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The value of rheumatoid arthritis autoantibodies in disease pathogenesis and treatment prognosis

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Citation

Moel, E. C. de. (2026, April 7). *The value of rheumatoid arthritis autoantibodies in disease pathogenesis and treatment prognosis*. Retrieved from <https://hdl.handle.net/1887/4302760>

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Note: To cite this publication please use the final published version (if applicable).



CHAPTER 4

In RA, becoming seronegative over the first year of treatment does not translate to better chances of drug-free remission

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Annals of the rheumatic diseases. 2018;77(12):1836-8.
doi: 10.1136/annrheumdis-2018-213823

LETTER

In rheumatoid arthritis (RA), it is becoming common to attempt to taper or stop medication, aiming for sustained drug-free remission (SDFR). Autoantibody seropositivity is a poor prognostic factor for this treatment goal. However, autoantibody levels may change and patients may become seronegative, sometimes termed ‘immunological remission’(1). Understanding how often this occurs and whether it is favourable for achieving SDFR is important to determine whether becoming seronegative is a meaningful prognostic marker for drug tapering decisions. Furthermore, it will elucidate pathways that lead to long-term resolution of the pathophysiology underlying RA.

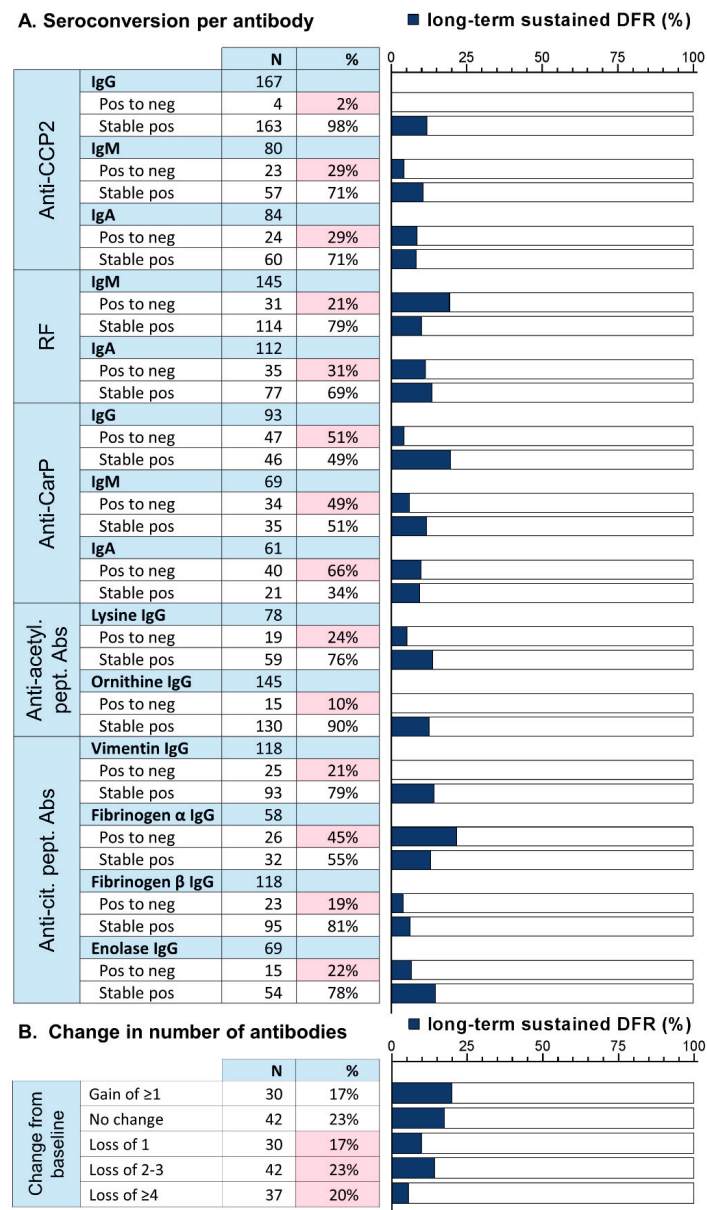
To that end, we investigated the relationship between seroconversion and SDFR. In baseline and 1-year serum of 381 patients with seropositive RA, we measured 14 RA-associated autoantibodies by ELISA(2): anti-CCP2 IgG, IgM and IgA; rheumatoid factor IgM and IgA; anti-CarP IgG, IgM and IgA; anti-acetylated lysine vimentin IgG and anti-acetylated ornithine vimentin IgG (Orgentec Diagnostika, Germany); and anti-citrullinated vimentin 59–74 IgG, anti-citrullinated fibrinogen β 36–52 and α 27–43 IgG, anti-citrullinated enolase 5–20 IgG. Patients originated from the IMPROVED study (3), a randomised controlled treat-to-target trial of early (<2 years) untreated RA, steered at disease activity score remission ($\text{DAS44} < 1.6$) and DFR, with initial treatment of methotrexate and high-dose prednisone. We investigated whether becoming seronegative over the first year of treatment improves chances of long-term SDFR, defined as remission lasting at least 1 year, starting at any time point and held until the last moment of that individual’s follow-up (maximum 5 years).

The prevalence of seroconversion from positive to negative between 0 and 12 months varied substantially depending on the autoantibody from 2% (anti-CCP2 IgG) to 66% (anti-CarP IgA) (**FIGURE 1**), occurring mostly in low-positive patients (**SUPPLEMENTARY TABLE S1**). Demographic and clinical characteristics at baseline and 1 year in patients with seroconversion versus those without did not show marked differences (**SUPPLEMENTARY TABLE S1**). Of the 359 patients who had outcome data available, 48 (13.4%) achieved long-term SDFR. Intriguingly, seroconversion from positive to negative was not associated with a greater chance of achieving long-term SDFR for any of the 14 antibodies tested (**FIGURE 1A**). To investigate whether these findings were influenced by low-positive patients whose autoantibody levels merely fluctuated around the cut-off, a sensitivity analysis was conducted including only patients whose baseline autoantibody levels were above the median, with similar results (**SUPPLEMENTARY FIGURE S1**). Of the 170 seropositive patients with complete antibody data at 0 and 12 months, only six (3.5%) seroconverted to completely seronegative by 12 months; 33% (2/6) of these completely seroconverted patients achieved long-term SDFR, compared with 11.6% (19/164) of patients who were positive for at least one antibody ($p=0.11$). Patients who seroconverted to negative for a larger number of autoantibodies did not achieve long-

term SDFR more often than those who seroconverted for fewer (**FIGURE 1B**). Relative changes in autoantibody levels between 0 and 12 months did not differ between patients with or without long-term SDFR (data not shown).

The clinical significance of seroconversion in RA and especially its relationship with long-term SDFR, an approximation of disease 'cure' of RA, is a topic of major interest. Previous studies found no association of seroconversion with remission or radiographic damage (4, 5). We here investigated the association between seroconversion and the most favourable long-term outcome of RA, SDFR, and found no association. Thus, it appears that seroconversion (as measured by current standards) does not identify a group of patients in whom the underlying immunopathology has been favourably modulated, that is, patients in true immunological remission, and is not superior to signals of low inflammatory load (e.g. by DAS (6)) for predicting successful drug tapering. Future studies are needed to identify whether other immunological parameters such as the numbers or phenotype of circulating autoreactive B or T cells might be a better reflection of disease persistence and markers for immunological remission.

FIGURE 1: (A) Number and percentage of baseline seropositive patients seroconverting ('Pos to Neg') or non-converting ('Stable pos') between 0 and 12 months are listed on the left, and the percentage of each subset subsequently reaching long-term sustained drug-free remission (DFR) is graphically depicted on the right. (B) Number and percentage of baseline seropositive patients reaching long-term sustained DFR, categorised by the amount of antibody reactivities that were lost (i.e. composite of positive-to-negative seroconversion) between 0 and 12 months. Anti-acetyl pept Abs, anti-acetylated peptide antibodies; Anti-cit pept Abs, anti-citrullinated peptide antibodies; RF, rheumatoid factor



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SUPPLEMENTARY FIGURES

Supplementary Table S1 (part 1 of 3): Demographic and clinical differences at baseline and 1 year, between patients that did not seroconvert (“Stable Pos”) and those that seroconverted between 0-12 months (“Pos-Neg”). Bold typeface indicates significance after correction for multiple testing by Holmes-Bonferroni methods for 14 tests (14 autoantibodies).

	anti-CCP2 IgG (range: 0-1600 aU/mL)			anti-CCP2 IgM (range: 0-1400 aU/mL)			anti-CCP2 IgA (range: 0-1160 aU/mL)			RF IgM (range: 0-200 aU/mL)			RF IgA (range: 0-200 aU/mL)		
	Stable Pos	Pos-Neg	p	Stable Pos	Pos-Neg	p	Stable Pos	Pos-Neg	p	Stable Pos	Pos-Neg	p	Stable Pos	Pos-Neg	p
N total	163	4		57	23		60	24		114	31		77	35	
Levels Baseline, med (IQR)	561 (230-1,226)	40 (33-81)	0.00	538 (381-990)	203 (115-273)	0.00	269 (102-657)	72 (44-156)	0.00	117 (76-200)	56 (31-81)	0.00	200 (94-200)	29 (21-50)	0.00
Age in years, mean ± SD	49 ± 12	56 ± 5	0.27	52 ± 13	52 ± 12	0.97	50 ± 12	53 ± 12	0.38	50 ± 13	53 ± 11	0.27	51 ± 11	52 ± 13	0.61
Symptom duration (weeks), med (IQR)	23 (10-38)	6 (4-7)	0.01	25 (9-42)	21 (11-32)	0.58	27 (10-48)	22 (6-28)	0.06	22 (10-36)	18 (9-30)	0.27	22 (11-42)	20 (8-32)	0.25
BMI (kg/m2), mean ± SD	26 ± 4	25 ± 6	0.66	26 ± 4	26 ± 5	0.82	26 ± 4	27 ± 5	0.66	25 ± 4	26 ± 4	0.32	26 ± 4	27 ± 5	0.08
Female gender (%)	112 (69%)	3 (75%)	0.79	38 (67%)	16 (70%)	0.80	37 (62%)	17 (71%)	0.43	78 (68%)	21 (68%)	0.94	46 (60%)	22 (63%)	0.75
Ever smoker (%)	83 (51%)	0 (0%)	0.04	31 (54%)	12 (52%)	0.86	38 (64%)	13 (54%)	0.38	59 (52%)	10 (32%)	0.05	56 (74%)	12 (34%)	0.00
Achieved early remission (%)	115 (71%)	1 (25%)	0.05	40 (70%)	17 (74%)	0.74	43 (72%)	14 (58%)	0.24	79 (69%)	17 (55%)	0.13	56 (73%)	24 (69%)	0.65
RAI index Baseline, med (IQR)	6 (4-9)	8 (4-11)	0.57	6 (4-8)	6 (4-10)	0.82	6 (3-8)	6 (4-10)	0.80	6 (4-9)	7 (6-12)	0.03	6 (4-8)	8 (4-11)	0.23

Supplementary Table S1 (part 1 of 3): Demographic and clinical differences at baseline and 1 year, between patients that did not seroconvert ("Stable Pos") and those that seroconverted between 0-12 months ("Pos-Neg"). Bold typeface indicates significance after correction for multiple testing by Holmes-Bonferroni methods for 14 tests (14 autoantibodies). (continued)

	anti-CCP2 IgG (range: 0-1600 aU/mL)			anti-CCP2 IgM (range: 0-1400 aU/mL)			anti-CCP2 IgA (range: 0-1160 aU/mL)			RF IgM (range: 0-200 aU/mL)			RF IgA (range: 0-200 aU/mL)		
	Stable Pos	Pos-Neg	p	Stable Pos	Pos-Neg	p	Stable Pos	Pos-Neg	p	Stable Pos	Pos-Neg	p	Stable Pos	Pos-Neg	p
N total	163	4	p	57	23	p	60	24	p	114	31	p	77	35	p
RAI index 1 year, med (IQR)	1 (0-3)	4 (0-8)	0.60	1 (0-3)	1 (0-2)	0.35	1 (0-3)	2 (0-3)	0.86	1 (0-4)	1 (0-4)	1.00	1 (0-4)	0 (0-2)	0.08
SIC Baseline, med (IQR)	5 (3-10)	6 (2-10)	0.78	5 (3-9)	5 (4-13)	0.56	5 (3-7)	6 (3-13)	0.57	5 (3-10)	5 (3-11)	0.43	5 (3-9)	7 (5-12)	0.05
SIC 1 year, med (IQR)	0 (0-1)	1 (0-5)	0.52	0 (0-1)	0 (0-0)	0.38	0 (0-1)	0 (0-2)	0.46	0 (0-1)	0 (0-2)	0.81	0 (0-2)	0 (0-2)	0.82
ESR (mm/h) Baseline, med (IQR)	26 (14-36)	45 (30-56)	0.09	30 (18-42)	24 (11-42)	0.34	29 (17-42)	26 (9-47)	0.54	29 (17-36)	28 (11-53)	0.94	29 (14-37)	28 (19-50)	0.50
ESR (mm/h) 1 year, med (IQR)	9 (4-19)	9 (4-58)	0.91	11 (6-19)	6 (2-12)	0.02	11 (6-19)	9 (4-25)	0.50	11 (5-24)	9 (2-15)	0.14	11 (5-25)	9 (2-14)	0.08
VAS (mm) Baseline, mean $\pm$ SD	43 $\pm$ 24	45 $\pm$ 17	0.84	42 $\pm$ 25	41 $\pm$ 26	0.91	42 $\pm$ 25	48 $\pm$ 24	0.35	42 $\pm$ 24	48 $\pm$ 21	0.24	43 $\pm$ 25	47 $\pm$ 24	0.47
VAS (mm) 1 year, mean $\pm$ SD	24 $\pm$ 23	38 $\pm$ 26	0.22	25 $\pm$ 24	19 $\pm$ 20	0.33	25 $\pm$ 25	16 $\pm$ 15	0.07	24 $\pm$ 23	22 $\pm$ 19	0.65	26 $\pm$ 23	19 $\pm$ 21	0.11
HAQ Baseline, mean $\pm$ SD	1.1 $\pm$ 0.7	1.2 $\pm$ 0.5	0.83	1 $\pm$ 0.7	1 $\pm$ 0.6	0.91	0.9 $\pm$ 0.7	1.3 $\pm$ 0.8	0.04	1 $\pm$ 0.7	1.5 $\pm$ 0.7	0.00	1.1 $\pm$ 0.6	1.3 $\pm$ 0.8	0.14
HAQ 1 year, mean $\pm$ SD	0.5 $\pm$ 0.5	0.5 $\pm$ 0.7	0.93	0.5 $\pm$ 0.6	0.3 $\pm$ 0.4	0.19	0.5 $\pm$ 0.6	0.4 $\pm$ 0.5	0.79	0.5 $\pm$ 0.6	0.6 $\pm$ 0.6	0.58	0.6 $\pm$ 0.6	0.4 $\pm$ 0.5	0.15
CRP Baseline, med (IQR)	11 (4-27)	22 (2-50)	0.94	14 (4-29)	9 (4-39)	0.73	12 (4-24)	11 (5-41)	0.43	11 (4-23)	16 (5-53)	0.22	11 (4-28)	11 (3-31)	0.93

Supplementary Table S1 (part 1 of 3): Demographic and clinical differences at baseline and 1 year, between patients that did not seroconvert ("Stable Pos") and those that seroconverted between 0-12 months ("Pos-Neg"). Bold typeface indicates significance after correction for multiple testing by Holmes-Bonferroni methods for 14 tests (14 autoantibodies). (continued)

	anti-CCP2 IgG (range: 0-1600 aU/mL)			anti-CCP2 IgM (range: 0-1400 aU/mL)			anti-CCP2 IgA (range: 0-1160 aU/mL)			RF IgM (range: 0-200 aU/mL)			RF IgA (range: 0-200 aU/mL)		
	Stable Pos	Pos-Neg	p	Stable Pos	Pos-Neg	p	Stable Pos	Pos-Neg	p	Stable Pos	Pos-Neg	p	Stable Pos	Pos-Neg	p
N total	163	4		57	23		60	24		114	31		77	35	
CRP 1 year, med (IQR)	4 (3-8)	4 (3-17)	0.95	4 (3-7)	3 (3-6)	0.19	3 (3-7)	6 (3-11)	0.33	4 (3-8)	3 (3-8)	0.10	4 (3-8)	3 (3-5)	0.01
DAS Baseline, mean $\pm$ SD	3.2 $\pm$ 0.9	3.4 $\pm$ 0.6	0.70	3.3 $\pm$ 1.1	3.3 $\pm$ 0.9	0.97	3.2 $\pm$ 1	3.2 $\pm$ 1	0.96	3.2 $\pm$ 0.9	3.5 $\pm$ 1	0.15	3.2 $\pm$ 1	3.5 $\pm$ 0.8	0.18
DAS 1 year, mean $\pm$ SD	1.5 $\pm$ 0.9	1.9 $\pm$ 1.5	0.42	1.6 $\pm$ 0.9	1.3 $\pm$ 0.8	0.16	1.6 $\pm$ 0.9	1.5 $\pm$ 0.8	0.66	1.6 $\pm$ 0.9	1.5 $\pm$ 1	0.62	1.7 $\pm$ 1	1.3 $\pm$ 0.8	0.04
Total SHS Baseline, med (IQR)	0.0 (0.0-0.5)	0.0 (0.0-4.5)	0.87	0.0 (0.0-2.0)	0.0 (0.0-0.0)	0.04	0.0 (0.0-0.9)	0.0 (0.0-1.5)	0.83	0.0 (0.0-0.6)	0.0 (0.0-0.6)	0.99	0.0 (0.0-2.0)	0.0 (0.0-0.0)	0.04
Total SHS 1 year, med (IQR)	0.0 (0.0-1.4)	0.0 (0.0-4.5)	0.94	0.0 (0.0-2.0)	0.0 (0.0-0.0)	0.03	0.0 (0.0-2.0)	0.0 (0.0-0.8)	0.20	0.0 (0.0-1.9)	0.0 (0.0-1.1)	0.74	0.0 (0.0-2.0)	0.0 (0.0-0.0)	0.03

P-values are based on t-tests, Mann Whitney tests, or Chi-squared tests for comparisons of means, medians, and frequencies, respectively. SD: standard deviation. Med: median. IQR: interquartile range. BMI: Body mass index. RAI: Ritchie-Articular Index. SIC: Swollen joint count. ESR: Erythrocyte sedimentation rate. VAS: Visual analogue scale. HAQ: Health assessment questionnaire. CRP: C-reactive protein. DAS: Disease activity score. SHS: Sharp-van de Heijde score. Acetyl: acetylated. Cit: citrullinated.

Supplementary Table S1 (part 2 of 3): Demographic and clinical differences at baseline and 1 year, between patients that did not seroconvert ("Stable Pos") and those that seroconverted between 0-12 months ("Pos-Neg"). Bold typeface indicates significance after correction for multiple testing by Holmes-Bonferroni methods for 14 tests (14 autoantibodies).

	anti-CarP IgG (range: 0-5272 aU/mL)				anti-CarP IgM (range: 0-3650 aU/mL)				anti-CarP IgA (range: 0-3100 aU/mL)				Anti-acetyl-L-lysine IgG (range: 0-1000 aU/mL)				Anti-acetyl-L-ornithine IgG (range: 0-1000 aU/mL)			
	Stable Pos	Pos-Neg	p		Stable Pos	Pos-Neg	p		Stable Pos	Pos-Neg	p		Stable Pos	Pos-Neg	p		Stable Pos	Pos-Neg	p	
N total	46	47			35	34			21	40			59	19			130	15		
Levels Baseline, med (IQR)	1,579 (1069-2,846)	1,123 (822-1,463)	0.00		3,650 (2375-3,650)	2,843 (2221-3,568)	0.04		2,478 (1591-2,912)	1,128 (955-1,479)	0.00		167 (75-532)	60 (50-74)	0.00		484 (180-1,000)	47 (40-74)	0.00	
Age in years, mean ± SD	48 ± 14	54 ± 10	0.04		52 ± 13	50 ± 14	0.65		52 ± 9	53 ± 13	0.90		49 ± 13	52 ± 12	0.51		49 ± 13	53 ± 10	0.19	
Symptom duration (weeks), med (IQR)	19 (8-32)	23 (9-38)	0.47		26 (10-56)	19 (7-29)	0.11		32 (19-63)	18 (8-28)	0.02		25 (8-36)	27 (18-44)	0.26		25 (10-44)	24 (6-32)	0.79	
BMI (kg/m2), mean ± SD	26 ± 4	25 ± 3	0.28		26 ± 4	26 ± 4	0.80		26 ± 4	26 ± 4	0.75		26 ± 4	26 ± 4	0.99		25 ± 4	27 ± 5	0.10	
Female gender (%)	23 (50%)	36 (77%)	0.01		20 (57%)	27 (79%)	0.05		12 (57%)	30 (75%)	0.15		40 (68%)	14 (74%)	0.63		83 (64%)	14 (93%)	0.02	
Ever smoker (%)	25 (54%)	25 (54%)	1.00		22 (63%)	16 (47%)	0.19		15 (71%)	24 (60%)	0.38		27 (47%)	10 (53%)	0.65		71 (55%)	5 (33%)	0.11	
Achieved early remission (%)	31 (67%)	29 (62%)	0.57		22 (63%)	21 (62%)	0.93		12 (57%)	27 (68%)	0.42		43 (73%)	12 (63%)	0.42		95 (73%)	6 (40%)	0.01	
RAI index Baseline, med (IQR)	6 (4-10)	7 (4-10)	0.54		7 (4-10)	7 (4-11)	0.76		7 (4-9)	6 (4-9)	0.91		6 (4-10)	6 (4-9)	0.71		6 (4-9)	10 (3-16)	0.14	
RAI index 1 year, med (IQR)	1 (0-2)	1 (0-3)	0.83		2 (0-3)	0 (0-3)	0.10		2 (0-3)	1 (0-3)	0.51		0 (0-2)	0 (0-2)	0.87		1 (0-2)	4 (1-7)	0.01	
SIC Baseline, med (IQR)	6 (2-13)	7 (4-12)	0.27		6 (4-14)	6 (3-14)	0.63		6 (4-11)	6 (3-12)	0.84		6 (3-12)	7 (5-11)	0.25		5 (3-10)	4 (2-15)	0.82	

Supplementary Table S1 (part 2 of 3): Demographic and clinical differences at baseline and 1 year, between patients that did not seroconvert ("Stable Pos") and those that seroconverted between 0-12 months ("Pos-Neg"). Bold typeface indicates significance after correction for multiple testing by Holmes-Bonferroni methods for 14 tests (14 autoantibodies). (continued)

	anti-CarP IgG (range: 0-5272 aU/mL)				anti-CarP IgM (range: 0-3650 aU/mL)				anti-CarP IgA (range: 0-3100 aU/mL)				Anti-acetyl-lysine IgG (range: 0-1000 aU/mL)				Anti-acetyl-ornithine IgG (range: 0-1000 aU/mL)			
	Stable Pos	Pos-Neg	p		Stable Pos	Pos-Neg	p		Stable Pos	Pos-Neg	p		Stable Pos	Pos-Neg	p		Stable Pos	Pos-Neg	p	
N total	46	47			35	34			21	40			59	19			130	15		
SJC 1 year, med (IQR)	0 (0-1)	0 (0-1)	0.42	0 (0-2)	0 (0-1)	0 (0-1)	0.53	1 (0-2)	0 (0-1)	0 (0-1)	0.08	0 (0-0)	0 (0-1)	0 (0-1)	0.40	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)	0.76
ESR (mm/h) Baseline, med (IQR)	25 (17-36)	29 (19-41)	0.49	29 (17-38)	29 (18-50)	0.75	32 (19-56)	29 (14-36)	0.35	26 (17-36)	33 (18-42)	0.24	26 (15-36)	28 (6-48)	0.66					
ESR (mm/h) 1 year, med (IQR)	10 (5-19)	9 (5-14)	0.44	11 (6-19)	9 (5-19)	0.80	14 (6-25)	9 (5-19)	0.19	9 (5-14)	0.54	9 (5-27)	0.54	9 (5-19)	0.92					
VAS (mm) Baseline, mean ± SD	50 ± 23	43 ± 24	0.17	42 ± 23	44 ± 26	0.78	43 ± 23	41 ± 25	0.80	43 ± 25	46 ± 28	0.71	44 ± 25	41 ± 20	0.71					
VAS (mm) 1 year, mean ± SD	22 ± 22	21 ± 19	0.89	24 ± 23	22 ± 23	0.74	30 ± 25	23 ± 22	0.30	24 ± 23	19 ± 25	0.44	22 ± 21	30 ± 21	0.16					
HAQ Baseline, mean ± SD	1.1 ± 0.6	1.1 ± 0.7	0.81	1 ± 0.6	1.2 ± 0.8	0.29	1.2 ± 0.5	1.2 ± 0.8	0.87	1.1 ± 0.7	1.3 ± 0.7	0.16	1.1 ± 0.7	1.4 ± 0.9	0.09					
HAQ 1 year, mean ± SD	0.4 ± 0.5	0.5 ± 0.5	0.47	0.6 ± 0.6	0.4 ± 0.5	0.15	0.6 ± 0.5	0.4 ± 0.6	0.21	0.5 ± 0.6	0.4 ± 0.6	0.66	0.5 ± 0.5	0.8 ± 0.7	0.06					
CRP Baseline, med (IQR)	13 (5-27)	11 (4-34)	0.78	13 (5-27)	11 (3-37)	0.88	17 (6-26)	13 (4-28)	0.85	11 (3-26)	16 (3-37)	0.62	11 (4-26)	7 (3-28)	0.64					
CRP 1 year, med (IQR)	5 (3-8)	3 (3-7)	0.82	4 (3-8)	3 (3-7)	0.64	3 (3-10)	3 (3-7)	0.69	3 (3-7)	3 (3-7)	0.63	4 (3-7)	4 (3-9)	0.39					
DAS Baseline, mean ± SD	3.4 ± 0.9	3.4 ± 1.1	0.77	3.4 ± 0.9	3.5 ± 1.1	0.73	3.4 ± 0.7	3.3 ± 1	0.80	3.2 ± 0.9	3.4 ± 0.9	0.42	3.2 ± 1	3.4 ± 1.2	0.52					

Supplementary Table S1 (part 2 of 3): Demographic and clinical differences at baseline and 1 year, between patients that did not seroconvert ("Stable Pos") and those that seroconverted between 0-12 months ("Pos-Neg"). Bold typeface indicates significance after correction for multiple testing by Holmes-Bonferroni methods for 14 tests (14 autoantibodies). (continued)

	anti-CarP IgG (range: 0-5272 aU/mL)		anti-CarP IgM (range: 0-3650 aU/mL)		anti-CarP IgA (range: 0-3100 aU/mL)		Anti-acetyl-lysine IgG (range: 0-1000 aU/mL)		Anti-acetyl-ornithine IgG (range: 0-1000 aU/mL)	
	Stable Pos	Pos-Neg	Stable Pos	Pos-Neg	Stable Pos	Pos-Neg	Stable Pos	Pos-Neg	Stable Pos	Pos-Neg
N total	46	47	35	34	21	40	59	19	130	15
	p		p		p		p		p	
DAS 1 year, mean $\pm$ SD	1.5 $\pm$ 0.8	1.5 $\pm$ 0.9	0.97	1.7 $\pm$ 0.9	0.26	1.7 $\pm$ 0.7	1.4 $\pm$ 1	0.37	1.4 $\pm$ 0.9	2 $\pm$ 1
										0.03
Total SHS	0.0	0.0	0.76	0.0	0.27	0.0	0.45	0.0	0.08	0.0
Baseline, med (IQR)	(0.0-0.8)	(0.0-1.0)	(0.0-2.0)	(0.0-0.5)	(0.0-0.1)	(0.0-2.0)	(0.0-2.0)	(0.0-0.0)	(0.0-0.5)	(0.0-0.0)
Total SHS 1 year, med (IQR)	0.0	0.0	0.88	0.0	0.34	0.0	0.45	0.0	0.04	0.0
	(0.0-2.0)	(0.0-2.0)	(0.0-2.0)	(0.0-1.3)	(0.0-0.9)	(0.0-2.0)	(0.0-2.0)	(0.0-0.0)	(0.0-1.0)	(0.0-0.0)

P-values are based on t-tests, Mann Whitney tests, or Chi-squared tests for comparisons of means, medians, and frequencies, respectively. SD: standard deviation. Med: median. IQR: interquartile range. BMI: Body mass index. RAI: Ritchie Articular Index. SJC: Swollen joint count. ESR: Erythrocyte sedimentation rate. VAS: Visual analogue scale. HAQ: Health assessment questionnaire. CRP: C-reactive protein. DAS: Disease activity score. SHS: Sharp-van de Heijde score. Acetyl: acetylated. Cit: citrullinated.

Supplementary Table S1 (part 3 of 3): Demographic and clinical differences at baseline and 1 year, between patients that did not seroconvert (“Stable Pos”) and those that seroconverted between 0-12 months (“Pos-Neg”). Bold typeface indicates significance after correction for multiple testing by Holmes-Bonferroni methods for 14 tests (14 autoantibodies).

	Cit-Vimentin IgG (range: 0-10,000 aU/mL)				Cit-Fibrinogen α IgG (range: 0-25,000 aU/mL)				Cit-Fibrinogen β IgG (range: 0-100,000 aU/mL)				Cit-Enolase IgG (range: 0-70,000 aU/mL)			
	Stable Pos	Pos-Neg	25	p	Stable Pos	Pos-Neg	26	p	Stable Pos	Pos-Neg	23	p	Stable Pos	Pos-Neg	15	p
N total	93				32				95				54			
Levels Baseline, med (IQR)	4,003 (2305-8,871)	1,671 (800-3,120)		0.00	6,357 (2871-14,730)	2,952 (1763-4,077)		0.00	25,874 (12578-57,366)	6,741 (3549-8,961)		0.00	32,972 (14634-70,000)	8,777 (6401-11,380)		0.00
Age in years, mean ± SD	48 ± 13	50 ± 9		0.56	50 ± 13	51 ± 12		0.79	50 ± 12	49 ± 14		0.85	51 ± 13	50 ± 10		0.88
Symptom duration (weeks), med (IQR)	26 (9-46)	23 (15-32)		0.80	27 (9-55)	23 (10-31)		0.14	26 (11-47)	20 (10-28)		0.21	26 (10-41)	32 (10-56)		0.31
BMI (kg/m2), mean ± SD	26 ± 4	27 ± 6		0.44	26 ± 4	26 ± 5		0.88	26 ± 4	25 ± 4		0.10	26 ± 4	24 ± 3		0.07
Female gender (%)	53 (57%)	20 (80%)		0.04	25 (78%)	18 (69%)		0.44	62 (65%)	18 (78%)		0.23	32 (59%)	8 (53%)		0.68
Ever smoker (%)	50 (54%)	14 (56%)		0.88	14 (44%)	15 (58%)		0.29	49 (52%)	10 (43%)		0.46	34 (64%)	9 (60%)		0.77
Achieved early remission (%)	63 (68%)	18 (72%)		0.68	23 (72%)	16 (62%)		0.40	68 (72%)	17 (74%)		0.82	33 (61%)	12 (80%)		0.17
RAI index Baseline, med (IQR)	6 (4-10)	6 (4-10)		0.75	6 (4-8)	6 (3-8)		0.86	6 (4-8)	8 (5-11)		0.12	6 (4-9)	5 (3-10)		0.79
RAI index 1 year, med (IQR)	1 (0-3)	1 (0-4)		0.58	1 (0-5)	1 (0-3)		0.75	1 (0-3)	0 (0-2)		0.13	2 (0-3)	1 (0-3)		0.67
SJC Baseline, med (IQR)	6 (3-10)	5 (3-12)		0.96	4 (2-7)	5 (3-13)		0.33	4 (3-8)	8 (4-12)		0.06	6 (3-14)	7 (4-12)		0.65

Supplementary Table S1 (part 3 of 3): Demographic and clinical differences at baseline and 1 year, between patients that did not seroconvert (“Stable Pos”) and those that seroconverted between 0-12 months (“Pos-Neg”). Bold typeface indicates significance after correction for multiple testing by Holmes-Bonferroni methods for 14 tests (14 autoantibodies). (continued)

	Cit-Vimentin IgG (range: 0-10,000 aU/mL)			Cit-Fibrinogen α IgG (range: 0-25,000 aU/mL)			Cit-Fibrinogen β IgG (range: 0-100,000 aU/mL)			Cit-End-lase IgG (range: 0-70,000 aU/mL)		
	Stable Pos	Pos-Neg	p	Stable Pos	Pos-Neg	p	Stable Pos	Pos-Neg	p	Stable Pos	Pos-Neg	p
N total	93	25		32	26		95	23		54	15	
SJC 1 year, med (IQR)	0 (0-1)	0 (0-1)	0.65	0 (0-1)	0 (0-1)	0.43	0 (0-1)	0 (0-0)	0.26	0 (0-1)	0 (0-4)	0.48
ESR (mm/h) Baseline, med (IQR)	25 (11-37)	28 (14-55)	0.43	31 (19-38)	31 (13-44)	0.90	26 (14-38)	30 (19-36)	0.57	28 (17-44)	32 (11-55)	0.94
ESR (mm/h) 1 year, med (IQR)	9 (5-18)	9 (3-20)	0.89	11 (6-29)	11 (4-17)	0.43	11 (5-18)	6 (2-14)	0.31	11 (6-25)	7 (2-14)	0.20
VAS (mm) Baseline, mean ± SD	44 ± 25	52 ± 24	0.18	39 ± 22	43 ± 25	0.51	43 ± 23	41 ± 28	0.71	49 ± 23	44 ± 30	0.44
VAS (mm) 1 year, mean ± SD	23 ± 23	25 ± 20	0.74	24 ± 24	24 ± 19	0.98	22 ± 21	21 ± 20	0.73	23 ± 22	28 ± 25	0.45
HAQ Baseline, mean ± SD	1.1 ± 0.7	1.2 ± 0.6	0.63	1 ± 0.7	1.2 ± 0.6	0.33	1 ± 0.7	1.3 ± 0.5	0.05	1.1 ± 0.7	1.2 ± 0.8	0.93
HAQ 1 year, mean ± SD	0.5 ± 0.6	0.5 ± 0.6	0.99	0.5 ± 0.6	0.6 ± 0.4	0.60	0.5 ± 0.5	0.3 ± 0.4	0.17	0.5 ± 0.5	0.5 ± 0.6	0.93
CRP Baseline, med (IQR)	13 (4-28)	12 (4-34)	0.81	12 (3-26)	17 (5-28)	0.32	13 (4-28)	13 (8-21)	0.99	14 (4-43)	21 (9-35)	0.56
CRP 1 year, med (IQR)	4 (3-7)	3 (3-8)	0.51	4 (3-8)	3 (3-7)	0.48	3 (3-7)	4 (3-7)	1.00	3 (3-7)	3 (3-7)	0.95
DAS Baseline, mean ± SD	3.3 ± 1	3.4 ± 1	0.51	3.1 ± 0.8	3.3 ± 1.2	0.57	3.2 ± 1	3.3 ± 0.7	0.41	3.4 ± 1	3.3 ± 1.2	0.70

Supplementary Table S1 (part 3 of 3): Demographic and clinical differences at baseline and 1 year, between patients that did not seroconvert (“Stable Pos”) and those that seroconverted between 0-12 months (“Pos-Neg”). Bold typeface indicates significance after correction for multiple testing by Holmes-Bonferroni methods for 14 tests (14 autoantibodies). (continued)

	Cit-Vimentin IgG (range: 0-10,000 aU/mL)			Cit-Fibrinogen α IgG (range: 0-25,000 aU/mL)			Cit-Fibrinogen β IgG (range: 0-100,000 aU/mL)			Cit-Enolase IgG (range: 0-70,000 aU/mL)		
	Stable Pos	Pos-Neg	p	Stable Pos	Pos-Neg	p	Stable Pos	Pos-Neg	p	Stable Pos	Pos-Neg	p
N total	93	25		32	26		95	23		54	15	
DAS 1 year, mean ± SD	1.5 ± 0.9	1.5 ± 0.9	0.78	1.7 ± 1	1.4 ± 0.7	0.31	1.5 ± 0.9	1.2 ± 0.8	0.16	1.6 ± 0.9	1.5 ± 1.1	0.61
Total SHS Baseline, med (IQR)	0.0 (0.0-0.4)	0.0 (0.0-0.0)	0.61	0.0 (0.0-0.4)	0.0 (0.0-2.0)	0.24	0.0 (0.0-0.5)	0.0 (0.0-0.0)	0.16	0.0 (0.0-0.8)	0.5 (0.0-2.6)	0.16
Total SHS 1 year, med (IQR)	0.0 (0.0-0.5)	0.0 (0.0-0.5)	0.93	0.0 (0.0-1.1)	0.0 (0.0-3.5)	0.31	0.0 (0.0-1.5)	0.0 (0.0-0.1)	0.38	0.0 (0.0-1.0)	0.8 (0.0-3.0)	0.12

P-values are based on t-tests, Mann Whitney tests, or Chi-squared tests for comparisons of means, medians, and frequencies, respectively. SD: standard deviation. Med: median. IQR: interquartile range. BMI: Body mass index. RAI: Richtie Articular Index. SIC: Swollen joint count. ESR: Erythrocyte sedimentation rate. VAS: Visual analogue scale. HAQ: Health assessment questionnaire. CRP: C-reactive protein. DAS: Disease activity score. SHS: Sharp-van de Heijde score. Acetyl: acetylated. Cit: citrullinated.

Supplementary Figure S1: Sensitivity analysis within patients with baseline antibody levels above the median for each antibody. Number and percentage of baseline patients seroconverting ("Pos to Neg") or non-converting ("Stable pos") between 0-12 months are listed on the left, and the percentage of each subset subsequently reaching long-term sustained DFR is graphically depicted on the right. Anti-acetyl. pept. Abs = anti-acetylated peptide antibodies. Anti-cit. pept. Abs = anti-citrullinated peptide antibodies.

