

# World Journal of *Hepatology*

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*WJH* covers topics concerning liver biology/pathology, cirrhosis and its complications, liver fibrosis, liver failure, portal hypertension, hepatitis B and C and inflammatory disorders, steatohepatitis and metabolic liver disease, hepatocellular carcinoma, biliary tract disease, autoimmune disease, cholestatic and biliary disease, transplantation, genetics, epidemiology, microbiology, molecular and cell biology, nutrition, geriatric and pediatric hepatology, diagnosis and screening, endoscopy, imaging, and advanced technology. Priority publication will be given to articles concerning diagnosis and treatment of hepatology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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## Risk of liver disease in methotrexate treated patients

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### Abstract

Methotrexate is the first line drug treatment for a

number of rheumatic and non-rheumatic diseases. It is effective in controlling disease activity and preventing disease-related damage, and significantly cheaper than many alternatives. Use in rheumatoid arthritis infers a significant morbidity and mortality benefit. Methotrexate is generally well tolerated but can cause symptomatic adverse events. Multiple serious adverse events have been attributed to methotrexate, based largely on older reports using high or daily doses, and subsequent case reports and circumstantial evidence. The risk with modern dosing regimens: Lower doses, weekly schedules, and concomitant folic acid is less clear. Clarification and dissemination of the actual risk is crucial so appropriate judgements can be made for patients who may benefit from this treatment. Methotrexate has been associated with a range of liver related adverse events ranging from asymptomatic transaminase elevations to fibrosis and fatal hepatic necrosis. Concern over potential liver toxicity has resulted in treatment avoidance, cessation, or recommendations for investigations which may be costly, invasive and unwarranted. Modern laboratory monitoring of liver blood tests may also influence the risk of more serious complications. The majority of present day studies report an approximate doubling of the relative risk of elevated transaminases in methotrexate treated patients but no increased risk of symptomatic or severe liver related adverse events. In this article we will review the evidence around methotrexate and liver related adverse events.

**Key words:** Liver disease; Transaminases; Fibrosis; Cirrhosis; Methotrexate; Hepatic

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**Core tip:** Methotrexate is a highly effective treatment for many diseases. In rheumatoid arthritis it controls symptoms, prevents damage, and reduces mortality. The risks of methotrexate use are often over-estimated. Methotrexate may result in asymptomatic transaminase elevations. Historically methotrexate has been infrequently associated with more severe liver adverse

events. With modern monitoring and management of liver blood tests serious liver related adverse events related to methotrexate use appear to be avoidable.

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## INTRODUCTION

Methotrexate, formerly known as amethopterin, is one of several folic acid antagonists originally utilised in children with acute leukaemia<sup>[1]</sup>. Successful use in adults, and children with other tumours followed shortly thereafter<sup>[2]</sup>. Use has increased dramatically since that time both in volume and in scope; methotrexate is now commonly used in the treatment of a wide range of malignant and non-malignant diseases<sup>[3]</sup>. The importance of methotrexate as a treatment option is emphasised by its prominent place on the World Health Organisation's List of Essential Medicines, a list of those critical basic medications which should be available to every healthcare system<sup>[4]</sup>. Indeed methotrexate is arguably one of pharmaceuticals greatest success stories, a medication which has found indications widely disparate from its original intention. Methotrexate is highly effective for a range of diseases which had been difficult to treat prior to its introduction, including rheumatoid arthritis, psoriasis, and Crohn's disease<sup>[3]</sup>. Methotrexate has transformed the management of rheumatoid arthritis (RA), dramatically altering the disease course, patient's quality of life, and reducing RA-related mortality<sup>[5,6]</sup>. Modern reviews and meta-analyses show methotrexate has similar or better efficacy to other available agents including biologic therapies<sup>[7]</sup>. No treatment is superior to methotrexate monotherapy for inhibiting radiographic progression, but combination therapy is superior for methotrexate failures<sup>[6]</sup>.

Despite this success, the potential adverse events associated with methotrexate attract considerable attention. Several reasons account for this, mainly stemming from notable toxicity with early use employing daily or high-dose therapeutic regimes. The translation of the adverse events associated with oncological dosing to those of modern low-dose methotrexate regimes for the treatment of autoimmune disease should not be automatic. Recent studies suggest methotrexate carries a similar risk of adverse events and toxicity to other agents, but combination therapy may have a higher rate of infection and liver-related adverse events<sup>[6-11]</sup>.

## METHOTREXATE RELATED ADVERSE EVENTS

The first papers on methotrexate use detailed the

acute toxicity associated with high dose therapy for cancer, and later long-term sequelae<sup>[1,12]</sup>. Later studies in non-malignant disease showed similar problems with high dose therapy but not so with lower doses, weekly regimens and concomitant use of folic acid<sup>[13,14]</sup>. The adverse events associated with methotrexate use can be divided into two broad subsets; those symptomatic but rarely life-threatening adverse events experienced by patients, and those rarely symptomatic (at least until the latter stages) but potentially life-threatening adverse events which require careful monitoring by physicians.

Symptomatic adverse events associated with methotrexate are reported relatively commonly. These include symptoms such as nausea, headaches, fatigue, mucositis, and hair loss<sup>[3]</sup>. For the majority of patients they are an acceptable accompaniment to their treatment, and a minor inconvenience compared to their previously debilitating disease symptoms. These adverse events are common with many medications and also shared by many of the diseases which methotrexate is used to treat. This can make it difficult in many cases to know if methotrexate is definitively the cause of the symptoms the patient is experiencing. However, distinguishing the precise source of the symptoms is often not needed, provided they can be tolerated or managed with symptomatic interventions. The occurrence rate using modern dosing schedules appear similar to the placebo arm in some clinical trials yet the perception of toxicity persists, and often apportioned to methotrexate<sup>[15]</sup>. More rarely patients will ultimately be unable to tolerate methotrexate due to intractable symptomatic adverse events leading to drug cessation.

The more serious and infrequent adverse events attributed to methotrexate use present more of a clinical dilemma. The evidence linking many of these events to methotrexate use is sometimes weak and circumstantial. Methotrexate has been utilised in clinical practice for a considerable period and the origin of the attribution of many of its associated adverse events lies in older studies which used daily dosing, or much higher doses for example 3 mg/kg per week, or 100 mg/wk<sup>[1,2,12-14]</sup>. More recent reports of isolated cases, case series, and observational studies where established beliefs may bias the findings and/or conclusions are inconclusive. There is no doubt that very high doses are toxic to the marrow, gingiva, and long-term the liver, hence the introduction of lower dose, less frequent schedules<sup>[1,12,13]</sup>. Examination of these potential risks using modern regimens requires thorough exploration in well designed and performed studies in order to establish robust evidence for what the risks are. Adverse events falling into this category include cytopenias, interstitial lung disease (or methotrexate pneumonitis), and indeed methotrexate related liver disease.

Methotrexate-induced lung disease is a good example, an entity widely believed to be common, serious and potentially fatal<sup>[3]</sup>. Incorrectly apportioning

blame on methotrexate can result in two potential risks to the patient: (1) denying them an effective drug; and (2) delaying the appropriate investigation and treatment of the real cause of their symptoms. Recent studies show this is in fact a rare occurrence and may not exist at all<sup>[8,9,11]</sup>. Furthermore, it appeared that any increased risk was likely due to a small increase in respiratory infections with methotrexate use, rather than interstitial lung disease<sup>[8]</sup>. This knowledge has the potential to significantly change clinical practice as cessation of methotrexate frequently occurs as a knee jerk reaction to any cough or dyspnoea.

The nature of liver disease related to methotrexate is similarly complex. It is well established that patients treated with methotrexate may develop abnormal liver blood tests, but the long-term consequences of modern dosing regimens in people with normal renal function are unknown<sup>[16]</sup>. Many such patients not treated with this agent can develop abnormal liver enzymes, potentially confounded by alcohol use, non-steroidal anti-inflammatory drugs, non-alcoholic fatty liver disease, and both related and unrelated *de novo* liver diseases<sup>[16,17]</sup>. Patients prescribed methotrexate have liver blood tests performed at intervals far in excess of the general population so the significance of minor or transient abnormalities in these test results remain uncertain<sup>[18]</sup>. This is of course a vital issue regarding what action, if any, should be taken when faced with an abnormal liver blood tests, as it clearly depends on what it signifies. Cessation of an effective drug due to a transient unrelated transaminase elevation is potentially harmful to patients, as is continuation of that agent in the face of a developing significant drug induced liver injury<sup>[19]</sup>.

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## EPIDEMIOLOGY OF METHOTREXATE RELATED LIVER DISEASE

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Reported rates of liver blood abnormalities during methotrexate treatment vary. Initial reports of hepatic toxicity, and death from hepatic toxicity, as well as cumulative incidences of 48.9% for elevated transaminases and 16.8% for transaminases elevated more than twice the upper limit of normal have been reported<sup>[12,16,20]</sup>. Hepatic toxicity is not universal with prolonged chemotherapeutic regimes and some demonstrated normal liver histology despite several months of therapy<sup>[12]</sup>. The reported rates of hepatic toxicity appear to have decreased progressively over time, likely related to refinements in dosing and monitoring strategies<sup>[13]</sup>. A 2009 systematic review of observational studies up to that time reported that elevated transaminases were found in 20% of patients treated with methotrexate for 1 year, with transaminases greater than twice the upper limit of normal in 13%<sup>[21]</sup>. Present day monitoring strategies and treatment regimens appear to have significantly lower risks than those which have been historically

associated with methotrexate use. Two high quality recent studies reported elevated transaminases in 22% but with as little as 1% having transaminases greater than twice the upper limit of normal<sup>[22,23]</sup>. A higher rate occurs when used in combination with other therapies<sup>[6,7,17]</sup>. A number of other risk factors for hepatotoxicity have been identified including obesity and hypercholesterolaemia<sup>[17]</sup>.

In contrast to the frequently reported transaminase elevations in methotrexate treated patients, reports of serious adverse liver outcomes in appropriately treated patients are harder to find in more recent times. An estimated 5-year risk of 1/1000 patients is likely to be an over-estimate based on the limited histological information available<sup>[19]</sup>. A study reported rates of mild liver fibrosis, severe fibrosis and cirrhosis based on liver biopsies performed before and after methotrexate use. Rates prior to methotrexate use were 9.1%, 0% and 0.3%. The corresponding results after methotrexate use were 15.3%, 1.3% and 0.5% respectively<sup>[16]</sup>. A literature review on biopsy proven liver abnormalities found that 3% of methotrexate treated patients developed histological abnormalities after one year of treatment. Importantly however, when the results were confined to those controlled studies of patients with baseline biopsies prior to the introduction of methotrexate no biopsy proven histological abnormalities were identified after 4 years of treatment<sup>[21]</sup>.

A recent meta-analysis of clinical trials demonstrated a cumulative incidence of liver adverse events of 11.2% in methotrexate treated patients compared to 6.3% in patients on other treatments<sup>[10]</sup>. Calculated incidence rates from this were 20/100 patient-years in methotrexate treated patients and 9/100 patient-years in patients on other treatments<sup>[10]</sup>. The majority of these adverse events were low grade liver enzyme elevations with an incidence rate of 16/100 patient-years in methotrexate treated patients compared to 8/100 patient-years in others<sup>[10]</sup>. The incidence rate of major liver enzyme elevations was 4/100 patient-years in methotrexate treated patients and 1/100 patient-years in other patients, which is concerning<sup>[10]</sup>. Reassuringly more serious liver complications did not occur in any methotrexate treated patients in these studies<sup>[10]</sup>. The short duration of clinical trials is universal, the mean duration of studies in this meta-analysis were 47 wk, therefore data from long-term registries with robust unbiased analyses are required.

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## PATHOGENESIS

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Any discussion of the mechanisms of potential methotrexate toxicity must begin with an appreciation of our understanding of methotrexate's mode of action. It is here that we reach a major impediment, though perhaps an informative one. We simply do not fully understand how methotrexate, and in particular low dose methotrexate, achieves its clinical effects<sup>[11]</sup>.

The oft quoted explanation that methotrexate is a dihydrofolate reductase inhibitor, while of course true, does not fully explain either the clinical efficacy or potential toxicities which we see with this agent. Low dose methotrexate has a multitude of biochemical effects at the most basic level including influences on T-cell apoptosis, cell proliferation and cytokine production<sup>[24]</sup>. Despite methotrexate's long historical use this remains an active area of research, in part due to a certain neglect of exploration of these pathways in the past, and in part due to the increasingly evident complexities of the effects of methotrexate.

A reduction in hepatic folate stores and toxicity due to a local folate deficiency is one possible toxic effect of methotrexate on the liver. A definitive relationship between folate depletion and hepatotoxicity has not been experimentally confirmed. However folic acid supplementation has been associated with a lower incidence of elevated transaminases<sup>[25]</sup>.

Early animal and clinical studies of high dose methotrexate demonstrated the development of liver fibrosis and cases of cirrhosis but subsequent low dose weekly regimens failed to demonstrate a similar effect<sup>[13,26]</sup>.

The histological appearance of the liver in methotrexate treated patients is generally graded according to the Roenigk classification system<sup>[27]</sup>. The system progressively classifies changes from early fatty infiltration and pleomorphism, through inflammation and necrosis, varying degrees of fibrosis and ultimately cirrhosis. Importantly none of these findings are unique to methotrexate and can be seen in other disease processes.

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## LIVER ADVERSE EVENTS WITH ANALAGOUS MEDICATIONS

One of the key tenets of causation is specificity<sup>[28]</sup>. If patients given alternative agents to methotrexate do not develop liver disease than this facet of evidence would strongly implicate methotrexate as a causative agent. If they do however, than this, while be no means definitive, raises a potential warning flag that we should reconsider our hypothesis. In inflammatory bowel disease thiopurines (azathioprine and 6-mercaptopurine) are the most commonly used alternatives to methotrexate. Hepatotoxicity due to thiopurines has been reported in 10%-17% of patients<sup>[29,30]</sup>. Risk factors for thiopurine induced hepatotoxicity appear to be similar to methotrexate with age, obesity, and concomitant medications implicated<sup>[29,30]</sup>. In randomised controlled trials comparing thiopurines with methotrexate hepatotoxicity appears to occur at a similar rate<sup>[31-33]</sup>. Leflunomide is often used in rheumatoid arthritis as an alternative to methotrexate and has been associated with a variety of similar complications to methotrexate. Pulmonary disease in particular has been associated with both agents,

however our work has illustrated that leflunomide may not be causative in this regard<sup>[34]</sup>. Leflunomide has also been associated with transaminase elevations with a similar frequency to methotrexate with elevations in 17% and elevations greater than twice the upper limit of normal in 1%-2%<sup>[22]</sup>. Combining both agents appears to have additive effects with transaminase elevations seen in 31% and those greater than twice the upper limit of normal in 5%<sup>[7,22]</sup>. Sulfasalazine, another agent used in similar settings also appears to show similar effects to leflunomide (and to methotrexate)<sup>[7]</sup>. Anti-tumour necrosis factor alpha agents have been reported as a relatively frequent cause of mild transaminase elevations, however, as with methotrexate, significant elevations occur relatively infrequently and are reported in less than 1% of patients<sup>[35]</sup>. Again similar to methotrexate, serious liver adverse events seen in association with these agents appear infrequent<sup>[36]</sup>.

All of this begs the question, what is the rate of transaminase elevations in a healthy population? Most laboratory tests define normality as lying within 2 standard deviations of the mean in a Gaussian distribution. In a normally distributed sample approximately 95% of values will lie within 2 standard deviations of the mean. Therefore 2.5% of the population will have transaminase levels above the normal range and 2.5% will have transaminase levels below the normal range. The importance of this is that the rate of "abnormality" is not zero and never can be if normality is defined in this manner. This must be born in mind in evaluating any reported rate of abnormalities. Since studies show a higher incidence of liver enzyme abnormalities and since there is well-documented hepatotoxic potential, understanding the relationship between the mild enzyme rises and long-term outcomes is necessary, but unclear at this time.

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## EFFICACY OF METHOTREXATE IN AUTOIMMUNE LIVER DISEASE

Methotrexate is a well-established treatment for a wide variety of autoimmune diseases<sup>[3]</sup>. Given the concern over the association between liver adverse events and methotrexate use it is perhaps understandable that the evaluation of methotrexate efficacy in autoimmune liver diseases has proceeded more slowly than in other disciplines. However the treatment depends on the cause and early studies in malignancy showed dramatic improvements in hepatic manifestations, coupled with longer term toxicity in some cases<sup>[1,12]</sup>.

Primary biliary cholangitis (previously primary biliary cirrhosis) (PBC) is perhaps the liver disease with the best established evidence for an autoimmune basis. PBC is characterised by early lymphocytic infiltration and granulomatous inflammation progressing to chronic damage and scarring resulting in the ultimate clinical manifestations of the disease. PBC is more common

in a variety of rheumatic diseases including Sjogren's syndrome, rheumatoid arthritis, and a number of other connective tissue diseases<sup>[37]</sup>. However, the full importance of autoimmunity in the disease pathogenesis has been questioned given the apparent lack of response of PBC to many traditional immunosuppressants<sup>[38]</sup>. Ursodeoxycholic acid is recommended as the first-line treatment option in PBC, however even its benefits are at best modest and a substantial number of patients do not respond<sup>[39-43]</sup>. There is therefore a significant unmet therapeutic need for safe and effective treatment options for PBC.

Given the suggested autoimmune basis of the disease and the proven efficacy of methotrexate in a number of the conditions associated with PBC it was perhaps a natural development to progress to studying this agent in PBC. The ultimate trigger for the initial use of methotrexate in PBC however was its apparent efficacy in early studies in primary sclerosing cholangitis (PSC)<sup>[44]</sup>. Methotrexate has been demonstrated to improve liver blood tests and liver histology in a long-term open label study of PBC patients with an inadequate response to ursodeoxycholic acid<sup>[45]</sup>. Despite these apparent benefits the more widespread use of methotrexate in these diseases is difficult to recommend given the lack of evidence for improvements in important outcomes such as mortality and progression to transplantation<sup>[46]</sup>. Of even greater difficulty is the lack of convincing evidence for efficacy in the randomised controlled trials of methotrexate in PBC<sup>[38,47]</sup>. The only commonality across the studies of methotrexate in PBC has been a lack of evidence of adverse events, including transaminase elevations<sup>[38,45]</sup>. This picture is complicated by the inherent difficulties in studying treatment efficacy in PBC, a disease with widely variable outcomes, a prolonged course prior to the development of end-stage disease, and a lack of definitive surrogate markers of disease progression. It has been suggested that another aspect of the difficulty may be related to subsets of responders and non-responders among patients with PBC<sup>[47]</sup>. While the use of methotrexate in PBC remains controversial, the lack of alternative treatment options and the good evidence regarding the drug's safety in this patient population may justify a therapeutic trial.

Primary sclerosing cholangitis (PSC) is in many ways even more challenging than PBC. In contrast to PBC, PSC is not a classical immune disease, lacking characteristic autoantibodies, but does certainly have an immune component, with evidence of T-lymphocyte driven inflammation<sup>[48]</sup>. The use of immunosuppressants in PSC has not demonstrated convincing evidence of favourable responses<sup>[49]</sup>. Methotrexate was first used in PSC in the 1980's with initial reports of good responses with early treatment initiation<sup>[50,51]</sup>. Results from a subsequent randomised controlled trial and case series were not encouraging however with evidence of improvement only in alkaline phosphatase levels<sup>[52,53]</sup>.

The utility of methotrexate in cholestatic liver

diseases remains uncertain. Based on the clinical trials in these diseases however we can obtain some reassurance about the overall liver safety of methotrexate given the lack of evidence of significant adverse events in this group predisposed to liver adverse outcomes.

## META-ANALYSIS

In view of the ongoing uncertainty over the risk of liver disease in methotrexate treated patients we recently performed a comprehensive meta-analysis of randomised controlled trials evaluating this issue<sup>[10]</sup>. We choose to limit our assessment to double-blind randomised controlled trials in order to eliminate the potential bias, both overt and covert, inherent in any situation in which a physician knows that a patient is prescribed, or potentially prescribed methotrexate<sup>[54]</sup>. Pre-existing perceptions among physicians regarding the liver toxicity of methotrexate are a major confounder in many of the previous assessments of methotrexate toxicities. An additional advantage of this methodology is that the very nature of a randomised controlled trial provides a large number of patients with similar clinical and demographic characteristics as a control group. Of course randomised controlled trials, and meta-analyses of such trials, have their own inherent limitations, including issues with generalizability to heterogeneous real world patient populations, and a limited period of follow-up<sup>[55]</sup>. Hence it is important to interpret such studies in conjunction with other forms of evidence such as that from observational studies<sup>[21]</sup>.

In our meta-analysis we included randomised controlled trials in which patients were prescribed methotrexate for rheumatoid arthritis, psoriasis, psoriatic arthritis, or inflammatory bowel disease<sup>[10]</sup>. A total of 32 studies with 13177 participants were included in the analysis, 6877 of these were prescribed methotrexate and 6300 comparator agents. The majority of included studies used active comparators to methotrexate, predominantly synthetic disease-modifying antirheumatic drugs (DMARDs) or biologic agents; there were also 5 studies with placebo comparators. The trial durations ranged from 24 to 104 wk with a mean duration of 47 wk. Liver adverse events were common in both cohorts, the cumulative incidence was 11.2% in methotrexate treated patients and 6.3% in the comparator group. This translated to an incidence rate of liver adverse events of 20/100 patient-years in methotrexate treated patients compared to 9/100 patient-years in the comparators giving an attributable risk of 11/100 patient years in methotrexate treated patients.

Our meta-analysis demonstrated that methotrexate use was associated with an increased relative risk (RR) of liver adverse events in this population of 2.19 (95%CI: 1.73-2.77). Additionally methotrexate use was associated with an increased risk of transaminase

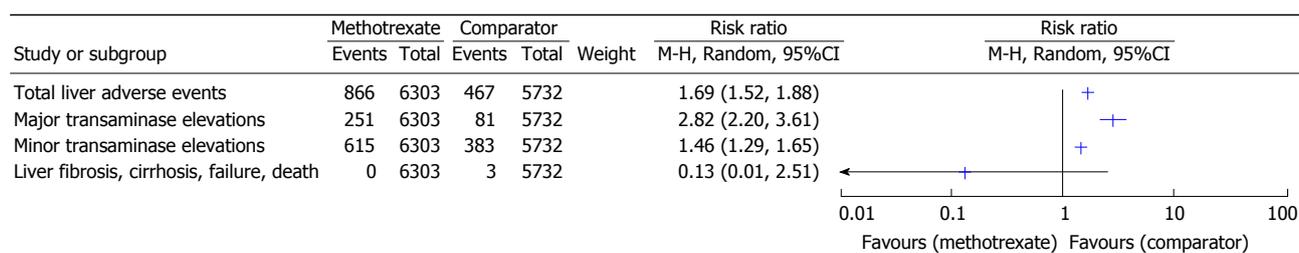


Figure 1 Risk of liver adverse events with methotrexate use.

elevation both less than or equal to three times the upper limit of normal, RR = 2.16 (95%CI: 1.67-2.79) and transaminases greater than three times the upper limit of normal, RR = 2.63 (95%CI: 1.90-3.64). The consistency in the increase risk across the various categories demonstrated by this portion of the meta-analysis was concerning, particularly given the utility of transaminases in predicting drug induced liver injury. We went on to analyse the hard endpoint of more serious liver outcomes, defined as hepatic failure, hepatic fibrosis, cirrhosis, or death due to liver disease. This was far more reassuring; methotrexate was not associated with any increased risk in these outcomes, RR = 0.12 (95%CI: 0.01-1.09). Indeed while not reaching statistical significance there was a strong trend towards less of these serious outcomes in methotrexate treated patients. The reasons why methotrexate could be associated with a possible reduction in serious outcomes but an increase in transaminase elevations are not immediately apparent. Methotrexate has shown potential efficacy in treating some autoimmune liver diseases<sup>[45,49]</sup>. Methotrexate induced transaminase elevations frequently prompt further investigations, potentially identifying concomitant diseases at an earlier stage, allowing earlier treatment and thus less progression to the hard endpoints evaluated in this outcome. However caution is required as only having surrogate measures of hepatic toxicity (transaminase elevations) with very few serious events is another major limitation. The main findings of the meta-analysis are summarised in Figure 1.

## MANAGEMENT OF ABNORMAL LIVER BLOOD TESTS IN METHOTREXATE TREATED PATIENTS

The management of abnormal liver blood tests in patients treated with methotrexate is a common clinical query. As with any management plan the key first step is in ensuring the correct diagnosis. Abnormal liver blood tests should never be presumed to be due to methotrexate. The available evidence indicates that methotrexate related liver adverse events are rarely serious, particularly in the short term, while many other causes of abnormal liver blood tests may be. An evaluation for other potential causes should follow identical pathways and similar rigor to that

applied to a patient who is not taking methotrexate. This investigative approach has been covered in detail elsewhere<sup>[56]</sup>.

If after exhaustive investigation no cause other than methotrexate is identifiable than the treatment approach recommended in guidelines depends on the degree of transaminase elevation. The baseline transaminase levels prior to methotrexate institution are also important; a previously elevated transaminase level that hasn't changed following institution of methotrexate is unlikely to need further intervention. The threshold for immediately interrupting methotrexate use differs by the respective guideline, however levels greater than 3 times the upper limit of normal are often used<sup>[57]</sup>. Persistent lower grade elevations may also require intervention particularly if the trend is for a progressive increase in the transaminases<sup>[18,57]</sup>.

Widely differing recommendations regarding the indication for a liver biopsy in methotrexate treated patients exist<sup>[58-60]</sup>. Increasingly a welcome move away from the routine performance of liver biopsies in methotrexate treated patients has accompanied a wider appreciation of the relative safety of this agent. Liver biopsy is the gold standard investigation as it allows direct assessment of liver histology, however it is imperfect and has a relatively high sampling error rate of 20%-30%<sup>[61]</sup>. In addition it is an invasive procedure, and like any such procedure carries with it risks of morbidity and indeed mortality; therefore it should only be performed when the results will be clinically useful<sup>[59]</sup>. In our practice a liver biopsy is infrequently clinically indicated and when it is performed is most commonly to investigate for another potential cause rather than investigation of suspected methotrexate induced hepatotoxicity.

Alternative methods of assessing for liver toxicity including procollagen III aminopeptide, multibiomarker scores, and transient elastography in our opinion have potential but remain experimental and we do not recommend their use in routine clinical practice at the present time<sup>[62]</sup>. A proposed approach to suspected methotrexate hepatotoxicity is outlined in Table 1. All of the suggestions in this table must be interpreted and modified in the light of the clinical scenario.

## CONCLUSION

Methotrexate is a highly effective treatment for a

**Table 1 Management of suspected methotrexate toxicity**

Transaminase monitoring	Commencing Adjusting dose Stable dose	Every 2 wk Every 2 wk Every 12 wk
Elevated transaminases	New persistent elevation New elevation greater than 3 times upper limit normal	Reduce methotrexate, investigate Withdraw methotrexate, investigate, methotrexate may be restarted after normalisation
Liver biopsy	Indication	Investigation of other potential causes of elevated transaminases Very rarely for confirmation of methotrexate induced toxicity

broad range of diseases. Concern over potential adverse events has limited the use of methotrexate in certain populations. Robust evidence of the true risk of the majority of methotrexate associated adverse events with modern dosing regimens in patients with normal renal function have been lacking. Methotrexate use is associated with an increased risk of elevated transaminase levels; however the risk of an increased risk of serious liver adverse events with modern methotrexate monitoring protocols appears to be extremely low at present. Long-term follow-up studies of patients with mild transaminase elevations are needed. Large increases are rare, should be taken seriously, and the medication stopped. Physicians and patients should be comfortable using methotrexate where clinically indicated.

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