

## Supplementary file

Supplementary table 1: Baseline characteristics and primary outcomes at year 1 and year 10 for RF-negative and ACPA-negative patients.

	<b>Sequential monotherapy</b>  <b>n=28</b>	<b>Step-up therapy</b>  <b>n=33</b>	<b>Initial combination with prednisone</b>  <b>n=34</b>	<b>Initial combination with infliximab</b>  <b>n=30</b>	<b>p-value</b>
<b>Baseline</b>					
Age (years), mean $\pm$ SD	55 $\pm$ 13	54 $\pm$ 16	58 $\pm$ 14	55 $\pm$ 15	
Female, n (%)	20 (71)	28 (85)	19 (56)	21 (70)	
Symptom duration (weeks), median (IQR)	19 (11-41)	27 (15-46)	22 (12-45)	22 (14-43)	
DAS, mean $\pm$ SD	4.9 $\pm$ 0.9	4.7 $\pm$ 0.9	4.5 $\pm$ 0.9	4.5 $\pm$ 1.1	
HAQ, mean $\pm$ SD	1.5 $\pm$ 0.7	1.4 $\pm$ 0.6	1.5 $\pm$ 0.7	1.5 $\pm$ 0.8	
Erosive disease, n (%)	19 (68)	22 (67)	21 (62)	22 (73)	
Smoker, n (%)	10 (36)	6 (18)	9 (26)	7 (23)	
<b>Year 1</b>					
SHS progression, median (IQR)	0 (0-0)	0 (0-0.9)	0 (0-1)	0 (0-0.5)	0.206
<b>Year 10</b>					
DAS, mean $\pm$ SD	1.6 $\pm$ 1.0	1.7 $\pm$ 0.8	1.4 $\pm$ 0.9	1.3 $\pm$ 0.8	0.090
HAQ, mean $\pm$ SD	0.6 $\pm$ 0.6	0.6 $\pm$ 0.7	0.5 $\pm$ 0.5	0.6 $\pm$ 0.4	0.575
DAS-Remission, n (%)	9 (32)	7 (21)	12 (35)	12 (40)	0.606
SHS progression, median (IQR)	0 (0-0.5)	0 (0-3.5)	0 (0-2.8)	0 (0-0.6)	0.762

ACPA: anti-citrullinated protein antibodies; RF: IgM rheumatoid factor; DAS: disease activity score;

HAQ: health assessment questionnaire (scale 0-3); Erosive disease: >0.5 erosion score on radiographs of hands and feet based on the Sharp van der Heijde score. Radiographs were assessed by two independent readers, and the mean score of both readers was used; SHS: Sharp van der Heijde score; IQR, interquartile range; SD, standard deviation.

Supplementary table 2: Functional ability and DAS-remission percentages during the first year for RF-negative and ACPA-negative patients according to the 4 strategy arms.

	<b>Sequential monotherapy</b>	<b>Step-up therapy</b>	<b>Initial combination with prednisone</b>	<b>Initial combination with infliximab</b>	<b>p-value</b>
	<b>n=28</b>	<b>n=33</b>	<b>n=34</b>	<b>n=30</b>	
<b>HAQ, mean ± SD</b>					
3 months	1.04±0.69	1.06±0.69	0.74±0.63	0.65±0.53	0.024
6 months	0.92±0.77	0.88±0.69	0.58±0.52	0.60±0.60	0.076
9 months	0.88±0.70	0.79±0.81	0.63±0.57	0.57±0.50	0.258
12 months	0.75±0.71	0.70±0.81	0.61±0.57	0.51±0.48	0.531
<b>DAS-remission, n (%)</b>					
3 months	1 (4)	1 (3)	3 (9)	4 (13)	0.417
6 months	5 (18)	6 (18)	8 (24)	8 (27)	0.806
9 months	5 (18)	6 (18)	6 (18)	11 (37)	0.210
12 months	9 (32)	8 (24)	9 (27)	11 (37)	0.805

ACPA: anti-citrullinated protein antibodies; RF: IgM rheumatoid factor; DAS: disease activity score;

HAQ: health assessment questionnaire (scale 0-3).

Supplementary table 3: Functional ability and DAS-remission percentages during the first year for RF-negative and ACPA-negative patients according to monotherapy and combination therapy.

	<b>Monotherapy</b>	<b>Combination therapy</b>	
	<b>n=61</b>	<b>n=64</b>	<b>p-value</b>
<b>HAQ, mean <math>\pm</math> SD</b>			
baseline	1.5 $\pm$ 0.6	1.5 $\pm$ 1.7	0.934
3 months	1.05 $\pm$ 0.68	0.70 $\pm$ 0.58	0.003
6 months	0.90 $\pm$ 0.72	0.59 $\pm$ 0.58	0.010
9 months	0.83 $\pm$ 0.75	0.60 $\pm$ 0.53	0.055
12 months	0.73 $\pm$ 0.76	0.56 $\pm$ 0.53	0.188
<b>DAS-remission, n (%)</b>			
3 months	2 (3)	7 (11)	0.166
6 months	11 (18)	16 (25)	0.370
9 months	11 (18)	17 (27)	0.252
12 months	17 (28)	20 (31)	0.824

ACPA: anti-citrullinated protein antibodies; RF: IgM rheumatoid factor; DAS: disease activity score; HAQ: health assessment questionnaire (scale 0-3).

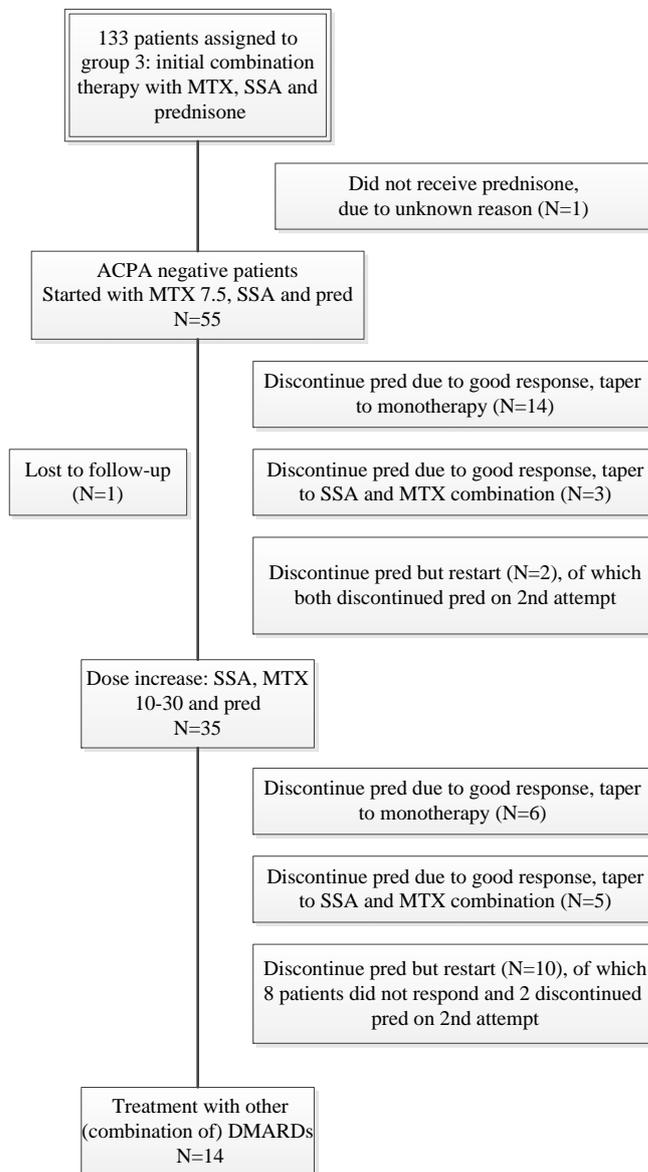
Supplementary table 4: Components of the disease activity score in patients who failed on the treatment steps in strategy arms 1 and 2, both starting with methotrexate monotherapy.

	<b>Failure on MTX at 3 months <i>15 mg weekly</i> N=64</b>	<b>Failure on MTX at 6 months <i>25 mg weekly</i> N=36</b>	<b>Failure on SSA at 9 months N=33</b>	<b>Failure on step 3 at 12 months N=21</b>
SJC	9 (4-14)	9 (4-12)	6 (2-10)	4 (3-11)
TJC	11 (7-16)	12 (8-17)	9 (5-17)	10 (7-16)
ESR	22 (12-32)	20 (13-29)	20 (14-41)	21 (12-24)
VAS	37 (20-51)	47 (26-55)	48 (25-69)	40 (20-65)

Numbers indicate median (interquartile range).

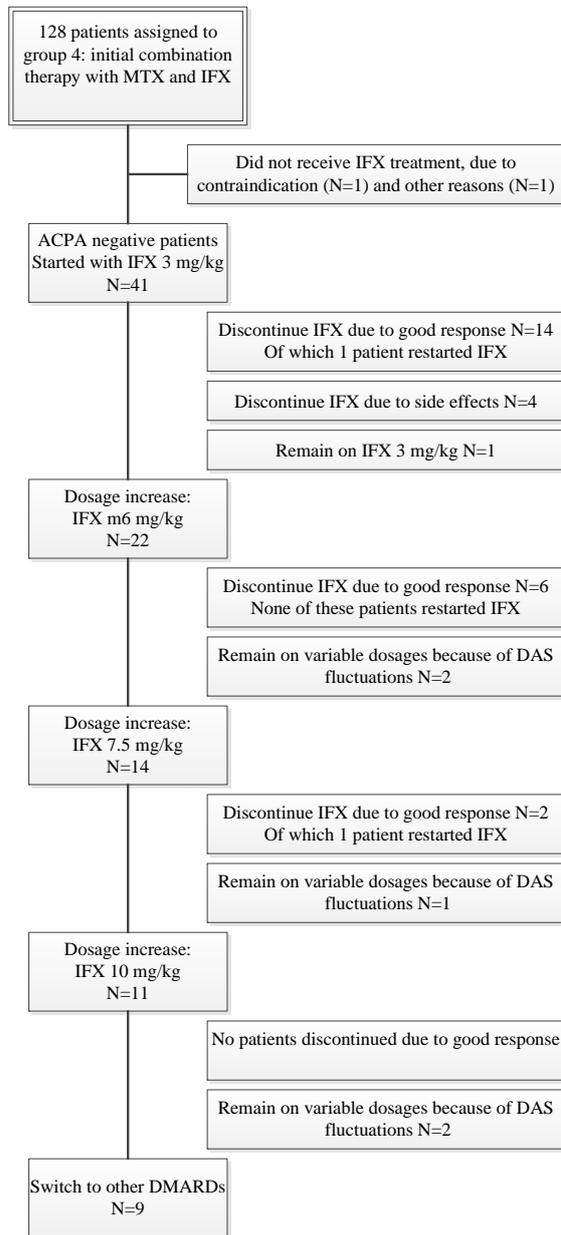
SJC: 44 swollen joint count; TJC: tender joint count (Ritchie articular index); ESR: erythrocyte sedimentation rate; VAS: patient's assessment of global health on a visual analogue scale (0-100 mm); MTX: methotrexate monotherapy; SSA: sulfasalazine (switching to SSA monotherapy in strategy arm 1, adding SSA to MTX in strategy arm 2); Step 3: leflunomide in strategy arm 1, adding hydroxychloroquine to MTX and SSA in strategy arm 2.

Supplementary figure 1: Flowchart of randomization arm 3 (initial combination with methotrexate, sulphasalazine and prednisone ) during year 1 and 2 of follow-up, stratified for ACPA-status.



ACPA, anti-citrullinated protein antibodies; DMARD, disease-modifying antirheumatic drugs; MTX, methotrexate; pred, prednisone; SSA, sulphasalazine

Supplementary figure 2: Flowchart of randomization arm 4 (initial combination with methotrexate and infliximab) during year 1 and 2 of follow-up, stratified for ACPA-status.



ACPA, anti-citrullinated protein antibodies; DAS, disease activity score; DMARD, disease-modifying antirheumatic drugs; IFX, infliximab; MTX, methotrexate.