METHOTREXATE (MTX) is probably the most commonly used disease-modifying anti-rheumatic drug (DMARD)/second-line agent in rheumatoid arthritis (RA). Further, its use is increasing in other rheumatic diseases. Between 1992 and 1996, over 400 articles about MTX and RA were published, indicating both its popularity and the research ongoing in its use (Medline Search, December 1996). This paper attempts to winnow through much of these data for the most practical and helpful articles. The following areas will be reviewed: mechanism of action; practical clinical pharmacology; efficacy; toxicity.

MECHANISM OF ACTION

While MTX inhibits dihydrofolate reductase (DHFR), it is intracellularly metabolized to polyglutamates which inhibit both DHFR and other folate-dependent enzymes, such as thymidylate synthetase and 5-aminoimidazole-carboxamide-ribonucleotide-transformylase (AICAR) [1–3]. Cronstein and Merrill [4] recently showed that MTX increases adenosine release, inhibits adenosine deaminase and, finally, inhibits neutrophil chemotaxis. This mechanism probably acts through MTX's inhibition of AICAR at nanomolar concentrations [2]. Other potential mechanisms of action include normalization of low interleukin-2 (IL-2) through an effect on polyamine synthesis, reduced IgM-rheumatoid factor (RF) production, decreased IL-1 production, secretion or binding, and decreased IL-6 activity [2, 4].

Summary

While immunosuppressive effects are clearly possible as mechanisms of action for MTX, the anti-inflammatory effects are likely to be particularly important at the doses used in RA.

PRACTICAL CLINICAL PHARMACOLOGY

Absorption

While the mean absolute bioavailability of MTX is 0.73, significant variability exists, ranging from 0.25 to 1.0 after 10 mg/m² MTX [5]. Compared to i.m. treatment, the mean relative bioavailability of a MTX solution was 0.87, that of the MTX tablet was 0.85, and that of MTX s.c. was 0.92. Once again, however, there was significant within-dosage form variability, ranging from 0.58 to 1.13 for the solution [6, 7]. On a practical basis, this means that patients who do not respond to oral tablet dosing may be switched to solution or s.c. therapy with the hope that a better response may occur.

Although initial data indicated the possibility that food affects MTX absorption, more recent data do not corroborate such an effect [7].

Summary. Absorption is generally good, but variable, and switching from oral to s.c. or i.m. injection can sometimes improve response.

Distribution and metabolism

As MTX albumin binding is 35–50%, drug displacement reactions are unlikely to be important [5].

Both MTX and 7-OH-MTX are polyglutamated after entering cells and accumulate therein as active DHFR inhibitors [8]. The accumulation of MTX polyglutamates intracellularly (e.g. in the liver) makes this a potentially significant contributor to this drug's mechanism of action or toxicity [9, 10].
MTX also accumulates in bone marrow precursors and gastrointestinal cell precursors, one would expect these cells to be vulnerable to MTX toxicity [11].

Although the ratio of synovial fluid to plasma concentrations approximates one, synovial membrane and bone concentrations are ~10 times plasma concentrations [5,12]. Despite this, plasma kinetics appear unaltered, making it unlikely that intra-articular MTX will yield an advantage over systemic therapy [12,13].

Summary. An understanding of MTX’s distribution and metabolism can help guide rational therapy with this drug.

CLEARANCE

MTX clearance decreases by a factor of approximately three as age increases from 7 to 15 yr, explaining why some children require larger doses than adults [14]. Further, both renal and metabolic MTX clearance decrease at night (by 50 and 14%, respectively), at least in children, supplying a rationale for changes in response (either efficacy or toxicity) with changes in dosing regimens [15].

The elimination half-life of MTX approximates 7 h, although some patients (17% in one study) have half-lives as long as 26 h [5]. Total MTX clearance is 80–90 ml/min/m², with renal tubular mechanisms playing the major role in MTX elimination [16,17]. Since renal clearance is MTX’s principal route of elimination, patients with renal failure should exhibit decreased overall MTX clearance. Compared with a mean renal clearance of 84.6 ml/min/m² in normal RA patients, renal clearance was 2.8 ml/min/m² in patients with severely impaired renal function [5,18]. Since MTX has low protein binding and high tissue distribution, haemodialysis or peritoneal dialysis would not be a very effective way to clear the drug [18]. On the other hand, biliary excretion may account for up to 30% of MTX excretion, thus giving patients with renal failure a ‘safety valve’ in which increasing biliary excretion may help compensate for decreasing renal excretion [19]. Furthermore, the biliary excretory route can be utilized to increase MTX blood clearance by using cholestyramine [20]. In contrast, probenecid can increase the MTX area under the plasma concentration vs time curve (AUC) by 25% in oncological doses [21]. Since neither the cholestyramine nor the probenecid interactions have been tested in RA patients, this information needs to be used with some care.

MTX–non-steroidal anti-inflammatory drug (NSAID) interactions have generated both significant interest and some controversy. Kinetically, aspirin consistently decreases both total and renal MTX clearance [22]. In contrast, no significant changes in MTX kinetics has been documented after etodolac, flurbiprofen or naproxen (despite some controversy with respect to naproxen) [22]. Ibuprofen has been associated with both increased MTX clearance and unchanged MTX clearance, while sulindac has affected metabolic but not renal clearance of MTX [22].

Clinically, many NSAIDs have been associated with case reports of clinically important adverse events after MTX [22]. These include: leucopenia after aspirin; gastrointestinal (GI) toxicity after azapropazole, indomethacin and naproxen; bone marrow hypoplasia or aplasia after diclofenac, ketoprofen and azapropazole; and renal failure after diclofenac, indomethacin and ketoprofen [22]. However, these interactions must be rare as Rooney et al. [23] found no difference in toxicity among 12 patients treated with MTX and aspirin as compared to 22 patients treated with MTX and other NSAIDs over 12 months. Although rare, serious NSAID–MTX adverse events can occur with any NSAID, including aspirin.

Summary

(a) Since renal clearance is the principal mechanism of MTX excretion, the use of MTX in renal insufficiency is hazardous, although not impossible.

(b) Since bile may, occasionally, account for a significant portion of MTX excretion, this pathway can be exploited to decrease MTX blood concentrations in the case of overdose, by using cholestyramine.

(c) In contrast, probenecid, which inhibits both renal and biliary excretory pathways, may be a way to improve the cost-effective use of MTX, although this has not been formally tested.

(d) Clinically important toxicities from aspirin and NSAID effects on MTX are rare, are not different for aspirin vs other NSAIDs, and are not well reflected by kinetic studies.

Other interactions

There have been at least seven documented cases of pancytopenia or other bone marrow suppression after the combined use of MTX and trimethoprim–sulphamethoxazole or trimethoprim [22,23]. The mechanism of this rare interaction is not well understood.

Likewise, a potential interaction between MTX and corticosteroids indicates that patients on long-term corticosteroids may have as much as a 20% decrease in MTX clearance, accompanied by a 24% decrease in renal clearance [24]. This potentially interesting interaction has been documented in a study of somewhat unconventional design and will need corroboration.

While the addition of hydroxychloroquine to MTX results in fewer aspartate aminotransferase elevations in an observational study, this has not yet been corroborated in a prospective controlled study and it is also not clear that decreasing the frequency or degree of AST elevations is protective against cirrhosis [25].
A positive interaction between folic acid and MTX shows that the addition of 1 mg/day folic acid decreases MTX-induced toxicity, particularly with respect to stomatitis, and GI side-effects [25–27].

**Summary**

Practically, these data indicate that one should be somewhat more careful when using trimethoprim-sulphamethoxazole combinations or trimethoprim in MTX-treated patients with urinary tract infections, and that folic acid can (and perhaps should) be used frequently to decrease MTX toxicity. The data on corticosteroid effects are not strong enough, in my view, to warrant a change in therapy and the use of hydroxychloroquine with MTX to decrease AST elevations is common, although its verity and long-term effectiveness are not proven.

**EFFICACY**

**Placebo-controlled studies**

Table I outlines the placebo-controlled studies of MTX for the treatment of RA [28–32]. The study of Anderson *et al.* [30] was a 13 week cross-over study examining i.m. rather than oral MTX. The patients treated with placebo had more swollen joints than the MTX group at baseline (26 vs 16), but the 9.1 mean swollen joint count decrease in the MTX group was statistically more than the 6.6 mean swollen joint count decrease among the placebo-treated patients. The mean change in erythrocyte sedimentation rate (ESR) was also more (24 mm in the MTX group vs 3 mm in the placebo-treated patients). The study of Furst *et al.* [32] had a parallel design and showed a dose-related effect, with 5 and 10 mm/m² being more effective in general than placebo. However, this study included a 12 day hospitalization during which all patients improved. Response was related to this improved post-hospitalization point, so placebo patients worsened (and returned to pre-hospitalization activity) while others remained stable (5 mg/m²) or improved further (10 mg/m²). The major effect occurred at 10 mg/m² (an average of ~17.5 mg/week) where a >50% improvement occurred in 6/11 measures. A dose response was demonstrated for 5–11 efficacy measures and for GI toxicity. Forty-eight patients in the study of Thompson *et al.* [31] used i.m. MTX (10 or 25 mg) vs i.m. placebo for only 6 weeks followed by collapse of the placebo patients into one of the active treatment arms for another 6 weeks. In essence, this was a cross-over trial, from placebo to either 10 or 25 mg MTX in ~16 patients. It showed improvement relative to placebo in all indices. The Weinblatt *et al.* study [29] was a cross-over study using oral MTX and allowing dose escalation from 7.5 to 15 mg a week. Joint swelling count among the MTX-treated patients improved more than placebo, whereas there was no difference between drug and placebo for joint tenderness. The study of Williams *et al.* [28] was by far the largest, comprising 189 patients. It was performed early in the use of MTX and required discontinuations of drug for mild elevations in liver function tests. Hence, 80 patients discontinued the drug, partially mitigating its size. Thirty-one per cent of patients discontinued MTX secondary to ‘drug toxicity’ as compared to 11% on placebo. In contrast, 21% of placebo patients discontinued the study secondary to ineffectiveness compared to only 3% of MTX-treated patients.

The meta-analysis of Tugwell *et al.* [33] demonstrated a 26–39% improved joint tenderness count and pain visual analogue scale (VAS), and 27% decreases in joint swelling counts and ESR compared to placebo.

**Positively controlled and combination trials**

Six double-blind positively controlled trials used MTX (Table II) and another five trials used MTX in combination (Table III) [35–44]. Three trials compared MTX vs gold sodium thiomalate (GST) [35, 37, 38]. Morassut *et al.* [38] used p.o. MTX (12.5 mg weekly) vs i.m. GST over 26 weeks. In general, the GST and MTX were equally effective and equally toxic, although there were sometimes trends for GST to improve more than MTX. For example, all nine efficacy measures improved statistically after GST, while seven of nine improved on MTX. The authors rightfully pointed out that the power to tell differences between treatments was small (there were only 17 patients on GST and 18 patients on MTX), so they declared the treatments equal. Six patients discontinued gold secondary to toxicity and three dis-
continued MTX for this reason. It is worth pointing out that this trial compared oral MTX at a relatively lower dose (12.5 mg) to standard doses of GST (50 mg). The data of Weinstein et al. [37] have appeared only in abstract. This group compared 25 mg i.m. MTX to 50 mg GST in two small groups of nine patients. Both substances were apparently equally effective, although MTX caused more elevations of liver enzymes. This study was never published as a full manuscript, so the details of any differences between this relatively high dose of MTX and gold have not become available. Rau et al. [35, 45] examined 15 mg i.m. MTX (a more standard dose) vs 50 mg of GST. Their trial is particularly useful as it compared radiological outcomes. The patients in this trial may have been slightly different from other studies as patients in this trial had ‘non-deforming’ RA in order to allow a more clear radiological assessment. Only 36 of 52 patients in the GST group completed the 1 yr study and only 34 of 50 patients in the MTX group did the same. This study showed that MTX and GST affected radiological progression equally. Weinblatt et al. [36] completed a large study comparing oral gold (auranofin) at 6–9 mg a day to oral MTX at 7.5–15 mg a day. During this 36 week study MTX was more effective than auranofin in all 10 variables for all patients remaining in the trial for at least 12 weeks. Four

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### TABLE II

<table>
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<tr>
<th>Ref.</th>
<th>Drugs</th>
<th>N</th>
<th>Duration (weeks)</th>
<th>Indicator variable</th>
<th>Efficacy</th>
<th>Toxicity</th>
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<td>35 Rau et al.</td>
<td>i.m. GST 50</td>
<td>34</td>
<td>52</td>
<td>X-ray*</td>
<td>MTX = GST</td>
<td>MTX ≤ GST</td>
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<tr>
<td>37 Weinstein et al.</td>
<td>i.m. MTX 15</td>
<td>44</td>
<td>–</td>
<td>–</td>
<td>SWJC</td>
<td>MTX = GST</td>
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<td>26</td>
<td>ESR</td>
<td>MTX = GST</td>
<td>MTX = GST</td>
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<tr>
<td>39 Hamdy et al.</td>
<td>p.o. GST 10</td>
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<td>24</td>
<td>ESR</td>
<td>MTX = AZA</td>
<td>MTX = AZA</td>
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<td>40 Williams et al.</td>
<td>p.o. MTX 7.5–15</td>
<td>67</td>
<td>31</td>
<td>–</td>
<td>–</td>
<td>MDTX = 50% in 3 of 4 variables</td>
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</tbody>
</table>

GST, gold sodium thiomalate; p.o., oral; SWJC, swollen joint count; ESR, erythrocyte sedimentation rate; AF, auranofin; AZA, azathioprine.

*Radiograph.

### TABLE III

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Drugs (mg)</th>
<th>N</th>
<th>Duration (weeks)</th>
<th>Indicator variable</th>
<th>Efficacy</th>
<th>Toxicity</th>
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<td>43 Ferraz et al.</td>
<td>MTX 7.5 MTX 7.5 + CO 250</td>
<td>34</td>
<td>24</td>
<td>JTC</td>
<td>Combo &gt; MTX</td>
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<td>44 O’Dell et al.</td>
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<td>36</td>
<td>50% improved</td>
<td>Combo &gt; Others</td>
<td>Combo = Others</td>
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<td>42 Tugwell et al.</td>
<td>MTX 12.5* MTX + CSA 2.97*</td>
<td>31</td>
<td>24</td>
<td>ACR improvement</td>
<td>MTX + CSA &gt; MTX</td>
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<td>41 Willkens et al.</td>
<td>AZA 50–150 MTX 5–15</td>
<td>67</td>
<td>24</td>
<td>% ≥ 30% in 3 of 4 variables</td>
<td>55%</td>
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</tbody>
</table>

N, number of patients per group; CO, chloroquine; JTC, joint tenderness count; Combo, combination; HCl, hydroxychloroquine; SSZ, sulphasalazine; SWJC, swollen joint count; CSA, cyclosporin; AF, auranofin; AZA, azathioprine.

*12.5 = average dose, ascertained by personal communication.
†2.97 = average dose in mg/kg/day.
MTX patients discontinued secondary to inefficacy compared to 13 patients taking auranofin (P = 0.047) and 7% of MTX patients discontinued therapy secondary to toxicity compared to 22% of the auranofin group (P < 0.01). Williams et al. [40], as part of a combination therapy trial (Table III), also compared MTX to auranofin. In their large trial, however, a fixed dose of auranofin (6 mg) and a low fixed dose of MTX (7.5 mg weekly) were compared. In that trial, the auranofin and MTX treatment showed equal efficacy.

Three trials compared azathioprine with MTX, one of those being part of a combination therapy study [34, 39, 41]. Hamdy et al. [39] only examined a very small group of patients, but commented that all nine efficacy parameters improved in both groups with a trend (not statistically significant) toward more rapid and greater improvement in the MTX-treated patients. Jeurissen et al.’s [34] 48 week trial showed that 12/13 efficacy measures improved in the MTX-treated group, while 6/13 measures improved statistically in the azathioprine-treated patients. In those patients who completed the trial, response was equivalent, but 64% of the patients discontinued azathioprine, while only 19% discontinued MTX. Overall, Jeurissen et al. felt that MTX was more effective than azathioprine. The third comparison between MTX and azathioprine was part of a combination therapy study in which Willkens et al. [41] compared azathioprine 50–150 mg a day and MTX 5–15 mg a week, to 5–7.5 mg MTX plus 50–100 mg azathioprine over 24 weeks. Willkens et al. used a >30% response in three of four efficacy variables as a combined response measure. Forty-four per cent of the azathioprine-treated patients improved by this amount, while 55% of the MTX-treated patients did the same. At 12 weeks, the MTX-treated group was statistically better than the azathioprine group, but this difference was gone by 24 weeks because, essentially, the azathioprine-treated patients were ‘responder enriched’. This is because a large number of azathioprine-treated patients discontinued the trial (38%) compared to only 7% discontinuing MTX. This implies that responders remained in the trial for the full 24 weeks, decreasing any differences that might have occurred early. The azathioprine-treated patients also experienced more toxicity than did the MTX group. Among the five combination therapy trials, only two utilized a ‘classical’ design comparing each drug separately to their combination [40, 41]. The other three trials (see below) utilized less conventional designs (Table III) [42–44].

In Willkens et al.’s study [41], a lower dose combination of MTX and azathioprine was compared to more usual and higher doses of each drug alone. The combination therapy fared as well as, but no better than, the MTX-alone group and better than the azathioprine-treated patients (58% vs 55% vs 44% response; see Table III). MTX alone was equally effective and no more toxic than the combination. Williams et al. [40] compared usual doses of auranofin, a low dose of MTX (7.5 mg a week), and their combination, in over 100 patients per group. All treatment regimens were equally effective even though a low dose of MTX was used. When examining discontinuations secondary to inefficacy on the other hand, MTX discontinuations (7%) and combination therapy discontinuations (2%) were equal and fewer than discontinuations among the auranofin-treated patients (13%) (P = 0.004). Tugwell et al. [42] employed a different design, utilizing patients who had ‘failed’ MTX secondary to continued disease activity at maximum tolerated dose (mean 12.5 mg/week). While continuing the MTX, cyclosporin at a mean final dose of 2.97 mg/kg/day or placebo was added. Sixteen per cent of the MTX plus placebo-treated patients improved by ACR improvement criteria, while 48% of the patients utilizing MTX plus cyclosporin improved by this combined measure (P < 0.001). Toxicity was also generally equal, although the serum creatinine increased more in the combination-treated group than the placebo-treated patients (0.14 mg/dl vs 0.05 mg/dl; P < 0.02). Ferraz et al. [43] compared low-dose MTX (7.5 mg weekly) to MTX (7.5 mg/week) and chloroquine (250 mg/day). The analysis examined only those patients who completed the trial. Three of the seven efficacy measures favoured the combination, while the other four did not, despite the low-dose MTX. Interestingly, 12 patients utilizing the combination experienced elevations of hepatic enzymes vs seven on MTX alone. O’Dell et al. [44] compared MTX to hydroxychloroquine plus sulphasalazine (HCQ/SSZ) to all three together. In 31–36 patients per group followed for 2 yr the well-defined response rate was 33% in the MTX group, 40% in the HCQ/SSZ-treated patients and 77% in the triple-combination group. The triple combination was clearly more effective, while the other two treatments were equivalent.

An interesting meta-analysis by Felson et al. [46] examined combination therapies in RA. They utilized a methodology which allowed two-way confidence intervals to be constructed so that comparisons could be made visually in two axes. In general, combination trials resulted in a marginal improvement over monotherapy in tender joint count (4%; P < 0.001) and no improvement in swollen joint count (1.7%; P = 0.008).

Observational studies indicate that more patients remain on MTX after 3 yr than other DMARDs [47]. Between 45 and 62% of patients remained on MTX after 3 yr compared to 18–62% on i.m. gold, 35% on hydroxychloroquine, and 11–39% on sulphasalazine.

Radiographic progression

Four studies, each small or with significant weaknesses, support the concept that MTX retards new bony damage in RA [45, 48]. In contrast, two studies, with similar weaknesses, do not do so [36]. Using individual patient data from these studies, a meta-analysis persuasively showed that MTX slowed the
appearance of new erosions more effectively than azathioprine and as effectively as i.m. gold [49].

Summary. MTX is effective for treating RA and it may slow the appearance of new erosions.

Off indication use

Controlled studies. Two well-controlled, blinded studies used MTX to treat psoriatic arthritis [50, 51]. In one, 21 hospitalized patients were given 1–3 mg/kg MTX every 10 days for 30 days compared to placebo. Patients given MTX had more improvement in joints and skin than did the placebo group [50]. In the other study, 37 patients responded to 7.5–15 mg weekly MTX orally better with respect to physician global and skin involvement, but did not separate MTX from placebo with respect to joint tenderness or swelling [51]. Double-blind, placebo-controlled studies of juvenile chronic arthritis (JCA) (also called juvenile RA) chronically suffer from a large placebo response. The use of MTX in JCA was no exception for it took three trials and a meta-analysis involving 127 children to separate 10 mg/week MTX from placebo [52]. In this case, 63% of the MTX-treated children responded, using a combined index, compared to 36% of placebo-treated patients.

Uncontrolled studies. MTX has been successfully utilized in uncontrolled studies of patients with systemic lupus erythematosus, inflammatory bowel disease, ankylosing spondylitis, temporal arteritis, Wegener’s granulomatosis, and systemic sclerosis [53–57]. One short controlled trial in systemic sclerosis was unsuccessful [58]. As usual, open studies are encouraging, but one must await well-controlled, blinded studies, some of which are presently being undertaken, to sort out the true place of MTX in the treatment of these diseases.

<table>
<thead>
<tr>
<th>TABLE IV</th>
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<tr>
<td>Adverse events when using methotrexate [48–50]</td>
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<table>
<thead>
<tr>
<th>Methotrexate dose (mg/week)</th>
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<td>Duration of use (months)</td>
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<table>
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<tr>
<th>Adverse events</th>
<th>%</th>
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<tr>
<td>Central nervous system (headache, fatigue, ‘fuzziness’, malaise)</td>
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<tr>
<td>Gastrointestinal (GI) Nausea, GI distress</td>
<td>3–74</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>19–65</td>
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<td>Hematological Anaemia</td>
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<td>Leucopenia</td>
<td>1–2</td>
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<td>Thrombocytopenia</td>
<td>2–21</td>
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<td>2–15</td>
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<td>Rash</td>
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<td>Liver Cirrhosis</td>
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<td>Pneumonitis (hypersensitivity)</td>
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<td>Pseudolymphoma</td>
<td>1–7</td>
</tr>
<tr>
<td>Teratogenicity</td>
<td>Definite</td>
</tr>
</tbody>
</table>

TOXICITY

Table IV outlines the range of MTX’s toxicities found in the medical literature.

Gastrointestinal toxicity including stomatitis, nausea and abdominal distress is most common [59, 60]. Central nervous system effects, including headache, fatigue, and malaise, are surprisingly common, but are frequently not volunteered. They occurred in up to 67% in one study [59–61].

Cirrhosis may occur, although its incidence is controversial [62, 63]. An ACR ad hoc committee recommended liver biopsies only after 5 yr or if liver function tests were frequently elevated [63]. Baseline CBC, liver function tests and serological tests for hepatitis B and C are recommended. Follow-ups are useful, with CBCs and liver function tests every 2–4 weeks initially and then every 4–8 weeks; serum creatinines should be done every 4–12 weeks [62, 63]. An analysis of the cost effectiveness of liver biopsy in MTX-treated patients with RA has been published [62]. Its claim that liver biopsies are not cost effective after 5 yr of treatment is based on an assumption that cirrhosis occurs in 1 out of 1000 cases. Unfortunately, some studies indicate more frequent cirrhosis (up to 3%), so that this article must be considered as somewhat speculative [63].

Haematological side-effects do occur, including occasional leucopenia and rare thrombocytopenia, although they are not a principal area of concern when using MTX (Table I) [61, 64]. Similarly, renal toxicity can occur, but is quite rare.

MTX interactions with NSAIDs raise some concern. These most frequently result in mild diminution in creatinine clearance and are extremely rare causes of clinical toxicity. No great difference exists between aspirin and other NSAIDs with respect to renal toxicity [22, 23, 48, 64]. Pulmonary hypersensitivity associated with severe hypoxaemia occurs in 1–7% of patients given MTX [59, 60, 64]. Thus far, it has usually been reversible, but is unpredictable. Recurrent pulmonary disease after re-treatment with MTX has been reported.

Teratogenicity is well documented after MTX and MTX has been used in combination with misoprostol as an abortifacient [65, 66]. Pseudolymphomas continue to be reported after MTX use (J. M. S. Davies, personal communication). The name pseudolymphoma comes from the appearance of the pathology which looks like a large cell lymphoma, but this lesion disappears when MTX is withdrawn (J. M. S. Davies, personal communication). Of course, the lymphoma is usually treated, but spontaneous large cell lymphoma usually recurs, while it does not recur after MTX withdrawal.

Opportunistic infections have repeatedly been reported after MTX use, including infection with Pneumocystis carinii, aspergillosis, cryptococcosis, nocardiosis and herpes zoster [67–70]. The issue of
whether MTX increases the incidence of bacterial infections in RA patients remains controversial [70].

While anaphylactic reactions have been reported to the Food and Drug Administration (FDA), only 5/24 reported cases were in patients with rheumatic diseases (two with JRA, one with polymyositis and two with RA) (FDA inquiry). In two cases, the patients were re-challenged without recurrence of symptoms. In the other three cases, no re-challenge was undertaken. The other 19 cases of anaphylaxis were in patients given MTX for malignancies.

Summary

MTX causes discontinuation of therapy less than other DMARDs. GI and central nervous system toxicities are most common, while rare pneumonitis and cirrhosis are most serious. The issues of pseudolymphoma and a tendency towards increased infections when using MTX are not yet settled.

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