Update on Methotrexate as the Anchor Drug for Rheumatoid Arthritis

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Abstract

Methotrexate has become the “anchor drug” for rheumatoid arthritis (RA), taken by far more patients than any other disease modifying anti-rheumatic drug (DMARD) or biological agent. Methotrexate has greater efficacy and effectiveness than any other non-biologic DMARD, and greater tolerability and safety than other DMARDs. The efficacy of methotrexate is comparable to biologic agents in parallel clinical trials of DMARD-naïve patients. Adequate responses to methotrexate monotherapy or combinations with other non-biologic DMARDs are seen in about two-thirds of patients with RA in usual care. The most efficacious treatments for RA reported in the rheumatology literature are seen in strategy trials with methotrexate as the anchor drug, without any biologic agent. Interpretation of significantly lower radiographic progression between methotrexate and biologic agents in clinical trials is overstated regarding clinic consequences. The admonition to patients to refrain entirely from consumption of alcohol while taking methotrexate may be unnecessary. Accurate information concerning methotrexate as the anchor drug for RA should lead to better understanding of optimal use and better patient outcomes in usual clinical care.

Methotrexate (MTX) has become the “anchor drug” for rheumatoid arthritis (RA), taken by far more patients than any other disease modifying anti-rheumatic drug (DMARD) or biological agent. For example, in the Quantitative Standard Monitoring of Patients with Rheumatoid Arthritis (QUEST-RA) international database, which now includes more than 30 countries, MTX was taken by 83% of patients with RA, compared to 23% for any biological agent (Table 1). More than 67% of patients with RA had taken MTX in each of 15 countries.

Prior to the 1990s, most reported patients with RA experienced unfavorable outcomes, including severe functional declines, progression of radiographic joint damage, joint replacement surgery, work disability, premature mortality and premature mortality and premature mortality. Considerably better outcomes have been reported in recent years, including reduced mortality rates in patients who respond to MTX. Without randomized data, it is not possible to state unequivocally that these improvements are due to widespread early and aggressive use of weekly low-dose MTX prior to joint damage, with a current goal to “treat to target” of remission or low disease activity. The findings may also reflect a possible secular trend toward milder disease, and biologic therapies have added further to better outcomes in RA. However, MTX may account for most of this improvement in the majority of patients.

Nonetheless, despite the importance of MTX in advances in therapy and outcomes, most of the rheumatology literature and scientific presentations over the last decade have emphasized biologic agents. Methotrexate continues to be regarded in many medical sources and patient materials, as a highly “toxic” therapy. In literature given to patients when filling a prescription for MTX, adverse effects of weekly low-dose MTX generally are not distinguished from those of high-dose MTX used in the treat-
ment of neoplastic disease. Many physicians express far greater concern about toxicities of weekly low-dose MTX than about antibiotics with as high a likelihood of adverse events, which often are prescribed over the telephone.

This review updates previous articles concerning the efficacy, effectiveness, tolerability, and safety of MTX as the “anchor drug” for RA (Table 2). We hope that this analytic review may improve clinically relevant interpretation of the favorable benefit-risk ratio of weekly low-dose MTX in contemporary care of RA for both physicians and patients.

### Table 1 Proportion of Patients with Rheumatoid Arthritis A Who Took Various Disease-modifying Antirheumatic Drugs (DMARDs) in the QUEST-RA Database; the Highest Percentage for Each Drug is Indicated in Bold, and the Lowest in Bold Italics

<table>
<thead>
<tr>
<th>Country</th>
<th>Delay to start DMARDs, months, median</th>
<th>DMARD exposure years, mean</th>
<th>Prednisone</th>
<th>MTX</th>
<th>HCQ</th>
<th>SSZ</th>
<th>LEF</th>
<th>Any biological agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argentina</td>
<td>13</td>
<td>3.7</td>
<td>83%</td>
<td>68%</td>
<td>49%</td>
<td>6%</td>
<td>16%</td>
<td>3%</td>
</tr>
<tr>
<td>Denmark</td>
<td>10</td>
<td>7.9</td>
<td>43%</td>
<td>85%</td>
<td>39%</td>
<td>64%</td>
<td>11%</td>
<td>23%</td>
</tr>
<tr>
<td>Finland</td>
<td>7</td>
<td>14.4</td>
<td>74%</td>
<td>85%</td>
<td>74%</td>
<td>84%</td>
<td>21%</td>
<td>17%</td>
</tr>
<tr>
<td>France</td>
<td>8</td>
<td>9.9</td>
<td>83%</td>
<td>86%</td>
<td>55%</td>
<td>49%</td>
<td>42%</td>
<td>53%</td>
</tr>
<tr>
<td>Germany</td>
<td>15</td>
<td>8.4</td>
<td>54%</td>
<td>78%</td>
<td>30%</td>
<td>36%</td>
<td>25%</td>
<td>29%</td>
</tr>
<tr>
<td>Ireland</td>
<td>11</td>
<td>6.3</td>
<td>71%</td>
<td>92%</td>
<td>15%</td>
<td>33%</td>
<td>24%</td>
<td>41%</td>
</tr>
<tr>
<td>Italy</td>
<td>9</td>
<td>7.1</td>
<td>69%</td>
<td>79%</td>
<td>42%</td>
<td>14%</td>
<td>31%</td>
<td>26%</td>
</tr>
<tr>
<td>Netherlands</td>
<td>5</td>
<td>8.1</td>
<td>26%</td>
<td>91%</td>
<td>28%</td>
<td>35%</td>
<td>6%</td>
<td>19%</td>
</tr>
<tr>
<td>Poland</td>
<td>4</td>
<td>7.2</td>
<td>69%</td>
<td>87%</td>
<td>34%</td>
<td>60%</td>
<td>18%</td>
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<tr>
<td>Serbia</td>
<td>11</td>
<td>6.6</td>
<td>88%</td>
<td>69%</td>
<td>55%</td>
<td>17%</td>
<td>7%</td>
<td>2%</td>
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<tr>
<td>Spain</td>
<td>14</td>
<td>7.3</td>
<td>67%</td>
<td>82%</td>
<td>43%</td>
<td>29%</td>
<td>34%</td>
<td>27%</td>
</tr>
<tr>
<td>Sweden</td>
<td>12</td>
<td>8.8</td>
<td>66%</td>
<td>83%</td>
<td>34%</td>
<td>62%</td>
<td>9%</td>
<td>31%</td>
</tr>
<tr>
<td>Turkey</td>
<td>12</td>
<td>8.9</td>
<td>69%</td>
<td>88%</td>
<td>27%</td>
<td>61%</td>
<td>22%</td>
<td>7%</td>
</tr>
<tr>
<td>UK</td>
<td>12</td>
<td>7.9</td>
<td>51%</td>
<td>67%</td>
<td>39%</td>
<td>46%</td>
<td>4%</td>
<td>16%</td>
</tr>
<tr>
<td>USA</td>
<td>9</td>
<td>7.9</td>
<td>77%</td>
<td>85%</td>
<td>49%</td>
<td>12%</td>
<td>19%</td>
<td>33%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>9</strong></td>
<td><strong>8.1</strong></td>
<td><strong>66%</strong></td>
<td><strong>83%</strong></td>
<td><strong>41%</strong></td>
<td><strong>43%</strong></td>
<td><strong>21%</strong></td>
<td><strong>23%</strong></td>
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</tbody>
</table>


### Table 2 Efficacy, Effectiveness, Tolerability, and Safety of Weekly Low Dose Methotrexate

1. Although a meta-analysis and systematic review of clinical trials suggest that the efficacy of other DMARDs is similar to that of methotrexate, in actual care, methotrexate has far greater long-term effectiveness than other DMARDs.
2. In parallel design trials, the efficacy of biologic agents is not substantially greater than that of methotrexate in groups of patients who took no prior DMARDs.
3. Adequate responses to methotrexate as monotherapy or in combination with other non-biologic DMARDs are seen in about two-thirds of patients with rheumatoid arthritis in usual care.
4. The most efficacious treatments for rheumatoid arthritis are found in “strategy trials” with methotrexate as the anchor drug, usually without any biologic agent.
5. Interpretation of significantly lower radiographic progression between methotrexate and biologic agents in clinical trials is overstated.
6. The admonition to patients to refrain entirely from consumption of alcohol while taking methotrexate may be unnecessary.
7. Frequent blood testing in patients who take methotrexate may be overused.

1. Although a meta-analysis and systematic review of clinical trials suggest that the efficacy of other DMARDs is similar to that of Methotrexate, in Actual Care, Methotrexate Has Far Greater Long-term Effectiveness than Other DMARDs

Methotrexate has greater effectiveness than other non-biologic DMARDs and equivalent effectiveness to biologic agents in most patients, as well as greater tolerability and safety than any other DMARD in the majority of RA patients. However, many clinical trials, as well as meta-analyses and systematic reviews, suggest that other DMARDs—including sulfasalazine and even injectable gold and d-
penicillamine—have similar efficacy and safety. These observations illustrate some of the limitations of clinical trials, which have been presented in a number of reports by many observers, including the authors, but usually are ignored in the medical literature. Indeed, clinical trials and meta-analyses of these trials are often regarded as providing the “best evidence” to guide clinical therapy, although recent reports recognize the potential value of well-performed observational, non-randomized studies.

One example of limitations of clinical trial and meta-analysis data to describe results in usual clinical care involves a meta-analysis of 66 clinical trials reported in 1990 concerning the efficacy of DMARDs in the treatment of RA, which included 117 treatment groups: 11 for antimalarial drugs (e.g., hydroxychloroquine), 23 for auranofin, 29 for injectable gold, 7 for MTX, 19 for d-penicillamine, 6 for sulfasalazine, and 22 for placebo. The meta-analysis indicated no significant differences between the efficacy of MTX compared to sulfasalazine, d-penicillamine, and injectable gold (Fig. 1). It was concluded that MTX was equivalent to these other DMARDs in efficacy for RA.

A second, more recent example of some pitfalls in interpretation of clinical trial data for clinical care can be seen in a systematic review of DMARDs reported in 2008, which concluded that there was moderate “evidence” that sulfasalazine, leflunomide, and MTX were equivalent in efficacy, with “no obvious major differences in adverse events and discontinuation rates” among these three DMARDs.

These conclusions differ from clinical care in the QUEST-RA database (Table 1), in which MTX was taken by 83% of patients, sulfasalazine by 43%, and leflunomide by 21% of patients (and hydroxychloroquine by 41% and biologic agents by 23%). These patterns were seen in countries in which patients do not pay for medications, so they could be explained only in small part on the basis of costs. Perhaps a strict methodologist may conclude that
the clinicians were in error and not practicing “evidence-based medicine.” Nevertheless, one might expect to see comparable usage in actual clinical care of three DMARDs that truly have similar efficacy, adverse events, and discontinuations over time, but this is not the case.

Results of the 1990 meta-analysis did not appear translated into actual clinical care over 5 years in a study from seven rheumatology practices reported in 1992 (Fig. 2A). A formal analysis of estimated continuation of 1,083 courses of six DMARDs over 60 months in 477 patients with RA indicated that approximately 80% of MTX courses were continued after 2 years, compared to 50% of courses of hydroxychloroquine, penicillamine, parenteral gold, and azathioprine and only 20% of courses of oral gold. After 5 years, approximately 60% of the MTX courses were continued, versus approximately 20% of the hydroxychloroquine, penicillamine, parenteral gold, and azathioprine courses, and virtually no course of oral gold (Fig. 2, Panel A).56

Nonetheless, the data from the meta-analysis were accurate for clinical care over 1 year of only the initial 447 DMARD courses, conditions that mimic clinical trials (Fig. 2B), in contrast to the above analyses of all DMARD courses over 5 years.56 Continuation rates of courses of all six DMARDs were similar over 12 months, including no difference between MTX versus parenteral versus oral gold (auranofin) (Fig. 2B). A 1-year clinical trial also indicated no significant differences between MTX versus oral gold,57 unlike 5-year results in clinical care (Fig. 2A).56 The absence of statistically significant differences between DMARD courses over 1 year (Fig. 2B) is similar to results of clinical trials in Figure 1 but differs considerably from the results seen in actual clinical care over 5 years (Fig. 2A).

A more recent study reported in 2005 analyzed all 248 patients with RA who began treatment with MTX between 1990 and 2003 under care of TP.58 The probability of continuing MTX over 5 years was 79% in 1,007 person-years. Severe laboratory abnormalities occurred in 2.9 per 100 person-years, and only two discontinuations resulted from laboratory abnormalities, both of WBC, possibly from other sources. Discontinuation was based in almost all cases on clinical findings, such as gastrointestinal or central nervous system intolerance, rather than laboratory tests, as few clinically significant laboratory abnormalities were seen. Weekly low-dose MTX appears among the safest treatments for RA and indeed as safe and well-tolerated as almost any medication available for care of any disease at this time.58

These observations indicate that data from short-term clinical trials may provide less accurate information about therapies in actual care than long-term observational studies, as a result of limitations of the clinical trial methodology. These limitations include a short term of 1 year or less, patient selection, inflexible dosage schedules, preordained discontinuation for any liver function abnormality (rather than 3 times the upper limit of normal as in recent trials), and others.33-52

Well-designed structured studies such as clinical trials and meta-analyses are more likely to be published in medical journals than observational studies, which necessarily cannot have as rigorous a design. This matter may remain an important barrier to awareness of optimal patient therapy in RA and other chronic diseases, as results of treatment by sophisticated specialists which result in improved long-term outcomes usually are neither captured in clinical trials nor published in the medical literature. As noted above, it has been suggested recently that strong observational studies may provide a high level of evidence comparable to clinical trials,54 a concept that is gaining advocacy.

2. In Parallel Design Trials, the Efficacy of Biologic Agents is Not Substantially Greater than that of Methotrexate in Groups of Patients Who Took No Prior DMARDs

Superior efficacy of biological therapies over MTX was documented initially in “step-up” registration clinical trials.59 In these trials, patients who experience incomplete responses to MTX are treated with MTX plus placebo, or MTX plus a biological agent such as infliximab,60 etanercept,61 adalimumab,62 or many others. In some senses, such trials are “weighted” to show efficacy for the additional agent in combination since patients are selected for incomplete responses or “failure” with MTX.

In “parallel” design clinical trials, in which the efficacy of two medications is compared in patients who have no prior exposure to either agent, treatment with MTX results in relatively similar outcomes to a biological agent. For example, in the early RA (ERA) trial61,63 conducted in patients who had RA of less than 3 years’ duration, after 12 months, ACR 20 responses were seen in 72% of patients who were randomized to 25 mg per week of etanercept compared to 65% of patients randomized to MTX (initiated at 7.5 mg per week although escalation to 20 mg per week was allowed) (p = 0.16). The etanercept group did respond more quickly and had slightly less radiographic progression, which, however, does not appear clinically important, as discussed below.

Similar results have been seen with many biological agents in parallel design clinical trials in patients who had no prior MTX. These studies indicate that if MTX is administered to patients with early disease and no prior MTX, results in most patients are quite similar to results with biologic agents, again with a marginal (but clinically unimportant) advantage for biologic agents to inhibit radiographic progression (see below). Definitive superiority of biological agents over MTX generally is seen only in clinical trials involving a step-up design,69 in which patients with prior incomplete responses to MTX are treated with a combination of MTX and a biologic agent, versus MTX monotherapy plus placebo. A limited response to MTX and...
significant advantage to a combination with another agent might be expected in these patients.

3. Adequate Responses to Methotrexate as Monotherapy or in Combination with Other Non-biologic DMARDs are Seen in About Two-thirds of Patients with Rheumatoid Arthritis in Usual Care

A study was made of all 93 patients with RA seen by the senior author (TP) at a weekly academic clinical setting at Vanderbilt University between 1996 and 2006, for whom 5 year follow-up data were available.44 All patients completed a multidimensional health assessment questionnaire (MDHAQ),65 with three 0 to 10 scores for physical function, pain, and patient global estimate, and RAPID3, an index of these three measures scored 0 to 30.66 All RA patients had an erythrocyte sedimentation rate (ESR) assessed. RAPID3 scores may be interpreted as: high severity greater than 12, moderate severity 6.1 to 12, low severity 3.1 to 6, and near remission less than or equal to 3. RAPID3 scores were not used to guide therapy before 2006.

An adequate response to MTX was defined as not having any subsequent treatment with a biologic agent over a period of 5 years (although some patients had treatment with other non-biologic DMARDs in combination with MTX). An incomplete response to MTX was defined as initiation of treatment with a biologic agent after MTX initiation. An adequate response was seen in 63 of the 93 patients (68%), and an incomplete response was seen in 30 of the 93 patients (32%) (Table 3). The subsequent biologic agent was initiated at a mean interval of 2.6 years after MTX had been begun. This interval was 5.4 years in 13 patients in the 1990s prior to availability of biologic agents in 1999 and 1.6 years in 17 patients in the 2000s, when biologic agents were available.44

In patients with subsequent adequate responses, baseline median ESR at initiation of MTX was 24 mm/hr, MDHAQ physical function 2.3, pain 4.1, patient global estimate 4.2 (all 0 to 10), and RAPID3 10.6 (0 to 30). By contrast, in subsequent incomplete responders, baseline median ESR was 28 mm/hr, MDHAQ physical function 3.2, pain 5.2, patient global estimate 5.5, and RAPID3 14.9, when MTX was begun. Therefore, patients with subsequent inadequate

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**Table 3** Measures and Indices in 63 Adequate Methotrexate (MTX) Responders and 30 Incomplete MTX Responders at MTX Initiation and Follow-up

<table>
<thead>
<tr>
<th>Measure (“abnormal” value)</th>
<th>63 Patients MTX-only: Adequate Responses—No Biological Agent</th>
<th>30 Patients Biologic Agents: Incomplete Response to MTX with Addition of Biologic Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MTX start</td>
<td>Follow-up mean 2.6 years later</td>
</tr>
<tr>
<td>ESR (mm/h) (≥ 28)</td>
<td>Median</td>
<td>% abnormal</td>
</tr>
<tr>
<td>MDHAQ-FN (0-10) (&gt; 2)</td>
<td>2.3</td>
<td>52%</td>
</tr>
<tr>
<td>Pain (0-10) (&gt; 2)</td>
<td>4.1</td>
<td>73%</td>
</tr>
<tr>
<td>Patient global (PTGL) (0-10) (&gt; 2)</td>
<td>4.2</td>
<td>75%</td>
</tr>
<tr>
<td>RAPID3 (0-30) (&gt; 6)</td>
<td>10.6</td>
<td>78%</td>
</tr>
</tbody>
</table>

MTX, methotrexate; ESR, erythrocyte sedimentation rate; MDHAQ-FN, physical function score on multidimensional health assessment questionnaire; RAPID3, routine assessment of patient index data 3.
MTX responses tended to have more severe baseline clinical status. In adequate MTX responders, RAPID3 scores fell from 10.6 to 3.6, just above the level for “remission” of 3. In incomplete responders to MTX, RAPID3 actually rose from 14.9 at initiation of MTX to 16.2 at initiation of the biologic agent, greater than the level for RAPID3 “high severity” of 12. By contrast, ESR fell similarly in both groups. Thus RAPID3 scores documented clinical status of “near remission” in adequate responders, compared to “high severity” in incomplete responders. These data indicate that 68% of patients had adequate responses to MTX over 5 years.

4. The Most Efficacious Treatments for Rheumatoid Arthritis are Found in Strategy Trials with Methotrexate as the Anchor Drug, Usually Without Any Biologic Agent

In recent years, a new design for RA clinical trials that may be termed a “strategy trial” has been developed. Strategy trials require adjustment of treatment with MTX monotherapy or combination with DMARDs or biological agents. Frequent visits are conducted, with quantitative assessment to aim toward a target, generally a disease activity score (DAS or DAS28) indicating low disease activity or remission. Some of the best reported results for treatment of RA have emerged from strategy trials, most without any biological agent.

In the TICORA (TIght COntrol for Rheumatoid Arthritis) trial, after 18 months of intensive versus routine care, 36/55 (65%) patients in an intensive management group had DAS less than 1.6, the criterion for remission, compared to 9/55 (16%) in the routine care group (odds ratio 9.7; limits of 95% CI, 3.9-23.9; p < 0.0001). In the BeSt (Behandel-Strategieën or “treatment strategies”) trial, after 2 years, no significant clinical differences were seen among 508 patients randomized to one of four treatment strategies: 1. sequential DMARD monotherapy; 2. step-up combination DMARD therapy; 3. initial combination therapy with tapered high-dose prednisone (COBRA strategy); and 4. initial combination therapy with infliximab, a tumor necrosis factor (TNF) antagonist biological agent. Over 2 to 5 years, an intensive therapy with combination DMARDs was applied to patients in all groups, and similar results in all groups were seen. In CAMERA (Computer Assisted Management in Early Rheumatoid Arthritis), 76 patients in the intensive strategy group (50%) achieved at least one period of remission during the 2-year trial, versus 55 patients (37%) in the conventional strategy group (p = 0.03), without any biological agents.

CIMESTRA (CIclosporine, MEthotrexate, STeroid in RA) involved treatment with MTX plus cyclosporine (combination therapy group) or MTX plus placebo-cyclosporine (monotherapy group) and intensive treatment of all patients with intra-articular betamethasone injections in all swollen joints. After 2 years, ACR20, ACR50 and ACR70 responses were 88%, 79%, and 59% of patients in the combination group, versus 72%, 62% and 54% in the monotherapy group—as high as seen in the rheumatology literature, but without biological agents. The TEAR (Treatment of Early Aggressive Rheumatoid Arthritis) trial, patients had similar responses at 48 weeks after randomization to one of four treatment arms: 1. immediate treatment with MTX plus etanercept; 2. immediate oral triple therapy (MTX plus sulfasalazine plus hydroxychloroquine); 3. step-up from MTX monotherapy to MTX plus etanercept at week 24 if the DAS28-ESR was greater than 3.2; 4. step-up from MTX monotherapy to triple therapy (MTX+SSZ+HCQ) if the DAS28-ESR was greater than 3.2. The investigators concluded that “initial use of MTX monotherapy with the addition of sulfasalazine plus hydroxychloroquine or etanercept, if necessary, after 6 months is a reasonable therapeutic strategy for patients with early RA.” This conclusion is supported by data from all RA strategy trials.

5. Interpretation of Significantly Lower Radiographic Progression between Methotrexate and Biologic Agents in Clinical Trials is Overstated

Almost all clinical trials with two arms that compare MTX to a biologic agent indicate a statistically significant advantage to biologic agents to slow radiographic progression. For example, analyses of the TEMPO trial indicated radiographic progression of 3.34 units according to the Sharp/van der Heijde scale in patients randomized to MTX, compared to 1.15 in patients randomized to etanercept, and 0.56 in patients randomized to the combination of MTX and etanercept (Fig. 3). However, analyses of TEMPO and similar trials ignore several features of the observed differences:

A. The total number of units in a Sharp/van der Heijde score is 448. Patients rarely are seen who have more than 50% of the maximum score, suggesting that...
some joints are spared in almost all patients or that a maximum level of damage may occur, and it may be suggested that actual maximum scores are actually 224. Radiographic changes of two units per year are statistically significant but clinically not detectable (Fig. 4). Differences must be at least five units to be appreciated clinically, and a clinically detectable minimal change at the rate presented would be seen only over 2.5 years. Two units involve 0.5% of actual maximum scores. Furthermore, radiographic scores tend to plateau over time, which explains why few patients have even 50% of maximum damage.

B. Results of clinical trials are presented for groups of patients, and probability plots of TEMPO trial data indicate that 70% to 80% of individual patients have similar levels of radiographic progression, whether treated with MTX or biologic agents, most show no progression (Fig. 5). Some show improved scores, which may be the result of “healing,” measurement error, or both. Similar data are seen in other clinical trials.

C. Radiographs are far less likely than functional status on a patient questionnaire, comorbidities, rheumatoid factor, ESR, joint counts, or extra-articular disease to be prognostic of severe outcomes of RA, such as work disability and mortality. In a review of all 84 reports that described predictors of premature mortality in RA, functional status was a significant predictor of mortality in 17 of 18 studies, while radiographs were significant in 5 of 18 studies. Therefore, a statistically significant change in radiographic scores may be clinically far less important in prognosis and course than changes in functional status.

Certainly, reduction in the rate of radiographic progression is desirable. Extensive evidence indicates that MTX inhibits this progression significantly, albeit not as effectively as a biological agent in 20% to 30% of patients (Fig. 5). Radiographs are correlated more significantly with laboratory tests than with physical function, but physical function is of considerably greater prognostic significance for work disability and mortality in RA than laboratory tests or radiographs. Reported differences in radiographic
progression as a single measure, after treatment with MTX versus all biologic agents, may be too minimal to justify additional costs and risks of biological therapy.

6. The Admonition to Patients to Refrain Entirely from Consumption of Alcohol While Taking Methotrexate may be Unnecessary

Methotrexate was introduced as a cytotoxic agent for cancer chemotherapy, administered in high doses, with a potential for hepatotoxicity. Therefore, patients who are treated with high-dose MTX were advised to refrain entirely from alcohol intake. A similar warning is still given by many physicians to patients who are treated with weekly low-dose MTX for RA.

It has become apparent over time that moderate alcohol intake may be well-tolerated by almost all patients who take weekly low-dose MTX, although patients with psoriatic arthritis may be more vulnerable to hepatic injury. A survey of 200 patients in the United Kingdom with 139 respondents (69%) indicated that 61% received advice about alcohol when given prescriptions for MTX. Among respondents, 36% reported no alcohol consumption, 20% < 1 unit/week, 33% 1-7 units, and 11% ≥ 8 units, including 4 patients > 21 units/week. The highest mean alanine transaminase (ALT) was 41 to 42 international units (IU) in all groups; an abnormal ALT > 40 IU or > 80 IU did not differ at all according to alcohol use, including those who consumed greater than 21 units/week.

In the senior author’s clinical care, in which weekly low-dose MTX with co-administration of folic acid was continued over 5 years by 80% of patients, the standard instruction to patients is “do not consume more alcohol than your doctor recommends,” i.e., up to two glasses per day. None of 248 patients monitored between 1990 and 2003 in the report cited above discontinued MTX due to elevated liver enzymes over the 13 years of observation. Only three patients were not treated with MTX because of “excessive alcohol use.”

One of these patients, a 61-year-old man with RA, readily acknowledged regular consumption of five drinks per day since age 15. He was treated with hydroxychloroquine with good control for several years. However, he presented with a severe RA flare on one visit. An extensive discussion led to a shared decision by doctor and patient to try MTX 7.5 mg weekly with careful monitoring of hepatic enzymes every 2 weeks, versus the usual practice of every 12 to 16 weeks. His RA was improved to remission status over 1 month, and no elevations of hepatic function enzymes were seen.

Only a minority of individuals who abuse ethanol develop fibrosis and cirrhosis. Patients who have no evidence of compromised liver function after more than 20 years of alcohol abuse may be regarded as having been selected as unlikely to experience hepatic damage with MTX. Moderate alcohol consumption is associated with longer general survival. More liver function abnormalities may be seen using a combination of MTX and leflunomide, but a reassessment concerning warnings about consumption of alcohol while taking MTX may be of value.

7. Frequent Blood Testing of Patients Who take Methotrexate may be Overused

American College of Rheumatology (ACR) guidelines for patients who are treated with MTX include monitoring a complete blood count, liver transaminase levels, and serum creatinine levels every 2 to 4 weeks for the first 3 months, every 8 to 12 weeks from 3 to 6 months, and every 12 weeks after 6 months. One rationale for this frequency involves evidence that elevated transaminase levels may be missed with less frequent monitoring. However, such elevations rarely, if ever, lead to changes in therapy and almost always resolve, sometimes with reduction in dosage and sometimes without changes in MTX dosage. Perhaps some elevations are due to intercurrent viral infections, rather than MTX.

Of course, as with all clinical decisions, certain individual patients with comorbidities, such as diabetes, renal disease, and so forth, may require frequent monitoring. Nonetheless, the standard practice in the senior author’s clinical care included an initial check for an idiosyncratic problem after 2 to 4 weeks but only every 3 to 6 months thereafter. As noted, no patient had MTX discontinued due to elevated liver function enzymes, and no patient had evidence of hepatic damage over 13 years. A reassessment concerning frequency of laboratory tests for patients taking MTX may be of value, particularly as costs of patients’ copayments rise and cause further economic hardship to many patients.

Conclusion

The information in this commentary strongly supports the efficacy, effectiveness, tolerability, and safety of weekly low-dose MTX with co-administration of folic acid as the “anchor drug” for RA. Overall, about 60% to 80% of patients experience adequate responses to MTX as monotherapy or combined with non-biologic DMARDs, with low disease activity. Many of those who have inadequate responses can be treated with combination of MTX and DMARDs, rather than MTX and a biologic agent. Nonetheless, MTX often is underestimated in information presented to rheumatologists, other physicians, and patients. Fewer than 20% of presentations at annual meetings of the European League Against Rheumatism (EULAR) and ACR are about MTX and other DMARDs, although about 80% of patients take such agents in most clinical settings, and most patients are adequately treated with MTX. The investigators hope that comments in this review and other articles in this supplement will provide a more balanced view of the importance and value of MTX in management of RA and other rheumatic diseases at this time.

Disclosure Statement

None of the authors have a financial or proprietary interest
in the subject matter or materials discussed, including, but not limited to, employment, consultancies, stock ownership, honoraria, and paid expert testimony.

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