Determinants of Functional Response in Rheumatoid Arthritis Therapy

A thesis

submitted by

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In fulfillment of the requirements

for the degree of

Master of Science

in

Clinical and Translational Science

TUFTS UNIVERSITY

Sackler School of Graduate Biomedical Sciences

May 2012

Abstract

Background: Rheumatoid arthritis (RA) is an inflammatory condition that primarily affects the joints of the hands. If disease activity cannot be suppressed effectively, synovitis leads to loss of function. In recent years, biological therapies have made functional improvement possible for many patients, if effective treatment is initiated promptly. Because biologicals are expensive and carry risk for adverse effects, identifying those patients who are at high risk for limited functional response would select a subgroup that may benefit from rapid treatment escalation.

Aim: To identify determinants of functional improvement during RA therapy.

Methods: We analyzed observational data of RA patients who were starting a new therapy at two outpatient clinics. Using linear regression, we examined the impact of baseline radiographic damage assessed by Total Sharp Score (TSS), physical function evaluated with the Health Assessment Questionnaire (HAQ), clinical and laboratory inflammation markers, therapy, and patient characteristics on functional improvement during therapy.

Results: We included 311 patients with a mean age of 61.5 years and average disease duration of 17.1 years in our analyses. Baseline radiographic damage (higher TSS) was significantly associated with HAQ worsening during a mean follow-up of 1.75 years. Over the entire TSS range (0-448 points), a 1 point elevation of TSS at baseline worsened HAQ by 0.002 units (95% CI 0.001-0.003). However, for baseline TSS scores between 30 and 70, HAQ progressed by 0.011 units per 1 unit rise in TSS (for men), versus 0.002 units for TSS>70. Patients with more baseline tender joints and those not

treated with biological therapies had more HAQ progression, but patients with higher baseline HAQ, and more swollen joints had HAQ improvement.

Conclusions: In a patient population with relatively low baseline radiographic damage despite 17 years of disease, a one point rise in TSS falling between 30 to 70 affects HAQ progression more so than TSS in other ranges. Our findings emphasize the importance of vigorous therapeutic efforts to prevent radiographic progression especially in this group.

Acknowledgements

I am very thankful to my mentors Dr. John Wong, Dr. John Griffith and Dr. Josef Smolen, whose guidance and tremendous support enabled me to accomplish this work.

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Introduction

Rheumatoid arthritis (RA) is a severe and frequently disabling condition. Due to chronic inflammation of the synovial joints, patients experience swelling, pain and stiffness, joint damage, and impaired physical function that significantly affects their quality of life.[1] If disease activity cannot be controlled, the capacity to be employed may be limited or lost.[2,3] With effective therapies that inhibit chronic inflammation, however, improvement has become possible in the majority of patients. The optimal use of synthetic disease modifying antirheumatic drugs (DMARDs), such as methotrexate (MTX), has dramatically ameliorated outcomes, and further improvement has been introduced with the development of biological drugs that target cytokines such as tumor necrosis factor and interleukin-6 receptor, T-cell co-stimulation or B-cells.

Physical function is the main determinant of patients' quality of life[1] and working capacity,[4-6] so improvement of function (or at least prevention of functional decline) is of utmost importance. However, physical function is comprised of reversible inflammatory and irreversible joint damage components, with the latter observable on radiographs.[7] Consequently, extensive radiographic damage at baseline may limit the achievable functional improvement in patients with advanced disease.[8] Up to now, only a few studies have investigated factors that influence physical function at the end of follow-up. Published analyses mostly have been developed from studies on patients participating in clinical trials.[9,10] However, clinical trial patients do not fully reflect those seen in routine clinical practice,[11] so it remains uncertain if these trial data linking radiologic joint damage to physical function also apply to the general RA patient population. Where

observational data have been analyzed, only long-term associations from a minimum of 3 years up to 12 years have been investigated,[12,13] but EULAR guidelines suggest evaluation of therapeutic response as early as 3 to 6 months after initiating a new therapy.[14] Thus assessing short-term change in function and their relationship to radiographic damage is pivotal.

The aim of the present study was to investigate factors that determined short-term functional change in a cohort of real life patients receiving treatment for RA. Among the predictors of functional response, our main interest was the effect of baseline radiographic damage on functional improvement during therapy.

Rheumatoid arthritis and disease assessment: see Appendix I

Methods

Patient Population

We used prospectively collected data from two rheumatology outpatient clinics. To evaluate response to initiation of a new therapy, patients who started either DMARDs or biological therapy between January 2000 and December 2006 were entered into a prospective database. Initiation of the new therapy was due to insufficient response to previous therapies (73%) or adverse events (27%). At each clinic visit, the following patient characteristics and disease activity variables were captured: swollen- and tender joint counts (SJC28, TJC28), acute phase reactants (C-reactive protein [CRP] and

erythrocyte sedimentation rate [ESR]) as well as patient global assessment- (PGA) and evaluator global assessment (EGA) of disease activity on a 100 mm visual analogue scale, and assessment of physical functioning (HAQ). Composite measures of inflammatory disease activity, such as the disease activity score DAS28,[15] the simplified and the clinical disease activity index (SDAI[16] and CDAI[17]) were calculated according to established formulae *(see Appendix I)*. X-rays were performed at baseline and approximately annually during follow-up.

Outcome and Main Predictor Variable

Outcome: HAQ-change. Our dependent variable of interest was the change in physical function between baseline and endpoint assessment, as measured by the Health-Assessment Questionnaire (HAQ).[18] This patient reported score of functionality is derived as the mean of the worst evaluation of 20 questions in 8 domains of physical function (dressing, rising, eating, walking, hygiene, reach, grip, and chores; *see Appendix I*). It uses an ordinal scale from 0 to 3, where higher values indicate worse function (allowing for a range of the variable “HAQ change” from -3 to +3. The minimally clinically important difference (MCID) in HAQ has been determined to be 0.22.[19]

Predictor: Baseline Radiographic Damage. The main independent variable was structural joint damage, as evaluated at baseline from x-rays of hands and feet that were assessed by use of the van der Heijde-modified Sharp Score (“Total Sharp Score”, TSS), a radiographic scoring system with a range from 0-448.[20] The score is the sum of the total erosion score (ES; range 0-280), reflecting bony damage, and the joint space narrowing score (JSN; 0-168), reflecting cartilage damage. Higher scores indicate more

structural damage *(see Appendix I)*. We implemented TSS in our model as a continuous variable and analyzed separate ranges of baseline TSS for their influence on HAQ change, testing the hypothesis that the impact (as expressed in the beta value of the regression) would vary between different levels of baseline radiographic damage. We explored predictor-response relationships in a generalized additive model and fitted a regression to piecewise linear ranges of TSS.

Statistical Analysis

To analyze changes in disease activity scores, HAQ and TSS between baseline and follow-up visits, we used t-tests. We used linear regression models and analysis of variance to explore univariate associations of change in HAQ score with TSS and HAQ at baseline, as well as baseline inflammation markers (CRP, ESR), numbers of swollen and tender joints, composite disease activity scores (DAS28, SDAI, CDAI), seropositivity, age, disease duration, and gender. To adjust treatment with DMARDs alone or in combination with biological agents, we included treatment as a categorical 3-level class variable (1) traditional disease modifying drugs other than methotrexate [DMARDs], (2) methotrexate [MTX] and (3) biologicals in combination with MTX or other DMARDs and tested for interaction between type of treatment and patient- or disease activity related factors. All variables that were statistically significant at a $p<0.05$ level in these analyses were considered candidates for the stepwise inclusion in the final multivariable model. In a multivariable linear regression model, we assessed the impact of baseline radiographic status and other factors on functional response to therapy. All

analyses were carried out by use of SAS 9.2. statistical software. (*Linear regression model: see Appendix II)*

Sample Size

Based on published data,[9,10,12,13,21] we estimated the correlation coefficient of the radiographic score at baseline with functional change during therapy to be at least 0.2. At a type I error-level of 0.05 in a two-sided test and for a statistical power of at least 90%, this required a sample size of 260 patients, given the low correlation coefficient.

Results

Study Population

In the 311 patients in our analysis, 81% were female, mean age was 61.5 years and average disease duration was 17.1 years (Table 1). At baseline, the mean disease activity (DAS28) was 3.6±1.4, with 42.5% having moderate (DAS28>3.2) and 16.5% having high (DAS28>5.1) disease activity. Baseline HAQ score was 0.9±0.7, and baseline Total Sharp Score (TSS) was 52.7±57.0, consisting of Joint Space Narrowing scores (JSN) of 36.4±32.4, and Erosion Scores of 16.3±27.9. The mean time of follow-up was 1.75±0.68 years, with an average of 9.2±5.9 months from baseline to visit 2, and 12.2±4.7 months from visit 2 to visit 3, respectively.

Disease characteristics during follow-up (Figure 1): Mean DAS28 as a measure of inflammation decreased significantly between baseline assessment and visit 2 (3.6 to 3.4; $p<0.001$) and between baseline and visit 3 (3.6 to 3.2; $p<0.001$). Similarly, HAQ measured physical function improved from baseline to visit 2 (after a mean interval of 9.2 months), but this improvement was not statistically significant. Between baseline and visit 3 however, HAQ decreased significantly (from 0.9 to 0.8; $p<0.05$). TSS increased significantly during follow-up (52.7 to 62.1; $p<0.001$). Figure 1 displays disease activity scores and HAQ during follow-up. For the regression model, we chose the 3rd visit as the endpoint after a mean follow-up of 1.75 years because HAQ change versus baseline became significant.

Regression Model

Table 2 specifies the regression model (R^2 of 0.32), parameter estimates and levels of significance of all included variables: baseline TSS and HAQ, numbers of swollen and tender joints, and gender, and therapy. Baseline HAQ was the strongest predictor of HAQ change. A higher HAQ score at treatment initiation predicted significantly more improvement after a 1.75 year follow-up. Similarly, a higher initial number of swollen joints predicted more HAQ change, while in contrast, every additional tender joint at baseline predicted less HAQ improvement. In general, functional improvement was less pronounced in women than in men. Importantly, women with radiographic scores between a TSS of 30 to 70 had less worsening of their HAQ than men with comparable TSS scores. However, for TSS >70, this difference between men and women was not confirmed.

We did not find a significant association between disease duration or age and functional change. Similarly, seropositivity for ACPA or RF, baseline laboratory markers of inflammation (CRP and ESR), and the composite disease activity scores DAS28, SDAI, CDAI were not significant in preliminary univariate analyses. Therefore, these variables were not included in the final model (see Table 2).

Treatment: Not unexpectedly, the type of therapy showed significant impact on functional improvement. Significant superiority of biologicals with MTX versus MTX monotherapy was evident, and, even more so, when biologicals were compared with other DMARDs (Table 2). Importantly, there was no interaction between treatment and any of the patient-related variables, so that a higher therapeutic benefit in a specific group of patients could not be identified, such as those with inflammation.

Baseline Radiographic Damage

Sharp Score at baseline was significantly associated with HAQ change. Overall, patients with higher TSS at baseline had less pronounced HAQ improvement. Over the whole range of the TSS from 0-448, a 1 point elevation (i.e., deterioration) of TSS led to a 0.002 (95% CI 0.001-0.003) point HAQ worsening (times the baseline HAQ), i.e., a smaller HAQ improvement would have occurred in an identical patient with the same baseline HAQ, swollen and tender joint counts, gender, and treatment but who had a 1 point higher TSS.

When applying the model separately on piecewise linear ranges of TSS, we did not find a significant association between baseline TSS below 30 with HAQ change, but for TSS between 30 and 70, HAQ function worsened by 0.011 points (times the baseline HAQ) at follow-up for every one point increase in baseline TSS for men. Above a baseline

TSS of 70, the influence was still significant, but the slope flattened with a one point increase in baseline TSS leading to a 0.002 point worsening increase in HAQ. Exploratory analyses showed a trend toward less HAQ worsening beyond TSS values of 200, but sparse data in the highest range did not allow for firm conclusions. Translating these findings into their clinical significance involves applying the minimally clinical important differences (MCID) in HAQ change ($\geq$0.22)[19] so that a 20 point higher baseline TSS for men with mild baseline radiographic damage (TSS between 30 and 70 points) would make a clinically important outcome difference after 1.75 years (when compared to the improvement that this patient would have without the 20 point higher baseline TSS). In men or women patients who have already accrued moderate to severe radiographic damage (TSS ≥70) at baseline, a higher baseline TSS still implies a clinically significantly worsened change in HAQ function over 1.75 years, but the initial TSS would need to be 110 points higher.

Linear regression model: see Appendix II

Discussion

Summary

In an observational cohort of “real life” patients, this analysis shows that gender, baseline tender and swollen joint counts, radiographic damage and therapy significantly affect functional improvement over 1.75 years of follow-up. Higher baseline radiographic damage led to worsening physical function (less improvement). A 1 point higher

baseline TSS had greater impact on functional improvement for patients with baseline TSS in the range of 30-70 than for patients with TSS from 0-29 or >70. Consequently, in patients who develop joint damage, preventing radiographic progression has the most dramatic impact on function at relatively early stages of radiographic damage.

Predictors of worsening HAQ included tender joint counts, therapy not including a biological agent, and a higher baseline HAQ which was the strongest factor. Factors that predicted functional improvement included tender joint count and female gender.

Importantly, the characteristics of the patients in our cohort differ substantially from clinical trial populations.[11] First, most patients had mean disease activity scores in the low to moderate range rather than high activity. Second, the baseline HAQ in our investigation was 0.9 and not 1.5-1.8 as in most clinical trials. Third, disease duration was substantially longer than those in clinical trials.

Despite these differences, our analysis provides confirmation of the impact of baseline function in a population whose disease duration is substantially longer and whose initial function is half as much impaired. In previous sub-analyses of clinical trial data,[9,22] greater joint damage at baseline has been linked to less improvement in physical function after treatment. A change of 1 point on the TSS scale contributed to 0.01 increase of irreversible disability on the 0-3 scale of the HAQ[22], similar to our finding for individuals with baseline TSS between 30 and 70 (1 TSS point corresponding to 0.011 HAQ change). A previous cross-sectional analysis of trial data[22] found a sigmoidal relationship between TSS and HAQ function but was limited to TSS scores ranging from 11 to 75. Our analysis also finds a sigmoidal relationship but over a broader range of structural damage (TSS from 0 to 302), and we specify the impact of

per-point TSS increase at baseline. Third, this analysis finds physical function at baseline to be significantly associated with functional response; indeed, it had an even stronger effect on HAQ improvement than the radiographic score at baseline which is consistent with previously reported analyses of trial data.[9]

Limitations

The relatively small R^2 of the final model must be considered a limitation. Our sample size was restricted to the number of patients initiating a new therapy, thereby likely mitigating our power to detect some associations. For example, in contrast to previous reports, we were unable to find a statistically significant relationship between baseline TSS 0-29 on HAQ change or a significant relationship between more effective treatment and inflammation on HAQ change because presumably ineffectively treated inflammation leads to future radiographic damage. Similarly, ideally, our analysis would examine HAQ change over 6 months to be consistent with current guidelines, but our population necessitated 1.75 years follow up for the change in HAQ to be statistically significant. Lastly, since piecewise linear fitting of the influence of TSS may lead to overfitting the local data these analyses may need further validation on an external dataset.

Conclusion

Our study contributes findings from a large real-life observational patient cohort that quantifies the influence of baseline radiographic damage and other patient- or therapy-related factors including baseline physical function on functional improvement over one

and one-half years. The model includes variables with face validity regarding their influence on functional improvement. It shows clearly that TSS at baseline was significantly associated with functional improvement during therapy, so structural damage also matters when patients are in moderate disease activity states and have lower baseline HAQ levels than the usual characteristics of clinical trial populations. Our model also specifies the influence of preexisting radiographic damage on HAQ improvement and differentiates influence based on TSS ranges. In addition, it corroborates earlier findings of the importance of baseline functional state in a cohort with relatively low functional impairment at the start of therapy. Finally, it confirms significant associations between baseline swollen and tender joint count and gender with functional improvement. The particular clinical value of our results lies in the identification of a patient group that is at high risk for limited functional response, in whom therapeutic approaches should be more aggressive to avert progressive irreversible disability.

Bibliography

1. Knittle KP, De Gucht V, Hurkmans EJ, et al. Effect of self-efficacy and physical activity goal achievement on arthritis pain and quality of life in patients with rheumatoid arthritis. Arthritis Care Res (Hoboken) 2011;63(11):1613-9.
2. Ter Wee MM, Usan H, et al. The effect of biological agents on work participation in rheumatoid arthritis patients: a systematic review. Ann Rheum Dis 2012;71(2):161-71. Epub 2011 Oct 13.
3. Kessler RC, Maclean JR, Petukhova M, et al. The effects of rheumatoid arthritis on labor force participation, work performance, and healthcare costs in two workplace samples. J Occup Environ Med 2008;50(1):88-98.
4. Kavanaugh A, Han C, Bala M. Functional status and radiographic joint damage are associated with health economic outcomes in patients with rheumatoid arthritis. J Rheumatol 2004;31(5):849-55.
5. Young A, Dixey J, Kulinskaya E, Cox N, Davies P, Devlin J, Emery P, Gough A, James D, Prouse P, Williams P, Winfield J. Which patients stop working because of rheumatoid arthritis? Results of five years' follow up in 732 patients from the Early RA Study (ERAS). Ann Rheum Dis 2002;61(4):335-40.
6. Smolen JS, Han C, van der Heijde D, Emery P, Bathon JM, Keystone E, Kalden JR, Schiff M, Bala M, Baker D, Han J, Maini RN, St Clair EW. Infliximab treatment maintains employability in patients with early rheumatoid arthritis. Arthritis Rheum 2006;54(3):716-22.
7. Aletaha D, Smolen J, Ward MM. Measuring function in rheumatoid arthritis: Identifying reversible and irreversible components. Arthritis Rheum 2006;54(9):2784-92.
8. Aletaha D, Strand V, Smolen JS, Ward MM. Treatment-related improvement in physical function varies with duration of rheumatoid arthritis: a pooled analysis of clinical trial results. Ann Rheum Dis 2008;67(2):238-43.
9. F C Breedveld, C Han, M Bala, et al. Association between baseline radiographic damage and improvement in physical function after treatment of patients with rheumatoid arthritis. Ann Rheum Dis 2005;64:52–55.
10. D van der Heijde, R Landewé, R van Vollenhoven, et al. Level of radiographic damage and radiographic progression are determinants of physical function: a longitudinal analysis of the TEMPO trial. Ann Rheum Dis 2008;67:1267-1270.
11. Sokka T, Pincus T. Most patients receiving routine care for rheumatoid arthritis in 2001 did not meet inclusion criteria for most recent clinical trials or american college of rheumatology criteria for remission. J Rheumatol 2003;30(6):1138-46.
12. Ødegård S, Landewé R, van der Heijde D, et al. Association of early radiographic damage with impaired physical function in rheumatoid arthritis: a ten-year, longitudinal observational study in 238 patients. Arthritis Rheum 2006;54(1):68-75.

13. 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 follow-up. Arthritis Rheum 2002;47(4):383-90.
14. Smolen JS, Landewé R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. Ann Rheum Dis 2010;69(6):964-75.
15. Prevoo ML, van't Hf MA, Kuper HH, et al. Modified disease activity scores that include twenty-eight joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38:44-48.
16. Smolen JS, Breedveld FC, Schiff MH, et al. A simplified disease activity index for rheumatoid arthritis for use in clinical practice. Rheumatology (Oxford) 2003;42:244-257.
17. Aletaha D, Nell VP, Stamm T, et al. Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical activity score. Arthritis Res Ther 2005;7:R796-806.
18. Fries JF, Spitz PW, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum 1980;23:137-145.
19. Tugwell P, Wells G, Strand V, et al. Clinical improvement as reflected in measures of function and health-related quality of life following treatment with leflunomide compared with methotrexate in patients with rheumatoid arthritis: Sensitivity and relative efficiency to detect a treatment effect in a twelve-month, placebo-controlled trial Arthritis & Rheumatism 2000;43(3):506–514.
20. van der Heijde DM, van Leeuwen MA, van Riel PL, et al. Radiographic progression on radiographs of hands and feet during the first 3 years of rheumatoid arthritis measured according to Sharp's method (van der Heijde modification). J Rheumatol 1995;22(9):1792-6.
21. Scott DL, Pugner K, Kaarela K, et al. The links between joint damage and disability in rheumatoid arthritis. Rheumatology (Oxford) 2000;39(2):122-32.
22. Smolen JS, Aletaha D, Grisar JC, et al. Estimation of a numerical value for joint damage-related physical disability in rheumatoid arthritis clinical trials. Ann Rheum Dis 2010;69(6):1058-64.

Tables

Age [yrs.]	63.5 (52.8, 70.3)
Disease duration [yrs.]	14.7 (10.2, 20.7)
Female [%]	81%
Methotrexate only [%]	66.9%
DMARDs other than methotrexate [%]	21.1%
Biological therapy [%]	12%
C-Reactive Protein [mg/dl]	0.6 (0.5, 1.4)
Swollen Joint Count (SJC28)	3.0 (1.0, 5.0)
Tender Joint Count (TJC28)	1.0 (0, 5.0)
Patient Pain Assessment [VAS]	29.0 (12.8, 47.3)
Patient Global Assessment [VAS]	30.0 (13.8, 49.0)
Evaluator Global Assessment [VAS]	24.0 (12.0, 39.0)
HAQ	0.9 (0.3, 1.4)
Disease Activity Score (DAS28)	3.5 (2.5, 4.6)
Simplified Disease Activity Score (SDAI)	12.0 (6.3, 20.1)
Clinical Disease Activity Score (CDAI)	10.3 (5.3, 18.6)
Total Sharp Score (TSS)	34.0 (16.1, 69.6)

Table 1. Patients' baseline characteristics. N=311. values are median (25^{th} and 75^{th} percentile), where applicable (otherwise percentages). VAS (visual analogue scale) ratings are on 0 to 10 centimeter scales.

Variable	**Beta (SE)**	**p-value**
Intercept	-0.8 (0.15)	0.61
Baseline Total Sharp Score (TSS): range 30-70	0.011 (0.004)	<0.01
range 71-400	0.002 (0.0006)	<0.01
Baseline physical function [HAQ]	-0.39 (0.05)	<0.0001
Number of swollen joints at baseline LN(SJC28+1)	-0.12 (0.04)	<0.01
Number of tender joints at baseline TJC28	0.03 (0.008)	<0.01
Female gender	0.26 (0.09)	<0.01
Interaction term: female * TSS (30-70)	-0.01 (0.004)	<0.05
Therapy: DMARDs other than MTX vs. biological therapy	0.19 (0.13)	<0.05
MTX monotherapy vs. biological therapy	0.08 (0.12)	<0.05

Table 2. Regression model. Dependent variable: change from baseline to visit 3, with a mean(SD) interval of 21.4 (6.7) months; LN(SJC28)…natural log of swollen joint count28; DMARDs… disease modifying antirheumatic drugs, MTX…methotrexate, HAQ…Health Assessment Questionnaire-Disability Index, TSS…Total Sharp Score

Figure

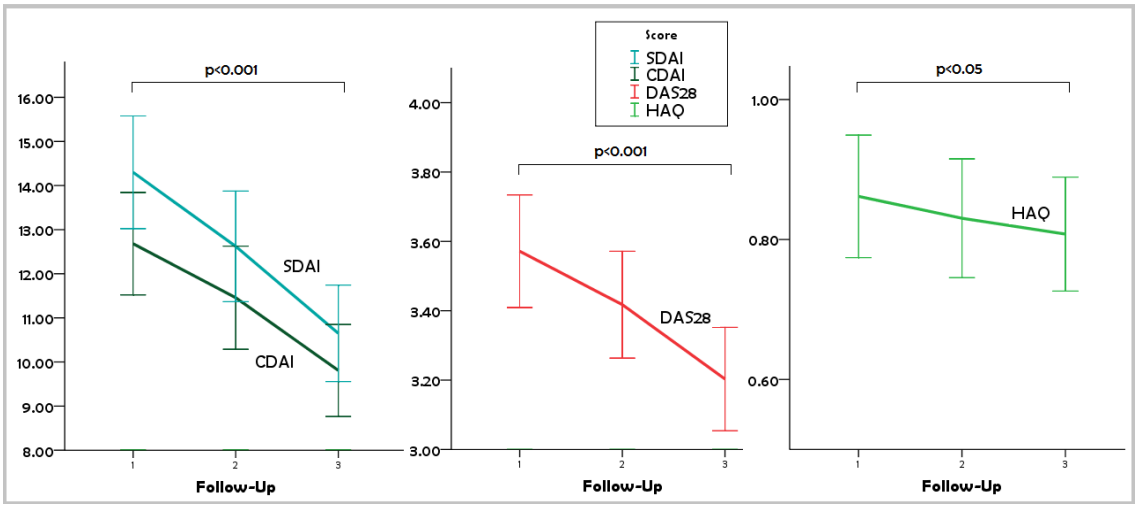


Figure 1. Disease activity scores and function during follow up.

CDAI…clinical disease activity index, SDAI…simplified disease activity index, DAS28…disease activity score using a 28-joint count, HAQ…health assessment questionnaire - disability index. The x-axis indicates follow-up assessments from baseline (visit 1) to visit 3. The mean time of follow-up was 1.75 years. The mean±SD time from baseline to visit 2 was 9.2±5.9 months, and the interval between visit 2 and 3 was 12.2±4.7 months.

Appendices

I. *Appendix I Background: Rheumatoid arthritis and disease assessment*
II. *Appendix II Methods: Linear regression model*

APPENDIX I

Rheumatoid Arthritis

Disease and Assessment; Therapeutic Options and Targets

Disease and Assessment, Therapeutic Options and Targets

Rheumatoid Arthritis – Epidemiology and Clinical Presentation

Rheumatoid arthritis (RA) is a chronic inflammatory disease of unknown origin, with a prevalence of 1% worldwide.[A1] It occurs more often in women than in men, with a reported ratio between 2:1 and 4:1.[A1,A2] The onset typically lies between the age of 40 and 50 years, with a characteristic presentation of acute tenderness and swelling in synovial joints. Synovitis shows a typical pattern with symmetrical involvement of the metacarpophalangeal joints (MCPs) and proximal interphalangeal joints (PIPs), predominantly of the hands.[A3] However, the clinical presentation can vary to a great extent, with a subset of patients experiencing an onset beyond the age of 60 years,[A4] or at a very early age. Also, a graduate start of symptoms over weeks to months has been described in approximately 50% of patients, while 15% have a highly acute onset with symptoms developing within days.[A1,A5] Lastly, joint involvement at early presentation can differ from the more characteristic pattern and instead show mono- or oligoarticular involvement, or affect some of the larger joints like shoulders or knees.[A2] The diagnostic criteria for RA have only recently been revised[A6], and are now based on the following: (a) synovitis in ≥1 joint, (b) lacking a more likely diagnosis, and (c) the achievement of ≥6 points out of 10 in four domains: (I) number and site of involved joints (range 0–5), (II) serological abnormality (range 0–3), (III) elevated acute-phase response (range 0–1) and (IV) symptom duration (two levels; range 0–1). The criteria and scores are enlisted in Table A1.

Once RA is suspected, appropriate therapy should be started promptly. In the last decade, therapeutic options have been significantly expanded, and also treatment concepts and targets have undergone a dramatic shift: In earlier years, the so-called „treatment pyramid“ symbolized a stepwise approach that started with non-steroid antiinflammatory drugs (NSAIDs)[A1,A7]. Only in case of progressive disease - documented by radiographic damage – therapy was intensified by disease modifying antirheumatic drugs (DMARDs). However, if synovitis cannot be suppressed by antiinflammatory drugs, chronic inflammation leads to pannus proliferation and progressive joint damage with loss of function. Typically, deformations of wrists and hands like the „swan-neck deformity“ (that results from flexion of the DIP and MCP joints, with hyperextension of the PIPs) are among the adverse outcomes of advanced disease that significantly limit function.[A1] Consequently, a rapid and aggressive treatment escalation, especially in early disease, is nowadays emphasized,[A8] since broad evidence supports a therapeutic window of opportunity for halting radiographic damage in early disease.[A9] Moreover, insufficiently treated chronic inflammation has been linked to increased cardiovascular risk[10] and a higher overall mortality.[A11,A12]

Therapeutic Options and Targets

Treatment Options: The first therapeutic step for a newly diagnosed patient is usually one of the traditional “synthetic” DMARDs. Among these agents, especially methotrexate has often been called the “anchor” drug for RA treatment due to it’s high effectiveness in a large proportion of patients.[A13-A15] However, in some cases, DMARDs cannot suppress disease activity sufficiently. Especially for these patients, RA treatment

has undergone tremendous progress in the last years. The armamentarium of available drugs that are licensed for DMARD-non-responders, has rapidly increased, since some of the pro-inflammatory cytokines, that have been linked to the development of disease, are used as therapeutic targets.[A16] Table A2 enlists the currently licenced agents and their target structures.

Economic Implications: Inflammatory rheumatic diseases in general have substantial financial implications.[A17-A20] In RA, biological antirheumatic drugs have led to marked improvements in disease activity and joint damage, but have dramatically raised direct medical costs.[A21] Contrariwise, since RA often affects people at an age of high work productivity, a decline in physical functioning is frequently linked to less working capacity.[A22,23] Therefore, the considerably more costly biological therapies appear to provide sufficient cost-effectiveness.[A24] Also, an “aggressive”, i.e., rapidly switching and adaptive approach was found cost-effective in comparison to a more conservative approach due to an offset of initially higher costs of intensive treatment by considerably lower costs of late sequelae.[A25]

Assessment of Disease Activity; Remission

Clinical Assessment - Disease Activity Scores

Clinical assessment and documentation of disease activity in RA is usually conducted by use of composite scores. Benefits of such measures are an increased power, easier interpretation of data,[A26] and the possibility of categorization into different disease activity states. If these indices employ measures related to long-term outcome and comprise patient-, physician- and biology- related measures, they can capture the

disease process very accurately.[A27,28] The most widespread used scores are the Disease Activity Score (DAS28),[A29] the Simplified Disease Activity Index (SDAI)[A30] and the Clinical Disease Activity Index (CDAI)[A31]. All of these include patient- reported evaluation of disease activity by visual analogue scale ratings (VAS). In addition, with the tender joint count (TJC), one other at least partly patient-based component is reflected. Formulae for derivation of disease activity scores are as follows:

Disease Activity Score using 28-joint counts:

$$DAS28^{A29} = 0{,}56 * \sqrt{TJC} + 0{,}28 * \sqrt{SJC} + 0{,}7 \times ln(ESR) + 0{,}0142 * PtVAS$$

Simplified Disease Activity Index:

$$SDAI^{A30} = TJC + SJC + PGA + CRP + EGA$$

Clinical Disease Activity Index:

$$CDAI^{A31} = TJC + SJC + PGA + EGA$$

Abbreviations: TJC…tender joint count, SJC…swollen joint count, ln…natural logarithm, ESR…erythrocyte sedimentation rate, ptVAS…patient assessment of global disease activity on a visual analogue scale, PGA…patient global assessment (VAS), CRP…C-reactive protein (mg/dl), EGA…evaluator global assessment (VAS)

Cut-off values to define remission and low disease activity have been provided and validated for all of the above mentioned scores. However, only very recently, a new set

of criteria has been validated for use as trial endpoint, the so called “Boolean-based definition”, that requires for a patient to be in remission that he or she must satisfy at any time point all of the following items: tender joint count ≤1, swollen joint count ≤1, C-reactive protein ≤1mg/dl, and a patient global assessment on a 0-10 scale of ≤1.[A32] Current consensus statements encourage either Boolean remission criteria, or alternatively, the use of index-based definition by an SDAI of ≤3.[A32]

Functional Assessment – The HAQ

RA patients experience a progressive decline of physical function, initially due to pain and inflammation and subsequently due to structural damage. Assessment of function in RA is predominantly the domain of the Health Assessment Questionnaire (HAQ)-score: The HAQ has been developed to measure the patient’s ability to perform activities of daily living. Introduced by Fries et al.,[A33] the score became a model of patient reported outcomes,[A34] with different versions that vary in length and items assessed. In our dataset, the HAQ-Disability-Index (HAQ-DI) is used, as outlined below (Figure A1). This version includes 20 questions to evaluate 8 different domains of physical function (dressing, rising, eating, walking, hygiene, reach, grip, and chores). The questions are rated by the patient on an ordinal scale from 0 to 3 (verbally anchored from „no difficulties“ to „unable to do“). The overall score is calculated as the mean of each domain’s worst evaluation. The range of the score is 0 to 3, higher scores express worse function. Functional remission has been defined as a HAQ score below 0.5.

X-Ray Assessment – The van der Heijde-Modified Sharp Score

The van der Heijde modified Sharp score (TSS, for “total Sharp Score”) is a radiographic scoring system with a range from 0-448. It is the sum of the Erosion Score (ES) and the Joint Space Narrowing (JSN) score in x-rays of hands and feet in RA patients[A35]. Higher scores indicate more damage. This method is the ‘gold-standard’ for assessing RA radiographs, and is used in the majority of clinical trials and observational studies. In each joint, individual erosions are scored from 0 to 5, depending on the involved surface area, with 1 point for a discrete but clearly present erosion, and 2 or 3 points for larger erosions. A 3 point score is used to describe large erosions that extend over the imaginary middle of the bone. A complete collapse of the joint or the affection of the full surface of the joint is rated with five points. There is a total of 16 areas for possible erosions per hand, the maximum erosion score for each hand is therefore 80 points. Similarly, in each foot, there are 6 erosion areas. In feet assessment, the ES has a range from zero to 10 for each joint, each side of the joint is independently scored from zero to 5. The maximal erosion score per foot is thus 60. JSN and (sub)luxation are again combined in a single score from zero to 4 points. Maximal total erosion score of both hands is 160. Maximal total erosion score of the feet is 120, total ES of hands and feet therefore maximum 280 points.

In addition, for each hand, there are 15 areas for JSN defined. JSN or joint-(sub)luxations are rated with a combined score, ranging from zero to 4 points. A normal joint space is scored 0. A generalized narrowing leaving more than 50% of the original joint space present is scored 2. A generalized narrowing that leaves less than 50% of the original joint space present is scored 3, also a subluxation is scored with 3 points. A

bony ankylosis or a complete luxation of the joint is scored 4. Maximal total narrowing/(sub)luxation score is 120 in the hands, and 48 points in the feet, with a sum of 168 for maximal total narrowing/(sub)luxation score of hands and feet. The maximal Total Sharp Score is the sum of all: 448 points. The Smallest Detectable Difference is between 5 and 8 points.[A36] Scoring sheets are shown in Figure A2.

Joint Damage and Physical Function in RA

Loss of function leads to reduced quality of life for the patient, and to considerable impact on societal costs of disease due to reduced work capacity. Biological drugs have significantly higher cost than DMARDs, yet their ability to keep patients in the working process leads to reduced societal cost of disease. Health economic models have been used to assess long-term benefit due to better outcome with biologicals. Therefore, since burden of disease and treatment outcome are primarily determined by the functional status of patients, the assessment of function in RA is crucial in the evaluation of individual patients as well as in health economic evaluations. Importantly, the HAQ score depends mainly on two contributory factors: current inflammatory disease activity, which is reversible and structural joint damage, which is irreversible. In any patient, the proportion of disability attributable to these two factors can vary considerably, yet result in the same overall HAQ score.[A37] Since HAQ is used in cost-effectiveness analyses as surrogate for cost and utility alike,[A38] evaluating the impact of TSS as HAQ's irreversible component may have important impact on health economic assessment.

Tables

	Score
Target population (who should be tested?): patients who	
1) have at least one joint with definite clinical synovitis (swelling)*	
2) with the synovitis not better explained by another disease†	
Classification criteria for RA (score-based algorithm: add score of categories A–D a score of ≥6/10 is needed for classification of a patient as having definite RA)	
A. Joint involvement	
1 large joint¶	0
2–10 large joints	1
1–3 small joints (with or without involvement of large joints)**	2
4–10 small joints (with or without involvement of large joints)	3
>10 joints (at least one small joint)††	5
B. Serology (at least 1 test result is needed for classification)	
Negative RF and negative ACPA	0
Low-positive RF or low-positive ACPA	2
High-positive RF or high-positive ACPA	3
C. Acute-phase reactants (at least one test result is needed for classification)	
Normal CRP and normal ESR 0	0
Abnormal CRP or normal ESR 1	1
D. Duration of symptoms	
<6 weeks	0
≥6 weeks	1

Table 1. The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for RA[6].

Agent	Target	Route of Application
Adalimumab	Human IgG anti TNF mAB	s.c.
Etanercept	Soluble TNF RC linked to IgG Fc fragment	s.c.
Infliximab	Chimeric monoclonal antibody (mAB) against TNF-	s.c.
Golimumab	Human anti TNF	s.c.
Certolizumab	Pegylated anti-TNF	s.c.
Anakinra	Recombinant IL-1 receptor antagonist	s.c.
Tocilizumab	Humanized anti IL-6 Rc mAb	i.v.
Rituximab	Chimeric anti-CD20 mAB	i.v.
Abatacept	Human CTLA4 linked to IgG Fc fragment	i.v.

Table 2. Biological agents licensed for RA treatment.

Figures Appendix I

Are you able to:	Without ANY difficulty	With SOME difficulty	With MUCH difficulty	UNABLE to do
DRESSING				
1. Dress yourself, including tying shoelaces and doing buttons?	0	1	2	3
2. Shampoo your hair?	0	1	2	3
ARISING				
3. Stand up from a straight chair?	0	1	2	3
4. Get in and out of bed?	0	1	2	3
EATING				
5. Cut your meat?	0	1	2	3
6. Lift a full cup or glass to your mouth?	0	1	2	3
7. Open a new milk carton?	0	1	2	3
WALKING				
8. Walk outdoors on flat ground?	0	1	2	3
9. Climb up five steps?	0	1	2	3
HYGIENE				
10. Wash and dry your body?	0	1	2	3
11. Take a tub bath?	0	1	2	3
12. Get on and off the toilet?	0	1	2	3
REACH				
13. Reach and get down a 5 pound object (such as a bag of sugar) from above your head?	0	1	2	3
14. Bend down to pick up clothing from the floor?	0	1	2	3
GRIP				
15. Open car doors?	0	1	2	3
16. Open previously opened jars?	0	1	2	3
17. Turn faucets on and off?	0	1	2	3
ACTIVITIES				
18. Run errands and shop?	0	1	2	3
19. Get in and out of a car?	0	1	2	3
20. Do chores such as vacuuming or yard work?	0	1	2	3

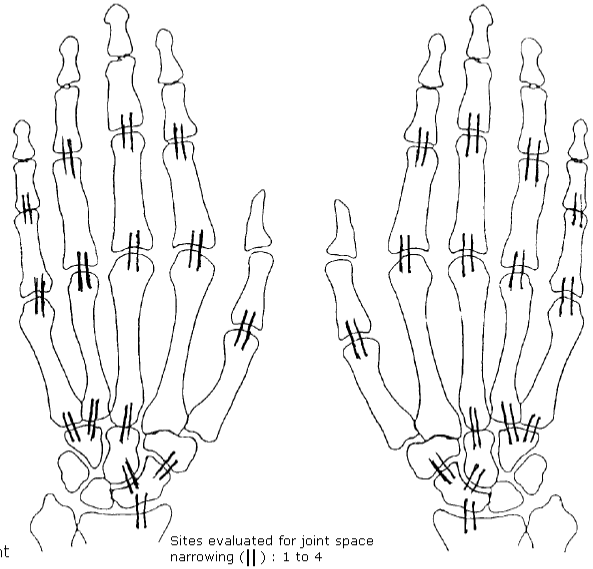
Figure A1. HAQ-DI, the Health Assessment Questionnaire - Disability Index, as used for patient-reported function scoring in RA patients.

Initials of the patient's name : _____ Date : _____ Visit : 1 2 3 4 5

File CHUS : _____

JOINT SPACE NARROWING

Defined periarticular osteopenia ☐



Score

Hands : _____

Feet : _____

Total : _____

Score

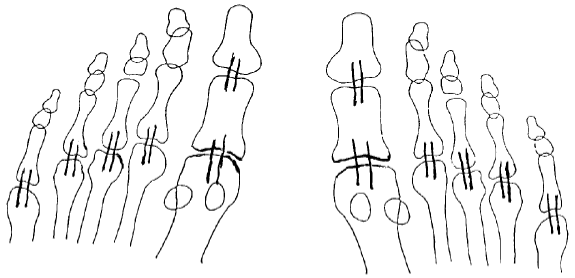
1 = Focal or not important enough to quote 2

2 = >50% space left (generalized narrowing)

3 = <50% space left or subluxation

4 = Complete ankylosis or luxation

Sites evaluated for joint space narrowing (||) : 1 to 4



Sites evaluated for joint space narrowing (||) : 1 to 4

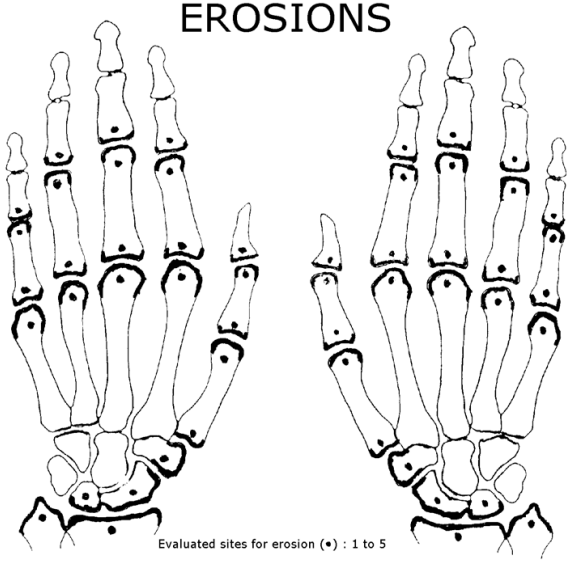
_____ Signature of the evaluator

_____ Date of the evaluation

Initials of the patient's name : _____ Date : _____ Visit : 1 2 3 4 5

File CHUS : _____

EROSIONS



Score

Hands : _____

Feet : _____

Total : _____

SCORE

Evaluated sites for erosion (•) : 1 to 5

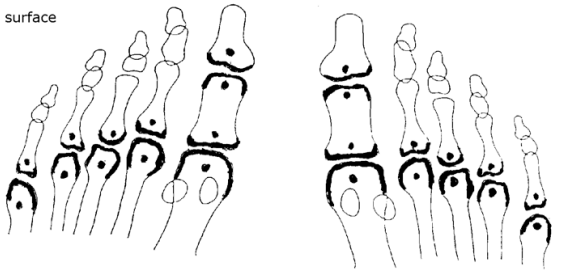
1 = Discreet lesion

2 to 4 = Surface dependant

3 = Reaches >50% of the joint surface

5 = Bone collapsus

P.S. The erosion noted can be caused by R.A. and arthrosis.



Evaluated sites for erosion (•) : 1 to 10 (5 for each side of the joint)

_____ Signature of the evaluator

_____ Date of the evaluation

Figure A2. Total Sharp Score

APPENDIX II

Methods: Linear Regression Model

Regression Model

We developed a multivariable regression model to assess the impact of baseline radiographic status on functional response to therapy. Our main predictor variable was Total Sharp Score at baseline (TSS), the dependent variable the change in HAQ score during follow-up. Given that the change in HAQ is a continuous variable, we fitted a linear regression. To approach this, we first tested the assumptions of a linear regression model, linearity, normality of residuals, and homoscedasticity.

Testing Model Assumptions

We tested model assumptions for linear regression (linearity, normality of residuals, homoscedasticity) by use of residual vs. predictor plots, Kernel-Density estimates and normal quantile-quantile (Q-Q) plots, and transformed variables, if necessary. We identified and checked potentially influential data by use of leverage points and DfBeta plots, and in case of significant distortion in the model, these observations were removed.

We found the assumptions for a linear regression fulfilled in all included variables, except for the SJC28 which had non-constant variance. We therefore used a log-transformed SJC28 term in the model. We also screened the dataset for high leverage observations (extreme observations or outliers), but did not have to exclude data on these grounds.

Linearity

For a first visual checking of linearity, we used residual versus predictor (RVP) plots to test if the linear fits for all variables were met. As displayed in Figure A3 below, fits were satisfactory, with no divergence or nonlinear pattern across the values.

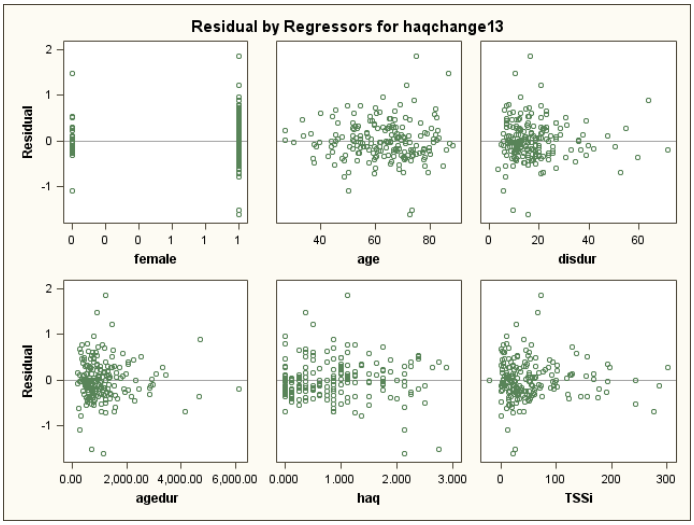
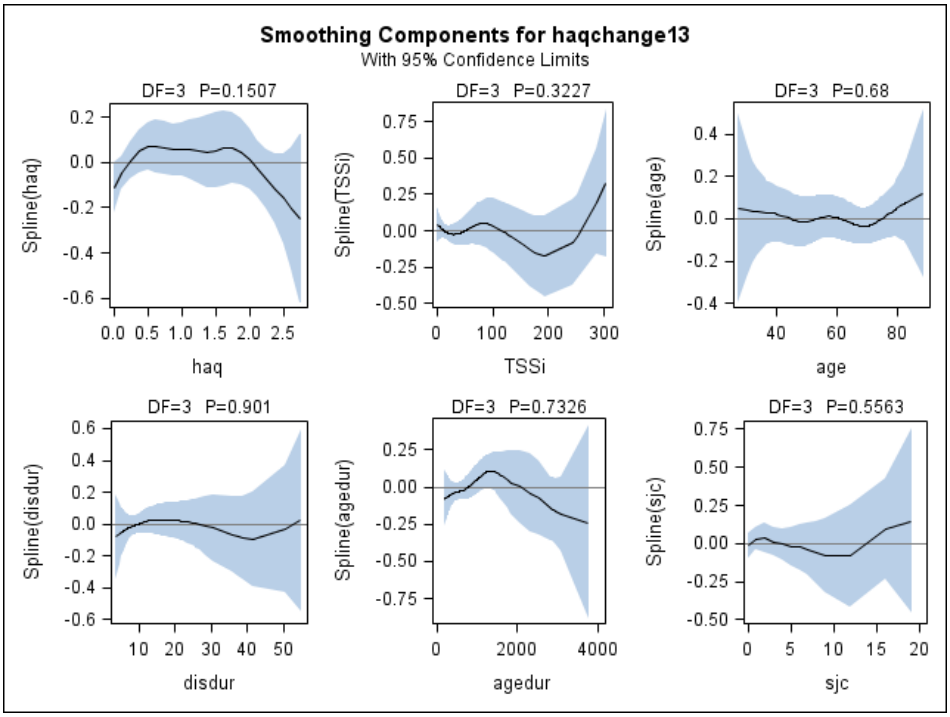


Figure A3. Residual versus predictor plots; Disdur…disease duration, agedur…interaction term between age and disease duration.

We also tested linearity by use of a proc gam model in SAS. The code is given below.

proc gam data=m;
model haqchange13=spline (tssi) spline (haq) spline (age) spline (disdur) spline (agedur) spline (sjc) param (tjc);**run**;
ods html;
ods graphics on;
Proc gam plots=components(clm);
model haqchange13=spline(tssi) spline (haq) spline (age) spline (disdur) spline (agedur) spline (sjc) spline (tjc); **run**;
ods graphics off;
ods html close;

Figure A4 below shows no significant pattern around the horizontal lines for each variable, indicating that linearity assumption was met. For some variables, however, relatively broad 95% confidence intervals (95% CI, blue areas) indicate sparse data in certain ranges, as for instance in very old or very young patients (>80 and <40 yrs. in the “age” variable).



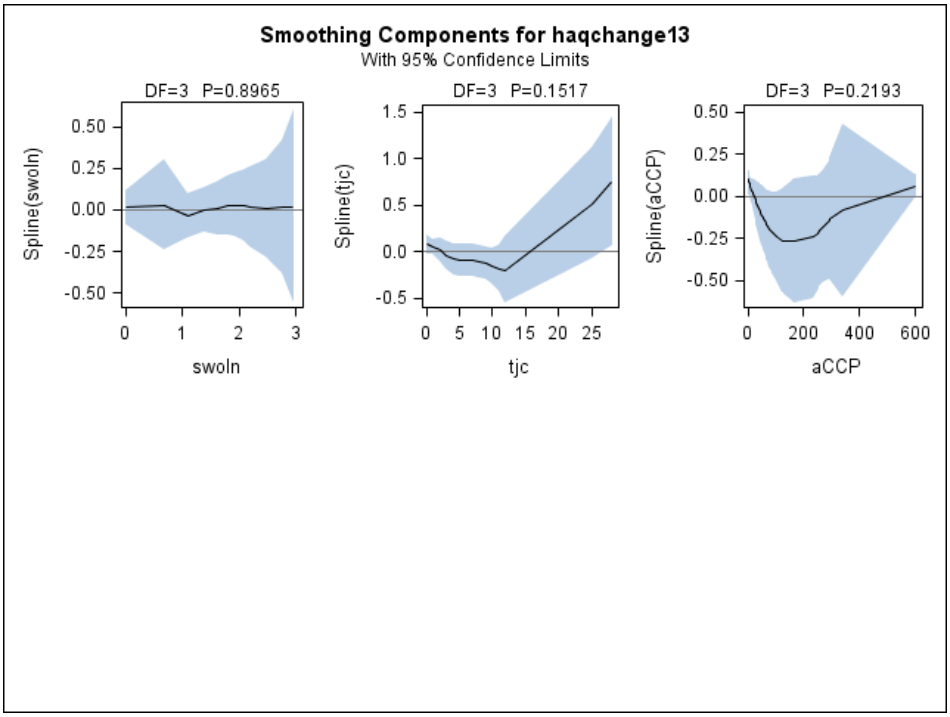


Figure A4. swoln…SJC28, log transformed variable (see below: "homoscedasticity"), tjc…tender joint count, aCCP… anti-cyclic citrullinated peptide antibodies, Disdur…disease duration, agedur…interaction term between age and disease duration.

Normality of Residuals

We tested the assumption of residual normality of the dependent variable by use of Kernel Density Function (Figure A5a), Histograms (Figure A5b), and Boxplots of Residuals (Figure A5c). As illustrated below, we found the assumption met.

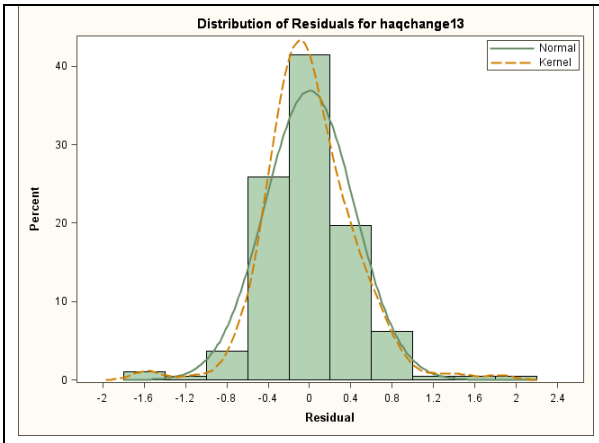


Figure A5a

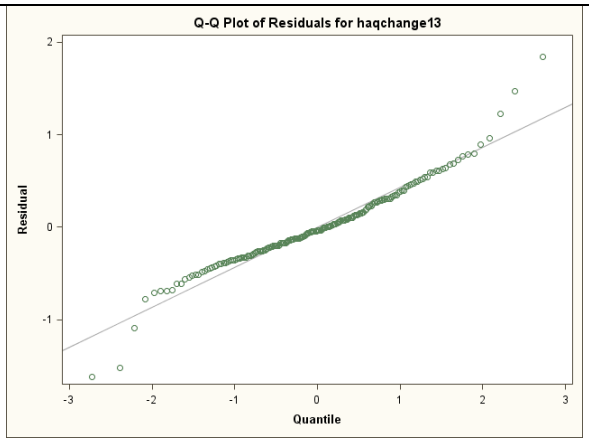


Figure A5b

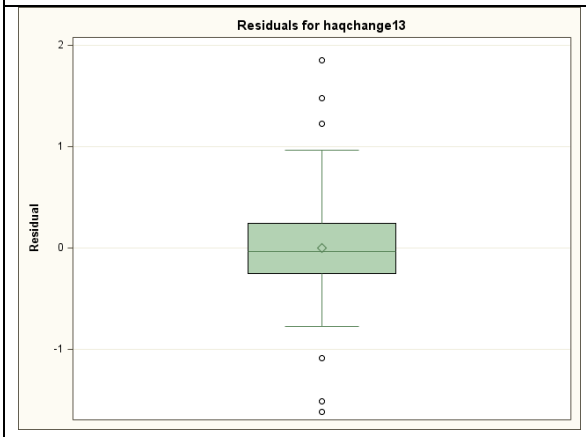


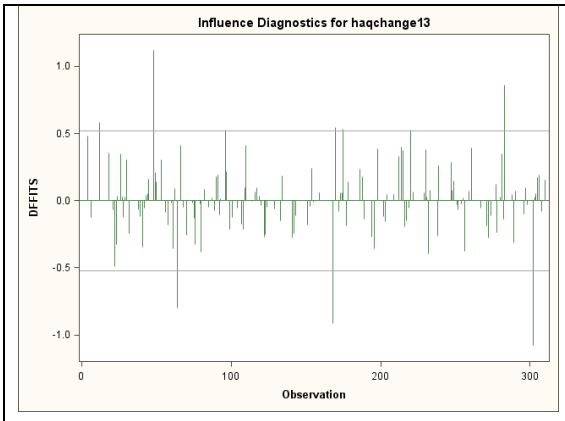
Figure A5c

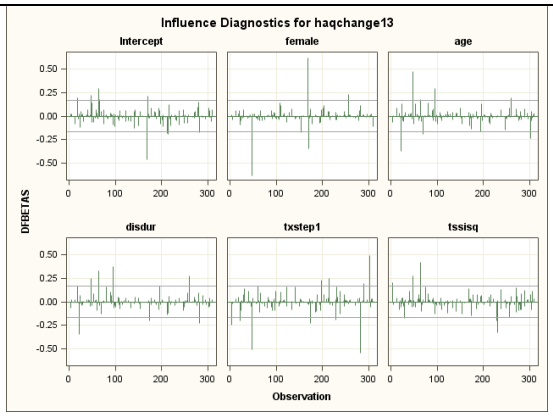
Homoscedasticity

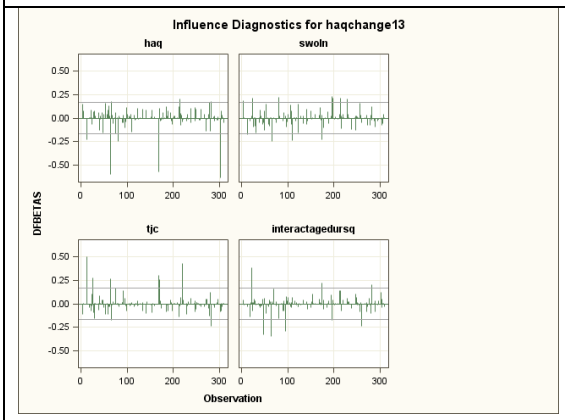
In a last step, we tested homoscedasticity, or homogeneity of variance in our variables. We found that for the independent predictor variable swollen joint count (SJC), a funnel in the residual vs. predicted plots indicated that this assumption was not met. We therefore transformed this variable to stabilize the variance and used the natural logarithm of SJC (ln(SJC) in our model. Given the fact of a number of patients with a SJC of zero at baseline, we further transformed the variable to “ln(SJC+1)” to avoid the problem of a natural logarithm of zero being infinity leading to missing / unusable data.

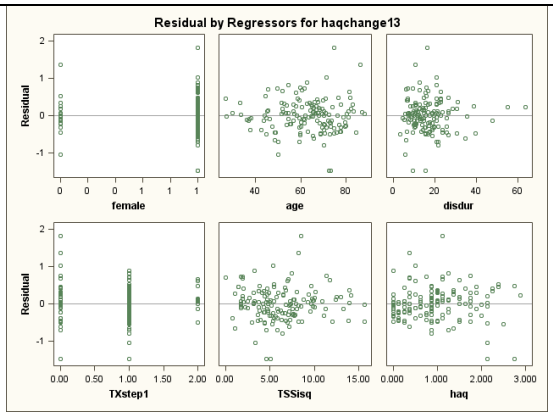
Influential Points – Dfbetas

In a next step, we screened the dataset for high leverage points. We used influence diagnostics to see, how much each of the coefficients would change, if each of the observations were omitted from the data set. Below (Figure A6) are displayed the DF Beta graphs for all included variables, we used of a threshold of 0.5 for a simple outlier and a threshold of 1.0 for high leverage points. We did not have to exclude any observations on grounds of these results.









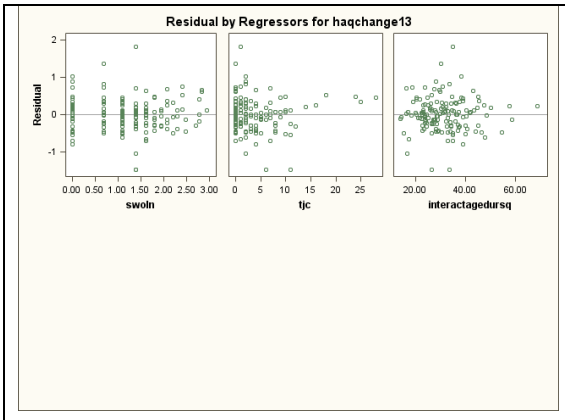


Figure A6. DF Beta

Fitting Piecewise Regression

The graphical display of TSS indicated different ranges of the variable with possibly differing influence, a visual impression that guided our attempt to split the whole range up in different intervals and fit a piecewise regression to TSS. This resulted in the use of 3 new variables, “TSS 0-29”, “TSS 30-70”, “TSS 71-400” (range indicates baseline value in all cases). Introducing these variables in the regression model enabled sub-analyses in addition to the exploration of overall influence of joint damage.

Final Model

As mentioned, we introduced therapy as a categorical class variable, with the 3 levels: (I) “traditional disease modifying drugs (DMARDs) other than methotrexate” (MTX), (II) “MTX” and (III) “biologicals in combination with DMARDs”. Thereby, our final model

was realized instead of a proc reg procedure in SAS in the form of a proc glm (“generalized linear model procedure”), as stated in the following:

```
proc glm; class txstep1;
model haqchange13=txstep1 haq tssi_lin30_70oo tssi_lin70_400oo ln_swollen_neu tjc  female
xfemtssi_lin30_70 /solution ;run;
```

The results of betas and levels of significance are stated in the main manuscript.

Internal Model Validation

We validated our model by use of bootstrap resampling. In this procedure, the distribution of betas in 10,000 random samples was investigated. Variables that were included in the final model had significant p-values (by threshold of <0.05) in 69% (TSS range 30-70) to 100% (baseline HAQ) of random samples.

Bibliography / Appendices

A1) Kelley, Harris, Ruddy, Sledge. Textbook of Rheumatology, 4th Edition. Saunders 1993

A2) Hochberg M, Silman A, Smolen J, et al., (Ed.) Practical Rheumatology. 3rd edition Philadelphia, Elsevier Mosby, 2004

A3) Fauci A, Langford C. Harrison's Rheumatology, 2nd Edition McGrawHill 2010

A4) Lance NJ, Curran JJ. Late-onset, seropositive, erosive rheumatoid arthritis. Semin Arthritis Rheum 1993;23(3):177-82.

A5) Fleming A, Crown JM, Corbett M. Early rheumatoid disease. I Onset. II Patterns of joint involvement. Ann Rheum Dis 1976;35:357-363.

A6) Aletaha D, Neogi T, Silman A, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative Ann Rheum Dis 2010;69:1580-1588 doi:10.1136/ard.2010.138461

A7) Verstappen SM, Jacobs JW, Bijlsma JW, et al. Five-year followup of rheumatoid arthritis patients after early treatment with disease-modifying antirheumatic drugs versus treatment according to the pyramid approach in the first year. Arthritis Rheum 2003;48(7):1797-807.

A8) Smolen JS, Aletaha D, Bijlsma JW, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. Ann Rheum Dis 2010;69(4):631-7.

A9) van Tuyl LH, Felson DT, Wells G, et al. Evidence for predictive validity of remission on long-term outcome in rheumatoid arthritis: a systematic review. Arthritis Care Res (Hoboken) 2010;62(1):108-17.

A10) Willers J, Hahn A. Cardiovascular risk in patients with rheumatoid arthritis: assessment of several traditional risk parameters and a German risk score model. Rheumatol Int 2011 [Epub ahead of print]

A11) Lassere MN, Rappo J, Portek IJ, et al. How many life-years are lost in patients with rheumatoid arthritis? Secular cause-specific and all-cause mortality in rheumatoid arthritis and their predictors in a long-term Australian cohort study. Intern Med J 2012 [Epub ahead of print]

A12) Mikuls TR, Fay BT, Michaud K, et al. Associations of disease activity and treatments with mortality in men with rheumatoid arthritis: results from the VARA registry. Rheumatology (Oxford) 2011;50(1):101-9.

A13) Bijlsma JW, Jacobs JW. Methotrexate: still the anchor drug in RA treatment. Joint Bone Spine 2009;76(5):452-4.

A14) Sokka T, Envalds M, Pincus T. Treatment of rheumatoid arthritis: a global perspective on the use of antirheumatic drugs. Mod Rheumatol 2008;18(3):228-39.

A15) Weinblatt ME, Coblyn JS, Fox DA et al. Efficacy of low-dose methotrexate in rheumatoid arthritis. N Engl J Med 1985;312:818-22.

A16) Harris ED Jr. Rheumatoid arthritis: pathophysiology and implications for therapy. N engl J Med 1990;322:1277-89.

A17) Fautrel B, Clarke AE, Guillemin F, et al. Costs of rheumatoid arthritis: new estimates from the human capital method and comparison to the willingness-to-pay method. Med Decis Making 2007;27:138-50.

A18) Jacobsson LTH, Lindroth Y, Marsal L, et al. Rheumatoid arthritis: what does it cost and what factors are driving those costs? Results of a survey in a community-derived population in Malmö, Sweden. Scand J Rheumatol 2007;36:179-83.

A19) Pugner KM, Scott DI, Holmes JW, et al. The costs of rheumatoid arthritis: an international long-term view. Semin Arthritis Rheum 2000;29:305-20.

A20) Fautrel B, Guillemin F. Cost of illness studies in rheumatic diseases. Curr Opin Rheumatol 2002;14:121-6.

A21) Michaud K, Messer J, Choi HK, et al. Direct medical costs and their predictors in patients with rheumatoid arthritis: a three-year study of 7,527 patients. Arthritis Rheum 2003;48:2750-62.

A22) Burton W, Morrison A, Maclean R, et al. Systematic review of studies of productivity loss due to rheumatoid arthritis. Occup Med (Lond) 2006;56:18-27.

A23) Shanahan EM, Smith M, Roberts-Thomson L, et al. Influence of rheumatoid arthritis on work participation in Australia. Intern Med J 2008;38:166-73.

A24) Schoels M, Wong J, Scott DL, et al. Economic aspects of treatment options in rheumatoid arthritis: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis 2010;69(6):995-1003.

A25) Grigor C, Capell H, Stirling A, et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. Lancet 2004;364:263–9.

A26) Fairclough DL. Summary measures and statistics for comparison of quality of life in a clinical trial of cancer therapy. Stat Med 1997;16:1197-1209.

A27) Goldsmith CH, Smythe HA, Helewa A. Interpretation and power of a pooled index. J Rheumatol 1993;20: 575-578.

A28) Van der Heijde DM, Van't Hof MA, Van Riel PL, et al. Validity of single variables and composite indices for measuring disease activity in rheumatoid arthritis. Ann Rheum Dis 1992;51:177-181.

A29) Prevoo MML, Van't Hof MA, Kuper HH, et al. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38: 48.

A30) Smolen JS, Breedveld FC, Kalden JR, et al. A simplified disease activity index for rheumatoid arthritis for use in clinical practice. Rheumatology (Oxford) 2003;42:244-257.

A31) Aletaha D, Nell V, Stamm T, et al. Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical activity score. Arthritis Research and Therapy 2005;7:R796-R806.

A32) Felson DT, Smolen JS, Wells G, et al. American College of Rheumatology/European League against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Ann Rheum Dis 2011;70(3):404-13.

A33) Fries JF, Spitz PW, Kraines RG, Holman HR Measurement of patient outcome in arthritis. Arthritis Rheum 1980;23:137-145.

A34) Bruce B, Fries JF. The Stanford Health Assessment Questionnaire: dimensions and practical applications. Health Qual Life Outcomes 2003;1:20.

A35) van der Heijde DM, van Leeuwen MA, van Riel PL, et al. Radiographic progression on radiographs of hands and feet during the first 3 years of rheumatoid arthritis measured according to Sharp's method (van der Heijde modification). J Rheumatol 1995;22(9):1792-6.

A36) Van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method. Journal of Rheumatology 2000;27:261-3.

A37) Aletaha D, Smolen J, Ward MM. Measuring Function in Rheumatoid Arthritis; Identifying Reversible and Irreversible Components. Arthritis and Rheum 2006;54(9):2784–2792.

A38) Boggs R, Sengupta N, Ashraf T. Estimating health utility from a physical function assessment in rheumatoid arthritis (RA) patients treated with adalimumab (HUMIRA). International Society of Pharmacoeconomics and Outcomes Research 2002.