Online Supplementary material for

Effects of treatment with etanercept *versus* methotrexate on sleep quality, fatigue and selected immune parameters in patients with active rheumatoid arthritis

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Supp. S1. *Screening procedure to prevent dropout after the first night of polysomnography*

To prevent dropout after the first night of polysomnography (PSG), eligible patients were screened before baseline to record the number of periodic leg movements (PLM) and sleep-disordered breathing (SDB) events using ambulatory 6–channel monitoring. Included in the study were all patients without specific SDB symptoms, such as snoring and suspected apnoea's, as well as symptomatic patients with an apnoea-hypopnoea index below 30 per hour of sleep and a PLM index below 20 per hour of sleep. Patients with a PLM index >20 per hour of sleep were able to participate in the study if they also had a periodic leg movement arousal index (PLMAI) below 10 per hour during the first adaptation night. As a result of this screening, no patient was excluded because of these criteria. Other exclusion criteria included history of restless legs syndrome, narcolepsy, parasomnia, hypersomnia, known sleep-wake rhythm disorder and a PLMAI of more than 10 per hour in the first adaptation night.

Supp.S2. *Multi-channel flow cytometry*

To block unspecific binding, peripheral blood mononuclear cells (PBMC) were treated with human immunoglobulin G (IgG; Flebogamma, Grifols, Los Angeles, California, USA). Stainings (incubation for 10 min at 4°C followed by washing with phosphate buffered saline/bovine serum albumin) were performed with the following anti-human antibodies: anti–CD3–Pacific blue (UCHT1), anti–CD4–APC–Cy7 (RPA–T4), αντι–CD8-Pacific orange (3B5), Caltag Laboratories, Hamburg, Germany), anti–CD19–APC (HIB19), anti–CD14vPE (M5E2), anti–CD22–FITC (HIB22) (all BD Biosciences, Heidelberg, Germany) and anti–CD20–PE–Cy7 (2H7) (BSV BioScience, Aachen, Germany). Acquisition and analysis were performed using an LSR II Flow Cytometer (BD Biosciences) and FlowJo software (Tree Star, Ashland, Oregon, USA).

Cytokine concentrations

Concentrations of interleukin (IL)–1β, IL–2, IL–4, IL–5, IL–6, IL–7, IL–8, IL–10, IL–12, IL–13, IL–17, interferon gamma (IFNγ), tumour necrosis factor (TNF), monocyte chemotactic protein–1 (MCP–1), macrophage inflammatory protein–1 beta (MIP–1β , also known as CCL4), granulocyte colony–stimulating factor (GCSF) and granulocyte-macrophage colony–stimulating factor (GMCSF) were quantified by multiplex suspension array (Bio-Rad Laboratories, Munich, Germany) according to the manufacturer's instructions.

Neuroendocrine immunological parameters

Concentrations of 17–OH–progesterone, 17β–estradiol, dehydroepiandrosterone (DHEA), free testosterone and neuropeptide Y (all IBL, Hamburg, Germany) were quantified in plasma samples by enzyme–linked immunosorbent assay and radioimmunoassay according to the manufacturer's instructions as described previously (1).

References

1. HÄRLE P, SARZI-PUTTINI P, CUTOLO M, STRAUB RH: No change of serum levels of leptin and adiponectin during anti-tumour necrosis factor antibody treatment with adalimumab in patients with rheumatoid arthritis. *Ann. Rheum. Dis.* 2006; 65: 9701.

Tab. S1. *Clinical and selected laboratory parameters* ([1]Differences in ETA vs MTX were estimated using covariance methods adjusted for baseline. CfB, change from baseline; CI, confidence interval; CRP, C-reactive protein; $DAS28_{CRP}$, 28-joint disease activity score; ETA, etanercept; IQR, interquartile range; MTX, methotrexate; SD, standard deviation; SJC, swollen joint count; TJC, tender joint count; V, variables compared between MTX and ETA groups; VAS, visual analogue scale.)

	baseline				week 8						week 16					difference[1] ETA vs MTX		
V	**n**	**M**	**SD**	**MTX vs. ETA, *p***	**n**	**M**	**SD**	**CfB±SD**	**CfB, *p***	**MTX vs. ETA, *p***	**n**	**M**	**SD**	**CfB±SD**	**CfB, *p***	**MTX vs. ETA, p**	**wk**	**CfB (adj)**	**95% CI**
100–mm $VAS_{disease\ activity}$																			
MTX	17	45.5	19.2	0.610	16	29.9	17.9	-15.7±16.3	<0.01	0.221	16	30.9	21.0	-14.4±16.0	<0.01	0.492	8	8.9	-1.8;19.6
ETA	17	49.2	22.5		16	22.8	14.5	-25.3±16.0	<0.01		16	26.0	19.1	-22.1±23.5	<0.01		16	7.1	-5.5;19.8
TJC (0–28 joints)																			
MTX	18	10.4	7.3	0.594	17	3.8	4.4	-9.0±55.1	0.51	0.900	14	4.4	4.0	-6.0±42.1	0.61	0.731	8	4.3	-22.7;31.4
ETA	17	11.9	9.1		17	4.0	3.3	-13.4±54.4	0.33		16	3.9	4.1	-19.0±48.6	0.14		16	9.9	-15.7;35.5
SJC (0–28 joints)																			
MTX	18	5.4	3.3	0.915	17	2.8	2.6	-2.6±2.8	<0.01	0.049	16	2.2	2.8	-3.6±4.1	<0.01	0.153	8	1.6	0.22;3.0
ETA	17	5.5	4.4		15	1.3	1.5	-4.5±4.2	<0.01		16	1.1	1.5	-4.3±6.8	<0.01		16	1.1	-0.5;2.7
CRP, mg/l, median (IQR)																			
MTX	18	0.9	1.1	0.175	17	0.7	1.0	-0.3±1.0	0.26	0.940	17	0.4	1.0	-0.5±1.2	0.11	0.943	8	0.3	-0.3;0.9
ETA	17	1.8	2.4		15	0.7	1.1	-1.2±1.8	0.02		17	0.5	0.8	-1.3±2.2	0.02		16	0.1	-0.5;0.7
$DAS28_{CRP}$																			
MTX	18	4.4	0.9	0.994	17	3.2	1.0	-1.2±1.2	<0.01	0.246	16	3.1	1.2	-1.4±1.6	<0.01	0.258	8	0.6	-0.2;1.3
ETA	17	4.4	1.7		13	2.7	1.3	-1.9±1.2	<0.01		16	2.7	1.1	-1.8±2.0	<0.01		16	0.5	-0.4;1.3

Tab. S2. *Patient–reported outcome measures* ([1]Differences in ETA vs MTX were estimated using covariance methods adjusted for baseline. CfB, change from baseline; CI, confidence interval; ETA, etanercept; HAQ-DI, Functional Disability Index of the Health Assessment Questionnaire; MFI–20, 20–item Multidimensional Fatigue Inventory; MTX, methotrexate; SF–36, 36–item Short–Form Health Survey; SD, standard deviation; V, variables compared between MTX and ETA groups.)

baseline					week 8						week 16						Difference[1] ETA vs. MTX		
V	**n**	**M**	**SD**	**MTX vs ETA, *p***	**n**	**M**	**SD**	**CfB±SD**	**CfB, *p***	**MTX vs. ETA, *p***	**n**	**M**	**SD**	**CfB±SD**	**CfB, *p***	**MTX vs. ETA, *p***	**wk**	**CfB (adj)**	**95% CI**
HAQ–DI																			
MTX	18	1.1	0.6	0.35	16	0.9	0.5	-0.4±0.3	<0,01	0.75	17	0.9	0.6	-0.3±0.4	<0,01	0.88	8	-0.1	-0.3;0.2
ETA	16	1.3	0.6		16	1.0	0.6	-3.4±0.4	<0,01		16	0.8	0.6	-0.4±0.4	<0,01		16	0.1	-0.2;0.3
SF–36 mental health																			
MTX	19	31.0	13.1	0.69	17	54.1	8.8	2.1±8.0	0.3	0.18	17	54.5	7.6	3.1±8.1	0.13	0.89	8	-5.9	-13.2;1.3
ETA	16	39.1	15.6		16	60.4	12.4	6.5±14.9	0.1		16	55.8	8.8	1.9±8.7	0.39		16	-0.1	-5.5;5.2
SF–36 physical health																			
MTX	19	43.4	41.5	0.96	17	55.1	16.8	13.4±14.6	<0,01	0.41	17	14.2	1.2	14.2±15.2	<0.01	0.98	8	-3.1	13.6;7.5
ETA	16	44.2	10.7		16	60.1	17.3	15.8±12.5	<0.01		16	55.6	15.9	11.4±12.5	<0.01		16	2.2	-7.7;12.1
SF–36 total																			
MTX	19	49.8	12.5	0.92	17	56.79	12.3	8.4±11.1	<0,01	0.25	17	57.5	13.15	9.6±11.9	<0.01	1.0	8	-4.9	-13.8;3.9
ETA	16	49.4	8.4		16	62.37	15.1	13.0±14.4	<0.01		16	57.5	13.63	8.1±11.2	0.01		16	1.1	-7.1;9.3
MFI–20 general fatigue																			
MTX	18	12.7	4.2	0.33	17	12.82	3.9	10.8±14.8	0.80		17	12.4	12.35	10.4±14.3	0.79	0.85	8	0.4	-1.6;3.7
ETA	16	13.9	4.0		16	11.75	2.7	9.8±13.7	0.07		16	12.1	12.13	10.4±13.8	0.10		16	0.8	-2.3;2.7
MFI–20 physical fatigue																			
MTX	18	13.1	3.6	0.1	17	12.71	3.5	-0.6±5.5	0.69	0.25	17	12.0	3.69	-1,4±5.2	0.29	0.73	8	1.4	-1.4;4.1
ETA	16	14.9	2.2		16	11.25	3.6	-3.6±4.0	<0.01		16	12.4	3.6	-2.4±3.6	0.02		16	-0.2	-3.1;2.6
MFI–20 reduced activity																			
MTX	18	11.2	4.7	0.39	17	11.24	4.7	-0.6±4.1	0.55	0.75	17	11.2	4.32	-0.1±5.5	0.96	0.94	8	-0.2	-3.2;2.7
ETA	16	12.4	3.3		16	11.75	3.5	-0.6±4.6	0.59		16	11.1	3.75	-1.3±4.3	0.24		16	0.4	-2.6;3.3
MFI–20 reduced motivation																			
MTX	18	8.8	3.5	0.24	17	9.41	3.2	0.5±4.3	0.65	0.76	17	9.4	3.41	0.2±3.1	0.76	0.98	8	0.6	-1.7;2.9
ETA	16	10.1	2.9		16	9.06	3.3	-1.1±3.4	0.23		16	9.4	3.44	-0.7±3.8	0.48		16	0.4	-1.9;2.6
MFI–20 mental fatigue																			
MTX	18	9.8	3.7	0.12	17	10.65	3.6	0.4±4.4	0.70	0.44	17	10.6	3.57	0.8±3.9	0.46	0.65	8	1.8	-1.0;4.6
ETA	16	11.8	3.6		16	9.56	4.4	-2.2±3.9	0.04		16	3.8	3.79	-1.7±3.2	0.05		16	1.6	-0.9;4.0

Tab. S3. *Selected sleep parameters* ([1]Differences in ETA vs MTX were estimated using covariance methods adjusted for baseline. CfB, change from baseline; CI, confidence interval; ETA, etanercept; MTX, methotrexate; REM, rapid eye movement sleep; S1–S4, sleep stages 1 to 4; TST, total sleep time; V, variables compared between MTX and ETA groups; WASO, wake time after sleep onset)

	baseline				week 8						week 16						difference[1] ETA vs. MTX		
V	**n**	**M**	**SD**		**n**	**M**	**SD**	**CfB±SD**	***p***	**MTX vs. ETA, *p***	**n**	**M**	**SD**	**CfB±SD**	***p***	**MTX vs. ETA, *p***	**wk**	**CfB (adj)**	**95% CI**
TST (min)																			
MTX	19	437.1	42.4	0.365	17	435.1	35.8	0.8±33.0	0.92	0.315	14	432.5	35.5	1.2±64.5	0.94	0.184	8	-15.3	-35.3;4.6
ETA	17	432.5	35.5		17	446.4	28.7	23.0±46.3	0.06		16	447.4	24.2	23.8±46.7	0.06		16	-15.1	-38.1;7.9
S1 (min)																			
MTX	19	72.3	48.1	0.980	17	62.9	45.2	-9.0±55.1	0.51	0.747	14	63.9	45.6	-6.0±42.1	0.61	0.555	8	4.3	-22.7;31.4
ETA	17	71.9	44.9		17	58.6	31.4	-13.4±54.4	0.33		16	55.7	28.6	-19.0±48.6	0.14		16	9.9	-15.7;35.5
S2 (min)																			
MTX	18	147.2	42.2	0.276	17	160.1	61.8	9.8±64.4	0.57	0.502	13	145.3	45.8	2.9±45.3	0.57	0.244	8	5.5	-31.5;42.5
ETA	17	130.8	45.2		17	148.3	37.2	17.5±54.4	0.20		16	167.9	54.5	38.5±41.9	<0.01		16	-31.3	-64.4;1.8
S3 (min)																			
MTX	19	45.6	20.0	0.954	17	45.9	16.3	2.1±17.2	0.62	0.813	14	41.2	13.1	-0.6±18.1	0.91	0.321	8	-0.8	-10.8;9.3
ETA	17	45.2	25.2		17	26.6	26.5	-2.5±12.8	0.43		16	48.2	22.9	6.8±23.6	0.27		16	-7.1	-20.4;6.9
S4 (min)																			
MTX	19	19.3	37.3	0.402	17	50.8	27.1	-0.8±24.2	0.89	0.392	14	53.2	26.0	-1.5±26.7	0.84	0.573	8	-12.1	-28.1;4.0
ETA	17	40.2	25.2		15	59.5	29.1	14.0±27.7	0.07		15	47.6	26.9	2.1±33.4	0.81		16	2.0	-16.3;20.2
REM (min)																			
MTX	19	69.6	24.2	0.566	17	71.6	21.4	2.9±23.4	0.62	0.517	14	74.8	13.3	-6.8±28.5	0.39	0.635	8	-2.1	-15.4;11.2
ETA	17	75.0	31.1		17	76.9	25.7	1.95±22.8	0.73		16	77.6	26.9	4.8±29.1	0.52		16	-2.0	-17.2;13.1
WASO (min)																			
MTX	19	36.3	24.7	0.943	17	30.4	20.7	-6.6±20.5	0.2	0.597	14	23.0	31.6	-18.0±38.3	0.10	0.296	8	0.62	-7.4;13.8
ETA	17	36.9	22.6		17	27.2	13.8	-9.7±22.2	0.09		16	33.0	18.8	-4.2±22.1	0.46		16	0.37	-29.9;7.9
WASO (min)																			
MTX	19	88.0	39.4	0.369	17	55.7	28.0	-28.4±41.4	0.01	0.780	14	59.8	31.3	-22.3±55.8	0.16	0.070	8	-6.72	-29.2;15.8
ETA	17	75.5	42.7		17	59.2	40.8	-16.3±39.5	0.11		16	40.3	25.3	-37.9±35.4	<0.01		16	19.0	-2.3;40.2
sleep efficiency (%)																			
MTX	19	84.0	7.7	0.148	17	84.0	7.9	-0.4±7.3	0.82	0.875	14	83.0	9.7	-1.3±13.5	0.71	0.320	8	-2.2	-7.9;3.5
ETA	17	79.3	11.4		17	83.4	10.7	4.2±10.4	0.12		16	86.5	9.1	8.1±9.7	<0.01		16	-5.1	-12.3;2.0

Supplemental material

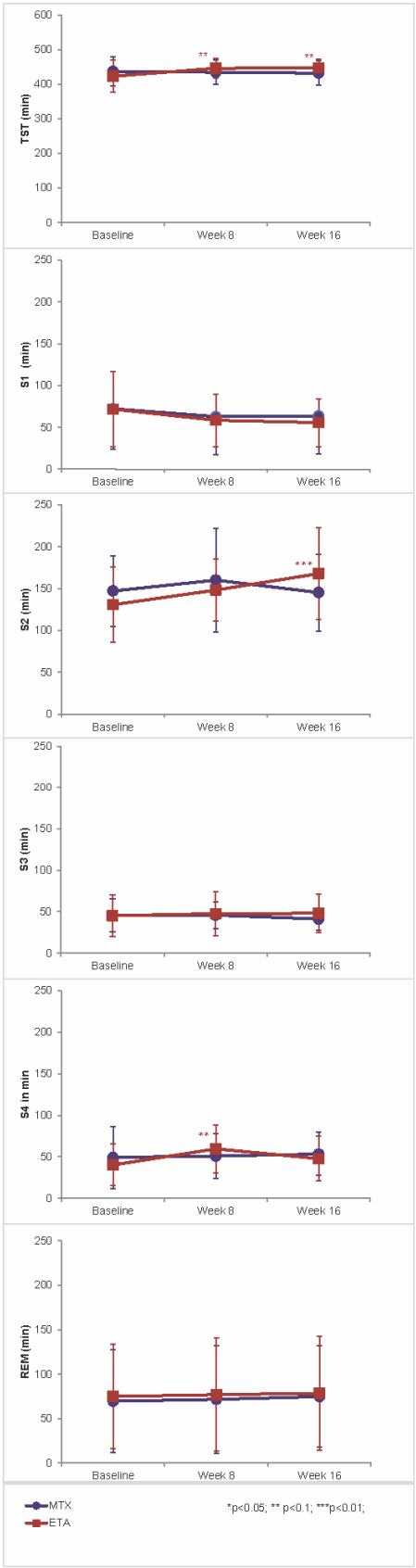


Fig. S1. *Comparison of sleep phases* (ETA, etanercept; MTX, methotrexate; REM, rapid eye movement sleep; S1–S4, sleep stages 1 to 4; TST, total sleep time)

Tab. S4. *Selected humoral, cellular and hormonal parameters* ([1]Differences in ETA vs MTX were estimated using covariance methods adjusted for baseline. CfB, change from baseline; CI, confidence interval; DHEA, dehydroepiandrosterone; ETA, etanercept; G-CSF, granulocyte colony-stimulating factor; GM–CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; MCAF, monocyte chemotactic and activating factor; IFN-γ, interferon gamma; MCP–1, monocyte chemoattractant protein–1; MIP–1β, macrophage inflammatory protein–1 beta; MTX, methotrexate; NPY, neuropeptide Y; PBMC, peripheral blood mononuclear cells; SD, standard deviation; TNF, tumour necrosis factor; V, variables compared between MTX and ETA groups)

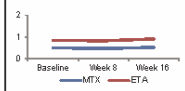
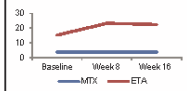
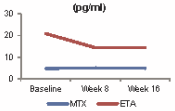
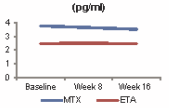
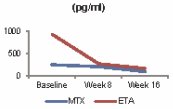
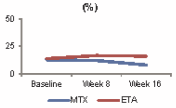
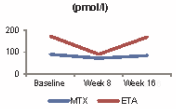
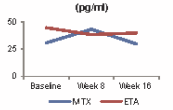
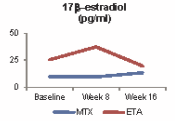
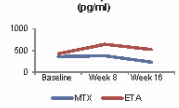
	baseline				week 8						week 16						difference[1] ETA vs. MTX		
V	**n**	**M**	**SD**	**MTX vs. ETA, *p***	**n**	**M**	**SD**	**CfB±SD**	***p***	**MTX vs. ETA, *p***	**n**	**M**	**SD**	**CfB±SD**	***p***	**MTX vs. ETA, *p***	**wk**	**CfB (adj)**	**95% CI**
NPY (pmol/l)																			
MTX	16	89.8	31.8	0.362	15	72.3	40.5	-21.4±30.7	0.02	0.223	16	84.2	40.5	-1.9±41.1	0.86	0.410	8	-8.0	-36.8;20.8
ETA	15	172.6	368.2		17	90.2	44.7	-88.0±372.3	0.38		15	168.2	400.2	-2.0±581.4	0.99		16	-95.7	-323.6;132.3
DHEA (ng/ml)																			
MTX	17	4.1	0.7	0.371	15	4.1	0.8	-0.09±0.5	0.49	0.716	16	4.4	0.6	0.21±0.47	0.47	0.588	8	-0.14	-0.54;0.25
ETA	15	4.3	0.8		17	4.2	1.0	0.04±0.52	0.75		15	4.2	1.0	-0.18±1.45	1.45		16	0.22	-0.46;0.90
free testosterone (pg/ml)																			
MTX	17	3.78	0.98	0.005	15	3.66	1.03	-0.12±0.22	0.07	0.020	16	3.53	0.98	0.16±0.40	0.15	0.018	8	-0.20	-0.46;0.05
ETA	15	2.48	1.42		17	2.51	1.55	0.06±0.34	0.25		15	2.47	1.38	0.01±2.17	0.98		16	0.98	-0.06;2.02
17β–estradiol (pg/ml)																			
MTX	16	9.7	6.2	0.03	15	9.7	6.4	-1.44±4.3	0.25	0.01	16	13.5	15.4	3.3±15.0	0.43	0.19	8	-20.2	-44.8;4.4
ETA	15	25.6	27.1		17	37.6	39.5	12.2±41.1	0.27		15	19.9	10.9	-6.9±31.2	0.42		16	-6.1	-18.0;5.7
17–OH–progesterone																			
MTX	17	0.50	0.31	0.07	15	0.46	0.23	-0.04±0.18	0.42	0.155	16	0.52	0.31	0.06±0.27	0.41	0.250	8	0.005	-0.11;012
ETA	15	0.34	0.13		17	0.36	0.16	0.03±0.18	0.50		15	0.39	0.31	0.05±0.37	0.64		16	0.07	-0.18;0.32
IL–1β (pg/ml)																			
MTX	17	17.0	12.9	0.125	16	21.2	12.4	4.4±12.3	0.19	0.276	16	21.0	11.8	4.1±12.0	0.21	0.199	8	-13.4	-43.2;16.3
ETA	15	75.7	153.1		17	35.4	49.4	-37.6±154.8	0.21		15	35.4	42.2	-0.8±12.2	0.81		16	3.2	-6.5;12.8
IL–2 (pg/ml)																			
MTX	17	38.9	27.6	0.66	16	32.9	21.5	-6.2±10.8	0.05	0.138	16	34.2	23.6	-5.2±9.5	0.05	0.191	8	13.2	-1.6;28.1
ETA	15	53.0	127.7		17	21.9	20.0	-33.3±127.5	0.33		15	23.3	21.6	3.5±8.8	0.17		16	-7.4	-14.9;0.19

	baseline				week 8						week 16						difference[1] ETA vs. MTX		
V	**n**	**M**	**SD**	**MTX vs. ETA, *p***	**n**	**M**	**SD**	**CfB±SD**	***p***	**MTX vs. ETA, *p***	**n**	**M**	**SD**	**CfB±SD**	***p***	**MTX vs. ETA, *p***	**wk**	**CfB (adj)**	**95% CI**
IL–4 (pg/ml)																			
MTX	17	4.8	2.8	0.076	16	5.1	3.3	0.23±0,6	0.18	0.021	16	4.8	2.8	-0.04±0.5	0.78	0.004	8	-4.4	-8.6;-0.23
ETA	15	16.2	25.5		17	9.3	6.2	-6.8±27.1	0.35		15	9.5	5.2	-0.07±2.8	0.93		16	0.02	-1.7;1.8
IL–5 (pg/ml)																			
MTX	17	3.8	0.0	0.138	16	3.8	0.0	0.0±0.0	n.a.	0.266	16	3.8	0.0	0.0±0.0	n.a.	0.212	8	4.4	-0.64;9.5
ETA	15	11.5	21.0		17	19.6	55.9	9.5±39.0	0.36		15	18.7	46.9	7.4±27.4	0.33		16	2.8	-1.0;6.6
IL–6 (pg/ml)																			
MTX	17	244.0	371.2	0.450	16	201.0	308.4	-40.5±138.1	0.27	0.093	14	87.9	179.4	-144.1±272.0	0.06	0.792	8	153.3	-21.7;328.4
ETA	15	692.7	2390.9		17	67.9	70.9	-626.0±2408.9	0.33		16	74.8	66.2	-0.14±35.9	0.99		16	-42.6	-119.9;34.8
IL–7 (pg/ml)																			
MTX	17	35.2	57.8	0.011	16	33.1	55.0	-4.5±10.8	0.13	0.031	14	34.2	61.8	-3.3±12.1	0.31	0.006	8	-67.7	-172.4;36.9
ETA	15	171	198.0		17	130.7	163.9	-35.3±234.4	0.57		16	124.2	104.4	0.7±37.9	0.94		16	1.2	-23.2;35.5
IL–8 (pg/ml)																			
MTX	17	30.8	37.0	0.199	16	43.0	82.9	-10.3±38.9	0.32	0.814	14	29.6	27.2	-7.7±28.9	0.27	0.181	8	-14.6	-23.9;-5.2
ETA	15	44.6	17.9		17	38.2	10.4	-6.5±18.7	0.20		16	39.6	7.0	-6.8±14.4	0.10		16	1.8	-17.6;21.1
IL–10 (pg/ml)																			
MTX	17	1.7	1.1	0.002	16	1.6	1.0	-0.08±0.24	0.23	0.037	14	1.6	0.9	-0.2±0.4	0.19	0.016	8	6.3	1.2;11.4
ETA	15	12.1	12.6		17	14.5	23.4	2.69±13.7	0.46		16	13.4	18.3	0.6±7.9	0.79		16	4.0	0.2;7.7
IL–12 (pg/ml)																			
MTX	17	102.5	89.4	0.164	16	82.5	82.2	-15.4±55.1	0.38	0.065	14	102.7	75.8	-2.5±39.9	0.81	0.221	8	-227.5	-456.8;-1.8
ETA	15	234.9	371.7		17	141.3	93.4	98.8±380.5	0.38		16	137.5	79.1	-5.8±43.5	0.63		16	-76.0	-144.0;-8.0
IL–13 (pg/ml)																			
MTX	17	7.4	0.0	0.294	16	7.4	0.0	0.0±0.0	n.a.	0.340	14	7.4	0.0	0.0±0.0	n.a.	n.a.	8	-0.5	-1.6;0.5
ETA	15	9.3	7.6		17	7.8	1.8	-1.59±7.9	0.49		16	7.4	0.0	00.0±0.0	n.a.		16	0	
IL–17 (pg/ml)																			
MTX	17	30.0	46.0	0.0005	16	25.8	44.0	1.4±6.2	0.41	0.0001	14	32.4	49.1	0.8±17.5	0.87	0.0005	8	6.0	-2.1;14.2
ETA	15	83.2	28.0		17	79.8	26.2	-3.9±10.0	0.15		16	84.8	15.8	-4.1±5.5	0.01		16	3.4	-9.6;16.4
GCSF (pg/ml)																			
MTX	17	77.2	42.2	0.255	16	74.9	43.5	-3.4±16.5	0.44	0.620	14	71.1	30.1	-9.0±19.8	0.10	0.314	8	0.05	-27.9;28.0
ETA	15	98.3	60.1		17	81.9	36.7	-14.5±64.8	0.41		16	85.6	31.9	-2.1±37.8	0.84		16	-9.1	-27.2;9.1

	baseline				week 8						week 16						difference[1] ETA vs. MTX		
V	**n**	**M**	**SD**	**MTX vs. ETA, *p***	**n**	**M**	**SD**	**CfB±SD**	***p***	**MTX vs. ETA, *p***	**n**	**M**	**SD**	**CfB±SD**	***p***	**MTX vs. ETA, *p***	**wk**	**CfB (adj)**	**95% CI**
GM–CSF (pg/ml)																			
MTX	17	0.4	0.0	0.284	16	0.4	0.0	0.0±0.0	n.a.	0.206	14	0.4	0.0	0.0±0.0	n.a.	0.153	8	-6.9	-18.6;4.7
ETA	15	118.3	60.1		17	6.8	20.0	-111.4±449.0	0.35		16	6.0	15.3	3.3±8.9	0.19		16	-9.1	-1.5;1.2
IFN-γ (pg/ml)																			
ETA	15	426.5	748.0	0.775	17	643.5	1,5450	254.5±1,003	0.34	0.546	15	524.2	1,109	92.7±545.5	0.54	0.355	8	-235.2	-727.1;256.6
MTX	17	356.4	624.3		16	379.6	789.2	3.1±434.6	0.98		16	234.9	582.8	-100.6±265.3	0.16		16	-178.7	-500.9;143.5
MCP1/MCAF (pg/ml)																			
MTX	17	131.9	73.4	0.436	16	135.6	76.0	-7.1±47.9	0.58	0.223	14	124.0	74.12	0.54±25.2	0.94	0.681	8	25.8	-31.4;83.1
ETA	15	194.5	318.1		17	103.6	71.9	-84.4±321.5	0.33		16	112.2	87.6	1.8±54.3	0.90		16	-0.0	-31.2;31.2
MIP–1β (pg/ml)																			
MTX	17	345.1	175.1	0.002	16	314.4	98.4	1.8±76.4	0.93	<0.001	14	340.2	124.9	4.0±82.3	0.85	<0.001	8	81.2	22.5;140.0
ETA	15	176.7	75.9		17	132.5	81.3	-44.2±57.0	<0.01		16	125.4	61.6	-48.2±56.2	<0.01		16	110.9	66.0;155.8
TNF (pg/ml)																			
MTX	17	105.9	177.5	0.149	16	92.6	167.1	-20.7±88.1	0.38	0.028	14	73.5	151.3	-38.5±86.8	0.11	0.004	8	-227.5	-456.8;-1.8
ETA	15	773.6	1852.4		17	315.2	351.3	-455.8±1927.8	0.38		16	319.8	269.8	21.7±78.9	0.32		16	-76.0	-144.0;-8.0
lymphocytes (% of PBMC)																			
MTX	20	37.8	33.9	0.644	28	43.1	32.2	22.4±31.0	<0.01	0.928	22	30.6	32.9	9.7±36.9	0.28	0.371	8	-0.89	-19.0;17.3
ETA	28	42.3	32.2		30	42.4	28.5	9.7±36.9	<0.01		22	39.3	31.1	21.8±33.9	<0.01		16	-11.5	-33.4;10.5
monocytes (% of PBMC)																			
MTX	10	16.5	15.2	0.966	14	17.2	12.0	0.4±10.3	0.92	0.641	11	15.7	18.6	-5.73±19.3	0.40	0.632	8	-0.19	-5.6;9.2
ETA	14	16.8	12.1		15	19.1	10.0	0.8±13.2	0.83		11	19.1	13.7	0.63±13.5	0.89		16	-5.9	-18.8;7.1
CD3+ T cells (% of lymphocytes)																			
MTX	10	56.5	30.5	0,707	14	68.9	26.3	3.9±22.7	0.62	0.249	11	42.7	36.1	-18.0±28.1	0.09	0.247	8	9.26	-5.4;23.9
ETA	14	60.8	24.4		15	58.8	19.6	-5.4±8.6	0.04		11	59.8	31.0	-5.6±31.8	0.59		16	-15.9	-45.3;13.4
CD3+/CD4+ T helper cells (% of lymphocytes)																			
MTX	10	39.4	23.3	0.956	14	46.6	20.5	0.1±13.3	0.99	0.201	11	25.4	34.5	-12.2±19.4	0.10	0.298	8	5.2	-5.9;16.3
ETA	14	38.9	17.0		15	38.1	13.7	-4.6±11.5	0.17		11	35.3	18.5	-4.6±11.9	0.26		16	-8.12	-23.7;7.4
CD3+/CD8+ cytotoxic T cells (% of lymphocytes)																			
MTX	10	12.8	9.5	0.800	14	12.2	8.0	-5.1±9.4	0.14	0.186	10	8.1	7.3	-6.4±7.4	0.03	0.064	8	-6.7	-12.6;-0.77
ETA	13	13.8	9.1		13	16.7	9.2	1.4±4.3	0.30		10	16.2	10.7	1.7±8.7	0.57		16	-9.2	-16.4;-2.0

	baseline				week 8						week 16						difference[1] ETA vs. MTX		
V	**n**	**M**	**SD**	**MTX vs. ETA, *p***	**n**	**M**	**SD**	**CfB±SD**	***p***	**MTX vs. ETA, *p***	**n**	**M**	**SD**	**CfB±SD**	***p***	**MTX vs. ETA, *p***	**wk**	**CfB (adj)**	**95% CI**
CD3-/CD19+ B cells (% of lymphocytes)																			
MTX	10	11.5	9.2	0.874	14	12.4	10.1	-1.0±9.4	0.77	0.943	11	8.1	7.8	-5.8±10.7	0.14	0.395	8	-2.4	-8.9;4.0
ETA	14	11.0	6.1		14	12.2	8.7	-5.8±10.7	0.31		11	10.7	6.2	1.9±7.2	0.43		16	-4.8	-11.6;2.1
CD22+ B cells (% of CD3-/CD19+ B cells)																			
MTX	16	47.9	42.6	0.323	22	73.7	33.5	1.5±22.3	0.82	0.809	18	49.2	45.2	26.2±34.2	0.02	0.665	8	-9.7	-29.2;9.7
ETA	28	61.0	41-2		24	71.3	34.2	11.7±32.6	0.11		20	55.4	42.9	-9.7	0.72		16	17.9	-12.9;48.8
CD20+/CD22+ B cells (%CD3-/CD19+ B cells)																			
MTX	8	45.8	43.8	0.538	11	67.4	34.9	-8.3±27.9	0.50	0.974	9	47.8	45.3	-24.2±35.9	0.16	0.937	8	-16.5	-47.1;14.1
ETA	14	57.5	40.6		12	66.9	33.5	-8.8±33.5	0.41		10	46.1	44.6	-10.2±47.8	0.54		16	21.0	-29.2;71.3

Fig. S2. *Selected humoral, cellular and hormonal parameters* (CfB, change from baseline; CI, confidence interval; DHEA, dehydroepiandrosterone; ETA, etanercept; G–CSF, granulocyte colony–stimulating factor; GM–CSF, granulocyte–macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; MCAF, monocyte chemotactic and activating factor; MCP–1, monocyte chemoattractant protein–1; MIP–1β, macrophage inflammatory protein–1 beta; MTX, methotrexate; PBMC, peripheral blood mononuclear cells; TNF, tumour necrosis factor; V, variables compared between MTX and ETA groups; *$p \leq 0.1$; **$p \leq 0.05$; ***$p \leq 0.01$; red flag, change from baseline for ETA; blue flag, change from baseline for MTX; black flag, MTX versus ETA)

Example of curve											
Description of the curves	MTX	no change	no change	no change	decrease	decrease	decrease	decrease & increase	increase & decrease	increase	increase & decrease
	ETA	no change	increase	decrease	no change	decrease	increase	decrease & increase	decrease	increase & decrease	increase & decrease
Parameters		DHEA 17–OH–progresterone	IL–5 IL–10** IL–17**/***	IL–1β IL–4* IL–7**/***/**** IL–13 GM–CSF MIP1β**/***	free testosteron**/***	IL–2 IL–6 GCSF MCP1/MCAF TNFα** CD3-/CD19+	CD3+/CD4+	NPY*	IL–8 lymphocytes* PBMC***/** CD3+/CD4+	17β-estradiol**	IFNγ CD22+ CD20+/22+ CD3-/CD19+ monocytes