Editorial

Should aggressive therapy for rheumatoid arthritis require early use of weekly low-dose methotrexate, as the first disease-modifying anti-rheumatic drug in most patients?

Therapy for rheumatoid arthritis (RA) has evolved substantially over the last two decades. During the 1980s it was recognized that most patients experienced poor outcomes over 10–20 yr, including radiographic progression [1], severe functional declines [2, 3], work disability [2, 4] and premature mortality [2]. During the 1990s, calls for an aggressive strategy [5–10], led to the introduction of disease-modifying anti-rheumatic drugs (DMARDs) in early RA, particularly weekly low-dose methotrexate [11, 12], often in combination [10, 13], to prevent long-term damage. Weekly low-dose methotrexate had greater efficacy [11, 12], lower toxicity [14, 15] and considerably greater long-term continuation than previously available DMARDs [16]. During the first years of the present century, evidence of reduced mortality outcomes [17, 18] and considerably better clinical status compared with previous decades [17–21] reflect the effectiveness of methotrexate. Introduction of targeted biological therapies further enhances the armamentarium of rheumatologists to implement aggressive treatment strategies [22, 23].

Clinical trials in patients with early RA with combination DMARDs [24–26] and with biological agents [27] indicate the value of aggressive therapy in early RA. However, formal clinical trials have not been conducted to determine whether similar advantages to aggressive therapy might be seen in patients with long-standing disease.

In this issue of *Rheumatology*, Symmons and colleagues address the absence of formal clinical trial data concerning aggressive treatment of patients with stable RA of 5 yr or longer. They report a well-designed clinical trial by the British Rheumatoid Outcome Study Group (BROSG), to compare ‘intensified’ hospital treatment, with ‘the aim of suppressing the inflammatory process completely’, versus symptom control/shared care using standard DMARD therapy, over 5 yr in five UK rheumatology centres [28]. The primary outcome measure was the health assessment questionnaire (HAQ) score, admirably chosen in recognition that disease activity measures, such as the number of swollen and tender joints, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) may improve over 5–10 yr, while measures of joint damage, radiographic scores and HAQ scores indicate disease progression [1, 2, 29–32]. The intensified arm included visits every 4 months with a goal of reducing the CRP to twice the normal value.

The results indicated that HAQ scores worsened similarly in both groups over 36 months, suggesting that the intensified treatment protocol in this study did not provide superior results to standard care. These observations may initially appear discouraging to rheumatologists who believe that ‘tight control’ will improve outcomes in patients with long-standing RA, particularly to strict adherents to a view that optimum ‘evidence-based medicine’ [33] is invariably derived from clinical trials rather than observational studies. However, the authors themselves offer five possible explanations for the observed absence of differences between the two groups [28]:

(i) patients in the intensified group did not have indications for treatment changes;
(ii) treatment changes were indicated, and physicians did not act or patients refused;
(iii) patients in the intensified group did have evidence of disease activity, but there was no resultant improvement;
(iv) patients in the intensified group had evidence of disease activity, treatment change and their condition improved, but there was no effect on outcome;
(v) patients in the standard therapy group had their treatment changed as often as the patients in the intensified group [28].

They reject the first three explanations, as patients in the intensified group did have indications for treatment changes, physicians did act and there was resultant improvement. Nonetheless, support appears for the fourth and fifth possible explanations. Improvement was seen in disease activity and symptom control in 90% of patients in the intensified group, but HAQ scores indicated progression of disability [28]. Furthermore, there is some evidence that patients in the standard care group had their treatment changed ‘more often than might have been anticipated’, i.e. 56% of patients, albeit fewer than the 90% in the intensified treatment group [28].

These findings suggest ‘contamination of the control’, as patients and physicians participating in a clinical trial involving an intensified therapy might have determined that ‘standard therapy’ might be more ‘intensified’. Indeed, symptom control in the standard therapy group was 64%, only 6% less than seen in the intensified group. In addition, ‘non-compliance’ was noted in 8% of patients in the intensified group, including 50% characterized by ‘no reason’, 25% by refusal of the patient and 25% by the consultant regarding change as unnecessary, which may have attenuated possible differences between the intensified and standard therapies.

Although the type of ‘intensified’ care delivered in this trial did not appear to provide significant benefit for patients with established RA of 5 yr or longer compared with ‘standard’ care, many rheumatologists would not necessarily regard the ‘intensified’ approach as sufficiently aggressive. Adjustments of therapy were made every 4 months in the ‘intensified’ group, compared with monthly adjustments in the TICORA clinical trial toward complete control of inflammation [26]. Furthermore, only 38% of patients in the ‘intensified’ group took methotrexate and 22% combination therapy [28], figures considerably
lower than seen in seven US rheumatology private practices even in 1992 [16], and even much lower than in recent series [21, 34].

Three important lessons from the BROS trial may be recognized:

(i) This clinical trial adds further evidence to the literature suggesting that partial control of disease activity does not prevent long-term damage in RA [1, 2, 29–32]. Improvement, albeit modest, was seen in the number of swollen joints, tender joints, ESR and composite disease activity scores (DAS). The authors rated 49% of patients in the intensified arm as ‘treatment success’, including 70% with symptom control, 67% with CRP less than twice upper limit of normal, 70% with no actively inflamed joints and 31% as good or moderate responders according to European League Against Rheumatism (EULAR) response criteria [28]. HAQ scores worsened similarly to the standard care group.

(ii) The BROS trial may present a further example in which longitudinal observational data from clinical studies [17–21] may sometimes provide more accurate information than a clinical trial [35, 36]. Although the clinical trial represents the optimal method for analysing an experimental versus a control group, many limitations are seen in clinical trials [35–37]. As illustrated in this study, the design of a clinical trial can greatly influence results, as the outcome might have differed if the ‘intensified’ group had included more aggressive treatment. Furthermore, the existence of a control group does not assure that a question will be answered definitively.

A number of recent observational reports indicate improved status of patients with established RA using aggressive therapies [17–21], although the possible contribution of RA becoming a milder disease cannot be excluded from these findings [21]. The results also illustrate a further methodological issue that often is overlooked— that statistically significant observations are not necessarily clinically significant. For example, patients in the intensified arm were statistically significantly more likely than patients in standard care to begin methotrexate therapy (odds ratio 1.93, 95% confidence interval 1.11, 3.37) or receive combination therapy (odds ratio 2.1, 95% confidence interval 1.13, 3.91). However, these odds ratios are based on an increase of patients who took methotrexate in the ‘intensified arm’ from 21% at baseline to 38%, and combination therapy increases from 7 to 22% [28], considerably fewer than even in 1992 [16], and as noted above in 2000 [21, 34]. Therefore, the statistically significant odds ratios do not recognize that relatively few patients in the ‘intensified’ group were taking neither methotrexate nor combination therapy. Many reports in the rheumatology literature present statistically significant information which is not clinically significant.

(iii) Perhaps the most important lesson of this trial is that it appears unlikely at this time to achieve the authors’ ‘aim of suppressing the inflammatory process completely’ [28] without most patients having an opportunity to be treated with methotrexate. The algorithm used in this study considered DMARDs in three categories: category 1, sulphasalazine and antimalarials; category 2, intramuscular gold and methotrexate; and category 3, penicillamine, azathioprine and leflunomide. Although this classification is traditional, several observers, including the authors, have suggested that methotrexate should be regarded in a different category from other DMARDs, as it has greater efficacy, effectiveness, safety and tolerability than any of the other DMARDs by a wide margin [38, 39]. Even in 1992, the likelihood of continuation of methotrexate over 5yr was 50% compared with 20% for injectable gold, penicillamine, hydroxychloroquine or azathioprine, and a recent series indicated continuation of methotrexate by 80% of patients after 5yr [15]. The effectiveness of widespread use of methotrexate has been documented with improved mortality outcomes [17, 18], and considerably better clinical status of consecutive patients seen in 2000 compared with 1985, with fewer than half the number of swollen joints, as well as modified health assessment questionnaire (MHAQ) and quantitative radiographic scores, compared with 15yr earlier [21].

Nonetheless, weekly low-dose methotrexate continues to be regarded by many general physicians as associated with toxicities similar to those of daily high-dose methotrexate. However, weekly low-dose methotrexate appears primarily an anti-inflammatory rather than an immunosuppressive agent [40], and low white blood cell counts and high liver enzymes are unusual, despite allowing patients up to two alcoholic beverages per day [15]. To be sure, 20% of patients discontinued methotrexate over 5yr, and many patients report mild toxicities, ranging from hair loss, gastrointestinal distress and central nervous system problems. However, the authors are not aware of any therapy for any rheumatic disease that is continued by 80% of patients after 5yr (other than low-dose prednisone, for which the toxicities also are often confused with high-dose prednisone [41]). Therefore, the efficacy, effectiveness, safety, tolerability and benefit-risk of methotrexate may be among the most favourable available for any drug for any chronic disease at this time.

We conclude that this BSO clinical trial does further confirm that incomplete control of inflammation does not prevent long-term damage in patients with RA. We are not convinced, however, that the strategies used in this trial ‘with the aim of suppressing the inflammatory process completely in patients with long established RA’ necessarily would meet that objective, and suggest that evidence from observational studies might be used to develop a more effective intensified programme. Although many might suggest that anti-tumour necrosis factor alpha (TNFα) therapies are required for optimal control of inflammation in all patients, it is well to remember that FIN-RACO, COBRA and TICORA, which did not include anti-TNFα therapy, showed better results than many studies involving biological therapies by including early patients, and anti-TNFα therapy invariably led to better results with the addition of methotrexate. We suggest that methotrexate should serve as the ‘anchor drug’ [14] for patients with RA, to be used early in almost all patients as the first DMARD and required in any protocol designed to provide aggressive therapy.

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