Immunoglobulin levels in methotrexate treated paediatric rheumatology patients

O J Rackham, J A Sills, J E Davidson

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 juvenile idiopathic arthritis (JIA), 17 had systemic onset JIA, nine had other connective tissue diseases. Fifty two were 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 juvenile idiopathic arthritis (JIA), 17 had systemic onset JIA, nine had other connective tissue diseases. Fifty two were treated with methotrexate, together with their 95% confidence intervals and mean fall in Ig.

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 IgG1 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, 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, juvenile rheumatoid arthritis, systemic lupus erythematosus, and dermatomyositis).
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. Several studies have shown a fall in immunoglobulin concentrations or B cell hyperactivity 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 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.

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