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

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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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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 (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-

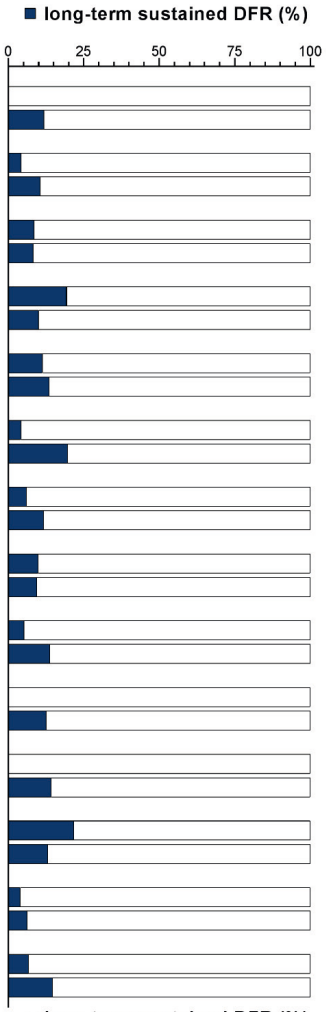
term SDFR more often than those who seroconverted for fewer (**FIGURE 1B**). Relative changes in autoantibody levels between 0 and 12 months did not differ between patients with or without long-term SDFR (data not shown).

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 F. 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*

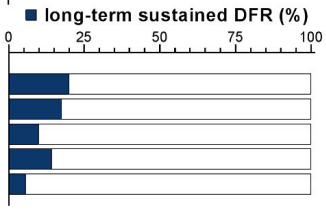
A. Seroconversion per antibody

		N	%
Anti-CCP2	**IgG**	167	
	Pos to neg	4	2%
	Stable pos	163	98%
	IgM	80	
	Pos to neg	23	29%
	Stable pos	57	71%
	IgA	84	
	Pos to neg	24	29%
	Stable pos	60	71%
RF	**IgM**	145	
	Pos to neg	31	21%
	Stable pos	114	79%
	IgA	112	
	Pos to neg	35	31%
	Stable pos	77	69%
Anti-CarP	**IgG**	93	
	Pos to neg	47	51%
	Stable pos	46	49%
	IgM	69	
	Pos to neg	34	49%
	Stable pos	35	51%
	IgA	61	
	Pos to neg	40	66%
	Stable pos	21	34%
Anti-acetyl. pept. Abs	**Lysine IgG**	78	
	Pos to neg	19	24%
	Stable pos	59	76%
	Ornithine IgG	145	
	Pos to neg	15	10%
	Stable pos	130	90%
Anti-cit. pept. Abs	**Vimentin IgG**	118	
	Pos to neg	25	21%
	Stable pos	93	79%
	Fibrinogen α IgG	58	
	Pos to neg	26	45%
	Stable pos	32	55%
	Fibrinogen β IgG	118	
	Pos to neg	23	19%
	Stable pos	95	81%
	Enolase IgG	69	
	Pos to neg	15	22%
	Stable pos	54	78%



B. Change in number of antibodies

		N	%
Change from baseline	Gain of ≥1	30	17%
	No change	42	23%
	Loss of 1	30	17%
	Loss of 2-3	42	23%
	Loss of ≥4	37	20%



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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		Stable Pos	Pos-Neg		Stable Pos	Pos-Neg		Stable Pos	Pos-Neg		Stable Pos	Pos-Neg	
N total	163	4	p	57	23	p	60	24	p	114	31	p	77	35	p
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		Stable Pos	Pos-Neg		Stable Pos	Pos-Neg		Stable Pos	Pos-Neg		Stable Pos	Pos-Neg	
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**
SJC 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
SJC 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 ± SD	43 ± 24	45 ± 17	0.84	42 ± 25	41 ± 26	0.91	42 ± 25	48 ± 24	0.35	42 ± 24	48 ± 21	0.24	43 ± 25	47 ± 24	0.47
VAS (mm) 1 year, mean ± SD	**24 ± 23**	**38 ± 26**	**0.22**	**25 ± 24**	**19 ± 20**	**0.33**	**25 ± 25**	**16 ± 15**	**0.07**	**24 ± 23**	**22 ± 19**	**0.65**	**26 ± 23**	**19 ± 21**	**0.11**
HAQ Baseline, mean ± SD	1.1 ± 0.7	1.2 ± 0.5	0.83	1 ± 0.7	1 ± 0.6	0.91	0.9 ± 0.7	1.3 ± 0.8	0.04	1 ± 0.7	1.5 ± 0.7	**0.00**	1.1 ± 0.6	1.3 ± 0.8	0.14
HAQ 1 year, mean ± SD	**0.5 ± 0.5**	**0.5 ± 0.7**	**0.93**	**0.5 ± 0.6**	**0.3 ± 0.4**	**0.19**	**0.5 ± 0.6**	**0.4 ± 0.5**	**0.79**	**0.5 ± 0.6**	**0.6 ± 0.6**	**0.58**	**0.6 ± 0.6**	**0.4 ± 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		Stable Pos	Pos-Neg		Stable Pos	Pos-Neg		Stable Pos	Pos-Neg		Stable Pos	Pos-Neg	
N total	163	4	p	57	23	p	60	24	p	114	31	p	77	35	p
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 ± SD	3.2 ± 0.9	3.4 ± 0.6	0.70	3.3 ± 1.1	3.3 ± 0.9	0.97	3.2 ± 1	3.2 ± 1	0.96	3.2 ± 0.9	3.5 ± 1	0.15	3.2 ± 1	3.5 ± 0.8	0.18
DAS 1 year, mean ± SD	**1.5 ± 0.9**	**1.9 ± 1.5**	**0.42**	**1.6 ± 0.9**	**1.3 ± 0.8**	**0.16**	**1.6 ± 0.9**	**1.5 ± 0.8**	**0.66**	**1.6 ± 0.9**	**1.5 ± 1**	**0.62**	**1.7 ± 1**	**1.3 ± 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: Richtie 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 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-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	p	35	34	p	21	40	p	59	19	p	130	15	p
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**
SJC 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		Stable Pos	Pos-Neg		Stable Pos	Pos-Neg		Stable Pos	Pos-Neg		Stable Pos	Pos-Neg	
N total	46	47	p	35	34	p	21	40	p	59	19	p	130	15	p
SJC 1 year, med (IQR)	**0 (0-1)**	**0 (0-1)**	**0.42**	**0 (0-2)**	**0 (0-1)**	**0.53**	**1 (0-2)**	**0 (0-1)**	**0.08**	**0 (0-0)**	**0 (0-1)**	**0.40**	**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)**	**9 (5-27)**	**0.54**	**9 (5-19)**	**9 (2-27)**	**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	p	35	34	p	21	40	p	59	19	p	130	15	p
DAS 1 year, mean ± SD	**1.5 ± 0.8**	**1.5 ± 0.9**	**0.97**	**1.7 ± 0.9**	**1.4 ± 0.9**	**0.26**	**1.7 ± 0.7**	**1.4 ± 1**	**0.37**	**1.4 ± 0.9**	**1.4 ± 1**	**0.97**	**1.4 ± 0.9**	**2 ± 1**	**0.03**
Total SHS Baseline, med (IQR)	0.0 (0.0-0.8)	0.0 (0.0-1.0)	0.76	0.0 (0.0-2.0)	0.0 (0.0-0.5)	0.27	0.0 (0.0-0.1)	0.0 (0.0-2.0)	0.45	0.0 (0.0-2.0)	0.0 (0.0-0.0)	0.08	0.0 (0.0-0.5)	0.0 (0.0-0.0)	0.13
Total SHS 1 year, med (IQR)	**0.0 (0.0-2.0)**	**0.0 (0.0-2.0)**	**0.88**	**0.0 (0.0-2.0)**	**0.0 (0.0-1.3)**	**0.34**	**0.0 (0.0-0.9)**	**0.0 (0.0-2.0)**	**0.45**	**0.0 (0.0-2.0)**	**0.0 (0.0-0.0)**	**0.04**	**0.0 (0.0-1.0)**	**0.0 (0.0-0.0)**	**0.24**

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. 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		Stable Pos	Pos-Neg		Stable Pos	Pos-Neg		Stable Pos	Pos-Neg	
N total	93	25	p	32	26	p	95	23	p	54	15	p
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)

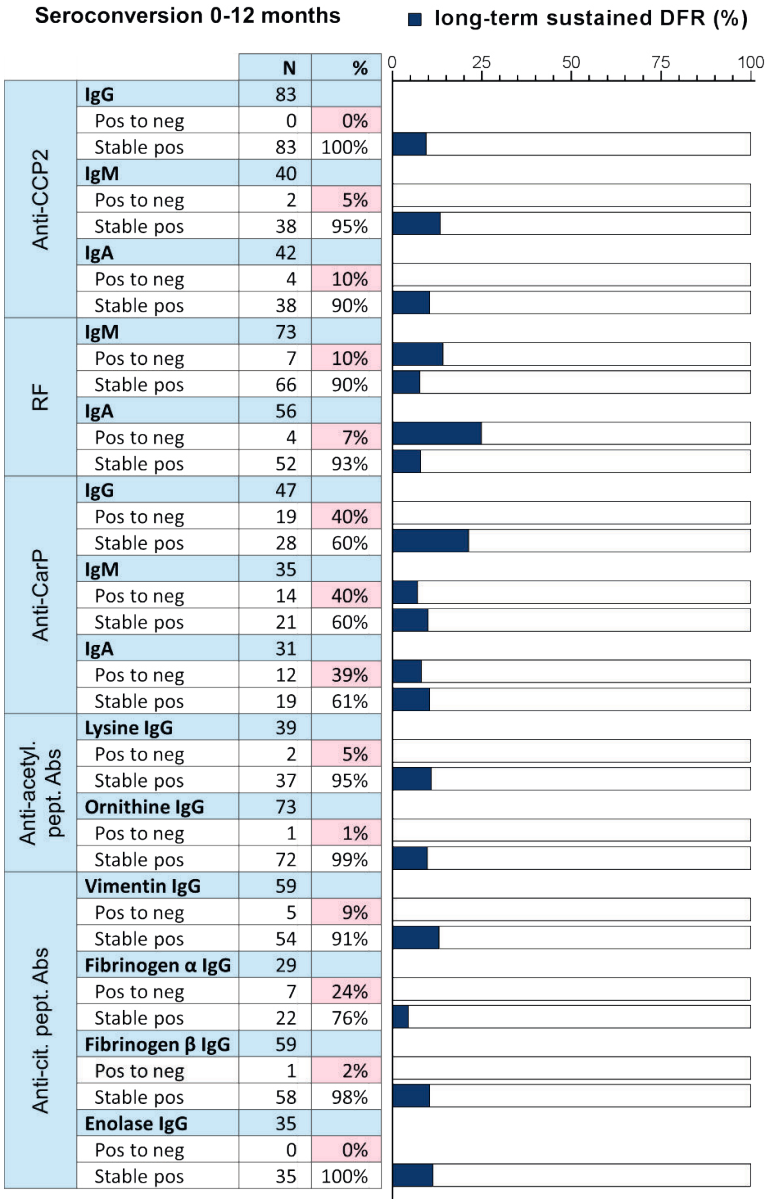
	Cit-Vimentin IgG (range: 0-10,000 aU/mL)			Cit-Fibrinogen α IgG (range: 0-25,000 aU/mL)			Cit-Fibrinogen β IgG (range: 0-100,000 aU/mL)			Cit-Enolase IgG (range: 0-70,000 aU/mL)		
	Stable Pos	Pos-Neg		Stable Pos	Pos-Neg		Stable Pos	Pos-Neg		Stable Pos	Pos-Neg	
N total	93	25	p	32	26	p	95	23	p	54	15	p
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		Stable Pos	Pos-Neg		Stable Pos	Pos-Neg		Stable Pos	Pos-Neg	
N total	93	25	p	32	26	p	95	23	p	54	15	p
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. 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 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.



		N	%
Anti-CCP2	**IgG**	83	
	Pos to neg	0	0%
	Stable pos	83	100%
	IgM	40	
	Pos to neg	2	5%
	Stable pos	38	95%
	IgA	42	
	Pos to neg	4	10%
	Stable pos	38	90%
RF	**IgM**	73	
	Pos to neg	7	10%
	Stable pos	66	90%
	IgA	56	
	Pos to neg	4	7%
	Stable pos	52	93%
Anti-CarP	**IgG**	47	
	Pos to neg	19	40%
	Stable pos	28	60%
	IgM	35	
	Pos to neg	14	40%
	Stable pos	21	60%
	IgA	31	
	Pos to neg	12	39%
	Stable pos	19	61%
Anti-acetyl. pept. Abs	**Lysine IgG**	39	
	Pos to neg	2	5%
	Stable pos	37	95%
	Ornithine IgG	73	
	Pos to neg	1	1%
	Stable pos	72	99%
Anti-cit. pept. Abs	**Vimentin IgG**	59	
	Pos to neg	5	9%
	Stable pos	54	91%
	Fibrinogen α IgG	29	
	Pos to neg	7	24%
	Stable pos	22	76%
	Fibrinogen β IgG	59	
	Pos to neg	1	2%
	Stable pos	58	98%
	Enolase IgG	35	
	Pos to neg	0	0%
	Stable pos	35	100%