Letters to the Editor

K. KAARELA, M. HAKALA, P. HANNONEN1, H. KAUTIAINEN, M. KORPELA2, M. LEIRISALO-REPO1, R. LUUKKAINEN2, T. MOTTONEN2, K. PUOLAKKA3

Rheumatism Foundation Hospital, Heinola, 1Jyväskylä Central Hospital, Jyväskylä, 2Tampere University Central Hospital, Tampere, 3Helsinki University Central Hospital, Helsinki, 4Kuopio University Central Hospital, Kuopio, 5Satakunta Central Hospital, Rauma, 6Turku University Central Hospital, Turku and 7Lappeenranta Central Hospital, Lappeenranta, Finland

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Correspondence to: K. Kaarela. E-mail: kalevi.kaarela@reuma.fi


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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 who, in the current environment, would be unnecessarily subjected to 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 required systematic observation and therapeutic decision-making based on the ACR50 response criteria. Patients not fulfilling the response criteria had their treatment switched to more 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.

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 became work-disabled over 5 yr, similar to higher rates of work disability in the past.

Long-term follow-up will reveal whether the Mayo clinic study [1] is one of those described by Verna Wright: ‘Clinicians may all too easily spend years writing ‘doing well’ in the notes of a patient who has become progressively more crippled before their eyes’ [8].

The authors have declared no conflicts of interest.
this pretrial response measure. Whether this response is adequate in terms of long-term disease control is a separate issue this study was not designed to address. Clearly, current thinking is towards complete eradication of any and all signs and symptoms of disease; we agree this is a legitimate goal, which, however, can be achieved with varying means in different patients, not all of whom require ‘aggressive treatment’ [3].

We agree with Kaarela and Pincus et al. that long-term follow up of this and every cohort of patients with RA will provide the true test of adequacy of our current treatment approaches. We hope that a more differentiated approach will identify those patients requiring aggressive treatment, sparing patients with milder disease the unwanted consequences of more aggressive management.

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E. L. Matteson, C. M. Weyand, J. G. Goronzy
Division of Rheumatology, Mayo Clinic College of Medicine, Rochester, MN and 1Lowance Center for Human Immunology, Emory University School of Medicine, Atlanta, GA, USA

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Correspondence to: E. L. Matteson. E-mail: matteson.eric@Mayo.edu


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Poststreptococcal reactive arthritis (PSRA): a plea for diagnostic criteria

Sir, With great interest we read the paper by Mackie and Keat on poststreptococcal reactive arthritis (PSRA) [1]. In their study they try to tackle the intriguing problem of defining PSRA, which is appreciated. However, one may question whether their objective, to find if PSRA is a discrete homogeneous syndrome, is methodologically answered properly by reviewing recent literature. One may consider first that the inclusion criteria of case reports, mainly characterized by presentation of arthritis and positive streptococcal (often only antistreptolysin-O) serology, induced heterogeneity. Another problem may well be publication bias. Some case reports are lacking in their study, even one paper from Rheumatology [2].

Additionally, we fully agree that there is a need for a homogeneous group of PSRA. One may start trying to homogenize the patient group by applying a set of criteria as proposed before [3]: Ayoub and Ahmed have proposed a set of clinical and serological PSRA criteria which may be used as a starter to find a set of criteria applicable for making a diagnosis of PSRA due (probably) to group A streptococci (GAS) [3]: (i) arthritis with acute onset and of non-migratory type; (ii) arthritis with a protracted course or of a recurrent type; (iii) arthritis with poor responsiveness to salicylates/non-steroidals; (iv) evidence of antecedent streptococcal infection; (v) not fulfilling Jones’s criteria on acute rheumatic fever; and (vi) absence of any of Jones’s major manifestations. In an attempt to separate GAS-induced from non-GAS-induced PSRA, one may apply (vii) lower antistreptolysin-O/antiDNase-B ratios as an additional tool [4]. Clearly, we need a homogeneous group of PSRA patients meeting validated diagnostic criteria. Future prospective studies are warranted to find out what proportion of a more homogeneous group of GAS-induced PSRA patients should or should not strictly adhere to penicillin prophylaxis for purposes of potentially recurrent arthritis or cardiac involvement. Could the authors explain their statement on the aforementioned application of diagnostic criteria, and possibly clarify the fulfilment within these criteria of the case reports they studied?

T. L. T. A. Jansen, M. Eede, A. Spoorenberg
Medical Centre Leeuwarden, Department of Rheumatology, POB 888, 8901 BR Leeuwarden, The Netherlands

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Correspondence to: T. L. T. A. Jansen. E-mail: T.Jansen@znb.nl


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Poststreptococcal reactive arthritis (PSRA): a plea for diagnostic criteria: reply

We are grateful to Dr Jansen and colleagues for their interesting and constructive letter. Naturally, we agree that retrospective literature review is not an appropriate methodology for defining a clinical syndrome, particularly given the likely publication bias implied by the geographical origins of the case reports we analysed. Our objective was not to formulate a definition of the poststreptococcal reactive arthritis but to investigate whether it appears to exist at all as a discrete entity. We found considerable heterogeneity within the existing literature, certainly more than the criteria proposed by Ayoub and Ahmed [1] might suggest. Furthermore, criteria thus framed in relation to acute rheumatic fever may be quite useful in paediatrics, but might potentially disguise the complexity of the relationship between the gastrointestinal tract, the immune system and the joints; for example, the onset of adult Still’s disease often features a sore throat.

A large prospective epidemiological study would be required to demonstrate whether there is a true association between arthritis and sore throats in general or streptococcal infections in particular. It is worth recalling that although Reiter’s syndrome was originally linked to genitourinary and gut infections by recognition of sporadic cases, the linkage is more securely based on epidemiological studies, albeit uncontrolled ones, such as those of Paronen and colleagues [2, 3] and Csonka [4]. Moreover, in another instance it was originally proposed that a specific form of arthritis may be linked to HIV infection, based on sporadic observa-