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TITLE PAGE

a) Title

Methotrexate for recurrent chronic rhinosinusitis with nasal polyps: A randomized controlled phase II clinical trial

b) Running title

MTX as maintenance therapy for CRSwNP

c) Authors

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d) Funding

This investigator-initiated project was funded by The Scientific and Technological Research Council of Turkey (TÜBİTAK) in the framework of the 3001-Starting R&D Projects Funding Program with project number 216S871. This budget covered all medical costs and insurance for the patients.

e) Conflict of Interest

The authors have no conflicts of interest to declare.

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/23131.

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g) Acknowledgements

The authors would like to thank Professor Sule Oktay, MD, for her consultancy for designing the trial and editing of the manuscript.

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Conception: ACC, MCE, YT, PK, MAA, FO; Design: MCE, YT, ACC, PK, MAA, FO; Materials and Data Collection: ACC, MCE, YT, MAA, FO, PK; Analysis and Interpretation: ACC, PK, MCE, YT, MAA, FO; Literature Review: ACC, MCE, YT, PK, MAA, FO; Writing: ACC, YT, PK, MAA, PK, FO, MCE; Critical Review: MCE, YT, PK, ACC, MAA, FO

i) **Keywords**

Nasal polyps, chronic rhinosinusitis, methylprednisolone, mometasone furoate, methotrexate, Phase II, clinical trial

Abstract

Objective: This randomized, controlled, open-label, phase 2 clinical trial aimed to assess the efficacy and safety of low-dose methotrexate (MTX) as maintenance therapy for recurrent postoperative chronic rhinosinusitis with nasal polyps (CRSwNP).

Methods: Forty-one patients with CRSwNP who experienced postoperative polyp recurrence(s) were randomly divided into three groups to receive one of the following treatments for eight weeks: daily intranasal mometasone furoate monohydrate 200 mcg (control [INCS arm, n=13]); daily per oral methylprednisolone 8 mg (oral corticosteroid [OCS] arm, n=14); and once weekly per oral 10 mg methotrexate (MTX arm, n=14). All patients were assessed at three clinical visits according to the Lund-Kennedy endoscopic grading system (LKES), visual analogue scale (VAS), Turkish version of the Sinonasal Outcome Test-22 (SNOT-22), peak nasal inspiratory flow (PNIF), butanol olfactory threshold test (BuOT), serum total immunoglobulin E (IgE) level, presence of peripheral eosinophilia, serum biochemical assays, and adverse events.

Results: All efficacy outcome measures significantly improved in all three groups, except for the non-recovery of peripheral eosinophilia in the INCS group. There was no significant difference among the groups in terms of LKES scores. Scores for the Turkish version of the SNOT-22, PNIF, BuOT, and serum IgE levels were also similar among the groups. However, total VAS scores recovered significantly better in the INCS group than in

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the MTX group. Serum biochemical assays remained normal in all groups. Adverse events were minor and observed only in the OCS group.

Conclusion: Low-dose MTX was a safe and effective maintenance therapy for patients with recurrent postoperative CRSwNP.

Keywords: Nasal polyps, chronic rhinosinusitis, methylprednisolone, mometasone furoate, methotrexate, Phase II, clinical trial

Level of Evidence: Level 2

TEXT

Background

The basis of chronic rhinosinusitis with nasal polyps (CRSwNP) treatment with medications is the use of intranasal corticosteroids (INCS) or oral corticosteroids (OCS). One-half of severe cases that do not respond to INCSs or OCSs are referred for functional endoscopic sinus surgery (FESS)[1,2]. Although FESS appears to be quite beneficial, with a success rate of 80–90%, the recurrence rate may reach 60% at 40 months postoperatively[3]. In 2020, The European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) [1] recommended using INCSs to prevent recurrences. However, the adjuvant use of INCSs may also lead to treatment failure, with a rate of 44%[4]; therefore, the short-term use of OCSs may, again, become compulsory[2]. In resistant cases in which short-term OCSs also fail because revision surgeries may cause major complications[5], there is usually no option other than re-administration or long-term or high-dose OCS, which raises concerns for the increased risk for adverse reactions[6-8]. Although a biologic, dupilumab, has recently been suggested for severe CRSwNP, particularly with type 2 inflammation or asthma comorbidity, with a relatively safe profile[1,9,10], dupilumab use is associated with eosinophilic adverse reactions that can cause vasculitis and pneumonia[11].

Methotrexate (MTX) has been shown to reduce nasal polyps by inhibiting angiogenesis in a dose-dependent manner, increasing apoptosis, and dominating various proinflammatory cytokines in nasal polyp tissue culture[12-15]. MTX, owing to having been an already in-use agent for various clinical indications, has been evident to be relatively safe, except for fetal toxicity and some infrequent severe adverse reactions such as bone marrow suppression. Two previous case reports have documented the regression of nasal polyps in patients who were treated with MTX for asthma and malignancy and coincidentally presented with nasal polyposis[16,17]. Inhibition of dihydrofolate reductase and T lymphocyte proliferation and triggering T lymphocyte apoptosis are among the autoinflammatory mechanism of MTX[18]. Because T helper 1, 2, and 17 cells play roles in the three different types of CRSwNP [1], MTX can be a promising treatment option.

Accordingly, we designed a phase II clinical trial to test the feasibility of using low-dose oral MTX as maintenance therapy in patients who experienced surgical and medical treatment failures.

Materials and Methods

The study was designed as an investigator-initiated, randomized, controlled, three-armed, parallel, and open-label phase II clinical trial (phase II RCT). The clinical trial protocol was approved by the Ethics Committee of Dokuz Eylul University (276-SBKAEK 2106/04-21) and the Turkish Medicines and Medical Devices Agency

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of the Ministry of Health (93189304-514.02.01-63343, 215-AKD-75), and registered to the *ClinicalTrials.gov (NCT* Number: NCT04532736). All procedures were performed in accordance with the ethical standards described by the Declaration of Helsinki. The CONSORT 2010 checklist was used while reporting our clinical trial.

Eligibility

Patient volunteers, 18 to 75 years of age, followed up in the Department of Otolaryngology of Dokuz Eylul University, School of Medicine (Izmir, Turkiye) and diagnosed with CRSwNP endoscopically, radiologically, and histologically according to the EPOS 2012 guidelines, who underwent FESS followed by appropriate medical treatment[2] (AMT), were assessed for eligibility (n=123). The patients who failed AMT and subsequent FESS and demonstrated postoperative recurrence of polyps were eligible. Exclusion criteria compromised absence of polyps on nasal endoscopy, exposure to OCS or MTX six months before recruitment, the experience of adverse reactions to any of the experimental drugs, comorbidities such as malignancy, rheumatological disorders, NSAID-sensitivity, immunodeficiency, ciliary dyskinesia, any types of allergies and positivity in skin prick tests, systemic comorbidities other than bronchial asthma, abnormalities in baseline safety parameters, pregnancy, a plan for pregnancy, and lactation. Forty-one eligible patients who provided written informed consent were enrolled in the study and randomly assigned (Figure 1). Asthma treatment was not modified during the study and consisted of inhaler therapy only and not leukotriene antagonists. Patients were recruited between September 2, 2017, and March 12, 2019, and followed up by May 5, 2019.

The medical therapy regimen in CRSwNP is a step-up therapy, according to the authors' routine clinical practice. The first step is using daily INCS, either mometasone furoate(200 mcg twice daily) or fluticasone furoate(110 mcg twice daily) for at least three months[19]. Non-responder volunteers are referred for bilateral FESS, as previously described[5,20], and independently from approving surgery or not, prescribed preoperative OCS (methylprednisolone, starting with a dose of 1mg/kg and 8 mg reduced every alternate day) [20]. Bilateral FESS refers to bilateral complete sinus opening consisting of uncinectomy, anterior and posterior ethmoidectomy, middle meatal antrostomy, sphenoidotomy, and frontal opening[2]. No advanced procedures, including Draf IIB or III, were performed.

Interventions

Eligible patients were randomly assigned into three groups to receive one of the following interventions for eight weeks: twice daily intranasal mometasone furoate monohydrate (200 mcg, Nasonex® aqueous nasal spray 0.05% 18g/140 dose, Merck Sharp Dohme [MSD] International GmBH, Singapur, License Number:13.09.1999-106/61) (group 1, control group, INCS arm [n = 13]); daily per oral 8 mg methylprednisolone (Prednol®, 4 mg 20 tablets, Mustafa Nevzat İlaç Sanayi A.Ş., İstanbul, License Number:12.05.1970-104/68) (group 2, OCS arm [n = 14]); and once weekly per oral 10 mg methotrexate (Emthexate® 2.5 mg 100 tablets, Teva Czech Industries s.r.o. Opava-Komarov, Czechia, License Number:13.12.2004-116/90) (group 3, MTX arm [n = 14]). Medicine boxes that were obliged to turn back to the investigators to reveal the number of remaining pills were utilized to monitor the treatment compliance of the individuals.

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Mometasone furoate was given in a standard clinical dose[21,22]. The arithmetic mean of two cumulative methylprednisolone doses suggested by Alobid et al. (270 mg)[23] and Ecevit et al. (720 mg)[20] was used to calculate the daily dose as 8 mg methylprednisolone.

The weekly dose of MTX 10 mg was chosen based on two anecdotal reports[16,17] and considering its well-known safe and low-dose (7.5-30 mg/week) prescription in standard indications[24]. Gastrointestinal disturbances and a slight deterioration in liver function were the two most commonly observed adverse effects with 8.8 mg/week (4.6 mg-18 mg) of methotrexate for an average of 36.5 weeks (27-132 weeks). Nevertheless, it has been stated that long-term use of methotrexate, such as 10.7 mg/week on average, is not associated with severe toxicity[25].

Outcomes

The primary efficacy outcome of the study was the sum score of the Lund-Kennedy endoscopic grading system (LKES)[26], which measured nasal polyps, discharge, edema, scarring, and crusting obtained from the bilateral nasal cavities. The secondary efficacy outcomes included: the total visual analog scale (VAS) score[20] in which smell, nasal discharge, nasal obstruction, facial pressure, and headache were scored between 0 (no complaint) and 10 (most annoying); the Turkish version of the Sinonasal Outcome Test-22 (SNOT-22)[27]; sum score of the peak nasal inspiratory flow (PNIF) and butanol olfactory threshold test (BuOT)[20] obtained from bilateral nasal cavities; serum total immunoglobulin E (IgE) level[28]; and the presence of peripheral eosinophilia (PE, > 500/mcl) in blood samples[29].

Safety outcomes addressed adverse and serious adverse events and serum biochemical parameters, including complete blood count, liver, renal, thyroid function tests, and glucose levels following an 8-hour fasting interval. Efficacy and safety outcomes were evaluated at three in-person clinical visits on days 1 (baseline), 28, and 56. Adverse events and serious adverse events were monitored by a telephone call on days 14 and 42, which were intended for this purpose only, as well as the second and third in-person clinical visits, but not the baseline visit.

No exacerbations were encountered.

Sample size

The sample size calculation was based on a controlled three-armed study[30]. Accordingly, the mean and standard deviation of the nasal polyp score was 5.86 ± 0.27 for the OCS arm and 6.16 ± 0.29 for the control arm[30]. Since there was no study with a similar design for MTX, the comparison of MTX and OCS effectiveness was inspired by an experimental study[13], quite similar to ours in terms of sample and outcome measures, and calculated by predicting the mean deviation values of the nasal polyp score for MTX arm. Hence, the mean and standard deviation of the nasal polyp score was estimated to be 5.40 ± 0.24 for the MTX arm. Assuming an ideal power of 80%, a 95% confidence interval[31,] and pooled standard deviation of 0.26 to observe differences among the groups, the sample size of each group was calculated to be 9 (PASS Sample Size Software 2019, NCSS, LLC, USA). However, considering potential drop-outs, missing data, variations, harms, and ethical considerations, it was decided to assign 14 patients to the MTX and OCS arms and 13 to the INCS arm.

Randomization

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For the first 24 patients, the randomization protocol consisted of two basic principles; blocking over time by coin toss and stratification according to sex. Accordingly, these patients were assigned to groups 2 and 3. The subsequent five male and five female patients were allocated to group 1. The subsequent patients were blocked into the groups by choosing one of the three envelopes written with the name of one of the three groups inside, ignoring sex.

Implementation

Two clinical otolaryngologists (ACC and MCE) generated the random allocation sequence, enrolled participants, and assigned participants to interventions. All visits were attended by ACC and MCE, and the outcome of each participant was accepted through the joint decision of two researchers.

Statistical methods

Categorical variables were presented with numbers and percentages and compared using the $\chi 2$ test. Continuous variables were presented using mean±standard deviation, median, and minimum-maximum values, and the Shapiro-Wilk test evaluated the normality of the continuous variables. Age comparison was performed using a one-way analysis of variance (ANOVA). Parametric repeated measurements in three groups, namely the sum score of LKES, the total score of the Turkish SNOT-22, VAS, and safety outcome measures, were analyzed using repeated-measures ANOVA for 3×3 model with a within and a between-subjects factor. The Statistical Package for the Social Sciences SPSS Version 22 (SPSS, Armonk, NY, USA) was used for this purpose. To analyze non-parametric variables of three independent groups' three repeated measurements, namely the BuOT, PNIF, and IgE, the non-parametric analysis of longitudinal data in factorial experiments program (F1-LD-F1design: https://rdrr.io/cran/nparLD/man/f1.ld.f1.html) was utilized[32].

The results were assessed with a 95% confidence interval and at the $p<0.05$ significance level. The patients with missing data were not included in the analyses.

Results

Participant flow and numbers analyzed

The number of participants who received MTX, OCS, and INCS was 14, 14, and 13, respectively. None of the patients was excluded after randomization, and none discontinued the intervention; however, a patient in the control group missed the second visit. Also, serum IgE values for two patients (INCS group, second visit) could not be assessed due to technical issues(Fig. 1). All participants' blood pressure and serum biochemical assay results were within normal ranges. The groups were similar in terms of baseline data(Table 1).

Outcomes and estimation

All outcome measures significantly improved in all three groups except for the non-recovery of peripheral eosinophilia (PE) in the control (INCS) group. The groups were similar in terms of the primary efficacy outcome measure. The Turkish version of the SNOT-22, PNIF, BuOT, and serum IgE levels were also similar between the groups (Table 2 and Supplementary Material 2). However, the total VAS scores recovered significantly better in the control (INCS) group than in the MTX group (Table 2 and Supplementary Material 2).

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Safety outcome parameters remained normal in all groups (Supplementary Material 1). Adverse events were experienced on the last visit in six patients allocated in the OCS arm, and these were marked as adverse reactions according to the causality assessment evaluation (Table 3).

Discussion

In the present study, all three maintenance treatment protocols (i.e., INCS, low-dose OCS, and low-dose MTX) successfully improved total scores for LKES, VAS, SNOT-22, PNIF, BuOT, and serum IgE in a treatment period of eight weeks. Regarding the primary efficacy outcome (LKES) of the study, none of the groups was found to be superior. However, regarding two secondary efficacy outcomes, peripheral eosinophilia responded only to OCS and MTX administration, and total VAS scores improved more in the INCS group than in the MTX group. Although we targeted to avoid adverse reactions by using low doses of OCS, adverse reactions were experienced solely in the OCS group. The INCS and MTX groups were shown to be safer. Considering the similarity of baseline measurements, patient characteristics, and demographic features, the outcome measures in the present phase II RCT are valid and applicable.

According to a recent meta-analysis evaluating the effects of INCS on CRSwNP, INCSs were beneficial for recovering all nasal symptoms[33]. INCSs, independent of the molecule type and delivery method, are also most useful for nasal symptoms and reducing the size of nasal polyps, and preventing recurrences after surgery in line with the suggestions of EPOS [1,2]. Although INCSs are usually well-tolerated, it has been proposed that they increase the risk for nose bleeds and local irritation (the sense of dry nose) mainly when high doses are administered. However, the adverse effects of INCS mostly remain local because of their negligible systemic bioavailability[33]. On the other hand, EPOS 2020[1] reported studies that used long-term (1 year) and higher doses of INCS without any adverse effects; however, the absolute benefit of the long-term and high-dose INCS remains to be confirmed. Additionally, the postoperative use of INCS as maintenance therapy may also lead to treatment failure in almost one-half of cases[1].

In terms of OCS, despite the 2012 version[2] was lack of dosing recommendations, EPOS 2020[1] recommended the short-term use of OCSs alone or with INCS for their significant impact on improving total nasal symptoms and polyp scores in those with CRSwNP. Nevertheless, there is still an enormous heterogeneity to what extent the dosing and duration of systemic steroids should be employed. Many authors, however, highlight the importance of monitoring the total dose instead[34,35]. Brescia et al.[19] managed CRSwNP participants for 36 months postoperatively, either by INCS or two cycles of OCS, and did not find any significant difference between the groups regarding recurrences[19]. Because RCTs that compare INCS and OCS head-to-head are exceptional, we ascribe importance to the literature[19], the results of which are similar to ours. The other study was a three-arm RCT[7], in which OCS, inhaled budesonide, and INCS were administered. Unlike our results, the authors recorded statistically significant improvements in the OCS and inhaler budesonide groups but not in the INCS group. However, OCS has been shown to adversely affect the functions of the hypothalamic-pituitary-adrenal axis[7]. No authors have commented on whether the frequency or severity of adverse reactions increases when OCS is added to INCS[36].

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On the other hand, in a recent review evaluating adverse reactions related to OCS use in asthma, the risk for various adverse reactions, such as infections, diabetes mellitus, osteoporosis and psychiatric disorders, was found to be higher in patients exposed to long-term use of OCS compared with controls[8]. Despite their well-established anti-inflammatory genomic and non-genomic effects, CS's therapeutic mechanisms of action on CRSwNP still have unexplained aspects[37]. Moreover, using CS for CRSwNP has emerged as a potential candidate for treatment resistance via receptor-related or non-receptor-related mechanisms, which can even be concluded in an obligation of revision surgery. Increasing the dose may break CS resistance in some cases, primarily when the resistance depends on receptor abnormalities [37]; however, adverse reactions may occur meanwhile[8]. Additionally, high doses of short-term OCS do not always guarantee treatment success. It has been reported that 30–50% of all CRSwNP patients managed with high doses of short-term OCS (50 mg/day prednisolone for 14 days) unfortunately cannot be treated in terms of nasal symptoms, polyp scores, and quality of life scales[36] and this is a proportion that we consider to be highly remarkable.

MTX, currently available for treating many diseases, has been shown to reduce nasal polyps in experimental studies[12-15] and in cases treated with MTX for asthma and malignancy in whom CRSwNP was present or coincidentally detected[16,17] through its autoinflammatory and immunosuppressive effects[18]. MTX causes extracellular adenosine accumulation and inhibits tumour necrosis factor-alpha-α and NF-κB via adenosine receptors. When adenosine binds to its receptor, it inhibits the synthesis of purine and pyrimidine and, thus, T lymphocyte and matrix metalloproteinase production[18]. Th 1, 2, and 17 cells and matrix metalloproteinases are essential to the pathogenesis of CRSwNP types, and some of them are also associated with CS resistance[1]. From another perspective, MTX reduces the expression of various adhesion molecules, such as vascular cell adhesion molecule-1[18], which is also expressed by fibroblasts in nasal polyp tissue and associated with polyp recurrence[1]. In a recent tissue culture study, MTX was demonstrated to be as efficient as OCS[13]. MTX is associated with minor adverse effects, which are encountered relatively frequently (30–80%) but mostly (65–95%) do not necessitate a permanent drop-out and, instead, can be eliminated by reducing or delaying dose or folate administration[39]. Because a low-dose MTX treatment is well-tolerated and safe and appears to be as effective as CS[13], it appears to be a promising maintenance therapy for severe, resistant, and recurrent CRSwNP, as revealed in our trial.

Our results demonstrate that methotrexate is safer than oral corticosteroids as maintenance therapy for postoperative recurrent chronic rhinosinusitis with nasal polyps. In addition, because being taken once a week, methotrexate seems to provide better patient compliance compared with daily corticosteroid pills, although we did not digitalize and statistically analyze this observation. Despite providing a safe treatment option, it should not be underestimated that methotrexate has an evidence-based confirmed teratogenic risk potential[24]. In order to refrain from any teratogenic outcome, methotrexate should not be prescribed to women whose pregnancy is confirmed, suspected, or planned.

Considering application routes, we emphasize that topical drug treatment applications are advantageous to reduce the systemic adverse reactions of drugs in CRSwNP. Despite topical dermatological formulations of methotrexate being available in a few countries except ours, to the best of our knowledge, the topical intranasal

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form has not been introduced yet[25] which made us use peroral forms methodologically. Although an increase in adverse reactions was not observed in this study related to oral MTX, studies that will focus on developing topical intranasal MTX formulations are suggested to be conducted.

Limitations

The major limitation of the study was that the clinical researchers and volunteers were not blinded. The long-term follow-up results and recurrence rates among the patients are unavailable, and local inflammatory mediators were not studied due to financial constraints. Additionally, since the study's most crucial goal was to reveal the non-inferiority of methotrexate as a maintenance treatment in terms of safety and efficacy compared to already in-use maintenance treatments, it may not fulfill the answer of whether methotrexate can decrease the necessity for revision surgery or biological agents in CRSwNP. Moreover, as known, the recurrence can occur after months to years, but eight weeks might not always have been long enough to observe it. Furthermore, the BuOT scores remained very low overall across all three interventions, even after being on maintenance therapy which may be due to the short follow-up period, as well. Considering the financial funder's and review board's approval terms and conditions, we had to limit the study time.

Besides, we recognized a numerical superiority regarding the presence of asthma and peripheral eosinophilia and the shortness of the interval between the last FESS and the initiation of intervention in the MTX group. The total VAS scores were also slightly higher in the MTX group. We suppose that our randomization method may be responsible for this minor heterogeneity because we prioritized assigning participants to the OCS and MTX groups. A previous study reported that the rate of polyp recurrences was greater in patients with CRSwNP when accompanied by asthma[38]. Hence, we speculate that the more complaints patients had, the sooner they were admitted to our department, which manifested as a shorter post-surgical interval, and numerical superiority of asthma comorbidity and, perhaps, peripheral eosinophilia in the MTX group[1].

Additionally, the EPOS guidelines[1,2] imply that the higher the VAS score is, the more severe the disease becomes. We speculate that this assumption might have happened to our MTX group. Nevertheless, we did not detect a statistically significant difference among the groups regarding these parameters. Therefore, even if we mistakenly introduced bias during randomization, we do not believe it affected our results.

We are also compelled to comment on the adequacy of our sample size. As known, phase II clinical research aims to demonstrate the investigational drug's optimal dose, effectivity, and tolerability regarding physiological aspects in a large sample size. However, we emphasize that our study was not designed to be a standard phase II clinical research of MTX to be licensed but as an investigation of the feasibility of re-purposing MTX, which has been previously licensed for many chronic diseases. We meticulously calculated the prior sample size. Therefore, we believe that the sample size of this phase II clinical research was adequate.

Another topic that we clarify is that medication compliance relies on the physician-patient trust relationship. Volunteering, being informed via signed informed consent, and effective communication established the basis of adherence. We ensured patient compliance here, similar to how we handle it in our daily clinical practice. Additionally, the patients returned their used medicine boxes to us when the intervention was completed.

Finally, it should be reminded that the current study is not a superiority phase III clinical trial. In our study, we designed a phase II clinical trial to investigate the efficacy and safety of methotrexate in comparison with

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traditional management alternatives such as INCS and oral corticosteroids. Our results claim that accomplishing a similar efficacy between three therapeutic arms does not mean that any of the arms can be ignored or that one can replace another.

Apart from that, our results concluded an excellent safety with methotrexate. In this regard, methotrexate was superior to oral corticosteroids. Nevertheless, we accept that the safety outcomes were similar between INCS and methotrexate. Another question emerges at this point about whether methotrexate may become superior to INCS in long-term use or not, which has to be investigated in further research. From this perspective, we believe that our results are encouraging and pioneering.

Conclusion

In this investigator-initiated phase II RCT, we demonstrated that administration of low-dose (10 mg) weekly MTX was as effective as standard-dose daily 200 mcg mometasone furoate and low-dose daily methylprednisolone 8 mg, and safer than methylprednisolone over an eight-week treatment period. Therefore, we recommend the use of weekly 10 mg oral MTX instead of daily 8 mg methylprednisolone as a safe and efficient alternative maintenance therapy in such cases.

Acknowledgments

The authors would like to thank Professor Sule Oktay, MD, for her consultancy in designing the trial and editing the manuscript.

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Tables

Table 1. Baseline demographic characteristics for each group and results of statistical analysis.

Table 1. Baseline demographic and clinical characteristics for each group, the result of statistical analysis, and the effect size.

Variables		**Group 1** **INCS (control)** **n=13**	**Group 2** **OCS** **n=14**	**Group 3** **MTX** **n=14**	***P***	***Effect size***
Gender	Number and percantage (F)	8 (61.5%)	8 (57.2%)	6 (42.8%)	*0.538* [a]	*0.174* [d]

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Presence of bronchial asthma	Number and percantage	6 (46.1%)	5 (35.7%)	8 (57.1%)	*0.524* [a]	*0.240* [d]
Age (years)	Mean ± SD	47.0±10.4	48.0±7.4	45.0±11.5	*0.714* [b]	*0.018* [e]
	Median	47	49.5	44		
	(min, max)	(29-69)	(36-57)	(29-70)		
FESS for CRSwP (numbers)	Mean ± SD	2.54±1.76	2.64±1.73	2.86±1.46	*0.678* [c]	*0.009*
	Median	2.0	2.0	2.5		
	(min, max)	(1-7)	(1-7)	(1-6)		
Interval between the last surgery and recruitment (days)	Mean ± SD	996.5±1041.1	1049.6±1152.3	701.9±343.6		
	Median	700	527.5	675.5	*0.953* [c]	*0.060*
	(min, max)	(159-3312)	(135-4365)	(129-1508)		

*INCS: Intranasal momatasone furoate, OCS: Oral metyhlprednisolone, MTX: Oral methotrexate, n: Number of patients, F.: Female, FESS: Functional endoscopic sinus surgery, CRSwP:Chronic rhinosinusitis with nasal polyposis, SD: Standard deviation, Min: Minimum, Max: Maximum, a: Pearson Chi Square test, b: One-way Analysis of variance (ANOVA) test, c: Kruskal-Wallis test, d: Cramer's v, e: Partial eta squared, *p<0.05*

Table 2. Primary and secondary outcome measures for each group and results of statistical analysis.

Table 2. Primary and secondary outcome measures for each group and results of statistical analysis.

	Group 1 Control (INCS)	**Group 2 OCS**	**Group 3 MTX**	***p***	**Pairwise comparison**	**Post-hoc *p***
Total score of LKES (mean±SD)						
Visit 1	7.5±3.1	9.6±3.1	9.0±3.0	$p_{between}$ *= 0.038* [a]*	***Group*** *1-2*	*0.467*
					Group *1-3*	*0.578*
Visit	5.9±2.7	6.9±3.0	6.9±4.0		***Group*** *2-3*	*1.000*

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2						
Visit 3	5.9±2.8	5.9±2.2	6.6±3.5			
Total score of VAS(mean±SD)						
Visit 1	22.7±10.8	27.6±13.3	31.4±12.5			
Visit 2	12.4±8.0	18.6±9.4	26.6±12.0	$p_{between} = 0.016^{a}$*	***Group*** $_{1-2}$	*0.360*
					Group $_{1-3}$**	*0.012**
					Group $_{2-3}$	*0.226*
Visit 3	13.5±6.6	14.8±9.5	23.7±11.1			
Total score of SNOT-22(mean±SD)						
Visit 1	47.2±19.9	45.4±17.7	57.1±22.7			
Visit 2	30.6±19.6	30.6±18.3	47.8±17.6	$p_{between} = 0.050^{a}$	***Group*** $_{1-2}$	*>0.05*
					Group $_{1-3}$	*>0.05*
					Group $_{2-3}$	*>0.05*
Visit 3	26.7±19.7	20.9±13.0	37.0±18.4			
Total score of PNIF						
Visit 1	80(50-210)	80(0-240)	70(10-210)			
Visit 2	95(50-360)	90(40-240)	92.5(20-210)	$p_{between} = 0.842^{b}$	***Group*** $_{1-2}$	*>0.05*
					Group $_{1-3}$	*>0.05*
					Group $_{2-3}$	*>0.05*
Visit 3	90(65-370)	95(50-240)	110(25-240)			
Total score of BuOT median(min-max)						
Visit 1	2(2-8)	2(2-5)	2(2-2)		***Group*** $_{1-2}$	*>0.05*
				$p_{between} = 0.003^{b}$*	***Group*** $_{1-3}$	*>0.05*
Visit 2	4(2-15)	2(2-5)	2(2-4)		***Group*** $_{2-3}$	*>0.05*

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Visit 3	4(2-16)	3.5(2-7)	2(2-4)			
Serum IgE level						
Visit 1	86(13-810)	146(14-2000)	130(26-2000)			
Visit 2	53.5(11-580)	128.5(9-2000)	100.5(25-2000)	$p_{between} = 0.738^{b}$*	***Group*** $_{1-2}$	*>0.05*
					Group $_{1-3}$	*>0.05*
					Group $_{2-3}$	*>0.05*
Visit 3	97(10-817)	96(11-2000)	85.5(19-2000)			
Presence of peripheral eosinophilia n (%)						
Visit 1	4 (30.8)	5 (35.7)	7 (50.0)			
				Group $_{1-2}$	*>0.05*	
Visit 2	4 (30.8)	5 (35.7)	5 (35.7)	***Group*** $_{1-3}$	*0.019**	
				Group $_{2-3}$	*>0.05*	
Visit 3	4 (30.8)	3 (21.4)	2 (14.3)			

INCS: Intranasal momatasone furoate, OCS: Oral metyhlprednisolone, MTX: Oral methotrexate, n: Number of patients, F: Female, FESS: Functional endoscopic sinus surgery, CRSwP:Chronic rhinosinusitis with nasal polyposis, LKES: Lund-Kennedy endoscopic grading system, VAS: Visual analog scale, SNOT-22: The Turkish version of Sinonasal Outcme Test-22, PNIF: Peak nasal inspiratory flow, BuOT: Butanol olfactory threshold test, IgE: Immunoglobuline E, PE: Peripheral eosinophilia, SD: Standard deviation, Min: Minimum, Max: Maximum

[a] *Repeated measure ANOVA control for between subject efffect on parametric condition*

[b] *Nonparametric Analysis of Longitudinal Data control for between subject efffect*

* $p<0.05$

*** The groups were similar regarding the baseline measurements. The statistical analyses of the baseline outcome measurements between the three groups were statistically non-significant.*

Table 3. Adverse events.

Table 3. Adverse events

	Severity	**Study Intervention Relationshi**	**Action Taken Regarding Study**	**Outcome of Adverse**	**Expected**

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					p	Intervention	Event	
				1=Mild *2=Moderate* *3=Severe* *4=Life threatening*	*1=Absolutely not related* *2=Possibly not related* *3=Possibly related* *4= Probably related* *5=Definitely related*	*0=None* *1=Dose adjustment* *2=Specific treatment required* *3=Hospitalisation* *4=Discontinued permenantly* *5 =Other*	*1=Resolved, no sequel* *2=Minor sequel* *3=Major sequel* *4=Still present-being treated* *5=Being treated-getting worse* *6=Death* *7=Unknown*	*1=Yes* *2=No*
ID*	**Event description**	**Age**	**Sex**					
1	Gastritis-like symptoms	36	M	1	4	2 (Consulted with gastroenterology, received oral treatment, treatment completed)	1	1
2	Gastritis-like symptoms	36	F	1	4	2 (Consulted with gastroenterology, received oral treatment, treatment completed)	1	1
3	Gastritis-	44	F	1	4	2 (Consulted	1	1

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	like symptoms					with gastroenterology, received oral treatment, treatment completed)		
4	Gastritis-like symptoms	51	M	1	4	2 (Consulted with gastroenterology, received oral treatment, treatment completed)	1	1
5	A few acne-like lesions on scalp	37	M	1	4	0 (Consulted with dermatology, gradually resolved in a month after the last visit)	1	1
6	Elevation of fasting serum glucose (128 mg/dl)	57	M	1	4	0 (Consulted with endocrinology, completely resolved ten days after the last visit)	1	1

** These six patients belonged to the OCS arm and experienced adverse events, shown in the table, during the last visit.*

Supplementary Material (Table) 1: Safety outcome measures for each group and results of statistical analysis.
Supplementary Material (Table) 2: Expanded version of the Table 2, Primary and secondary outcome measures for each group and results of statistical analysis.

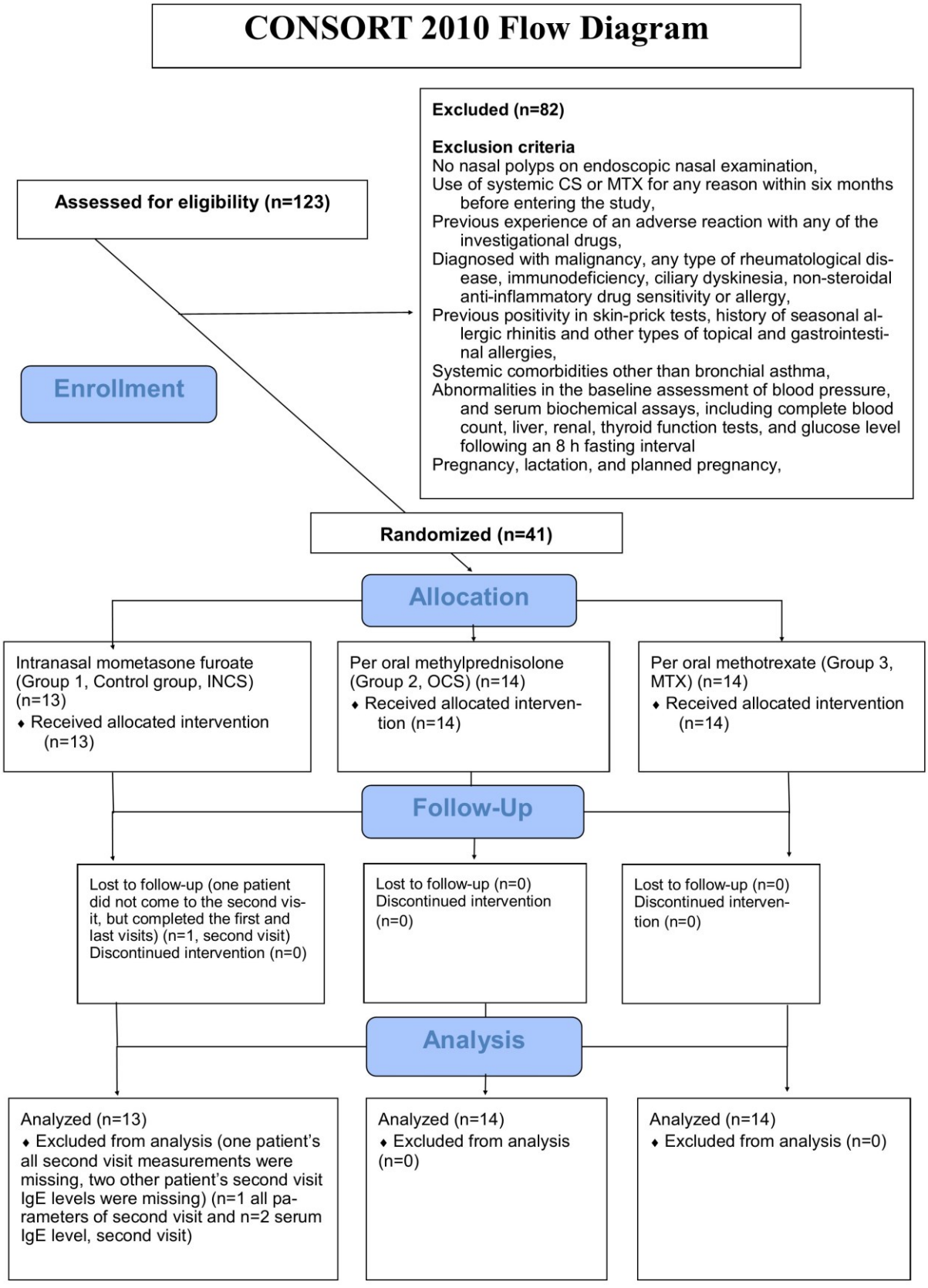
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Figure Legends

Figure 1. Consort flow diagram.



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