Underestimation of the efficacy, effectiveness, tolerability, and safety of weekly low-dose methotrexate in information presented to physicians and patients

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ABSTRACT

Ten specific examples of the underestimation of the efficacy, effectiveness and tolerability, and overestimation of adverse events of weekly, low-dose methotrexate, administered with folic acid, in treatment of rheumatic diseases are summarised. These examples include: 1) meta-analyses of clinical trials suggest that methotrexate has an efficacy similar to other disease-modifying anti-rheumatic drugs (DMARDs); 2) information in textbooks and websites may overstate adverse events and drug interactions associated with weekly low-dose methotrexate; 3) information presented to patients when filling a prescription for methotrexate underestimates “side effects” of RA and overstates those of methotrexate; 4) an admonition to patients to refrain entirely from consumption of alcohol while taking methotrexate may be unnecessary; 5) frequent blood testing in patients who take methotrexate may be unnecessary; 6) eligibility of only a small minority of patients for clinical trials to compare biologic agents and methotrexate; 7) Step-up design in most comparisons of biologic agents with methotrexate includes only patients who had experienced an incomplete response to methotrexate; 8) in parallel design trials, the efficacy of biologic agents is not substantially greater than that of methotrexate; 9) low, inflexible dosage schedules of methotrexate and requirement for withdrawal with minimal liver function abnormalities in many clinical trials may underestimate efficacy, effectiveness, tolerability and safety; 10) interpretation of clinical trial results may overstate the clinical significance of lower radiographic progression in patients treated with biologic agents versus patients treated with methotrexate. More accurate interpretation of information for physicians and other health professionals, as well as patients, concerning use of weekly low-dose methotrexate in contemporary care could improve care and outcomes for patients with RA and other rheumatic diseases.

Introduction

Contemporary treatment of patients with rheumatoid arthritis (RA) is based in large part on the ascendancy of methotrexate as the “anchor drug” (1, 2). Weekly low-dose methotrexate, administered with folic acid, has greater efficacy, effectiveness, tolerability, and safety than any previously available disease-modifying anti-rheumatic drug (DMARD) (3) (see article by Sokka in this Supplement). Methotrexate responses in the majority of previously-untrated individual patients with RA are similar to those seen with biologic agents (see article by Rau in this Supplement), although about 20% to 40% of patients experience incomplete responses and/or adverse events with methotrexate, and require other DMARDs and/or biologic agents to control inflammation.

Most RA patients at most rheumatology settings take methotrexate, along with biologic agents. For example, in the Quantitative Standard Monitoring of Patients with Rheumatoid Arthritis (QUEST-RA) international database, which now includes more than 8,000 patients from more than 30 countries, methotrexate use was reported for more than 75% of patients with RA, far more than the proportion of patients treated with biologic agents (Table I) (4). More than 67% of patients had taken methotrexate in each of 15 countries.

Courses of weekly low-dose methotrexate (administered with folic acid) are continued longer than reported for most available medications for any chronic disease. In 1992 (5), before bi-
Table I. The use of disease-modifying antirheumatic drugs (DMARDs) in the QUEST-RA countries; the highest percentage for each drug is indicated in bold, and the lowest in bold italics (adapted from (4)).

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


Oligo-clinical agents became available, more than 50% of patients were reported to continue their courses of methotrexate therapy for at least 5 years, a continuation rate considerably higher than reported for individual biologic agents (6). A recent report from one site indicated that methotrexate was continued for more than 5 years by about 80% of patients, including some in whom the dose was reduced, and some in whom biologic agents were added, with a policy of allowing up to 2 alcoholic drinks per day (7). Therefore, the benefit: risk ratio for weekly low-dose methotrexate appears to be as favourable as for most medications, such as anti-hypertensive agents, anti-depressants, or other widely-used prescription and over the counter medications.

Most reported patients with RA in the 1980s experienced unfavourable outcomes, including severe functional declines (8, 9), radiographic joint damage (10), joint replacement surgery (11), work disability (8, 12), and premature death (8, 9, 13). Considerably better status has been reported in recent years (14-18), including reduced mortality rates in patients who respond to methotrexate (19, 20). These improvements may be explained as much by the widespread use of weekly low-dose methotrexate, used aggressively prior to joint damage (21-27) with a current goal to “treat to target” of remission (28-30) or at least low disease activity, as by biologic therapies, albeit also possibly reflecting a possible secular trend toward milder disease (31-33). Nonetheless, despite the importance of methotrexate in advances in therapy and outcomes, most of the rheumatology literature and scientific presentations over the last decade have emphasised biologic agents. In a resulting knowledge void, methotrexate continues to be regarded in many medical sources and patient materials, as a highly “toxic” therapy. Even at this time, adverse effects of weekly low-dose methotrexate often are viewed as comparable to those of high-dose methotrexate used in the treatment of neoplastic disease. Many physicians express far greater concern about toxicities of weekly low-dose methotrexate than about antibiotics that often are prescribed over the telephone with a higher likelihood of adverse events.

This review presents (Table II) 10 examples of underestimation of the efficacy, effectiveness, tolerability, and safety of methotrexate in information presented to physicians and patients. The authors do not question the accuracy of the published information but suggest that many interpretations have led to a distorted underestimation of efficacy, tolerability and effectiveness of weekly low-dose methotrexate, and an overestimation of the likelihood of adverse events, particularly if folic acid is co-administered. Underestimation of the benefit: risk ratio of methotrexate in information presented to physicians and patients may inhibit optimal care for patients with RA. We hope that this essay may improve clinically relevant interpretations of the value and importance of weekly low-dose methotrexate in contemporary care for physicians and patients.

1. Meta-analyses suggest that methotrexate has efficacy similar to other DMARDs

A meta-analysis of 66 clinical trials concerning the efficacy of DMARDs in the treatment of RA, reported in 1990 (34), included 117 treatment groups: 11 for antimalarial drugs (e.g. hydroxychloroquine), 23 for auranofin, 29 for injectable gold, 7 for methotrexate, 19 for d-penicillamine, 6 for sulfasalazine, and 22 for placebo. The meta-analysis indicated no significant differences between the efficacy of sulfasalazine, d-penicillamine, methotrexate, and injectable gold (Fig. 1) (34). Therefore, it was concluded that methotrexate and other DMARDs were equivalent in efficacy for RA.

The conclusion from the meta-analysis appeared inconsistent with a clinical impression at the time that methotrexate was becoming the most prominent DMARD used for RA (35), because of greater effectiveness, tolerability, and safety compared to other DMARDs. Therefore, a formal analysis was conducted of estimated duration of continuation of 1083 courses of 6 DMARDs over 60 months in 477 patients with RA in 7 rheumatology practices (5). Estimated continuation rates provide a composite surrogate of long-term effectiveness, tolerability, and safety of any medication.
Low-dose methotrexate efficacy / T. Pincus et al.

Table II. Ten specific examples indicating underestimation of efficacy, effectiveness and tolerability, and overestimation of adverse events of weekly-low dose methotrexate.

<table>
<thead>
<tr>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Meta-analyses of clinical trials suggest that methotrexate has efficacy similar to other disease-modifying anti-rheumatic drugs (DMARDs)</td>
</tr>
<tr>
<td>2. Information in textbooks and websites may overstate adverse events and possible drug interactions associated with weekly low-dose methotrexate</td>
</tr>
<tr>
<td>3. Information presented to patients when filling a prescription for methotrexate understates side effects of RA and overstates those of methotrexate</td>
</tr>
<tr>
<td>4. An admonition to patients to refrain entirely from consumption of alcohol while taking methotrexate may be unnecessary</td>
</tr>
<tr>
<td>5. Frequent blood testing in patients who take methotrexate may be overused</td>
</tr>
<tr>
<td>6. Eligibility of only a small minority of patients for clinical trials to compare biologic agents and methotrexate</td>
</tr>
<tr>
<td>7. Step-up design in most comparisons of biologic agents with methotrexate includes only patients who had experienced an incomplete response to methotrexate</td>
</tr>
<tr>
<td>8. In parallel design trials, the efficacy of biologic agents is not substantially greater than that of methotrexate</td>
</tr>
<tr>
<td>9. Low, inflexible dosage schedules of methotrexate and requirement for withdrawal with minimal liver function abnormalities in many clinical trials may underestimate efficacy, effectiveness, tolerability and safety</td>
</tr>
<tr>
<td>10. Interpretation of clinical trial results may overstate the clinical significance of lower radiographic progression in patients treated with biologic agents versus patients treated with methotrexate.</td>
</tr>
</tbody>
</table>

Composite Treatment Effect
(in standard units)

![Composite Treatment Effect Graph](image)

Fig. 1. Meta-analysis to compare standard composite treatment effect of various disease-modifying antirheumatic drugs (DMARDs) for rheumatoid arthritis (34).

Approximately 80% of methotrexate 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 (Fig. 2, Panel A). After 5 years, approximately 60% of the methotrexate 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) (4).

Results from the clinical cohort were compared more directly to results of the meta-analysis by further analysis of a subset within the clinical cohort of only the initial 447 DMARD courses over only 1 year, conditions that mimic clinical trials (5), in contrast to the initial analysis, which had included all DMARD courses over 5 years. Continuation rates of courses of all 6 DMARDs were similar, including evidence of no difference between methotrexate versus parenteral or oral gold (auranofin) (Fig. 2, Panel b), an observation also made in a direct comparison in a 1-year clinical trial (36). The absence of statistically significant differences between DMARD courses over 1 year seen in Fig. 2, Panel b mimics the results of clinical trials in Figure 1, but differs considerably from the results seen in actual clinical practice over 5 years as shown in Fig. 2, Panel a.

A similar difference in conclusions concerning the benefit-risk ratio of methotrexate from a systemic review versus clinical observation was seen recently. A systemic review reported in 2008 (37) concluded that there was moderate “evidence” that sulfasalazine, as well as leflunomide, were equivalent to methotrexate in efficacy, with “no obvious major differences in adverse events and discontinuation rates” among these 3 DMARDs (37). By contrast, evidence from clinical care in the QUEST-RA database (Table I) indicated that methotrexate was taken by 83% of patients, sulfasalazine by 43%, and leflunomide by 21% of patients (4). These patterns were seen in countries in which patients do not pay for medication (4), so they cannot be explained on the basis of costs. Although a strict methodologist may conclude that the clinicians were in error and not practicing “evidence-based medicine,” one might expect to see comparable usage in actual clinical care of 3 DMARDs with similar efficacy, adverse events, and discontinuations.

These observations challenge the generally accepted view that a systematic review or meta-analysis of clinical trials provides the “best evidence” to guide clinical therapy (38, 39). Data from short-term clinical trials may provide less accurate information about therapies than long-term observational studies, as a result of limitations seen in the clinical trial methodology, including a short-term of 1 year or less, patient selection, inflexible dosage schedules,
preordained discontinuation for any liver function abnormality, and others
(40). Limitations of clinical trials have been presented in a number of reports
by several observers (41-51), including the authors (40, 52-57), but usually
are ignored in the medical literature. Well-designed structured studies such
as clinical trials and meta-analyses are more likely to be published in med-
cal journals than observational stud-
ies, which necessarily cannot have as
rigorous a design. This problem may
remain an important barrier to optimal
patient therapy in RA and other diseas-
es, as actions of the most sophisticated
specialists, which result in improved
long-term outcomes, are less likely to
be published than clinical trials.

2. Information in textbooks and
websites may overstate adverse
events and drug interactions
associated with weekly low-dose
methotrexate

A paragraph from the Goodman
and Gilman Textbook of Pharmacology,
2006 edition (section IV, chapter 26,
page 690) (58), states the following
emphasis added):

“Although aspirin is regarded as
the standard against which other
drugs should be compared for the
treatment of rheumatoid arthri-
tis, many clinicians favour the use
of other NSAIDs perceived to have
better gastrointestinal tolerability,
even though this perception remains
unproven by convincing clinical tri-
als. Patients with progressive or
resistant disease require therapy
with more toxic, second-line drugs,
such as antimalarials, glucocortic-
oids, methotrexate, or immuno-
suppressive agents. In the United
States, methotrexate is the second-
line drug used most frequently, while
in Europe, sulfasalazine is generally
preferable.

“The pharmacologic management of
mild rheumatoid arthritis is geared to-
wards symptomatic relief through the
use of NSAIDs. Although they have
anti-inflammatory effects, they do not
prevent or delay joint deformity.
Thus, there now is a trend to use dis-
ease-modifying anti-rheumatic drugs
earlier in the course of the disease
... The use of these agents early in
the course of the disease should be
weighed against their potentially
serious adverse effects. Therapy is
tailored to the individual patient, but
short-term glucocorticoids often are
used to bring the level of inflamma-
tion under control. Glucocorticoids
are not suitable for long-term use
because of adrenal suppression, so
methotrexate, sulfasalazine, or low-
dose immunosuppressants commonly
are used early in the course of the
disease. Should these agents be in-
effective, TNF-receptor antagonists
or IL-1-receptor antagonists may be
administered. The combination of
NSAIDs with these agents is increas-
ingly common.”

Several comments in this “authorita-
tive” pharmacology textbook are at var-
iance with clinical practice and stand-
ards of care at this time, including:

a) Aspirin has not been regarded as the
“standard” treatment of rheumatoid
arthritis for nearly 2 decades.
b) Second-line drugs—including antimal-
arials, low-dose glucocorticoids and
weekly low-dose methotrexate—may
not be “more toxic than NSAIDs” and
may, in fact, be less toxic.
c) Symptomatic relief is no longer the
standard of care in management of
rheumatoid arthritis.
d) A comment that the combination of
NSAIDs with biologic agents “is increas-
ingly common,” is not evi-
dence-based. Indeed, NSAIDs are
less commonly used in RA at this
time than in earlier periods.

Although better information for physi-
cians might appear a reasonable hope
with availability of a personal digital
assistant (PDA) and other hand-held
devices, it is disappointing that the
Medscape application (“app”) concern-
ng methotrexate on the iPhone states:
“Interaction Detail: Infliximab and
methotrexate both increase immuno-
suppressive effects; risk of infection.
High likelihood serious or life-threaten-
ing interaction. Contraindicated un-
less benefits outweigh risks and no al-
ternatives available.” By contrast, the
manufacturer’s package insert states:
“Infliximab, in combination with meth-
otrexate, is indicated to reduce the signs
and symptoms of rheumatoid arthritis
in patients who have had an inadequate
response to methotrexate, and informa-
tion for patients: “REMICADE is used
in combination with methotrexate for
patients with moderate to severe rheu-
matoid arthritis.” Relatively little qual-
ity control of some messages in these
textbooks and websites. Much informa-
tion presented to the medical commu-
nity (and patients) may substantially un-
derestimate methotrexate as the “anchor
drug” in contemporary management of
RA and overestimate adverse events.
3. Information presented to patients when filling a prescription for methotrexate understates “side effects” of RA and overstates those of methotrexate

Underestimation of methotrexate effectiveness and overestimation of adverse events in a standard pharmacology resource is reflected in information presented to patients when filling a prescription for methotrexate. For example, information for patients concerning methotrexate at the website for drugstore.com (http://www.drugstore.com/pharmacy/prices.drugprice.asp?ncdc=00555057202&txr=1Z5006) includes the following comments:

“WARNING: METHOTREXATE 2.5mg MAY CAUSE SEVERE AND SOMETIMES FATAL SIDE EFFECTS INCLUDING BONE MARROW, BLOOD, LIVER, LUNG, KIDNEY, OR SKIN PROBLEMS...
YOUR DOCTOR WILL PERFORM LAB TESTS TO CHECK FOR SIDE EFFECTS while you take methotrexate 2.5mg...
ADDITIONAL MONITORING OF YOUR DOSE OR CONDITION may be needed if you are taking azathioprine, …leflunomide, …sulfasalazine, …nonsteroidal anti-inflammatories drugs (NSAIDs) (such as ibuprofen, naproxen), …corticosteroids (such as prednisone), cyclosporine, …folic acid…”

This information for patients contains several important nuances that present unnecessary concerns, not justified by evidence in the opinion of the authors, including:

a) As with all such documents, no distinction is made between adverse events seen with versus weekly low-dose methotrexate used to treat inflammatory diseases versus high-dose methotrexate used to treat neoplastic disease. As noted above, weekly low-dose methotrexate is associated with long-term tolerability and risk of side effects lower than that of most available medications for any indication, particularly with co-administration of folic acid would, in marked contrast to high-dose methotrexate.

b) The warning infers that concomitant use of NSAIDs or salicylates with methotrexate appears undesirable, on the basis of in vitro protein binding interactions. Ironically, methotrexate is commonly used in combination with salicylates and other NSAIDs in clinical practice. Indeed, it has been documented that the combination of courses of an NSAID and DMARD continued over the longest periods in RA involved methotrexate and zero-order release aspirin (5, 59). Nonetheless, at least 3 patients of the senior author were forced to go to 2 different pharmacies to fill prescriptions for methotrexate at one and for an NSAID at another, on the basis of well-meaning warnings. However, the findings and clinical practice suggest that in vitro observations are not clinically important.

c) The upper-case letters used to state that “YOUR DOCTOR WILL PERFORM LAB TESTS TO CHECK FOR SIDE EFFECTS” are accurate – although the report in which methotrexate was continued by 80% of patients over 5 years indicated that most discontinuations of methotrexate were for clinical adverse events, such as oral ulcers, gastrointestinal distress and/or central nervous system problems, rather for laboratory abnormalities (7).

d) It is noted that “additional monitoring of your dose or condition may be needed” with leflunomide, sulfasalazine, corticosteroids, salicylates, cyclosporine – although all have been documented to be used effectively over long periods in combination with methotrexate.

Nonetheless, such warnings are provided to all patients when filling a methotrexate prescription, without balanced information concerning the “side effects” of rheumatoid arthritis (60) – i.e. the likelihood that persistent inflammation will lead to progressive disease if no medication is not taken.

4. The admonition to patients to refrain entirely from consumption of alcohol while taking methotrexate may be unnecessary

Methotrexate certainly has potential hepatotoxicity in high doses. Therefore, patients who are treated with high-dose methotrexate are advised to refrain entirely from alcohol intake. A similar warning was given by many physicians to patients who were treated with weekly low-dose methotrexate for RA, and continues to be the practice of some rheumatologists. However, over time, it has become apparent that moderate alcohol intake may be well-tolerated by many patients who take weekly low-dose methotrexate, although patients with psoriatic arthritis may be more vulnerable to hepatic injury (61). A survey of 200 patients in the UK with 139 respondents (69%) indicated that 61% received advice about alcohol when given prescriptions for methotrexate (62). Among respondents, 36% reported no alcohol consumption, 20%<1 unit/week, 33% 1–7 units, 11% ≥8 units, including 4 patients >21 units/week. The highest mean alanine transaminase (ALT) was 41–42 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 with >21 units/week (62).

In the senior author’s clinical care, in which weekly low-dose methotrexate with co-administration of folic acid was continued over 5 years by 80% of patients (7), the standard instruction to patients was “do not consume more alcohol than your doctor,” i.e. up to 2 glasses per day. No patient discontinued methotrexate due to elevated liver enzymes over the 13 years of observation (7). Only 2 patients were not treated with methotrexate because of “excessive alcohol use.”

One patient, age 61, who readily acknowledged regular consumption of 5 drinks per day since age 15, presented with a severe RA flare after reasonable control with hydroxychloroquine. An extensive discussion led to a mutual decision by doctor and patient to try methotrexate 7.5mg 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 (63). Patients who have no evi-
idence of compromised liver function after more than 20 years of alcohol abuse may be regarded as having selected themselves as unlikely to experience hepatic damage with methotrexate. As moderate alcohol consumption is associated with longer general survival, a reassessment concerning warnings about consumption of alcohol while taking methotrexate may be of value.

5. Frequent blood testing of patients who take methotrexate may be overused

The American College of Rheumatology (ACR) guidelines for patients who are treated with methotrexate 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 (64). 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, as it has been extensively reported that they almost always resolve without changes in methotrexate therapy.

The standard practice in the senior author’s clinical care (7) 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 discontinuation of methotrexate due to elevated liver function enzymes, and no patient had evidence of hepatic damage over 13 years (7). A reassessment concerning frequency of laboratory tests for patients taking methotrexate may be of value, particularly as costs of patient copayments rise and cause further economic hardship to many patients.

6. Eligibility of only a small minority of patients for clinical trials to compare biologic agents and methotrexate

All clinical trial designs list inclusion and exclusion criteria. Most clinical trials that were conducted in patients who had RA during the 1990s (65-86) listed similar inclusion criteria, such as 6 or more swollen joints, 6 or more tender joints, an erythrocyte sedimentation rate (ESR) of 28 mm/h or more, or morning stiffness of 45 minutes or more (87, 88). These findings were common in patients who had active RA in the 1980s, but are not common at this time (18). Very few of today’s patients with RA seen in the US and Western countries are eligible to participate in most clinical trials.

Cross-sectional studies were conducted in the early 2000s of 2 cohorts of consecutive patients with RA in Nashville, TN, to study the proportion of patients who were eligible to participate in major clinical trials (87, 88). The first cohort of 232 patients had early RA of less than 3 years’ duration and was identified in a large, multi-rheumatologist private practice setting (Fig. 3). In this cohort, only 37 of all 232 patients (16%) met inclusion criteria for the ERA clinical trial of methotrexate versus etanercept (67, 89).

The second cohort included 152 patients with long-standing RA who had been monitored over 1 to 18 years at a weekly academic rheumatology clinic (88). This cohort was analysed according to basic inclusion criteria for the Anti-Tumour Necrosis Factor Trial in RA with Concomitant Therapy (ATTRACT) study of infliximab plus methotrexate versus methotrexate only (Fig. 4) (69, 90). Only 5% of patients met these inclusion criteria. Of course, at least 50% of the patients had experienced prior adequate responses to methotrexate and therefore were not appropriate to participate in a clinical trial of a new biologic agent. These observations and confirmation at other sites (91, 92) suggest that current inclusion criteria for RA clinical trials may be too restrictive and often do not apply to most patients seen in contemporary clinical settings in the US and Western countries. Problems introduced by exclusion criteria are seen in the previous examples of differences between patients who are taking their first DMARD versus any DMARD course (see Fig. 2). Furthermore, 40% to 60% of patients with RA have a normal ESR (87, 93, 94) and therefore would be ineligible for clinical trials according to this criterion. It may be appropriate to consider inclusion of patients who have fewer than 6 swollen joints or 6 tender joints – perhaps patients who have as few as 2 swollen joints – particularly with remission as the objective of current clinical care.

7. Step-up design in most comparisons of biologic agents with methotrexate includes only patients who had experienced an incomplete response to methotrexate

Patients who were studied in initial
ATTRACT Trial clinical inclusion criteria

Criteria:  
- ≥ 8 tender joints and ≥ 6 swollen joints  
- 2 of 3: Morning stiffness ≥ 45 min, ESR ≥ 28 mm/hour, CRP ≥ 2.0 mg/dL  
- MTX dose ≥ 12.5 mg/week

Fig. 4. Analysis of eligibility for the ATTRACT clinical trial, which established the efficacy of infliximab+methotrexate versus methotrexate-only (69,90), among 152 patients with long-standing RA who had been monitored over 1 to 18 years at a weekly academic rheumatology clinic (88). Only 5% of patients met these inclusion criteria.

and many subsequent clinical trials to compare the efficacy of methotrexate versus biologic therapies were selected for having experienced incomplete responses to methotrexate with continued moderate to high disease activity (95,96). This type of trial design is known as a “step-up” design (96), in which patients are randomised to an additional medication in combination with the medication to which responses were incomplete.

A “step-up” design is appropriate when patients experience incomplete responses to a standard of care, such as methotrexate as the anchor drug for RA. In theory, patients who had either adequate responses or no response to methotrexate were excluded. However, no formal criteria generally have been specified for “incomplete” or “adequate” or “no” response to methotrexate, which has been determined on the basis of “gestalt” impression of the rheumatologist and/or study coordinator. Patients who are classified as insufficient responders may well have once been previous ACR20 or ACR50 responders (97). Formal criteria for a stable response according to multidimensional health assessment questionnaires (MDHAQ) scores have been used in a recent clinical trial involving prednisone (98).

A “step-up” design has been applied in clinical trials involving all biologic agents that have been approved for marketing in the US and European and Asian countries, including the ATTRACT study (69,90), etanercept (99), infliximab (69,90), anakinra (70), adalimumab (100), abatacept (101), rituximab (102), certolizumab (103), golimumab (104), and tocilizumab (105). The reports do clearly state that the patients were selected for incomplete responses to methotrexate. However, derivative “marketing messages” often understate or omit mention of the selection process for patients in these clinical trials, and may be interpreted as suggesting that all patients respond with significantly greater efficacy to biologic agents compared to methotrexate.

In any approach to therapy, it would be anticipated that at least a few patients who had an incomplete response to a given medication would respond to addition of a second medication for any given indication. For example, if patients who experienced an incomplete response to an antibiotic for an infection or an antihypertensive agent for elevated blood pressure are given an additional antibiotic or antihypertensive agent, would it not be expected that some might experience improved results compared to patients who continued the same medication with a placebo? To be sure, improved results would not be seen if the second agent had no efficacy whatsoever. At the same time, evidence of improvement from a “step-up” trial does not indicate that the second (biologic) agent would have greater efficacy in all individual patients, particularly if most patients are not included because they had adequate responses to the first agent (methotrexate). Selection of patients for incomplete responses to one agent favours demonstration of significant efficacy for the new agent.

8. In parallel design trials, the efficacy of biologic agents is not substantially greater than that of methotrexate

In “parallel” design clinical trials – studies comparing efficacy of 2 medications, in which the patients have no prior exposure to either agent – results with methotrexate and biologic agents appear quite similar (see article in this Supplement by Rau). One example of a parallel design clinical trial is the early RA (ERA) trial (67,89) conducted in patients who had RA of less than 3 years’ duration, which established that etanercept 25mg twice a week had slightly greater efficacy than methotrexate, which had slightly greater efficacy than etanercept 10mg twice a week. Similar results have been seen in clinical trials with parallel design involving leflunomide, infliximab, adalimumab, and many others. These studies indicate that if methotrexate is administered to patients with early disease, results in most patients are quite similar to results with biologic agents, with only marginal advantage for biologic agents to inhibit radiographic progression.

9. Low, inflexible dosage schedules of methotrexate and requirement for withdrawal with minimal liver function abnormalities in many clinical trials may underestimate efficacy, effectiveness, tolerability and safety

In order to standardise protocols to mimic “scientific” conditions with minimal variation, clinical trial designs incorporate an inflexible dosage sched-
In almost all clinical trials, patients continued methotrexate and patients were treated with fixed low dosages and were required to be withdrawn for slightly abnormal liver function tests. Furthermore, co-administration of folic acid often was not included. By contrast, in standard clinical care, co-administration of folic acid is standard, the dosage of methotrexate has risen over the years (35) (see article in this Supplement by Sokka), and patients continue methotrexate with elevated liver enzymes to twice and sometimes three times normal levels, even with high dosages. The fixed low dosages of methotrexate and requirement for withdrawal with minimal abnormalities in clinical trials may explain, in part, underestimation of the efficacy of methotrexate and may explain, for example, why auranofin and methotrexate had similar efficacy in one clinical trial (36).

Methotrexate may also be administered parenterally in patients with inadequate responses or tolerability. At one site in the UK, 10% of RA patients took parenteral methotrexate, 75% of whom met criteria for the use of anti-tumour necrosis factor (TNF) agents. DAS response rates were similar to those seen in responders to oral methotrexate. The authors advocate consideration of parenteral methotrexate in all RA patients unresponsive to oral therapy prior to treatment with anti-TNF therapy, particularly in patients with low or high body mass index (106). The option of parenteral methotrexate was not available in some early clinical trials.

10. Interpretation of clinical trial results may overstate the clinical significance of lower radiographic progression in patients treated with biologic agents versus patients treated with methotrexate

In almost all clinical trials, a statistically significant advantage is seen to treatment with biologic agents compared to methotrexate in retardation of radiographic progression. These findings have been reported in trials with both step-up and parallel clinical designs. For example, analyses of the TEMPO trial indicated radiographic progression of 3.34 units according to the Sharp/van der Heijde scale in patients randomised to methotrexate, compared to 1.15 in patients randomised to etanercept, and 0.56 in patients randomised to the combination of methotrexate and etanercept (Fig. 5) (107). However, these analyses ignore several features of the observed differences:

a) The total number of units in a Sharp/van der Heijde score is 448 (107). 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 only 224. Nonetheless, radiographic changes of 2 units per year are statistically significant but clinically unimportant (Fig. 6) (108, 109), and 2 units would represent less than 1% of actual maximum scores. A clinically detectable minimal change at the rate presented would be seen only over 10 years, as differences must be at least 20 units to be appreciated clinically.

To be sure, reduction in the rate of radiographic progression is desirable, but it has been documented extensively that methotrexate inhibits radiographic progression considerably (18, 110). Reported differences in radiographic progression after treatment with methotrexate versus all biologic agents may not be sufficient to justify additional costs and risks of biological therapy.

b) Results of clinical trials are presented for groups of patients, and probability plots of TEMPO trial data indicate that 70% to 90% of individual patients have similar levels of radiographic progression with methotrexate or biologic agents, many showing no progression (Fig. 7) (107, 111). Some show improved scores, which may be the result of “healing” and/or measurement error. Similar data are seen in all clinical trials, as most individual patients have similar levels of radiographic progression with methotrexate or biologic agents.

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 (112). In a review of all 84 reports which described predictors of premature mortality in RA, functional status was a significant predictor of mortality in analyses in 17 of 18 studies, versus radiographs, which were significant in 5 of 18 studies (112). Therefore, a statistically significant change in radiographic scores may be clinically unimportant in prognosis.

Ironically, biologic agents were superior to methotrexate in groups of patients compared for improvement in functional status on a health assessment questionnaire (HAQ) at levels similar to differences in radiographic progression. However, these differences generally are not emphasised in presentations to rheumatologists nearly so much as structural changes seen in radiographs. Radiographs are correlated with laboratory tests, which are of highest prognostic significance in RA.

Conclusions
Taken together, the 10 factors addressed in this commentary indicate strongly that the efficacy, effectiveness, tolerability, and safety of weekly low-dose methotrexate with co-administration of folic acid generally is underestimated in information presented to rheumatologists, other physicians, and patients. Although the data are accurate, the interpretation is skewed against methotrexate. Fewer than 20% of presentations at annual meetings of the European League Against Rheumatism (EULAR) and ACR are about methotrexate and other DMARDs, although about 80% of patients take such agents in most clinical settings, and most patients are adequately treated with methotrexate. The authors hope that comments in this review and other articles in this Supplement will provide a more balanced view of the importance and value of methotrexate in management of rheumatic diseases at this time.

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