Evaluation of anti-TNF levels and anti-TNF antibodies in rheumatic diseases treated with adalimumab, etanercept and infliximab. Results from a local registry

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Different Monoclonal Autoantibodies against biological therapies, with different immunogenicity reaction, according with origin,

**Murins**

**Chimerics:**
- Infliximab
- Rituximab

**Humans:**
- Adalimumab
- Golimumab

**Humanized:**
- Tocilizumab
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Chimerics:
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**Fusion Proteins**:
- Etanercept
- Abatacept
ANTI-TNF IMMUNOGENICITY

Where arise the anti-TNF antibody response in classic anti-TNF drugs

- INF, ADA: Variable region
- ETN: Hinge fusion protein region
To analyze the clinical relevance of serum levels of adalimumab (ADA), etanercept (ETN) and infliximab (INF) and the production of, anti-ADA, anti-ETN or anti-INF antibodies from a local registry of patients with rheumatic diseases.
ANTI-TNF IMMUNOGENICITY: Material and Methods

- Epidemiological and Clinical characteristics:
  - Sex, age
  - Time of disease evolution
  - Previous anti-TNF

- Clinical activity index:
  - Peripheral arthritis (RA, PsA): DAS28-ESR, SDAI
  - Spondilitis (AE): BASDAI, BASFI

- Responders:
  - RA, PsA: DAS28-ESR≤3 or SDAI≤3.3
  - AE: BASDAI≤4
ANTI-TNF IMMUNOGENICITY: Material and Methods

- Serum levels of anti-TNF and anti-TNF antibodies:
  - ELISA kit. Promonitor®-ADA, ETN, INF. Proteomika, Derio, Vizcaya. Spain
  - Distributed by Menarini Diagnóstics S.A®, Badalona, Barcelona, Spain

- Cut-off levels:
  - ADA: <0.002 mg/L to >8 U/mL
  - ETN: <0.052 mg/L to >138 U/mL
  - INF: <0.053 mg/L to >37 U/mL

- Serum samples were collected at the time of infusion of INF or the same day before injection for ADA or ETN, and stored frozen until analysis.
ANTI-TNF IMMUNOGENICITY: RESULTS
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- Nº consecutive patients included: 81
- Nº tests anti-TNF antibodies analyzed: 99
- Women: 74%
- Mean age: 55±15 years (16-78)
- Time on treatment: > 6 months
- Anti-TNF:
  - ADA: 56 tests in 48 patients
  - INF: 31 tests in 21 patients
  - ETN: 12 tests in 12 patients
ANTI-TNF IMMUNOGENICITY: Results

Diagnosis of patients was:

- RA: 49%
- AE: 35%
- PsA: 11%
- Others: 5%

Was the first anti-TNF received:

- INF: 24 (96%)
- ADA: 37 (76%)
- ETN: 5 (42%)
ANTI-TNF IMMUNOGENICITY: Results

Average time of treatment:

- Whole population: 31±22 months (median: 25)
- ADA: 23.9 months (median: 21)
- ETN: 41.6 months (median: 34)
- INF: 43.7 months (median: 42)
Anti-TNF antibodies were detected:

- Whole population: 9/81 patients (11%)
- INF: 4/25 patients (16%)
- ADA: 5/49 patients (10%)
- ETN: 0/12 patients (0%)

![Bar chart showing immunogenicity of Anti-TNF antibodies for different drugs: Infliximab (16%), Adalimumab (10%), Etanercept (0%).]
ANTI-TNF IMMUNOGENICITY: **Results**

Anti-TNF antibodies were detected:

- **Whole population:** 9/81 patients (11%)
- **INF:** 4/25 patients (16%)
- **ADA:** 5/49 patients (10%)
- **ETN:** 0/12 patients (0%)

- **Infusion reaction in INF group:** 3/4 (75%) patients (all of 3 patients with high level of Abs)
Characteristics in responders (DSA28-28≤3) and non-responders patients with RA o PsA, receiving INF.

<table>
<thead>
<tr>
<th></th>
<th>Responders (n: 18)</th>
<th>Non Responders (n: 8)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>INF level, mean (range)</td>
<td>20.22±18.06 (3.60-73.21)</td>
<td>0.16±0.34 (0.04-1.14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anti-INF-Abs</td>
<td>0%</td>
<td>62.5%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>DAS28-ESR (mean)</td>
<td>2.55</td>
<td>3.76</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Responders, have significative superior level of INF, no presence of antibodies and mean DAS28 of clinical remission.
ANTI-TNF IMMUNOGENICITY: **Results**

Characteristics in **responders** (DSA28-28≤3) and **non-responders** patients with RA or PsA, receiving ADA.

<table>
<thead>
<tr>
<th></th>
<th>Responders (n: 28)</th>
<th>Non Responders (n: 15)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ADA-level mean (range)</strong></td>
<td>9.49±4.96 (1.56-19.84)</td>
<td>2.70±3.41 (0.002-11.28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Anti-ADA-Abs</strong></td>
<td>0%</td>
<td>23%</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>DAS28-ESR (mean)</strong></td>
<td>2.48</td>
<td>4.34</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Characteristics in **responders** (DSA28-28≤3 or SDAI≤3.3) and **non-responders** patients with RA or PsA, receiving ETN.

<table>
<thead>
<tr>
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<th>Responders (n: 6)</th>
<th>Non Responders (n: 6)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ETN-level mean (range)</strong></td>
<td>2,69±0.51 (1,48- 3,90)</td>
<td>3,69±0.96 (1,45-5,94)</td>
<td>0.3412</td>
</tr>
<tr>
<td>Anti-ETN-Abs</td>
<td>0%</td>
<td>0%</td>
<td>ns</td>
</tr>
<tr>
<td><strong>DAS28-ESR / SDAI (mean)</strong></td>
<td>1,88 / 2,33</td>
<td>3,10 / 5,45</td>
<td>0.002 / 0.016</td>
</tr>
</tbody>
</table>
ANTI-TNF IMMUNOGENICITY: Conclusions

1. Serum anti-TNF antibodies were detected in 16% of patients receiving treatment with INF, 10% of patients treated with ADA and were not detected (0%) in patients receiving ETN.

2. Patients responders receiving ADA or INF have absence of Abs and significantly higher serum concentrations of anti-TNF, and clinical response than non-responders.

3. Immunogenicity can induce inefficacy in patients on treatment with ADA or INF.

4. For patients receiving ETN other causes than immunogenicity must be involved for inefficacy.