Effect of corticosteroids on tissue eosinophilia in chronic rhinosinusitis: a systematic review and meta-analysis

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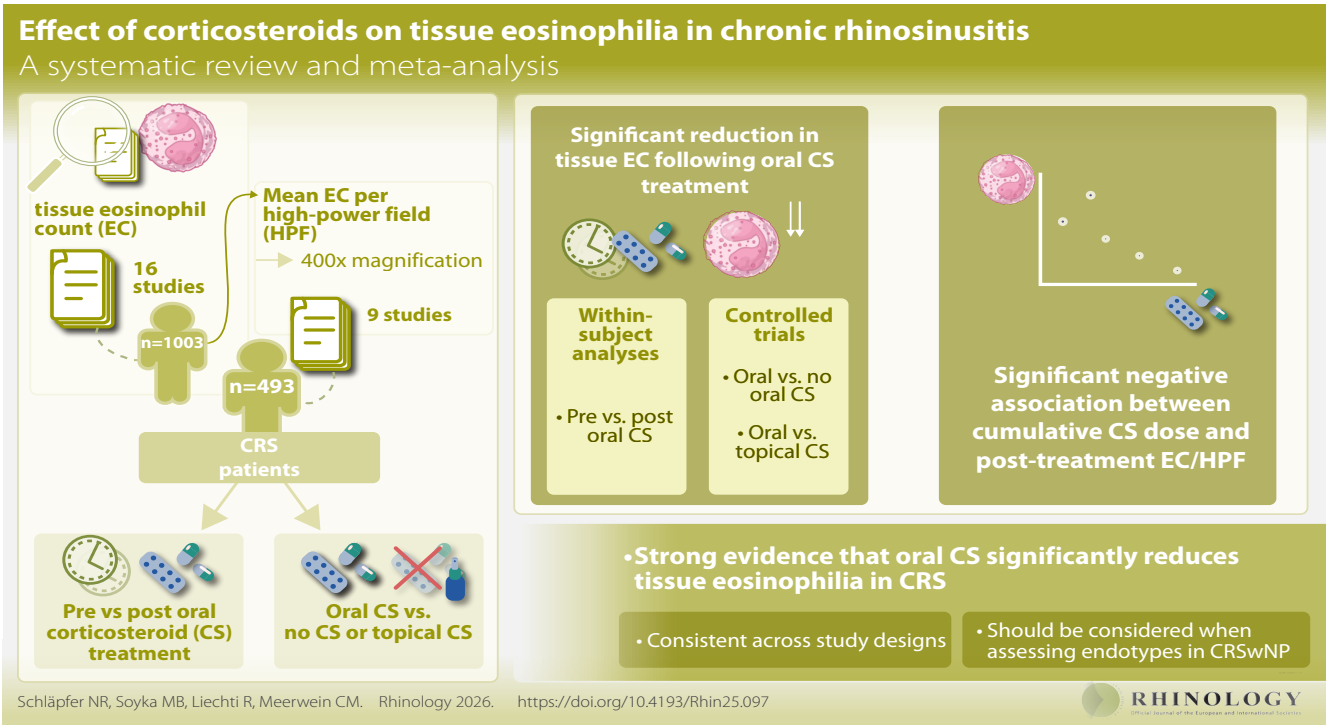

Abstract

Introduction: This systematic review and meta-analysis evaluated the effect of oral corticosteroid (CS) treatment on tissue eosinophil count (EC) in chronic rhinosinusitis (CRS) patients.

Methodology: A comprehensive database search identified 16 studies with 1,003 patients for the systematic review. Nine studies with 493 patients reporting mean tissue EC per high-power field (HPF) with 400x magnification were included in the meta-analysis. Within-subject (pre- vs. post CS treatment) and controlled comparisons (oral CS vs. no CS or topical CS) were analyzed.

Results: Results showed a significant reduction in tissue EC following oral CS treatment in both within-subject analyses and controlled trials. A similar effect was found when comparing oral vs. topical CS treatment. Meta-regression showed a significant negative association between cumulative CS dose and post-treatment EC/HPF.

Conclusion: These findings provide strong evidence that oral CS significantly reduces tissue eosinophilia in CRS, including comparisons with topical CS. The effect was consistent across study designs and should be considered when assessing endotypes in CRS with nasal polyps.

Key words: rhinosinusitis, corticosteroids, eosinophilia

Introduction

Chronic rhinosinusitis (CRS) is a prevalent condition that significantly impacts both quality of life and the healthcare system, with substantial economic implications [1–4]. Accurate diagnosis and characterization of CRS are essential for initiating appropriate treatment and guiding long-term management strategies. According to EPOS guidelines 2020, primary diffuse CRS is classified as type 2 or non-type 2 endotype [5]. Studies have shown that patients with a type 2 endotype generally respond less effectively to current treatment protocols, resulting in poorer disease control compared to those with a non-type 2 endotype (5). In recent years, the advent of biologics has revolutionized the management of severe uncontrolled type 2 CRS. Biologics target key drivers of type 2 inflammation, thereby attenuating inflammation, reducing polyp size, reversing tissue remodeling, and lowering recurrence rates [6–8]. However, biologics remain expensive and are therefore regulated by well-defined eligibility criteria. According to EPOS/EUFOREA 2023 criteria, patients with bilateral nasal polyps and a history of functional endoscopic sinus surgery (FESS) may be considered for biologic therapy if they fulfill at least three of the following criteria: evidence of type 2 inflammation (e.g., tissue eosinophils ≥ 10/HPF, blood eosinophils ≥ 150 cells/µL, or total IgE ≥ 100 kU/L), need for systemic corticosteroid (CS) treatment, significantly impaired quality of life (e.g., score of ≥40 in the 22-item SinoNasal Outcome Test (SNOT-22)), anosmia, and/or comorbid asthma requiring regular inhaled corticosteroids [9]. One possible indicator of type 2 inflammation is tissue eosinophilia, which can be assessed histologically in nasal polyp biopsies. These tissue samples can be obtained either in the setting of an outpatient clinic or during FESS. However, blood eosinophil counts alone may suffice in many cases to establish a type 2 endotype, especially in the presence of late-onset eosinophilic asthma, anosmia, and good response to corticosteroids [10].

Preoperative administration of short course oral CS in the treatment of CRS is well established in clinical practice [11,12]. It has been demonstrated that preoperative CS reduce polyp volume, minimize intraoperative bleeding, improve surgical field visibility, and shorten operation duration [13–15]. However, guidelines regarding optimal dosage and duration of CS therapy remain lacking. Additionally, several studies have shown that CS administration reduces the infiltration and survival of eosinophils by inhibiting the expression of pro-eosinophil cytokines -such as interleukin 5 and granulocyte/macrophage colony-stimulating factor - and by inducing apoptosis [16–20]. This CS-induced reduction in tissue eosinophils may complicate endotyping based on nasal biopsies, whether obtained through a preoperative biopsy or during surgery, as eosinophils ≥10/HPF represent a threshold for biologic eligibility. Consequently, patients may be incorrectly excluded from receiving biologic treatment.

This study aims to conduct a systematic review and meta-analysis of the current literature to evaluate the effect of CS treatment on tissue eosinophilia in CRS patients.

Materials and methods

This systematic review and meta-analysis was written according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) checklist [21,22]. No ethical approval was required for this study.

Search strategy and selection criteria

The PubMed, Embase, Cochrane Library, Web of Science, ProQuest, and Scopus databases were searched for studies comparing tissue eosinophil counts (EC) in CRS patients with or without oral CS treatment. Keyword selection was based on the PICO model [23]. Keywords used in the literature search were (rhinosinusitis OR chronic rhinosinusitis OR sinusitis OR chronic sinusitis) AND (eosinophil*) AND (steroid* OR corticosteroid* OR glucocorticoid* OR prednisone OR prednisolone) AND (oral OR systemic).

Data collection was performed according to the principles laid out by the Cochrane Collaboration [24]. Two reviewers (CMM, NRS) independently screened titles and abstracts for eligibility. Both randomized clinical trials and observational studies were considered for inclusion.

The inclusion criteria consisted of studies assessing the effect of oral CS treatment on tissue eosinophilia in patients with chronic rhinosinusitis. Exclusion criteria were review articles, studies only examining postoperative oral or topical CS treatment, preclinical studies, languages other than English, French, or German, no availability of full text or letters. For the meta-analysis, only studies evaluating mean EC/HPF at the magnification of 400x and oral CS treatment for a duration of 7 to 14 days were included. Disagreements on eligibility of full-text articles were resolved by consensus or by discussion with a third reviewer (MBS).

Data extraction

Two reviewers (CMM, NRS) independently performed data extraction. The following baseline characteristics were extracted from the included studies: first author, year of publication, country, study design, number of included patients, mean age, eligibility criteria, CS treatment protocol, control protocol, and tissue EC with or without CS treatment.

Risk of bias assessment

Two reviewers (CMM, NRS) independently assessed the methodological quality of the included randomized controlled trials (RCTs) using the RoB 2 tool on the specific outcome "effect of oral CS on tissue eosinophilia" [25]. In RCTs used exclusively for the within-subject analysis, the risk of bias assessment for the randomization process was marked as not applicable, as the analysis

Table 1. Summary of the systematic literature review.

Author, year	Country	Study design	Number of patients (n)		Mean age (range or SD)	Eligibility criteria	CS treatment protocol	Control protocol	Tissue sampling	Outcome	Oral CS reduces EC
			Inter-vention	Control							
Jankowski, 2003	France	Retrospective chart analysis	83	123	45 (8 - 77)	Isolated NP, NP + asthma or AERD	Oral CS during the last 2 months before surgery, either short course or long-lasting treatment, no product or dosage implications	No preoperative oral CS	NP biopsy during FESS, specific location NR	Significant lower eosinophil infiltration ratio after oral CS treatment compared to control group.	+
Kroflic, 2006	Slovenia	RCT	20	20	51 (13.6)	NP + AERD or AR, non-allergic NP	1 mg/kg/day methylprednisolone (≈1.25 mg/kg of prednisone) for 7 days	Inhalation of max. 20 mg/day furosemide for 7 days	Most superficial NP biopsies pre- and 7 days post-CS treatment	Significant lower EC after oral CS treatment without affecting mast cells or edema, while furosemide treatment does not significantly impact inflammatory cell counts.	+
Pujols, 2008	Spain	RCT	20	7	51 (2)	Severe NP (according to EP3OS guidelines66 ± asthma or AERD	30 mg prednisone daily for 4 days followed by a tapering of 5 mg every 2 days and intranasal budesonide (400 µg BID) for 2 weeks (w2), followed by intranasal budesonide (400 µg BID) alone for 10 additional weeks (w12)	No oral CS for 2 weeks following randomization (no treatment for 6 weeks in total)	NP biopsies obtained before (w0) and after 2 weeks (w2) and 12 weeks (w12) of CS treatment, specific location NR	Significant lower EC after oral CS treatment at w2 and w12 compared to baseline (w0).	+
Won, 2012	Korea	Prospective, non-randomized case series	47	47	42 (15 - 72)	Newly diagnosed NP, no CS or antihistamine within the past 4 weeks	20 mg prednisolone (≈20 mg prednisone) daily for 2 weeks	Same patients pre-treatment	NP biopsies pre- and post-CS treatment, specific location or timepoint NR	Significant lower eosinophil infiltration ratio 2 weeks post-oral CS treatment compared to pre-oral CS treatment.	+
Alobid, 2014	Spain	RCT	67	22	48.8 (13.6)	CRSwNP (according to EPOS 2012 criteria [67])	After a 4-week corticosteroid washout period (w0), prednisone for 2 weeks (w2) (30 mg daily for four days followed by a 2-day reduction of 5 mg) and intranasal budesonide (400 µg BID) for 12 weeks (w12)	After a 4-week corticosteroid washout period (w0), no CS treatment for 2 weeks	NP biopsies before (w0) and after 2 weeks of CS treatment (w2), specific location NR	Significant lower EC after oral CS treatment at w2 and w12 compared to baseline (w0) and compared to the control group.	+
Edward, 2013	USA	Prospective, non-randomized cohort study	12	12	44.3 (13)	CRSwNP, AERD (not further classified)	30 mg prednisone daily for 1 week prior to surgery	No oral CS 3 months prior to enrollment	NPs and ethmoid sinus mucosa for intervention and tissue from sphenoid rostrum and peripheral regions of this sinus for control during FESS.	Significant lower eosinophil infiltration ratio after oral CS treatment at 1 week compared to control group.	+
Hong, 2014	Korea	Retrospective chart analysis	6	20	48 (NR)	CRSwNP (according to diagnostic criteria of the American Academy of Otorhinolaryngology-Head and Neck Surgery68), no systemic CS for at least 1 month prior to study enrollment	15 mg prednisolone (≈15 mg prednisone) daily for 10 days prior to surgery, topical steroid 6 weeks prior to surgery (no product or dosage implications)	No oral CS prior to surgery, topical steroid 6 weeks prior to surgery (no product or dosage implication)	NP biopsies during FESS, specific location NR	Significantly lower EC after oral CS treatment at 10 days compared to control group.	+
De Borja, 2015	Spain	Retrospective case series	18	18	52.9 (3.7)	CRSwNP ± asthma or AERD	30 mg of prednisone daily for 4 days followed by a 2-day tapered reduction of 5 mg (total of 2 week) and intranasal budesonide (400 µg BID) for 12 weeks	Same patients pre-treatment	NP biopsies obtained before (w0) and after 2 weeks (w2) and 12 weeks (w12) of CS treatment, specific location NR	Significant lower EC after oral CS treatment at w2 and w12 compared to baseline (w0).	+

Table 1. Summary of the systematic literature review. *continued.*

Author, year	Country	Study design	Number of patients (n)		Mean age (range or SD)	Eligibility criteria	CS treatment protocol	Control protocol	Tissue sampling	Outcome	Oral CS reduces EC
			Inter-vention	Control							
Fujimoto, 2019	Japan	Retrospective chart analysis	11	31	54.8 (29 - 77)	Probable ECRS (according to JESREC diagnostic criteria69)	0.5 mg of bethametasone (=5 mg prednisone) daily for 7 days prior to surgery	No oral CS prior to surgery	NP biopsies during FESS, specific location NR	EC not different after oral CS treatment for 7 days compared to control group.	-
Zheng, 2019	China	Prospective cohort study	26	26	35.5 (18 – 64)	CRSwNP (according to EPOS 2012 criteria70), no oral or nasal CS 4 weeks before study	30 mg of prednisone daily for 7 days prior to surgery	Same patients pre-treatment	NP biopsies obtained before (d0) and after 8 days (d8) of CS treatment, specific location NR	EC not different 7 days post-oral CS treatment compared to pre-oral CS treatment.	-
Akiyama, 2019	Japan	RCT	21	23	53.4 (29 – 77)	ECRS: according to JESREC diagnostic criteria69), no systemic CS within 3 months before biopsy	0.3 mg/kg prednisolone daily 7 days prior to surgery, continuation of topical CS, antihistamines,or antileukotrienes if used before study	0.3 mg/kg prednisolone daily 3 days prior to surgery, continuation of topical CS, antihistamines, or antileukotrienes if used before study	Most superficial part of middle meatus polyp pre-CS treatment and during FESS post-CS treatment	EC slightly decreased post-oral CS treatment compared to pre-oral CS treatment, without reaching statistical significance, regardless of duration of CS administration (3 days or 7days) and no significant difference post-oral CS treatment between groups.	-
Zhang, 2019	China	RCT	26 (Group A)	30 (Group B) 29 (Group C)	43 (11)	Eosinophilic CRSwNP (according to EPOS 2012 criteria70), no oral CS treatment within the last 3 months	Group A:24 mg of methylprednisolone, (= 30 mg prednisone) daily for 2 weeks prior to surgery	Group B: 1 mg/2 mL Pulmicort (budesonide inhalation suspension = BIS) Respules transnasally twice daily for 2 weeks. Group C: budesonide nasal spray = BNS (256 µg BID) for 2 weeks	NP biopsies obtained 1 week before (w1) and after 2 weeks (w2) of CS treatment, specific location NR	Significant lower eosinophil infiltration ratio in all 3 groups (methylprednisolone, BIS and BNS) compared to baseline (before treatment).	+
Xu, 2020	China	RCT	40 (Group A)	38 (Group B) 39 (Group C)	44.1 (12)	CRSwNP (according to EPOS 2012 criteria70), systemic CS or antibiotics 1 month or local CS 2 weeks before randomization	Group A: 24 mg methylprednisolone, (= 30 mg prednisone) daily AND budesonide nasal spray (128 µg BID) for 7 days	Group B: intranasal budesonide suspension, 1 mg/d and budesonide nasal spray, 256 mg/d. Group C: budesonide nasal spray, 256 mg/d for one week	NP biopsies at the end of 7-day treatment, specific location NR	Significantly lower EC 7 days post-oral CS treatment compared to pre-oral CS treatment. EC compared to the control group NR.	+
Radajewski, 2021	Poland	Prospective controlled study	42	23	47.4 (12.7)	CRSwNP (according to EPOS 2020 criteria [5])	40 mg of prednisone daily for 7 days prior to surgery plus topical steroids (no product or dosage implications)	Only topical steroids (no product or dosage implications)	NP biopsies from nasal middle meatus during FESS	Significantly lower EC after oral CS treatment for 7 days compared to control group.	+
Suzuki, 2021	Japan	Retrospective, controlled study	28	9	55.8 (12.6)	AERD	5 mg of prednisolone (= 5 mg prednisone) daily, for 8 days prior to surgery	No oral CS prior to surgery	NP biopsies during FESS, specific location NR	73.3% decrease of EC after oral CS treatment for 8 days compared to control group.	+
Wierzchowska, 2023	Poland	Retrospective, controlled study	15	15	NR	CRS (according to EPOS 2020 criteria [5])	40 mg of prednisone daily for 7 days prior to surgery	Only topical steroids (no product or dosage implication)	NP or from ethmoid cavity during FESS	Significantly lower EC after oral CS treatment for 7 days compared to control group.	+
Total			482	532	46.4 (11.3)						In 13/16 studies oral CS led to a EC reduction

involved only pre- and post-treatment comparisons within the same group, and no between-group randomization was performed.For non-randomized studies, the two reviewers (CMM, NRS) assessed the risk of bias for the specific outcome, "effect of oral CS on tissue eosinophilia," using the Newcastle-Ottawa Scale (NOS) [26]. Studies with an NOS score < 7 were considered to have a high risk of bias, whereas those with a score ≥ 7 were considered to have a low risk of bias. Thus, studies with a NOS score < 7 were excluded for the systematic review and the meta-analysis. Disagreements were resolved by consensus with MBS.

Study outcome

The primary outcome of the meta-analysis was the effect of oral CS treatment on mean tissue EC within the same individual (within-subject analysis: pre- vs. post-CS treatment). Secondary outcomes included the effect of oral CS on mean tissue EC in controlled studies, comparing it to no oral CS or topical CS treatment.

In cases where studies reporting EC per multiple high-power fields (HPF) at the magnification of 400x, tissue EC values were corrected to one HPF. HPF conventionally uses the 40x lens, giving an overall magnification of 400x with a 10x eyepiece. According to Cree et al. one HPF corresponds to 0.24mm^2 [27]. This factor was used for the correction of results given in EC/mm^2. For studies using corticosteroids other than prednisone, the equivalent dose for prednisone was calculated for easier comparison.

Statistical analysis

Information about continuous variables was presented as means with standard deviation (SD), or information was converted to mean and SD using the methods suggested by Luo et al. [28]. Weighted mean calculations were performed for the synthesis of continuous variables to account for differences in study sizes. Dichotomous variables were presented as counts and percentages. Effects of oral CS treatment on tissue EC were pooled using the (random effects) inverse variance weighting method and presented as mean difference (MD) with a corresponding 95% confidence interval (95% CI). Heterogeneity between studies was assessed by visual inspection of forest plots (overlap of 95% CI) and by the I^2 statistic for heterogeneity. A mixed-effects meta-regression analysis was conducted using the restricted maximum likelihood (REML) estimator to evaluate the relationship between cumulative CS dose and post-treatment tissue EC/HPF. Residual heterogeneity was quantified using τ^2, I^2, and H^2, while the proportion of variance explained by the model was assessed using R^2. Statistical significance was determined using tests for residual heterogeneity (*QE*) and moderator effects (*QM*). Analyses were conducted using Review Manager (RevMan, version 5.3.5) and the R Statistical Software (version 4.4.3; R Core Team 2025) with the metafor package (version 4.8.0, Viechtbauer 2010). A p-value below 0.05 was considered statistically significant.

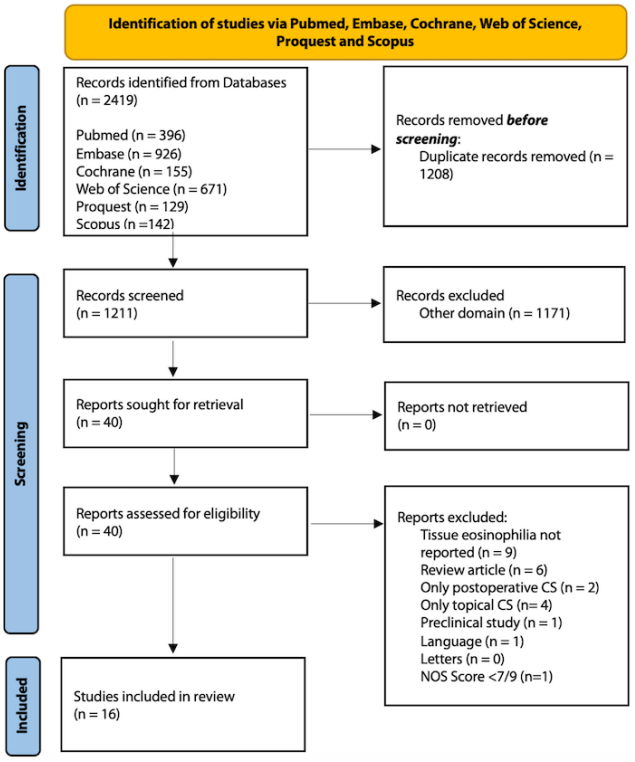

Figure 1. PRISMA 2020 flow diagram of the database search (December 10th, 2024). Abbreviations: CS corticosteroids, NOS Newcastle-Ottawa Scale.

Results

Study selection

Figure 1 presents the flowchart of the literature search and study selection. We identified a total of 2,419 articles in our initial search. A total of 2,379 studies were excluded after removing duplicates (n = 1,208) and title and abstract screening (n = 1,171). The remaining 40 articles were assessed for eligibility. Twenty-four articles were excluded because they did not meet inclusion criteria. Finally, a total of 16 articles were included: 6 RCTs; 4 prospective and 6 retrospective, non-randomized controlled studies (29–44). Among the 16 studies analyzed, 8 were conducted in Western/European populations (France, n = 1; Slovenia, n = 1; Spain, n = 3; USA, n = 1; and Poland, n = 2),

Table 1 Legend. Abbreviations: AERD Aspirin-exacerbated respiratory disease, AR allergic rhinitis, BID two times a day, CRSwNP chronic rhinosinusitis with nasal polyps, CS corticosteroids, EC eosinophil count, ECRS eosinophilic chronic rhinosinusitis, FESS functional endoscopic sinus surgery, NP nasal polyps, NR not reported, RCT randomized controlled trial, SD standard deviation.

Figure 2. Risk of bias assessment according to version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2) on the specific outcome "effect of oral CS on tissue eosinophilia". Abbreviations: CS corticosteroids.

while 8 focused on Asian populations (Korea, n=2; Japan, n = 3; and China, n = 3).

Study characteristics

The 16 included studies encompassed 1,014 patients with a weighted mean age of 46.4 years (SD 11.3 years). Of these 16 studies, 9 studies with a total of 493 patients were included in the meta-analysis. All studies included adult patients, except for one study that included both adult and pediatric patients, and another study that did not provide age information for the included patients [44,45]. Oral CS administration ranged from 5 mg to 70 mg Prednisone equivalent daily (mean 23.3 mg/day, SD 11.3) ranging from 3 to 14 days (mean 9.7 days, SD 3.3). Details on study type, number of patients, mean age, eligibility criteria, timing and dosage of oral CS administration, timing and type of tissue sampling and main study outcome are listed in Table 1.

Risk of bias assessment

The risk of bias assessment was specifically applied to the outcome "effect of oral CS treatment on tissue EC" for each study. The rating for non-randomized studies using the Newcastle-Ottawa Scale (NOS) is shown in Table 2. All non-randomized studies (n = 10) showed a score ≥ 7 and were therefore considered to have a low risk of bias. The rating for randomized studies (n = 6) using the RoB 2 tool is shown in Figure 2. In two studies, only within-subject data analysis was possible; therefore, the assessment of the randomization process was marked as not applicable. One study reported five patients lost to follow-up (16% loss to follow-up), while another study presented tissue EC data in a bar chart without providing absolute or relative values [40,41]. Therefore, the overall risk of bias is in these studies is rated as "some concerns". All studies included in the meta-analysis were assessed as having a low risk of bias.

Table 2. Risk of bias assessment according to the Newcastle-Ottawa Scale for non-randomized studies on the specific outcome "effect of oral CS on tissue eosinophilia".

Study	Selection Max. 4 stars	Comparability Max. 2 stars	Outcome Max. 3 stars	Total Score/ quality Max. 9 stars
Jankowski, 2003	★★★★	★	★★	7 / high quality
Won, 2012	★★★	★	★★★	7 / high quality
Edward, 2013	★★★★	★	★★★	8 / high quality
Hong, 2014	★★★	★★	★★★	8 / high quality
De Borja, 2015	★★★	★	★★★	7 / high quality
Fujimoto, 2019	★★★	★	★★★	7 / high quality
Zheng, 2019	★★★	★	★★★	7 / high quality
Radajewski, 2021	★★★★	★	★★★	8 / high quality
Suzuki, 2021	★★★★		★★★	7 / high quality
Wierzchowska, 2023	★★★★	★	★★★	8 / high quality

Qualitative synthesis

Of a total of 16 studies, 13 reported a significant reduction in tissue eosinophilia following oral CS treatment. However, three studies found no significant reduction after seven days of oral CS treatment [37–39]. Two of these studies used a low-dose treatment regimen (Fujimoto et al. used 5 mg/day; Akiyama et al. administered Prednisolone at 0.3 mg/kg, with doses ranging from 10 mg/day to 25 mg/day based on body weight) [37,39]. It is worth noting that Akiyama used a control group that received oral CS for 3 days, rather than patients who had no oral CS treatment. In the intraindividual comparison within the same subjects, tissue EC slightly decreased after oral CS treatment compared to before treatment; however, the reduction did not reach statistical significance [39]. In contrast, Zheng et al. administered 30mg /day of prednisone for 7 days without revealing significant tissue EC reduction.

Five studies compared oral CS with topical steroids (three non-randomized studies and two RCTs) [35,39–42,44]. All these studies demonstrated a significant reduction in tissue EC compared to patients treated with topical CS alone. One RCT investigated tissue EC after oral CS treatment for 7 days with 1 mg/kg/day methylprednisolone (=1.25 mg/kg of prednisone) compared to inhalation of max. 20 mg/day furosemide for 7 days. The results

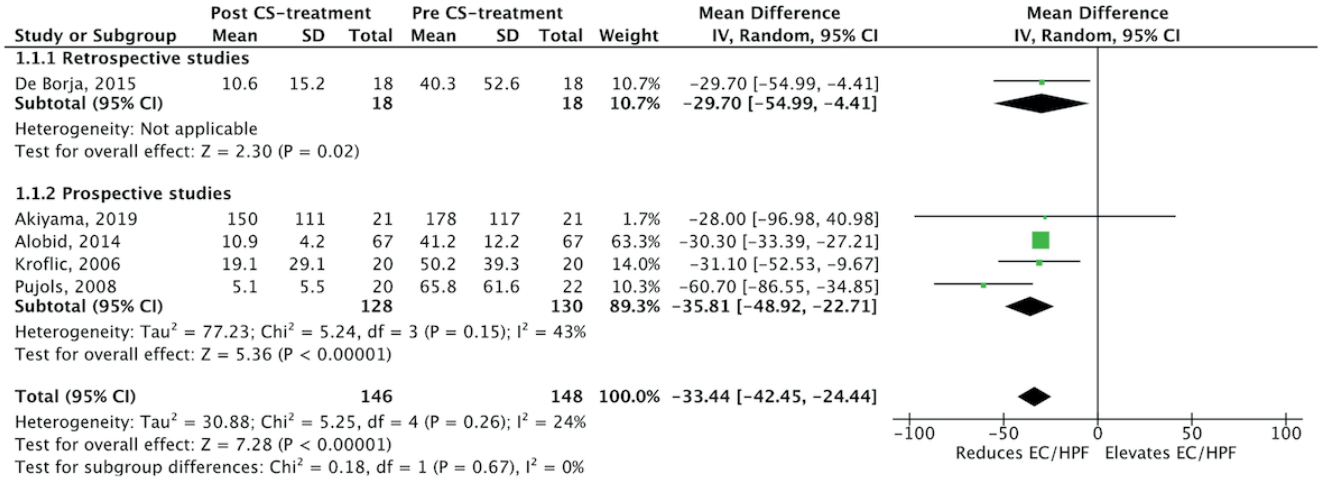

Figure 3. Forest plot depicting effect estimates regarding tissue eosinophilia pre- and post-CS treatment, limited to within-subject data analysis. Results are stratified according to the study design (prospective and retrospective studies). Abbreviations: EC CS corticosteroids, eosinophil count.

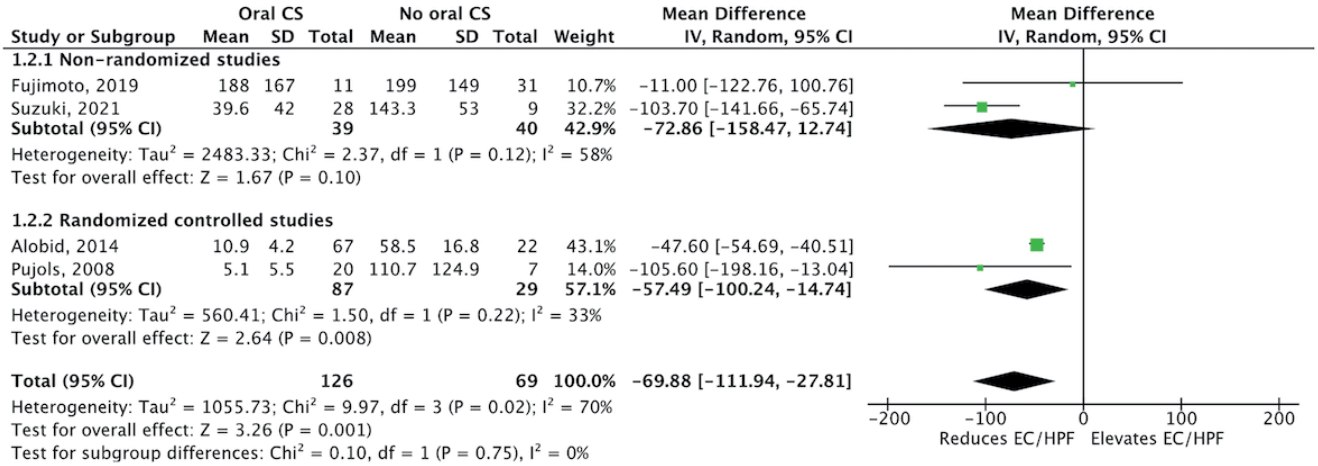

Figure 4. Forest plot depicting effect estimates regarding tissue eosinophilia in controlled studies (CS-treated vs. non-CS treated groups). Results are stratified according to the study design (observational and randomized controlled studies). Abbreviations: CS corticosteroids, EC eosinophil count.

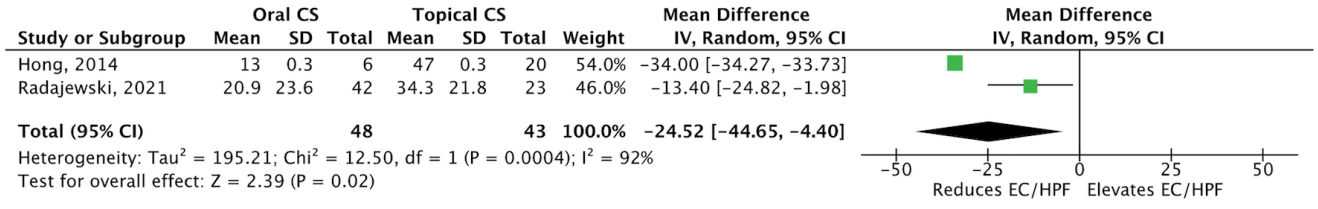

Figure 5. Forest plot depicting effect estimates regarding tissue eosinophilia in controlled studies (oral CS-treated vs. topical CS-treated groups). Abbreviations: CS corticosteroids, EC eosinophil count.

showed a significant reduction in tissue EC in the oral CS-treated group. Patients in the CS-treated group (within-subject analysis) showed a significant reduction in tissue EC after treatment compared to pre-treatment levels [30].

Meta-analysis results

Seven studies were excluded due to data being reported in a format unsuitable for statistical calculations, leaving a total of 9 studies for meta-analysis [30,31,33,35–37,39,42,43]. Pujols et at. reported results in EC/mm² [31]. For comparison to EC/HPF, a correction factor 0.24 was used for results given in EC/mm² as described in

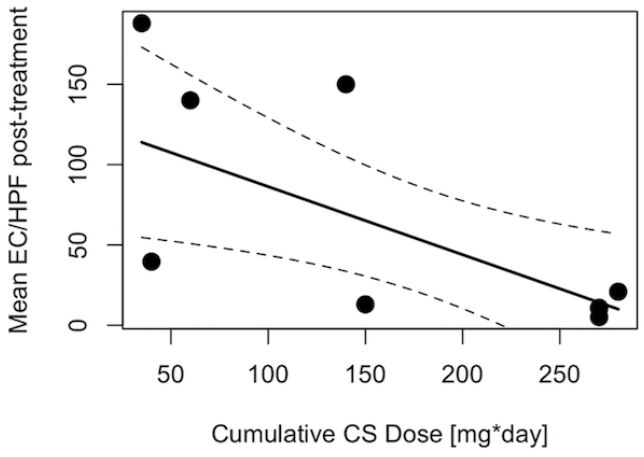

Figure 6. Dose-response curve and meta-regression of cumulative CS dose (mg∗day) and post-treatment mean EC/HPF. The solid line represents the fitted regression model, and the dashed lines indicate the 95% CI. A significant negative association was observed (β = −0.4239, p=0.0136), suggesting that higher cumulative CS doses are associated with lower post-treatment EC. Abbreviations: CI confidence interval, CS corticosteroids, EC eosinophil count, HPF high-power field.

the "Materials and Methods" section. Two studies counted eosinophils per 10 HPF at the magnification of 400x, therefore mean values were divided by 10 to reach comparability between studies [30,35].

Two RCTs comparing oral CS treatment to no oral CS treatment also reported on intraindividual tissue ECs before and after treatment within the same subjects [31,33]. Therefore, the data of these studies were included in both the within-subject analysis and the controlled (control = no oral CS) analysis. Another study used furosemide as a control, while another compared 7-day versus 3-day oral CS treatment, which therefore could not be included in the meta-analysis for controlled studies [30,39]. However, both studies provided pre- and post-treatment tissue EC data, which were used for within-subject analysis in the present study.

Within-subject analysis

Five studies, involving 148 patients, compared tissue EC before and after CS treatment (within-subject analysis) [30,31,33,36,39]. Two patients were lost to follow-up. Studies were stratified into pro- and retrospective studies.

The overall analysis, combining both retro- and prospective data, showed a pooled MD of -33.44 EC/HPF (95% CI [24.4, 42.4 EC/HPF], $p < 0.00001$), confirming a statistically highly significant reduction in tissue EC after CS treatment. Heterogeneity across all studies was low ($I^2 = 26\%$).

The only retrospective study revealed a MD of -29.70 EC/HPF (95% CI [4.4, 54.9 EC/HPF], $p = 0.02$), indicating a significant EC reduction post-treatment [36]. Among the prospective studies, four studies contributed to the analysis, with a pooled MD of -35.81 EC/HPF (95% CI [22.7, 48.9 EC/HPF], $p < 0.00001$), demonstrating a consistent and significant reduction post-CS treatment [30,31,33,39]. Heterogeneity within this subgroup was moderate ($I^2 = 43\%$). The test for subgroup differences showed no significant distinction between retro- and prospective studies ($\chi^2 = 0.18$, $p = 0.67$, $I^2 = 0\%$). The forest plot is presented in Figure 3.

Controlled studies (control = no oral CS)

For the analysis of controlled studies, in which the control groups did not receive oral CS, four studies were included [31,33,37,43]. A total of 126 patients received oral CS, while 69 patients did not. The studies were further stratified into non-randomized studies and randomized controlled trials (RCTs).

The overall effect of oral CS treatment resulted in a significant tissue EC reduction with a pooled MD of -69.88 EC/HPF (95% CI [27.8, 111.9 EC/HPF], $p = 0.001$). The total heterogeneity across all studies was substantial ($I^2 = 70\%$).

In the subgroup of non-randomized studies, the overall effect of oral CS treatment on tissue EC was not significant with a pooled MD of -72.86 EC/HPF (95% CI [12.7,158.5 EC/HPF], $p = 0.10$). Heterogeneity within this subgroup was substantial ($I^2 = 58\%$). In contrast, the RCT subgroup indicated a significant EC reduction after oral CS treatment with a pooled MD of -57.49 EC/HPF (95% CI [14.7, 100.2 EC/HPF], $p = 0.008$) and a moderate heterogeneity of $I^2 = 33\%$. The test for subgroup differences resulted in $\chi^2 = 0.10$ ($p = 0.75$), indicating no significant difference between the non-randomized and randomized subgroups. The forest plot is presented in Figure 4.

Controlled studies (control = topical CS)

Two studies, where the control groups received topical CS, were included into the meta-analysis [35,42]. 48 patients were treated with CS, whereas 43 did not receive oral CS, but were treated with topical CS. Oral CS treatment resulted in a significantly greater reduction in tissue EC compared to topical CS treatment with a pooled MD -24.5 EC/HPF (95% CI [4.4, 44.7 EC/HPF], $p < 0.001$). Heterogeneity was high with $I^2 = 92\%$. The forest plot is presented in Figure 5.

Dose-response analysis

A total of eight studies provided precise CS dosage data, enabling a dose-response analysis [31,33,35–37,39,42,43]. One study reported tissue EC at two distinct time points: 3 days and 7 days post-CS treatment, resulting in a total of 9 datasets available for meta-regression ($\kappa = 9$) [39]. A mixed-effects meta-regression analysis was conducted to assess the association between cumulative CS dose and mean EC/HPF post-treatment. The residual heterogeneity was estimated using REML ($\tau 2 = 2'259.42$, SE = 1'343.95). The analysis revealed substantial between-study variability ($I^2 = 99.79\%$, $H^2 = 482.75$), with the moderator ac-

counting for 40.64% of the heterogeneity (R^2 = 40.64%). The test for residual heterogeneity was statistically significant ($QE(7) = 104.50$, $p < 0.0001$), indicating the presence of unexplained variance. Meta-regression results demonstrated a significant negative association between cumulative CS dose and EC/HPF ($\beta = -0.4239$, SE = 0.1718, $p = 0.0136$), suggesting that higher CS doses were associated with lower post-treatment eosinophil counts. The fitted regression model and confidence intervals are displayed in Figure 6.

Discussion

Summary of main findings

This systematic review and meta-analysis found that oral CS treatment significantly reduces EC in patients with CRS, with consistent effects across study designs. The reduction was greater with higher cumulative CS doses and remained significant compared to topical CS treatment. These results underscore the need for individualized CS dosing strategies. This is the first meta-analysis to compare oral CS effects on tissue EC in CRS, aligning with broader evidence from eosinophilic diseases and carrying important implications for accurate CRS endotyping and treatment planning [20,46–48].

Strengths and limitations of the evidence

A key strength of this study is the comprehensive inclusion of both randomized controlled trials (RCTs) and non-randomized studies, enhancing the robustness of the findings. The within-subject comparison controls for inter-individual variability, including factors such as responsiveness to CS treatment, baseline differences and genetics. The latter is particularly noteworthy, as studies have shown ethnic differences in type 2 inflammation, with a lower prevalence and reduced severity in Asian populations [49,50]. This design is less susceptible to confounding factors and provides higher statistical power. However, when evaluating the efficacy of CS treatment in reducing mean tissue EC, a between-group comparison provides stronger determination of cause-and-effect relationship and better controls for time-dependent effects. Furthermore, the significant dose-response relationship across different study designs reinforces these results. Together, our findings underscore the significant impact of oral CS treatment on tissue EC while emphasizing the importance of study design in interpreting the results.

Regarding limitations, the heterogeneity in CS regimens, treatment durations and EC reporting across studies presumably contributes to the variability in results. Some studies employed short-term, high-dose oral CS protocols, while others used lower doses or incorporated a tapering regimen. The duration of CS administration also varied, ranging from as short as three days to as long as several weeks, potentially influencing the extent of eosinophil reduction. Additionally, several studies combined oral CS with topical steroids, further complicating direct comparisons between treatment effects. Additional topical therapy could enhance the reduction of tissue EC, as previous studies looking at nasal polyposis or allergic rhinitis patients have demonstrated that topical CS treatment alone can decrease tissue EC [51–56]. These findings suggest that the combined use of oral and topical CS may potentiate the effect on tissue eosinophilia. While all included studies investigated patients with nasal polyps, there was variability in the specific phenotypes and terminology used (e.g., chronic rhinosinusitis with nasal polyps (CRSwNP), AERD, ECRS, or severe NP), as well as in the anatomical sites of biopsy. This variability in phenotype and sampling site may impact the generalizability of the findings and is acknowledged as a limitation.

Some studies reported tissue EC in non-standardized formats, requiring conversions that could introduce minor inaccuracies. Furthermore, although all studies included in the meta-analysis reported a mean EC/HPF value, Fujimoto et al. and Akiyama et al. presented notably higher mean EC/HPF compared to the others [37,39]. This discrepancy may be attributed to the fact that both studies explicitly stated that histological analysis was performed in eosinophil-rich areas. Furthermore, it is worth noting that tissue eosinophilia may vary depending on the anatomical site of biopsy, as reported in previous research [57,58]. Only four studies in present systematic review specifically analyzed inflamed mucosa samples from the ethmoid or middle meatus, whereas the other articles did not specify the exact site of biopsy [34,39,42,44]. The wide variability in baseline eosinophil counts underscores the importance of interpreting MDs within the context of individual study populations.

These inconsistencies in treatment protocols and tissue EC reporting complicate direct comparisons and may explain the variability in tissue EC reductions observed across studies. While the dose-response analysis aimed to account for variability of CS dose and treatment duration, a substantial residual heterogeneity of the meta-regression (I^2 = 99.79%) remained, again indicating that additional factors may influence treatment response. The proportion of heterogeneity explained by CS dose (R^2 = 40.64%) suggests that while dose plays a major role, further studies are needed to explore additional moderators that may contribute to variability in treatment response.

Implications for practice

Biologic treatments targeting key drivers of type 2 inflammation have emerged as promising therapeutic options, significantly altering the clinical course of severe CRS phenotypes [59]. However, oral CS treatment remains a widely used and essential treatment for affected individuals, effectively reducing nasal mucosal inflammation [60]. Our findings confirm that oral CS does lead to a significant reduction in tissue EC levels. Given that tissue eosinophilia serves as a one of other criteria for biologic therapy eligibility, clinicians should be aware that the use of oral CS may

suppress tissue EC levels and lead to potential misclassification of endotypes. This highlights the importance of carefully timing biomarker assessment to avoid underestimating the extent of type 2 inflammation and its relevance for treatment selection. However, the diagnostic value of tissue biopsy itself should be weighed critically, since peripheral blood eosinophil counts often serve as a practical and accessible surrogate for treatment guidance in routine clinical settings.

Moreover, the routine use of oral CS in patients with CRSwNP should be reconsidered. Emerging evidence suggests that the long-term benefits of oral CS are limited, whereas the potential for cumulative adverse effects is substantial [61,62]. A multicenter randomized trial, for example, found no meaningful long-term improvement following postoperative oral CS administration in CRSwNP patients, raising doubts about the added value of such interventions [61]. These findings, alongside growing concern about the long-term harms of repeated corticosteroid exposure, support a more cautious, individualized approach to oral CS use—especially when alternative perioperative strategies (e.g., Anti-Trendelenburg positioning, mean arterial pressure control, tranexamic acid administration, or transoral pterygopalatine fossa infiltration) are available to optimize the surgical field without systemic steroid use [63,64]. These findings, combined with growing concerns about cumulative corticosteroid side effects, call for a careful reconsideration of routine oral CS use in CRSwNP management.

Implications for research

Future research should aim to standardize treatment protocols and EC reporting to facilitate comparability between studies. Standardized methodologies including detailed reporting of additional topical CS treatment will enhance the reliability and generalizability of findings across different patient populations. As highlighted in a recent review, a significant number of patients remain unresponsive to CS treatment, leading to inadequate disease control. According to this article, assessment of CS sensitivity includes clinical evaluation, biomarker analysis, and genetic profiling [65]. Such stratification has practical relevance, as demonstrated by one study included in the current analysis, which found a significant reduction in tissue EC only in CS-sensitive patients. In this study, patients were classified as either CS-sensitive or CS-insensitive based on a previously described method that utilized clinical parameters [38]. Future research should take this aspect into account when defining study eligibility criteria.

Conclusion

This systematic review and meta-analysis demonstrates that oral CS treatment significantly reduces tissue eosinophilia in CRS patients. The observed reduction in eosinophils may influence endotyping and subsequent treatment decisions, highlighting the need for caution when using tissue EC to guide biologic therapy eligibility.

Conflict of interest

MBS is a consultant for different companies including Sanofi, GSK, Astra Zeneca, MSD, Novartis. CMM is consultant for Sanofi, GSK and Astra Zeneca.

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Authors' contributions

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Statement for availability of data and materials

Data supporting the findings of this study are available from the original published studies included in this systematic review and meta-analysis. Relevant citations and sources are listed in the manuscript.

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