

Low-dose methotrexate may be the best starting option for patients initiating treatment with adalimumab

Some medicines used to treat inflammatory diseases such as rheumatoid arthritis may have different efficacy and safety depending on the dose used.

INTRODUCTION

Rheumatoid arthritis is a chronic inflammatory disease that affects a person's joints, causing pain and disability. Methotrexate is commonly used in patients with rheumatoid arthritis, both on its own and in combination with a class of drugs called biologics. Despite having been used for many years in patients with rheumatoid arthritis, how methotrexate works against the disease is not exactly known. When used in combination with biologic drugs, it is thought that methotrexate can additionally help to prevent the development of antibodies to the biologic, which the body's immune system sometimes recognises as a foreign protein, and can therefore help to maintain efficacy. The dose of methotrexate used can vary widely, from 7.5 mg to 25 mg a week.

WHAT DID THE AUTHORS HOPE TO FIND?

The authors wanted to see whether the dose of methotrexate used in combination with a biologic drug called adalimumab has an impact on the overall efficacy and safety in patients with early rheumatoid arthritis, and if it was possible to identify an optimum dose that should be used.

WHO WAS STUDIED?

The study included 395 patients diagnosed with early rheumatoid arthritis. All patients were over the age of 18, had suffered from severe rheumatoid arthritis for less than 1 year, and had not previously received methotrexate or a biologic drug, or more than one other type of disease-modifying anti-rheumatic drug (usually called DMARDs).

HOW WAS THE STUDY CONDUCTED?

This was a randomised, double-blind trial, which means that patients were assigned by chance to one of four treatment groups to receive one of four different doses of methotrexate in combination with a biologic drug called adalimumab and folic acid. Using chance in this way means that the groups will be similar and will allow the treatment under investigation (different doses of methotrexate) to be compared objectively. During the treatment neither patients nor their doctors knew which group they were in.

A series of assessments were performed at baseline and over the next 26 weeks. These recorded clinical and functional status, including functional ability, whether there was any progression or joint damage, and patient quality of life. Safety issues were also recorded. Blood samples were also taken to work out whether patients developed antibodies to adalimumab – a phenomenon which can affect the efficacy of biologic drugs.

WHAT WERE THE MAIN FINDINGS OF THE STUDY?

The study found that more patients saw an improvement in their rheumatoid arthritis disease score with increasing doses of methotrexate, and were more likely to achieve remission. There were fewer antibodies to adalimumab with increasing doses of methotrexate. No difference in progression of joint damage was seen between the different groups, suggesting that methotrexate dose may not affect this. The study also found that patients experienced more side effects with increasing methotrexate dose; people were more likely to have an infection while taking a high dose of methotrexate, but these were not serious.

The authors concluded that higher doses of methotrexate may be more likely to result in better clinical outcomes, although not in joint progression. For patients with early RA starting adalimumab combination therapy, it may be possible to achieve clinical results with a lower initial dose of methotrexate than had previously been thought – perhaps as low as 10 mg a week.

ARE THESE FINDINGS NEW?

Yes – this is the first blinded, controlled clinical trial that has tried to find out the lowest effective dose of methotrexate in combination with biologic therapy in patients with early, active rheumatoid arthritis of the type often seen in clinical practice. Determining the best methotrexate starting dose in these patients provides an important insight into the optimal management of these patients for doctors in clinical practice.

HOW RELIABLE ARE THE FINDINGS?

There are some limitations which may affect how reliable the findings are. The study looked at different doses of methotrexate in patients with early and aggressive disease who had not received a biologic drug before, and these results may not apply to patients who have received many other drugs previously, or who have had their disease for longer. Also, some of the results seen may be specific to adalimumab, and methotrexate might not behave in exactly the same way in combination with other biologic drugs.

Patients receiving the highest dose in the study (20 mg) actually started at 10 mg a week and had their dose gradually increased over 8 weeks to try to help prevent side effects, which means that the results for these patients include some time at a lower dose. The authors also acknowledged that not investigating doses higher than 20 mg may affect how useful these results are, as doses greater than this are often used in clinical practice.

WHAT DO THE AUTHORS PLAN ON DOING WITH THIS INFORMATION?

This information will be used to support doctors in choosing lower doses of methotrexate for their patients. Further studies may be undertaken to see if the same results can be repeated with other biologic drugs or in different groups of patients.

WHAT DOES THIS MEAN FOR ME?

Patients with rheumatoid arthritis who are taking a biologic drug will often receive methotrexate as well because it is thought that it can help to achieve better results than when biologics are used on their own, but it may also increase the number of side effects seen. These results might mean that doctors try lower doses of methotrexate to start with. Patients who are concerned should speak to their doctor.

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