SHORT REPORT

Immunoglobulin levels in methotrexate treated paediatric rheumatology patients

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Arch Dis Child 2002;87:147–148

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 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 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 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 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 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.

The concentrations of IgG, IgA, and IgM were compared 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. 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,

Abbreviations: CRP, C reactive protein; ESR, erythrocyte sedimentation rate; Ig, immunoglobulin; JIA, juvenile idiopathic arthritis
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 clini-
cal 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 sim-
ply 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 func-
tional 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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Accepted 14 March 2002

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| Table 1 Mean immunoglobulin levels (g/l) pre- and post-treatment |
|-------------------|-------------------|-------------------|-------------------|
|                   | Pre-treatment Ig  | Post-treatment Ig | Mean fall in      |
|                   | (95% CI) (n=54)   | (95% CI) (n=59)   | 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)        | Diagnosis         |
|                   | Pre   | Post | Pre   | Post |
| Patient 1         | 9.78  | 5.98 | 114   | 3    | Systemic JIA |
| Patient 2         | 10.4  | 6.16 | 54    | 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.