

SUPPLEMENTARY APPENDIX S1

Results

Study population and baseline characteristics

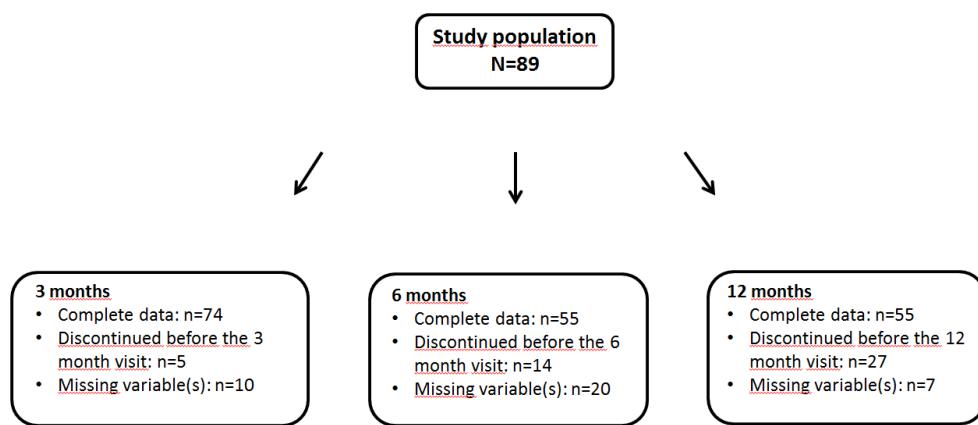


Figure S1. Overview of the study population and missing variables at the 3-, 6- and 12 months visits.

Missing variable(s) indicates that one or more of the ultrasound sum scores, clinical disease activity composite scores and/or inflammatory markers were missing in patients who were still in the study.

Sensitivity analyses using completer data

Table S1. Associations at 3, 6 and 12 months between etanercept serum concentration and improvement from baseline in clinical disease activity-, GS/PD ultrasound scores and biochemical inflammatory markers.

| | 3 months | | | 6 months | | | 12 months | | |
|--|---|-------------------|------|---|------------------|------|---|------------------|------|
| | Median (IQR) /Mean (SD) change from baseline | β (95% CI) | P | Median (IQR) /Mean (SD) change from baseline | β (95% CI) | P | Median (IQR) /Mean (SD) change from baseline | β (95% CI) | P |
| Delta sum GS ultrasound score | -7.0 (-14.0, -1.0) | -1.7 (-4.0, 0.6) | 0.14 | -9.0 (-15.0, -3.5) | -0.4 (-2.8, 2.0) | 0.76 | -12.0 (-19.5, -3.0) | -1.7 (-4.6, 1.2) | 0.25 |
| Delta sum PD ultrasound score | -4.0 (-12.0, -1.0) | -0.5 (-2.4, 1.4) | 0.61 | -5.0 (-12.5, -1.0) | -0.6 (-3.1, 1.9) | 0.65 | -6.0 (-15.0, -2.0) | -0.7 (-3.3, 1.8) | 0.56 |
| Delta DAS28-ESR | -1.1 (1.0) | -0.2 (-0.5, -0.0) | 0.05 | -1.2 (1.1) | 0.0 (-0.2, 0.3) | 0.85 | -1.3 (1.2) | -0.1 (-0.3, 0.2) | 0.61 |
| Delta SDAI | -6.9 (-12.2, -3.5) | -1.8 (-3.5, 0.0) | 0.05 | -8.3 (-12.2, -2.8) | -0.3 (-2.7, 2.1) | 0.81 | -8.6 (-13.8, -2.8) | -0.7 (-3.1, 1.7) | 0.57 |
| Delta Calprotectin ($\mu\text{g/L}$) | 477 (-1012, -169) | -146 (-386, 94) | 0.23 | -496 (-1120, -185) | -126 (-402, 150) | 0.36 | -469 (-1004, -142) | -180 (-485, 125) | 0.24 |
| Delta CRP (mg/L) | -2 (-7, 0) | -1.7 (-4.6, 1.2) | 0.24 | -2 (-7, 0) | -0.8 (-4.5, 2.8) | 0.64 | -3 (-8, 0) | -1.6 (-4.9, 1.7) | 0.34 |

Multivariate linear regression analyses, adjusted for age, gender, disease duration and prior use of biologic disease-modifying antirheumatic drug (yes/no). CRP, C-Reactive Protein; DAS28, 28-joint Disease Activity Score; ESR, Erythrocyte Sedimentation Rate; GS, Grayscale; IQR, interquartile range; PD, Power Doppler; SD, standard deviation; SDAI, Simplified Disease Activity Index.

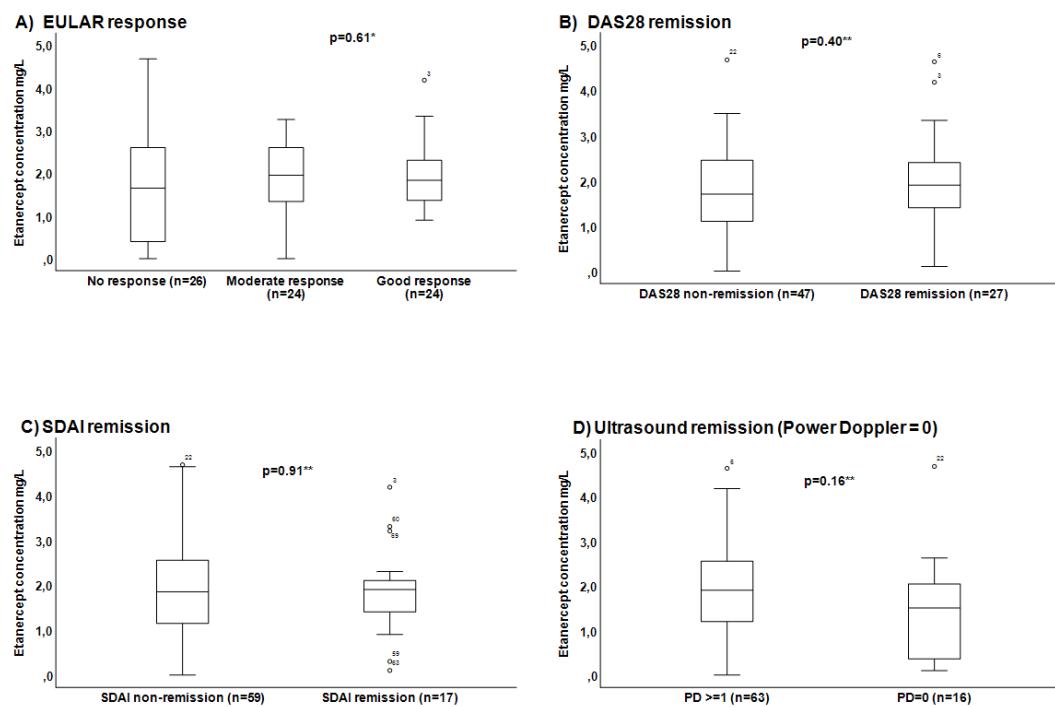


Figure S2 A-D. Etanercept concentrations in patients with response/remission vs. non-response/non-remission at 3 months.

A) EULAR good, moderate or non-response at 3 months. B) DAS28 remission ($\text{DAS28} < 2.6$) vs. non-remission ($\text{DAS28} \geq 2.6$) at 3 months. C) SDAI remission ($\text{SDAI} \leq 3.3$) vs. non-remission ($\text{SDAI} > 3.3$) at 3 months. D) PD ultrasound remission (Power Doppler=0) vs PD ultrasound activity (Power Doppler ≥ 1) at 3 months. *Kruskal-Wallis test. **Mann-Whitney U test. DAS28, Disease Activity Score 28 joints; EULAR, European League Against Rheumatism; PD, Power Doppler; SDAI, Simplified Disease Activity Index.

TableS2. Predictive value of etanercept concentration at 1 or 3 months for response/remission at 6 and 12 months.

| | 1 month etanercept concentration | | 3 month etanercept concentration | |
|--|----------------------------------|----------------------------|----------------------------------|----------------------------|
| | 6 months, AUC (95% CI) | 12 months, AUC (95% CI) | 6 months, AUC (95% CI) | 12 months, AUC (95% CI) |
| EULAR good/ moderate response | 0.49 (0.35 , 0.64) | 0.58 (0.42 , 0.73) | 0.53 (0.37 , 0.68) | 0.51 (0.36 , 0.67) |
| DAS28 remission | 0.49 (0.35 , 0.63) | 0.57 (0.42 , 0.73) | 0.47 (0.33 , 0.61) | 0.64 (0.49 , 0.79) |
| SDAI remission | 0.53 (0.37, 0.68) | 0.60 (0.43 , 0.76) | 0.54 (0.40 , 0.68) | 0.59 (0.44 , 0.75) |
| Ultrasound remission | 0.49 (0.34 , 0.64) | 0.52 (0.35 , 0.69) | 0.41 (0.24 , 0.58) | 0.44 (0.27 , 0.60) |

AUC, Area Under Curve; CI, Confidence Interval; DAS28, Disease Activity Score 28 joints; EULAR, European League Against Rheumatism; SDAI, Simplified Disease Activity Index.

Robustness analyses of multivariable linear regression analyses and mixed effect regression model

Table S3. Associations at 3, 6 and 12 months and in longitudinal analyses, between etanercept serum concentration and biochemical inflammatory markers.

| | 3 months | | 6 months | | 12 months | | Mixed effect regression model | |
|--------------------------------------|----------------------|-------------|---------------------|------|---------------------|------|-------------------------------|--------|
| | β (95% CI) | P* | β (95% CI) | P* | β (95% CI) | P* | β (95% CI) | P† |
| Log Calprotectin ($\mu\text{g/L}$) | -0.13 (-0.21, -0.05) | 0.02 | -0.05 (-0.14, 0.04) | 0.26 | -0.07 (-0.15, 0.01) | 0.09 | -0.10 (-0.14, -0.06) | <0.001 |
| Log CRP (mg/L) | -0.1 (-0.2, 0.1) | 0.38 | 0.0 (-0.1, 0.2) | 0.64 | -0.1 (-0.2, 0.0) | 0.23 | -0.07 (-0.13, 0.00) | 0.05 |

Robustness analyses using log-transformed variables for continuous biochemical inflammatory markers, adjusted for baseline value of the marker, age, gender, disease duration and prior use of biologic disease-modifying antirheumatic drug (yes/no). The P-values denote *the P-value in cross-sectional linear regression analyses, † P-value in mixed effect linear regression model. CI, confidence interval CRP, C-Reactive Protein.