Wide variability in rheumatoid arthritis drug suggests alternative dosing should be considered

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Methotrexate (MTX) is commonly used to treat rheumatoid arthritis (RA) and is suggested as the "anchor" drug in treating the disease. Despite its widespread use, the understanding of its mechanism of action and pharmacokinetics is limited. Since joint damage occurs early in the course of RA and is largely irreversible, understanding the time it takes for stable levels of MTX to be reached could be useful in effectively controlling RA and preventing long-term damage. A new study examining levels of MTX metabolites in red blood cells was published in the November issue of *Arthritis & Rheumatism*.

MTX is normally taken orally and is rapidly taken up into a variety of cells, including red blood cells, where it remains long after being eliminated from blood serum. Once inside red blood cells, the drug can assume up to five different forms, which are known as MTXGlu1-5 (MTX polyglutamates) These can be measured inside red blood cells and are thought to be representative of concentrations within other cells, such as lymphocytes. Within the cell, MTX polyglutamates bind to and inhibit several important enzymes, playing a role in a number of anti-inflammatory actions and pathways.

The dose of MTX varies and is unpredictable from patient to patient, but because it disappears rapidly from blood plasma, measurement in plasma can't be used to monitor concentrations of the drug. However, MTX polyglutamate concentrations can be measured in red blood cells.

Patients with RA are normally started on low doses of MTX, with increasing amounts based on response to treatment, but valuable time may be lost with this method, resulting in unnecessary joint damage.

Led by Lisa Stamp and Murray Barclay of the University of Otago in Christchuch, New Zealand and supported by the Health Research Council of New Zealand, researchers examined the levels of MTX polyglutamates in the red blood cells of 10 patients who were beginning treatment with low-dose oral MTX and 10 patients who were stopping treatment. They used high-performance liquid chromatography to detect MTX polyglutamate concentrations in blood samples for an average of 40 weeks.

In most of the patients beginning therapy, the various forms of MTX polyglutamates were detectable in red blood cells between one and eight weeks following administration of the first dose. The median time until 90 percent of the maximum stable level of the drug was reached was 27.5 weeks. The authors note that starting with higher doses may cause some patients to discontinue therapy due to nausea. This might be avoided by injecting the drug, which has been shown to improve the clinical response at 24 weeks compared to oral therapy, but it is not known if this improvement occurred earlier compared to oral administration.

It took approximately 20 weeks for MTX polyglutamates to be undetectable in red blood cells. Elimination of the drug may be more rapid than accumulation due to the lifespan of red blood cells, which have a lifespan of about 120 days. As they gradually die out they are replaced with new cells which causes a "dilutional effect" when MTX is stopped. The lifespan of red blood cells may also contribute somehow to the delay in reaching stable levels of MTX polyglutamates. In any case, the fact that it takes so long for MTX to be eliminated after stopping treatment has implications for discontinuing it prior to surgery,

conception and when an infection is present. "Although newly produced cells will not be exposed to MTX, existing cells will clearly continue to be affected by MTX for a considerable length of time," the authors note.

Although it was small, the study provides information as to how the different forms of MTX are accumulated and eliminated from red blood cells, which is quite variable and may limit the usefulness of MTX polyglutamates detection in these cells as an effective monitoring tool. The authors conclude that if MTX polyglutamate concentrations correlate with MTX efficacy, it may be necessary to consider either injecting the drug or rapidly increasing oral doses in order to reach stable levels.

Source: Wiley