0.79$). Similarly, ICS use did not significantly affect asthma symptom control ($p = 0.56$) or FeNO ($p = 0.25$). The mean duration of dupilumab treatment was 77 weeks, injection intervals among patients ranged from 2 to 10 weeks. There was no significant impact of dupilumab injection intervals on INCS adherence in our cohort ($p = 0.30$). There was an overall significant association between dupilumab treatment duration and CRSwNP symptom control ($p = 0.03$), with patients in the 'controlled' symptom group having a longer average duration of dupilumab treatment. However, the post-hoc multiple comparison test showed no statistical significance between the groups ($p = 0.06$). Dupilumab treatment duration did not affect asthma symptom control ($p = 0.70$) or medication adherence to INCS ($p = 0.20$) or ICS ($p = 0.66$). The results are displayed in Figure 1. Further details on the results can be found in the online supplement. Most patients attributed the reduction to a perceived lack of additional benefit. Limitations of the study include the variability in dosing intervals, the lack of data on adherence changes over time and the small sample size with even smaller subgroups [9]. A larger, more homogeneous population would be needed to more precisely assess the impact of INCS/ICS adherence on symptom control in dupilumab-treated CRSwNP patients.

The main goal of the study was to investigate adherence to topical corticosteroids in CRSwNP patients who respond to dupilumab treatment and assess the impact of a reduced compliance on symptom control. In conclusion, most patients reported a decreased medication adherence, and we could not show a detrimental effect for CRSwNP patients on dupilumab therapy when reducing INCS and ICS.

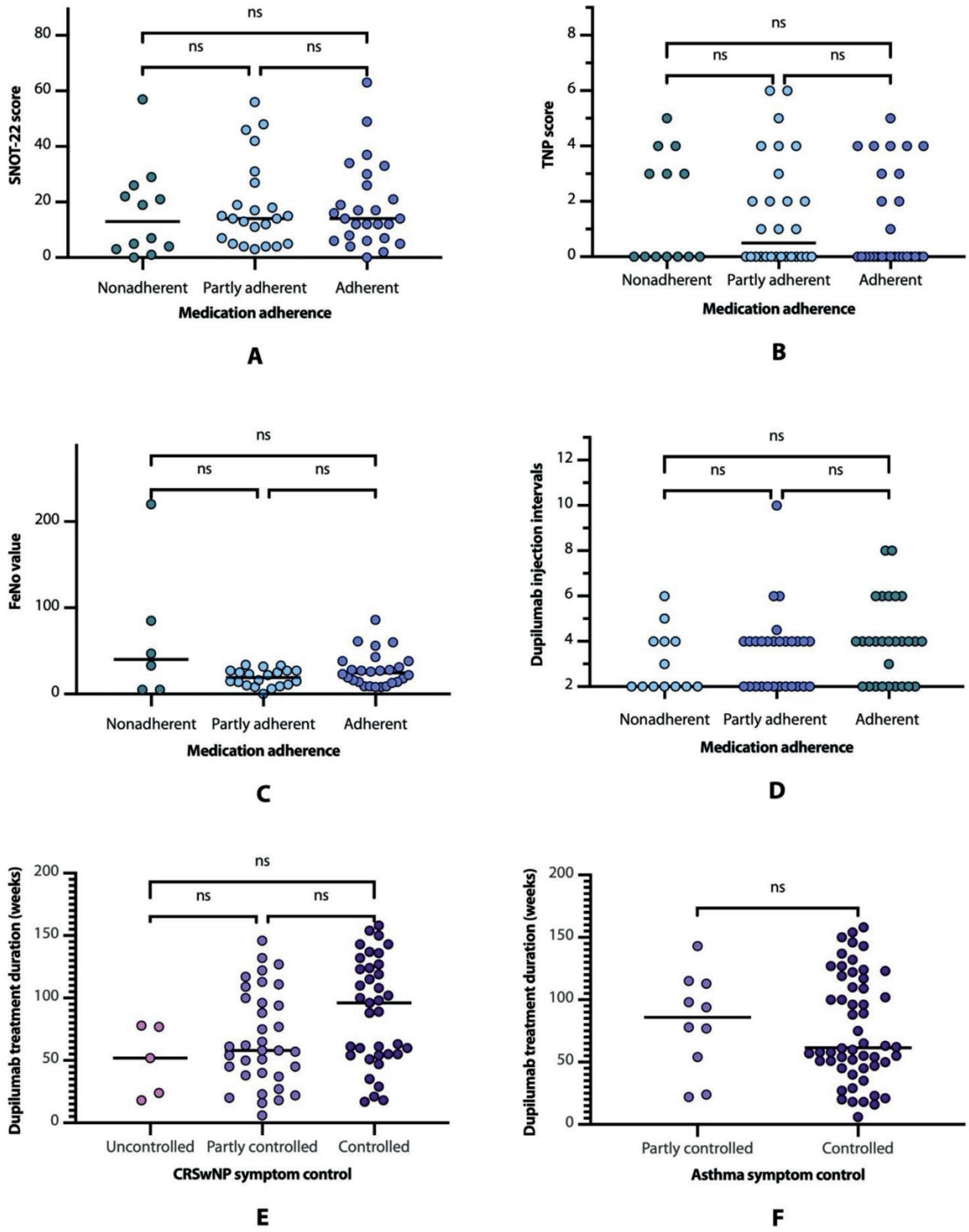

Figure 1. Association between medication adherence to INCS and ICS and SNOT-22 score, TNPS, dupilumab injection intervals and FeNO and between CRSwNP and asthma symptom control and dupilumab treatment duration.

Authorship contribution

SMM: conceptualization, ethical approval, investigation, data curation, formal analysis, writing – original draft. CB: Data curation, formal analysis, writing – original draft. AY: investigation, writing – original draft. UCS: conceptualization, supervision, writing – review & editing. CMM: formal analysis, writing – review & editing. MBS: conceptualization, supervision, investigation, writing – original draft.

Conflict of interest

The authors have no competing interests to declare.

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Table 1. Distribution of patients regarding CRSwNP and asthma symptom control and medication adherence to INCS and ICS.

Condition	Adherence	Controlled (%)	Partly controlled (%)	Uncontrolled (%)
CRSwNP	Adherent (INCS)	14 (20.3%)	12 (17.4%)	2 (2.9%)
	Partly adherent (INCS)	15 (21.7%)	12 (17.4%)	1 (1.4%)
	Nonadherent (INCS)	5 (7.2%)	7 (10.1%)	1 (1.4%)
Asthma	Adherent (ICS)	23 (43.4%)	4 (7.5%)	0 (0.0%)
	Partly adherent (ICS)	16 (30.2%)	5 (9.4%)	0 (0.0%)
	Nonadherent (ICS)	5 (9.4%)	0 (0.0%)	0 (0.0%)

$p = 0.88$ for CRSwNP and $p = 0.56$ for asthma.

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This manuscript contains online supplementary material

SUPPLEMENTARY MATERIAL

Materials and methods

Study design and setting

The present study was a single-center cohort study performed retrospectively at the department of Otorhinolaryngology and Head&Neck Surgery at the University Hospital of Zurich, Switzerland. Eligible patients were interviewed by telephone between March 16, 2023, and June 1, 2023.

Patients

All patients over 18 years of age diagnosed with chronic rhinosinusitis with nasal polyps (CRSwNP) undergoing intranasal corticosteroids (INCS) and/or inhaled corticosteroids (ICS) and biologic therapy treated at the department of Otorhinolaryngology and Head&Neck surgery at the University Hospital of Zurich between March and June 2023 were identified as population of interest. Identification of patients was performed through the clinical information system (KISIM), as well as the review of their medical history. Exclusion criteria were incompletely documented topical corticosteroid prescription (e.g. without specific dosage), interrupted biologic therapy during the period of interest and the use of additional systemic corticosteroids (apart from so-called short-term, single-use rescue treatment due to an exacerbation of CRSwNP).

Data collection

All eligible patients were subjected to the same interview protocol by telephone. This included questions about their current pharmacological therapy regarding CRSwNP and, if present, asthma. Thereby, each patient was instructed to specify the exact medication with the corresponding dosage and frequency of application. The dosage and frequency were grouped into the categories adherent (medication taken as prescribed), partly adherent (medication taken at a reduced dosage and/or frequency) and nonadherent (medication not taken). We then grouped the patients regarding their symptom control, according to the European Position Paper on Rhinosinusitis and Nasal Polyps 2020 (EPOS) and the Global Initiative for Asthma (GINA) symptom control tools [1, 2], into the categories controlled, partly controlled and uncontrolled. Therefore, they were requested to rank their CRSwNP symptoms using the Numeric Rating Scale (NRS), a verbal rating scale where 0 indicates no symptoms and 10 represents the worst possible severity. The scale included nasal blockage, rhinorrhoea and postnasal drip, facial pain or pressure, smell, sleep disturbance or fatigue during the last month and needed rescue treatment in the last six months [1]. The TNPS of their last nasal endoscopy, their last SNOT-22 score, the dupilumab injection intervals and treatment duration were noted from KISIM. Regarding asthma, patients were asked about any daytime symptoms, night waking, need of using SABA reliever and activity limitation due to the condition during the last month [2]. In addition, their last FeNO value was noted.

Statistical analysis

Fisher's exact test was applied to determine whether there was an association between medication adherence to INCS and ICS and symptom control of CRSwNP and asthma respectively. Shapiro-Wilk normality test, Mann-Whitney-U test and Kruskal-Wallis test were applied to determine whether there was an association between medication adherence to topical corticosteroids and dupilumab intervals, TNPS, SNOT-22 score and FeNO. Shapiro-Wilk normality test, one-way ANOVA, Kruskal-Wallis-test and Mann-Whitney-U-test were applied to assess the association between dupilumab treatment duration and CRSwNP and asthma symptom control and medication adherence. A statistical significance level of $p < 0.05$ was used. Analyses were performed using GraphPad PRISM software (version 10.2.1) and RStudio software (version 2024.04.2+764).

Ethics

The study was submitted to the ethics committee of the canton of Zurich (BASEC number 2022-02153) in December 2022 and approved in January 2023.

Patients were given information about the study by email or mail a few weeks prior to the telephone survey and informed consent was then acquired verbally shortly before each interview.

Results

Patient characteristics

Of 131 eligible patients identified in KISIM, 32 were excluded due to not meeting the required conditions (interrupted biologic treatment, no definitive CRSwNP diagnosis or incomplete topical corticosteroid documentation). 10 patients could not be contacted and 5 refused to participate. The biologics prescribed in the cohort were dupilumab, mepolizumab and tezepelumab, with 91.7% of patients treated with dupilumab alone, 3.6% treated with dupilumab combined with mepolizumab, 3.6% treated with mepolizumab alone and 1.2% treated with dupilumab combined with tezepelumab. We then decided to only include patients undergoing dupilumab treatment alone, excluding 7 more patients, leaving 77 eligible patients. The patients were between 25 and 77 years old, with an average of 52.3 years. 54 (70.1%) were males and 23 (29.9%) females. 64 (83.1%) patients were also diagnosed with asthma. Patients' last appointment, including FeNO, TNPS, and SNOT-22 assessments, occurred within a 4-month timeframe relative to the interview.

Topical corticosteroids prescription

69 (89.6%) patients had been prescribed INCS and 56 (72.7%) ICS, with 48 (62.3%) patients receiving both. The INCS prescribed in our cohort were either nasal sprays or rinses. The prescribed topical corticosteroids were budesonide, fluticasone, ciclesonide, mometasone, budesonide combined with formoterol, beclomethasone combined with formoterol, fluticasone combined with either formoterol, salmeterol or vilanterol and fluticasone furoate combined with umeclidinium and vilanterol. Of the patients with the INCS prescription, 8 did not complete their SNOT-22 score survey. Of the patients with the ICS prescription, 4 had no FeNO documented in their last consult. TNPS, dupilumab intervals and treatment duration were documented for all of the patients.

Medication adherence

Out of all patients, 52 (67.5%) reported using topical corticosteroids below the prescribed dosage and/or frequency. For INCS, 28 (40.6%) patients were adherent to the prescription, 28 (40.6%) were partly adherent and 13 (18.8%) patients were nonadherent. For ICS, 29 (51.8%) were adherent, 21 (37.5%) were partly adherent and 6 (10.7%) were nonadherent. The results are displayed in Figure S1.

Symptom control

According to EPOS, 37 (48.1%) patients were controlled, 35 (45.5%) were partly controlled, and 5 (6.5%) were uncontrolled regarding CRSwNP [(1)]. 5 patients needed rescue treatment during the previous 6 months, all of them reported a positive outcome afterwards (no persisting symptoms). For asthma, following GINA guidelines, 54 (84.4%) patients were controlled, and 10 (15.6%) were partly controlled, with no patients being uncontrolled [(2)]. The results are displayed in Figure S1.

The mean SNOT-22 score in our cohort was 17.7, with a median of 14, and the mean TNPS was 1.5, with a median of 0. The distribution of TNPS among patients is displayed in Table S1. The mean FeNO was 27.5, with a median of 22.5.

Association between medication adherence and symptom control

No significant association was found between INCS use and the degree of symptom control of CRSwNP ($p = 0.88$), SNOT-22 score ($p = 0.81$), or TNPS ($p = 0.79$). Similarly, ICS use did not significantly affect asthma symptom control ($p = 0.56$) or FeNO value ($p = 0.25$).

Dupilumab treatment

Patients started their dupilumab treatment between 3 years and 6 weeks before the interview. The mean duration of dupilumab treatment was 76.6 weeks, with a median duration of 63 weeks. Dupilumab injection intervals among patients ranged from 2 to 10 weeks, with specific intervals of 2, 3, 4, 4.5, 5, 6, 8, and 10 weeks, with 36.4% of patients having an interval of 2 weeks and 42.9% of patients having one of 4 weeks. There was no significant impact of dupilumab injection intervals on INCS adherence in our cohort ($p = 0.30$). There was an overall significant association between dupilumab treatment duration and CRSwNP symptom control ($p = 0.03$), with longer treatment duration in the controlled group. However, the post-hoc multiple comparison test showed no statistical significance between the groups ($p = 0.06$ comparing the controlled and the partly controlled group). Dupilumab treatment duration did not affect asthma symptom control ($p = 0.70$) or medication adherence to INCS ($p = 0.20$) or ICS ($p = 0.66$).

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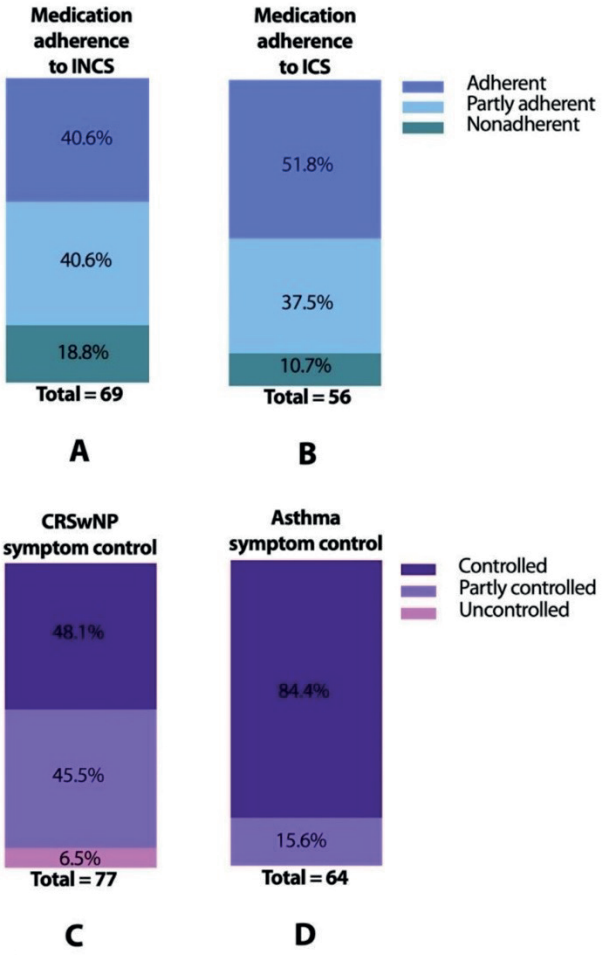

Figure S1. Distribution of medication adherence to INCS and ICS and of CRSwNP and asthma symptom control among patients.

Table S1. Distribution of TNPS among patients.

TNPS	Number of patients	Percentage (%)
0	43	55.8
1	5	6.5
2	6	7.8
3	6	7.8
4	10	13
5	4	5.2
6	3	3.9
7	0	0.0
8	0	0.0