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How aggressive should initial therapy for rheumatoid arthritis be? Factors associated with response to 'non-aggressive' DMARD treatment and perspective from a 2-yr open label trial

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***Objective*. To determine what baseline factors might be associated with response to an initial mild treatment regimen in patients with early rheumatoid arthritis (RA).**

***Methods*. Open label 2-yr study of 111 consecutive patients with early RA of duration less than 1 yr. None of the patients had previously received disease-modifying anti-rheumatic drugs (DMARDs). All patients were assigned to receive hydroxychloroquine (HCQ) at enrolment, and could also take non-steroidal anti-inflammatory drugs (NSAIDs) and prednisone. At any point during follow-up, patients not fulfilling the American College of Rheumatology (ACR) 50 criteria for improvement and/or who were taking prednisone >10 mg/day were considered treatment failures and therapy changed to methotrexate (MTX), 7.5–20 mg/week. Clinical, laboratory and immunogenetic factors potentially predictive of treatment assignment at month 24 were evaluated.**

***Results*. After 24 months of follow-up, a majority of patients (56/94) were either still on solo DMARD therapy with HCQ ($n = 49$) or off DMARD therapy with controlled/quiescent disease ($n = 4$), and 38 patients were taking MTX (including 11 in combination with other DMARDs). At month 24, all but 9 patients met ACR50 criteria for treatment response. Features present at enrolment which were predictors of MTX therapy at month 24 were high pain score, baseline rheumatoid factor titre >1:40, higher number of swollen joints, and poor patient global assessment. The presence of HLA-C7*xx* at enrolment was also predictive of need for MTX therapy.**

***Conclusions*. This study suggests that even milder treatment with HCQ is greatly beneficial in patients with early RA. There continue to be very few consistently reliable predictors of treatment needs in patients with this disease.**

KEY WORDS: Early rheumatoid arthritis, Treatment.

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease associated with long-term disability and premature mortality. RA is one of the most common causes of disability. After 12 yr of disease, more than 80% of patients are partially disabled, and 16% are completely disabled [1]. Disease-specific factors including extent of joint involvement and the presence of extra-articular disease manifestations are highly correlated with disease course and survival [2–5].

Treatment decisions in RA are individualized and depend largely on the disease activity at the time of presentation. However, most patients have a variable clinical course, spontaneous disease fluctuations occur commonly, and disease course may be different in women and men. Women with RA are more likely to have erosive disease than men (72 *vs* 55%), and the erosions occur earlier in women than in men [6]. While onset may be abrupt, gradual onset is most common. These issues make initial treatment decisions in RA critical but difficult when their relationship to long-term outcomes is considered. Based on current understanding of the disease and its course, there is a general belief that to reduce long-term morbidity and disability, earlier control of the disease process is essential. This has led to more aggressive treatment such as the earlier institution of disease-remitting therapy, although specific treatment recommendations for individual patients are very discretionary. Identification of patients who are destined to have a rather benign disease course and may not need aggressive treatment would not only protect these patients from excessive treatment with its attendant potential toxicity, but would also have socio-economic implications.

In the context of a study of possible prognostic markers that might play a role in predicting the course of RA, we devised a standardized treatment algorithm for treatment of these patients, evaluating radiographs at 2 yr as the primary outcome measure [7]. This treatment algorithm was designed to avoid initial over-treatment, permitting identification of patients who can be managed with less aggressive or even rather minimal treatment. Treatment was escalated to achieve control of symptoms in those patients with persistently active disease.

Patients and methods

Patients

One-hundred and eleven patients age 18 to 75 yr fulfilling the American College of Rheumatology (ACR) criteria for

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classification of RA with disease duration of less than 1 yr were enrolled in the study [8]. All patients were disease-modifying anti-rheumatic drug (DMARD) naïve at screening (i.e. had never taken any standard DMARD including gold, hydroxychloroquine (HCQ), methotrexate (MTX), sulphasalazine, etc. prior to enrolment). All patients gave written informed consent for study participation.

Study design and treatment algorithm

This was an open label study. All patients were treated according to a standardized algorithm using a step-up approach which was intended to avoid over-treatment and represented the standard of care at the time of study initiation. All patients initially received HCQ at 200 mg twice a day as the initial DMARD and, if deemed needed by the treating physician, a non-steroidal anti-inflammatory agent (NSAID); low-dose prednisone (<10 mg per day) was used in addition if it was felt necessary for initial disease control. In order to adhere to usual practice as closely as possible, decisions about specific NSAIDs and prednisone use were left to the treating physicians. Formal assessment of disease activity was performed according to the study protocol at month 6, month 12 and month 24, including number of painful and swollen joints, Westergren sedimentation rate, patient and physician global assessment on a 10 cm visual analogue scale (VAS; 0 = no disease activity, 10 = very active disease), pain assessment (0 = no pain, 3 = worst possible pain), duration of morning stiffness (in min), patient-derived functional assessment with the Health Assessment Questionnaire for RA (HAQ; 0 = no impairment, 3 = severe impairment) and the presence of extra-articular disease manifestations. Response to treatment was assessed at each visit, at a minimum every 6 months for 24 months in total.

According to the study protocol, initial HCQ therapy was changed to MTX at doses of 7.5–20 mg a week (and folic acid, 1 mg/day) if the response to initial treatment failed to fulfil a pre-set definition of treatment response. In addition, patients requiring >10 mg of prednisone a day were considered non-responders. Patients were seen at more frequent intervals according to need and patient and physician preference, usually between 6 and 12 weeks after enrolment, and often every 3 months thereafter. An initial change of HCQ therapy to MTX was permitted at any point during follow-up if formal assessment according to the outcome measures revealed that the treatment response was inadequate, so that some patients who had an initial response to therapy but subsequently flared and did not fulfil the response criteria compared with the previous visit were switched to MTX. Other DMARDs could then be used if the patient responded poorly to this regimen according to patient and treating physician preference.

A treatment response was defined according to the ACR50 as 50% or greater improvement in criteria 1 and 2, and at least three of five criteria in point 3 of the categories of RA disease activity as defined below [9]:

1: At least 50% improvement in the number of tender joints.
2: At least 50% improvement in the number of swollen joints.
3: At least 50% improvement in at least three of the five following criteria:
   (a) patient assessment of physical function
   (b) patient global assessment of disease activity
   (c) physician global assessment of disease activity
   (d) patient assessment of pain
   (e) erythrocyte sedimentation rate.

Immunogenetic predictors of outcome

The following were evaluated as possible predictors of outcome: HLA-DRB1*, homozygous shared epitope, HLA-DRB1*04, HLA-DRB1*04/04 *vs* non-HLA-DRB1*04, HLA-DRB1*04/04 *vs* non HLA-DRB1*04/04, HLA-DRB1*01 or *04 *vs* non-HLA-DRB1*01 or *04; frequencies of $CD4^{+}CD28^{null}$ T cells, adrenergic-β2 receptor, CD14 antigen, cytotoxic T-lymphocyte-associated protein 4 (CD152), cytotoxic T-lymphocyte-associated protein 4 (CD152), IgE high-affinity receptor 1 β-chain, Fc fragment intracellular adhesion molecule 1 (CD54), interferon-γ receptor 1, interleukin-10, interleukin-4, interleukin-4 receptor (CD124), VCAM1, interleukin-5 receptor α-chain (CDw125), interleukin-6, interleukin-9, lymphotoxin-α (tumour necrosis factor-β), small inducible cytokine A11 (eotaxin), selectin E (ELAM1, CD62E), selectin P (CD62P), tumour necrosis factor-α, cytokine X, vascular cell adhesion molecule 1 (CD106); single nucleotide polymorphisms ADRB2, CD14, CTLA4, FCER1B, ICAM1, IFNGR1, IL10, IL4, IL4R, IL5RA, IL6, IL9, LTA, SCYA11, SELE, SELP, TNF. The details of these assays are contained in Goronzy *et al*. [7].

Radiographic assessment

Radiographs of the hands and wrists were obtained at baseline, month 12 and month 24, but were not included as response criteria. A single radiologist expert in musculoskeletal radiography who was blinded to the treatment assignment read and scored all radiographs according to the method described by Sharp *et al*. [10]. Details of the radiological assessment and outcome are contained in a separate report [7].

Statistical methods

Descriptive statistics were used to characterize the demographics of the cohort. Variables were compared between baseline and 24 months using paired *t*-tests or signed rank tests as appropriate. To study the associations between these variables and the end of study treatment assignment logistic regression models were constructed for the odds of non-response to HCQ (i.e. for the odds of having switched the patient from HCQ to MTX within 24 months). Unadjusted odds ratios and 95% confidence intervals are reported for each potential predictor of interest. Additionally, we present a multiple logistic regression model that includes both factors found to be significant univariately.

Approval of the research was required and obtained from the Mayo Clinic Institutional Review Board.

Results

Demographics

Approximately 70% of the study population were female and 58% had a positive rheumatoid factor (Table 1).

Treatment

A total of 94 of the 111 patients completed the 2-yr follow-up period. The treatment assignment at month 0, and according to

TABLE 1. Patient demographics

	Mean (±S.D.) or median (min.–max.) or *N* (%)
Age (yr)	51.5 ± 13.4
Female gender	78 (70%)
Symptoms (yr)	0.4 (0.1–2.6)
RF positive	64 (58%)
RF titre	112 (20–2240)

RF, rheumatoid factor; S.D., standard deviation.

TABLE 2. Disease parameters

	Enrolment Mean (±S.D.) or median (min.–max.) or *N* (%)	6 months Mean (±S.D.) or median (min.–max.) or *N* (%)	12 months Mean (±S.D.) or median (min.–max.) or *N* (%)	24 months Mean (±S.D.) or median (min.–max.) or *N* (%)	*P*-value Comparing 24 month result with baseline result
Morning stiffness (min)	120 (0–360)	15 (0–360)	15 (0–360)	10 (0–360)	<0.001
Patient global assessment (scale 0–10)	5.3 (±2.3)	2.9 (±2.1)	2.2 (±2.0)	2.3 (±1.9)	<0.001
Physician global assessment (scale 0–10)	4.9 (±2.1)	2.4 (±2.0)	2.0 (±1.8)	1.9 (±1.9)	<0.001
Number of swollen joints	24.6 (±16.5)	NA	10.1 (±10.5)	9.2 (±10.7)	<0.001
Number of tender joints	23.0 (±17.4)	NA	7.1 (±9.6)	6.5 (±8.1)	<0.001
ESR (mm/h)	28.0 (±20.5)	16.8 (±18.6)	14.8 (±15.2)	16.5 (±21.2)	<0.001
HAQ disability (range 0.0–3.0)	1.140 (±0.639)	0.545 (±0.574)	0.459 (±0.545)	0.400 (±0.496)	<0.001
Pain (range 0.0–3.0)	1.588 (±0.700)	0.788 (±0.693)	0.634 (±0.577)	0.736 (±0.663)	<0.001
Erosions (maximum score 160)	0 (0–42)	NA	0 (0–61)	1 (0–64)	<0.001
Erosions (no. with ≥1 erosion)	26 (26%)	NA	41 (46%)	52 (59%)	
Joint space narrowing (max. score 120)	0 (0–37)	NA	0 (0–18)	0 (0–51)	<0.001
Joint space narrowing (no. with score ≥1)	21 (21%)	NA	24 (26%)	31 (36%)	
Prednisone users (no. of patients)	28 (25%)	55 (52%)	43 (43%)	26 (31%)	0.851*
Prednisone dose (mg/day)	8.6 (±4.5)	6.3 (±2.9)	6.1 (±3.5)	5.6 (±3.4)	<0.001
Hydroxychloroquine (no. of patients)	111 (100%)	78 (74%)	68 (68%)	49 (52%)	
Methotrexate (no. of patients)	0	27 (26%)	27 (27%)	38 (40%)	
No DMARD therapy (no. of patients)	0	0	0	4 (4%)	

Non-responders according to the ACR50 response criteria taking HCQ were switched to MTX and/or given additional prednisone and/or sulphasalazine (see text).

**P*-value for prednisone use based on sign test. All other *P*-values based on paired *t*-tests or signed rank tests as appropriate.

N, number; S.D., standard deviation; ESR, Westergren sedimentation rate; HAQ, Health Assessment Questionnaire; DMARD, disease-modifying anti-rheumatic drug.

response to treatment at months 6, 12 and 24, is contained in Table 2. Forty-nine of the 94 patients were either still on HCQ as a single DMARD at 24 months or off treatment ($n = 4$) with control of disease. Nine of the 94 patients available for evaluation at month 24 were considered to be non-responders according to the treatment algorithm irrespective of the escalating treatment during the 2-yr treatment period. Of these, eight patients were taking MTX (including two on solo DMARD therapy with MTX, four on MTX + HCQ + prednisone, two on MTX + HCQ + sulphazalazine 2000–3000 mg day + prednisone) and one patient, who had been considered a treatment responder on HCQ + prednisone at months 6, 12, and 18 was a non-responder at month 24; MTX was added to the treatment regimen of this patient at the completion of the month 24 visit. Seventeen patients dropped out during the trial, including six during the first 6 months (no further information is available for these patients), and 11 after month 6. Of these, six were treatment responders and five were not. According to the protocol, non-responders were first switched to solo DMARD therapy with MTX, and if not responsive to MTX could be switched to other DMARDs or have other DMARDs added to the MTX. By the end of the study, 38 patients were on MTX (10.0–22.5 mg/week; average dose 16.25 mg/week), including 11 on combination DMARD therapy (four patients taking HCQ + MTX; six patients taking HCQ + MTX + sulphasalazine, 2000–3000 mg/day; and one patient on MTX + minocycline 100 mg b.i.d.). One patient who was considered a non-responder at month 6 refused to switch therapy to MTX at that time point, but was a responder at both month 12 and month 24, and was included in the analysis.

At baseline, 28 (25%) patients were on oral prednisone therapy usually initiated by the referring physician. This number rose to 55 (52%) patients at month 6 at a mean dose of 6 mg/day, declined to 43 (43%) at month 12, and by month 24, a total of 26 (31%) patients were on prednisone (Table 2). Of patients taking prednisone at baseline, the drug was continued in 11, discontinued in 13 and for 4 patients there was no information. There was no meaningful difference in the number of patients taking prednisone at the end of the study compared with baseline, although among users the prednisone dose was lower at month 24 than at baseline (Table 2). Only 7 of the 49 patients regarded as responders at month 24 were still on low-dose steroids (mean prednisone dose 3.4 mg/day).

Clinical disease course

The disease was active in all patients at the time of study entry, as assessed by tender and swollen joint counts, morning stiffness and patient and physician global assessments (Table 2). There was clinically and statistically meaningful improvement in all disease outcome parameters at month 24. A 50–75% improvement was seen for most of the disease activity parameters. The tender and swollen joint counts after 2 yr were 6.5 and 9.2. Between one and four symptomatic extra-articular disease manifestations occurred in 27 patients (24.3%). These included keratoconjunctivitis sicca (10 patients), peripheral neuropathy (4 patients), cutaneous vasculitis (1 patient), carpal tunnel syndrome (10 patients), fever (1 patient), pleuritis (1 patient), myopathy (2 patient), pulmonary fibrosis (1 patient), episcleritis (1 patient) and subcutaneous nodules (2 patients). Felty's syndrome was not diagnosed in any patient. Because of its strong association with wrist synovitis and subsequent compression, carpal tunnel syndrome was not further considered in the analysis of extra-articular disease if it was the sole extra-articular manifestation, which included only the 21 patients without this condition. There was no change in diagnosis of RA during follow-up and no patient underwent joint surgery during the 2 yr observation period.

Radiographic findings

The majority (74%) of all patients did not have any RA-specific findings on hand radiographs at baseline. The median erosion and joint space narrowing counts were 0, although there were a few patients who already had erosive changes; one patient had 31 and another 42 erosions (Table 2). On average, patients had about one additional erosion in wrist, metacarpophalangeal (MCP) or proximal interphalangeal (PIP) joints during the 2-yr observation period. The dynamics of progression of erosion were nearly

TABLE 3. Possible predictors and treatment assignment at month 24: categorical variables*

Variables		*N*	Treatment at month 24: HCQ/no erosions, *N* (%)	MTX/no erosions, *N* (%)	HCQ/erosions, *N* (%)	MTX/erosions, *N* (%)
Responding at 6 months	No	20	1 (5.0)	9 (45.0)	0 (0.0)	10 (50.0)
	Yes	70	24 (34.3)	9 (12.9)	24 (34.3)	13 (18.6)
HLA-C7*xx*	0	39	14 (35.9)	4 (10.3)	12 (30.8)	9 (23.1)
	1	28	6 (21.4)	8 (28.6)	6 (21.4)	8 (28.6)
	2	4	0 (0.0)	2 (50.0)	0 (0.0)	2 (50.0)
Initial RF ≥1:40	No	38	13 (34.2)	11 (29.0)	8 (21.0)	6 (15.8)
	Yes	53	12 (22.6)	7 (13.2)	16 (30.2)	18 (34.0)
Peak RF ≥40	No	32	12 (37.5)	9 (28.1)	8 (25.0)	3 (9.4)
	Yes	59	13 (22.0)	9 (15.2)	16 (27.1)	21 (35.6)
HLA-DR-4	No	33	9 (27.3)	11 (33.3)	7 (21.2)	6 (18.2)
	Yes	58	16 (27.6)	7 (12.1)	17 (29.3)	18 (31.0)
HLA-DR-4 '04X'	No	33	9 (27.3)	11 (33.3)	7 (21.2)	6 (18.2)
	Yes	19	2 (10.5)	3 (15.8)	6 (31.6)	8 (42.1)
HLA-DR4 '0104' and '04X'	No	33	9 (27.3)	11 (33.3)	7 (21.2)	6 (18.2)
	Yes	11	0 (0.0)	3 (27.3)	5 (45.4)	3 (27.3)
Prednisone user at baseline	No	66	17 (25.8)	11 (16.7)	22 (33.3)	16 (24.2)
	Yes	25	8 (32.0)	7 (28.0)	2 (8.0)	8 (32.0)
Gender	Female	61	19 (31.2)	13 (21.3)	14 (23.0)	15 (24.6)
	Male	30	6 (20.0)	5 (16.7)	10 (33.3)	9 (30.0)
Extraarticular manifestations	No	72	19 (26.4)	19 (26.4)	12 (16.7)	22 (30.6)
	Yes	19	6 (31.6)	5 (26.3)	6 (31.6)	2 (10.5)

*None of the other immunogenetic parameters studied were predictive of treatment assignment at month 24 (data not shown; see Methods). %, per cent of patients in the study.

**N = number of patients for whom complete information was available regarding erosions for each of the variables studied.

S.D., standard deviation; HCQ, hydroxychloroquine (as solo DMARD therapy); MTX, methotrexate (including 11 patients on combination DMARD therapy; see text); RF, rheumatoid factor.

HLA-C7*xx* key: 0 = HLA-Ci ne 7 and HLA-Cii ne 7; 1 = HLA-Ci or HLA-Cii = 7; 2 = HLA-Ci and HLA-Cii = 7.

TABLE 4. Continuous variables by final treatment assignment and erosions

Variables	Treatment at month 24: HCQ/no erosions (N = 25) (mean ± S.D.)	MTX/no erosions (N = 18) (mean ± S.D.)	HCQ/erosions (N = 24) (mean ± S.D.)	MTX/erosions (N = 24) (mean ± S.D.)
Age (yr)	50.7 ± 13.5	44.8 ± 12.4	50.9 ± 14.0	57.2 ± 12.6
Pain (0–3)	1.39 ± 0.79	1.58 ± 0.65	1.42 ± 0.76	1.77 ± 0.57
HAQ function (0–3)	0.98 ± 0.69	1.11 ± 0.70	1.10 ± 0.75	1.28 ± 0.55
Swollen joints (*N*; range 0–62)	20.9 ± 15.4	22.2 ± 13.6	20.7 ± 10.9	30.8 ± 23.4
Tender joints (*N*; range 0–62)	22.7 ± 18.0	20.9 ± 13.5	18.0 ± 13.6	26.5 ± 21.3
Morning stiffness (minutes)	233 ± 380	114 ± 88.6	271 ± 382	398 ± 492
Patient global assessment (0–10)	4.87 ± 2.89	5.43 ± 2.12	4.87 ± 2.25	5.99 ± 1.83
Physician global assessment (0–10)	4.37 ± 2.32	4.81 ± 2.15	4.60 ± 1.88	5.55 ± 2.43
Sedimentation rate mm/1 h (Westergren)	26.6 ± 22.2	26.1 ± 19.5	28.2 ± 18.1	36.3 ± 24.0

S.D., standard deviation; HAQ, Health Assessment Questionnaire, HCQ, hydroxychloroquine (as solo DMARD therapy); MTX, methotrexate (including 11 patients on combination DMARD therapy; see text).

identical in the patients remaining on HCQ and those taking MTX or other DMARD at month 24, suggesting that clinical response, even if restrictively defined, did not predict radiographic outcome after 2 yr (data contained in [7]). Of the 11 patients who were on combination DMARD therapy including MTX at the end of the study, 4 were in the group with no erosions, and 7 were in the group with erosions (Tables 3 and 4).

Baseline laboratory and clinical factors predictive of treatment at month 24

Frequencies of the categorical and continuous variables according to the final treatment assignment at month 24 are shown in Tables 3 and 4. Among the 70 patients responding at 6 months, 49 (70%) remained responsive at 24 months, and hence were still on HCQ at the end of the study. We then performed a formal analysis of possible predictors of treatment assignment at month 24 to the two treatment groups, HCQ and MTX. In both of these analyses, presence of HLA-C7*xx* and a high HAQ pain score were successful predictors of being switched from HCQ to MTX therapy (Table 5). No other factor examined, including use of prednisone, radiographic erosions or the presence of extra-articular disease manifestations, was predictive of treatment assignment at month 24 (Table 5).

Discussion

We evaluated the clinical response of patients with early RA enrolled into an observation of routine initial therapy with NSAIDs and HCQ followed for a 2-yr period. Depending on

TABLE 5. Odds ratios for treatment assignment to methotrexate at month 24: unadjusted logistic regression models for non-response to HCQ at 24 months.

Condition	Odds ratio (95% CI)	*P*-value
Age	1.01 (0.98, 1.04)	0.70
Male	1.03 (0.44, 2.44)	0.94
HLA-C7*xx* (positive)	3.40 (1.31, 8.87)	0.01
RF >1:40	1.24 (0.54, 2.82)	0.62
Peak RF >40	1.90 (0.79, 4.54)	0.15
HLA-DR4	0.66 (0.29, 1.54)	0.34
HLA-DR where DR = 04X	1.16 (0.37, 3.58)	0.80
HLA-DR where DR = 0104	1.01 (0.26, 3.94)	0.99
HAQ pain	1.85 (1.01, 3.40)	0.05
HAQ function	1.49 (0.79, 2.79)	0.21
Swollen joints	1.02 (1.00, 1.05)	0.10
Tender joints	1.01 (0.99, 1.04)	0.30
Morning stiffness (duration)	1.00 (1.00, 1.00)	0.75
Patient global assessment	1.17 (0.98, 1.40)	0.08
Physician global assessment	1.16 (0.96, 1.40)	0.13
Sedimentation rate (Westergren)	1.01 (0.99, 1.03)	0.36
Prednisone user	1.95 (0.77, 4.95)	0.16
Extra-articular manifestations*	0.75 (0.27, 2.07)	0.57

*All conditions are as present at baseline other than presence of extra-articular manifestations, which are any incident during the 24 months of follow-up.

TABLE 5. Odds ratios for treatment assignment to methotrexate at month 24: multiple logistic regression model for non-response to HCQ at 24 months.

Condition	*N*	Odds ratio (95% C.I.)	*P*-value
HLA-C7*xx* (presence of)	72	3.38 (1.22, 9.35)	0.019
Pain	94	2.52 (1.16, 5.46)	0.019

response, treatment could be intensified, with addition of MTX if the disease was not well controlled (if patients did not achieve at least an ACR50 response assessed at follow-up every 6 months for 2 yr). A majority of patients (56) were still on HCQ as solo DMARD therapy at the end of the 24 month study or off DMARDs, while 38 were on MTX. All but nine patients had meaningful clinical improvement as assessed by the ACR50 criteria by year 2 of the study.

A unique aspect of this study is the use of an extensive set of clinical activity and immunogenetic markers which predicted successful treatment 24 month after initiation of therapy. The measures we chose to accomplish this aim included parameters identified in other studies as important, including several that have been identified as predictors of especially poor outcome. The presence of HLA-C7*xx* and a high HAQ pain score were the only strong predictors of being switched from HCQ to MTX therapy by the end of the study. This association of this class I MHC gene has not previously been identified as a marker of RA severity. Presence of a baseline rheumatoid factor titre >1:40, a higher number of swollen joints and worse patient global assessment were more weakly associated with MTX use at month 24 (Table 5). The weak association with RF may be a result of the low incidence of RF at baseline (present in 59% of patients at baseline, a figure typical of studies of early RA). We observed that patients who were on HCQ and considered treatment responders at month 6 were most likely to be on HCQ at month 24 (Table 3). None of the other clinical markers examined such as baseline morning stiffness, swollen joint count, HAQ pain or disability score nor laboratory markers of an acute phase response were predictive of ultimate treatment assignment in our study. These markers also have not been very consistent or reliable in other studies.

The study design we employed to examine these questions was based on several longitudinal studies that described the progression of erosive joint damage. Most patients with early RA who develop erosions do so within the first 2 yr of RA, although authors disagree about the rate of progression. There is general consensus that the 2-yr disease duration time-point is a watershed in the course of the disease [11]. Patients who have non-erosive disease after 2 yr tend to not develop erosions during the disease, or at least have rather non-destructive disease, while patients who have developed erosions within the first 2 yr, have further progression with continued follow-up.

In more recent years, efforts to improve the outcome in patients with RA have concentrated on the early stages of the disease. DMARD treatment in the early stages of the disease can slow the progression and change the long-term course of the disease [12–19]. More aggressive combination therapies with different DMARDs including tumour necrosis factor-α inhibitors and perhaps general use of low-dose prednisone in the early stages of the disease have been advocated to capitalize on this critical time period [11].

We attempted to address the issue of which patients could benefit by a non-aggressive initial treatment approach by standardizing initial treatment to a mild DMARD, HCQ and accelerating therapy as clinically indicated, assessing prognostic markers which in the future may help to avoid over-treatment in those patients who do not need it. A large subset of our patients had an overall good prognosis, frequently on rather mild treatment. After 2 yr, 49 of the 94 available patients were still on a mild treatment regimen with HCQ and NSAIDs or were off DMARDs and were considered by the treating physician as doing satisfactorily using rather strict clinical response criteria, indicating that disease activity was well controlled in these patients. These patients had a mean tender joint count of 4.6. Only seven of these patients were on low-dose steroids. While current treatment goals are for no active joints, still 47 of the 94 patients did not develop new erosions during the 2-yr period [7]. Our examination of the 17 patients who dropped out of the study prematurely revealed that most (11/17) had responded to treatment according to the pre-defined response criteria, possibly suggesting that patients with milder disease were less motivated to follow through with the study and more likely to drop out of it. It is unlikely therefore that the study was overly biased by retention of individuals with mild disease as opposed to more severe disease.

The present study suggests that early aggressive treatment may not be needed for all patients with RA, and is in concert with other studies which have suggested that even milder, less aggressive treatment with DMARDs such as HCQ and sulphasalazine, and perhaps even low-dose corticosteroids, is capable of improving clinical outcomes and reducing erosive disease [12, 14, 16, 20, 21]. Certainly many studies have demonstrated the value of MTX, the 'fall back' DMARD in this study, in controlling disease symptoms, reducing the development of erosions and improving life expectancy [14, 16–18, 20–24].

Prognostic markers that allow identification of those patients in whom disease activity can be controlled by minimal therapy are clearly of interest and these markers may be different from those that predict erosive disease. Our prospective study used clearly defined outcome measures and a pre-defined treatment algorithm to address this question. These parameters include the number of joints with active disease, the degree of acute phase response and rheumatoid factor positivity. Genetic factors associated with increased risk of developing erosions in other studies include HLA-DRB1 polymorphisms, but were not predictive of treatment assignment in our study [25–30]. The HLA-C7*xx* was, however, predictive; the significance of this finding remains to be fully elucidated.

While acute phase reactants including the sedimentation rate and C-reactive protein have been suggested by some as the strongest predictor of radiographic progression, the risk of functional disability correlates less well with acute phase reactants,

and better with age and HAQ score, pain, as well as global assessments [30–33]. Work disability is associated with these same factors and socio-demographic indicators including educational achievement, physical job demands and total joint count [34, 35]. One of the reasons may be that these clinical markers reflect disease activity and therefore directly influence the treatment approach by the physician. In our study design, we had required a step-up treatment approach to control disease activity, to optimize management of the patient and to reflect normal practice behaviour. It is possible that this type of approach in treatment has already compensated for the impact of these clinical disease activity markers.

Approximately 50% of the patients enrolled in this study were maintained on what is generally considered non-aggressive therapy with HCQ with or without low-dose corticosteroid therapy with good control of clinical disease despite the use of rigorous criteria for treatment response. The tender and swollen joint count after 2 yr was 6.5 and 9.2. This is somewhat difficult to compare with more recent treatment studies that use a simplified 0/1 scoring system; however, our results appear to be in the same range, suggesting that patients in this study were not under-treated. Further, approximately 50% of all patients did not develop any erosions during the 2-yr follow-up, clearly indicating that there is a substantial proportion of patients where over-treatment can be avoided. This observation highlights the need for better prognostic markers to make early treatment decisions in RA. Our study demonstrates that there are still very few consistently reliable predictors of long-term treatment needs in patients with this disease.

Identification of markers of very poor prognosis among DMARD naïve and DMARD treated patients with refractory early disease remains a major challenge [36, 37]. At the same time, we have treatment options at our disposal that have the potential to prevent functional and radiographic deterioration and improve life expectancy. Rheumatoid factor positivity, and in this study rheumatoid factor titre, has consistently been a valuable prognostic indicator. Extra-articular disease occurred in a small number of patients; their impact on clinical outcome and treatment assignment at 2 yr could not be assessed.

Ultimately, we believe that this study suggests that even milder forms of treatment are greatly beneficial and reduce the disease burden substantially, including development of erosive disease. Longer-term studies will demonstrate whether this improvement is sustained over time. Clearly, at this point, we must conclude that initial therapy for RA need not, of necessity, be 'aggressive' for a large subset of patients. Neither, however, may DMARD therapy be neglected. We are engaged in a long-term follow-up of these patients, which should yield further information about the role of these factors in predicting the long-term course and treatment of the disease. While there is considerable debate about the relative risks and benefits of the use of low-dose prednisone in the management of early RA, we could not determine whether the use of this drug has an impact on the ultimate treatment assignment by 24 months of follow-up, given the two treatment options HCQ or MTX, or on the development of erosions [7]. Whether the outcome of such a trial evaluating treatment assignment and outcomes such as erosions in a cohort of patients with early RA by comparing, for example, HCQ or even MTX to a biological therapy (with or without low-dose prednisone) would be similar to our results is of course uncertain. In the meantime, early referral to specialist care and continued efforts of early arthritis clinics have an increasingly important role in improving the long-term care and disease outcome of patients with RA, optimizing outcome and minimizing side-effects, and in all cases must be embraced by the medical community.

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