Predicting responses in patients with rheumatoid arthritis to disease-modifying agents using baseline clinical data

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Abstract

Objective

The optimal treatment for active rheumatoid arthritis (RA) is unresolved, particularly in early RA. We used data from an observational cohort to develop the simple predictor algorithm and evaluated its application in two completed clinical trials in early and established RA. We assessed whether using a simple algorithm can identify patients who have persisting active disease despite treatment with disease-modifying drugs (DMARDs). We also examined if patients who have lower likelihoods of persisting active RA are likely to benefit from intensive treatment.

Methods

We developed a simple predictive score for persisting disease activity using conventional clinical assessments in an observational cohort of patients with early RA (ERAN). It was tested in two trials in early (CARDERA) and established (TACIT) RA. Persistent disease activity was defined as disease activity score for 28 joints (DAS28) >3.2 at both 6 and 12 months.

Results

Regression modelling identified three main predictors of persisting active disease in ERAN; tender joint counts, health assessment questionnaire (HAQ) scores and ESR. We dichotomised these predictors (≥6 tender joint counts, ≥1.0 HAQ ≥20 mm/h ESR) in a four-point prediction score. This simple prediction score predicted persisting active disease in the ERAN cohort and both CARDERA and TACIT trials. Patients with high scores were more likely to have persistently active disease at 6 and 12 months. The relationship was weaker in TACIT because no patients were without any predictive factors.

Conclusion

Combining tender joint counts, ESR and HAQ in a simple predictive score prospectively identifies patients with higher risks of persistent disease activity over the next 12 months. More patients with all three risk factors had persistent active disease than those with none or one risk factor.

Key words

outcome, early rheumatoid arthritis, treatment response, health utility

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Introduction

The optimal treatment for active rheumatoid arthritis (RA) is unresolved, particularly in early RA. Monotherapy with methotrexate and other disease-modifying anti-rheumatic drugs (DMARDs) is often insufficient. Initial intensive management with either combination DMARDs or DMARD monotherapy with biologics like tumour necrosis factor (TNF) inhibitors, though more effective, risks over-treating some patients (1). The uncertainty about which RA patients need intensive treatment is reflected in divergent advice from management guidelines (2-4).

One way to minimise uncertainty is to use response predictors to judge if intensive treatment is needed. Several clinical variables predict poor treatment outcomes, including longer disease durations, female gender, high disability and disease activity levels, rheumatoid factor positivity and smoking (5-8). Treatment response predictors have been studied in detail in early RA. Studies show responses to methotrexate and other DMARDs are predicted by rheumatoid factor and anti-citrullinated peptide antibody positivity, female gender, disease activity, disability scores, genetic risks and smoking status (9-14).

Clinical trials in RA usually enrol patients with active disease identified with simple assessments, like 6 or more tender and swollen joints and ESRs of 28mm/h or more (15). Not all early RA patients need intensive treatment and a simple algorithm using commonly recorded clinical assessments may identify early RA patients likely to respond poorly to initial DMARD monotherapy. The goal using DMARDs is sustained low disease activity. We therefore designed an algorithm to identify patients with persistent active disease (DAS28 ≥3.2) at 6 and 12 months despite DMARDs. Data from an observational cohort (16) helped develop a simple predictor algorithm. We evaluated it using published clinical trials in early (17) and established RA (18). We asked two specific questions. Firstly, can a simple algorithm identify patients who with persisting active disease despite DMARDs? Secondly, will patients at higher risk of persistent disease activity benefit from intensive treatment?

Methods

Observational study

We studied data collected from 2002–2007 in patients from the Early RA Network (ERAN) observational cohort. This inception cohort of patients with newly diagnosed RA was recruited from 19 UK centres. It reflected contemporary routine care. 62% fulfilled four or more ACR criteria for RA at first visit. Most patients (97%) received DMARDs; 91% received initial DMARD monotherapy (usually sulfasalazine or methotrexate); 9% received DMARD combinations; details of these ERAN patients have been previously reported (16).

Clinical trials

We studied patients in two trials. The first, in early RA, was the combination anti-rheumatic drugs in early RA (CARDERA) trial. The second, in established RA, was the tumour-necrosis-factor inhibitors against combination intensive therapy with conventional disease-modifying anti-rheumatic drugs in established RA (TACIT) trial.

CARDERA recruited active RA patients of less than 24 months' duration meeting the 1987 ACR classification criteria. They had active disease with three of the following: ≥3 swollen joints, ≥6 tender joints, ≥45 minutes morning stiffness and an erythrocyte sedimentation rate (ESR) >28mm/h. It compared methotrexate monotherapy, methotrexate with cyclosporine, methotrexate with steroid or all three drugs (17). The trial lasted 24 months.

TACIT recruited patients with active RA (18). Patients met the 1987 ACR classification criteria for RA and had active disease (two DAS28 scores over 5.1 at least one month apart). They received combination DMARDs, with tumour necrosis factor inhibitors given to non-responders after 6 months, or initial tumour necrosis factor inhibitors with DMARD monotherapy. The trial lasted 12 months.

Approval

Ethical approval was obtained for ERAN from the Trent Research Ethics Committee (ref. 01/4/047), for CARDERA from the South East Multicentre Research Ethics Committee (ref.

MREC (1) 99/04), and for TACIT from the University College London Hospital research ethics committee ref. 07/Q0505/57). All patients gave written, informed consent.

Data analysed

Patient demographics (age, sex, disease duration), Disease Activity Score for 28-joints (DAS28) and its components, disability using the health assessment questionnaire (HAQ), treatments with disease-modifying drugs (DMARDs), biologics and steroids were available for analysis in all studies. In ERAN rheumatoid factor and baseline smoking status was also analysed.

Persistent disease activity

Persistent disease activity was defined as a DAS28 of greater than 3.2 at both 6 and 12 month visits (19).

Statistical analysis

Predictors of persistent disease activity in ERAN were assessed using logistic multiple regression and expressed as odds ratios (OR) with 95% confidence intervals (CI). The baseline explanatory variables considered were sex, tender joint count, swollen joint count, ESR, DAS28 and HAQ. As DAS28 was strongly associated with all other variables it was not included in the model. Chi-squared tests compared the proportion of patients with low disease activity scores. Statistical analyses were performed using SPSS v. 17 (SPSS Inc). *P*-values of less than 0.05 were considered statistically significant.

Results

Patient cohorts

We studied 155 patients in the observational cohort (ERAN) who had completed 12 months' follow-up and who had had clinical data collected at 0, 6 and 12 months. The CARDERA trial enrolled 465 patients with early RA; we evaluated 377 patients where complete data were available. The TACIT trial enrolled 205 patients with established RA; we evaluated 179 patients with all data available. Baseline characteristics of each group are shown in Table I.

Table I. Baseline patient characteristics in the ERAN and CARDERA studies.

Characteristics	ERAN cohort (n=155)	CARDERA trial (n=465)	TACIT trial (n=205)
Mean age (SD)	56 (14)	54 (13)	57 (12)
Women (%)	101 (65%)	325 (70%)	152 (74%)
Tender joints	8 (7)	11.8 (7.6)	17 (7)
Swollen joints	6 (6)	9.9 (6.3)	11 (6)
ESR	30 (25)	41 (29)	32 (25)
Health Assessment Questionnaire	1.1 (0.8)	1.6 (0.7)	1.8 (0.6)
DAS28	4.7 (1.6)	5.8 (1.3)	6.3 (0.9)

Table II. Overall predictors of persistently active disease in ERAN patients.

Predictor	Unadjusted		Adjusted	
	OR (95% CI)	Significance	OR (95% CI)	Significance
Tender joint count	1.16 (1.09, 1.23)	<0.01	1.11 (1.04, 1.19)	<0.01
HAQ	3.83 (2.23, 6.54)	<0.01	2.10 (1.16, 3.81)	<0.02
ESR	1.06 (1.03, 1.08)	<0.01	1.05 (1.02, 1.08)	<0.01
Swollen joint count	1.13 (1.05, 1.21)	<0.01	-	NS

Developing simple predictive model using observational data

Regression modelling assessed the effects of individual predictors of persisting active disease (DAS28 >3.2 at 6 and 12 months) using ERAN data. An unadjusted regression model showed initial tender joint counts, HAQ, ESR and swollen joint counts were all predictive factors (Table II). Age, gender, smoking and rheumatoid factor status did not show significant relationships. Variables which remained significantly associated at 5% level with persisting active disease in univariate analysis were subsequently included in a multivariable logistic regression model. This adjusted model showed the three key predictors of persisting active disease comprised tender joint counts, HAQ and ESR (Table II).

This regression model was subsequently transformed into a simple practical score by dichotomising these three key predictors. We used cut-offs of ≥6 tender joint counts, ≥1.0 HAQ and ≥20 mm/h ESR as simple predictors, based on clinical utility. All three dichotomised variables showed significant associations in unadjusted and adjusted models (data not shown). We combined these three simple predictors into a four point prediction score (0–3). It showed strong relationships to all patients in the ERAN cohort and also those patients in the ERAN cohort who had been treated with methotrexate (Table III).

Confirmatory studies using clinical trial data

The simple predictors score developed in the observational cohort showed similar relationships in patients in the CARDERA trial (Table IV); only 20% of patients with no initial predictors had persistent active disease, compared with 80% of patients with all three initial predictors. There was a similar, though weaker relationship in the TACIT trial; this was mainly because no TACIT patients fell into the lowest prediction category without any predictive factors. In both trials, patients with high scores were more likely to have persistently active disease at 6 and 12 months (Table IV).

We also evaluated the impact of treatment type. In CARDERA 90% of patients with all three poor predictive factors who received methotrexate monotherapy had persistently active disease. This was reduced to 76% in the triple therapy group (Table IV). There was no difference in the predictive capacity for different treatment strategies in TACIT.

Initial predictors, remission, and treatment intensities in clinical trial patients

In both the CARDERA and TACIT trials there were significant overall relationships between remissions at trial end-points (24 and 12 months, respectively) and initial predictive factors.

Table III. Simplified predictors of persistently active disease at 6 and 12 months in the ERAN cohort.

Patients	DAS28 at 6 and 12 months	Combination of TJ ≥6, HAQ ≥1.0 and ESR ≥20*				Significance
		0	1	2	3	
All treatments	≤3.2	21	27	9	4	χ^2=51.2; DF=3; p<0.01
	>3.2	5	16	38	36	
	Percent with active disease	19%	37%	81%	90%	
Methotrexate monotherapy	≤3.2	5	7	5	2	χ^2=11.6; DF=3; p<0.01
	>3.2	3	7	15	20	
	Percent with active disease	38%	50%	75%	91%	

*These variables were measured at baseline.

Table IV. Applying simplified predictors of persistently active disease to clinical trial patients.

Trial	DAS28 at 6 and 12 months	Combination of TJ ≥6, HAQ ≥1.0 and ESR ≥20*				Significance
		0	1	2	3	
CARDERA (All treatments)	≤3.2	8	25	40	24	χ^2=41.1;DF=3; p<0.01
	>3.2	2	29	99	150	
	Percent with active disease	20%	54%	71%	86%	
CARDERA (Methotrexate monotherapy)	≤3.2	2	2	10	3	χ^2=14.9; DF=3; p<0.01
	>3.2	0	8	26	41	
	Percent with active disease	0%	80%	72%	93%	
CARDERA (Triple therapy)	≤3.2	1	11	14	9	χ^2=8.9; DF=3; p<0.05
	>3.2	0	7	26	28	
	Percent with active disease	0%	39%	65%	76%	
TACIT (All treatment)	≤3.2	-	8	31	40	χ^2=5.9; DF=2; p=0.05
	>3.2	-	2	38	60	
	Percent with active disease	-	20%	55%	60%	

*These variables were measured at baseline

When different treatments were evaluated, these relationships were not seen with methotrexate monotherapy in the CARDERA trial and the DMARD strategy in the TACIT trial. They only occurred with triple therapy in CARDERA and the biologic strategy in TACIT.

Discussion

Our results show combining three initial clinical assessments before a new treatment is started in RA patients – tender joint count, ESR and HAQ – produce a simple algorithm which prospectively identified patients with higher risk of persistent disease activity over 12 months. The predictive value was similar in ERAN and CARDERA patients and comparable in TACIT patients. Substantially more patients with all three risk factors had persisting active disease than those with none or one risk factor. Our approach falls within the framework for prognostic studies recommended by the Progress Partnership (20).

Previous research shows genetic predictors appear important in determining responses to methotrexate and other DMARDs in early RA, particularly genes associated with methotrexate metabolism (21). There has also been extensive interest in identifying general prognostic indicators in early RA (22) and predictors of erosive progression (23, 24), functional disability (25, 26], extra-articular disease (27) and remission (28, 29). A different approach is using synovial pathobiology, but this is at a more developmental stage (30). None of these previous studies have focused on simple clinical algorithms of the sort we have developed.

A critical issue when treating patients with active RA is whether all patients are likely to benefit from intensive treatment. Although we were able to identify patients likely to fail to have their RA controlled with current treatment strategies, there was evidence that patients with all risk profiles benefitted from intensive treatment. TACIT showed patients with only one risk predictor had substantial benefit from the biologic strategy with 75% achieving remission at the trial end-point. Interestingly, Markusse *et al*. (31) suggested that benefits from intensive treatment should be extended to all patients and not restricted to poor prognosis patients. However, this perspective is controversial (32).

Our study has several strengths. In particular we studied large numbers of patients and replicated our findings across two clinical trials in both early and established RA. It also has a number of limitations. We did not include genetic predictors, which may be crucial predictors of response. Second, we did not evaluate rheumatoid factor isotypes or anti-citrullinated peptide antibodies, which may also be important response predictors. Third, using simple predictors failed to identify all patients with persistently active disease. This is partly because intensive treatments used in CARDERA and TACIT trials did not

prevent a substantial proportion of persistently active disease. Finally, our patients were enrolled before the introduction of new diagnostic criteria for the classification of early RA (33), although there is uncertainty about the impact of these criteria when used to prospectively identify patients with early RA (34, 35). However, there is growing evidence the new criteria change the exact nature of patients classified as having RA, particularly patients with seronegative disease (36, 37). In addition the clinical phenotype and frequency of RA may also be changing over time (38). It is possible these changes in classification and disease phenotype could alter the impact of our prognostic criteria.

We conclude RA patients have variable outcomes to treatment with DMARDs and biologics, which can in part be predicted using a simple algorithm. This concept builds on previous research about the predictive value of high DAS28 scores (38) and high HAQ scores [39]. This indicates that patients may not need identical treatment regimens; treatments should be individualised. However, the ability of the treatments used in this study to control RA, given in a range of settings during the last 10–15 years, seems incomplete. There is substantial supportive evidence in studies of biologics in a range of routine clinical practice settings (41, 42). Consequently, we consider most patients with active RA need to follow an intensive treatment regimen. Our findings suggest treatment intensities are still sub-optimal and there is a need to identify more effective treatment modalities and combinations of new and existing agents.

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