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

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

**Conflict of Interest:**

Dr. Chan has nothing to disclose.

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To the Editor,

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

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

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

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

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

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

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

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

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

asthma outcomes, despite there being no reduction in blood eosinophils, but no polyp biospies were reported.[9]

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

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

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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 proprionate 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

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