

Supplemental Online Content

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eFigure 1. Flow Chart

eTable 1. Response in ADAb Unclassified Patients

eTable 2. Retention Rates by Drug and Visits

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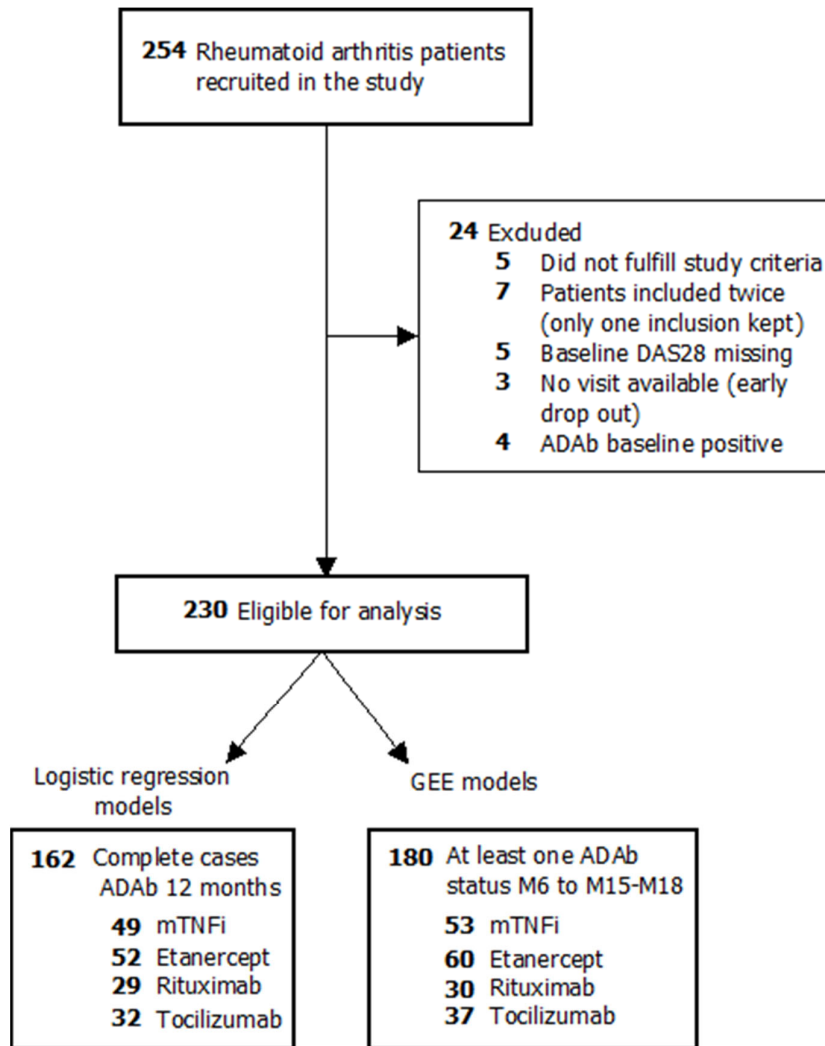
eTable 4. Association of EULAR Response With Clinical and Demographic Variables at Each Visit From M6 to M15-M18 (Univariate GEE Models)

eFigure 2. Drug Concentration Compared Between ADAb Positive and Negative and Between Responders and Non-Responders in Etanercept-Treated Patients

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This supplemental material has been provided by the authors to give readers additional information about their work.

eFigure 1: Flow Chart



eTable 1: Response in ADAb Unclassified Patients: n (%)

| | All bDMARDs | mTNFi | ETN | RTX | TCZ |
|---|-------------|-----------|-----------|---------|-----------|
| N of ADAb overall unclassified | 66 | 18 | 30 | 1 | 17 |
| Responders in ADAb unclassified | 16 (24.2%) | 4 (22.2%) | 8 (26.7%) | 0 (0%) | 4 (23.5%) |
| | | | | | |
| N of ADAb transient/persistent unclassified | 78 | 27 | 30 | 2 | 19 |
| Responders in ADAb unclassified | 17 (21.8%) | 4 (14.8%) | 8 (26.7%) | 1 (50%) | 4 (21.1%) |
| | | | | | |

eTable 2: Retention Rates by Drug and Visits

| bDMARD | M1 | M3 | M6 | M12 | M15-18 |
|---------------|------------|-----------|-----------|------------|---------------|
| All bDMARDs | 230 (100%) | 220 (96%) | 188 (82%) | 155 (67%) | 93 (40%) |
| mTNFi | 68 (100%) | 64 (94%) | 55 (81%) | 42 (62%) | 24 (35%) |
| Etanercept | 82 (100%) | 77 (94%) | 65 (79%) | 55 (67%) | 33 (40%) |
| Rituximab | 30 (100%) | 30 (100%) | 30 (100%) | 27 (90%) | 10 (33%) |
| Tocilizumab | 50 (100%) | 49 (98%) | 38 (76%) | 30 (60%) | 25 (50%) |

eTable 3: Association of Therapy Response With ADAb Status at M6 (Univariate Logistic Regression)

| | | All bDMARDs N=188 OR (95% CI) | mTNFi N=58 OR (95% CI) | Etanercept N=63 OR (95% CI) | Rituximab N=30 OR (95% CI) | Tocilizumab N=37 OR (95% CI) |
|---|----------|-------------------------------------|------------------------------|-----------------------------------|----------------------------------|------------------------------------|
| Model 1 : ADAb status M6 | Negative | reference | reference | reference | reference | reference |
| | Positive | 0.40 [0.20-0.80] | 0.50 [0.17-1.48] | 0.35 [0.05-2.9] | 0.82 [0.19-3.56] | 0.41 [0.07-2.46] |

eTable 4: Association of EULAR Response With Clinical and Demographic Variables at Each Visit From M6 to M15-M18 (Univariate GEE Models)

| Variable | p-value | FDR |
|---|----------------------------|-----------------------------|
| DAS28 baseline | 9.2*10⁻⁷ | 1,75*10⁻⁵ |
| BMI (<25 or >=25 kg/m2) (visits) | 0.0018 | 0,0171 |
| RF baseline | 0.0043 | 0,02723 |
| Age at inclusion | 0.012 | 0,057 |
| White blood cells (visits) | 0.015 | 0,057 |
| Neutrophils (visits) | 0.02 | 0,06333 |
| Familial history autoimmunity | 0.034 | 0,0923 |
| Medical and surgical history | 0.062 | 0,1473 |
| Creatinine (visits) | 0.12 | 0,2533 |
| Packyears (0,[1-15), >=15) | 0.2 | 0,38 |
| Smoke (ever/never) | 0.42 | 0,7255 |
| Smoke (No/current/quit) | 0.5 | 0,7917 |
| ALAT baseline | 0.66 | 0,9263 |
| Lymphocytes (visits) | 0.74 | 0,9263 |
| Cigarettes per day (0,[1-10), >=10) | 0.77 | 0,9263 |
| ASAT baseline | 0.78 | 0,9263 |
| Sex | 0.87 | 0,9724 |
| Disease duration (years) | 0.99 | 1 |
| ACPA | 1 | 1 |

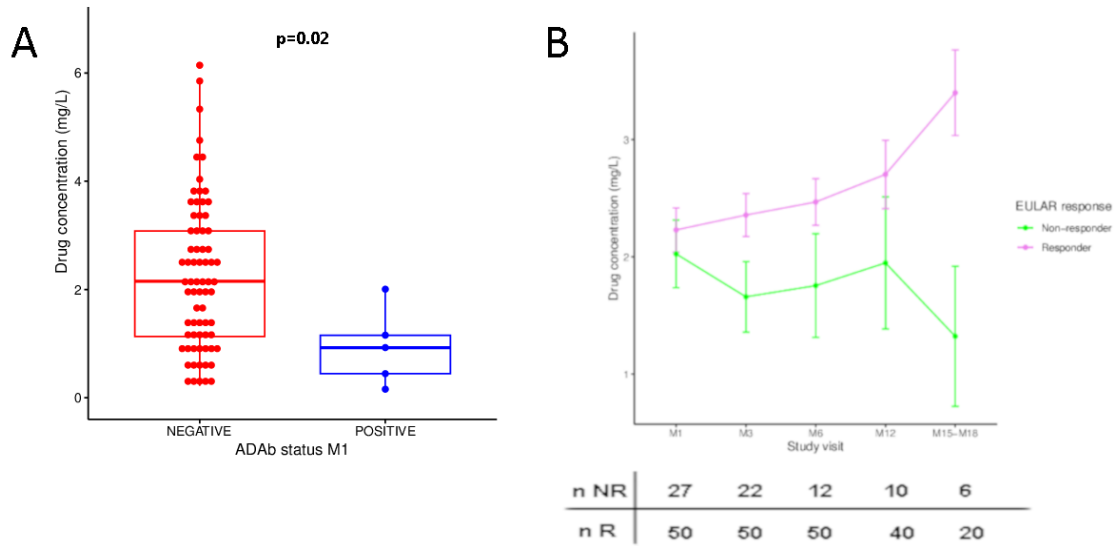
Variables with FDR<6% are shown in bold.

FDR: False discovery rate.

eFigure 2: Drug Concentration Compared Between ADAb Positive and Negative and Between Responders and Non-Responders in Etanercept-Treated Patients

Serum drug concentration were measured using Elisa.

- (A) Drug levels at month 1 visit for ADAb positive and negative patients. The other visits are not shown because all patients were ADAb negative after month 1.
- (B) Drug levels at each visit for EULAR responder and non-responder patients.



eTable 5: Association of ADAb Status at M12 and ADAb Persistency With Methotrexate Comedication (Model 1: Univariate Logistic Regression; Model 2: Polytomous Logistic Regression).

Etanercept was not analyzed in model 2 because no persistent ADAb were developed by etanercept-treated patients.

| | | All bDMARDs N=165 | | mTNFi N=50 | | Etanercept N=52 | Rituximab N=29 | | Tocilizumab N=34 | |
|---|-----------------------------|--|----------------------------------|-------------------------|-------------------------|--------------------|--|-------------------------|-------------------------|-------------------------|
| | MTX comedication | OR (95% CI) | | OR (95% CI) | | OR (95% CI) | OR (95% CI) | | OR (95% CI) | |
| Model 1 : ADAb status M12 | No | reference | | reference | | reference | reference | | reference | |
| | Yes | 0.50 [0.25-1.00] | | 0.23 [0.06-0.87] | | 0.51 [0.08-3.46] | 0.8 [0.16-3.88] | | 1.05 [0.17-6.60] | |
| | | | | | | | | | | |
| | | All bDMARDs (no Etanercept) N=101 | | mTNFi N=41 | | Etanercept NA | Rituximab N=28 | | Tocilizumab N=32 | |
| | | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) |
| | MTX comedication | trans vs neg | pers vs neg | trans vs neg | pers vs neg | NA | trans vs neg | pers vs neg | trans vs neg | pers vs neg |
| Model 2 : ADAb transient or persistent M12 | No | refer. | refer. | refer. | refer. | NA | refer. | refer. | refer. | reference |
| | Yes | 0.88 [0.21- 3.69] | 0.36 [0.13- 0.97] | 0.30 [0.04- 2.42] | 0.28 [0.06- 1.35] | NA | 3699 [0.9*1 0 ⁻³⁴ - 1.5*10 ⁴ 0 | 0.32 [0.05- 1.85] | 0.53 [0.04- 7.05] | 1.05 [0.09- 11.6] |