Clinical and Serological Predictors of Remission in Rheumatoid Arthritis Are Dependent on Treatment Regimen

Margaret H.Y. Ma, Ian C. Scott, Chanaka Dahanayake, Andrew P. Cope, and David L. Scott

ABSTRACT. ***Objective.*** Early intensive treatment is now the cornerstone for the management of rheumatoid arthritis (RA). In the era of personalized medicine, when treatment is becoming more individualized, it is unclear from the current literature whether all patients with RA benefit equally from such intensive therapies. We investigated the benefit of different treatment regimens on remission rates when stratified to clinical and serological factors.

Methods. The Combination Anti-rheumatic Drugs in Early Rheumatoid Arthritis (CARDERA) trial recruited patients with RA of less than 2 years' duration who had active disease. The trial compared 4 treatment regimens: methotrexate monotherapy, 2 different double therapy regimens (methotrexate and cyclosporine or methotrexate and prednisolone) and 3-drug therapy. Clinical predictors included age, male sex, and tender joint count (TJC) and serological biomarkers included rheumatoid factor (RF) and anticitrullinated protein antibodies (ACPA).

Results. Patients who were male, over 50 years, had ≥ 6 TJC, were RF-IgM–positive, or ACPA-positive were more likely to achieve remission at 24 months using 3-drug therapy compared to monotherapy (OR 2.99, 4.95, 2.71, 2.54, and 3.52, respectively). There were no differences in response to monotherapy and 3-drug therapy if patients were female, under 50 years, had < 6 TJC, or were seronegative.

Conclusion. Early intensive regimens have become the gold standard in the treatment of early RA. Our study suggests that this intensive approach is only superior to monotherapy in certain subsets of patients. Although these are unlikely to be the only predictors of treatment response, our study brings us a step closer to achieving personalized medicine in RA. (First Release June 15 2014; J Rheumatol 2014;41:1298–1303; doi:10.3899/jrheum.131401)

Key Indexing Terms:
RHEUMATOID ARTHRITIS
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Rheumatoid arthritis (RA) is a heterogeneous disease with diverse outcomes. Early intensive combination treatment regimens aiming at achieving remission have been shown to reduce disease activity, structural damage, and longterm disability[1,2,3,4,5,6,7]. This approach is now widely adopted as first-line treatment in routine clinical practice both nationally and internationally[8,9,10]. In an era when personalized medicine is becoming a possibility, treatment of patients with RA should be more individualized. It is unclear from the current literature whether all patients with RA benefit equally from such intensive therapies.

We have shown previously that age, sex, and baseline tender joint counts (TJC) predict remission at 24 months[11]. By using these baseline clinical variables, we developed a remission score that predicted the likelihood of achieving remission at 24 months. While the scores are relevant to both clinical trial and routine practice settings, their interaction with treatment was not explored.

Serological biomarkers including rheumatoid factor (RF) and anticitrullinated protein antibodies (ACPA) play important roles in the diagnosis of RA[12]. The presence of these antibodies is associated with radiographic damage, high disease activity, and extraarticular manifestations[13,14,15]. There is emerging evidence that serological status can predict treatment response in biological therapies[16,17]; however, evidence in intensive therapy with disease-modifying antirheumatic drugs (DMARD) is limited[18]. In our current study, we assessed the role of ACPA and RF status as predictors of remission and evaluated whether clinical and serological biomarkers

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predict remission in response to different DMARD regimens.

MATERIALS AND METHODS

Patients and samples. The Combination Anti-rheumatic Drugs in Early Rheumatoid Arthritis (CARDERA) trial recruited patients with RA of less than 2 years' disease duration who had active disease. Details have been published[19]. The trial compared 4 treatment regimens: methotrexate (MTX) monotherapy, 2 different double-therapy regimens [MTX and cyclosporine (CSA) or MTX and prednisolone], and 3-drug therapy (MTX, CSA, and prednisolone). Serum samples were taken at baseline.

Autoantibody analysis. RF-IgM was determined using commercially available ELISA kits (Euroimmun) and expressed as relative units per ml (RU/ml). Testing was performed according to the manufacturer's instructions, at a sample dilution of 1:200. The upper limit of the normal range (ULN) recommended by Euroimmun is 20 RU/ml. Anticyclic citrullinated peptide antibodies (anti-CCP; IgG) were measured using an ELISA-based kit from Axis-Shield that detects autoantibodies toward a synthetic cyclic peptide containing modified arginine residues (CCP2 peptides). Testing was performed according to the manufacturer's instructions, at a sample dilution of 1:100. The cutoff value for anti-CCP antibody positivity was 5 U/ml.

Remission score. The development of the remission score has been published[11]. In brief, we used the CARDERA randomized controlled trial (RCT) to develop a predictive model for 24-month remission. This model was then validated using data from a UK observational cohort (Early RA Network, ERAN). Remission was defined as 28-joint Disease Activity Score < 2.6. Logistic regression models were used to estimate the associations between remission and potential baseline predictors. Multivariate logistic regression analyses showed age, sex, and tender joint count (TJC) were independently associated with 24-month remission. The multivariate remission score developed using the trial data correctly classified 80% of patients. The remission score was 0.37 + [–0.03 × age] + [1.1 × sex (1 for males and 0 otherwise)] + [–0.07 × Baseline 28TJC]. By combining data from the trial and ERAN, we also developed a simplified remission score that showed that younger men (< 50 years) with a TJC of 5 or lower were most likely to achieve 24-month remission. The effect of treatment was not considered in this article because treatment differed considerably between the 2 study groups.

Statistical analysis. Data were analyzed using SPSS v20. Analyses were restricted to those individuals with complete data at 24 months and with available serum samples. Remission was defined as DAS28 < 2.6 at 24 months. Individual variables were assessed descriptively as median values and interquartile ranges. Categorical data were analyzed using chi-square test if the number of patients was 10 or more, or Fisher's exact test if there were fewer than 10 per group. Multiple testing was adjusted by using Bonferroni method.

The remission score was 0.37 + [–0.03 × age] + [1.1 × sex (1 for males and 0 otherwise)] + [–0.07 × Baseline 28TJC][11]. A higher value indicates a higher probability that the patient will achieve remission at 24 months. Logistic regression modeling was carried out to assess the ability of the remission score to predict remission at 24 months when stratified into different treatment groups. This was adjusted for treatment center.

Sex, age, and baseline TJC were dichotomized using thresholds from our previous study[11]: sex, age (< 50 or ≥ 50 years), and TJC < 6 or ≥ 6. Logistic regression models were used to estimate the associations between treatment regimens and point remission at 24 months when stratified by these clinical predictors and serological biomarkers. The effects of treatment on remission rates were first explored. This showed no difference between double vs monotherapy (OR 0.852, 95% CI 0.435–1.67, p = ns). The effect of 3-drug therapy compared to monotherapy was OR 2.22, 95% CI 1.11–4.46 (p = 0.025). The models were therefore restricted to monotherapy versus 3-drug therapy with adjustment for treatment center. To explore the interaction between clinical and serological status, serological status models were also adjusted for baseline DAS28, sex, and age.

RESULTS

Study population. In the CARDERA trial, 467 patients were randomized; 378 patients had complete data for 24 months of followup. Analysis was restricted to the 351 patients from this group who had baseline serum samples available. Table 1 summarizes their baseline characteristics. There was no difference in baseline DAS28 between patients when stratified according to RF-IgM and to ACPA status: mean initial DAS28 (SD) of RF-IgM–negative and –positive patients were 5.86 (1.27) and 5.73 (1.29), respectively, and of ACPA-negative and ACPA-positive patients were 5.84 (1.36) and 5.69 (1.27), respectively.

DAS28 remission rates at 24 months. In total, 16/87 patients (18%), 29/180 (16%), and 30/90 (33%) achieved remission at 24 months using monotherapy, double therapy, and 3-drug therapy, respectively. There were no differences between serological status and remission rates at 24 months: 10/44 (23%) of RF-IgM–negative and 14/88 (16%) of ACPA-negative patients achieved remission, whereas 65/313 (21%) of RF-IgM–positive and 60/262 (23%) of ACPA-positive achieved remission (chi-square p > 0.05).

The remission score and clinical predictors of remission by treatment group. The mean (SD) remission score was –1.7 (0.84). The remission score predicted treatment response in monotherapy, double, and 3-drug therapy (OR 3.07, 95% CI 1.35–6.96, p = 0.007; OR 1.99, 95% CI 1.19–3.32, p = 0.008; and OR 4.42, 95% CI 1.90–8.94, p < 0.0001, respectively). This was adjusted for treatment center.

The individual clinical predictors were then dichotomized: sex, age (< 50 or ≥ 50 years), and TJC < 6 or ≥ 6. There were 245 female patients and 113 male, 122 were < 50, 236 were ≥ 50 years, 88 had fewer than 6 tender joints, and 270 had 6 or more tender joints. Figure 1 shows treatment responses when stratified to different clinical predictors. Females achieved low levels of remission across

Table 1. Baseline patient characteristics in 358 patients with complete 2-year data and available serum samples.

Clinical Features	Baseline Data
Female, n (%)	245 (68)
Median age at onset, yrs (IQR)	54 (46, 63)
Rheumatoid nodules, n (%)	80 (22)
Median baseline DAS28 (IQR)	5.78 (4.88, 6.76)
Median baseline HAQ (IQR)	1.62 (1.12, 2.03)
Median Larsen score (IQR)	6.5 (2.3, 16)
RF-IgM positivity, n (%)	313 (87)
ACPA positivity, n (%)	258 (72)

IQR: interquartile range; DAS28: 28-joint Disease Activity Score; HAQ: Health Assessment Questionnaire; RF-IgM: rheumatoid factor-IgM isotype; ACPA: anticitrullinated protein antibodies.

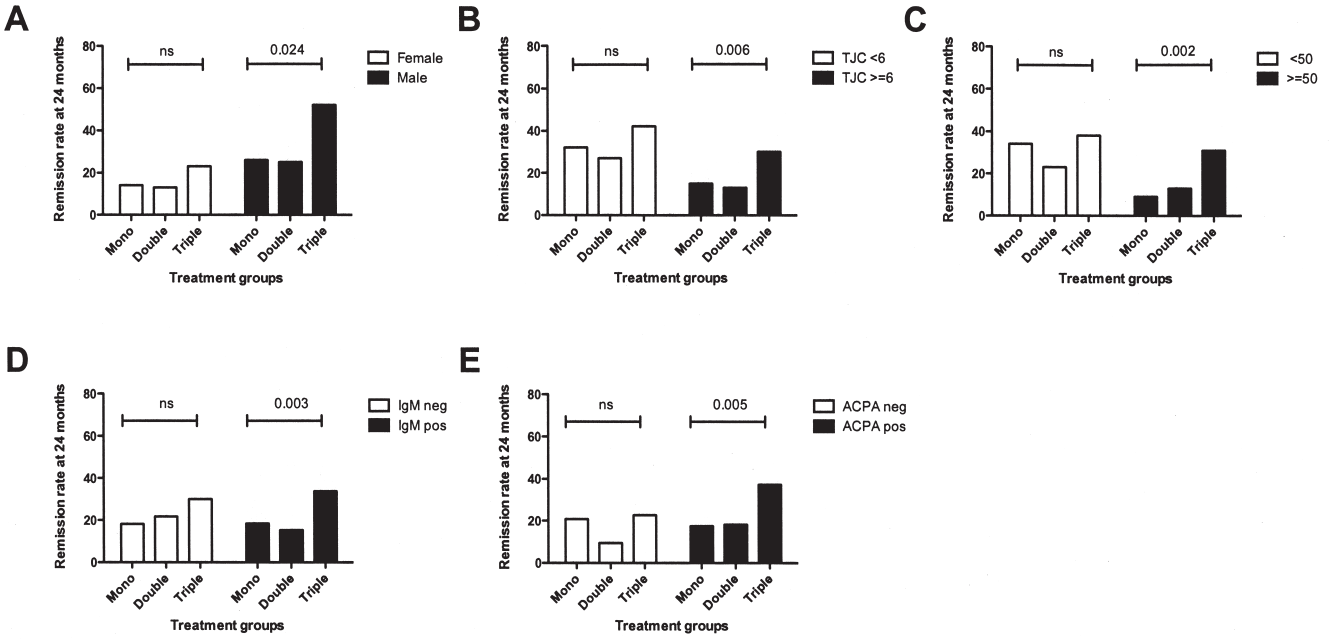

Figure 1. Remission rates at 24 months in different treatment groups according to clinical and serological predictors: (A) sex, (B) tender joint count (TJC), (C) age (years), (D) rheumatoid factor–IgM, and (E) antibodies to anticitrullinated protein (ACPA). Multiple testing was adjusted using the Bonferroni method. Mono: methotrexate (MTX) monotherapy; double therapy: MTX and prednisolone or MTX and cyclosporine (CSA); triple therapy: MTX, CSA, and prednisolone.

all treatment arms and responded to a similar extent to monotherapy, double-drug, and 3-drug therapy [8/14 (14%), 17/131 13%, 13/57 23%, respectively, $p > 0.05$]. Males responded better to 3-drug therapy (17/33, 52%) compared to monotherapy and double therapy (8/31, 26%; 12/49, 25%). Patients with lower TJC responded to a similar extent across all the treatment groups: monotherapy (6/19, 32%), double therapy (12/44, 27%), and 3-drug therapy (10/24, 42%, p = ns). Patients with more than 6 TJC achieved higher remission rates with 3-drug therapy (20/66, 30%) when compared to monotherapy (10/68, 15%) and double therapy (17/136, 13%). Patients under 50 years achieved similar high rates of remission across all the treatment groups: monotherapy (11/32, 34%), double therapy (14/61 23%), and 3-drug therapy (11/29 38%, p = ns). Patients over 50 years of age achieved higher remission rates using 3-drug therapy (19/61, 31%) when compared to monotherapy (5/55, 9%) and double therapy (15/119, 13%).

Using logistic regression modeling, patients who were male, over 50 years, or had ≥ 6 TJC were more likely to achieve remission at 24 months using 3-drug therapy compared to monotherapy (OR 2.99, 4.95, and 2.71, respectively, Table 2). There were no differences in response to monotherapy and 3-drug therapy if patients were female, under 50 years, or had fewer than 6 tender joints (Table 2).

Serological predictors of remission by treatment group. When stratified according to different treatment groups, serological status did have an effect on remission rates (Figure 1). In RF-IgM–negative patients, there was no difference in point remission rates between monotherapy, double therapy, and 3-drug therapies, respectively [2/11 (18%), 5/23 (22%), and 3/10 (30%), $p > 0.05$]. In RF-IgM–positive patients, fewer patients achieved remission using monotherapy and double therapy (14/76, 18% and 24/157, 15%) compared to 3-drug therapy (27/80, 34%, p = 0.02). In ACPA-negative patients, 5/24 (21%), 4/42 (10%), and 5/22 (23%) achieved remission using monotherapy, double therapy, and 3-drug therapies, respectively ($p > 0.05$). In ACPA-positive patients, more patients achieved remission

Table 2. Predictive value of achieving remission at 24 months using 3-drug therapy (methotrexate, cyclosporine, and prednisolone) compared to methotrexate monotherapy, adjusted for treatment region.

Predictors of Response	OR	95% CI	p
Female	1.80	0.68–4.78	NS
Male	2.99	1.01–8.90	0.049
Over 50 years old	4.95	1.66–14.75	0.004
Under 50 years old	1.09	0.38–3.16	NS
≥ 6 TJC	1.56	0.43–5.63	NS
< 6 TJC	2.71	1.11–6.60	0.028
RF-IgM–negative	1.49	0.17, 12.46	NS
RF-IgM–positive	2.28	1.08, 4.85	0.032
ACPA-negative	1.03	0.25, 4.30	NS
ACPA-positive	2.99	1.29, 6.97	0.011

RF-IgM: rheumatoid factor–IgM isotype; ACPA: anticitrullinated protein antibodies; TJC: tender joint count; NS: not significant.

using 3-drug therapy (25/67, 37%) than monotherapy (11/63, 17%) and double therapy (24/132, 18%; p = 0.007).

The level of seropositivity was next explored. Patients were stratified into low-positive (< 3 × ULN) and high-positive (≥ 3 × ULN), according to thresholds adopted in the American College of Rheumatology (ACR) criteria for RA in 2010[12]. In low-positive RF-IgM, there was no difference between remission rates in the different treatment groups: monotherapy 2/8 (25%), double therapy 0/15 (0%), and 3-drug therapy 1/3 (33%, p = ns). In high-positive RF-IgM, more patients achieved remission with 3-drug therapy [26/77 (33.8%)] than monotherapy [12/68 (17.6%)] and double therapy [24/142 (16.9%, p = 0.01)]. In low-positive ACPA, there was no significant difference in remission rates between the treatment groups: monotherapy 3/5 (60%), double therapy 1/13 (7.7%), and 3-drug therapy 2/9 (22%, p = ns). In contrast, in the high-positive ACPA group, more patients achieved remission with 3-drug therapy [23/58 (39.7%)] when compared to monotherapy [23/76 (13.8%)] and double therapy (23/119, 19.3%, p = 0.001) groups.

The associations of treatment regimens and remission according to serological status are summarized in Table 2. The benefit of 3-drug therapy is only apparent in RF IgM–positive (OR 2.28, 95% CI 1.08-4.85) and ACPA-positive patients (OR 2.99, 95% CI 1.29-6.97). The effect size increased when adjusted for clinical factors (DAS28, age, and sex), suggesting that the effects of the clinical and serological biomarkers were cumulative (OR 2.54 and 3.52, respectively, Table 3).

Serological status and ACR core set remission measures. To explore the effects of the individual components of DAS28, the threshold levels for remission according to the ACR core set measures were used[12,20]. At 24 months, in total, 44.7% of patients achieved TJC28 ≤ 1, 22.9% had no swollen joints, 56.2% had erythrocyte sedimentation rate ≤ 20, and 23.2% had physician's global assessment ≤ 10. There were no differences between monotherapy and 3-drug therapy in any of the 4 components at 24 months between RF-IgM–positive and RF-IgM–negative patients (Table 4). Among ACPA-positive patients, more achieved TJC28 and SJC28 thresholds of remission in the 3-drug therapy group than in monotherapy groups at 24 months than did ACPA-negative patients (Table 4).

Table 3. The use of serological status to predict remission at 24 months using 3-drug therapy (methotrexate, cyclosporine, and prednisolone) compared to methotrexate monotherapy. Adjusted for treatment region, baseline DAS28, sex, and age.

Predictors of Response	OR	95% CI	p
RF-IgM–negative	1.17	0.58, 23.9	NS
RF-IgM–positive	2.54	1.12, 5.76	0.026
ACPA-negative	0.91	0.19, 4.28	NS
ACPA-positive	3.52	1.37, 9.03	0.009

DAS28: 28-joint Disease Activity Score; RF-IgM: rheumatoid factor–IgM isotype; ACPA: anticitrullinated protein antibodies; NS: not significant.

DISCUSSION

Early intensive combination regimens have become the gold standard in the treatment of early RA. Our study suggests that this approach is only superior to monotherapy in certain subsets of patients. Stratifying patients according to sex, age, TJC, RF-IgM positivity, and ACPA positivity can predict those subjects more likely to achieve remission states after 24 months of combination treatment.

Intensive DMARD therapies are associated with increased drug toxicity[21]. A personalized, tailored approach in which each patient receives the appropriate intensity of treatment for as long as needed is the goal. We have shown previously that female patients of older age with high TJC were less likely to achieve remission, and many other studies have shown similar findings[22,23,24,25,26,27]. However, it may be an oversimplification to suggest that patients with poor prognostic factors will respond to intensive therapies. The current study suggests that males respond better to 3-drug therapy compared to monotherapy, whereas females respond worse to all treatment regimes. Conversely, patients over 50 years and with more than 6 tender joints respond better to 3-drug therapy than monotherapy, but younger patients with a lower TJC respond well to all treatment regimens.

Prediction matrices using serological status exist to predict risk of rapid radiological progression using different DMARD and biological treatment regimens[28]. Other studies have shown conflicting results using serological status to predict anti-tumor necrosis factor response[16,17,29]. However, no model exists for predicting clinical response to intensive DMARD regimens. Our study demonstrates that the remission rates of different DMARD regimens are dependent on serological status in patients with early RA. This suggests that there may be fundamental differences in the disease of these subsets of patients, and treatment regimens should be separated according to serological status.

The main limitation of our study is that it is a posthoc analysis of an RCT. The findings of our study will require validation in an independent cohort. The treatments used in the RCT (MTX, CSA, and short-term high-dose prednisolone) are not widely used as initial combinations in contemporary RA treatment. Our findings might not be generalizable to all intensive combination therapies. However, it is a well-recognized combination, and many RCT have demonstrated its efficacy[30,31,32,33,34]. CSA is infrequently used in RA, though there is extensive evidence for its use, which has been summarized in a Cochrane review by Wells, *et al*[34]. Although they are effective and relatively safe, other DMARD, such as sulfasalazine and hydroxychloroquine, are usually given in combination with MTX. In addition, our

Table 4. Comparing the effects of methotrexate monotherapy and 3-drug therapy (methotrexate, cyclosporine, and prednisolone) in achieving remission scores in the individual components of DAS28 at 24 months when taking serological status into account. Except for p values, data are n (%).

Serological Status	Treatment Regimens	TJC at 24 Months ≤ 1	p	SJC at 24 Months < 1	p	ESR at 24 Months ≤ 20	p	PGA at 24 Months ≤ 10	p
RF-IgM-negative	Monotherapy	4/8 (50)	NS	1/4 (25)	NS	7/15 (47)	NS	4/6 (67)	NS
	3-drug	4/8 (50)		3/4 (75)		8/15 (53)		2/6 (33)	
RF-IgM-positive	Monotherapy	37/87 (43)	NS	16/42 (38)	NS	42/89 (47)	NS	17/41 (42)	NS
	3-drug	50/87 (58)		26/42 (62)		47/89 (53)		24/41 (59)	
ACPA-negative	Monotherapy	14/25 (56)	NS	5/10 (50)	NS	12/27 (44)	NS	7/13 (54)	NS
	3-drug	11/25 (44)		5/10 (50)		15/27 (56)		6/13 (46)	
ACPA-positive	Monotherapy	27/70 (39)	0.015	12/36 (33)	0.033	37/76 (49)	NS	14/34 (41)	NS
	3-drug	43/70 (61)		24/36 (67)		39/76 (51)		20/34 (59)	

TJC: tender joint count; SJC: swollen joint count; ESR: erythrocyte sedimentation rate; PGA: patient global assessment; RF-IgM: rheumatoid factor-IgM isotype; ACPA: anticitrullinated protein antibodies; NS: not significant; DAS28: 28-joint Disease Activity Score.

study used fixed treatment regimens rather than the treat-to-target approach that is now widely used in early RA management. Our findings suggest further research is needed to assess the benefits and risks of treat-to-target strategies in ACPA-negative disease. We used the DAS28 remission criteria because it is readily achievable in clinical practice. Stricter remission criteria may be preferable in the longer term, such as the ACR/European League Against Rheumatism (EULAR) Boolean remission criteria. Finally, the patients enrolled in CARDERA had more severe early RA than is generally seen in current routine practice.

This study shows a role in a range of conventional clinical and serological biomarkers in predicting treatment responses to combination DMARD therapy. The results suggest that initial combination therapy may only be useful in certain subsets of patients with early RA. Although other genetic and laboratory biomarkers are likely to be required to achieve a personalized approach to treatment of RA, our study does challenge the established view that all patients with RA should be given intensive combination treatment. Our study favors the more cautious approach in the 2013 EULAR guidance.

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