SHORT REPORT

Immunoglobulin levels in methotrexate treated paediatric rheumatology patients

O J Rackham, J A Sills, J E Davidson

....

Retrospective review of serum immunoglobulin levels in 78 methotrexate treated paediatric rheumatology patients showed that IgG, IgA, and IgM levels fell significantly by 26%, 21%, and 17% respectively while on methotrexate. Six patients with systemic disease showed a fall in IgG to below the normal range.

The effects of methotrexate on serum immunoglobulin (Ig) concentrations in paediatric rheumatology patients have not previously been studied. In our unit it has been noted anecdotally that Ig levels can fall in these patients, sometimes to below the normal range. If this is confirmed it may have implications on what we must tell patients and their families regarding methotrexate and immunosuppression.

This study was carried out to determine the effect of methotrexate on serum immunoglobulin concentrations in paediatric rheumatology patients.

METHODS

This was essentially a retrospective case note review. All the patients under the care of the paediatric rheumatologists at Alder Hey Children's Hospital who are being or have been treated with methotrexate in the past two years were included. They were identified from the consultants' and rheumatology research nurses' lists and from pharmacy records, yielding 78 names. Fifty two had polyarticular juvenile idiopathic arthritis (JIA), 17 had systemic onset JIA, and nine had other connective tissue diseases. Fifty two were on standard low dose methotrexate (10 mg/m²), and 26 on medium dose (15–20 mg/m²).

The case notes were examined and immunoglobulin concentrations pretreatment and more than three months after treatment with methotrexate was commenced were obtained. Where possible results were sought from other hospitals where these patients are seen jointly as shared care. Results were also obtained prospectively when patients were having their routine blood monitoring. No extra blood sampling was done.

The concentrations of IgG, IgA, and IgM were compared pre- and post-treatment. Where there was a fall in IgG to below the normal range, IgG subclasses were also measured. The results were analysed using a two tailed *t* test.

RESULTS

There was a statistically significant fall in IgG, IgA, and IgM by 26%, 21%, and 17% respectively during treatment with methotrexate. Table 1 shows the mean serum IgG, IgA, and IgM concentrations before and during treatment with methotrexate, together with their 95% confidence intervals and mean fall in Ig.

In 38 patients, both pre- and post-treatment Ig levels were measured. The mean fall in these paired samples was the same as the overall mean fall, so the results for the whole group have been quoted. In the paired samples the fall in IgG was 27% (p = 0.0001). The fall in the paired samples in IgA was 23% and in IgM 17%, but because of the smaller sample size this did not quite reach statistical significance (p = 0.054 and p = 0.058 respectively).

The fall was greater in patients receiving subcutaneous compared to those receiving oral methotrexate. This difference was only statistically significant for IgG: oral subgroup mean fall in IgG 2.59 g/l (95% CI: 1.38 to 3.79), subcutaneous subgroup mean fall in IgG 6.27 g/l (95% CI: 2.83 to 9.72) (p = 0.028). Pretreatment Ig levels were the same in both subgroups.

In addition there was a subgroup of six patients who had a fall in IgG from within or above normal limits to below normal levels. All six of these had systemic disease. Two were on low dose and four on medium dose methotrexate. None were on other disease modifying agents. Table 2 summarises their results and diagnoses, together with concomitant erythrocyte sedimentation rate (ESR) measurements. Four of these patients also had their IgG subclasses measured. All showed a fall in IgG1 to subnormal levels. One also showed a fall in IgG3 to below normal.

There was no correlation between the changes in IgG and the changes in inflammatory markers in those patients who had C reactive protein (CRP) and/or ESR measured both pre- and post-treatment at the same time that Igs were measured. The correlation coefficient for the percentage fall in IgG and the percentage fall in CRP was 0.41 (n = 25). The correlation coefficient for the percentage fall in IgG and the percentage fall in ESR was 0.39 (n = 24).

DISCUSSION

Methotrexate is one of a number of cytotoxic drugs used in non-malignant disease. Folates (in particular tetrahydrofolate) are essential for the synthesis of purine nucleotides and thymidylate, which in turn are essential for DNA synthesis and cell division. Methotrexate acts by inhibiting dihydrofolate reductase and depleting intracellular stores of tetrahydrofolate. Cytotoxic drugs act predominantly on rapidly dividing cells such as lymphocytes. This is the basis of their desired anti-inflammatory action, but also means that they have an immunosuppressive action. Methotrexate is absorbed from the gastrointestinal tract, probably via a folate carrier system. However, increasing the dose above a certain level does not necessarily increase the absorption, presumably because the carrier becomes saturated. Methotrexate may also be given intramuscularly, intravenously, intrathecally, or, as in a third of our patients, subcutaneously.

Methotrexate has traditionally been used as a second line, disease modifying agent in a number of paediatric rheumatological conditions (for example, juvenile idiopathic arthritis,

....

Table 1   Mean immunoglobulin levels (g/l) pre- and post-treatment

	Pre-treatment Ig (95% CI) (n=54)	Post-treatment Ig (95% CI) (n=59)	Mean fall in Ig (%)	p value
IgG	15.25 (13.99 to 16.51)	11.22 (10.29 to 12.15)	4.03 (26)	<0.0001
IgA	1.76 (1.51 to 2.01)	1.39 (1.17 to 1.60)	0.37 (21)	0.028
IgM	1.46 (1.31 to 1.62)	1.22 (1.07 to 1.36)	0.25 (17)	0.026

Table 2   Pre- and post-treatment data for the subgroup of patients who showed a fall in IgG to below normal levels

	IgG (g/l)		ESR (mm/h)		
	Pre	Post	Pre	Post	Diagnosis
Patient 1	9.78	5.98	114	3	Systemic JIA
Patient 2	10.4	6.16		54	Systemic JIA
Patient 3	9.04	4.52	65	1	Systemic JIA
Patient 4	17.3	5.11	2	1	Polymyositis overlap
Patient 5	10.3	5.36	7	1	Juvenile dermatomyositis
Patient 6	9.49	5.77	12	2	Panniculitis with systemic disease

Normal range for IgG is age dependent. For patients 3 and 5 it was 6.13–15.5 g/l, for patients 1, 2, 4, and 6 it was 6.26–13.9 g/l.

juvenile dermatomyositis). There is now a trend towards the earlier use of methotrexate and at higher doses.

The effects of methotrexate on B cell function have been shown in vitro.[1] Several studies have shown a fall in immunoglobulin concentrations[2][3] or B cell hyperactivity[4] with sulphasalazine. However, there is no published research on the effects of methotrexate on serum immunoglobulins.

In paediatric rheumatology patients being treated with methotrexate, there is a statistically significant fall in serum immunoglobulins. None of these patients had clinical evidence of infection during the period of the study. The clinical significance of this is uncertain. There is a greater fall in IgG in patients receiving subcutaneous compared to oral methotrexate. This may be a dose related effect as the subcutaneous doses were, in general, higher than the oral doses.

It is possible that the fall in immunoglobulin levels is simply in parallel with a fall in other inflammatory markers. This was not found to be the case in our patients. The fall to subnormal levels in a subgroup with systemic JIA and other connective tissue disorders also makes this unlikely. While these patients showed a fall to below the normal range, the level at which clinical problems occur is not easily predicted from total Ig levels alone. It may be helpful to measure functional antibody levels in these patients. A larger, prospective study with comparison of other inflammatory markers and functional antibody levels is needed to examine the clinical significance of these findings.

. . . .
Authors' affiliations
O J Rackham, J A Sills, J E Davidson, Department of Rheumatology, Alder Hey Children's Hospital, Eaton Road, Liverpool, UK

Correspondence to: Dr O J Rackham, Department of Rheumatology, Alder Hey Children's Hospital, Eaton Road, Liverpool L12 2AP, UK; ojrackham@talk21.com

REFERENCES
1 **Rosenthal GJ**, Weigand GW, Germolec DR, et al. Suppression of B cell function by methotrexate and trimetrexate. Evidence for inhibition of purine biosynthesis as a major mechanism of action. J Immunol 1988;**141**:410–16.
2 **van Rossum MA**, Fiselier TJ, Franssen MJ, et al. Effects of sulfasalazine treatment on serum immunoglobulin levels in children with juvenile chronic arthritis. Scand J Rheumatol 2001;**30**:25–30.
3 **Chalmers IM**, Sitar DS, Hunter T. A one-year, open, prospective study of sulfasalazine in the treatment of rheumatoid arthritis: adverse reactions and clinical response in relation to laboratory variables, drug and metabolite serum levels, and acetylator status. J Rheumatol 1990;**17**:764–70.
4 **Imai F**, Suzuki T, Ishibashi T, et al. Effect of sulfasalazine on B cell hyperactivity in patients with rheumatoid arthritis. J Rheumatol 1994;**21**:612–15.