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Drug management of early rheumatoid arthritis – 2008☆

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Modern therapy of rheumatoid arthritis (RA) is based on recognition of the severity of the natural history of disease, with early and aggressive treatment strategies. Methotrexate is the anchor drug, with addition of other disease-modifying anti-rheumatic drugs (DMARDs) in combinations, and biological targeted therapies. The approach emphasizes 'tight control', aiming for remission and low disease activity according to quantitative monitoring. In this chapter, we review selected randomized controlled studies for data concerning early versus delayed therapies. We present a historical perspective for the treatment of early RA using early RA cohorts from Finland as an example. Finally, we discuss principles of contemporary treatment of early RA in 2008.

The history of rheumatoid arthritis (RA) includes a long period from the 1950s through to the mid-1980s in which RA was regarded 'in the majority of patients as a disease with a good prognosis', based in large part on epidemiological data [1]. This traditional teaching was that RA could be controlled in most patients with bed rest [2], aspirin, and alternative non-steroidal anti-inflammatory drugs (NSAIDs). However, it was recognized during the mid-1980s from clinical cohorts that short-term drug efficacy was not translated into long-term effectiveness, as most patients experienced severe functional declines [3], radiographic progression [4], work disability [5], and premature mortality [3]. These reports led to calls for early and aggressive use of disease modifying anti-rheumatic drugs (DMARDs) [6–9].

Randomized clinical trials (RCTs) have provided invaluable data to help advance the treatment of RA and other rheumatic diseases. However, RCTs involve only selected patients, as inclusion and exclusion

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criteria frequently leave fewer than 10% of patients eligible for participation [10,11]. Furthermore, short duration of follow-up, inflexible dosage of study medications, and other limitations may limit generalizability and translation of the results to clinical practice [12]. Nonetheless, observations from RCTs support early versus delayed drug treatment in RA.

Data from clinical cohorts and observational studies indicate that status and outcomes of RA patients have improved over the past decades concomitantly with implementation of early and active treatment strategies. Improvements have been seen in disease activity [13,14], functional capacity [14–17], radiographic scores [14,18,19], and other clinical measures [14], including lower mortality rates in patients who responded to methotrexate (MTX) [20,21] and to biological therapies [22], lower rates of joint replacement surgery at this time compared to earlier decades [23–28], and lower work disability rates in patients who responded to DMARDs [29]. On the other hand, high levels of disease activity are still seen in many clinics in many countries [30].

A concept of early RA

The term 'rheumatoid arthritis' is used to describe a syndrome that may result in a destructive symmetrical polyarthritis and is often associated with the presence of rheumatoid factor [31]. Identification of RA in the early stages is both important and difficult. Criteria for RA have been developed since 1907 [32]. However, even the current set of criteria, the American Rheumatism Association (now the American College of Rheumatology, ACR) 1987 revised criteria [33], do not differentiate individual patients with early RA from those with other types of recent-onset inflammatory polyarthritides [34,35]; these criteria were developed for established disease.

The time frame of 'early' RA may range up to 5 years of symptoms in some studies [36]. At this time, 'early RA' is defined as $\leq$6–24 months of symptoms. The median duration of symptoms at the time of enrollment in most clinical early-RA cohorts was 5–8 months [37–39]. Very early RA has been defined with a maximum duration of symptoms of 12 weeks [40].

As noted above, a definite diagnosis of RA cannot usually be confirmed at early stages of the disease. Accordingly, it has been suggested that early inflammatory polyarthritis should not be called 'early RA' but rather simply 'early arthritis' [31]. Nevertheless, we use the term 'early RA' in this chapter, recognizing that some patients may develop other rheumatic diagnoses, and even a spontaneous self-limited process, although the majority of the patients are likely to develop a progressive, destructive symmetrical polyarthritis.

Early versus delayed drug treatments in randomized controlled trials of early RA

The benefits of early versus delayed treatment have been documented in studies of intramuscular (IM) gold [41], auranofin [42], sulphasalazine (SSZ) [43,44], and hydroxychloroquine (HCQ) [45]. Disease duration at the time of DMARD initiation was the primary predictor of the response to DMARD treatment in a meta-analysis [46]. One study concluded that very early treatment with MTX may postpone the development of RA [47].

The Finnish RA Combination Therapy Trial, termed the FIN-RACo study, enrolled 195 patients with early active RA in 1993–1995 [48]. The patients were randomized to two treatment arms for 2 years: 97 received a combination of MTX, SSZ, HCQ, and prednisolone, while 98 received single-drug therapy with SSZ (with or without prednisolone), in which MTX was later substituted in 51 patients.

The primary outcome measure of the FIN-RACo study was remission, which was more strict than the ACR criteria [49] and was defined as no tender and no swollen joints, morning stiffness $\leq$15 minutes, no pain, and normal erythrocyte sedimentation rate. According to these strict criteria, the frequency of remission was 37% in the combination group, and 18% in the single-drug group at 2 years ($P = 0.003$) [48]. It is noteworthy that delay in instituting therapy played a major role in the monotherapy group results: 35% of the patients with a short delay (0–4 months) were in remission at 2 years in the monotherapy group, while the corresponding figure in patients with a long delay (>4 months) was only 11% ($P = 0.021$). The frequency of remission was similar in patients with short (0–4 months) and long delay (>4 months) in instituting the therapy in the combination group.