Predictive factors for outcome of rheumatoid arthritis

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CHAPTER 10

The window of opportunity in ACPA-positive rheumatoid arthritis is not explained by ACPA characteristics

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Very early therapy of rheumatoid arthritis (RA) with disease-modifying anti-rheumatic drugs is associated with lower levels of joint destruction and a higher chance on achieving remission.[1-5] Having symptoms for >12 weeks at treatment initiation is a strong and independent risk factor for a persistent disease course.[1,3-5] These observations have led to the concept of the 'window of opportunity'.[2] This hypothesis presumes that underlying disease processes are not fully matured in the very early stage of arthritis, making modulation more successful. However, putative biological mechanisms remain unexplored.

Anti-cyclic citrullinated protein antibodies (ACPA) precede arthritis development and are associated with a severe disease course.[6] We hypothesized that the ACPA-response broadens within the very early phase of RA and in doing so limits the 'window of opportunity'. Therefore it was examined whether patients that are assessed within 12 weeks of symptom onset have a less broadened ACPA-response than patients with longer symptom duration.

309 ACPA-positive patients (defined by anti-CCP2-positivity) fulfilling the 1987-ACR criteria for RA and included in the Leiden Early Arthritis Clinic[7] were studied on the association between symptom duration and the progression in joint destruction over 7.5 years, with symptom onset as starting point.[3] Yearly radiographs of hands and feet were scored according to the Sharp-van der Heijde method.[7] A repeated measurement analysis was used with a random person and time effect; the fixed effect of time was modeled with linear spline functions with knots at each year.[3] Adjustments were made for age, gender and treatment strategy. RA patients that presented with <12 weeks or ≥12 weeks of symptoms were compared for level, isotype-usage and fine specificity of ACPA at inclusion. Antibody reactivity against peptides derived from human proteins (the citrullinated (Cit) and the uncitrullinated form of two linear peptides derived from vimentin (Vim1-16:STCitS VSSS SYCitCit MFGG and Vim59-74:VYAT CitSSA VCitLCit SSVP), two linear peptides derived from fibrinogen (Fibα27-43:FLAE GGGV Cit GPR VVER H and Fibβ36-52:NEEG FFSA CitGHR PLDK K), one linear peptide derived from α-enolase (Eno5-20:KIHA CitEIF DSCitG NPTV) and Myelin Basic Protein (MBP)) were determined by ELISA and described previously.[3,7-9] Anti-CCP3 and anti-MCV were also measured by ELISA (Quanta Lite CCP version 3.1 for IgG/IgA, Inova Diagnostics San Diego, USA and Orgentec Diagnostika, Mainz, Germany).

RA patients that presented <12 weeks of symptom onset had less progression in joint destruction over 7.5 years (p=0.04) (Figure 1). Patients with symptoms <12 weeks revealed no differences in anti-CCP2 level, isotype usage or fine-specificity recognition profile compared to patients with longer symptom duration (Table 1).

To our knowledge this is the first study investigating ACPA-characteristics in relation to the so-called 'window of opportunity'. Recently published data showed a trend for less joint destruction in ACPA-positive RA patients presenting with symptoms <12weeks.[3] In the present study the radiographic data were extended. No clear differences were observed with respect to ACPA-characteristics in relation to symptom duration. Although it cannot be excluded that other ACPA-characteristics, such as glycosylation patterns or other 'fine-specificities', would show

Table 1. ACPA characteristics at inclusion of ACPA-positive RA patients with symptoms for <12 or ≥12 weeks

	<12 weeks		≥12 weeks			
Anti-CCP2 levels*					P-value	
Median (AU) IQR	766 285-1711		642 215-1560		0.5	
Fine-specificity	<12 weeks		≥12 weeks		OR	95% CI
cVim1-16- cVim1-16+	54 8	87.1% 12.9%	177 26	87.2% 12.8%	0.99	0.42-2.32
cVim59-74- cVim59-74+	30 32	48.4% 51.6%	100 106	48.5% 51.5%	0.99	0.56-1.75
cFib-α – cFib-α +	40 22	64.5% 35.5%	156 50	75.5% 24.3%	0.58	0.32-1.07
cFib-β – cFib-β +	13 48	21.3% 78.7%	60 136	30.6% 69.4%	0.61	0.31-1.22
cEno5-20 – cEno5-20 +	40 22	64.5% 35.5%	139 67	67.5% 32.5%	0.88	0.48-1.59
MBP – MBP +	19 43	30.6% 69.4%	74 132	35.9% 64.1%	0.79	0.43-1.45
MCV – MCV +	3 58	4.9% 95.1%	10 191	5.0% 95.0%	0.99	0.26-3.71
CCP3 – CCP3 +	2 59	3.3% 96.7%	14 188	6.9% 93.1%	0.46	0.10-2.06
0-4 peptides** 5-8 peptides**	24 35	40.7% 59.3%	97 92	51.3% 48.7%	0.65	0.36-1.18
ACPA isotype usage***					OR	95% CI
IgM-ACPA – IgM-ACPA +	13 26	33.3% 66.7%	52 102	33.8% 66.2%	0.98	0.47-2.07
IgA-ACPA – IgA-ACPA +	14 24	35.9% 64.1%	50 104	32.5% 67.5%	1.17	0.56-2.43
IgG1-ACPA – IgG1-ACPA +	0 39	0% 100%	2 152	1.3% 98.7%	N/A	N/A
IgG2-ACPA – IgG2-ACPA +	3 36	7.7% 92.3%	26 128	16.9% 78.0%	0.41	0.12-1.43
IgG3-ACPA – IgG3-ACPA+	16 23	41.0% 59.0%	63 91	40.9% 59.1%	1.01	0.49-2.05
IgG4-ACPA – IgG4-ACPA +	0 39	0% 100%	6 148	3.9% 96.1%	N/A	N/A
0-4 isotypes 5-6 isotypes	14 25	35.9% 64.1%	55 99	35.7% 64.3%	1.01	0.49-2.10

Fine-specificity data were assessed in patients included between 1993 and 2006. Fine-specificity data were missing for 61 patients. Isotype data were determined previously in patients included between 1993 and March 2004 and are therefore missing in 116 patients. *Difference in anti-CCP2 levels was analyzed using Mann-Whitney test. IQR=interquartile range. cVim=citrullinated vimentin; cFib=citrullinated fibrinogen; cEno5-20=citrullinated Enolase 5-20; MBP=myelin basic protein; MCV=mutated citrullinated vimentin.**8 peptides were included for the high versus low recognition analyses: cVim1-16, cVim59-74, cFib-α, cFib-β, cEno5-20, MBP, MCV, CCP3. ***ACPA isotypes were measured using anti-CCP2 peptides

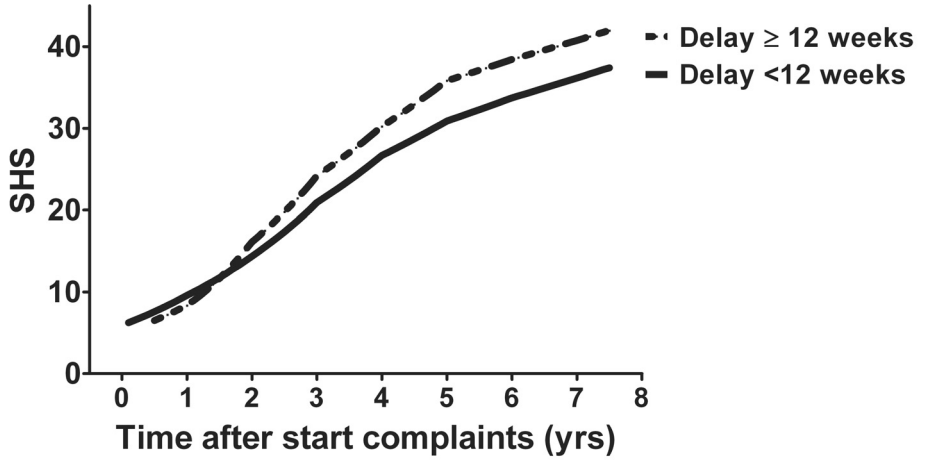

Figure 1. Joint destruction (Sharp/van der Heijde scores) over time in ACPA-positive RA patients with <12 or ≥12 weeks of symptoms at first presentation at the rheumatologist. The date of symptom onset is used as starting point. 70 ACPA-positive patients (22.7%) presented <12 weeks (median after 8 weeks of symptoms) and 239 ACPA-positive patients presented after ≥12 weeks of symptoms (median symptom duration at first presentation at 27 weeks). The RA patients studied were included in the Leiden Early Arthritis Clinic between 1993 and 2006

differences, our data indicate that the 'window of opportunity' is not reflected in the maturation of the ACPA-response.

A longitudinal study-design with regular assessments of ACPA-characteristics within the same patients would be more appropriate than a cross-sectional study. However, as ACPA-positive RA patients often present relatively late (only 22.7% of the ACPA-positive RA patients visited a rheumatologist <12 weeks of symptom onset), it will be difficult to obtain adequate patient numbers.

In conclusion, ACPA-positive RA patients with symptoms <12 weeks have less progressive disease than patients with a longer symptom duration. However, the broadness of the ACPA-response is not different between these groups; indicating that maturation of the autoantibody response occurs even earlier.[10]

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