Review

Aspects of early arthritis

Traditional DMARD therapy: is it sufficient?

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Abstract

There is increasing evidence for beneficial effects of early DMARD (disease-modifying antirheumatic drug) therapy over delayed treatment in patients who present with arthritis of recent onset. However, no universal consensus exists concerning the choice of initial drug or whether single drugs or combinations should be given as initial treatments. Recent studies have focused on the benefits of various strategies in which treatments were tailored to achieve low levels of disease activity, as assessed using validated response criteria. These studies demonstrated superiority of 'aggressive' over 'conventional' approaches. Whether the inclusion of tumour necrosis factor antagonists or other biologic targeted therapies in such strategies confers additional benefits in terms of improved long-term outcomes must be clarified by further studies. Assessment of risks in the individual patient, allowing individual 'tailoring' of the initial treatment, would be desirable.

Introduction

Diagnostic and treatment paradigms for rheumatoid arthritis (RA) and other potentially destructive arthritides have changed over recent years. Based on recognition of the risks that these diseases convey for patients in terms of quality of life and mortality [1-4], it has become a 'mantra' to diagnose and treat as early as possible [5]. Parallel to this development it has been recognized that conventional criteria for classification of destructive arthritides such as RA or psoriatic arthritis are not applicable to the early stages of these diseases [6,7]. However, many practicing physicians, in particular when they are less familiar with the multifaceted clinical appearances of these diseases, may be reluctant to begin administering potentially harmful drugs before a threshold of diagnostic certainty (such as the 'four criteria fulfilment' of the classification criteria for RA [8]) has been reached. On the other hand it has been recognized that delaying treatment, especially in high(er) risk patients, or inadequate treatment that does not control disease activity sufficiently may be quite detrimental in the long run [9].

Which strategies of treatment for early (rheumatoid) arthritis are optimal in which patients remains a subject of debate. Some evidence can be derived from studies published during recent years. This review focuses on the results of such studies and their possible implications for future therapeutic directions. It must be borne in mind, however, that most of these studies included patients with 'rheumatoid arthritis' in its early stages; the term 'early arthritis', on the other hand, encompasses a broader spectrum of diseases, which may differ from RA both in prognosis and response to therapy and in long-term outcomes.

Are there advantages of early DMARD treatment?

The hallmark of RA is the destructive inflammatory process, which – by virtue of the (bone and cartilage) damage induced in afflicted joints – leads to functional impairment and disability. The destruction is essentially irreversible, and repeated periods of active inflammation in a particular joint add further damage to pre-existing destruction. It is therefore clear that preventing, retarding, or halting damage early may have significant long-term benefits. Disease-modifying anti-rheumatic drugs (DMARDs) are the mainstay of RA therapy because of their significant effect on inflammation, damage and function. Their benefit in terms of preservation of joint structure as well as preventing disability in RA (mostly of long disease duration) is well established. Meta-analyses and retrospective analyses of large patient cohorts have revealed that responses to DMARDs or their retention rates are better in the early stages of the disease [10,11]. Two studies conducted in the mid-1990s suggested benefit from instituting DMARDs earlier than after the then customary waiting period of up to several years [12,13]. Egsmose and coworkers [12] conducted a double-blind, placebo-controlled trial in patients with RA of under 2 years duration; patients were treated with auranofin or treatment was delayed,

ACR = American College of Rheumatology; DAS = Disease Activity Score; DMARD = disease-modifying antirheumatic drug; EULAR = European League against Rheumatism; HAQ = Health Assessment Questionnaire; RA = rheumatoid arthritis; TNF = tumour necrosis factor.

employing placebo for 8 months instead. Clinical and radiological benefit was seen for the DMARD-treated group at 2 and 5 years. Van der Heide and coworkers [13] randomized 238 consecutive patients with early RA to receive DMARDs (hydroxychloroquine, intramuscular gold, or oral methotrexate; 7.5–15 mg/week) either immediately or with a delay, in an open-label manner. Both functional and clinical outcomes significantly favoured early DMARD treatment, and the control group had almost four times more treatment discontinuations. The observations of these studies have since been confirmed by numerous others, in which treatment with DMARDs was started earlier than 2 years after onset [14-19] or even earlier than 3 months [20]. Whether some DMARDs are more efficacious than others in such early (or very early) disease remains a matter of debate.

These studies suggest benefit from early therapy compared with a delayed start of DMARD therapy, at least during the initial year(s) of RA. Longer term extensions of these studies demonstrate that after the initial 'head start' conferred by early (aggressive) therapy, the rates of clinical success in the 'conventional' and 'aggressive' treatment groups converge [21-23]. Analysis of radiological progression rates, however, revealed a preserved advantage (despite identical clinical outcome) in the aggressively (and early) treated patients [21,22]. In the Utrecht cohort [23], in which 'aggressive' treatment was not mandated by the protocol and in which 'time to DMARD' was the principal difference between the two groups, the radiological damage scores in both groups approached each other and appeared to be identical during later stages. Thus, it remains to be determined whether the benefit observed after 1 or 2 years of early treatment may remain clinically relevant after 1 or 2 decades.

The complexities of the problem are highlighted by a report on 5-year outcomes in the Norfolk Arthritis Register [24]. In this inception cohort, patients with early inflammatory polyarthritis (not RA) were included and followed regularly over an extended period [25]. This initiative is remarkable in that it included patients with any kind of arthritis who were then assessed by a trained research team and followed as completely and comprehensively as possible over the following years. The 5-year radiological outcomes of 335 patients indicated that patients who were DMARD treated had worse radiological outcomes than patients who were never treated with DMARDs or in whom DMARD start was delayed for over 12 months. However, the patients without DMARD treatment or with delayed treatment had milder disease at baseline, as indicated by several parameters such as age at onset, delay to presentation, sex, maximal early morning stiffness, rheumatoid factor titre, Health Assessment Questionnaire (HAQ), C-reactive protein, and number of swollen and tender joints. After adjustment for these severity indicators, early initiation (before 6 months of disease) resulted in the most favourable outcome in severe RA, whereas in 'mild' cases treatment delay did not adversely affect radiological progression. Early (versus later) treatment also appeared to be beneficial in patients who were erosion free at the time of the first film (which was taken up to 1 year after onset of disease) in terms of influencing radiographic outcome at 5 years.

How aggressive should initial therapy be?

In a remarkable reversal of therapeutic paradigms, the cautious approach employed until the late 20th century, known as the 'therapeutic pyramid' [26], has been reversed to call for an early, optimally effective initial (DMARD) treatment. Given the possible toxicity of such an aggressive approach, as soon as 'remission' or a 'low disease activity stage' is reached the dosage should be reduced to the lowest level required to maintain this disease state.

Several investigations have addressed the issue of whether initial aggressive treatment of early RA confers benefits over more conservative strategies. The COBRA trial [15] compared initial therapy with methotrexate (7.5 mg/week), sulfasalazine (2 g/day) and prednisolone (starting with 60 mg/day and tapering over 6 months) versus sulfasalazine monotherapy (without steroids) over 1 year in patients with RA of duration under 2 years. The FIN-RACo trial [27] employed sulfasalazine, methotrexate, hydroxychloroquine and prednisolone in combination (maximum doses: 2 g/day, 15 mg/week, 300 mg/day and 10 mg/day, respectively) in patients with RA of duration under 2 years for 2 years. The 'single DMARD group' patients were sequentially treated with sulfasalazine, followed by methotrexate and then azathioprine (or, if deemed necessary, auranofin, hydroxychloroquine, injectable gold, penicillamine, or podophyllotoxin) if clinical response was insufficient. This single treatment group also permitted use of up to 10 mg/day prednisolone. In another Dutch study, van Jaarsveld and coworkers [28] compared hydroxychloroquine (if necessary replaced by auranofin) with intramuscular gold (if necessary replaced by D-penicillamine) and methotrexate (if necessary replaced by sulfasalazine) over 2 years in patients with disease duration under 1 year. Therapy with sulfasalazine, methotrexate and hydroxychloroquine as single DMARDs was compared with methotrexate plus sulfasalazine or methotrexate plus hydroxychloroquine and triple therapy by Calgüneri and coworkers [29] over 2 years. Proudman and coworkers [30] administered sulfasalazine (supplemented with intra-articular or intramuscular steroids if clinically indicated during the observation period of 1 year) and compared this strategy with a combination of methotrexate and cyclosporine A in patients with RA of duration under 1 year. The combination group received initial intra-articular steroids and subsequently received intra-articular or intramuscular steroid injections if joints were clinically active. Two studies [31,32] compared methotrexate, sulfasalazine and the two agents combined in RA patients of duration under 1 year and at high risk for aggressive disease (rheumatoid factor and/or shared epitope positivity) over 1 year.

Benefit of the more aggressive approach over the 'conservative' treatment was demonstrated in the COBRA [15] and FIN-RACo [27] studies as well as in the studies conducted by van Jaarsveld [28], Calgüneri [29] and Proudman [30] and their groups. However, the studies comparing the sulfasalazine/methotrexate combination versus the single agents [31,32] were unable to identify better outcomes for any treatment arm over the others, although there was a nonsignificant trend in favour of combination therapy.

Important points to be considered in interpreting the findings of these studies relate to the choice of the DMARDs used in the 'aggressive' or combination arms as well as to the use of steroids. Thus, although van Jaarsveld and coworkers [28] employed DMARDs early in all three arms, hydroxychloroquine (regarded to be the least potent of the three drugs [33]) and intramuscular gold (which has a significant delay until onset of its effect [34]) were demonstrated to be inferior to methotrexate with its (relatively) quick onset of action and greater potency. Both the COBRA study [15] and the FIN-RACo trial [27] mandated steroid use from the start in the aggressive arms, and although in the latter study the permitted steroid dose was identical and the amount of steroid use was higher in the single DMARD group, steroids were introduced rather late in this group, at up to 93 weeks from baseline [35]. The study conducted by Proudman and coworkers [30] employed both a potent DMARD (methotrexate) and a steroid in all patients in the 'aggressive' arm, whereas in the comparator group only 66% of patients received steroids at all, with a cumulative dose of about one-third that in the aggressive treatment group. In contrast, the two trials employing sulfasalazine and methotrexate compared two DMARDs with similar characteristics in terms of time to onset of treatment effects as well as efficacy in established RA [36,37]. Thus, a difference in efficacy between the two agents would have been more difficult to detect. Moreover, recent data have indicated that the combination of sulfasalazine and methotrexate should yield little benefit because of their biologic interactions [38].

Importantly, in all trials using aggressive approaches to initial treatment of arthritis, all patients – including those treated with intensive DMARD (and steroid) regimens – deteriorated with respect to radiological score. No significant differences, in terms of either number of patients with radiographic progression or damage scores, were reported by van Jaarsveld [28], Maillefert [39], Calgüneri [29] and Proudman [30] and their groups. Arrest of progression in terms of joint and bone destruction was achieved in only about half of these early RA patients. Only the COBRA [15] and the Fin-RACo trials [27] reported radiographic benefits in the high intensity treatment groups, although the results of the COBRA trial, in particular, make it very much likely that this difference was attributable mainly to the early and intensive use of steroids rather than the combination of DMARDs.

Taken together, a benefit not only of early but also of aggressive treatment in patients presenting with arthritis of short duration, at least for the clinical course, seems achievable, particularly when highly active DMARDs (sulfasalazine or methotrexate) are combined with (sufficient doses of) steroids. However, unequivocal benefit of combination therapy with ('conventional') DMARDs is yet to be demonstrated. Furthermore, even using these intensive treatment regimens, only a fraction of patients achieved the 'ideal' goal, namely halted progression and elimination of clinical activity ('remission'). Moreover, in terms of radiological outcome, progression was observed in a substantial number of patients despite use of these strategies.

Is therapeutic success a question of treatment strategy?

A recently published study examined the influence of a strategy of 'tight control in RA' (TICORA) [40]. A total of 110 patients with RA of duration under 5 years who had not received combination therapy were randomly assigned to 'tight' or 'routine' control. A Disease Activity Score (DAS)44 [41] of 2.4 or less was defined as the aim in the TICORA group, and this was examined monthly. Therapy was escalated according to a predefined strategy: sulfasalazine 500 mg/day increased to 40 mg/kg/day; progressing to combined sulfasalazine, methotrexate 7.5 mg/week and hydroxychloroquine 200-400 mg/day; progressing to triple therapy with methotrexate up to 25 mg/week; progressing to triple therapy with sulfasalazine up to 5 g/day followed by addition of prednisolone 7.5 mg/day; progressing to cyclosporin A at 2-5 mg/kg per day plus methotrexate 25 mg/week; followed by a change to alternative DMARD (leflunomide or sodium aurothiomalate) if the DAS44 score was above 2.4. These therapies were given in addition to intra-articular steroid injections. In the 'routine' group patients were seen every 3 months without formal assessment or feedback on disease activity scores; therapy adaptation was thus performed based on the clinical judgement of the rheumatologist. The TICORA group had significantly more remissions and European League against Rheumatism (EULAR) responses as well as American College of Rheumatology (ACR)70 responses. Indicators of quality of life (HAQ, 12-item Short Form) and X-ray progression were also in favour of the TICORA strategy (although there still was median [interquartile range] progression by 4.5 [1-9.875] points in the Sharp-van der Heijde score [42] in the TICORA group; in the routine group this progression was 8.5 [2-15.5]). Remarkably, this intensive monitoring strategy resulted in a higher treatment retention rate, a lower rate of discontinuations due to side effects, and lower costs per patient (based on lower admission costs) than the routine control over the 18 months of observation.

Can biologics add efficacy in early rheumatoid arthritis?

In several clinical trials highly potent biologics, such as tumour necrosis factor (TNF) antagonists, have effectively improved clinical activity and slowed radiological deterioration

in established disease [43,44]. All three commercially available TNF antagonists have been tested in methotrexate-naïve RA patients, although the disease would not necessarily be regarded as 'early' because patients were included up to 3 years after disease onset [45-47]. These three trials yielded remarkably similar results: the TNF antagonists and methotrexate exhibited comparable clinical efficacy, with similar response rates as estimated by ACR or EULAR criteria. The combination of etanercept, infliximab and adalimumab with methotrexate was more effective than monotherapy. In addition, at least for infliximab, it has been demonstrated that, even in cases in which clinical activity was not optimally suppressed ('poor response'), radiographic progression appeared to be significantly retarded in comparison with methotrexate [48].

These results raise expectations that addition of biologics to the treatment regimen in early RA might be superior to the results obtained with DMARD combinations or DMARDs (single or in combination) with steroids. In addition, the results of the TICORA strategy [40] (adaptation of treatment according to response, with clearly defined aims to reach thresholds for low disease activity or remission) indicate superiority of the intensive control/intensive DMARD/steroid strategy, with good tolerability.

A recently published study combined these approaches [49]. In an open four arm design, patients with early RA (duration under 2 years) were assigned to receive one of four treatment strategies. Similar to the TICORA strategy, the aim was to reduce the DAS44 score to values below 2.4. A total of 508 patients were allocated to receive one of four strategies. The first arm (group 1) was the 'sequential monotherapy' arm: methotrexate up to 25-30 mg/week; progressing to sulfasalazine; progressing to leflunomide; progressing to methotrexate plus infliximab; progressing to gold plus methylprednisolone; and finally progressing to methotrexate plus cyclosporin A and prednisone. The second arm (group 2), the 'step-up combination therapy' arm, involved the following: methotrexate increased to 25-30 mg/week; progressing to addition of sulfasalazine, hydroxychloroquine and prednisone, always added to the current combination; progressing to a switch to methotrexate plus infliximab; progressing to a switch to methotrexate with cyclosporine A and prednisone; progressing to a switch to leflunomide. The 'step-down therapy' arm (group 3) was initially adapted from the COBRA scheme [15]; the following protocol was followed in case of insufficient response: increase of methotrexate to 25-30 mg/week; progressing to addition of cyclosporine A and prednisone; progressing to switch to methotrexate plus infliximab; progressing to switch to leflunomide monotherapy; progressing to switch to gold plus methylprednisolone; and progressing to switch to azathioprine plus prednisone. In the final arm (group 4) patients were admininstered initial infliximab plus methotrexate (with increased infliximab dose in the case of insufficient response).

Treatment was stepped up if the DAS44 score was above 2.4 at any visit; if the DAS44 score was below 2.4 for two consecutive (three monthly) visits, treatment was reduced to the 'previous step'. The end-points in this study were functional capacity according to HAQ and radiological progression. A total of 491 patients (97%) completed the first year, and the aim of a DAS44 score below 2.4 was reached by significantly more patients in groups 3 and 4 than in group 1 (71% and 74% versus 53%; $P = 0.004$). Moreover, retention of initial treatment was significantly more frequent in groups 3 and 4 due to good response. The HAQ was significantly more improved in groups 3 and 4 compared with group 1 after 12 months. In addition, the pace of HAQ improvement was more rapid in these groups (improvement by over 60% after 3 months) than in groups 1 and 2 (only modest improvement after 3 months; marked improvement only after 9-12 months, but still less than in the two 'intensive' groups). In terms of radiological outcomes, the results were similar: patients in groups 3 and 4 had significantly better radiological outcomes at 12 months than did those receiving the two less intense treatment strategies.

Of interest is the observation that 50% of patients in the infliximab group could stop the biologic at the end of year 1 because of persistent low disease activity. In group 1 (sequential monotherapy), 20% needed methotrexate plus infliximab. In groups 2 and 3 fewer than 10% were treated with methotrexate plus infliximab. This trend continued in the second year of the study, with 26%, 10%, 11% and 19% of patients on infliximab in groups 1-4 (unpublished personal communication).

Conclusion

DMARD treatment is clearly beneficial in early arthritis patients, among whom many will develop destructive arthritis classifiable as RA. Delaying treatment is justified (if at all) only in those who present with very mild disease less than 3 months from disease onset. Arthritis that is persistent for more than 12 weeks is unlikely to remit spontaneously [50]; many of these patients will progress to develop RA and patients with significant initial disease activity benefit from an early start of DMARD, even if 'conventional treatment' is used. The 'best' initial treatment seems to be less a matter of drug choice and more a question of whether treatment aims ('remission' or 'low disease activity' as defined by available scores [41,51-55]) are strictly followed. The initial addition of

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steroids to any such treatment should be strongly encouraged [35,56]. The biologics, in particular TNF antagonists, appear to confer additional benefits. In early arthritis patients with high disease activity and/or risk factors for adverse outcomes (e.g. [high titre] rheumatoid factor or anti-cyclic citrullinated peptide antibodies [9]), a 'preventively aggressive' strategy including the entire drug armamentarium available seems justified.

Competing interests

The authors declare that they have no competing interests.

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