Using Predicted Disease Outcome to Provide Differentiated Treatment of Early Rheumatoid Arthritis

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ABSTRACT. ***Objective***. To determine the usefulness of a prediction model for making treatment decisions in early rheumatoid arthritis (RA).

Methods. In 152 patients with early RA, progression of radiological damage during the first year [Sharp-van der Heijde (SH) score > 0] was assessed and used to define actual disease outcome. Available variables at baseline were entered in a multivariate regression analysis with progression score as dependent variable. This model was used to predict disease outcome in every patient. Using the standard deviations of the predicted disease outcome, patients were divided into 3 groups: (1) severe disease: high probability (≥ 0.8) for progression > 0, (2) mild disease: high probability (≥ 0.8) for progression ≤ 0, and (3) not classified: no high probability for either option. It was determined how many patients could be classified by using this model.

Results. One hundred nine patients (71.7%) showed joint damage progression during the first year. Baseline variables available were: age, sex, duration of symptoms, duration of morning stiffness, patient's global assessment of disease activity, Health Assessment Questionnaire score, swollen and painful joint count, bilateral compression pain in metatarsophalangeals, rheumatoid factor positivity, erythrocyte sedimentation rate, shared epitope positivity, SH-score, and the presence of erosions. The R^2 value (≈ variation explained) of the prediction model was 0.36. By using this model 46.3% of patients could be classified as having severe disease, 0% as having mild disease, and 53.7% could not be classified.

Conclusion. To be able to make treatment decisions in early RA based on predicted disease outcome, a better prediction of disease outcome is needed, making the search for better prognostic variables urgent. (First Release July 15 2006; J Rheumatol 2006;33:1747–53)

Key Indexing Terms:
RHEUMATOID ARTHRITIS EARLY ARTHRITIS DISEASE PROGRESSION
PREDICTION COMBINATION DRUG THERAPY EARLY INTERVENTION

Over the last decade several studies have shown that early treatment of rheumatoid arthritis (RA) with disease modifying antirheumatic drugs (DMARD) results in more effective suppression of disease activity and substantial reduction of joint damage[1-3]. Even a brief delay of 3-9 months to start of DMARD therapy already has significant negative effect on radiological outcome after 2 years[4,5]. Based on these observations DMARD therapy currently is started as soon as a patient is diagnosed with RA.

This early start poses problems. It has been shown that early, aggressive intervention of RA with a combination of DMARD can modify longterm disease outcome independent of the treatment in the following years[6,7]. This indicates that there is a period very early in the course of RA during which radiological progression rates can be "reset" and therapeutic interventions can actually modify disease outcome. On the other hand, good clinical responses and prevention of progression of joint damage can be achieved with early DMARD monotherapy in a substantial proportion of patients. The results of the ERA trial, comparing etanercept and methotrexate (MTX) in patients with early RA, showed that among patients who received MTX monotherapy 60% had no increase of erosions, compared with 72% of patients who received etanercept 25 mg ($p = 0.007$)[8]. These observations are confirmed by the results of the BeSt study, a randomized, single-blinded clinical trial comparing 4 different treatment strategies in early RA. To achieve low disease activity, treatment was adjusted less often in the groups treated more aggressively with combination therapy including either prednisone or infliximab. However, in the group that started with monotherapy, persistent low disease activity could be maintained in 33% of patients over a period of 2 years with MTX monotherapy[9].

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Thus, although there is strong evidence for starting treatment early in the course of RA, these results also indicate that to achieve good clinical and radiological responses most aggressive strategies are not necessary for all patients. Supposing that patients with relatively mild RA need less aggressive and less toxic treatment strategies than patients with severe erosive disease, both subsets of patients should be identified at the moment of diagnosis. This way both subsets of patients will directly receive appropriate treatment with respect to expected disease outcome: an individual, "tailor-made" treatment strategy. In order to provide a tailor-made treatment strategy clinicians should ideally have at their disposal a set of baseline variables that accurately predicts disease outcome for every individual patient presenting with RA.

Of all aspects of RA, those resulting in physical impairment, such as joint damage and cumulative disease activity, are particularly specific for the disease and are highly associated with functional ability. Joint damage, disease activity, and functional ability are all used as outcome indicators[10,11]. Of these, joint damage is determined objectively and represents the cumulative effects of the disease on the joints at any point in time[11]. Several studies investigating factors predicting radiographic progression have shown that a combination of predicting factors can correctly identify up to 83% of patients with progressive erosive disease[12]. The question is whether and to what extent one can rely on (a combination of) these prognostic factors when addressing therapeutic questions in the individual patient with RA. Predictive variables have to meet stringent requirements for use in the prospective situation since by definition these variables are identified in other cohorts. Apart from correctly identifying a group of patients with severe disease retrospectively, a prediction model should guarantee a clinician enough certainty about the predicted disease outcome in the individual patient with RA to make therapeutic decisions.

The aim of our study was to evaluate the usefulness of a prediction model for making treatment decisions in early RA. Aggressive treatment was defined as directly starting with a combination of DMARD, including MTX and either a high-dose prednisone or a tumor necrosis factor (TNF)-inhibitor. We defined disease outcome by the presence (severe RA) or absence (mild RA) of joint damage progression. The main goal was to predict disease outcome in every individual patient as accurately as possible with all available predictive variables. In order to rely on a prediction model for therapeutic decisions, it was assumed that a clinician should have at least 80% certainty about the predicted disease outcome in the individual patient. With this assumption, the percentage of patients with early RA that could be classified as probably having severe disease or as probably having mild disease was evaluated. The remainder of patients without high probability for either mild or severe disease could not be classified as having mild or severe disease.

MATERIALS AND METHODS

Patients were selected from the Early Arthritis Clinic (EAC) of the Leiden University Medical Center (LUMC). The EAC was started in 1993 at the Department of Rheumatology of the LUMC, the only rheumatology clinic for rheumatic disease patients in an area with 300,000 inhabitants. The general practitioners in the area were encouraged to refer patients to the EAC if at least 2 of the following 3 features were present: joint pain, joint swelling, or reduced joint mobility. All patients were offered an appointment within 2 weeks of referral. The patients were included in the EAC if arthritis was confirmed by a rheumatologist, the duration of symptoms was < 2 years, and the patient had not seen a rheumatologist elsewhere for the same problem.

For our analysis a group of patients with early RA was selected that was not treated aggressively, i.e., starting with DMARD monotherapy, to evaluate whether a prediction model could reliably identify those patients who would develop progressive disease without aggressive initial treatment. Therefore we selected, from the patients included in the EAC between 1993 and 1999, all patients who presented at the outpatient clinic with RA or with probable RA and in whom diagnosis of RA was confirmed at 3 months after presentation. Patients had to have at least one year of followup and radiographs of hands and feet at baseline and after one year had to be available. Twelve percent of the EAC cohort fulfilled these criteria (n = 152). Definite RA was defined by the criteria of the American College of Rheumatology[13], but without the criterion that the symptoms must be of 6 weeks' duration, and observed by a physician. Of the included patients 85% received DMARD therapy during the first year after diagnosis [starting with: chloroquine (40%), sulfasalazine (SSZ) (30%), or other drugs (30%)]. Of all patients, 14 (9.2%) received a combination of DMARD during the first year, most (n = 9) a combination of an antimalarial drug with another DMARD (n = 3 antimalarial + MTX, n = 5 antimalarial + cyclosporine, n = 1 antimalarial + experimental peptide vaccination strategy). Other combinations used were: SSZ and low-dose prednisone (n = 2), MTX and low-dose prednisone (n = 2), and SSZ + interferon-ß (n = 1). A combination of DMARD was started after a mean period of 24 weeks after presentation. No patient was treated with a combination of drugs directly after presentation.

Baseline and followup assessments. At the first visit a standard diagnostic evaluation was performed according to the EAC protocol. All available potentially prognostic variables[10-12] from the patient's history, physical, and laboratory examination were used for the current analysis: age, sex, duration of symptoms at presentation, duration of morning stiffness, Health Assessment Questionnaire (HAQ) score, patient's assessment of disease activity, Ritchie Articular Index score[14], total swollen joint count, bilateral compression pain in the metatarsophalangeal (MTP) joints, erythrocyte sedimentation rate (ESR), IgM rheumatoid factor (IgM-RF) positivity, shared epitope (SE) hetero- or homozygosity, radiologic damage according to Sharp-van der Heijde (SH), and the presence of erosions on radiographs.

For the presence of arthritis 54 joints were assessed. Maximum swollen joint count was 22 since the proximal and distal interphalangeal joints, metacarpophalangeal (MCP) joints, and MTP joints were each scored as one joint (i.e., one left and one right). The presence of IgM-RF was measured at study entry by ELISA. Every value ≥ 5 units was considered positive. DNA isolation and HLA-DQ and DR typing were performed at study entry. Radiographs of hands and feet taken at study entry and after one year followup were scored in random order for the presence of erosions and narrowing by an experienced rheumatologist blinded for clinical data. The reported scores are the SH total damage scores[15,16]. Disease outcome after one year was defined by progression of radiological damage, determined as the difference between the SH score at one year and baseline. In order to evaluate currently available variables predicting disease outcome, 2 subsets of patients were identified: (1) patients with severe disease: patients with progression of radiological damage (progression score > 0); and (2) patients with mild disease: patients without progression of radiological damage (progression score ≤ 0).

Statistical analysis. Regression analysis. A regression analysis was performed to predict disease outcome for every individual patient. As we explicitly preferred to predict progression of radiological damage for every individual

patient as accurately as possible, we performed linear regression with progression of joint damage (continuous) as dependent variable. Both continuous variables (age, visual analog scale disease activity, duration of morning stiffness, swollen joint count, Ritchie, ESR, HAQ, SH score) and categorical variables (duration of symptoms > or ≤ 6 weeks, IgM-RF positivity, SE, bilateral compression pain MTP, and presence of erosions) were entered as covariates. Univariate as well as multivariate linear regressions were performed to determine the strength of correlation of the baseline variables with disease outcome. After entering the baseline variables, it was tested if the DMARD therapy given did have an additional effect on the outcome. The multivariate linear regression was used to predict disease outcome after one year for all individual patients. The positive predictive value (PPV) for mild versus severe disease was calculated. The R^2 (≈ variation explained) was calculated. With a sample size of 152 persons, given $\alpha = 0.05$ and with a power of 90%, each predictive variable with a correlation ≥ 0.26 with the dependent variable was detected (R2 = 0.07). For each patient, the predicted progression score and the predicted standard deviation, both obtained from the multivariate linear regression analysis, were used to calculate the predicted probability for severe disease (progression score > 0).

Prediction model. In order to rely on a prediction model for therapeutic decisions it was assumed that a clinician should have at least 80% certainty about the predicted disease outcome in the individual patient. Only those patients for whom 80% certainty about the predicted outcome could be guaranteed [only those patients for whom 80% of the standard deviation was > 0 (high probability for severe disease) and those patients for whom 80% of the standard deviation was < 0 (high probability for mild disease)] were identified as classifiable patients. Consequently 3 groups of patients were defined: (1) probably severe disease: high predicted probability (≥ 0.8) for progression of radiological damage (progression score > 0); (2) probably mild disease: high predicted probability (≥ 0.8) for absence of progression of radiological damage (progression score ≤ 0); and (3) not classifiable: predicted probability for severe disease between 0.2 and 0.8. In order to evaluate the effect of the prediction model on therapeutic decision-making it was calculated which percentage of patients was in each of the defined groups.

Hypothetical prediction model. We also studied how the percentage of unclassifiable patients changed with the R^2 of a model. We started with the assumptions that the predicted score and the actual score were bivariate normally distributed, with the mean chosen such that the percentage of patients with progression was equal to the percentage in our dataset. Under these assumptions, for different values of R the expected percentage of patients in the 3 groups as above (probably severe disease, probably mild disease, and not classifiable) could be calculated analytically. It was determined which R^2 value is needed to obtain a prediction model with < 20% of patients in the group not classifiable.

RESULTS

The baseline characteristics of the 152 patients in the study are shown in Table 1. The major radiographic findings are shown in Table 2. Fifty-seven patients (38%) presented with erosive damage at baseline. During the first year of followup another 48 patients developed erosive damage. Of all patients, 109 (71.7%) showed progression of radiological damage during the first year. Median progression of the SH score was 4 (interquartile range 0-14).

Table 3 shows the results of the univariate and multivariate linear regression analyses of all the available baseline variables. Of all baseline variables the following had significant correlation with progression of radiological damage in the univariate analysis: patient's global assessment of disease activity, total swollen joint count, Ritchie score, IgM-RF positivity, ESR, SH score, and presence of erosions. Total swollen joint count and IgM-RF positivity both had significant correlation with progression of radiological damage in the multivariate analysis. If the duration of symptoms at presentation exceeded 6 weeks, the progression score increased by 9.4 points (p = 0.06). In total 11 patients (12%) had a symptom duration < 6 weeks.

Patients who received no DMARD were compared with the patients who received a combination of drugs and the patients who were treated with one DMARD at a time. Of all variables used in the prediction model, a significant difference was found only for the proportion of patients positive for IgM-RF: of patients who did not receive a DMARD 28% were IgM-RF-positive, of patients who received one DMARD at a time 67% were IgM-RF-positive, and of patients who received a combination 72% were IgM-RF-positive. Patients did not differ significantly for progression scores during the first year (p = 0.493), although median progression was slightly higher for those who received DMARD monotherapy (6.5) compared to those who received combination therapy (3.5) and those who did not receive DMARD (2.0). Since the observed difference could be based on confounding by indication, it was analyzed whether treatment as defined above (none/one DMARD/combination therapy) contributed significantly to joint damage progression in a regression analysis, but no significant association was found [unstandardized regression coefficient (URC) 0.034; p = 0.934]. In a multivariate analysis with IgM-RF and treatment (none/one DMARD/combination), IgM-RF was still significantly contributing to joint damage progression, and treatment was not

Table 1. Baseline characteristics of patients with early RA (n = 152).

Median age (IQR), yrs	66 (55–76)
No. (%) female	103 (68)
Median symptom duration at first visit (IQR), wks	22 (11–45)
No. (%) IgM rheumatoid factor-positive	93 (61)
Median no. swollen joints (IQR)	6 (4–8)
No. (%) patients with erosions in hands or feet	57 (38)
HLA-DRB1 shared epitope (SE), no. (%)*	
SE +/+	31 (22)
SE +/–	65 (46)
SE –/–	45 (32)

IQR: Interquartile range. * Available from 141 patients.

Table 2. Radiographic results.

	Baseline	One Year Followup
No. (%) with erosions	57 (37.5)	104 (68.4)
Sharp-van der Heijde score, median (IQR)	1 (0–4)	8 (1–18)
Progression of Sharp-van der Heijde score, median (IQR)	—	4 (0–14)
No. with progression of radiological damage (%)	—	109 (71.7)

IQR: Interquartile range.

Table 3. Regression analysis of baseline variables.

Baseline Variables	Univariate Analysis		Multiple Regression Analysis $R^2 = 0.363$ (n = 95*)	
	URC**	p	URC**	p
Age	–0.1	0.568	–0.1	0.390
Sex	2.1	0.488	1.2	0.715
Duration of symptoms at presentation > 6 wks	6.2	0.129	9.4	0.060
VAS for disease activity***	1.1	0.032	0.9	0.123
Duration of morning stiffness	0.0	0.588	0.0	0.982
Total swollen joint count	1.3	0.005	1.7	0.010
Ritchie score	0.4	0.025	–0.0	0.893
Bilateral compression pain MTP	4.0	0.161	6.0	0.086
IgM-RF positivity	11.0	< 0.001	10.2	0.003
ESR	0.1	0.028	0.1	0.277
Shared epitope-positive†	5.1	0.120	0.7	0.835
HAQ††	–0.2	0.933	–3.4	0.207
Sharp-van der Heijde score	0.4	0.006	0.3	0.312
Presence of erosions	7.2	0.015	1.2	0.974

* n = 95: patients for whom all variables are available; ** The unstandardized regression coefficent (URC) describes the amount of increase in progression of joint damage per unit of the baseline variable, i.e., one more swollen joint at baseline accounts for 1.3 points in progression score during the first year; *** available for 105 patients; † available for 141 patients; †† available for 130 patients. VAS: visual analog scale; MTP: metatarsophalangeal; ESR: erythrocyte sedimentation rate; HAQ: Health Assessment Questionnaire.

(URC treatment 0.377, p = 0.344; URC IgM-RF 11.6, p < 0.001). In line with this, treatment did not significantly change the outcome of the multivariate regression analysis (data not shown).

With the multivariate model, presence of progression of radiological damage turned out to be predicted correctly in 75.3% of patients (PPV). The R^2 value of the multivariate regression analysis was 0.363 (R = 0.602). Patients for whom all variables were available (n = 95) were not significantly different in baseline characteristics from the total cohort except for HAQ score (mean value 1.06 for patients with all variables available vs 1.3 for patients with some variables missing; p = 0.03).

The multivariate regression analysis was used to predict disease outcome (i.e., progression score), yielding an individual predicted progression score for every patient and the individual predicted probability on radiological damage (progression > 0). Figure 1 shows the predicted progression scores versus the actual progression scores for the 95 patients for whom all variables were available. The histogram of residuals (predicted progression score minus actual progression score) was approximately normally distributed.

Next, the 95 patients were rearranged in 3 groups based on the predicted probability of radiological damage (probably severe disease, probably mild disease, not classifiable; Table 4). As shown in Table 4, 46.3% of patients could be classified as probably having severe disease, 0% as probably having mild disease, and 53.7% as not classifiable (a probability between 0.2 and 0.8). Apparently, the currently available predictive factors have better potential in identifying patients with severe disease compared to patients with mild disease: of 26 patients without actual progression of radiological damage only 6 had a predicted progression score ≤ 0.

Finally, the relation between the R^2 of a model and the per-

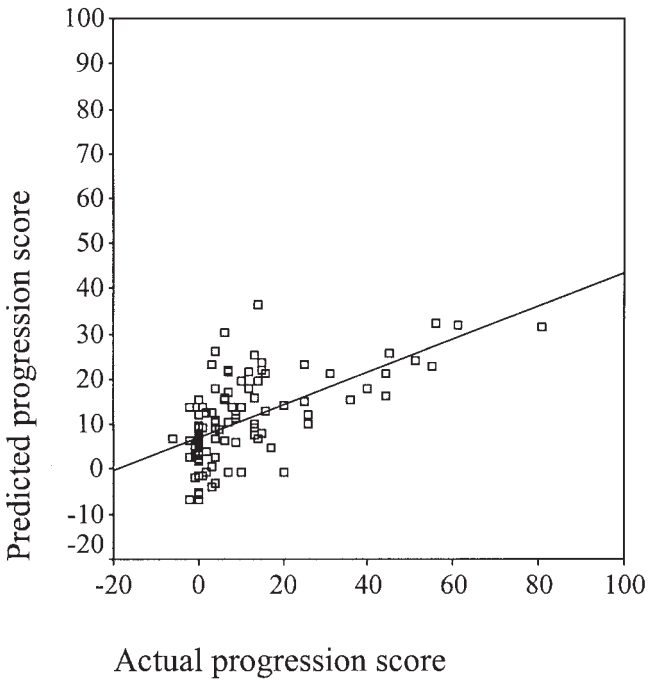

Figure 1. Actual versus predicted Sharp/van der Heijde score for progression of radiological damage for patients for whom all variables were available (n = 95).

Table 4. Evaluation of accuracy of prognostic model based on EAC cohort in classification of patients as having mild or severe disease; n = 95; R = 0.602, R^2 = 0.363, positive predictive value 75.3%.

Classification by Prediction Model*	Actual Disease Outcome		Total No. Classified (%)	Total No. Classified Correctly (%)	Total No. Not Classified (%)
	Mild	Severe			
	26	69			
Mild disease	0	0	0 (0)	0 (0)	
Severe disease	3	41	44 (46)	41 (43)	
Not classified	23	28	—	—	51 (54)

* Classification when taking into account that 80% certainty about predicted outcome is needed for therapeutic decisions. EAC: Early Arthritis Clinic.

Table 5. Evaluation of accuracy of hypothetical prognostic models; percentage of patients classified as having either mild or severe disease.

R^2 of Hypothetical Model	Disease Classification by Hypothetical Prediction Model	Actual Disease Outcome, %	
		Mild (28%)	Severe (72%)
R^2 = 0.49	Mild	9	3
	Severe	4	45
	Not classified	15	24
R^2 = 0.64	Mild	12	2
	Severe	3	50
	Not classified	13	20
R^2 = 0.9	Mild	19	1
	Severe	1	61
	Not classified	8	10

centage of patients not classifiable is shown in Table 5. In the case of R = 0.95 (R^2 = 0.9) in total 82% could be classified as having probably mild or severe disease. As shown by the data it was possible to identify patients with mild disease under the assumption of normally distributed actual and predicted progression scores.

DISCUSSION

A prediction model that could accurately identify subsets of patients with mild or severe disease in the early phase of RA would allow a clinician to make a conscious choice between different treatment strategies at the moment that DMARD therapy is started. Our main finding is that currently available prognostic variables in early RA are not sufficient to supply "tailor-made treatment" of RA in the majority of patients. If the power of the prediction model is optimized in a hypothetical situation (R = 0.95), differentiated therapeutic decisions would be possible in up to 82% of patients, validating the search for more and better prognostic variables.

A drawback of our study is that the prediction model was developed retrospectively and that it was not validated in another — ultimately prospective — cohort, possibly introducing bias in the identification of the prognostic variables. However, we chose to use all available and possibly prognostic baseline variables without any selection of variables. The baseline variables used in the regression analysis have been indicated as predictive factors for outcome of RA in many studies. The variables that correlated most strongly with disease outcome (IgM-RF positivity, swollen joint count, and disease duration) have also been identified as strong predictors of disease outcome by others[10,11,17-21], implying that selection bias most likely is not a major problem. In theory, bias may have occurred since the current analysis was carried out in a Caucasian population derived from one geographic area, but we are not aware of a specific phenotype of RA or specific risk factors in the population under study.

As shown in Table 4, the currently available predictive factors have better potential in identifying patients with severe disease compared to patients with mild disease. Twenty out of the 26 patients with actual mild disease (absence of progression of radiological damage) had a predicted progression > 0. Of these 20 patients, baseline variables were comparable to the baseline variables of the total cohort except for the following: median ESR of 33 (compared to 40 in the total cohort), median patient's global assessment of disease activity of 3.0 (compared to 4.9 in the total cohort), median Ritchie score of 8 (compared to 10 in the total cohort), 45% IgM-RF-positive (compared to 61.2% in the total cohort), 45% SE-negative (compared to 31.9% in the total cohort), median SH score of 0 (compared to 37.5% with median SH score of 1) and 25% presented with erosive disease. Thus, although these patients compared favorably with respect to the mentioned variables they did not differ from the total cohort with respect to duration of symptoms and total swollen joint count, 2 variables that have been identified by our model as correlating strongly with disease outcome. However, since only a minority of all patients (12%) had a symptom duration < 6 weeks the contribution of this variable in the prediction model to identify individual patients is limited.

A possible explanation for difficulties in identifying mild RA in general could be that predictors of disease outcome in early RA (IgM-RF positivity, swollen joint count, and disease duration) are sensitive but not specific for severe RA. As demonstrated by several prediction models developed in prospective observational studies, the percentage correctly classified with mild disease (specificity) is inversely related to the percentage of patients with severe disease: the higher the

Table 6. Prediction of radiological outcome in early RA: characteristics of prediction models in different studies.

Study	No. of Patients	Duration of Followup, yrs	Definition of Outcome	Proportion with Severe Outcome (%)	PPV* (%)	Sensitivity (%)	Specificity (%)
van der Heijde[19]	147	2	Progression of joint damage ≥ 3	69	83	88	59
van Zeben[21]	132 women	6 (mean)	Erosion score > 20	—	76**	52	76
			> 60	—	78**	88	48
Combe[24]	191	3	Progression, yes/no	41	72	71	74
Dixey[25]	866	3	Erosive disease, yes/no	58	68	78	52
			Severity of erosions	23	77	42	96

* PPV = positive predictive value; ** proportion classified correctly (accuracy).

one, the lower the other (Table 6). In general, prediction of mild disease is more difficult than prediction of severe disease in the subgroup with early RA (Table 6).

The results of the hypothetical prediction model show that it is possible to identify patients with mild disease under the assumption that actual and predicted progression scores are normally distributed. This assumption is justified by the fact that residuals of actual and predicted progression scores are both distributed approximately normally. In order to improve our results as well in the cohort as in the analytical calculations we performed the same analysis by using log-transformed actual and predicted progression scores, but this did not improve either the percentage of patients classified correctly or the comparability of results between the actual cohort and the analytical calculations.

In the 95 patients selected for the regression analysis 69 patients (73%) turned out to have progression of radiological damage, whereas 26 patients (27%) had no progression of radiological damage during the first year. As the treatment of patients with RA has changed considerably over the last 2 decades the treatment prescribed to this group of patients is currently considered insufficient. Earlier and more aggressive intervention has been shown to result in lower joint damage progression rates[6,22]. However, in the BeSt study, which compared aggressive and targeted treatment strategies, the proportion of patients with sequential monotherapy (starting with MTX) that showed progression of total SH score was 71%, a proportion very similar to the 73% in our study[23]. In addition, given the high PPV of the described model, the number of patients incorrectly identified as having severe disease is low, independent of the proportion of patients with actual severe disease.

By using the developed prediction model, 44 patients (46.3%) would have been classified as having high probability for severe (i.e., progressive) disease. Only 3 patients (7%) were incorrectly identified as having severe disease. This latter proportion is surprisingly low, since it was assumed that 80% certainty about the predicted disease outcome was required. The remainder of patients (53.7%) could not be classified as having either mild or severe disease.

Assuming that there are 2 possible treatment strategies for patients with early RA — (1) conventional treatment, for example DMARD monotherapy such as MTX, or (2) aggressive and eventually more expensive treatment, such as a combination of conventional DMARD or the combination of MTX and TNF-blocking drugs — these results lead to 3 different options in clinical practice.

The first option is to start with conventional therapy in all patients. Obviously this option rules out any possible benefit of early combination therapy. The second option is to start directly with combination therapy in all patients. In this case 69 patients with severe disease may be treated adequately, whereas all patients with mild disease will be overtreated and no patient will be undertreated. The last option is to start with combination therapy only in patients identified as having severe disease, while the remainder of patients will start with monotherapy. This way, 64 patients (67%) will receive adequate therapy (41 patients with severe disease and 23 patients with mild disease). In total, 28 of the patients with severe disease (41%) will be undertreated. Of all patients receiving aggressive treatment, 7% (3 patients) will be overtreated. Overall, the risk of overtreatment varies from 7% to 27%, whereas the risk of undertreatment varies from 55% (28 out of 51) to 73%. Thus, by using a prediction model based on currently available predictive factors to differentiate treatment in individual patients the risk of overtreatment is 5–6 times less than the risk of undertreatment. Consequently, in the current situation a case can be made for aggressive intervention in all patients presenting with RA.

In summary, individualized treatment of early RA based on predicted disease outcome is currently possible in 46% of patients in our cohort. With better prediction models for disease outcome, individualized treatment of early RA becomes possible in up to 80% of patients, validating the search for better prognostic variables.

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