Mepolizumab in adolescents with severe eosinophilic asthma not eligible for Omalizumab: one centre's early clinical experience

Keywords: Monoclonal antibody, asthma, eosinophils, pulmonary function, fractional exhaled nitric oxide, asthma control test, paediatric asthma quality of life questionnaire

ABSTRACT

Objective

To evaluate Mepolizumab for adolescents with severe eosinophilic asthma who failed on or were ineligible for Omalizumab.

Methods

Retrospective observational study assessing the effect of Mepolizumab on asthma attacks, blood eosinophil count, pulmonary function (fractional exhaled nitric oxide concentration (FeNO), forced expiratory volume in 1s (FEV_1)), Asthma Control Test (ACT) and Paediatric Asthma Quality of Life Questionnaire (PAQLQ) scores. Data evaluated during the first 4 and after 12 months.

Results

Seven adolescents (mean age 13.9±1.9, range 11-17 years; sex 5M:2F) received 12 Mepolizumab doses (100mg monthly subcutaneous injection) with no serious adverse reactions. Twelve months pre-Mepolizumab, mean number of severe asthma attacks per child requiring high dose oral steroids was 5.0±1.73 (4 hospitalised, mean hospitalisations 1.8±0.96). Reduced frequency of severe attacks, mean 1.1±1.07, 3.1±3.13 after 4 and 12 doses. One patient hospitalised twice, 1 avoided severe

attacks. Blood eosinophils decreased in all (mean pre-treatment 0.8±0.64 x 10^9, 0.1±0.06 x 10^9 cells/L after 3 or 4 doses). After 3 doses, PAQLQ scores improved/remained static in 5/7 patients (71%), mean ΔPAQLQ 0.9±1.84. After 4 doses, ACT improved in 5/7 patients (71%), mean ΔACT 3.0±4.55, FEV_1 z-score improved in 2/7 patients (29%), mean ΔFEV_1 z-score -0.2±0.68. After 12 doses, ACT improved in 3/7 patients (43%) from baseline, mean ΔACT 1.7±7.25. FEV_1 z-score improved in 2/7 patients, mean ΔFEV_1 z-score -2.2±2.14. Mean ΔFeNO -15±29, -37±126 ppb after 4 and 12 doses.

Conclusion

Mepolizumab is well tolerated, reduces exacerbation risk, may improve asthma control and quality of life but does not improve lung function.

INTRODUCTION

Omalizumab is a recombinant monoclonal antibody (IgG1) targeting IgE for use in severe allergic asthma. However, it is not a suitable treatment in some patients because of their IgE level and/or weight [1], and a small number of eligible patients do not respond to it [2]. Mepolizumab, an anti-interleukin-5 (IL-5) monoclonal antibody is an emerging therapy approved for use in adults with severe refractory eosinophilic asthma [3,4] and has been shown to reduce asthma attacks in adults and adolescents [5,6,7]. Mepolizumab has been accepted by NICE and the Scottish Medicines Commission for restricted use as an add-on treatment for severe refractory eosinophilic asthma in adult patients, and more recently for use in children from 6 years in the EU [3,8]. Although 28 adolescents who were 12 years and upwards were eligible for inclusion in the pivotal studies, only 19 adolescents aged 12-17 years old were treated with Mepolizumab [9,10,11].

In our experience, children with severe eosinophilic asthma who are poorly responsive to standard therapies, are not eligible for Omalizumab or fail to respond to it, are clinically difficult to manage. Our paediatric centre obtained local approval for use of Mepolizumab as an unlicensed medicine in such adolescents with severe eosinophilic asthma. Here we review our experience of Mepolizumab on acute asthma attacks, asthma control (Asthma Control Test, (ACT)) [12], pulmonary function (fractional exhaled nitric oxide concentration (FeNO) and forced expiratory volume in 1s (FEV_1)), blood eosinophil count, and quality of life (Paediatric Asthma Quality of Life Questionnaire (PAQLQ)). We performed an initial evaluation after 4 months as is recommended for Omalizumab [13] and after 12 months treatment.

METHODS

Study participants

We retrospectively analysed data from adolescents offered Mepolizumab at the Royal Hospital for Children, Glasgow between October 2016 – January 2018. Adolescents were offered Mepolizumab if they had severe eosinophilic asthma and were not eligible for Omalizumab (n=7).

Eosinophilic asthma was defined as a blood eosinophil count >300 cells/μL or fractional exhaled nitric oxide concentration (FeNO) ≥50 ppb in the previous year [9]. All adolescents received high-dose inhaled corticosteroids (ICS), long-acting beta-adrenoceptor agonist (LABA) and had a history of ≥3 severe asthma attacks needing systemic corticosteroids in the previous year. Six adolescents received leukotriene receptor antagonists, 3 received slow-release oral theophylline and 4 received daily oral steroids. All had low ACT scores (mean 10.4) prior to Mepolizumab.

Each patient received 12 Mepolizumab doses of 100 mg administered subcutaneously at monthly intervals, with evaluation after 4 and 12 doses. Long-term medications were not adjusted during Mepolizumab treatment.

Pulmonary function testing

Pulmonary function was measured using a Jaeger Masterscreen Body Plethysmograph (Jaeger V5.4, Germany) and FeNO measured with an electrochemical analyser (Aerocrine NIOX MINO, Sweden) by an experienced paediatric physiologist in accordance with American Thoracic Society (ATS)/European Respiratory Society (ERS) standards [14,15,16].

Consent

As Mepolizumab is an unlicensed drug in adolescents, informed verbal consent was obtained. As this study was a retrospective review of results from our clinical practice, we did not seek informed consent for review of anonymised patient data.

Statistical analysis

Data expressed as means and SDs. Forced expiratory volume in 1 s (FEV_1) expressed as z-scores using GLI reference ranges [17].

RESULTS

Seven adolescents (mean age 13.9±1.9, range 11-17 years; 5 males, 2 females; mean weight 62.0±10.04 kg, range 51-77 kg) were offered Mepolizumab. Four had IgE-weight combinations above the manufacturer's recommended treatment boundaries for Omalizumab (mean IgE level 1512 IU/ml, range 1031-2229 IU/ml). Three had previously received Omalizumab: one failed to respond and two developed allergic reactions resulting in treatment discontinuation.

Blood eosinophil count evaluated after 3 or 4 Mepolizumab doses and decreased in all patients (mean pre-treatment 0.8±0.64 x 10^9 cells/L to mean 0.1±0.06 x 10^9 cells/L at the 3rd or 4^{th} Mepolizumab dose). FEV_1 z-score improved in only 2/7 patients (29%) after 4 Mepolizumab doses (mean ΔFEV1 z-score -0.2±0.68). ACT score improved in 5/7 (71%) after 4 Mepolizumab doses with a mean ΔACT score of 3.0±4.55. PAQLQ scores were assessed after the initial 3 Mepolizumab doses and improved or remained static in 5/7 patients (71%), mean ΔPAQLQ score of 0.9±1.84.

After 12 months of Mepolizumab, FEV1 z-score improved from baseline in 2/7 (29%) (mean ΔFEV1 z-score -2.2±2.14). In 3/7 patients (43%), the FEV_1 z-score deteriorated with a year of Mepolizumab treatment and remained static in 2/7 patients. ACT improved from baseline in only 3/7 patients (43%), with a mean ΔACT score 1.7±7.25. Mean ΔFeNO after 4 Mepolizumab doses was -15±29 ppb and after 12 doses was -37±126 ppb. No serious adverse effects reported.

Episodes of asthma attacks in relation to treatment timelines for each patient are shown in figure 1. Mean number of asthma attacks requiring high dose oral steroids in the 12 months prior to Mepolizumab was 5.0±1.73. Four patients required hospitalisation for severe attacks during this time:2 admitted once, 1 admitted twice, 1 admitted three times. Prior to Mepolizumab treatment, mean number of hospitalisations for these patients was 1.8±0.96. During treatment, only 1 patient required 2 hospitalisations for asthma attacks after 1 and 11 Mepolizumab doses. There was reduced frequency of severe attacks requiring high dose oral steroids (mean 1.1±1.07 after 4 doses and mean 3.1±3.13 after 12 doses) with 1 patient (14%) having no severe attacks during Mepolizumab treatment. Although there was an overall improvement in the frequency of hospitalisations and severe attacks during Mepolizumab, 2 patients (patients 6 and 7) appear to be non-responders.

DISCUSSION

In these adolescents with eosinophilic asthma not eligible for Omalizumab or who had not benefited from it, Mepolizumab reduced asthma attacks in frequency or severity for the majority, similar to findings reported in adults and limited data available in adolescents [5,6,7]. We confirmed that while Mepolizumab reduced eosinophils to zero, those with a higher baseline eosinophil blood count did not respond better. There was less response of FeNO to Mepolizumab, consistent with findings by

Halder *et al* [18] and Pavord *et al* [5], confirming a weak correlation between these markers and suggesting two different inflammatory pathways [19]. We found that Mepolizumab did not bring any consistent improvement in lung function, ACT or PAQLQ scores. However, all patients subjectively reported positive feedback on their asthma control. Review at 4 and 12 months highlight that a 4-month evaluation as is performed for Omalizumab, is not sufficient time to assess the effect of Mepolizumab on asthma attacks and we recommend a 12-month evaluation.

Limitations

This was a retrospective review of a small number of adolescents managed with Mepolizumab within clinical practice with no control group.

CONCLUSION

Mepolizumab 100mg given subcutaneously at monthly intervals was well tolerated in adolescents with severe eosinophilic asthma who were either ineligible for or who had failed on Omalizumab. Over a 12-month period of evaluation, it had a positive effect on reducing risk of asthma exacerbations. Further studies comparing the effectiveness of Omalizumab and Mepolizumab in children who are eligible for both will be required to determine who best to use these drugs in children with severe asthma.

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Figure 1

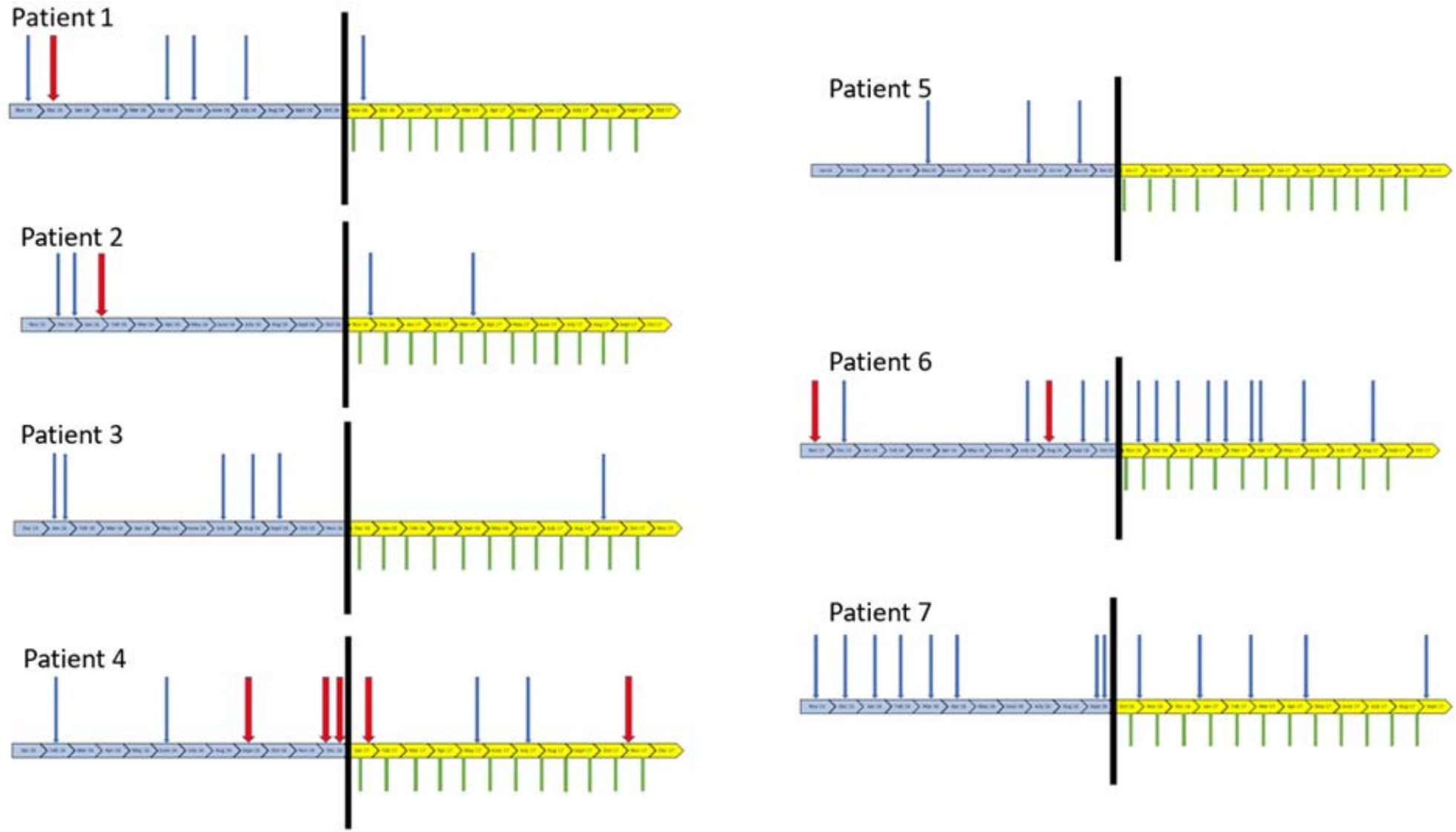
Patient 1
Patient 2
Patient 3
Patient 4
Patient 5
Patient 6
Patient 7

Figure 1 legend

Illustration of asthma attacks over time. The blue part of each timeline represents 12 months pre-Mepolizumab and yellow represents 12 months during Mepolizumab treatment (each subunit being 1 month), with the vertical black line highlighting commencement of Mepolizumab. Vertical green lines highlight when Mepolizumab was given. The red arrows represent hospitalisations for severe asthma attacks and the blues arrows represent patient reported asthma attacks requiring a course of oral steroids.