A matrix risk model for the prediction of rapid radiographic progression in patients with rheumatoid arthritis receiving different dynamic treatment strategies: post hoc analyses from the BeSt study

K Visser,[1] Y P M Goekoop-Ruiterman,[2] J K de Vries-Bouwstra,[3] H K Ronday,[2] P E H Seys,[4] P J S M Kerstens,[5] T W J Huizinga,[1] B A C Dijkmans,[3] C F Allaart[1]

[1]Leiden University Medical Center, Leiden, The Netherlands
[2]HAGA Hospital, The Hague, The Netherlands
[3]VUMC, Amsterdam, The Netherlands
[4]Franciscus Hospital, Roosendaal, The Netherlands
[5]JBI, Amsterdam, The Netherlands

Correspondence to
Dr K Visser, Department of Rheumatology C1-R, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, The Netherlands; k.visser@lumc.nl

ABSTRACT

Objectives To develop a matrix model for the prediction of rapid radiographic progression (RRP) in subpopulations of patients with recent-onset rheumatoid arthritis (RA) receiving different dynamic treatment strategies.

Methods Data from 465 patients with recent-onset RA randomised to receive initial monotherapy or combination therapy were used. Predictors for RRP (increase in Sharp-van der Heijde score ≥5 after 1 year) were identified by multivariate logistic regression analysis. For subpopulations, the estimated risk of RRP per treatment group and the number needed to treat (NNT) were visualised in a matrix.

Results The presence of autoantibodies, baseline C-reactive protein (CRP) level, erosion score and treatment group were significant independent predictors of RRP in the matrix. Combination therapy was associated with a markedly reduced risk of RRP. The positive and negative predictive values of the matrix were 62% and 91%, respectively. The NNT with initial combination therapy to prevent one patient from RRP with monotherapy was in the range 2–3, 3–7 and 7–25 for patients with a high, intermediate and low predicted risk, respectively.

Conclusion The matrix model visualises the risk of RRP for subpopulations of patients with recent-onset RA if treated dynamically with initial monotherapy or combination therapy. Rheumatologists might use the matrix for weighing their initial treatment choice.

INTRODUCTION

A major goal in the treatment of rheumatoid arthritis (RA) is to prevent joint damage progression and thus prevent long-term disability.[1] At the group level, initial combination therapies including either prednisone or a tumour necrosis factor (TNF) inhibiting agent are more effective in achieving that goal than initial disease-modifying antirheumatic drug (DMARD) monotherapy.[2–5] Several predictive factors for radiographic progression have previously been reported to help identify the patients at risk of a more severe disease course who might benefit from such therapies.[6–9] However, in clinical practice it is still difficult to translate this evidence into treatment choices for individual patients with recently diagnosed RA. This is probably due to the fear of toxicity of DMARD plus prednisone combinations and the cost of TNF-blocking therapies.[10] Furthermore, most existing algorithms assessing the

risk for joint damage progression have not included treatment, yet treatment is one of the most important determinants of radiographic outcome.[11–14] A recent model which did include treatment was based on a static treatment study not reflecting the dynamics of clinical practice, where treatment is adjusted if the initial therapy fails to achieve low disease activity.[15]

We therefore set out to develop a matrix risk model for the prediction of rapid radiographic progression (RRP) based on a cohort of patients with recent-onset RA who were dynamically treated aimed at a low disease activity (disease activity score (DAS) ≤2.4).[3] We identified baseline predictors for RRP in subsets of patients treated according to various treatment strategies which could help physicians in making their initial treatment choice.

METHODS

Patients and treatment

Data from patients with recent-onset RA randomised to four different treatment strategies were used.[3] All patients were DMARD-naïve and fulfilled the 1987 American College of Rheumatology criteria for RA.[16] In groups 1 (n=126) and 2 (n=121), patients started with initial methotrexate monotherapy which could be switched to or extended with other DMARDs. In group 3 (n=133), patients started with a combination of methotrexate, sulfasalazine, hydroxychloroquine and a tapered high-dose prednisone. In group 4 (n=128), patients started with a combination of methotrexate and infliximab. Every 3 months the treatment was adjusted according to a fixed protocol, aiming at a DAS ≤2.4.[17] Groups 1 and 2 were combined for the current analyses.

Statistical analysis

As outcome, RRP was defined as an increase in the Sharp-van der Heijde score (SHS) of ≥5 after 1 year, corresponding to the smallest detectable change and expert opinion on clinically relevant progression.[18 19] Baseline characteristics were compared between patients with and without RRP per treatment group using univariate logistic regression analysis. In a multivariate analysis with backward selection including the variable treatment group, significant independent predictors for RRP were identified using a p value of >0.10 as removal

criterion. Possible interactions with treatment were explored. More information on the baseline and outcome variables is available in the online supplement.

Matrix construction

To construct the matrix, the final regression model was fitted with all variables categorised, based on clinically relevant cut-offs and tertiles. The predicted risk of RRP was calculated for all possible risk factor combinations and presented in visual matrices for each treatment group. In addition, for the initial combination therapies compared with initial monotherapy, the risk differences were converted into numbers needed to treat (NNTs) and likewise presented in a matrix.

Discriminative/predictive ability and internal validation

The area under the receiver operating characteristics (ROC) curve was calculated (area under the curve (AUC)) and the positive and negative predictive values (PPV, NPV) of the model were explored. The predicted risk for the monotherapy group was compared with the observed radiographic progression after 5 years of continued DAS-guided treatment. Additional information can be found in the online supplement.

SPSS Version 16.0 software (SPSS, Chicago, Illinois, USA) was used for all analyses.

RESULTS

The baseline characteristics of 465 of 508 patients (92%) for whom radiographs were available are shown in table S1 in the online supplement.

Univariate analysis

RRP was observed in 75/224 patients (33%) in the initial monotherapy group, in 16/120 patients (13%) in the initial combination with prednisone group and in 11/121 patients (9%) in the initial combination with infliximab group. Significant univariate predictors of RRP in all three treatment groups were C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), SHS and the erosion score at baseline (see table S2 in the online supplement). The presence of rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPAs) were only significant univariate predictors in the monotherapy group.

Multivariate and fitted logistic regression analysis

In addition to the univariate predictors, age, gender, body mass index, symptom duration, swollen joint count, DAS, health assessment questionnaire and treatment group were also entered into the multivariate analysis. Because of colinearity, a merged variable including both RF and ACPA status was constructed and the erosion score, which is easier to perform, was included instead of the total SHS.

Independent significant predictors for RRP were the baseline erosion score, RF/ACPA, CRP and treatment group. A comparable model was found if ESR was included instead of CRP. No significant interaction was present between each independent predictor and the variable treatment group. The final model with all variables categorised is shown in table 1. Categorising the variables decreased the explained variance (Nagelkerke's R^2) from 0.33 to 0.31 in the CRP model and from 0.30 to 0.29 in the ESR model. Treatment alone accounted for one-third of the prediction of RRP ($R^2=0.11$ in both models). The R^2 of the model with RF or ACPA as dichotomous variables instead of combined was 0.28.

Table 1 Independent predictive variables for rapid radiographic progression (RRP) in the final fitted multivariate logistic regression model with all variables categorised

Predictor of RRP	OR (95% CI) (model including CRP)	OR (95% CI) (model including ESR)
RF/ACPA		
Both negative	Reference	Reference
One positive	2.47 (1.01 to 6.07)	2.64 (1.10 to 6.33)
Both positive	4.04 (1.92 to 8.48)	3.99 (1.91 to 8.33)
Erosions		
0	Reference	Reference
1–4	1.35 (0.59 to 3.06)	1.19 (0.54 to 2.60)
≥4	3.82 (1.64 to 8.89)	2.97 (1.33 to 6.63)
CRP (mg/l)		
<10	Reference	–
10–35	1.54 (0.74 to 3.22)	–
≥35	4.76 (2.32 to 9.73)	–
ESR (mm/h)		
<21	–	Reference
21–50	–	0.80 (0.41 to 1.58)
≥50	–	2.73 (1.40 to 5.33)
Treatment		
Monotherapy	Reference	Reference
Combined with prednisone	0.20 (0.10 to 0.40)	0.30 (0.15 to 0.57)
Combined with infliximab	0.14 (0.07 to 0.30)	0.14 (0.07 to 0.31)

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RF/ACPAs, rheumatoid factor/anti-citrullinated protein antibodies.

Matrix models

The matrices show the percentage predicted risk of RRP after 1 year of dynamic treatment with initial monotherapy or initial combination therapy for patients with specific risk profiles, indicated by the coloured boxes in figure 1. Matrices including ESR instead of CRP had comparable results (data not shown). The matrices of the initial combination therapy groups showed an overall reduced risk compared with the initial monotherapy matrix, especially in patients with an unfavourable risk profile. For example, the upper right box in figure 1A–C shows that, for a patient who is RF and ACPA positive and has a high CRP level and already has erosions at baseline, the predicted risk for RRP is 78% with initial monotherapy which is reduced to 42% or 34% with initial combination therapy including prednisone or infliximab, respectively.

NNT matrix

The risk reduction associated with treatment choice can be demonstrated more clearly by calculating the corresponding NNT with initial combination therapy to prevent one patient from RRP. For the example given above, the NNT is 1/(78–42)×100=2.8 (95% CI 2 to 5) patients for the combination with prednisone and 1/(78–34)×100=2.3 (95% CI 2 to 4) patients for the combination with infliximab. Figure 2 shows that the NNTs are low for patients with bad prognostic factors, indicating that the risk of RRP for these patients can be largely reduced with initial combination therapy. The NNT is 2–3 for patients with a high risk (≥50%) for RRP, 3–7 for patients with an intermediate risk (20–50%) and 7–25 for patients with a low predicted risk (<20%).

Discriminative/predictive ability and internal validation

An extended description of the following results can be found in the online supplement. For the model including CRP and ESR,
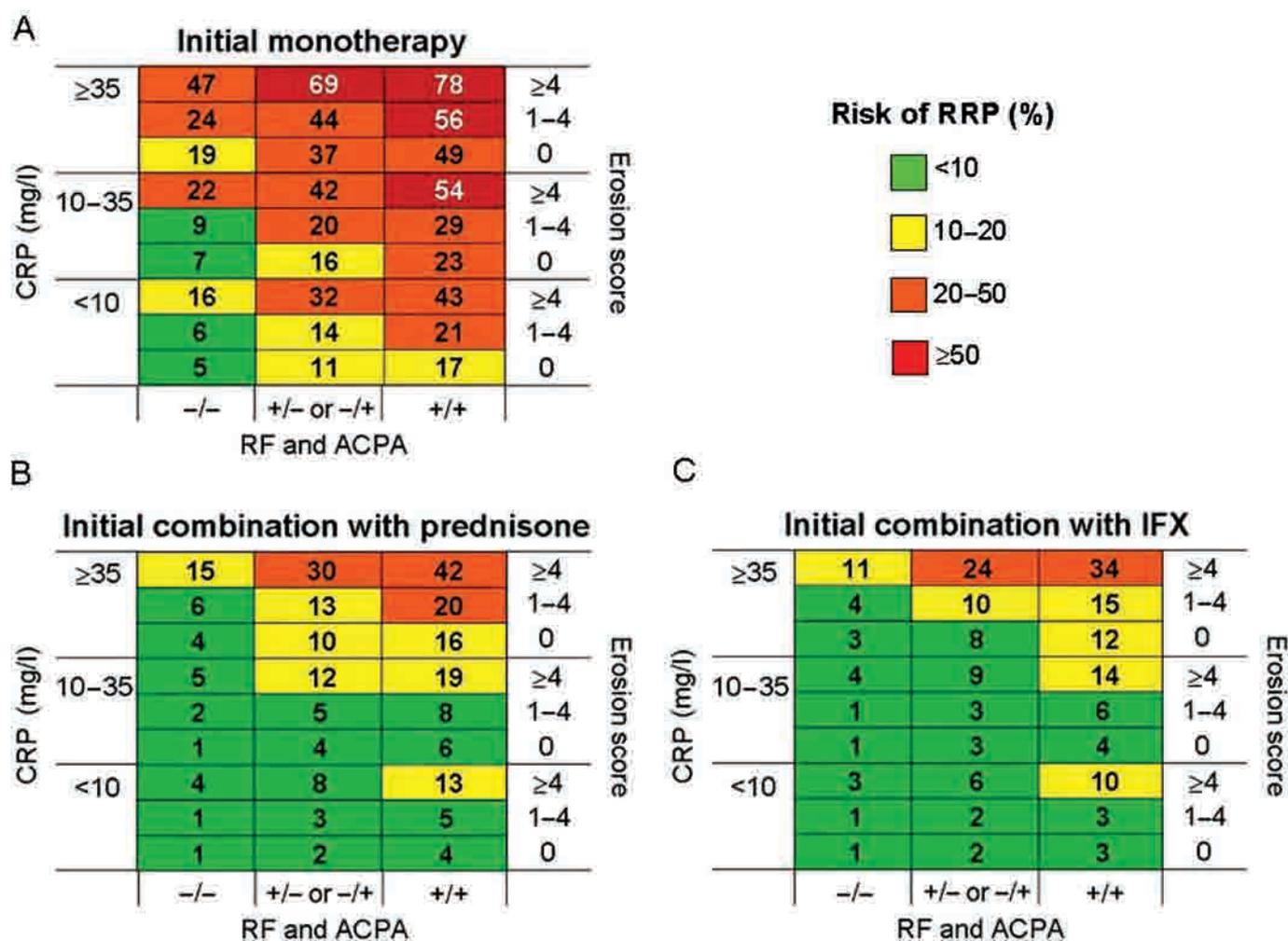
Figure 1 Matrix model including C-reactive protein (CRP) with predicted risk (in percentages) of rapid radiographic progression (RRP) in subpopulations of patients with recent-onset rheumatoid arthritis (RA) per treatment strategy. (A) Initial methotrexate monotherapy. (B) Initial disease-modifying antirheumatic drug (DMARD) combination therapy with prednisone. (C) Initial combination therapy with infliximab (IFX). Red boxes represent a high risk ($\geq$50%), orange boxes an intermediate risk (20–50%), yellow boxes a low risk (10–20%) and green boxes a very low risk (<10%) of RRP. ACPA, anti-citrullinated protein antibodies; RF, rheumatoid factor.
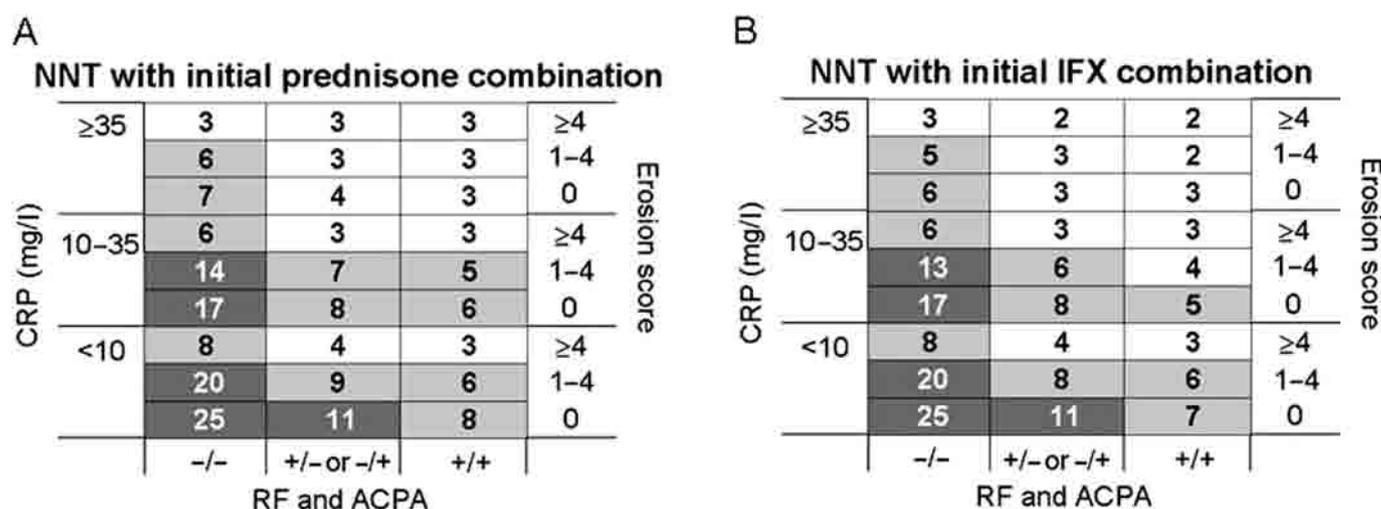
Figure 2 Matrix model with numbers needed to treat (NNTs) with initial combination therapy to prevent one patient from progression if treated with initial monotherapy. (A) Initial combination therapy with prednisone. (B) Initial combination therapy with infliximab (IFX). The NNT is <5 in the uncoloured boxes, 5–10 in the light grey boxes and >10 in the dark grey boxes. ACPA, anti-citrullinated protein antibodies; CRP, C-reactive protein; RF, rheumatoid factor.

the AUCs of the ROC curves were 0.81 (95% CI 0.77 to 0.86) and 0.80 (95% CI 0.75 to 0.85), respectively, indicating a reasonable discriminative ability (see figure S1 in online supplement). The model reliably classified 52% of the patients with a PPV of 62% and NPV of 91% (see table S3 in online supplement). The validity of the prediction after 5 years of continued DAS-steered treatment is shown in figure S2 in the online supplement.

DISCUSSION

To help rheumatologists decide how to start treatment in patients with recently diagnosed RA, we developed a matrix model from which the risk for RRP in patients with specific combinations of risk factors, if treated with different treatment strategies, can be assessed with a limited number of easily accessible clinical variables. In addition, the matrix gives insight into the risks of initial overtreatment by showing NNTs.

The current matrix is based on a dynamic treatment cohort where 3-monthly treatment adjustments were aimed at achieving and maintaining a DAS ≤2.4, closely resembling clinical practice. Our results showed that, in a tight control setting with frequent treatment adjustments, previously reported predictive variables such as the baseline erosion score, CRP, ESR, RF and ACPA still predict RRP after 1 year.[7 8 11 14 20] It is also clear that the initial treatment choice is a main determinant of RRP and therefore should be included in a useful prediction model.

Our matrix confirms that, with initial combination therapy with infliximab or prednisone, the risk of RRP is markedly reduced in comparison with initial monotherapy, especially in patients with an unfavourable risk profile.[21] This observation carries even more weight considering that, in the dynamic treatment design, patients on initial monotherapy could receive more intensive treatment within a relatively short time period.[3] Moreover, initial combination therapy could be tapered and stopped in approximately 50% of the patients once a low disease activity was achieved.[22] In this respect, the NNT allows consideration of whether to prevent RRP in one patient; initial temporary overtreatment in others is acceptable.

External validation in other dynamic treatment cohorts will be needed to increase the generalisability of the results. The general RA population probably represents a group of patients with a better prognosis and a lower prevalence of RRP than those included in the BeSt study.[23] Consequently, and because the matrix is better at predicting who will not have RRP, the NPV will be even higher in the general population of patients with recent-onset RA.

In conclusion, our matrix model offers the possibility of assessing the risk of RRP for each patient with a specific combination of risk factors. It requires only a few easily accessible variables, includes relevant initial treatment options, it has been developed in a cohort resembling the dynamics of daily practice and is visually attractive and easy to use. It could therefore be a useful tool to help rheumatologists choose the optimal initial treatment for their patients with recently diagnosed RA.

REFERENCES

1. **Finckh A**, Liang MH, van Herckenrode CM, *et al.* Long-term impact of early treatment on radiographic progression in rheumatoid arthritis: a meta-analysis. *Arthritis Rheum* 2006;**55**:864–72.
2. **Breedveld FC**, Weisman MH, Kavanaugh AF, *et al.* The PREMIER study: a multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. *Arthritis Rheum* 2006;**54**:26–37.
3. **Goekoop-Ruiterman YP**, de Vries-Bouwstra JK, Allaart CF, *et al.* Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. *Arthritis Rheum* 2005;**52**:3381–90.
4. **Korpela M**, Laasonen L, Hannonen P, *et al.* Retardation of joint damage in patients with early rheumatoid arthritis by initial aggressive treatment with disease-modifying antirheumatic drugs: five-year experience from the FIN-RACo study. *Arthritis Rheum* 2004;**50**:2072–81.
5. **Landewé RB**, Boers M, Verhoeven AC, *et al.* COBRA combination therapy in patients with early rheumatoid arthritis: long-term structural benefits of a brief intervention. *Arthritis Rheum* 2002;**46**:347–56.
6. **Berglin E**, Johansson T, Sundin U, *et al.* Radiological outcome in rheumatoid arthritis is predicted by presence of antibodies against cyclic citrullinated peptide before and at disease onset, and by IgA-RF at disease onset. *Ann Rheum Dis* 2006;**65**:453–8.
7. **Courvoisier N**, Dougados M, Cantagrel A, *et al.* Prognostic factors of 10-year radiographic outcome in early rheumatoid arthritis: a prospective study. *Arthritis Res Ther* 2008;**10**:R106.
8. **Lindqvist E**, Eberhardt K, Bendtzen K, *et al.* Prognostic laboratory markers of joint damage in rheumatoid arthritis. *Ann Rheum Dis* 2005;**64**:196–201.
9. **Machold KP**, Stamm TA, Nell VP, *et al.* Very recent onset rheumatoid arthritis: clinical and serological patient characteristics associated with radiographic progression over the first years of disease. *Rheumatology (Oxford)* 2007;**46**:342–9.
10. **Van der Goes MC**, Jacobs JW, Boers M, *et al.* Patients' and rheumatologists' perspectives on glucocorticoids and exercise to improve the implementation of the EULAR recommendations on the management of systemic glucocorticoid therapy in rheumatic diseases. *Ann Rheum Dis* 2009;(In Press).
11. **Combe B**, Dougados M, Goupille P, *et al.* Prognostic factors for radiographic damage in early rheumatoid arthritis: a multiparameter prospective study. *Arthritis Rheum* 2001;**44**:1736–43.
12. **Drossaers-Bakker KW**, Zwinderman AH, Vliet Vlieland TP, *et al.* Long-term outcome in rheumatoid arthritis: a simple algorithm of baseline parameters can predict radiographic damage, disability, and disease course at 12-year followup. *Arthritis Rheum* 2002;**47**:383–90.
13. **Goekoop-Ruiterman YP**, de Vries-Bouwstra JK, Allaart CF, *et al.* Comparison of treatment strategies in early rheumatoid arthritis: a randomized trial. *Ann Intern Med* 2007;**146**:406–15.
14. **Syversen SW**, Gaarder PI, Goll GL, *et al.* High anti-cyclic citrullinated peptide levels and an algorithm of four variables predict radiographic progression in patients with rheumatoid arthritis: results from a 10-year longitudinal study. *Ann Rheum Dis* 2008;**67**:212–7.

15. **Vastesaeger N**, Xu S, Aletaha D, *et al.* A pilot risk model for the prediction of rapid radiographic progression in rheumatoid arthritis. *Rheumatology (Oxford)* 2009;**48**:1114–21.
16. **Arnett FC**, Edworthy SM, Bloch DA, *et al.* The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;**31**:315–24.
17. **van der Heijde DM**, van 't Hof M, van Riel PL, *et al.* Development of a disease activity score based on judgment in clinical practice by rheumatologists. *J Rheumatol* 1993;**20**:579–81.
18. **Bruynesteyn K**, Boers M, Kostense P, *et al.* Deciding on progression of joint damage in paired films of individual patients: smallest detectable difference or change. *Ann Rheum Dis* 2005;**64**:179–82.
19. **Bruynesteyn K**, van der Heijde D, Boers M, *et al.* Determination of the minimal clinically important difference in rheumatoid arthritis joint damage of the Sharp/van der Heijde and Larsen/Scott scoring methods by clinical experts and comparison with the smallest detectable difference. *Arthritis Rheum* 2002;**46**:913–20.
20. **Forslind K**, Ahlmén M, Eberhardt K, *et al*. Prediction of radiological outcome in early rheumatoid arthritis in clinical practice: role of antibodies to citrullinated peptides (anti-CCP). *Ann Rheum Dis* 2004;**63**:1090–5.
21. **Smolen JS**, Van Der Heijde DM, St Clair EW, *et al*. Predictors of joint damage in patients with early rheumatoid arthritis treated with high-dose methotrexate with or without concomitant infliximab: results from the ASPIRE trial. *Arthritis Rheum* 2006;**54**:702–10.
22. **van der Kooij SM**, le Cessie S, Goekoop-Ruiterman YP, *et al.* Clinical and radiological efficacy of initial vs delayed treatment with infliximab plus methotrexate in patients with early rheumatoid arthritis. *Ann Rheum Dis* 2009;**68**:1153–8.
23. **Goekoop-Ruiterman YP**, de Vries-Bouwstra JK, Kerstens PJ, *et al.* DAS-driven therapy versus routine care in patients with recent-onset active rheumatoid arthritis. *Ann Rheum Dis* 2010;**69**:65–9.