Towards prevention of rheumatoid arthritis

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CHAPTER 2

Long-term outcome of RA defined according to the 2010-classification criteria

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ABSTRACT

Objective

The 2010 ACR/EULAR-criteria for RA have been thoroughly studied for the test characteristics but it is unclear whether '2010-RA' has a different phenotype than '1987-RA' when assessing the severity of the disease course. Therefore this study compared two long-term disease outcomes.

Methods

1502 early arthritis patients that had no other diagnoses than RA or UA were studied on fulfilling the 1987-ACR-criteria, 2010-criteria or both. The severity of joint damage was studied with yearly radiographs over 7-years. Achieving DMARD-free sustained remission was assessed over 10-years follow-up. Multivariate normal regression and Cox-proportional hazard regression were used, adjusting for age, gender and treatment.

Results

550 patients fulfilled the 1987-criteria, 788 patients the 2010-criteria and 489 both criteria sets. Patients fulfilling the 2010-criteria developed less severe radiological joint damage (p=0.023) and achieved DMARD-free sustained remission more often (HR=1.18 (0.93-1.50)) than patients fulfilling the 1987-critera, though the latter was not statistically significant. All 1987+2010-patients were ACPA-negative. When also applying the radiologic criterion of the 2010-criteria half of the 1987+2010- patients became 2010-criteria positive, but results on the long-term outcome remained similar.

Conclusion

'2010-RA' has a milder disease course than '1987-RA'. This may have important implications for basic scientific studies and clinical trials in RA.

INTRODUCTION

Presently Rheumatoid Arthritis (RA) can be classified according to either the 1987 ACR-criteria or the 2010 ACR/EULAR-criteria. Both sets of criteria are being used and multiple studies have evaluated the performance of the 2010-criteria[1-5]. A formal meta-analysis on the test-characteristic is in progress (personal communication H. Radner), but the current impression is that the 2010-criteria, compared to the 1987-criteria, are more sensitive and less specific in classifying RA[1]. It is yet insufficiently clear whether the phenotype of RA is different when the disease is classified according to the 2010-criteria or the 1987-criteria. Several studies observed that some disease characteristics at disease onset of 2010 RA-patients were milder than of 1987 RA-patients[2-5]. Some authors reported that erosions at baseline and after 2-years are more often present in 1987-RA compared to 2010-RA[2,4-6]. Together, these data lead to the presumption that RA defined according to the 2010-criteria is milder in nature than that defined according to the 1987-criteria, but there is insufficient data to draw definite conclusions on this matter. Particularly, there are no studies comparing the long-term outcome of RA-patients when RA is classified either to the 1987-criteria or the 2010-criteria. The most characteristic hallmarks of RA are progression of joint damage and disease persistency. We aimed to compare these two long-term disease outcomes in relation to the classification of RA and performed the present longitudinal study to this end.

METHODS

Patients

Early arthritis patients included in the Leiden Early Arthritis Clinic Cohort[7] between 1993 and May 2011 were studied. Inclusion took place when arthritis was confirmed at physical examination and symptom duration was <2 years. At the first visit, patients and rheumatologists completed questionnaires, physical examination was performed, and serum and radiographs were taken. Follow-up visits were performed yearly. For further description see reference [7]. The treatment differed for different inclusion periods. Patients included between 1993 and 1995 were initially treated with NSAIDs, patients included between 1996 and 1998 were initially treated with chloroquine or sulphasalazine and patients included after 1999 were promptly treated with methotrexate or sulphasalazine. The inclusion period was used as a proxy for the applied treatment strategy in the analyses.

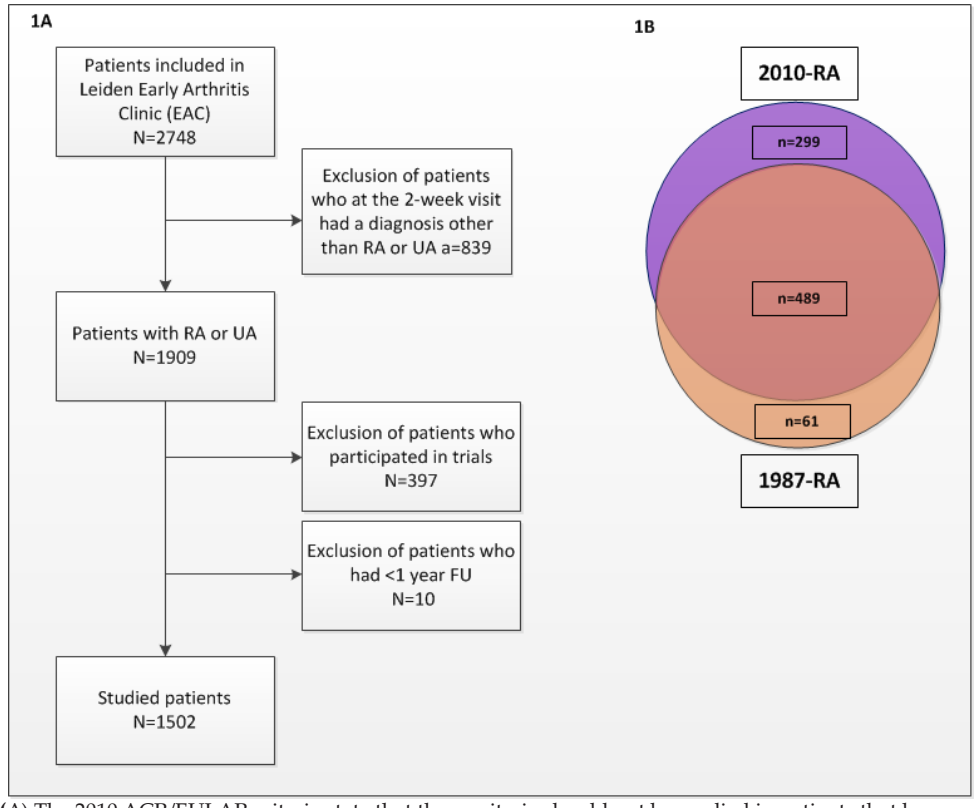
Of all 2748 included early arthritis patients, patients that at first visits had a clear diagnosis other than RA or undifferentiated arthritis were excluded (n=839), which is in line with the 2010-criteria. Patients that were treated in randomized clinical trials were

excluded (n=397) as the treatment of these patients was more tightly controlled and the medications used more potent; affecting the disease course . Patients with a follow-up <1 year were also excluded (n=10). Thus, 1502 patients were studied (Figure 1A) and classified on fulfilling the 1987 ACR-criteria and/or the 2010 ACR/EULAR-criteria.

Outcome

Two outcome measures were studied. The first was the severity of radiological damage during 7-years of follow-up. Hand and feet X-rays were taken at baseline and yearly thereafter and scored according to the Sharp-van der Heijde method by two

Figure 1: Flowchart of patient selection (A) and the number of patients studied that fulfilled the 1987 and/or 2010 classification criteria at baseline.



(A) The 2010 ACR/EULAR criteria state that these criteria should not be applied in patients that have other diagnoses. For this reason patients that at the 2-week visit (when the results of laboratory and radiological evaluations were known) had clear rheumatologic diagnoses were excluded. Patients that were treated according to trial protocols were excluded as well, as treatment strategies of these patients differed from the other patients. However, the trial-patients were included in a sensitivity analysis.
(B) Of the 1502 patients studied, 489 fulfilled both criteria sets for RA at the 2-week visit. 299 patients fulfilled only the 2010-criteria and 61 patients fulfilled only the 1987-criteria. 714 patients fulfilled none of the criteria sets for RA.

readers with known time order, blinded to clinical data. Intraclass-observer correlation coefficients (ICC) within the readers were 0.91 and 0.87 and between the two readers 0.89.

The second outcome was achieving a DMARD-free sustained remission during 10-years of follow-up. Remission was defined as the sustained absence of synovitis (by physical examination) after discontinuation of DMARD-therapy. Synovitis had to be absent for the entire period of follow-up and at least during one year[8]; in general these patients were also discharged from the outpatient clinic. Patients that achieved such a remission but relapsed (n=13) were included in the non-remission group. This stringent definition of remission is the best possible outcome of RA as it approximates 'cure'; it is the opposite of disease persistency. Medical files of all patients were studied on remission, and this was determined until the fifth of April, 2012.

Statistical analyses

Analyses on remission were done using a Cox proportional hazard regression analysis[8]. Analyses on joint destruction were done using a multivariate normal regression analysis as described previously, including all radiographs in one analysis and taking advantage of serial measurements[9]. Another advantage is that it allowed to study all patients, also in case of missing radiographs, preventing selection bias that would be induced by a completers-only-analysis[10]. All analyses were adjusted for age, gender, and treatment strategy. First the long-term outcomes of patients with RA according to the 1987-criteria and RA according to the 2010-criteria were compared. In this analysis, patients that fulfilled both criteria sets were included in both groups. Subsequently all patients were split in three groups (1987+2010-, 1987-2010+ and 1987+2010+) and analyses repeated. SPSS version 20.0 was used. P values <0.05 were considered significant.

RESULTS

Baseline characteristics

Of the 1502 patients studied, 550 patients fulfilled the 1987-criteria, 788 patients the 2010-criteria by having ≥6 points and 489 patients fulfilled both criteria (Figure 1B). Table 1 presents the baseline characteristics. Overall, no large differences were seen between 1987-RA and 2010-RA, but 2010+ patients experienced less morning stiffness than 1987+ patients (median 60 versus 90 minutes) and had slightly lower CRP levels. When comparing the three subgroups, it was observed that all 1987+2010- patients were ACPA-negative.

Table 1: Baseline characteristics of patients classified with RA according to either the 1987 and/or the 2010-criteria

Patient characteristic	1987-RA (n=550)	2010-RA (n=788)	1987-/2010+ (n=299)	1987+/2010+ (n=489)	1987+/2010- (n=61)
Age at inclusion, years, mean ± SD	57.9 ± 16.2	56.6 ± 16.4	54.7 ± 16.4	57.8 ± 16.2	58.9 ± 15.8
Female sex	377 (68.5)	536 (68.0)	198 (66.2)	338 (69.1)	39 (63.9)
Symptom duration in weeks, median (IQR)	21.9 (12.7-38.1)	19.9 (10.6-37.3)*	15.0 (5.9-31.3)	22.0 (13.0-40.0)	15.7 (10.8-31.8)
Symptom duration < 12 weeks	120 (23.5)	221 (29.7)*	119 (41.2)	102 (22.4)	18 (33.3)
Swollen joint count of 66 joints, median (IQR)	10.0 (6.0-15.0)	9.0 (4.0-15.0)	4.0 (2.0-10.0)	11.0 (7.0-16.0)	6.0 (4.0-8.0)
Acute onset of symptoms	287 (53.8)	408 (53.5)	159 (55.4)	249 (52.3)	38 (66.7)
Onset of symptoms in small joints	306 (57.0)	443 (57.2)	170 (57.2)	273 (57.1)	33 (55.9)
Symmetric onset of symptoms	377 (74.8)	519 (71.8)	183 (66.8)	336 (74.8)	41 (74.5)
RF positive	307 (55.9)	444 (56.5)	138 (46.3)	306 (62.7)	1 (1.6)
ACPA positive	264 (52.3)	379 (52.1)	115(41.7)	264 (58.5)	0 (0)
ESR, mm/hour, mean ± SD	41.1 ± 28.8	38.1 ± 28.2	32.0 ± 26.3	42.0 ± 28.7	34.7 ± 28.8
CRP, mg/L, median (IQR)	19.0 (8.0-42.8)	16.0(6.0-37.0)*	12.0 (4.0-26.3)	19.0 (9.0-43.0)	19.0 (6.5-37.0)
Morning stiffness, minutes, median (IQR)	90 (60-180)	60 (30-120)*	30 (10-82.5)	90 (60-180)	90 (60-150)
HAQ (0-3), median (IQR)	1.0 (0.6-1.6)	1.0 (0.5-1.5)	0.8 (0.4-1.4)	1.0 (0.6-1.6)	0.9 (0.6-1.3)
Erosive joints, median (IQR)	3 (1-7)	3 (1-6)	1.5 (0-4)	4 (1-7)	4 (1-6)

Unless indicated otherwise, values are the number (%) of patients. *p<0.05 for comparison between 1987-RA and 2010-RA (Student t-test or Mann-Whitney U-test as applicable). Some data were missing: for symptom duration (n=48), for acute onset of symptoms (n=29), for symptom onset in small joints (n=15), for symmetric onset of symptoms (n=71), for RF (n=2), for ACPA (n=68), for ESR (n=3), for CRP (n=35), for morning stiffness (n=24) and for HAQ (n=138).

Comparison of 1987 and 2010 RA

RA-patients according to the 2010-criteria had less severe radiological joint destruction over 7-years of disease than RA-patients classified using the 1987-criteria (p=0.023, Figure 2A). When evaluating DMARD-free sustained remission, more remission was achieved in 2010+ RA-patients than in 1987+ RA-patients, though this difference was not statistically significant (HR=1.18(0.93-1.50) p=0.17, Figure 2B).

Subanalyses

Subsequently, the RA-patients were stratified in three groups (1987+2010-, 1987-2010+, 1987+2010+) and the analyses were repeated. As presented in Figure 2C&D, 1987+2010+ RA-patients developed more severe joint destruction and achieved DMARD-free sustained remission less often than patients fulfilling one criteria set for RA ($p<0.001$ for both outcomes and comparison of three groups). Moreover, when analysing these subgroups in more detail, the severity of joint damage was not different between the 1987+2010+ and 1987+/2010- patients (p=0.35) but differed between the 1987+2010+ and 1987-/2010+ patients, $p<0.001$, Figures 2C&D). Interestingly, 1987+2010- RA-patients achieved DMARD-free sustained remission most frequently. However, this small subgroup contained only ACPA-negative patients. When the analysis was also adjusted for ACPA, this effect was no longer present (Figure 2F).

Thus far the 2010-criteria were applied using the point system. When applying the radiological criterion for RA-specific erosiveness (≥3 erosive joints)[11,12] in addition to the point system, 30 of the 61 1987+2010- RA were now 2010-criteria positive. All analyses on joint damage and remission were repeated; this did not influence the results (Supplementary Figures 1 and-2).

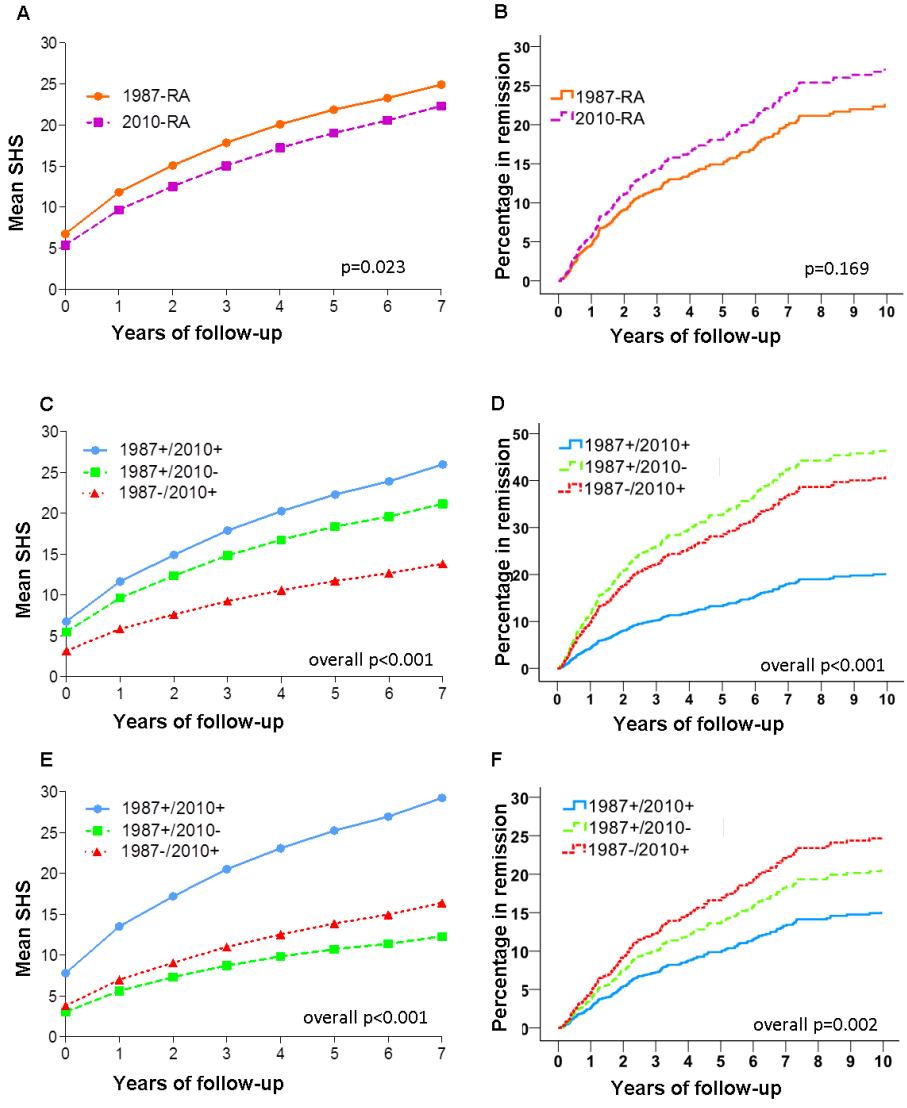
Finally, all analyses were repeated including the 397 patients that were treated in clinical trials, yielding similar results as described above (data not shown).

DISCUSSION

The present study evaluated the long-term outcome of patients classified to the 1987-criteria or the 2010-criteria and observed a statistically significant difference in the severity of joint damage and a non-significant difference with regard to disease persistency. For both outcomes, patients classified as RA using the 2010-criteria had a less severe disease course. Thereby the present data suggest that RA, when using the most recent classification criteria, has become a milder disease.

This observation might fit within the observations that the 2010-classification

Figure 2: Comparison of long-term outcomes of RA according to fulfillment of the 1987- and/or 2010 classification criteria for RA.



All analyses were adjusted for age, gender and treatment. Depicted in A, C and E are the predicted (by the multivariate normal regression model) Sharp-van der Heijde scores during 7-years of follow-up. Depicted in B,D,F are the percentage of patients achieving DMARD-free sustained remission
A-B: Comparison of patients fulfilling the 1987-criteria and patients fulfilling the 2010-criteria. C-D: Comparison of patients fulfilling either one or both criteria sets for RA. E-F: Comparison of patients fulfilling either one or both criteria sets for RA, after also adjusting for the presence of ACPA.
C,D,E,F; Presented are the overall p-values when comparing three groups.
For comparisons of subgroups with the 1987+2010+ patients as reference the results were for C: 1987+/2010+ versus 1987+/2010- p=0.35, 1987+/2010+ versus 1987-/2010+ p<0.001. D:1987+/2010+ versus 1987+/2010- p<0.001, 1987+/2010+ versus 1987-/2010+ p<0.001: E: 1987+/2010+ versus 1987+/2010- p=0.14, 1987+/2010+ versus 1987-/2010+ p<0.001. F:1987+/2010+ versus 1987+/2010- p=0.21, 1987+/2010+ versus 1987-/2010+ p<0.001.

criteria have a lower specificity than the 1987-criteria and can be positive in patients that later on have other diagnoses (associated with a less destructive course)[1,5,6,13-15]. Alternatively patients fulfilling the 2010-criteria, in particular the 1987-2010+ patients, may simply represent a milder set of patients. The milder outcome observed was not due to an earlier diagnosis and earlier treatment initiation, as the 2010-criteria were applied after the follow-up data were obtained.

In our study we did not observe large differences in baseline characteristics, though the 1987-RA patients experienced more morning stiffness than 2010-RA patients. This may be a consequence of morning stiffness being part of the 1987-criteria. Adding morning stiffness as an additional adjustment factor to the analyses did not gave different results (data not shown); hence the findings done were not driven by this baseline difference.

The 2010-criteria were derived with MTX-usage as outcome; by using this outcome some level of circularity could not be prevented. Advantages of the two outcomes used here is that they are independent of any set of classification criteria and therefore do not suffer from circle reasoning.

A limitation is that patients were treated. Ideally, the present study question was evaluated in patients that were not treated over many years, as this completely represents the natural disease course. We excluded patients that were treated in clinical trials and studied only patients treated according to routine care. Nonetheless the treatment strategies used in these patients had changed over time, therefore analyses were adjusted for these differences in treatment. Importantly, the proportion of 1987+ and 2010+ patients was similar for the different inclusion periods (data not shown). Moreover, including patients who were treated in clinical trials did not influence the findings.

All 1987+2010-patients were ACPA-negative, which is in line with another recent report[16]. When the radiological criterion of the 2010-criteria was also applied, half of this group of patients became 2010-criteria positive. This supports the relevance of the radiological criterion as the frequency of this misclassification reduced.

In conclusion, the present longitudinal study showed that RA classified according to the 2010-criteria has less severe joint destruction and is less often persistent than RA classified according to the 1987-criteria. This may have important implications, both for basic scientific studies and randomized clinical trials in RA.

SUPPLEMENTARY DATA

Supplementary data is available at the website of Annals of the Rheumatic Diseases

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