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Approaches to the treatment of early rheumatoid arthritis with disease-modifying antirheumatic drugs

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This paper reviews recent approaches to treatment of early rheumatoid arthritis (RA) with disease-modifying antirheumatic drugs (DMARDs). The literature on treatment the early RA published between 1995 and 2007 was accessed through the PubMed database from the National Library of Medicine. Keywords were 'early rheumatoid arthritis', 'disease-modifying antirheumatic drugs', 'biologic agents' and 'combination therapy'. Only results of trials on human subjects that directly measured the effects of DMARDs or biological agents on clinical, laboratory parameters and radiological progression of early RA were selected. Combination therapy suppresses RA activity and radiological progression more effectively than monotherapy. If better control of RA is evident after 3–6 months of treatment with the combination of DMARDs, one must still decide whether to stop the first DMARD, stop the second, or continue with the combination. Combination therapy biological agents (infliximab, adalimumab) with methotrexate and etanercept therapy alone may induce remission in many patients with early RA. It is a method of choice in patients with an adverse prognosis. The main indications for combination therapy 'standard' DMARDs or combination 1 DMARDs with a biological agent are such variables as detection of a shared epitope, increase of concentration of anticyclic citrullinated peptide antibodies, rheumatoid factor, C-reactive protein, 28-joint disease activity score, Sharp score and presence of erosion in joints. The majority of rheumatologists believe that patients with RA should be treated with DMARDs earlier rather than later in the disease process. Further trials should establish the optimal approaches to early RA therapy.

Introduction

Rheumatoid arthritis (RA) is an autoimmune disorder, characterized by symmetrical erosive arthritis and a wide spectrum of systemic damages. It affects about 0.5–1% of the population worldwide [1] and is associated with significant disordering of physical function and decrease of quality of life.

The main aim of treatment of early RA should now be to achieve clinical remission, in order to prevent structural damage and physical disability.

As recently as 10 years ago, many patients with RA would receive only a nonsteroidal anti-inflammatory drug and low-dose corticosteroids until damage to their joints was documented [2]. The majority of rheumatologists now believe that patients with RA should be treated with disease-modifying antirheumatic drugs (DMARDs) earlier rather than later in the disease process. 'DMARDs' includes disease-modifying antirheumatic drugs such as methotrexate (MTX), sulfasalazine (SSZ), leflunomide, hydroxychloroquine (HCQ) and gold, but also the tumour necrosis factor (TNF)-blockers infliximab and etanercept and other biological agents [3]. Early referral (at <3 months) and early DMARD treatment enable the course of RA to be changed [4]. Well-designed, long-term, controlled clinical trials have allowed determination of which combinations, dosage schedules and sequences of administration are most beneficial and least toxic [5].

This paper reviews recent approaches to the treatment of early RA with DMARDs.

Methods

The literature on treatment the early RA published between 1995 and 2007 was accessed through the PubMed database from the National Library of Medicine. Keywords were 'early rheumatoid arthritis', 'disease-modifying antirheumatic drugs', 'biologic agents' and 'combination therapy'. Only results of trials on human subjects that directly measured the effects of DMARDs or biological agents on clinical, laboratory parameters and radiological progression of early RA were selected.

Results

As a search of the literature has shown, rheumatologists and other treating physicians use two main treatment approaches in early RA: monotherapy and combination therapy.

DMARD therapy of early RA

SSZ, MTX and HCQ are the most commonly used traditional DMARDs [6]. Very important studies regarding therapy of the early RA patients are quoted in Table 1.

The first line of treatment in early RA often involves MTX monotherapy [7]. So, for example, The North American Cohort of Patients with Early RA (SONORA), which included patients with symptoms for >3 but <12 months, indicated that MTX was the most frequently prescribed DMARD, being taken by more than half of patients [8]. The study by Stenger *et al*. has shown that early 'aggressive' drug treatment, using SSZ and/or MTX, aimed at reduction of the C-reactive protein (CRP) level, significantly reduces radiographic progression in RA [9].

The recent PROable rheumatoid arthritis Methotrexate *vs.* Placebo Treatment (PROMPT) study, a double-blind, placebo-controlled, randomized, multicentre trial in 110 participants with undifferentiated (with undetermined diagnosis) RA, was conducted to determine whether participants would benefit from treatment with MTX. After 30 months, the group taking MTX showed somewhat less radiographic progression. The protective effect of MTX was greatest in subjects seropositive for anticyclic citrullinated peptide (anti-CCP) antibodies [10].

Lard *et al*. compared 79 patients diagnosed with probable or definite RA whose treatment (chloroquine or SSZ) started within 15 days of referral with 109 patients after a delay of about 4 months. After 2 years, the early treatment group had less radiological joint damage [median Sharp score 3.5; 95% confidence interval (CI) 1, 7] than the delayed treatment group (median Sharp score 10; 95% CI 5, 15; $P < 0.05$). The median area under the curve of the 2-year disease activity score was lower in the early treatment group (64 units; 95% CI 59, 69) compared with the delayed treatment group (73 units; 95% CI 69, 77; $P = 0.002$) [11]. The beneficial effect of early DMARD treatment on the radiological progression of joint damage was still present at 4 years. However, the rate of joint destruction from 1 to 4 years did not differ between the delayed and early treatment groups. Joint destruction in both groups positively correlated with the presence of the shared epitope (SE) [12].

The studies by Lard *et al*. and Emery *et al*. have shown that early treatment by traditional DMARDs improves long-term outcomes and quality of life more than delayed treatment until 3 months [13].

Nell *et al*. compared the changes of 28-joint disease activity score (DAS28) over time of patients with very early RA (<3 months) with those with late–early RA (from 6 months to 3 years). Patients in both groups had high

Table 1

Comparison of efficiency of combination therapy and monotherapy with disease-modifying antirheumatic drugs (DMARDs)

Trial	Therapy	Result
van Dongen H *et al*./PROMPT-study [10]	MTX or placebo	MTX showed somewhat less radiographic progression at 30 months
Boers *et al*./COBRA [16]	Step-down combination therapy with SSZ, MTX, prednisolone or SSZ monotherapy	Combination treatment during the 4–5 years had greater decrease of Sharp progression rate
Hetland *et al*./CIMESTRA study [17]	MTX + cyclosporine + intra-articular glucocorticoid betamethasone	Delay to progression of erosions in patients at 2 years
Möttönen *et al*./FIN-RACo [18, 19]	Combination of DMARDs (SSZ, MTX, HCQ), and prednisolone or a single DMARD with or without prednisolone	Combination of 3 DMARDs for the first 2 years limits peripheral joint damage (Larsen scores) for at least 5 years
Smolen *et al*./ATTRACT [26]	INF + MTX	Significant benefit with regard to the destructive process, clinically relevant improvement in physical function and quality of life
St Clair *et al*./ASPIRE [28] Quinn *et al*. [29]	INF + MTX or MTX	Combination therapy with MTX and INF provided greater clinical and functional benefits and significant reduction in MRI evidence of synovitis and erosions at 1 year
Genovese MC *et al*./ERA trial [31]	ETN or MTX	Profound reduction in radiographic progression of joint damage and reduction in signs of disease at 1 and 2 years
Goekoop-Ruiterman *et al*./BeSt [33]	Sequential monotherapy (group 1), step-up combination therapy (group 2), initial combination therapy with tapered high-dose prednisone (group 3), or initial combination therapy with infliximab (group 4)	Groups 3 and 4 showed more rapid clinical improvement and less progression of joint damage during the first year
Breedveld *et al*./PRIEMER [35]	Adalimumab + MTX or adalimumab or MTX	Combination therapy provided disease remission (DAS28 < 2.6) and ACR70 response for 49% patients, rates approximately twice those found among patients receiving either monotherapy at 2 years

MTX, methotrexate; SSZ, sulfasalazine; HCQ, hydroxychloroquine; INF, infliximab; ETN, etanercept; DAS28, 28-joint disease activity score; ACR, American College of Rheumatology.

disease activity according to DAS28 scores. Although both groups had statistically significant improvement over time, the DAS28 in the very early group decreased into the low activity range, whereas in the late–early group it reached a plateau in the moderate activity range. The largest difference in relative improvement occurred during the first year. During the second and third years, improvement trends in these groups were parallel [14].

The Combinatietharapie Bij Reumatoide Arthritis (COBRA) trial in patients with early RA (<2 years) compared efficacy of combination therapy by SSZ (2 g day^{-1}) with prednisolone (initially 60 mg day^{-1}, tapered in 6-weekly steps to 7.5 mg day^{-1}) and MTX (7.5 mg $week^{-1}$ with a cancellation by 40 weeks) in a step-down approach with SSZ monotherapy. The analysis of results testified that combined therapy suppresses RA activity more effectively than monotherapy by SSZ (by 28 weeks) [15]. During the 4–5-year follow-up period, the time-averaged DAS28 decreased 0.17 points per year in the SSZ group and 0.07 in the COBRA group. The Sharp progression rate was 8.6 points per year in the SSZ group and 5.6 in the COBRA group. The between-group difference in the rate of radiological progression was 3.7 points per year. Independent baseline predictors of radiological progression over time (apart from treatment allocation) were rheumatoid factor (RF) positivity, Sharp score and DAS28. The authors have shown that an initial 6-month cycle of intensive combination treatment that includes high-dose corticosteroids results in sustained suppression of the rate of radiological progression in patients with early RA [16].

The Cyclosporine, Methotrexate, Steroid in RA (CIMESTRA) study investigators applied intra-articular glucocorticoid betamethasone to swollen joints (maximum four joints or 4 ml per visit) in combination with step-up treatment with either MTX 7.5 mg $week^{-1}$ and placebo-ciclosporin 2.5 mg kg^{-1} of body (monotherapy) or MTX plus ciclosporin (combination therapy) in patients with early RA (<6 months' duration). Continuous MTX and intra-articular corticosteroid treatment resulted in excellent clinical response and disease control at 2 years, and the radiographic erosive progression was minimal. Addition of ciclosporin did not have any additional effect on remission rate and radiographic outcome [17].

In the FINnish Rheumatoid Arthritis Combination therapy (FIN-RACo) trial, patients with recent-onset RA (median duration 6 months) were randomly assigned to receive either (i) a combination of DMARDs (SSZ, MTX, HCQ), and prednisolone or (ii) a single DMARD with or without prednisolone. At 2 years, 40% of the patients in the combination-DMARD group and 18% in the single-DMARD group had achieved remission ($P < 0.009$). The frequency of achieving remission in the combination-DMARD group after 2 years was similar in patients with short (0–4 months) and long (>4 months) delay periods (approximately 42% in each group), whereas the corresponding frequencies in the single-DMARD group were eight of 23 patients (35%) and seven of 63 patients (11%) ($P = 0.021$). The delay to therapy (cut-point of 4 months) was therefore the only significant predictor for remission in patients treated using the single-DMARD strategy, whereas no variable was a significant predictor for remission in those treated using the combination-DMARD strategy [18]. At 5 years ($n = 160$), the corresponding percentages of remissions in the combination-DMARD group and in single-DMARD group were 28 and 22%, respectively (P = NS). The median Larsen radiological damage scores at baseline, 2 years and 5 years in the combination-DMARD and single-DMARD groups were 0 and 2 ($P = 0.50$), 4 and 12 ($P = 0.005$) and 11 and 24 ($P = 0.001$), respectively. The frequencies of adverse events were similar in both treatment groups [19]. The authors concluded that the delay of a few months from the onset of symptoms to institution of therapy decreases the ability of the traditional single-drug strategy to induce remission in early RA. Aggressive initial treatment of early RA with the combination of three DMARDs for the first 2 years limits peripheral joint damage for at least 5 years [20].

If better control of RA is evident after 3–6 months' treatment with the combination of DMARDs, one must still decide whether to stop the first DMARD, stop the second, or continue with the combination. In the absence of major toxicity, it is possible to continue the combination if the patient has had a good response, thus inadvertently embarking on prolonged combined DMARD therapy [5].

Recent research has provided new information on genetic markers predicting rapid progression of joint destruction; the role of serology, in particular, antibodies to citrullinated peptides in diagnosing RA; the utility of radiographic techniques in detecting both early synovitis and bone erosion; and the value of combination therapy in controlling signs, symptoms and radiographic progression [21]. The Norfolk Arthritis Register (NOAR) study, in which RA patients with 3 months of symptom onset participated, showed that although the peak incidence of first erosions is in the first 24 months, individuals who are non-erosive at 24 months have an ongoing risk of becoming erosive that does not decline with time. CRP and RF titre >1/160 was the strongest predictor of radiological progression. Patients who were SE– responded less to treatment than those who were SE+. All these factors were the cause of early beginning of treatment of DMARDs [22].

Leflunomide and biological agents in early RA

The development of drugs for RA resumed a few years ago with the introduction of leflunomide (inhibitor of pyrimidine synthesis) and the biological agents. Unlike the older DMARDs (apart from the cytotoxics), the newer drugs have been designed with strict reference to RA pathophysiology, and the intended action of these agents is highly likely to be the explanation for their observed efficacy. Proinflammatory cytokines, such as interleukin (IL)-1 and TNF,

play an important role in maintaining the chronicity of RA and mediating tissue damage [23]. The anti-TNF and IL-1 therapies exert their anti-inflammatory action by neutralizing the activities of TNF-α and IL-1, respectively [24].

Three biological agents that inhibit TNF-α are approved for treating RA. Infliximab (INF) is a chimeric (human/mouse) monoclonal antibody and adalimumab is a humanized monoclonal antibody. Etanercept (ETN) is a fusion protein comprising two soluble human TNF-α receptors linked to the Fc fragment of human immunoglobulin G1 [25].

As seen in the anti-TNFalpha trial in RA with concomitant therapy (ATTRACT) study, combination therapy with MTX (20 mg $week^{-1}$) and INF (3 mg kg^{-1} INF or 10 mg kg^{-1} INF every 4 or 8 weeks) at 54 weeks for patients with active early RA provided significant benefit with regard to the destructive process [26]. The combination therapy of INF plus MTX provided significant, clinically relevant improvement in physical function and quality of life, accompanied by inhibition of progressive joint damage and sustained improvement in the signs and symptoms of RA [27]. These data have been confirmed in the international study Active Controlled Study of Patients Receiving Infliximab for Treatment of Rheumatoid Arthritis of Early Onset (ASPIRE), in which 1049 patients have been included. Patients in the MTX 3 mg kg^{-1} INF and MTX 6 mg kg^{-1} INF groups also showed less radiographic progression than those receiving MTX alone. For patients with active RA in its early stages, combination therapy with MTX and INF also provided greater clinical and functional benefits than treatment with MTX monotherapy [28]. Quinn *et al*. showed that remission induction with INF plus MTX provided a significant reduction in magnetic resonance imaging evidence of synovitis and erosions at 1 year [29]. However, the use of TNF blocking agents may be valid only in a limited number of patients with the most severe RA [30].

The Early Rheumatoid Arthritis (ERA) trial compared monotherapy with ETN or MTX in patients with early erosive RA. Over the initial period of 12, and subsequently 24 months, both treatments were associated with a profound reduction in radiographic progression of joint damage, as well as a reduction in signs and symptoms of disease. ETN showed slight superiority to MTX in reducing subsequent radiographic erosions and in the rapidity of the clinical response [31].

Goekoop-Ruiterman *et al*. determined treatment preferences among patients with recent-onset RA participating in a randomized controlled Behandel Stategienn (BeSt) trial comparing four therapeutic strategies. Of 508 participants, treated for an average of 2.2 years with either sequential monotherapy (MTX, and then SSZ or Leflunomid or MTX + INF) (group 1), step-up combination therapy (MTX + SSZ + HCQ + corticosteroids → MTX + INF) (group 2), initial combination therapy (MTX + SSZ) with tapered high-dose prednisolone (group 3), or initial combination therapy MTX with INF (group 4), 440 patients (87%) completed the questionnaire. Almost half expressed no preference or aversion for a particular treatment group, 33% had hoped for assignment to group 4 and 38% had hoped against assignment to group 3. This negative perception was much less prominent in patients actually in group 3. Nevertheless, 50% of patients in group 3 disliked having to take prednisolone, whereas only 8% in group 4 disliked going to the hospital for intravenous treatment. Within the limitations of this retrospective study, patients clearly preferred initial combination therapy with INF and disliked taking prednisolone. After actual exposure, this preference remained, but the perception of prednisolone improved [32]. Groups 3 and 4 showed more rapid clinical improvement during the first year. All groups improved further to a mean functional ability score of 0.6, and 42% were in remission (P = NS) during the second year. Progression of joint damage remained better suppressed in groups 3 and 4 (median scores of 2.0, 2.0, 1.0 and 1.0 in groups 1, 2, 3 and 4, respectively; $P = 0.004$). It is remarkable that in 53% of patients after elimination of INF in group 4, the effect of therapy on MTX monotherapy persisted [33].

Clinical guidelines recommend the use of TNF blockers as treatment options for adults with RA that continue to have clinically active disease that has not responded adequately to two conventional DMARDs [34]. However, the Prospective Multi-Center Randomized, double-blind, Active Comparator, Parallel-Groups Study comparing the Fully Human Monoclonal Anti-TNF antibody D2E7 given Every Second Week, with Methotrexate Given Weekly and the Combination of D2E7 and methotrexate Administered Over 2 years In Patients With Early Rheumatoid Arthritis (PRIEMER) study compared the efficacy and safety of adalimumab plus MTX *vs.* MTX monotherapy or adalimumab monotherapy in 799 patients with early, aggressive RA who had not previously received MTX treatment. Treatments included adalimumab 40 mg subcutaneously every other week plus oral MTX, adalimumab 40 mg subcutaneously every other week, and weekly oral MTX. In total, the combination therapy with adalimumab (40 mg subcutaneously every other week) plus oral MTX (up to 20 mg $week^{-1}$) was significantly superior to either MTX alone or adalimumab alone in improving signs and symptoms of disease, inhibiting radiographic progression, and effecting clinical remission. After 2 years of treatment, 49% of patients receiving combination therapy exhibited disease remission (DAS28 < 2.6), and 49% exhibited a major clinical response [American College of Rheumatology (ACR) 70 response for at least six continuous months], rates approximately twice those found among patients receiving either monotherapy [35].

There is a hope that more aggressive use of conventional DMARDs and biological agents will result in less disability and a higher proportion of patients achieving remission [36].

Discussion and conclusion

The main approaches to management of early RA are early 'aggressive' treatment, before irreversible joint damage occurs, using monotherapy or combinations of DMARDs. As research studies have shown, there is a 'window of opportunity' to help patients with RA – 3–4 months' disease duration. DMARD monotherapy and biological agent monotherapy can be initial treatment in early RA. However, many researchers consider the combined therapy to be the most effective treatment for early RA patients, particularly if disease duration is >4 months. Combination therapy can be used in the following different ways: (i) a continuous approach, when the doctor prescribes two or more DMARDs for continual treatment; (ii) a step-up approach, in which the rheumatologist begins with monotherapy and adds subsequent DMARDs if adequate efficacy is not achieved; and (iii) a step-down approach, in with the rheumatologist initiates several DMARDs at the onset, excluding the most toxic or most expensive once goals are achieved (Table 1). A number of experts attribute the effect of combination therapy to the powerful anti-inflammatory action of glucocorticoids, which puts in question the opportunity to achieve remission in the majority RA patients by 'standard' DMARDs. Combination therapy biological agents (INF, adalimumab) with MTX and etanercept therapy alone may induce remission in many patients with early RA. It is a method of choice in patients with an adverse prognosis. The main indications for combination therapy 'standard' DMARDs or combination 1 DMARDs with biological agents are such variables as detection of SE, increase of concentration of anti-CCP antibodies, RF, CRP, DAS28, Sharp score and presence of erosion in joints. Hence, at onset of treatment it is necessary to take into account the duration and severity of disease. Further trials should establish the optimal approaches to early RA therapy.

Competing interests

None declared

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