

Total Cumulative Dose of Methotrexate is Not the Same as Continuous Cumulative Dose: A Clinician's Perspective

Methotrexate is the most frequently used systemic therapy for psoriasis with well documented efficacy.^[1] However, long-term hepatotoxicity is the major concern. The exact degree of risk attributable to methotrexate in the development of hepatotoxicity in patients with psoriasis is unknown. Recent studies, however, demonstrated that hepatic fibrosis and cirrhosis are considerably less common than initially reported.^[2,3] As compared with rheumatology, the dermatology guidelines are somewhat stricter as hepatotoxicity is greater in patients with psoriasis than in patients with rheumatoid arthritis.^[4] This is because of associated comorbidities like metabolic syndrome (obesity, diabetes, and dyslipidaemia), alcohol,^[5] and psoriasis itself^[6] which act as a contributory factor in hepatotoxicity.

Earlier, liver biopsy was recommended in all patients after a total cumulative dose of 1 to 1.5 gm of methotrexate.^[7] However, recent literature suggests that this stringent approach is not necessary in patients without any pre-existing risk factors for hepatotoxicity and 3.5 to 4.0 gm (instead of 1.0–1.5 gm) of cumulative methotrexate may be a more appropriate time frame for the first liver biopsy.^[8] These cut-offs values are arbitrary and based on experience. Recently updated methotrexate guidelines from the National Psoriasis Foundation suggest that patients be divided into two groups, those with risk factors for hepatotoxicity and those without.^[9]

Psoriasis is chronic inflammatory dermatoses that has a waxing and waning course and the patients often go into remission. Therefore, when indicated, methotrexate is used as intermittent therapy during disease activity and discontinuation/tapering off once remission is achieved. The concept of intermittent therapy^[10] and rotational therapy^[11] arose from an effort to reduce the total cumulative dose, thereby minimising adverse effects. This also helps in keeping it available for potential future use should the need arise. Anyways, psoriasis has natural tendency of intermittent remissions and relapses. An effective drug like methotrexate is therefore used intermittently as per these relapses. Hence, the concept is based on the reasoning that long periods without methotrexate may allow some hepatic changes to improve or even reverse completely. There is an increasing body of evidence that psoriasis patients without risk factors on long-term, low dosage, once-weekly methotrexate have only a modest risk of significant fibrosis.^[12,13]

The pathogenesis of cumulative methotrexate hepatotoxicity is not completely understood. Studies have shown that the pathologic fibrotic changes observed with methotrexate treatment are mostly non-aggressive^[14] and

potentially reversible after withdrawal of methotrexate treatment, defined as a period of 6 months or more without administration of methotrexate.^[15] Moreover, a systematic review of liver abnormalities in patients with psoriasis on methotrexate showed that cumulative dose and duration of methotrexate therapy were not associated with fibrosis/cirrhosis on biopsy (as independent variables). It was concluded that methotrexate increases the risk of fibrosis but not in everyone and/or not on its own alone.^[15] Also, a study on 26 years' experience with low-dose long-term methotrexate showed no obvious relation between cumulative dose or duration of methotrexate therapy and the frequency or severity of side effects.^[16] The cumulative dose in the study ranged between 120 and 10,235 mg (mean 3394 mg). In a systematic review^[17] on long term safety of methotrexate monotherapy in patients with rheumatoid arthritis, it was concluded based on 27 prospective studies that the prevalence of raised liver enzymes (more than twice the upper limit of normal) is close to 13% of patients, out of which 3.7% of patients stopped methotrexate permanently owing to liver toxicity (level 2b). In the same article, data based on 10 prospective studies regarding the risk for liver fibrosis/cirrhosis showed an incidence of fibrosis of 2.7% after 4 years of methotrexate (level 2a).^[17] This systematic literature search on methotrexate monotherapy with relatively low-dose use during at least 2 years shows favourable long-term safety. This experience on rheumatoid arthritis patients, though not applicable directly in psoriasis patients, gives some insight. In rheumatoid arthritis the doses are usually continuous, whereas in psoriasis, in a large majority of cases, its use is comparatively shorter in continuity and repeated whenever there is moderate to severe relapse as seen in study by Kumar *et al.*^[10] In another study by Radmanesh *et al.*,^[18] where daily 2.5 mg of methotrexate was compared with weekly 15 mg methotrexate in generalized plaque psoriasis, the liver enzyme abnormalities were less common in those who received methotrexate weekly. This indirectly suggests that a continuous exposure to methotrexate will have a different effect on liver than an intermittent exposure.

Considering safety of methotrexate as seen in above mentioned studies on psoriasis and rheumatoid arthritis, the question of cumulative toxicity has to be addressed on two aspects, a) duration of treatment, and b) total dose used. Further, lack of definite correlation between cumulative dose and hepatotoxicity, and the apparently reversible nature of hepatic changes including fibrosis produced by methotrexate in a large majority, we suggest the concept of continuous cumulative dose of methotrexate, in addition to total cumulative dose.

- Total cumulative dose: Sum of all the doses ever taken by the patient
- Continuous cumulative dose: Sum of all doses taken continuously (weekly) by the patient, or with drug-free period less than 6 months.

We postulate that it is probably the continuous cumulative dose taken by the patient over a period of time that determines the onset and progression of liver damage. In practice, the majority of the adverse effects seen after starting methotrexate are mild and transient, including changes in blood counts, elevation of serum transaminases, and gastrointestinal intolerance. It is well known that liver is an organ with tremendous regenerative capacity.^[19] Therefore, determining the cut-off value of continuous cumulative dose till the point of onset of irreversible liver damage is suggested. This concept is based on clinical experience and the well observed recovery of liver function when methotrexate is used intermittently and it needs proper study to confirm it. Beyond the cut-off value, discontinuation of therapy (drug-holiday/wash-out period) or switching to other therapy depending on the disease activity could be done so as to allow recovery. This could further reduce the risk of methotrexate induced hepatotoxicity and allow safer therapeutics. In addition, the fear of side effects due to past dosage of methotrexate can be alleviated in the mind of the treating dermatologist with a reasonable gap of 6 months. This period of 6 months is though arbitrary, but seems adequate for reversal of drug-induced changes, viz. steatosis and steatohepatitis. As a corollary, we also suggest while taking the drug history, two separate points, (a) continuous cumulative dose, (b) total cumulative dose, should be recorded in context of cumulative dose of methotrexate.

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Conflicts of interest

There are no conflicts of interest.

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