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CHAPTER 2.

Towards personalized treatment: predictors of short term HAQ response in recent onset active RA are different from predictors of rapid radiological progression

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ABSTRACT

Objective

Personalized treatment depends on the treatment goals. Current prediction models to guide initial treatment choices focus on radiological damage progression. However, for some patients this outcome is less relevant, whereas short-term functional ability is relevant to all. Do these various treatment goals share the same predictors?

Methods

Data of 497 patients from the BeSt study, randomized to initial mono- or combination therapy, were used. Predictors of short-term functional disability (HAQ >=1 after three months of treatment) were identified with logistic regression analyses. Predicted risks of a HAQ >=1 were determined per treatment group and for each subpopulation.

Results

At baseline, 76% of patients had a HAQ >=1 (mean 1.7 ± 0.5). After three months of treatment this was 40% (mean HAQ 1.5 ± 0.5). Baseline HAQ, pain, Ritchie Articular Index and treatment group were significant independent predictors for a HAQ >=1; presence of rheumatoid factor, anti-cyclic citrullinated peptide antibodies and baseline radiological damage (known predictors for radiological damage) were not. With cut-offs of 35% and 60%, the risk of a HAQ score >=1 was high for 47% and low for 20% of the patients treated with initial monotherapy. Risks were markedly reduced in combination therapy groups, also in unfavorable risk profiles.

Conclusion

In recent onset active RA, baseline HAQ, pain and initial treatment are predictors for HAQ >=1 after three months. Known predictors of radiological damage were not predictive of short term functional disability. The choice of the best initial treatment thus depends on the relevance of various outcome measures for an individual patient.

INTRODUCTION

In early rheumatoid arthritis (RA), personalized treatment aims at choosing the best treatment to achieve the most relevant goal for the individual patient. There is no single 'gold standard' quantitative measure to assess and monitor clinical outcomes.(1) Risk models help to identify predictors for the specific disease outcome that the treatment needs to prevent. Previous models have focused on prediction of radiological damage and long-term functional disability, which are interrelated.(2-5) For some patients, long-term outcomes may be less relevant than for others. For younger patients, prevention of future radiological joint damage is more important than for patients who present with RA later in life. However, rapid improvement in symptoms and a return to normal daily functioning including maintenance or work ability, is important for all patients.(6;7) We wondered if the known outcome predictors for radiological damage and long-term functional disability are also associated with short-term functional disability. To accommodate optimal treatment choices for such patients, we developed a risk model to predict functional disability after three months of various treatment strategies.

PATIENTS AND METHODS

Patients

Clinical data of 508 recent-onset RA patients, included in the BeSt study, were used. All patients were DMARD-naïve and fulfilled the 1987 American College of Rheumatology criteria for RA. For the present analysis, strategy groups 1 and 2 were combined since patients achieved the relevant outcome (Health assessment Questionnaire (HAQ) score at three months) on the same initial treatment, i.e. methotrexate monotherapy. In strategy 3 patients started with a combination of methotrexate, sulphasalazine and a tapered high dose of prednisone and in strategy 4 patients started with a combination of methotrexate and infliximab. More details on the BeSt study design were previously published.(8)

Statistical analysis

Insufficient functional outcome was defined as HAQ score >=1, considered to represent mild functional ability in previous papers (3;9). Baseline characteristics were compared between patients with a HAQ >=1 and a HAQ <1 after three months of treatment, per treatment group. Differences were tested using the chi-square test for categorical data and either one-way analysis of variance or Kruskal-Wallis test for continuous data, depending on the distribution of the tested variable. Univariate variables (table S2 online supplement) showing an association (p<0.10) with a HAQ score >=1 were entered as possible predictors in a multivariate logistic regression as well as possible confounding variables. With a backward selection procedure, using a p-value of 0.10 as the removal criterion, significant independent predictors were identified. As colinearity or overlap existed between several variables identified as predictors in the univariate regression analysis, multiple multivariate analyses were performed and a final model chosen for further analysis based on the explained variation (Nagelkerke's R^2).

To construct the matrix, the final regression model was fitted with all variables categorized based on tertiles. In addition, numbers needed to treat (NNT) with initial combination therapy were calculated to illustrate the effect of initial treatment choice.

Discriminative ability of the model and internal validation

A receiver operating characteristics (ROC) curve was fitted, the area under the curve (AUC) calculated, and the positive and negative predictive values (PPN, NPV) of the model were explored. To investigate the internal validation of the model, the predicted risk of a HAQ >=1 for the monotherapy group was compared with the observed HAQ scores after three and twelve months of treatment. For all analyses, SPSS version 16.0 software (SPSS, Chicago, IL) was used.

RESULTS

The baseline characteristics for 497 of 508 patients, for whom both baseline and three months follow-up HAQ scores were available, are shown in table S1 in the online supplement.

Treatment, female gender, disease activity score (DAS), HAQ, Ritichie Articular Index (RAI), tender joint count (TJC), VAS disease activity, VAS pain, VAS morning stiffness, VAS global health, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and body mass index (BMI) were significant univariate predictors of HAQ >=1 after 3 months (table 2). Anti-citrullinated protein antibodies (ACPA) and rheumatoid factor (RF) positivity, swollen joint count (SJC), and erosion and joint space narrowing scores were not predictors of short- term disability.

The multivariate logistic regression analysis showed that treatment, HAQ baseline, VAS pain and RAI were independent significant predictors of a HAQ score >=1 after three months. The final model was fitted with these variables categorized (table 1). The explained variation remained just 0.29. Other possibly unknown or unmeasured factors might explain the remaining variance.

The results were presented in a visual matrix model, separately for each treatment group (figure 1). Each percentage in the boxes in the matrix represents the chance of having a HAQ score >=1 after three months of treatment, for a specific risk profile. Compared to initial monotherapy, patients in the initial combination therapy with prednisone and infliximab group, had an overall significant reduced risk (odds ratio: 0.30, 95% CI: 0.18-0.50 and 0.36, 95% CI: 0.21-0.60, respectively) of having a HAQ >=1 after three months of treatment. There was no difference between the two combination groups (p=0.293).

The effect of initial treatment choice on the risk of a HAQ >=1 is also well illustrated by calculating the NNT. Overall, the number needed to treat with initial combination therapy to prevent one patient from having a HAQ >=1 if treated with monotherapy, ranged from 3-7, to 3-5, to 4-11 for patients with a high, intermediate or low predicted risk, respectively (Figures 2A and 2B). Since the NNT is similar for the different risk profiles, it seems that initial treatment choice is the most important determinant of early functional improvement.

The AUC of the ROC curve for the matrix model was 0.78 (95% CI = 0.74-0.82), indicating an acceptable discriminative ability. The model reliably classified 67% of the patients when cut-offs of <35% (low risk) and >60% (high risk) were used, with a PPV and NPV of 71% and 74% respectively. Validity of the prediction after one year of continued DAS-steered treatment is shown in figure S3 in the online supplement.

DISCUSSION

Personalized treatment in recent onset RA should aim at preventing the disease outcome that is most relevant for the individual patient, and for some long term radiological damage is not the most relevant. For many, early functional improvement is. We found that baseline HAQ, high VAS pain, high RAI and initial treatment choice were predictive of an insufficient improvement in functional ability defined as HAQ >=1 after three months of treatment. Based on these findings we developed a matrix model that might help rheumatologists choose the right initial treatment when aiming at improvement of functional ability. For generalisability of the results, external validation in other dynamic treatment cohorts will be needed.

Interestingly, we found that presence of autoantibodies, CRP or ESR level and baseline erosion score, known predictors of rapid radiological progression or long-term functional disability(2;3;5;10), were not predictive of short term functional disability. Baseline HAQ, pain and RAI were also found to be predictive of long-term functional disability in previous studies.(3;11) Since predictive factors for short term functional disability differ from those found for radiological progression, and only partially overlap with those of long-term functional outcome, long-term and short-term functional disability are likely to be different concepts. Long-term functional impairment is more related to joint damage, whereas in short-term disability, joint swelling and tenderness might be more influential.(4;12) Personalized treatment can be achieved by using the relevant risk model, depending on whether the treatment goal is prevention of short term disability or long-term radiological damage and disability. However, it appears that for many patients the initial treatment choice will achieve both. The current model for short-term functional disability and a previous prediction model for rapid radiological progression (5) both show that the risks for adverse outcomes are reduced if the initial treatment is with combination therapy.

Many rheumatologists start treatment of newly diagnosed RA patients with monotherapy and switch to a combination of medication if the treatment response is insufficient. However, an early treatment response is beneficial for both rapid functional improvement and prevention of radiological damage. Studies have shown that at a group level, patients

with active RA benefit most from initial combination therapy, in having earlier functional improvement and less radiological damage than with initial DMARD monotherapy.(5;14;15) We therefore propose that the EULAR recommendations for the management of RA (13), which state that 'MTX should be *part of* the first treatment strategy in patients with active RA' should be followed by starting with initial combination therapy.

In conclusion, the predictors of early functional impairment (after three months of treatment) are different from predictors for radiological damage. For an individual patient the optimal initial treatment is therefore dependent on the treatment goal and requires use of the relevant risk model. In most cases, initial combination therapy is the best choice to ensure earlier functional improvement and less radiological damage progression.

REFERENCES

(1) Pincus T, Sokka T. Quantitative measures for assessing rheumatoid arthritis in clinical trials and clinical care. Best Pract Res Clin Rheumatol 2003 Oct;17(5):753-81.

(2) Combe B, Dougados M, Goupille P, Cantagrel A, Eliaou JF, Sibilia J, et al. Prognostic factors for radiographic damage in early rheumatoid arthritis: a multiparameter prospective study. Arthritis Rheum 2001 Aug;44(8):1736-43.

(3) Combe B, Cantagrel A, Goupille P, Bozonnat MC, Sibilia J, Eliaou JF, et al. Predictive factors of 5-year health assessment questionnaire disability in early rheumatoid arthritis. J Rheumatol 2003 Nov;30(11):2344-9.

(4) Scott DL, Smith C, Kingsley G. Joint damage and disability in rheumatoid arthritis: an updated systematic review. Clin Exp Rheumatol 2003 Sep;21(5 Suppl 31):S20-S27.

(5) Visser K, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Ronday HK, Seys PE, Kerstens PJ, et al. 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. Ann Rheum Dis 2010 Jul;69(7):1333-7.

(6) Raterman HG, Hoving JL, Nurmohamed MT, Herenius MM, Sluiter JK, Lems WF, et al. Work ability: a new outcome measure in rheumatoid arthritis? Scand J Rheumatol 2010 Mar;39(2):127-31.

(7) Puolakka K, Kautiainen H, Mottonen T, Hannonen P, Korpela M, Hakala M, et al. Early suppression of disease activity is essential for maintenance of work capacity in patients with recent-onset rheumatoid arthritis: five-year experience from the FIN-RACo trial. Arthritis Rheum 2005 Jan;52(1):36-41.

(8) Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, van Zeben D., Kerstens PJ, Hazes JM, 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 Nov;52(11):3381-90.

(9) Sokka T, Krishnan E, Hakkinen A, Hannonen P. Functional disability in rheumatoid arthritis patients compared with a community population in Finland. Arthritis Rheum 2003 Jan;48(1):59-63.

(10) Berglin E, Johansson T, Sundin U, Jidell E, Wadell G, Hallmans G, 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 Apr;65(4):453-8.

(11) Lindqvist E, Saxne T, Geborek P, Eberhardt K. Ten year outcome in a cohort of patients with early rheumatoid arthritis: health status, disease process, and damage. Ann Rheum Dis 2002 Dec;61(12):1055-9.

(12) Aletaha D, Smolen J, Ward MM. Measuring function in rheumatoid arthritis: Identifying reversible and irreversible components. Arthritis Rheum 2006 Sep;54(9):2784-92.

(13) Smolen JS, Landewe R, Breedveld FC, Dougados M, Emery P, Gaujoux-Viala C, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. Ann Rheum Dis 2010 Jun;69(6):964-75.

(14) Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van VR, 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 Jan;54(1):26-37.

(15) Korpela M, Laasonen L, Hannonen P, Kautiainen H, Leirisalo-Repo M, Hakala M, 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 Jul;50(7):2072-81.

Table 1. Independent predictive variables of a HAQ score >= 1 after three months of treatment in the final fitted multivariate logistic regression model with all variables categorized.

Baseline predictor of HAQ		**OR (95% CI)**
Treatment	mono	*ref*
	combo prednisone	0.30 (0.18-0.50)
	combo infliximab	0.36 (0.21-0.60)
HAQ	< 1.38	*ref*
(tertiles)	1.38- 2.00	2.60 (1.61-4.18)
	> 2.00	5.27 (2.94-9.46)
VAS pain	< 40	*ref*
(tertiles)	40-60	2.20 (1.28-3.80)
	> 60	2.70 (1.43-5.09)
RAI	< 10	*ref*
(tertiles)	10-16	1.73 (1.02-2.95)
	> 16	2.66 (1.50-4.71)

A.

Initial monotherapy

HAQ score	<40	40-60	>60	RAI
> 2	73	89	88	> 16
	64	80	83	10–16
	51	70	74	<10
1.4 - 2	58	75	79	> 16
	47	66	70	10–16
	34	53	58	<10
< 1.4	34	53	58	> 16
	25	43	48	10–16
	16	30	35	<10

VAS pain

B.

Initial combination therapy with prednisone

HAQ score	<40	40-60	>60	RAI
> 2	45	64	69	> 16
	35	54	59	10–16
	23	40	45	<10
1.4 - 2	29	47	52	> 16
	21	37	41	10–16
	13	25	29	<10
< 1.4	14	25	29	> 16
	9	18	21	10–16
	5	11	14	<10

VAS pain

C.

Initial combination therapy with infliximab

HAQ score	<40	40-60	>60	RAI
> 2	50	68	73	> 16
	39	58	63	10–16
	27	45	50	<10
1.4 - 2	25	46	51	> 16
	24	41	46	10–16
	15	29	33	<10
< 1.4	16	29	33	> 16
	11	21	25	10–16
	7	13	16	<10

VAS pain

Figure 1. Matrix model with predicted risks (in %) of a HAQ score >= 1 after three months of treatment per treatment strategy; A. Initial monotherapy. B. Initial combination therapy with prednisone. C. Initial combination therapy with infliximab. The dark grey boxes represent a high risk (≥60%), grey boxes an intermediate risk (35-60%), light grey boxes a low risk (10-34%) and white boxes a very low risk (<10%).

A.

Initial combination therapy with prednisone

HAQ score		<40	40-60	>60	RAI
	> 2	4	4	5	> 16
		3	4	4	10-16
		4	3	3	<10
	1.4 - 2	3	4	4	> 16
		4	3	3	10-16
		5	4	3	<10
	< 1.4	5	4	3	> 16
		6	4	4	10-16
		9	5	5	<10

VAS pain

B.

Initial combination therapy with infliximab

HAQ score		<40	40-60	>60	RAI
	> 2	4	5	7	> 16
		4	5	5	10-16
		4	4	4	<10
	1.4 - 2	3	3	4	> 16
		4	4	4	10-16
		5	4	4	<10
	< 1.4	6	4	4	> 16
		7	5	4	10-16
		11	6	5	<10

VAS pain

Figure 2. Matrix model with numbers needed to treat (NNT) with initial combination therapy in order to prevent one patient from achieving a HAQ score >= 1 if treated with initial monotherapy. A. Initial combination therapy with prednisone and B. Initial combination therapy with infliximab. The dark grey boxes represent a NNT >10, the light grey boxes a NNT 5-10 and the uncolored boxes a NNT < 5.

S1. Baseline characteristics of 497 out of 508 recent-onset RA patients in the BeSt study. Patients were randomized to initial monotherapy or initial combination therapy including prednisone or infliximab.

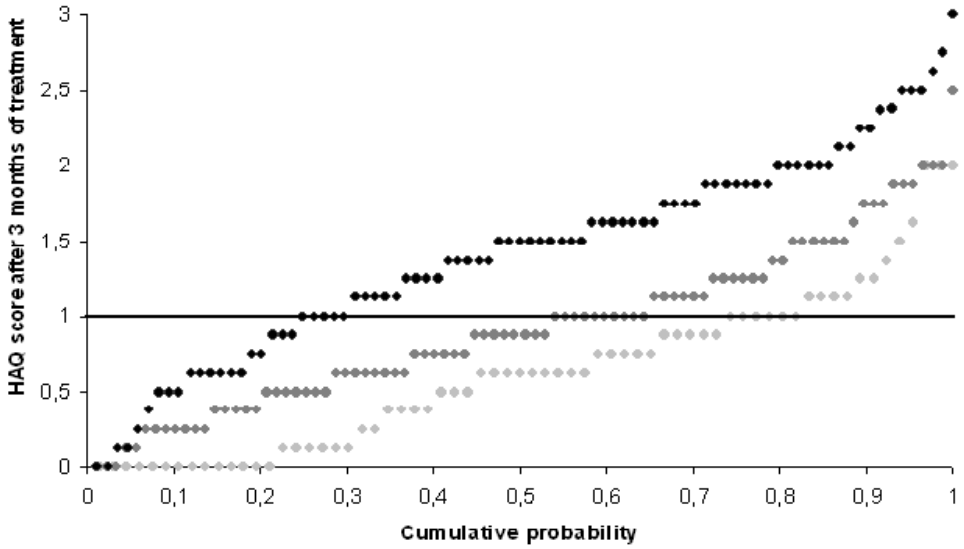
Baseline characteristics	**MTX monotherapy (n=239)**	**Combination therapy with prednisone (n=131)**	**Combination therapy with infliximab (n=127)**
Age, mean ± SD years	54 (13)	55 (14)	54 (14)
Female gender, no. (%)	167 (70)	86 (66)	84 (66)
Symptom duration, median (IQR) weeks	25 (14-55)	23 (15-53)	23 (13-46)
DAS, mean ± SD	4.5 (0.9)	4.4 (0.9)	4.3 (0.9)
HAQ, mean ± SD	1.4 (0.6)	1.4 (0.7)	1.4 (0.7)
RAI, median (IQR)	14 (9-18)	13 (9-19)	11 (8-17)
SJC, median (IQR)	14 (10-20)	14 (10-18)	13 (9-17)
TJC, median (IQR)	22 (14-31)	22 (13-33)	19 (12-22)
VAS disease activity, mean ± SD	59 (23)	59 (24)	62 (20)
VAS pain, mean ± SD	53 (22)	54 (23)	54 (21)
VAS morning stiffness, mean ± SD	59 (23)	59 (26)	60 (24)
VAS global health, mean ± SD	52 (20)	50 (22)	55 (19)
BMI, mean ± SD	26 (4)	26 (4)	26 (4)
CRP, median (IQR) mg/L	22 (9-59)	21 (10-57)	21 (7-44)
ESR, median (IQR) mm/hr	38 (21-58)	35 (17-45)	36 (19-58)
Total SHS, median (IQR)	4.0 (1.5-8.8)	3.5 (1.5-8.5)	4.0 (1.5-8.8)
Erosion score, median (IQR)	2.0 (0.5-4.5)	2.0 (0.5-4.5)	2.0 (0.5-5.0)
Narrowing score, median (IQR)	2.0 (0-4.3)	1.5 (0-4.0)	1.5 (0-3.6)
Erosive (>=1), no. (%)	165 (71)	92 (71)	92 (73)
RF positive, no. (%)	156 (65)	85 (65)	81 (64)
ACPA positive, no. (%)	143 (63)	67 (55)	82 (66)
Smoking yes, no. (%)	92 (39)	44 (34)	40 (32)

DAS, disease activity score; HAQ, Health assessment Questionnaire; RAI, Ritchie Articular Index; SJC, swollen joint count; TJC, tender joint count; VAS, visual analogue scale; BMI, body mass index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; SHS, Sharp- van der Heijde Score; RF, rheumatoid factor; ACPA, anti-cyclic citrullinated peptide antibodies

S2. Univariate predictive variables of a HAQ score >= 1 after three months of treatment. Odds ratios with 95% confidence intervals are shown. *P-value <0.05.

Predictor of a HAQ score >= 1	**Odds ratio (95% CI)**
Treatment	0.60 (0.48-0.76)*
Age	1.00 (0.99-1.01)
Female gender	0.56 (0.38- 0.83)*
Symptom duration	1.00 (1.00-1.00)
DAS	1.90 (1.51-2.38)*
HAQ	4.24 (3.03-5.92)*
RAI	1.09 (1.06-1.12)*
SJC	1.02 (1.00-1.05)
TJC	1.04 (1.02-1.05)*
VAS disease activity	1.02 (1.01-1.02)*
VAS pain	1.02 (1.01-1.03)*
VAS morning stiffness	1.02 (1.01-1.03)*
VAS global health	1.02 (1.00-1.03)*
BMI	1.08 (1.03-1.13)*
CRP	1.01 (1.00-1.01)*
ESR	1.01 (1.00-1.02)*
Total SHS	1.00 (0.98-1.02)
Erosion score	0.99 (0.96-1.03)
Narrowing score	1.03 (0.98-1.07)
Erosions	0.75 (0.50-1.12)
RF positive	0.96 (0.66-1.39)
ACPA positive	0.92 (0.63-1.34)
SE	1.25 (0.82-1.91)
Smoking yes	1.42(0.98-2.06)

A.



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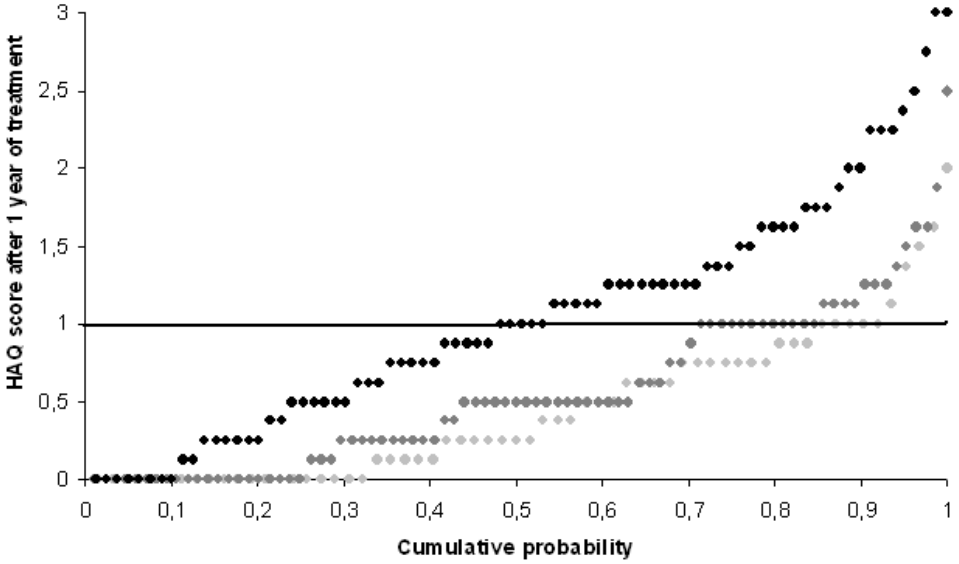

S3. HAQ scores for patients with a low (light grey dots), intermediate (dark grey dots) and a high (black dots) predicted risk of a HAQ score >= 1 after three months of treatment, if treated with initial monotherapy. A. HAQ scores after three months of treatment and B. HAQ scores after one year of treatment.