Mepolizumab for eosinophilic chronic sinusitis with nasal polyposis: real-life experience*

Firas Kassem[1,2,#], Ronit Cohen-Confino[2,3,#], Keren Meir-Shafrir[3], Idit Lachover-Roth[2,3], Anat Cohen-Engler[2,3], Benjamin Nageris[1,2], Yossi Rosman[2,3]

[1] ENT department, Meir medical center, Israel

[2] Sackler school of medicine, Tel-Aviv university, Israel

[3] Allergy and clinical immunology unit, Meir medical center, Israel

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# Both authors contributed equally

To the Editor:

Nasal polyps (NP) are benign, mostly eosinophilic inflammatory masses, arising from the mucosa of the nose and paranasal sinuses. Primary diffuse chronic rhinosinusitis (CRS) with type 2 inflammation (eosinophilic CRS (eCRS), formally known as CRS with nasal polyposis) is diagnosed based on the presence of chronic sino-nasal symptoms, including nasal obstruction and discharge and visualization of polyps in the nasal cavity [(1)]. Symptoms substantially affect quality of life (QOL). Nasal steroids provide only minor relief and extensive endoscopic sinus surgery (ESS) is often necessary [(1,2)]. Most patients experience recurrent NP after extensive ESS and repeated surgery is needed. Although well-established in eosinophilic asthma [(3)], information regarding anti – IL5 treatment in cases of eCRS is scarce [(2,4,5)]. This study evaluated the effect of mepolizumab (100-300mg sc monthly) for at least one year for the prevention of ESS in cases of eCRS.

This study was a retrospective review of prospectively collected data. It included patients with eCRS and severe eosinophilic asthma, either candidate for or immediately after extensive ESS in the Meir Medical Center, Kfar Saba, Israel. As conventional treatment and surgery failed, treatment with anti-IL5 was initiated. Monthly follow-up was performed routinely, including medical anamnesis focused on nasal symptoms, exacerbations requiring use of systemic steroids and/or antibiotics and need for emergency department visits or hospital admissions. NP were graded by imaging according to Lund-Mackay staging (6) before treatment and after, when indicated. Endoscopy scoring according to Meltzer et al. [(7)] was performed by an ENT specialist before and during follow-up. Lung function was evaluated using spirometry. QOL was assessed with the SNOT-22 questioners before treatment and after one year of mepolizumab.

Differences were analyzed using paired t-test. $P < 0.05$ was considered statistically significant. Analyses were performed using SPSS version 25 (IBM Corp., Armonk, NY, USA).

The study was approved by the local Institutional Ethics Committee.

Eleven patients with severe eCRS were treated with mepolizumab.

All patients were treated with mepolizumab, on top of nasal irrigation and topical steroids, and prospectively followed for an average period of 17.4±5.5 months.

Demographic data are summarized in Table 1. Two patients had EGPA, and another had hyper-eosinophilic syndrome with sinus, lung and intestinal involvement. Six patients had allergic sensitization and five suffered from non-steroidal drug exacerbating respiratory disease.

Mepolizumab significantly improved FEV1 (74.7%±22.7 vs. 91.3%±21.9, p=0.03), and reduced need for chronic systemic steroids (45% vs. 9% patients on chronic steroid treatment), antibiotics (1.3 vs. 0.83 courses per year on average) and emergency visits (1.1 vs. 0.1 visits per year on average).

Nasal symptoms outcomes are summarized in Figure 1. Mepolizumab improved nasal obstruction in 6/11 patients, nasal discharge in 5/11, olfaction in 4/10 and facial pain in 2/3. Endoscopic NP score improved in 6 patients, did not change in 4 patients and got worse in one patient. Overall, a non-significant improvement was noted after mepolizumab treatment (3±1.15 vs 2.1±1.3, p=0.1).

A clinically significant improvement (more than nine points) in QOL as measured by SNOT 22 was seen in seven patients. Overall, mepolizumab improved QOL but this improvement was not statistically significant (55.7±23.6 vs 34.1±27.7 p=0.07) possibly due to the small sample size (Table 2).

Treatment failure was noted in 4/11 patients during follow-up. Three needed extensive ESS despite mepolizumab, due to lack of improvement in nasal symptoms, with significant negative

Table 1. Demographic characteristics.

Patient	Sex	Age	Co-morbidity (excluding asthma)	Num. previous FESS	Endoscopic Polyposis score (0-4)	CT Score (LM, 0-24)	Max Eos. (cells/µl)	Mepolozumab dose (mg)	Follow up (months)
1	F	38	-	0	NA	14	1400	100	23
2	M	15	-	1	3	24	5500	100	35
3	F	67	-	0	4	22	1450	100	21
4	F	41	Hyper-eosinophilic syndrome	1	4	20	3100	300	19
5	M	64	EGPA	1	3	20	9800	300	23
6	F	45	-	3	3	20	1800	100	20
7	F	46	-	1	3	24	800	100	25
8	F	22	-	1	1*	22	1400	100	23
9	M	60	-	3	1*	24	600	100	17
10	M	58	-	4	4	22	600	100	12
11	M	82	EGPA	0	4	24	2800	300	12

* Patients 8-9 were evaluated immediately after nasal surgery

Table 2. Quality of life questionnaire (SNOT-22) before and after mepolizumab treatment (supp.)

Name	SNOT 22 Before (0-110)	SNOT 22 After (0-110)	SNOT 22 rhinology domain* before (0-35)	SNOT 22 rhinology domain after (0-35)
1	40	39	22	v
2	58	16	20	10
3	73	25	25	20
4	92	100	26	26
5	60	31	15	5
6	22	6	18	5
7	72	17	20	8
8	74	70	29	25
9	12	12	7	5
10	50	30	20	15
11	60	30	25	16

* questions 1-3, 6, 21-22

effects on QOL and need for recurrent courses of systemic steroids. Mepolizumab was continued after surgery in two patients with good clinical outcomes to-date. In the third, with hyper-eosinophilic syndrome, treatment with mepolizumab was stopped and systemic steroids were administered. In the fourth patient, mepolizumab was switched to benralizumab with improved clinical outcomes and no need for sinus surgery to date. No side effects to mepolizumab were noted.

IL-5 is the critical factor that promotes eosinophil development and survival [8]. Mepolizumab, a monoclonal antibody targeting IL-5, is approved for treating severe eosinophilic asthma (100 mg sc, monthly) and EGPA (300 mg sc, monthly)[3,9]. Although IL-5 appears to have a key role in the pathogenesis of eCRS, data regarding usefulness of mepolizumab are lacking. There are only two randomized trials regarding high-dose (750 mg IV, monthly) mepolizumab in patients with severe eCRS [4,5]. Mepolizumab, although significantly better than placebo, failed to prevent surgery in about 70% of treated patients. A phase 3 trial of 100 mg mepolizumab sc. monthly is ongoing.

The current study evaluated the effect of mepolizumab (100-300 mg sc, monthly) in 11 patients with eCRS. Although clinical outcomes and QOL improved, 4/11 patients required nasal surgery or change in treatment due to lack of improvement in nasal symptoms. This can be explained as follows: Some of the clinical outcome improvements may be due to improved lung function and not improved nasal symptoms. When focused specifically on nasal symptoms and polyposis scores, improvement was less evident. Moreover, most patients were treated with the dose approved for asthma. One can argue that although effective in asthma, the dose for eCRS should be higher, as in EGPA. Finally, it may be possible that mepolizumab is effective in cases of eCRS, but is insufficient for preventing surgery in some severe cases.

This study had several limitations. It was a retrospective uncontrolled trial with a small sample size, which precludes drawing strong conclusions. Due to Israeli healthcare system rules and FDA approval, mepolizumab was available only to eCRS patients with coexisting severe eosinophilic asthma or EGPA. Although all patients had eosinophilic asthma, they differed in other co-morbidities, leading to different treatment doses. Finally, due to the retrospective nature of the study, some data are lacking. Nevertheless, this is the first real-life study evaluating the effect of s.c mepolizumab in cases of eCRS.

In conclusion, we found that sc mepolizumab (100-300 mg,

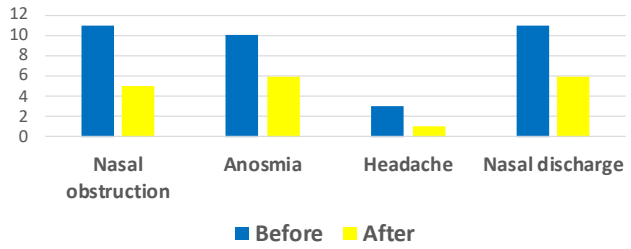

Figure 1. Nasal symptoms, before and after follow-up.

monthly) improved QOL and exacerbations in a small case series of patients with eCRS and co-morbid eosinophilic asthma, but failed to prevent ESS in about 25% of patients. Additional large-scale, controlled trials are needed in order to conclude the role of anti-IL-5 in general and mepolizumab specifically, in cases of severe, recurrent eCRS.

Conflict of interest

On behalf of all authors, we declare no conflict of interest.

Authorship contribution

FK, YR: drafting the work; FK, MSK, LRI, CEA: Acquisition, analysis and interpretation of data for the work; CCR, BN, YR: Substantial contributions to the conception or design of the work; CCR, MSK, CEA, BN: revising it critically for important intellectual content; FK, CCR, MSK, LRI, CEA, BN, YR: final approval of the version to be published and agreement to be accountable for all aspects of the work.

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List of abbreviations

CRS - Chronic rhinosinusitis; eCRS - Eosinophilic chronic rhinosinusitis; EGPA - Eosinophilic granulomatosis with polyangiitis; ESS - Endoscopic sinus surgery; NP - Nasal polyps; QOL - Quality of life.

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Yossi Rosman, MD
Allergy & Clinical Immunology Unit
Meir General Hospital
Kfar-Saba
Israel 44281

Tel: +972-9-7472718
Fax: +972-9-7472362
E-mail: rosmanyossi@gmail.com