The role of oral methotrexate as a steroid sparing agent in refractory eosinophilic asthma

David Bilocca[1,2], B Hargadon[1,2], ID Pavord[3], RH Green[1,2],
CE Brightling[1,2], P Bradding[1,2], AJ Wardlaw[1,2], N Martin[1,2],
AC Murphy[1,2] and S Siddiqui[1,2]

Abstract

The use of oral methotrexate for refractory eosinophilic asthma in a tertiary asthma referral centre, Glenfield Hospital, Leicester, was evaluated between January 2006 and December 2014. The patients ($n = 61$) were carefully phenotyped at baseline with markers of airway inflammation. In addition, a structured oral methotrexate proforma was utilized to evaluate response to therapy and adverse events. Oral steroid withdrawal was attempted 3 months after commencing treatment. Several outcomes were evaluated at 12 months, including both efficacy and adverse effects; 15% ($n = 9/61$) responded by achieving a decrease in daily oral corticosteroid dose (mean 8.43 (± 8.76) mg), although we were unable to identify factors that predicted a treatment response. There were no other significant changes in any other clinical outcome measures. There was a high rate of adverse events (19/61 (31%)), primarily gastrointestinal/hepatitis. Our findings support the use of biological agents in preference to using oral methotrexate as a steroid sparing agent at the first instance. In the event of failure of these agents, oral methotrexate remains a therapeutic option, which can be considered in highly specialist severe asthma centres.

Background

Severe refractory asthma, defined as poor asthma control, while adherent to high-intensity treatment, and ensuring exclusion of alternative diagnoses.[1]

The current management of refractory eosinophilic asthma focuses around the optimization of extra-pulmonary factors, corticosteroid sparing agents that can be divided into highly selective biological agents or traditional disease-modifying agents such as oral methotrexate.

A recent European respiratory society (ERS)/ American thoracic Society (ATS) position statement[2] suggested that oral methotrexate may have limited value in severe asthma. However, it concluded that a small benefit in oral corticosteroid reduction may be evident and suggested its use in highly specialized asthma centres with experience in this field.

[1] Institute for Lung Health, Glenfield Hospital, University Hospitals of Leicester National Health Service Trust, Leicester, UK
[2] Department of Infection, Immunity and Inflammation, University of Leicester, Leicester, UK
[3] NDM Research Building, Oxford University, UK

Corresponding author:
David Bilocca, Institute for Lung Health, Glenfield Hospital, University Hospitals of Leicester National Health Service Trust, Leicester, UK.
Email: dbilocca@yahoo.com

Table 1. Demographics and response to therapy of the audit population.

	Responders (N = 9/61)	Non-responders (N = 52/61)	p-Value
Age (years) $\pm$ SD	47.6 $\pm$ 8.2	53.9 $\pm$ 11.4	0.071
Sex (male:female)	3:6	18:34	0.94
Age onset (years) $\pm$ SD	27.9 $\pm$ 17.4	30.4 $\pm$ 17.5	0.36
Disease duration (years) $\pm$ SD	23.1 $\pm$ 14.3	20.5 $\pm$ 11.0	0.11
BMI (kg/m^2) $\pm$ SD	34.2 $\pm$ 6.8	29.7 $\pm$ 5.7	0.03
Atopic status	3/9	18/52	1
Nasal polyps	3/9	6/52	0.12
Serum total IgE (KU) $\pm$ SD	169.1 $\pm$ 200.5	335.1 $\pm$ 453	0.16
Asthma treatment step			
Step 4	0/9	4/52	0.39
Step 5	9/9	48/52	0.39
Prednisolone dose (mg/24 h) $\pm$ SD	15 $\pm$ 2.89	15.7 $\pm$ 8.9	0.42
ACQ-6 (baseline) $\pm$ SD	2.92 $\pm$ 1.22	4.14 $\pm$ 1.45	0.039
Post-BD FEV$_1$ (baseline) $\pm$ SD	2.2 $\pm$ 0.44	1.96 $\pm$ 0.74	0.20
Post-BD FEV$_1$/FVC $\pm$ SD	73.3 $\pm$ 10.0	71.6 $\pm$ 13.5	0.30
Sputum eosinophils (%) median (Q1–Q3)	12.33 (3.1–33.2)	4.0 (0.89–9.4)	0.18
Sputum neutrophils (%) $\pm$ SD	56.6 $\pm$ 24.1	64.7 $\pm$ 23.3	0.237
Blood eosinophils 10^9 $\pm$ SD	0.34 $\pm$ 0.25	0.68 $\pm$ 1.35	0.313

BD: bronchodilator; ACQ-6: six-item Juniper Asthma Control Score; BMI: body mass index; SD: standard deviation.

We sought to evaluate the (i) use of methotrexate, (ii) efficacy and (iii) adverse events in a refractory eosinophilic asthma population.

Methods

Patients started on oral methotrexate for refractory asthma were identified using a combination of (i) clinical letters and (ii) a difficult asthma clinic database. Patients were included if they had been (i) initiated on oral methotrexate between January 2006 and December 2014 and (ii) had at least 12 months of prospective follow-up data.

Eighty-three patients were identified meeting the entry criteria of whom and 61 patients had complete prospective follow-up data (see Table 1 for clinical characteristics).

All patients considered to be suitable for methotrexate treatment met the criteria of refractory asthma.[1] Patients were systematically screened to exclude other possible conditions and ensuring adherence to treatment through repeat prescription data and where available serum prednisolone and cortisol levels. None of the study population were established on biological agents.

Four patients (6.5%) were on Global Initiative for Asthma step 4 treatment,[3] while the remainder (n = 57, 93.5%) were on maintenance oral corticosteroids. The primary indication to initiate methotrexate was to reduce oral corticosteroid burden without loss of asthma control. A response to methotrexate was defined a priori as (i) a reduction in the daily maintenance oral corticosteroid dose of at least 2.5 mg while keeping stable asthma control and/or (ii) a decrease in exacerbation frequency, defined qualitatively via review of clinical letters over 12 months.

A standard methotrexate protocol (see supplementary file) that incorporated (i) healthcare utilization, (ii) symptoms, (iii) medication and (iv) biomarker assessments at baseline, 8 weeks and 16 weeks was utilized to evaluate clinical response, and in addition, a specialist consultant pharmacist evaluated potential side effects and safety bloods (full blood count, liver function tests and urea/electrolytes every week for 6 weeks and then monthly) in each patient. Prednisolone dose reduction was attempted after months, and efficacy was assessed between 4 months and 1 year. Parametric data were analysed using *t*-tests and analysis of variance, while Mann–Whitney and Kruskal–Wallis tests were used for non-parametric variables. A *p*-value of <0.05 was deemed statistically significant.

Results

Fifteen per cent (n = 9/61) of patients responded, with all of them having achieved corticosteroid dose reduction.

In the responder group, a mean ($\pm$ standard deviation) daily oral corticosteroid dose decrease of 8.43 mg ($\pm$ 8.76) was achieved (mean baseline dose 15 mg $\pm$ 2.89 versus 6.25 mg $\pm$ 2.09 after 12 months, $p = 0.001$).

There were no significant improvements in post-bronchodilator forced expiratory volume (FEV_1), Juniper Asthma Control Score (ACQ-6) and sputum eosinophil percentages. In addition, we failed to identify any improvement in qualitative exacerbations over a 12-month period. 'One potential confounder of our interpretation is that the responder population had a significantly lower ACQ-6 at baseline, when compared to non-responders'.

A high rate of adverse events was recorded in patients receiving methotrexate; 19/61 (31%) patients had to stop the drug, the commonest reasons being severe gastrointestinal (GI) symptoms (including reversible colitis ($n = 1$), upper GI bleed ($n = 1$)) and transiently elevated hepatic transaminases ($n = 6/61$ (10%)).

Conclusion

Oral methotrexate in refractory eosinophilic asthma has a small steroid sparing effect in responders, independent of the degree of baseline eosinophilic inflammation. We demonstrated a mean oral corticosteroid dose reduction of 8.43 mg/day in a small (15%) responder population, while having a high rate of adverse events (31%), which included colitis and upper GI bleeding in two cases.

Our findings support the use of biological agents in preference to using oral methotrexate as a steroid sparing agent at the first instance. In the event of failure of these agents, oral methotrexate remains a therapeutic option, which can be considered in highly specialist severe asthma centres.

Authors' note

Declaration of conflicting interests

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Supplemental material

Supplementary material for this article is available online.

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