Disability measured by the modified health assessment questionnaire in early rheumatoid arthritis: prognostic factors after two years of follow-up

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Abstract

Objective

To analyze the rate and baseline prognostic factors of disability measured by the modified HAQ (MHAQ), in a series of patients with early rheumatoid arthritis (RA) after two years of therapy with a structured algorithm using disease-modifying anti-rheumatic drugs (DMARDs).

Methods

One hundred and five patients (81% female) with early RA (disease duration <2 years) treated with the same therapeutic protocol using gold salts and methotrexate in a step-up strategy, together with methylprednisolone (4 mg/day), were followed up for two years. The outcome was the absence of disability (MHAQ=0) after two years of DMARD therapy. Clinical, biological, immunogenetic and radiographic data (Larsen score) were analyzed at study entry and at 12 and 24 months of follow-up.

Results

The MHAQ decreased significantly at 6 months after initiation of DMARD therapy and the reduction was maintained at 24 months (mean±SD: 0.97±0.56 at baseline, 0.51± 0.57 at month 6 and 0.45±0.5 at month 24). No disability (MHAQ=0) was observed in 26.6% of patients after two years of follow-up. Age, MHAQ>0.5, DAS28>5.1, VAS pain, positive rheumatoid factor and ESR at baseline were associated with disability in the univariate analysis. In the logistic regression analysis, only age (OR: 1.058, 95%CI 1.017; 1.101 p<0.006), rheumatoid factor status (OR: 3.772 95%CI 1.204; 11.813, p<0.02) and MHAQ>0.5 (OR:4.023, 95%CI 1.373; 11.783, p<0.02) were associated with disability (MHAQ>0) at two years.

Conclusion

In a series of early RA patients treated with a structured algorithm using DMARDs and very low doses of glucocorticoids, no disability was observed in a quarter of patients after two years. Age, rheumatoid factor positivity and MHAQ>0.5 were independent predictors of disability at two years.

Key words

Early rheumatoid arthritis, disability, health assessment questionnaire (HAQ), prognostic factors.

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Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease of unknown etiology which is associated with progressive joint destruction, significant disability and long-term reductions in quality of life together with substantial social and economic costs (1).

In the last decade, the measurement of disability and quality of life has attracted increasing attention. Disability measured by self-reported questionnaires is one of the main outcome measures in clinical trials and observational studies in RA (2). Periodic assessment of physical function has also been recommended for daily clinical practice (3). It is accepted that disability improves after the introduction of antirheumatic therapy, especially in early stages of RA, but worsens over the course of the disease (4). Different process variables in the course of RA may contribute to disability; inflammatory activity is the main contributor in early RA, whereas structural damage also plays an important role in longstanding disease (5).

The Health Assessment Questionnaire (HAQ) is the instrument most-commonly used to measure disability in RA. The HAQ analyses the capacity to perform different activities of daily living (6) and is a valid, accepted tool for measuring disability in RA (4, 5). The HAQ has been found to predict work disability (7), joint replacement (8) and even mortality (2, 9-10). In addition, baseline HAQ is the best predictive factor of 5-year quality of life in early RA (11). Most studies of prognostic factors of disability in RA have used the HAQ to measure functional capacity (12).

The modified HAQ (MHAQ) is a shortened version of the HAQ that reduces the original number of items in order to improve feasibility in daily practice (13). Although the MHAQ and HAQ scores are not interchangeable, both are sensitive to change in clinical trials (14, 15). However, to our knowledge there are no studies on prognostic factors of disability in RA using the MHAQ.

Prognostic factors of radiographic progression (16, 17) and clinical remission (18) in a series of patients with early RA in a clinical setting have recently been reported by our group. The objective of this study was to analyze the prevalence and prognostic factors of disability measured by the MHAQ after a follow up of two years in this cohort of patients with early RA after the introduction of a structured therapeutic strategy with DMARDs and low doses of glucocorticoids.

Patients and methods

Patients

Patients fulfilling the American College of Rheumatology (ACR: formerly the American Rheumatism Association) criteria for the classification of RA, with symptoms for <24 months were enrolled in the study. All were out-patients attending the rheumatology units of the Hospital Clinic of Barcelona or the Hospital Parc Tauli of Sabadell between 1998 and 2003 and were followed for two years. Patients previously treated with DMARDs or prednisone or equivalent at a dose >10 mg/day were excluded. Hospital Clinic ethical committee approval was obtained.

Study design

This was an open-label study, where all patients were treated according to a therapeutic protocol with early introduction of DMARDs, using a step-up approach. In all cases, intramuscular sodium aurothiomalate at a dose of 50 mg/week was prescribed as the first-choice DMARD, together with methylprednisolone 4 mg/day. Non-steroidal anti-inflammatory drugs and intraarticular steroid therapy were used according to clinical judgment. Methotrexate at an increasing dose of 7.5 to 20 mg was introduced if adverse effects without clinical improvement or no ACR20 response were observed at month 6. Methotrexate was also added if patients showed high disease activity according to physician judgment during the first six months. If an ACR50 response at 6 months was achieved, gold salts were scheduled every 2-3 weeks, but if a patient had an ACR20 response but no ACR50 response, combination therapy with sodium aurothiomalate and methotrexate was initiated. Oral steroid therapy was tapered according to clinical judgment. After the first year of therapy, patients were treated according

to the criteria of the attending physician, but with an aggressive approach, with the initiation of other DMARDs in cases with a poor response to previous DMARDs. Biological therapy was instituted in a few patients with a poor response to DMARD therapy.

At study entry, demographic characteristics, disease duration, serum rheumatoid factor measured by nephelometry (NV <25 UI/L), anti-cyclic citrullinated peptide antibodies (CCP) measured by a second-generation ELISA test (Immunoscan, Eurodiagnostica)(NV<50 UI/l) and DRB1 genotype determined by direct DNA sequencing, were analyzed. At baseline and at 6, 12, 18 and 24 months the following parameters were recorded: pain using a visual analogue scale (VAS), the 28 tender and swollen joint count, patient and physician assessment of disease status on a Likert scale, the 28-joint disease activity score (DAS28), functional status using the MHAQ, and the erythrocyte sedimentation rate and C reactive protein measured by nephelometry. The therapeutic response was analyzed according to both ACR (19) and EULAR (20) criteria.

Disability criteria

Disability was measured according to the MHAQ (13), which includes eight questions on the activities of daily living. Each item scores from 0 (fully able to perform such activity) to 3 (not able to perform it). The final score is the mean of the score of all eight items. Disability was considered as an MHAQ >0.

Radiographic evaluation

Radiographs of hands and feet were obtained at months 0, 12 and 24, graded by the modified Larsen method (21). Thirty-two joints were assessed: bilateral thumb interphalangeal (IP) joints, proximal IP joints 2-5 of hands, metacarpophalangeal joints 1-5, first toe IP joints, metatarsophalangeal joints 2-5 and wrists. Each wrist was considered a unit and its score was multiplied by 5. The Larsen score ranged from 0 to 200.

Statistical methods

The outcome variable was functional disability at 2 years of follow-up measured by the MHAQ. The *t*-test was used to evaluate continuous variables in the univariate analysis and the chi-square test to evaluate qualitative variables. A general linear model for repeated measures was applied to assess differences in MHAQ scores between different time points. Binary logistic regression was carried out using a hierarchical modeling method. Effect modifying variables were considered as those showing significance ($p<0.05$) or at least trends ($p<0.1$) in the univariate analyses between baseline characteristics and 6-month clinical response. Clinically relevant interactions were included and the forward stepwise conditional technique was used to obtain the final model. Spearman correlation analyses were performed to avoid instability in the binary logistic regression model. All calculations were carried out using the SPSS 12.0.

Results

One hundred and fifteen patients were initially enrolled. Ten patients did not complete the 2 year follow-up for various reasons: transfer out (1 patient), irregular or lost follow-up (6 patients), death (2 patients) and doubts about disease duration at inclusion (1 patient). The final cohort was 105 patients. Demographic and clinical characteristics are shown in Table I. Most patients were female (81%) and handworkers. At inclusion, the mean age was 55±14.9 and the disease duration was 10±6.7 months. There was a high prevalence of positive rheumatoid factor, anti-CCP and shared epitope. The evolution of clinical, biological and radiographic parameters in the different time point assessments, together with the rates of ACR and EULAR therapeutic responses are shown in Table II. DAS28 decreased significantly from a mean of 5.6±0.91 at inclusion to 3.8±1.3 and 3.4±1.28 at 12 and 24 months, respectively. The mean Larsen score was 1.23±2.7 at inclusion and 6.08±9.34 at 24 months. Drug therapies administered during the follow-up are shown in Table III.

Table I. Baseline characteristics of 105 patients with early RA.

Women (%)		81
Age (yr), mean± S.D.		55 ± 14.9
Disease duration (months), mean±S.D.		10 ± 6.7
Handwork (%)		81.7
Marital status (%)	Single	11.6
	Married	73.8
	Widowed	11.6
	Divorced	2.9
Educational level (%)	No formal education	13.8
	Primary education	46.5
	Secondary education	26.7
	University education	12.8
Occupational status (%)	Housewife	24.7
	Active	41.6
	Temporary out-of-work	13.8
	Handicapped	3
	Retired	13.8
Rheumatoid factor-positive (%)		73.3
Anti-CCP positive (%)		70.4
Shared epitope (%)		70.6
Shared epitope homozygosity (%)		20.6
HLA-DRB1-04 (%)		44.1
HLA-DRB1-04 homozygosity (%)		3.9
Larsen score, mean±S.D.		1.2 ± 2.7

SD: standard deviation.

Table II. Clinical and biological characteristics and rates of clinical response of patients during follow-up.

	Baseline	6 months	12 months	18 months	24 months
28 tender joint count	10.1 (5.9)	4.3 (5.6)	3.5 (4.7)	2.9 (4.1)	2.7 (4)
28 swollen joint count	8.3 (4.1)	3.3 (4.4)	2.6 (3.3)	2.2 (3.3)	2.2 (3.4)
Patient's global assessment	57.8 (15.1)	41.3 (19.2)	40.5 (17.4)	39.1 (18)	37.2 (18.3)
Physician's global assessment	55.8 (13.9)	38.3 (19.8)	36.9 (18.9)	33.6 (19.5)	32.8 (18)
VAS pain (mm)	51.3 (21.6)	31 (24.5)	31.9 (23.9)	29.8 (24.1)	28.8 (21.1)
ESR (mm/h)	39.5 (24.5)	27.1 (21.2)	25.5 (18.9)	23 (14.1)	22.9 (15.8)
C-reactive protein (mg/dL)	2.8 (2.9)	1.6 (3.2)	1.3 (1.6)	1.2 (1.4)	1.2 (1.5)
Hemoglobin (mg/dL)	127.4 (13.9)	128.9 (14.8)	130.2 (14.2)	130 (13.7)	130.8 (12.9)
Larsen score	1.23 (2.69)	–	3.46 (6.74)	–	6.08 (9.34)
MHAQ >0.5 (%)	67.3	31.6	38	30.9	33
MHAQ =0 (%)	1.9	24.5	21	23.8	26.6
MHAQ	0.97 (0.56)	0.51 (0.57)	0.51 (0.5)	0.45 (0.49)	0.45 (0.5)
DAS_28	5.66 (0.91)	4.01 (1.43)	3.83 (1.32)	3.57 (1.25)	3.46 (1.28)
ACR20 response (%)	–	70	73.3	75	70.5
ACR50 response (%)	–	51	41.7	56.2	52.4
Whole EULAR response (%)	–	74.2	78.1	79.1	81.9
Good EULAR response (%)	–	30.7	35.2	41.9	21.9

Variables expressed as mean (SD) except when indicated.

Table III. Drug therapies administered at one and two years of follow-up.

	Gold salts monotherapy	Gold salts and methotrexate	Methotrexate monotherapy	Methotrexate combined[1]	Other DMARDs	No DMARDs	Methyl-prednisolone
One year follow-up	50.5%	10.5%	23.8%	1.9%[2]	1.2%[4]	12.4%	67.5%
Two year follow-up	28.6%	10.5%	21.9%	12.4%[3]	12.4%[5]	14.2%	62.5%

[1]Other DMARDs combined other than gold; [2]Leflunomide n=1, Infliximab n=1; [3]Leflunomide n=1, Cyclosporine A n=4, Infliximab n=5, Adalimumab n=1, Hydroxychloroquine n=1. [4]Leflunomide n=1; [5]Leflunomide n=6, Leflunomide + Infliximab n=2, Etanercept n=1, Cyclosporine A n=1, Hydroxychloroquine n=1.

Prevalence and evolution of disability

Disability measured by the MHAQ decreased significantly at 6 months after initiation of DMARD therapy (0.97±0.56 *vs*. 0.51±0.57, $p<0.0005$) and the improvement was maintained at 24 months, when 26.6% of patients showed no disability (MHAQ=0). The percentage of disability at the different time points is shown in Table II.

Prognostic markers of disability

In the univariate analysis (Table IV), the baseline parameters associated with disability (HAQ>0) at two years were: age, female gender, MHAQ, VAS pain, DAS28>5.1, MHAQ>0.5, rheumatoid factor and ESR. A non-statistically significant trend was observed for patient's global assessment, hemoglobin and marital status (widowed) (Table IV). Other demographic variables, such as higher percentages of handworkers, lower educational level and a lower percentage of patients in active work in the disabled group, showed non-statistically significant differences. However, in the multiple regression analysis, the only independent baseline factors associated with disability (MHAQ>0) were: age (OR: 1.058, 95%CI 1.017; 1.101, $p<0.006$), positive rheumatoid factor (OR: 3.772, 95%CI 1.204; 11.813, $p<0.02$) and MHAQ>0.5 (OR: 4.023, 95%CI 1.373; 11.783, $p<0.02$) (Table V). The sensitivity and specificity of the multivariate model were 70.1% and 64%, respectively. Positive and negative predictive values were 83.9% and 44.4%. Patients aged ≥65 years at inclusion with positive rheumatoid factor and a MHAQ score above 0.5 had an 83.9% probability of having a MHAQ above 0 at 24 months of follow-up.

Discussion

This study focuses on the frequency and prognostic factors of disability in a cohort of early RA patients treated with a structured therapy with DMARDs and very low doses of glucocorticoids after two years of follow-up using the MHAQ. Disability improved significantly during the first six months after the introduction of antirheumatic therapy and this improvement was maintained at 24 months. Older age, positive rheumatoid factor and disability (MHAQ>0.5) at baseline were independent predictors of disability at 24 months of follow-up.

Disability is considered one of the most important outcome measures in RA. The introduction of the HAQ more than 25 years ago (6) simplified the measure of disability in clinical practice and has become the most frequent tool for measuring difficulties in performing activities of daily living in both observational studies and clinical trials in RA. The shortened version of the HAQ, the MHAQ, was introduced in 1983 (13) and reduced the questionnaire from 20 to eight items. The correlation between the two questionnaires is very high, but they are not interchangeable (14) and MHAQ scores are lower than those of the HAQ (14, 22-24). Some studies have suggested that the MHAQ is not the most appropriate tool for patients with RA in view

Table IV. Baseline characteristics in patients with and without disability at the end of follow-up (24 month). Results of the univariate analysis.

	24 months: mHAQ = 0		24 months: mHAQ >0		Mean difference[¶]	OR	LB 95% IC	UB 95% IC	*p*-value
Female (%)	68		87			3.14	1.05	9.37	0.05
Age (years)*	48.6	(14.1)	57.4	(13.9)	-8.89		-15.34	-2.44	0.01
Disease duration (months)*	8.5	(4.7)	10.17	(7.3)	-1.7		-4.27	0.87	NS
Marital status (widowed) (%)	4.2		14.7			3.97	0.48	32.76	0.08
Handworkers (%)	72		83.8			2.02	0.68	5.97	NS
Universitary studies (%)	20.8		10.6			0.45	0.13	1.59	NS
Active work patients (%)	58.3		36.4			0.41	0.16	1.06	NS
HLA-DRB1-04 (%)									
Heterozygote	41.7		44.8			1.14	0.44	2.92	NS
Homozygote	4.2		3			0.71	0.06	8.18	NS
Shared epitope									
Heterozygote	45.8		52.2			1.29	0.51	3.29	NS
Homozygote	25		20.9			0.79	0.26	2.37	NS
RF+ (>25 UI/l) (%)	56		81.2			3.38	1.25	9.14	0.01
Anti-CCP+ (> 50 UI/l) (%)	60.9		76.6			2.1	0.76	5.81	NS
ESR (mm/h)*	30.5	(22.5)	43.3	(25)	-12.79		-24.12	-1.46	0.03
C-reactive protein (mg/dL)*	2.1	(2.5)	3.1	(3.1)	-0.99		-2.38	0.4	NS
Hemoglobin*	131.5	(13.8)	126	(13.7)	5.53		-0.82	11.89	0.09
28 tender joint count*	8.8	(6.6)	10.5	(5.8)	-1.68		-4.46	1.11	NS
28 swollen joint count*	9	(5.3)	7.7	(3.7)	1.21		-1.13	3.54	NS
Patient's global assessment*	53.2	(16)	59.5	(14.9)	-6.35		-13.44	0.73	0.08
Physician's global assessment*	53.2	(14.9)	56.6	(14.1)	-3.37		-10.03	3.3	NS
VAS pain (mm)*	39.4	(20.4)	55.9	(20.1)	-16.57		-25.93	-7.20	0.00
DAS28*	5.28	(1.1)	5.77	(0.83)	-0.49		-0.98	0.00	0.05
DAS28 (> 5.1) (%)	56		80.9			3.32	1.23	8.99	0.02
MHAQ*	0.7	(0.5)	1.08	(0.53)	-0.38		-0.62	-0.13	0.00
MHAQ (> 0.5) (%)	48		76.5			3.52	1.34	9.23	0.01
Larsen score*	1	(2.02)	1.29	(3.03)	-0.29		1.59	1.01	NS

[¶] Mean difference in quantitative variables *Expressed as mean (Standard deviation); NS: not statistically significant; LB: lower bound; UB: upper bound; RF: rheumatoid factor.

of the lower sensitivity to change (22-24) and the greater ceiling effect (14, 22, 23), both of which effects increase in more disabled patients. In addition, the MHAQ has a higher probability of a floor effect, when patients with a zero score are, in reality, not without disability (25). New adaptations of the MHAQ, such as the 10-ADL MDHAQ, which includes two extra questions (walking 2 miles and participating in sports), have been developed in order to counteract this floor effect (26). However the MHAQ has demonstrated sensitivity to change in both clinical trials (15, 27-32) and observational studies (14, 33) and, like the HAQ, is a strong predictor of mortality in RA (34, 35). We use the MHAQ to measure disability in daily clinical practice.

There are several studies on the evolution of disability in early RA and its prognostic factors, but almost all have used the original HAQ (12, 36-39). To our knowledge, there are no longitudinal studies on disability measured by the MHAQ in a homogeneous cohort of early RA patients. Previous studies of disability using the HAQ in early RA showed a significant improvement in disability during the first months after the introduction of antirheumatic therapy, both in clinical trials (40-46) and observational studies (4, 12, 36, 37, 47, 48) although Eberhardt *et al*. found a non significant improvement in disability in a study in which the median change in the HAQ during a 5 year follow-up was not significant, but a high variability in the HAQ score between patients was observed (38). Similar results were observed in our cohort, in whom the most significant reduction in disability was observed in the first six months after the introduction of DMARDs and glucocorticoids, with a slight improvement thereafter until the end of the two year follow-up. The proportion of patients without disability (MHAQ=0) rose from 1.9% at baseline to 26.6% at 24 months, a frequency similar to that observed at 6 months (24.5%), indicating that most patients without disability achieved this status early in the course of therapy. The percentage of patients without disability is

Table V. Multivariate model results for functional status at 2 years.

	Coefficient	S.E.	OR	95% CI	*p*-value
Age	0.056	0.020	1.058	1.017-1.101	0.006
Baseline RF (+)	1.328	0.582	3.772	1.204-11.813	0.023
Baseline mHAQ (> 0.5)	1.392	0.548	4.023	1.373-11.783	0.011
Constant	-3.804	1.309	0.022		0.004

SE: standard error; OR: odds ratio; 95% CI: confidence interval.

Table VI. Studies of prognostic factors of disability in early RA using the original HAQ to measure disability

Author	Number of patients	Disease duration at entry	Disability outcome	Time of follow-up	Prognostic factors[¶]
Van der Heide A *et al*. (36)	95	<1year	HAQ	1 year	HAQ and VAS pain at baseline
Bansback N *et al*. (37)	985	<2 years	HAQ≥1.5	5 years	HAQ at 12 month and functional class III/IV at month 12, Economic status, radiological damage at inclusion[**], hemoglobin at inclusion,
Combe B *et al*. (12)	191	<1 year	HAQ≥1	5 years	HAQ, Ritchie score, erosions[*], ESR, and CRP, all at inclusion
Eberhardt KB *et al*. (38)	63	<1 year	HAQ ≥1	5 years	HAQ at inclusion, gender, education level
Lindqvist E *et al*. (39).	183	<2 years	HAQ>1	10 years	Mean HAQ of the first 3 years

[*]Sharp method modified by van der Heijde. [**]Larsen method. [¶]Prognostic factors based on multivariate analysis.

difficult to compare with other series with early RA, which were measured using the HAQ. Using the MHAQ, Stucky *et al*. reported 29% of patients with MHAQ=0 in a cohort of patients with RA, most treated with DMARDs, with a median disease duration of 5 years (23), a percentage similar to that observed in our cohort. In a cross-sectional study of patients with longstanding disease, with a median duration of arthritis of 10 years, as expected, only 12.4% of patients were not disabled (MHAQ=0) (49).

Several studies have attempted to identify prognostic factors of disability in RA, although the results are conflicting. Van der Heide *et al*. (36) found that the HAQ score and VAS pain at inclusion were the best predictive factors for HAQ at one year of follow-up in patients with early RA. Other observational studies of early RA or recent-onset polyarthritis found different prognostic factors at ≥5 years of follow-up, including age (47), gender (38, 47), the time lag before consulting a rheumatologist (47), economic status (37), education (38), clinical disease activity(12, 47), ESR (12, 50) and CRP (12) or radiographic damage at baseline (12, 37). However, the level of disability at baseline or after the first years of follow-up emerges as the most important predictor of long term disability in almost all studies (12, 37-39, 51).

There are no studies on prognostic factors of disability in early RA using the MHAQ. In our cohort, only older age, positive rheumatoid factor and disability (MHAQ>0.5) at baseline were associated with disability at 24 months. This is in accordance with studies using the HAQ to measure disability, in which older patients were likely to be disabled, not only in RA (47) but also in the general population (52). In addition, patients with seropositive disease were associated with a higher degree of disability (53). Interestingly, baseline MHAQ was also associated with disability at the end of follow-up, with the highest odds ratio in the multivariate analysis. Similar results are observed using the HAQ. Table VI shows five studies (12, 36-39) on prognostic factors of disability in patients with early RA measured by the original HAQ. HAQ scores at baseline or different combinations of HAQ scores during the first years of disease course were the main predictors of disability at the end of follow-up in all these studies.

The results of this study emphasize that prognostic markers in early RA may differ in accordance with the type of outcome variable analyzed. The prognostic factors of disability were different from the prognostic factors of other outcome measures, as previously reported (54). As suggested by Pincus, two clusters of measures have been identified in RA; radiographs are closely correlated with disease duration, laboratory measures and joint deformity; in contrast, radiographs have a lesser correlation with age, joint swelling, joint tenderness, functional status and pain which are, in turn closely correlated with each other (55). In our cohort, the prognostic markers of radiographic progression were gender (female), DRB1 genotype (DRB04) and cyclic citrullinated peptide antibodies (16, 17), and the prognostic factors of remission were disease activity score at baseline and a good therapeutic response during the first months of therapy (18).

In conclusion, in a cohort of patients with early RA, a DMARD strategy improved disability, especially in the first months after the introduction of antirheumatic therapy. Although the use of the MHAQ as a measure of disability is controversial and may have some limitations, this questionnaire is sensitive to clinical change in this population. The MHAQ may be a useful tool to predict future disability in early RA. Age, rheumatoid factor status and MHAQ >0.5 at baseline independently predict disability at two years.

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