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Disconnect between effects of mepolizumab on severe eosinophilic asthma and chronic rhinosinusitis with nasal polyps

Chan, Rory; Kuo, Chris RuiWen; Lipworth, Brian

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1 **Disconnect between effects of mepolizumab on severe eosinophilic asthma and chronic**
2 **rhinosinusitis with nasal polyps**

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4 Rory Chan, MBChB, r.chan@dundee.ac.uk

5 Chris RuiWen Kuo, MBChB, r.kuo@dundee.ac.uk

6 Brian Lipworth, MD, b.j.lipworth@dundee.ac.uk

7

8 **Affiliation:** Scottish Centre for Respiratory Research, School of Medicine, University of Dundee,
9 Ninewells Hospital, Dundee, DD1 9SY

10

11 **Correspondence:**

12 Dr Brian Lipworth

13 Scottish Centre for Respiratory Research and Rhinology Mega-clinic

14 Ninewells Hospital and Medical School

15 University of Dundee, DD1 9SY

16 Scotland, UK

17 b.j.lipworth@dundee.ac.uk

18

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20 **Clinical Implications:** Mepolizumab improves control of asthma but not nasal polyposis

21 **Conflict of Interest:**

22 Dr. Chan has nothing to disclose.

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30 To the Editor,

31 Mepolizumab is a humanised interleukin 5 (IL-5) antagonist monoclonal antibody used for the
32 treatment of uncontrolled severe eosinophilic asthma (SEA). Increased IL-5 expression and local
33 eosinophilic inflammation have a key role in the pathogenesis of SEA and chronic rhinosinusitis and
34 nasal polyps (CRSwNP).¹ Targeting IL-5 with mepolizumab (MEPO) which is a central protagonist of
35 eosinophilic type 2 inflammation (T2) has achieved good results in reducing asthma exacerbations.^{2,3}

36 Here we present a series of six retrospective cases of never smokers with uncontrolled SEA and
37 concomitant CRSwNP, in relation to their disconnected response to MEPO at the standard
38 subcutaneous dose of 100mg every four weeks (q4w) which was administered under supervision. In
39 this case series, MEPO was commenced for the treatment of SEA as it does not yet have a license for
40 CRSwNP. Patient demographics are summarised in the table. All patients had negative MPO or PR3
41 antibodies and negative *Aspergillus fumigatus* IgE and IgG antibodies. Asthma control questionnaire
42 (ACQ-6), spirometry, CT sinuses, nasal endoscopy (30 degree oblique rigid Hopkins 3.0mm endoscope)
43 and blood eosinophil count are all routinely performed in our regional rhinology mega-clinic.

44 CRSwNP burden was initially assessed endoscopically according to Lildholdt scoring with all
45 endoscopies being performed by at least one of the authors.⁴ Lildholt et al graded severity of nasal
46 polyps using a 0 - 3 point system for each nostril i.e. total score out of 6. A score of 1 implies mild
47 polyposis i.e. small polyps not reaching the upper edge of the inferior turbinate. A score of 2 suggests
48 moderate polyposis where medium sized polyps reach between the upper and lower edge of the
49 inferior turbinate. Finally, a score of 3 advocates severe polyposis i.e. large polyps reaching below the
50 lower edge of the inferior turbinate. A patient with severe bilateral nasal polyposis would therefore
51 have a maximum score of 6. CRSwNP burden was subsequently assessed radiologically using CT Lund-
52 Mackay scoring (out of 24).

53 In one study 38/54 (70%) patients did not respond to iv MEPO 750mg, with response measured as a
54 reduced need for nasal polyp surgery.⁵ In the second study, 8/20 (40%) did not respond to iv MEPO
55 750mg, with response described as a reduction in total polyp score.⁶ In this case series, the mean
56 duration of MEPO treatment was 9 months. We observed a significant improvement in asthma control
57 from a mean ACQ-6 of 3.4 before versus 0.3 after MEPO. An ACQ score of less than 0.75 denotes good
58 control and more than 1.5 denotes poor control. Moreover ACQ score is a strong predictor of future
59 exacerbation risk.⁷ The mean number of asthma exacerbations requiring oral corticosteroids (OCS) in
60 the ensuing 12 months fell from 4 before treatment to 1 after treatment. Blood eosinophils fell in all
61 cases as expected with anti-IL5 treatment from a mean of 1393 to 120 cells/ul.

62 However, the improvements in asthma control were not mirrored by CRSwNP. Mean endoscopic NP
63 score pre-treatment was 5 and remained unchanged after treatment (table). The mean number of
64 CRSwNP exacerbations requiring OCS in the 12 months was also unchanged pre and post treatment.
65 Furthermore, all patients had persistent anosmia pre and post MEPO. Pointedly, these observations
66 were noted in a patient cohort with a high nasal polyp burden reflected by a mean Lund-Mackay score
67 of 21/24 in addition to a high blood eosinophil count, thus representing a group who would be
68 expected to receive benefit from MEPO.

69 Our indication for OCS for a CRSwNP exacerbation would be worsening blockage and anosmia
70 together with increased often purulent secretions. Patients are normally referred from primary or
71 secondary care to our specialist rhinology mega-clinic where we are supported by specialist ENT
72 nurses and have access to point-of-care nasal endoscopy. Our patients with severe disease following
73 several oral steroid pulses are also usually offered the option of seeing an ENT surgeon (in the same
74 clinic) to discuss the merits and risks of surgery. Inevitably most patients opt for medical polypectomy
75 with our standard Tayside polyp-clear regimen of 2 weeks of oral prednisolone 25mg daily and 3 days
76 of azithromycin 500mg daily and fluticasone nasules 400µg twice daily.

77 Patient 2 was the only one with evidence of airway obstruction in terms of low FEV1 %. It is well
78 recognised frequent exacerbations in conjunction with preserved lung function may occur in patients
79 with SEA. Patient 6 had previously been commenced on omalizumab therapy for severe atopic asthma
80 but was subsequently switched to mepolizumab as their control worsened requiring frequent courses
81 of OCS.

82 Our clinical experience with MEPO for SEA with concomitant CRSwNP therefore differs from the
83 results achieved from previous studies.^{5, 6} Our patients responded favourably to MEPO in terms of
84 asthma control, but their CRSwNP disease persisted and, in some cases, continued to worsen. To
85 further elucidate this point, patient 4 underwent functional endoscopic sinus surgery (FESS) alongside
86 MEPO for asthma but experienced NP recurrence within four months. Similarly, patient 1 underwent
87 FESS prior to commencing MEPO but still experienced worsening endoscopic and clinical outcomes
88 having had clear ethmoid and sphenoid cavities in the immediate postoperative period. It is also worth
89 pointing out that while patients 1 and 2 experienced no exacerbations of CRSwNP requiring OCS per
90 se they still had a high Lund Mackay score.

91 This observed disconnect in MEPO response between upper and lower airways could perhaps be
92 explained by an insufficient dose of MEPO resulting in lack of efficacy for the treatment of eosinophilic
93 CRSwNP. Two randomised controlled trials (RCT) demonstrated that intravenous MEPO 750mg q4w
94 reduced NP size or the need for FESS, but the dose was much higher than the standard subcutaneous
95 100mg q4w dose used here.^{5, 6} There is an ongoing RCT looking at MEPO in CRSwNP using the standard
96 100mg subcutaneous dose (NCT03085797). Interestingly Laidlaw et al recently reported on a
97 disconnect between depletion of blood and tissue eosinophils with Dexamipexole over 6 months
98 with no change in polyp size or improvement in symptoms.⁸ Two phase 3 studies with dupilumab, an
99 IL-4 receptor alpha monoclonal antibody in CRSwNP as add on therapy to nasal corticosteroid spray
100 showed that it significantly improves endoscopic, radiological, clinical, patient-reported sino-nasal and

101 asthma outcomes, despite there being no reduction in blood eosinophils, but no polyp biopsies were
102 reported.⁹

103 We appreciate there are limitations to interpreting our study. First, we did not perform CT scans after
104 MEPO as this is not part of our routine clinic follow-up protocol to avoid unnecessary ionising
105 radiation. Second, we did not record formal symptom scores such as SNOT-22 or objective smell
106 testing because this is not usually performed in our NHS clinic. However, none of our patients
107 spontaneously reported any recovery in their sense of smell. Nonetheless it can be seen that our
108 patients overall had an appreciable NP burden based on their endoscopy and CT scores. Finally we
109 would like to emphasise that this was a real world retrospective case series based on case note review
110 and as such may not reflect results from prospective RCTs or prospective real life follow up trials.

111 In conclusion standard doses of MEPO significantly improved asthma control but not NP in our
112 cohort of uncontrolled SEA patients with concomitant CRSwNP.

113

114 Word count 1,193

115 Rory Chan MB ChB, Chris RuiWen Kuo MB ChB, Brian Lipworth MD

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117

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144 blind, placebo-controlled, parallel-group phase 3 trials. *The Lancet* 2019.

145

146 Table – patient demographics and clinical parameters pre and post mepolizumab

Patient	1	2	3	4	5	6
Age	49	37	53	61	58	65
Gender	F	F	M	F	F	M
AERD	+	+	-	+	-	-
Medications	BUD/FM ML FPN	FF/VIL, UMEC ML, FEX FPN	Pred 25mg BUD/FM, TIO FPN	FF/VIL ML, FEX FPN	FF/VIL, UMEC ML, CET FPN/AZEL	Pred 2.5mg, AZI FF/VIL, UMEC CROMO FPN
Total IgE kU/L	94	60	423	270	94	420
Pre MEPO						
ACQ-6	2.3	3.9	3.6	5.5	3	2.3
Eos cells/uL	1540	1330	1380	1520	1760	830
FEV1 %	92	63	109	118	96	81
Asthma exac [#]	4	4	4	4	6	4
CRSwNP exac [#]	0	0	2	2	2	1
LM score	23	21	23	19	24	14
NP score	0*	5	6	6	6	5
Post MEPO						
ACQ6	0	0.3	1	0	0	0.7
Eos cells/uL	90	90	340	90	80	30
FEV1 %	93	77	101	107	96	70
Asthma exac [#]	0	0	1	1	0	2
CRSwNP exac [#]	0	0	2	2	1	2
NP score	2	5	6	6	6	6

ACQ = asthma control questionnaire, AERD = aspirin-exacerbated respiratory disease, AZEL = azelastine nasal spray, AZI = azithromycin, BUD = budesonide, CET = cetirizine, CROMO = sodium cromoglicate, CRSwNP = chronic rhinosinusitis with nasal polyps, Eos = eosinophils, exac = exacerbations, FEV1 = forced expiratory volume in 1 second, FM = formoterol, FPN = fluticasone propionate nasal spray, FF = fluticasone furoate, IgE = Immunoglobulin E, LM = Lund Mackay score, MEPO = mepolizumab, ML = montelukast, NP = nasal polyp, TIO = tiotropium, UMEC = umeclidinium, VIL = vilanterol, # denotes number of asthma or CRSwNP exacerbations requiring oral corticosteroids in the preceding 12 months, * patient underwent surgical polypectomy prior to MEPO