Annals of Internal Medicine | ORIGINAL RESEARCH

Treatment of Chronic Rhinosinusitis With Nasal Polyposis With Oral Steroids Followed by Topical Steroids

A Randomized Trial

Sriram Vaidyanathan, MBBS; Martyn Barnes, MBChB; Peter Williamson, MBChB; Pippa Hopkinson; Peter T. Donnan, MD; and Brian Lipworth, MD

Background: Chronic rhinosinusitis (CRS) with nasal polyposis is common. The long-term efficacy and safety of approaches to medical management are not well-known.

Objective: To evaluate the efficacy and safety of a 2-week regimen of oral steroid therapy followed by 26 weeks of sequential topical steroid maintenance therapy.

Design: Parallel randomized trial with computer-generated block randomization and central allocation. Patients and investigators were blinded to group assignment. (ClinicalTrials.gov registration number: NCT00788749)

Setting: A specialty rhinology clinic in Tayside, Scotland.

Patients: 60 adults with CRS and moderate-sized or larger nasal polyps who were referred by their primary physicians for specialty care.

Interventions: Patients were randomly assigned in a 1:1 ratio to receive oral prednisolone, 25 mg/d, or placebo for 2 weeks, followed in both groups by fluticasone propionate nasal drops, 400 μg twice daily, for 8 weeks and then fluticasone propionate nasal spray, 200 μg twice daily, for 18 weeks.

Measurements: Polyp grading (primary outcome), hyposmia score, quality of life, symptoms, nasal patency, adrenal function, and bone turnover.

Results: The mean decrease in polyp grade from baseline to 2 weeks was 2.1 units (SD, 1.1) in the prednisolone group and 0.1 unit (SD, 1.0) in the placebo group (mean difference between groups, −1.8 units [95% CI, −2.4 to −1.2 units]; $P < 0.001$). The difference between groups was −1.08 units (CI, −1.74 to −0.42 unit; $P = 0.001$) at 10 weeks and −0.8 unit (CI, −1.8 to 0.2 unit; $P = 0.11$) at 28 weeks. The mean decrease in hyposmia score from baseline to 2 weeks was 31.12 mm (SD, 30.1) in the prednisolone group and 1.41 mm (SD, 30.6) in the placebo group (mean difference between groups, −28.33 mm [CI, −42.71 to −13.96 mm]; $P = 0.002$). The difference between groups was −16.06 mm (CI, −30.99 to −1.13 mm; $P = 0.03$) at 10 weeks and −12.13 mm (CI, −30.55 to 6.29 mm; $P = 0.19$) at 28 weeks. Prednisolone therapy resulted in transient suppression of adrenal function and increase in bone turnover after 2 weeks, with a return to baseline at 10 and 28 weeks.

Limitations: Patients were referred from primary care to a single-center rhinology clinic, which limits the generalizability of results. Serial measurements of surrogates of nasal inflammation (such as nitric oxide or cytokine levels) were not performed.

Conclusion: Initial oral steroid therapy followed by topical steroid therapy seems to be more effective over 6 months than topical steroid therapy alone in decreasing polyp size and improving olfaction in patients referred for specialty care of CRS with at least moderate nasal polyposis.

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For author affiliations, see end of text.

Chronic rhinosinusitis (CRS) is one of the most common chronic disorders in the developed world, affecting 32 million persons (16.3% of the population) in the United States alone (1). Annual health care costs for CRS are estimated at $6 billion, which is probably an underestimate because of the indirect costs from lost productivity and the effect on general and lower airway health outcomes (1–3). Chronic rhinosinusitis with nasal polyposis, a distinct pathologic subtype of CRS with an estimated prevalence of 3% to 5%, has a greater burden of symptoms and a higher relapse rate after treatment (4, 5). This condition is managed by various practitioners, including primary care physicians, otolaryngologists, respiratory physicians, and allergologists.

Despite the high prevalence and significant morbidity associated with CRS with nasal polyposis, evidence to guide practitioners on initiation and maintenance of therapy is limited. Current international guidelines (5) recommend that primary care physicians diagnose CRS with nasal polyposis on the basis of such symptoms as nasal blockage, discharge, facial pain or pressure, and reduction in the sense of smell for more than 12 weeks. Topical steroids are recommended for CRS, with or without nasal polyposis, along with nasal saline douching and antiallergy medications as needed (5). Referral to an otolaryngologist is recommended if no response is observed after 3

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Context

Chronic rhinosinusitis with nasal polyposis is a common problem resulting in nasal blockage, facial pain, and hyposmia. Responses to therapy are frequently incomplete, and relapses are common. Although oral steroids are recommended only when specialty care is required, little is known about their efficacy.

Contribution

Patients with at least moderate-sized nasal polyps and chronic rhinosinusitis were randomly assigned to receive 2 weeks of therapy with oral steroids or placebo, followed in both groups by sequential steroid nasal drops and spray. Over 28 weeks of therapy, a greater reduction in the size of polyps and greater improvement in olfaction were observed after induction therapy with oral steroids.

Caution

The diagnosis of chronic rhinosinusitis with nasal polyposis was made by otorhinolaryngologists at a specialty clinic, and the applicability of these findings to patients seen only in primary care is unclear.

Implication

An initial course of oral steroids seems to be effective in reducing polyp size and improving olfaction in some patients with chronic rhinosinusitis and nasal polyps.

—The Editors

months of these treatments. Under these guidelines, oral steroids are reserved for use by otolaryngologists, and only for severe CRS with nasal polyposis or for refractory cases (2, 5).

Monotherapy with intranasal corticosteroids can lead to a steady loss of symptom control in the long term (6–8). Chronic rhinosinusitis with nasal polyposis is characterized by frequent relapses, which prompt repeated referrals to secondary care for rescue therapy (5). We hypothesize that this is partly attributable to the inability of topical therapies to effectively penetrate the ostiomeatal complex (the outflow tract of the paranasal sinuses) and reestablish physiologic sinus drainage. Surgical treatment temporarily relieves ostiomeatal complex blockage, but it is not curative and serves primarily to facilitate the penetration of topical steroid therapy. In addition, surgery should be reserved for cases that are refractory to maximum medical therapy because of the potential for orbital and intracranial complications (5). A short course of oral steroids, known as *medical polypectomy*, might improve the long-term efficacy of topical therapy; however, data to support this practice are lacking. Furthermore, despite the high prevalence of concomitant asthma and use of inhaled corticosteroids, no data on long-term systemic steroid burden in these patients are available.

We hypothesized that initial therapy with oral steroids would lead to a greater and sustained reduction in polyp size and an improvement in olfaction, nasal airflow, and quality-of-life variables. On this basis, we conducted the first randomized clinical trial to evaluate the efficacy and safety of a treatment regimen that comprised a 2-week course of oral steroids followed by a 26-week course of intranasal steroids.

METHODS

We conducted a parallel, randomized, controlled trial in which patients who had CRS with nasal polyposis received either oral prednisolone or placebo for the first 2 weeks, followed in both groups by fluticasone nasal drops for 8 weeks and then fluticasone nasal spray for 18 weeks.

Setting and Participants

We recruited nonsmoking adults who had CRS with nasal polyposis, with or without asthma, from a single-center specialty clinic in Tayside, Scotland, to which patients were referred for assessment by their primary care physicians. Ear, nose, and throat specialists diagnosed CRS with nasal polyposis on the basis of the European Position Paper on Rhinosinusitis and Nasal Polyps 2007 criteria (5). Inclusion criteria were the presence on nasoendoscopy of bilateral moderate-sized to large nasal polyps (grade >1) according to the Lildholdt scale (0, no nasal polyps; 1, small polyps confined to the middle meatus; 2, moderate-sized polyps not crossing the lower edge of the inferior turbinate; 3, large polyps crossing the lower edge of the inferior turbinate) (9) and at least 2 of anterior or posterior nasal discharge, nasal obstruction, or decreased sense of smell for more than 12 weeks. Exclusion criteria included treatment with an oral corticosteroid in the past 3 months, sinus surgery in the past year, recent upper respiratory tract infection, mechanical nasal airway obstruction of more than 50% due to septal deviation, or pregnancy or lactation. The institutional review board of the Tayside Committee on Medical Research Ethics approved our study, and all participants gave written informed consent.

Our study was conducted in accordance with the current revision of the 1964 Declaration of Helsinki and guidelines laid down by the International Conference on Harmonization for good clinical practice in clinical trials. Serious adverse events were defined as noted in **Appendix Table 1** (available at www.annals.org).

Random Assignment and Interventions

An independent, off-site clinical trials pharmacist (Pharmacy Production Unit, Western Infirmary, Glasgow, United Kingdom) used a computer-generated random allocation sequence to randomize the trial, using block randomization with a block size of 4. The same pharmacist masked and blinded the 25-mg prednisolone tablet and an identical placebo tablet to double-blind the study from the investigator and participants. Tablets were distributed in sealed opaque envelopes at the research unit, in sequential

order, by a laboratory technician who was not directly involved with the study.

After a screening visit, eligible patients entered a 2-week period during which therapy for CRS with nasal polyposis was stopped. Patients were randomly allocated in a 1:1 ratio to receive either prednisolone, 25 mg/d, or an identical placebo for 2 weeks, followed in both groups by fluticasone propionate nasal drops (Flixonase nasule, Allen & Hanburys, Uxbridge, United Kingdom), 400 μg twice daily, for 8 weeks and then fluticasone propionate nasal spray (Flixonase nasal spray, Allen & Hanburys), 200 μg twice daily, for a further 18 weeks. From screening until the end of the study, no other rhinitis medications were permitted, including antihistamines, leukotriene receptor antagonists, intranasal corticosteroids, or nasal decongestants. No antibiotics were permitted during the study.

Outcomes and Measurements

Baseline Measurements

To characterize upper and lower airway disease and identify potential predictive factors that could influence therapeutic effectiveness, we established the presence and severity of asthma by history, spirometry (SuperSpiro, Micro Medical, Chatham Maritime, United Kingdom) (10), body plethysmography (Jaeger MasterScreen, CareFusion, Basingstoke, United Kingdom) (11), tidal and nasal nitric oxide levels (Niox, Aerocrine, Solna, Sweden) (12), and bronchial methacholine challenge (13). Aspirin sensitivity was diagnosed by history and nasal lysine–aspirin challenge (14). The extent of rhinosinusitis was staged by using the modified Lund–Mackay system to score computed tomography scans of the paranasal sinuses on the basis of reconstructed axial and coronal sections (15); percentage of opacification was scored for each of the maxillary, frontal, anterior ethmoid, posterior ethmoid, and sphenoid sinuses as 0%, 1 (1% to 25%), 2 (26% to 50%), 3 (51% to 75%), 4 (76% to 99%), or 5 (100%), and the scores were summed for each patient. Atopy was evaluated by total serum IgE levels and by radioallergosorbent testing for specific IgE to grass pollen, house dust mites, cats, dogs, or *Aspergillus* and IgG to *Aspergillus*. Polyp biopsies were performed to determine tissue eosinophil count. Specific levels of IgE to serum *Staphylococcus aureus* enterotoxins A and B and toxic shock syndrome toxin 1 were also measured with the UniCAP assay (Phadia, Uppsala, Sweden); the interassay coefficient of variation was 4.3%.

Longitudinal Measurements

Primary and secondary efficacy and safety outcomes were measured at random assignment (baseline) and after each treatment period (2, 10, and 28 weeks from baseline).

Our primary outcome measure was nasoendoscopic polyp grading. Nasoendoscopy was performed by using a 2.7-mm 30-degree endoscope (Karl Storz-Endoskope, Tuttlingen, Germany) with an integrated endoscopy camera system (LCH 01-D, Xion Medical, Berlin, Germany). Standard video sequences were stored on a computer and viewed by 2 independent observers, who were blinded to patient, treatment, and sequence. Disagreements were resolved by discussion. Interrater reliability (±SE), assessed by using a weighted κ score, was 0.75 ± 0.079. Secondary efficacy outcome measures were a 100-mm hyposmia visual analogue scale and the Pocket Smell Test (Sensonics, Haddon Heights, New Jersey) (16) for the subjective and objective assessment of olfaction, respectively; total nasal symptoms score (17); peak nasal inspiratory flow rate (5); the Juniper mini Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) (18); and serum eosinophil-derived neurotoxin and high-sensitivity C-reactive protein levels, which were measured by using commercially available enzyme-linked immunosorbent assays (Immunodiagnostik AG, Bensheim, Germany, and Kalon Biological, Guildford, United Kingdom).

Secondary safety measures included overnight (10:00 p.m. to 8:00 a.m.) urinary free cortisol; overnight urinary cortisol corrected for creatinine (no fluticasone cross-sensitivity); 8:00 a.m. serum cortisol; low-dose, 1-μg adrenocorticotropic hormone–stimulation test; and markers of bone turnover (serum osteocalcin by immunoradiometric assay and procollagen-1 *N*-terminal peptide and procollagen-3 *N*-terminal peptide by radioimmunoassay). **Appendix Table 2** (available at www.annals.org) presents the coefficients of variation for the assays.

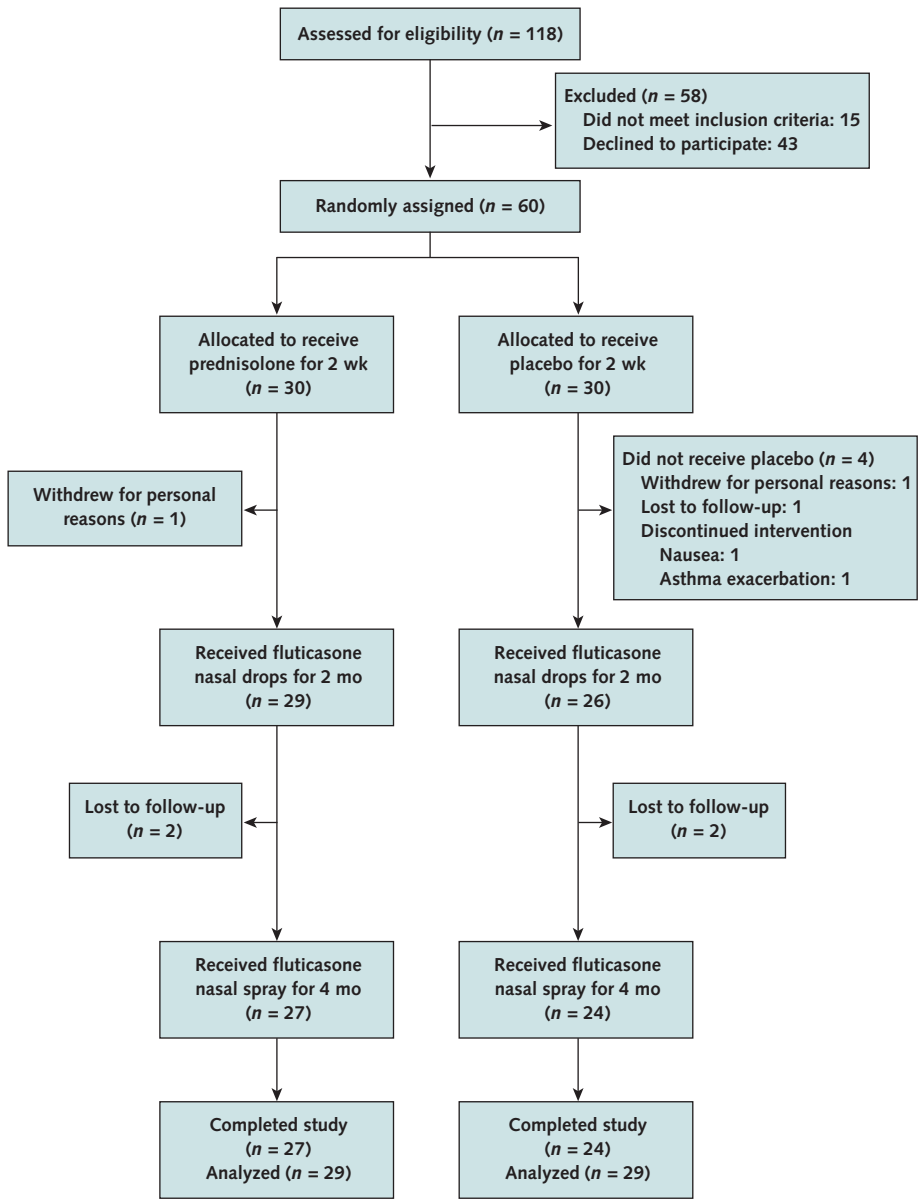
Sample Size

We estimated that with a parallel design and a sample size of 30 participants in each group, our study would be powered at greater than 90%, with a 2-tailed α value of 0.05, to detect a 0.5-unit difference in polyp grading between randomized treatments at 2 weeks (assumed SD, 0.4) (19). This would also provide greater than 90% power to detect a 6-mm improvement (minimal important difference) in the hyposmia visual analogue scale score. Minimal important differences were estimated to be 1 unit for polyp grading and 6 mm on the hyposmia visual analogue scale, on the basis of consensus and the Cohen small effect size, respectively (20).

Statistical Analysis

We included all patients who received the allocated intervention in the analysis. To estimate overall treatment effects between groups, repeated-measures outcomes were analyzed by using random-effects models. These allow for the correlation of measurements over time and allow some measurements to be missing, assuming they are missing at random. The effect of time was modeled with polynomials, and the best fit was obtained by using the Akaike Information Criterion. This criterion was also used to assess random intercepts and random slopes in all models. All models were adjusted for age and sex. Safety outcomes were also adjusted for baseline. The outcomes were assessed for deviations from normal distributions, and suitable transformations were applied. Model-based predicted means were calculated by fitting treatment-by-time interactions, and all random-effects models were implemented by using the

Figure 1. **Study flow diagram.**



PROC MIXED command in SAS, version 9.1 (SAS Institute, Cary, North Carolina). In the random-effects models, time (in weeks) was found to fit a cubic best (smallest Akaike Information Criterion), along with random intercepts and random coefficients. Most outcomes, including the primary outcome of polyp grading, had a reasonably normal distribution. Natural log transformations were applied to the results of overnight urinary cortisol corrected for creatinine, total nasal symptom score, and assays for serum high-sensitivity C-reactive protein and serum procollagen-1 *N*-terminal peptide. The square-root transformation worked best for the mini-RQLQ, and the reciprocal worked best for serum procollagen-3 *N*-terminal peptide assay results. The number of missing measurements varied by outcome, with 7% missing for the main outcome; this is small and unlikely to introduce major biases.

Participants in either treatment group who had an improvement of more than 1 minimal important difference in either polyp grading or hyposmia visual analogue scale at the end of 6 months were classified as responders. Minimal important differences are described elsewhere (17, 18) for the mini-RQLQ (0.7 unit), peak nasal inspiratory flow (6 L/min), and total nasal symptom score (0.55 units) but were not used to estimate response. Responders and non-

responders were compared by using unpaired *t* tests for all interval variables and Pearson chi-square tests for categorical data for oral steroid induction, age, duration of rhinitis, previous sinus surgery, historical and challenge-based aspirin intolerance, serum IgE level, systemic and tissue eosinophilia, presence of asthma, spirometry, body plethysmography, bronchial methacholine challenge, nasal and tidal nitric oxide level, and paranasal sinus computed tomography scan scores.

Role of the Funding Source

This study was funded by the Chief Scientist Office, Scotland; National Health Service Tayside Small Grants Scheme; and an Anonymous Trust grant from the University of Dundee. The funding sources were not involved in the study design, data collection, interpretation, or writing of the report.

RESULTS

We conducted our study from January 2005 to February 2008. Of the 118 patients screened, 60 were randomly assigned and 51 completed the study (**Figure 1**). Three patients in the prednisolone group and 4 in the placebo group had previously received oral steroids; in these patients, steroid therapy was last given a mean of 14 months (range, 6 to 24 months) and 12 months (range, 8 to 18 months), respectively, before recruitment. Similarly, 9 patients in the prednisolone group and 10 in the placebo group had previously received oral antibiotics; this therapy was last given 17 months (range, 2 to 30 months) and 14 months (range, 3 to 25 months), respectively, before recruitment. Baseline characteristics, including demographic characteristics; disease duration; upper and lower airway inflammation; airway caliber; and indexes of severity, such as aspirin sensitivity, atopy, and asthma, were similar in both treatment groups (**Table 1**).

Efficacy Outcomes

Table 2 and **Figure 2** present values at each time point, and changes in primary and secondary efficacy outcomes. In the prednisolone group, 3% of the data for polyp grad-

Table 1. **Participant Characteristics at Baseline**

Variable	Prednisolone Group (*n* = 30)	Placebo Group (*n* = 30)
Mean age (range), *y*	49 (24–70)	52 (17–78)
Men, *n (%)*	14 (47)	20 (67)
Mean duration of rhinosinusitis (SD), *y*	11 (11)	17 (15)
Previous surgery, *n (%)*	7 (23)	9 (30)
Previous oral steroid therapy, *n (%)*	3 (10)	4 (13)
Previous oral antibiotic therapy, *n (%)*	9 (30)	10 (33)
History of aspirin intolerance, *n (%)*	7 (23)	6 (20)
Positive nasal lysine–aspirin challenge, *n (%)*	16 (53)	15 (50)
Atopy, *n (%)**	13 (43)	16 (53)
House dust mites	12 (40)	12 (50)
Grass pollen	5 (17)	6 (20)
Cat	9 (30)	8 (26)
Dog	9 (30)	7 (23)
Aspergillus	2 (6)	3 (10)
Serum IgE level, *kU/L*†	93.32 (58.88–147.91)	101.71 (56.23–177.83)
Blood eosinophil count, × 10^9 *cells/L*†	0.34 (0.27–0.42)	0.35 (0.28–0.43)
Tissue eosinophil count, *cells/4HPF*†	70.79 (35.48–141.25)	41.16 (20.63–82.13)
Aspergillus IgG level, *mg/L*†‡	9.60 (4.70–19.60)	12.81 (9.71–16.88)
Asthma, *n (%)*	11 (37)	16 (53)
Median inhaled corticosteroid dose (IQR), *μg*§	400 (400–800)	700 (400–1250)
Spirometry findings		
Mean FEV_1 (SD), *% predicted*	95.6 (15.8)	93.2 (17.2)
Mean $FEF_{25–75}$ (SD), *% predicted*	78.7 (26.3)	75.6 (29.6)
Mean FEV_1–FVC ratio (SD), *%*	74 (9)	83 (9)
Mean specific airways resistance (SD), *% predicted*	97.4 (52.7)	103.3 (67.2)
Airway hyperresponsiveness, *n (%)*‖	9 (30)	11 (37)
Methacholine PC_{20}, *mg/L*†	1.20 (0.56–2.58)	1.60 (0.96–1.75)
Exhaled nitric oxide, *ppb*†	28.32 (20.14–39.45)	32.35 (23.66–44.26)
Nasal nitric oxide, *ppb*†	426.58 (338.84–524.81)	392.28 (295.12–501.19)
Mean CT score (SD)	25.1 (10.8)	22.5 (10.6)
Serum IgE to *Staphylococcus aureus* enterotoxin A, *kUA/L*†	0.04 (0.02–0.07)	0.06 (0.03–0.10)
Serum IgE to *S. aureus* enterotoxin B, *kUA/L*†	0.05 (0.02–0.14)	0.05 (0.03–0.10)
Serum IgE to *S. aureus* enterotoxin toxic shock syndrome toxin 1, *kUA/L*†	0.26 (0.14–0.46)	0.24 (0.13–0.43)

4HPF = 4 high-power fields; CT = computed tomography; $FEF_{25–75}$ = forced expiratory flow, 25%–75%; IQR = interquartile range; PC_{20} = provocative concentration causing a 20% decrease in postdiluent baseline FEV_1; ppb = parts per billion.
* Positive result on serum radioallergosorbent test for total IgE (>100 kU/L) or a positive specific IgE result (>0.35 kU/L).
† Geometric mean (95% CI).
‡ Normal range, 0–40 mg/L.
§ Expressed as chlorofluorocarbon beclomethasone dipropionate equivalent units.
‖ Defined as a positive methacholine bronchial challenge.

Table 2. **Overall Treatment Effect From Mixed Models and Comparisons at Each Time Point for Efficacy Outcomes**

Variable	Prednisolone Group		Placebo Group		Predicted Mean Difference (95% CI)	*P* Value*
	Participants, *n*	Mean Value (95% CI)	Participants, *n*	Mean Value (95% CI)		
Polyp grade (scale of 0–6)					−1.1 (−1.5 to −0.6)	<0.001
Baseline	30	4.7 (1.0)	30	4.8 (0.90)	−0.0 (−0.6 to 0.6)	0.94
After tablets	29	2.6 (2.1 to 3.1)†	29	4.7 (4.4 to 5.0)	−1.8 (−2.4 to −1.2)	<0.001
After nasal drops	27	2.2 (1.6 to 2.8)‡	26	3.2 (2.8 to 3.5)§	−1.1 (−1.7 to −0.4)	0.001
After nasal spray	26	2.8 (2.2 to 3.4)§	24	3.3 (2.8 to 3.7)§	−0.8 (−1.8 to 0.2)	0.11
Hyposmia VAS (0–100 mm)					−15.40 (−25.85 to −4.95)	0.004
Baseline	30	58.64 (31.12)	30	53.14 (32.34)	1.98 (−12.09 to 16.05)	0.78
After tablets	29	27.52 (18.37 to 38.53)†	29	54.55 (41.29 to 69.64)	−28.33 (−42.71 to −13.96)	0.002
After nasal drops	27	27.24 (17.41 to 39.25)‡	26	38.12 (26.31 to 52.10)§	−16.06 (−30.99 to −1.13)	0.03
After nasal spray	26	29.27 (19.84 to 40.53)‡	24	41.33 (28.96 to 55.92)	−12.13 (−30.55 to 6.29)	0.19
Pocket Smell Test score (scale of 0–3)					0.62 (0.19 to 1.04)	0.005
Baseline	30	1.65 (1.48)	30	1.54 (1.42)	0.26 (−0.32 to 0.84)	0.38
After tablets	29	2.50 (2.13 to 2.86)‡	29	1.58 (1.03 to 2.13)	0.87 (0.30 to 1.45)	0.003
After nasal drops	27	2.50 (2.13 to 2.86)‡	26	2.04 (1.53 to 2.55)§	0.33 (−0.30 to 0.97)	0.30
After nasal spray	27	2.31 (1.84 to 2.78)§	24	1.67 (1.12 to 2.21)	0.68 (−0.23 to 1.58)	0.140
Total nasal symptom score					0.41 (0.21 to 0.74)‖	0.009
Baseline	30	3.39 (2.7)	30	3.26 (2.6)	1.32 (0.62 to 2.71)‖	0.31
After tablets	29	1.03 (0.40 to 1.67)†	28	3.22 (1.86 to 4.57)	0.15 (0.02 to 0.40)‖	0.001
After nasal drops	27	1.14 (0.69 to 1.59)†	26	1.30 (0.69 to 1.91)‡	1.86 (0.85 to 3.98)‖	0.07
After nasal spray	27	1.00 (0.58 to 1.41)†	24	1.54 (0.95 to 2.14)§	0.80 (0.26 to 2.15)‖	0.81
Mini-RQLQ score					−0.14 (−0.28 to −0.04)	<0.001
Baseline	30	1.62 (1.05)	30	2.17 (1.68)	−0.03 (−0.15 to 0.00)	0.11
After tablets	29	0.75 (0.33 to 1.16)†	29	1.73 (1.21 to 2.24)	−0.25 (−0.52 to −0.08)	<0.001
After nasal drops	27	0.75 (0.46 to 1.03)†	26	0.69 (0.45 to 0.94)†	0.00 (−0.05 to 0.05)	0.100
After nasal spray	26	0.66 (0.45 to 0.87)†	24	1.08 (0.72 to 1.44)‡	−0.05 (−0.24 to 0.00)	0.110
PNIF rate, *L/min*					29.39 (11.33 to 47.46)	0.002
Baseline	30	107.08 (38.01)	30	122.35 (68.1)	4.72 (−20.32 to 29.77)	0.71
After tablets	29	146.67 (129.43 to 163.90)†	29	132.94 (100.08 to 165.80)	46.89 (22.49 to 71.28)	<0.001
After nasal drops	27	148.33 (131.77 to 164.93)†	26	160.29 (125.91 to 194.67)‡	3.11 (−23.98 to 30.21)	0.82
After nasal spray	26	146.88 (129.00 to 164.75)†	24	146.47 (110.34 to 182.59)	19.48 (−21.48 to 60.43)	0.35
Serum EDN level, *ng/L*‖					8.51 (−15.19 to −1.84)	0.010
Baseline	30	32.22 (25.28 to 38.31)	30	31.21 (23.26 to 40.50)	−1.99 (−11.08 to 7.11)	0.67
After tablets	28	25.28 (19.43 to 32.89)‡	29	32.90 (25.63 to 42.52)	−13.06 (−22.15 to −3.97)	0.005
After nasal drops	27	30.48 (24.25 to 38.05)	26	29.86 (24.08 to 37.27)	0.85 (−9.48 to 11.19)	0.87
After nasal spray	26	31.12 (18.37 to 37.01)	24	38.32 (30.48 to 48.50)	−5.54 (−20.85 to 9.76)	0.47
Serum hs-CRP level, *mg/L*‖					0.47 (0.34 to 0.66)	<0.001
Baseline	30	0.77 (0.53 to 1.11)	30	1.13 (0.75 to 1.70)	0.60 (0.38 to 0.93)	0.02
After tablets	28	0.59 (0.46 to 0.78)	29	1.00 (0.65 to 1.51)	0.40 (0.26 to 0.63)	<0.001
After nasal drops	27	0.96 (0.66 to 1.40)	26	1.20 (0.82 to 1.76)	0.75 (0.46 to 1.22)	0.24
After nasal spray	26	0.96 (0.68 to 1.36)	24	1.12 (0.77 to 1.64)	0.80 (0.42 to 1.52)	0.49

EDN = eosinophil-derived neurotoxin; hs-CRP = high-sensitivity C-reactive protein; RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire; PNIF = peak nasal inspiratory flow; VAS = visual analogue scale.

* By *t* test for treatment comparison in random-intercept mixed models adjusted for age, sex, and time as a cubic function. The first *P* value for each variable is for the overall treatment effect over 28 weeks.

† $P < 0.001$ for within-participant comparison with baseline value.

‡ $P < 0.01$ for within-participant comparison with baseline value.

§ $P < 0.05$ for within-participant comparison with baseline value.

‖ Geometric mean (95% CI).

ing were missing at 2 weeks, 7% at 10 weeks, and 4% at 28 weeks, whereas in the placebo group, 7% of the data were missing at 2 weeks, 7% at 10 weeks, and 4% at 28 weeks. The mean decrease in polyp grade from baseline to 2 weeks was 2.1 units (SD, 1.1) for the prednisolone group and 0.1 unit (SD, 1.0) for the placebo group (mean difference between groups, −1.8 units [95% CI, −2.4 to −1.2 units]; $P < 0.001$). The difference between groups was −1.08 units (CI, −1.74 to −0.42 unit; $P = 0.001$) at 10 weeks and −0.8 unit (CI, −1.8 to 0.2 unit; $P = 0.11$) at 28

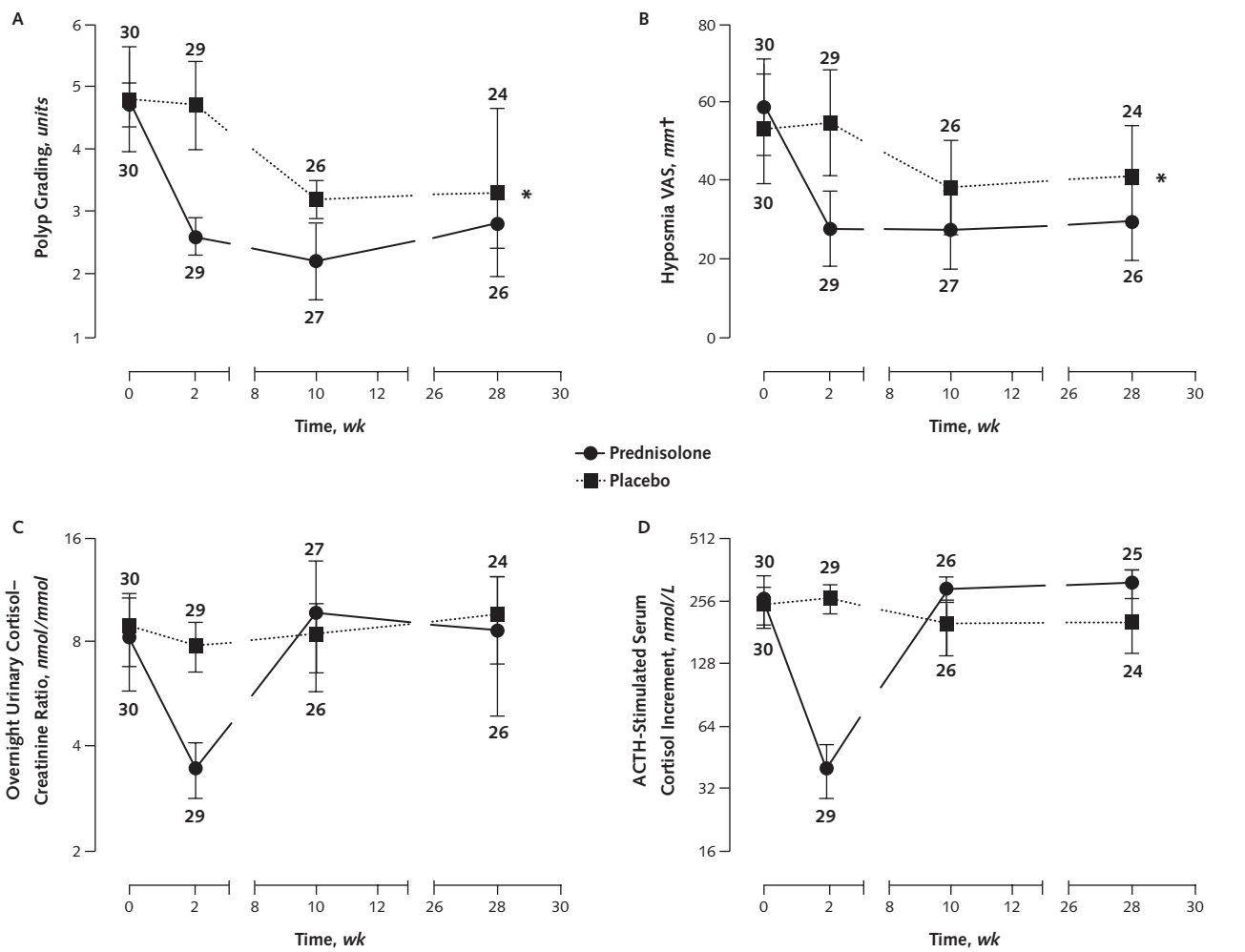
weeks. The mean decrease in hyposmia score from baseline to 2 weeks was 31.12 mm (SD, 30.1) in the prednisolone group and 1.41 mm (SD, 30.6) in the placebo group (mean difference between groups, −28.33 mm [CI, −42.71 to −13.96 mm]; $P = 0.002$). The difference between groups was −16.06 mm (CI, −30.99 to −1.13 mm; $P = 0.03$) at 10 weeks and −12.13 mm (CI, −30.55 to 6.29 mm; $P = 0.19$) at 28 weeks.

Baseline characteristics did not differ between responders and nonresponders (**Appendix Table 3**, available at www.annals.org). Twenty-five participants (83%) in the prednisolone group improved by more than the minimal important difference in either polyp grade or hyposmia visual analogue scale at the end of 28 weeks compared with 17 participants (57%) in the placebo group. Oral prednisolone therapy did not change levels of *S. aureus* enterotoxin–specific IgE ($P > 0.05$).

Safety Outcomes

After random assignment, 1 participant withdrew because of nausea and 1 had an asthma exacerbation (listed as "other medical reasons" in **Figure 1**). Thirty-seven participants (19 in the prednisolone group and 18 in the placebo group) reported an adverse event. Adverse events did not differ between groups (**Appendix Table 1**). No adverse events defined as serious by our protocol were reported. Basal and dynamic adrenal function were suppressed by oral prednisolone but recovered after the switch to nasal drops (**Table 3** and **Figure 2**). Overnight urinary cortisol corrected for creatinine was suppressed to 50% and adrenocorticotropic hormone–stimulated serum cortisol to 86% of baseline values after 2 weeks of oral prednisolone therapy. At 10 and 28 weeks, however, no significant residual adrenal suppression (compared with baseline) was observed. Markers of osteoblast activity showed a similar transient decrement during oral ste-

Figure 2. **Mean values for efficacy and safety outcomes after each stage of treatment.**



Panels A and B show mean values (±SE) for efficacy variables. Panels C and D show mean values (±SE) for safety variables (basal and dynamic adrenocortical function). ACTH = adrenocorticotropic hormone; VAS = visual analogue scale.
* Overall significant mean difference between groups.
† Scale of 0 to 100 mm.

Table 3. **Overall Treatment Effect From Mixed Models and Comparisons at Each Time Point for Safety Outcomes**

Variable	Prednisolone Group		Placebo Group		Predicted Mean Difference (95% CI)	*P* Value*
	Participants, *n*	Mean Value (95% CI)†	Participants, *n*	Mean Value (95% CI)†		
Overnight urinary cortisol–creatinine ratio, *nmol/mmol*†						
Baseline	30	8.07 (6.27 to 10.40)	30	8.70 (7.04 to 10.73)	0.93 (0.71 to 1.21)	0.58
After tablets	29	3.14 (2.47 to 3.97)‡	29	7.62 (6.39 to 9.09)	0.51 (0.35 to 0.75)	<0.001
After nasal drops	27	7.74 (5.79 to 10.37)	26	7.48 (5.98 to 9.35)	1.19 (0.80 to 1.74)	0.38
After nasal spray	26	8.51 (6.36 to 11.35)	24	8.14 (6.38 to 10.42)	1.16 (0.71 to 1.90)	0.55
Pre-ACTH serum cortisol level at 8 a.m., *nmol/L*						
Baseline	30	435.03 (168.1)	30	391.25 (166.10)	22.88 (–41.32, −87.08)	0.48
After tablets	29	184.76 (152.61 to 216.91)‡	29	327.81 (284.53 to 371.08)	−171.70 (–262.10 to −81.30)	<0.001
After nasal drops	27	387.01 (329.13 to 444.89)	26	345.46 (303.60 to 387.31)	10.34 (–82.50 to 103.20)	0.83
After nasal spray	26	370.96 (313.86 to 428.06)	25	353.57 (308.38 to 398.75)	−9.09 (–112.81 to 94.63)	0.86
Post-ACTH serum cortisol level, *nmol/L*						
Baseline	30	736.56 (245.02)	30	661.77 (238.10)	47.94 (–18.64 to –114.53)	0.160
After tablets	29	225.83 (191.96 to 259.70)‡	29	616.23 (584.65 to 647.81)	−442.80 (–536.60 to –349.10)	<0.001
After nasal drops	26	670.01 (606.53 to 733.49)	26	590.47 (544.34 to 636.60)	52.41 (–43.61 to 148.4)	0.28
After nasal spray	25	684.98 (627.87 to 742.10)	24	611.00 (570.71 to 651.30)	39.40 (–66.10 to 144.89)	0.46
ACTH-stimulated serum cortisol increment, *nmol/L*						
Baseline	30	289.51 (215.40)	30	246.26 (195.40)	24.53 (–179.91 to –89.62)	0.43
After tablets	29	39.22 (26.39 to 52.04)‡	29	273.34 (231.57 to 315.11)	−271.10 (–357.70 to –184.60)	<0.001
After nasal drops	26	294.88 (249.82 to 339.94)	26	207.32 (146.28 to 268.36)	52.14 (–36.52 to 140.8)	0.25
After nasal spray	25	309.30 (258.63 to 359.96)	24	219.06 (157.80 to 280.32)	67.33 (–32.57 to 167.23)	0.180
Serum osteocalcin level, *nmol/L*						
Baseline	30	1.06 (0.38)	30	1.23 (0.45)	−0.16 (–0.35 to –0.03)	0.100
After tablets	29	0.72 (0.55 to 0.88)‡	29	1.15 (0.97 to 1.32)	−0.22 (–0.49 to 0.04)	0.090
After nasal drops	27	1.03 (0.89 to 1.18)	26	1.33 (1.14 to 1.52)	−0.10 (–0.38 to 0.18)	0.49
After nasal spray	26	1.08 (0.91 to 1.24)	24	1.39 (1.11 to 1.68)	−0.12 (–0.52 to 0.27)	0.54
Serum P1NP level, *μg/L*						
Baseline	30	31.13 (9.63)	30	36.78 (9.75)	0.83 (0.71 to –0.98)†	0.020
After tablets	29	23.40 (20.70 to 26.09)§	29	38.31 (33.13 to 43.48)	0.76 (0.61 to 0.95)†	0.020
After nasal drops	27	28.40 (24.96 to 31.85)	26	39.45 (33.23 to 45.67)	0.87 (0.69 to 1.10)†	0.24
After nasal spray	26	30.81 (27.02 to 34.59)	24	41.39 (31.92 to 50.85)	0.93 (0.68 to 1.26)†	0.62
Serum P3NP level, *μg/L*						
Baseline	30	2.38 (0.51)	30	2.67 (0.60)	0.06 (0.00 to –0.11)	0.040
After tablets	29	2.18 (1.96 to 2.40)‡	29	2.78 (2.38 to 3.18)	0.12 (0.04 to 0.19)	0.002
After nasal drops	27	2.42 (2.23 to 2.61)	26	2.89 (2.31 to 3.47)	0.02 (–0.06 to 0.10)	0.57
After nasal spray	26	2.50 (2.27 to 2.74)	24	3.03 (2.47 to 3.59)	0.02 (–0.08 to 0.11)	0.73

ACTH = adrenocorticotropic hormone; P1NP = procollagen-1 *N*-terminal peptide; P3NP = procollagen-3 *N*-terminal peptide.
* By *t* test for treatment comparison in random-intercept mixed models adjusted for age, sex, and time as a cubic function, analyzed as change from baseline values.
† Geometric mean (95% CI). Mean differences (95% CIs and *P* values) represent geometric mean fold change.
‡ $P < 0.05$ for within-participant comparison with baseline value.
§ $P < 0.01$ for within-participant comparison with baseline value.

roid therapy, with a return to baseline with subsequent topical treatment (**Table 3**).

DISCUSSION

Our single-center study shows that in patients with CRS with nasal polyposis (polyp grade >1), an initial 2 weeks of oral prednisolone therapy significantly improves polyp size and hyposmia score compared with placebo. Benefits remained evident at 28 weeks without an increase in adverse steroid effects. Clinical markers of severity, such as aspirin intolerance, atopy, duration of illness, and concomitant asthma, did not differ between responders and nonresponders.

To our knowledge, no previous randomized, controlled trial has evaluated the long-term effects of oral steroid therapy for CRS with nasal polyposis. Previous studies

have either lacked placebo control or were short-term only. In a trial by Benítez and colleagues (21), 63 participants who received oral prednisolone therapy for 2 weeks, tapered from an initial dose of 30 mg/d, followed by intranasal budesonide, 400 μg, for 12 weeks showed overall symptom improvement, whereas the 21 participants in the control group received no treatment over a 2-week period and were not followed afterwards. In a 2-week randomized, controlled trial, Hissaria and colleagues (22) evaluated the efficacy of oral prednisolone, 50 mg, versus placebo for CRS with nasal polyposis. Neither trial specifically examined the role of oral steroid therapy in improving the efficacy of subsequent long-term topical steroids or comprehensively evaluated efficacy or safety.

We chose an oral prednisolone dosage of 25 mg/d because it provides a good systemic anti-inflammatory effect and is available as a single, once-daily tablet. This regimen is frequently used in our clinical practice to aid adherence and reduce the potential side effects of higher doses, such as sleep disturbance. Of note, no adverse events attributable to oral steroids were reported in our study. We hypothesized that improvement in outcomes of CRS with nasal polyposis disease would require adequate clearance of the ostiomeatal complex, and therefore the initial steroid therapy was followed by 8 weeks of intranasal drop therapy. Nasal drops provide better deposition to the ostiomeatal complex and have lower systemic bioavailability than nasal sprays (23, 24); however, they are relatively expensive and not universally available. For this reason, patients were maintained on therapy with intranasal spray for the remainder of the study.

Our study demonstrates a parallel and sustained improvement in both polyp size and the hyposmia visual analogue scale score, as seen in the short-term study by Hissaria and colleagues (22). Improved olfaction was also supported by the results of the Pocket Smell Test in the prednisolone group, although this did not reach statistical significance between groups. Nasal obstruction and hyposmia are the 2 primary symptoms of CRS with nasal polyposis, and they substantially affect quality of life (5, 25). Chronic rhinosinusitis with nasal polyposis causes olfactory impairment from mechanical obstruction and sensorineural defects secondary to mucosal inflammation (26). Although evidence indicates that oral steroids have a direct stimulatory effect on olfactory neurons, the sustained improvement in olfaction that we observed suggests that a reduction in local mucosal inflammation and edema is a more likely mechanism. We also found reductions in systemic markers of eosinophil activation (eosinophil-derived neurotoxin) and inflammation (high-sensitivity C-reactive protein) with systemic but not topical corticosteroid therapy, which further supports our hypothesis that the reduction in polyp size and improved sense of smell was due to local anti-inflammatory effects rather than systemic steroid spillover.

Although we demonstrated additional long-term efficacy with initial oral steroid therapy, this must be weighed against potential adverse steroid effects. In keeping with other series, more than 50% of our cohort had concomitant asthma treated with inhaled corticosteroids (5). To our knowledge, no long-term studies have evaluated the hypothalamic–pituitary–adrenal axis or bone turnover in patients who have CRS with nasal polyposis. However, it is reassuring that we found no residual adrenal suppression or reduction in osteoblast activity with our treatment regimen at 10 or 28 weeks.

Our study has limitations. We did not perform serial measurements of nasal inflammation by using surrogates, such as nitric oxide, eosinophils in repeated biopsy specimens, or cytokines obtained from nasal lavage. Although many studies describe these measures, their clinical relevance remains unclear (5, 27, 28). Instead, a clinically meaningful set of subjective, objective, and quality-of-life efficacy outcomes were used. Ostiomeatal complex assessment with serial computed tomography would have been desirable. However, this does not reflect routine clinical practice in the United Kingdom; most patients who have CRS with nasal polyposis are treated in primary care, where such investigations are not readily accessible. Serial scanning would also expose patients to excessive radiation doses and provide little more clinical information than polyp grading. The Juniper mini-RQLQ was used as a quality-of-life assessment tool, in conjunction with a hyposmia visual analogue scale. The mini-RQLQ is a validated, reliable instrument that is shorter and easier to administer than more extensive, disease-specific measures, such as the 31-item Rhinosinusitis Outcome Measure (22). The mini-RQLQ was also considered to be a comprehensive means of evaluating quality of life, because 50% of our patients were atopic. Although our study size was sufficient to demonstrate many benefits of steroid therapy in the setting of a single referral center, larger, multicenter trials with longer follow-up are warranted.

Future studies should consider whether an induction and maintenance approach should be considered at the point of first diagnosis of CRS with nasal polyposis (for example, in primary care) and whether it is beneficial in milder disease, in which ostiomeatal complex obstruction is less severe. Short-term nasal decongestants may further improve access of intranasal corticosteroids and could be assessed alone or in conjunction with prednisolone induction. Finally, larger long-term studies are required to assess whether steroid induction can delay or reduce the need for surgical intervention and influence postsurgical recurrence rates.

In conclusion, we found that an initial 2-week course of oral steroid therapy followed by topical steroids seems more effective over 28 weeks than topical therapy alone in decreasing polyp size and improving olfaction for the treatment of CRS with nasal polyposis above grade 1, without sustained adverse effects. Although further research is required to assess the efficacy

and safety of this approach in other settings, we believe these results are an important step in developing robust treatment approaches for this common but relatively understudied condition.

From Ninewells Hospital and University of Dundee, Dundee, United Kingdom.

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Requests for Single Reprints: Brian Lipworth, MD, Asthma & Allergy Research Group, Centre for Cardiovascular and Lung Biology, Division of Medical Sciences, Ninewells Hospital and University of Dundee, Dundee DD1 9SY, United Kingdom.

Current author addresses and author contributions are available at www.annals.org.

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Current Author Addresses: Drs. Vaidyanathan, Barnes, Williamson, and Lipworth and Ms. Hopkinson: Asthma & Allergy Research Group, Centre for Cardiovascular and Lung Biology, Division of Medical Sciences, Ninewells Hospital and University of Dundee, Dundee DD1 9SY, United Kingdom.

Dr. Donnan: Dundee Epidemiology and Biostatistics Unit, Division of Clinical and Population Sciences, and Education, Ninewells Hospital and University of Dundee, Dundee DD2 4BF, United Kingdom.

Author Contributions: Conception and design: S. Vaidyanathan, M. Barnes, P. Donnan, B. Lipworth.

Analysis and interpretation of the data: S. Vaidyanathan, M. Barnes, P. Williamson, P. Donnan, B. Lipworth.

Drafting of the article: S. Vaidyanathan, M. Barnes, P. Williamson, P. Donnan, B. Lipworth.

Critical revision of the article for important intellectual content: S. Vaidyanathan, M. Barnes, P. Williamson, P. Donnan, B. Lipworth.

Final approval of the article: S. Vaidyanathan, M. Barnes, P. Williamson, P. Donnan, B. Lipworth.

Provision of study materials or patients: M. Barnes, B. Lipworth.

Statistical expertise: S. Vaidyanathan, M. Barnes, P. Donnan, B. Lipworth.

Obtaining of funding: S. Vaidyanathan, M. Barnes, B. Lipworth.

Administrative, technical, or logistic support: S. Vaidyanathan, M. Barnes, P. Williamson, P. Hopkinson, B. Lipworth.

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Appendix Table 1. **Adverse Events***

Adverse Event	Prednisolone Group, *n*	Placebo Group, *n*
Epistaxis triggered by nasal spray	2	1
Viral rhinitis	6	6
Facial pain	1	1
Tonsillitis	0	1
Headache	2	1
Influenza-like symptoms	2	5
Rash	1	1
Conjunctivitis	1	0
Musculoskeletal pain	4	4
Nausea	0	1
Asthma exacerbation	0	1

* 37 participants (19 in the prednisolone group and 18 in the placebo group) reported an adverse event. No serious adverse events were reported; these were defined as an event causing the death of the participant, a life-threatening event, hospitalization, persistent or significant disability affecting important life functions, a congenital anomaly or birth defect in the offspring of a woman treated before or during pregnancy, pregnancy, and important medical events requiring urgent and intensive intervention to prevent 1 of the serious adverse events listed above.

Appendix Table 2. **Coefficients of Variation for Assays**

Substance (Unit of Measure)	Coefficients of Variation, %	
	Intra-assay	Interassay
Serum EDN (ng/L)	9.1	20
Serum hs-CRP (mg/L)	8.5	16
Serum cortisol (nmol/L)	9	6.2
Serum creatinine (mmol/L)	2.9	4.8
Serum osteocalcin (nmol/L)	NA	10
Serum P1NP (μg/L)	5.8	6.4
Serum P3NP (μg/L)	3	4.6

EDN = eosinophil-derived neurotoxin; hs-CRP = high-sensitivity C-reactive protein; NA = not available; P1NP = procollagen-1 *N*-terminal peptide; P3NP = procollagen-3 *N*-terminal peptide.

Appendix Table 3. **Baseline Characteristics of Responders and Nonresponders at 6 Months***

Variable	Responders (n = 42)	Nonresponders (n = 18)	P Value†
Steroid induction group, *n (%)*	25 (60)	5 (17)	0.030
Mean age (SD), *y*	51 (13)	49 (13)	0.55
Previous surgery, *n (%)*	9 (22)	7 (39)	0.160
Mean duration of rhinosinusitis (SD), *y*	14 (13)	17 (14)	0.53
History of aspirin intolerance, *n (%)*	10 (24)	3 (17)	0.54
Positive nasal lysine–aspirin challenge, *n (%)*	20 (48)	11 (61)	0.34
Atopic, *n (%)*	13 (43)	16 (53)	0.44
Mean serum IgE level, *kU/L*‡	109.17 (87.36–136.5)	70.79 (54.45–92.02)	0.31
Blood eosinophil count, $\times 10^9$ *cells/L*‡	0.33 (0.30–0.36)	0.40 (0.37–0.43)	0.25
Tissue eosinophil count, *cells/4HPF*‡	64 (41–102)	28 (7–117)	0.31
Aspergillus IgG level, *mg/L*‡§	11.35 (9.08–14.18)	9.88 (6.29–15.51)	0.78
Asthma, *n (%)*	19 (45)	8 (44)	0.95
Spirometry			
Mean FEV_1 (SD), *% predicted*	92.9 (16.9)	98.8 (14.7)	0.190
Mean $FEF_{25–75}$ (SD), *% predicted*	73.7 (27.3)	85.3 (27.3)	0.140
Mean FEV_1–FVC (SD), *%*	74 (6.5)	76 (8.4)	0.61
Mean specific airways resistance (SD), *% predicted*	106.1 (63.0)	88.6 (60.9)	
Airway hyperresponsiveness, *n (%)*‖	15 (36)	5 (29)	0.64
Mean methacholine PC_{20} (SD), *mg/L*‡	1.28 (1.04–1.57)	1.82 (1.07–3.09)	0.55
Mean CT score (SD)	23 (2)	22 (3.5)	0.72

4HPF = 4 high-power fields; CT = computed tomography; $FEF_{25–75}$ = forced expiratory flow, 25%–75%; IQR = interquartile range; PC_{20} = provocative concentration causing a 20% decrease in postdiluent baseline FEV_1.

* Responders were participants in both groups and were defined as having more than 1 minimal important difference improvement in their polyp score (1 unit) or anosmia visual analogue score (6 mm).

† *P* values for comparisons between responders and nonresponders by using unpaired *t* tests for all interval variables and Pearson chi-square tests for categorical data.

‡ Geometric mean (95% CI).

§ Normal range, 0–40 mg/L.

‖ Defined as a positive methacholine bronchial challenge.