deformity and radiographic scores [5]. For example, in 100 patients over 5 yr, joint tenderness, swelling and ESR were partially improved while joint deformity and scores for radiographic damage indicated disease progression (Fig. 1) [6].

Statistical significance of improved measures of inflammatory activity does not necessarily indicate clinical significance of the observations [7]. Aggressive treatment strategies for early RA have been advocated, with a goal beyond statistical significance toward remission [2, 8–10]. We would have treated most of these patients with methotrexate and anticipated many fewer swollen and tender joints. Methotrexate is the disease-modifying anti-rheumatic drug (DMARD) that is significantly more likely to be continued at 5 yr over 5 yr, joint tenderness, swelling and ESR were partially improved while joint deformity and scores for radiographic damage indicated disease progression (Fig. 1) [6].

Statistical significance of improved measures of inflammatory activity does not necessarily indicate clinical significance of the observations [7]. Aggressive treatment strategies for early RA have been advocated, with a goal beyond statistical significance toward remission [2, 8–10]. We would have treated most of these patients with methotrexate and anticipated many fewer swollen and tender joints. Methotrexate is the disease-modifying anti-rheumatic drug (DMARD) that is significantly more likely to be continued at 5 yr because of greater efficacy and tolerability and fewer adverse events than any other DMARD [11, 12], including hydroxychloroquine. Methotrexate appears the ‘anchor drug’ of choice for most patients with early RA [13], including those with a level of severity described in the cohort of Matteson et al. [1].

At this time, evidence of improved long-term outcomes in RA with aggressive treatment strategies is emerging, including radiographic damage [14], functional capacity [15], work disability [16] and survival [17, 18]. However, these reports remain unusual, and many patients continue to experience ‘side-effects’ of the disease [19].

We certainly admire the effort of Matteson et al. to collect rigorous data in standard clinical care, which we have advocated [20]. However, we suggest a reassessment of the hydroxychloroquine treatment strategy in these patients with early RA.

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How aggressive should initial therapy for rheumatoid arthritis be? The Finnish experience

Sir, We read with interest the report of Matteson et al. [1] concerning 2-yr results of hydroxychloroquine (HCQ) treatment in 111 patients with early rheumatoid arthritis (RA). After 2 yr of follow-up, inflammatory activity decreased statistically significantly, but the percentage of patients with erosions increased from 26% to 59%. At 2 yr the mean number of swollen joints was nine, and 38 patients (40% of 94 who completed 2 yr) did not apparently have an ACR50 response. Despite these findings, the authors suggest that treatment with HCQ is ‘greatly beneficial in patients with early RA’.

A Finnish cohort from Heinola was one of the first prospective cohorts of patients with recent-onset (<6 months) RA. One hundred and three RF-positive patients were enrolled in this cohort in 1973–1975. At the time of diagnosis, 31% of patients began HCQ, 51% gold sodium thiomalate, 5% a combination of these, and 2% penicillin; 85% were taking these drugs at the 1-yr visit and 76% at the 3-yr visit [2]. However, these treatments did not
Letters to the Editor

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How aggressive should initial therapy for rheumatoid arthritis be? Reply

We thank Kaarela et al. and Pincus et al. for their comments regarding our experience with a cohort of patients with early rheumatoid arthritis (RA) treated with what most would regard as non-aggressive DMARD therapy [1]. In our study, we noted that after 24 months of follow-up a majority of patients (60%) was either still on solo DMARD therapy with hydroxychloroquine (HCQ) or off DMARD therapy with controlled/quiescent disease. The remaining 40% of patients were taking methotrexate (MTX) (including 11 in combination with other DMARDs). At month 24, 90% of all patients met American College of Rheumatology (ACR) 50 criteria for treatment response.

Kaarela et al. miss the intention and focus of our study. That patients with RA should receive early treatment with DMARDs to prevent disability and other RA related disease complications is undisputed, and was not the subject of this trial. However, the question of how ‘aggressive’ this therapy should be remains to be resolved. There is a significant subset of patients with RA who appear to have a milder disease course and do not require overly aggressive treatment and attendant costs and side-effects, especially with chemotherapeutics and expensive anticytokine therapies. The purpose of this study was to make an attempt to identify this subset of patients.

Kaarela et al. suggest that the Mayo Clinic study will, in effect, watch passively as the patient becomes ‘progressively more crippled before their eyes’. This is incorrect. In fact, our study design mandated more aggressive treatment for patients who appear to have a milder disease course and do not require overly aggressive therapy, initially with MTX, according to the treatment protocol.

Kaarela et al. are concerned that we conclude ‘HCQ prevents erosions’. Our study was not a placebo-controlled trial of HCQ effect. The study design was not to test this question, but rather to identify which patients did well on minimal (HCQ) treatment. Clearly a substantial number did.

Kaarela et al. provide a summary of two of their studies, which as many others, demonstrate that aggressive treatment is helpful in RA. We certainly agree that aggressive treatment is indicated in those patients who require it, and may even lead to remission in a variable number of them. Who these patients are is at issue, and is unanswered in their studies. The claim implicit in Kaarela’s argument that most patients will develop severe erosive disease appears somewhat contradicted by their own findings. Among 103 patients followed for 20 yr, they detected a high Larsen score or HAQ in 30 (29%), and 16 (15%) of the patients underwent arthroplasty, a perhaps less disputed measure of poor outcome [2]. We do agree that patients who respond poorly have higher rates of work disability and poor outcomes; for this reason our study design mandated more aggressive treatment for patients responding poorly to initial treatment [1].

Pincus et al. also express concerns similar to Kaarela et al., and believe that our patients are undertreated with HCQ. They maintain that the treatment response was inadequate, portending increased disability and joint damage in the future. Again, to the point of our study, our clinical response parameter was the ACR50, with patients being switched to MTX if they failed to meet prevent severe joint damage or amyloidosis in most patients over the subsequent 20 yr [2–4]. In fact, HCQ has never been shown to prevent erosions in RA [5].

In the Finnish Rheumatoid Arthritis Combination Therapy trial (FIN-RACo) study, 195 patients with early RA were randomized to receive a combination of methotrexate (MTX), sulphasalazine (SSZ), HCQ and prednisolone vs SSZ only (with or without prednisolone), which could be switched to MTX or to another single anti-rheumatic drug [6]. At the 2-yr visit, 75% of patients who received combinations and 58% of patients who received a single DMARD therapy had ACR50 responses. Furthermore, remission was observed in 37% and 18% respectively. The importance of early remission was emphasized with the observation that all patients who met remission criteria during the first 6 months continued working for 5 yr, in contrast to work disability in 22% of patients who met ACR20 or ACR50 responses [7]. Furthermore, 54% of patients who improved less than ACR20 in 22% of patients who met ACR20 or ACR50 responses [7]. Long-term follow-up will reveal whether the Mayo clinic study [1] is one of those described by Verna Wright: ‘Clinicians became work-disabled over 5 yr, similar to higher rates of work disability that all patients who met remission criteria during the first 6 months. Remission was observed in 37% and 18% respectively. The single DMARD therapy had ACR50 responses. Furthermore, 54% of patients who improved less than ACR20 became work-disabled over 5 yr, similar to higher rates of work disability in the past.

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