Nuove sfide nel trattamento dell’AR con farmaci biologici

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RHEU-1155037-0000-REM-W-06/2017
Biologic agents for treatment of Rheumatoid Arthritis
EU Approval Timelines

Adapted from European Medicines Agency website
Treatment changes and improved outcomes in RA: an overview of a large inception cohort from 1989 to 2009

Wietske Kievit¹, Jaap Fransen¹, Maarten C. de Waal Malefijt², Alfons A. den Broeder³ and Piet L. C. M. van Riel¹

Rheumatology 2013;52:1500-8

Fig. 1 Proportions of patients receiving different drug treatments (A) and the mean MTX dose (B) over time.

- Medication use
- Methotrexate dose
- Median joint damage progression

(DAS28) Functional Disability (HAQ) Orthopedic surgery
Biologic agents and survival: data from RABBIT register

|                             | Unadjusted HR | Adjusted HR: 6 (rituximab 12) months risk window approach | Adjusted HR: Ever exposed approach |  
|-----------------------------|---------------|-----------------------------------------------------------|-----------------------------------|---
|                             | HR 95% CI     | HR 95% CI  p Value                                        | HR 95% CI  p Value               | Deaths | PYRS |
|-----------------------------|---------------|-----------------------------------------------------------|-----------------------------------|---|
| Methotrexate                | Ref.          | Ref.                                                      | Ref.                              | 96t/78† | 7012t/6469† |
| Other synth. DMARDs        | 2.53 1.95 to 3.28 | 1.14 0.86 to 1.51 0.36                                   | 0.98 0.60 to 1.59 0.92            | 126t/31† | 3513t/1581† |
| TNFα inhibitors             | 0.77 0.61 to 0.98 | 0.64 0.50 to 0.81 0.0007                                  | NA                                | 182†    | 16 843†    |
| Rituximab                   | 1.01 0.70 to 1.46 | 0.57 0.39 to 0.84 0.0062                                  | NA                                | 36†     | 25 999†    |
| TNFα inhibitors or rituximab| NA            | NA                                                       | 0.77 0.60 to 0.97 0.0312          | 330†    | 22 370†    |
| Other biologics             | 1.02 0.68 to 1.52 | 0.64 0.42 to 0.99 0.043                                  | 0.91 0.66 to 1.25 0.54            | 25t/51† | 1654t/2806† |
| DAS28>4.1 for > 6 (12) months after discontinuation of a biologic without start of a new one | NA | NA | 2.08 1.59 to 2.72 <0.0001 | 86† | 1812† |

Cost-effectiveness of RA treatment along with patients subset

Fautrel B. Rheumatology 2012
Biologics in RA: a reappraisal
data from LORHEN register

Survival on Treatment

Next stages in RA treatment with biological agents

- is response to different biologic agents predictable?

- is biologic agent-free remission a possible treatment goal?
Biomarkers still an unmet need in RA

- ESR and CRP are associated with disease activity
- ACPA and RF with disease severity
- No reliable indicator of response to therapy

«Forget personalised medicine and focus on abating disease activity»

Prediction of Therapeutic Responses to Tocilizumab in Patients With Rheumatoid Arthritis: Biomarkers Identified by Analysis of Gene Expression in Peripheral Blood Mononuclear Cells Using Genome-Wide DNA Microarray

Yoshie Sanayama, Kei Ikeda, Yukari Saito, Shin-ichiro Kagami, Mieko Yamagata, Shunsuke Furuta, Daisuke Kashiwakuma, Itsuo Iwamoto, Takeshi Umibe, Yasushi Nawata, Ryutaro Matsumura, Takao Sugiyama, Makoto Sueishi, Masaki Hiraguri, Ken Nonaka, Osamu Ohara, Hiroshi Nakajima
Circulating miRNAs as potential biomarkers of therapy effectiveness in rheumatoid arthritis patients treated with anti-TNFα

Carmen Castro-Villegas1, Carlos Pérez-Sánchez1, Alejandro Escudero1, Ileana Filipescu2, Miriam Verdu1, Patricia Ruiz-Limón1, Ma Angeles Aguirre1, Yolanda Jiménez-Gomez1, Pilar Font1, Antonio Rodríguez-Ariza1, Juan Ramon Peinado3, Eduardo Collantes-Estévez1, Rocío González-Conejero4, Constantino Martinez2, Nuria Barbarroja1 and Chary López-Pedrera1*
RF/ACPA status and response to Rituximab

Mean ΔDAS28 (bars: SEM) during the first 6 months for seropositive and seronegative patients.

Chatzidionysiou K et al. Ann Rheum Dis 2011;70:1575-1580
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Original article

Rheumatoid factor and response to TNF antagonists in rheumatoid arthritis: Systematic review and meta-analysis of observational studies

Eva Salgado\textsuperscript{a,}, José Ramón Maneiro\textsuperscript{a}, Loreto Carmona\textsuperscript{a, b}, Juan Gómez-Reino\textsuperscript{c}

Joint Bone Spine
Volume 81, Issue 1, January 2014, Pages 41–50
Synovial B cells: production of autoantibodies

Synovial lymphoid neogenesis and response to TNFα inhibitors

**Table 3. Clinicopathological predictors of moderate or good EULAR responses**

<table>
<thead>
<tr>
<th>Effect</th>
<th>Response (good or moderate vs. no response) (n=86)</th>
<th>Unadjusted</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>Odds Ratio (95CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>CD68+ cells/mm²</td>
<td>linear</td>
<td>1.000 (0.999;1.000)</td>
<td>0.4452</td>
</tr>
<tr>
<td>CD3+ cells/mm²</td>
<td>linear</td>
<td>1.000 (0.998;1.001)</td>
<td>0.3418</td>
</tr>
<tr>
<td>CD20+ cells/mm²</td>
<td>linear</td>
<td>1.000 (0.997;1.002)</td>
<td>0.8162</td>
</tr>
<tr>
<td>RA duration</td>
<td>linear</td>
<td>1.002 (0.996;1.008)</td>
<td>0.5285</td>
</tr>
<tr>
<td>Previous anti-TNF use</td>
<td>(+)</td>
<td>9 (75.00)</td>
<td>0.947</td>
</tr>
<tr>
<td></td>
<td>(-)</td>
<td>57 (76.00)</td>
<td>0.231 (1.380)</td>
</tr>
<tr>
<td>DAS28</td>
<td>linear</td>
<td>1.391 (0.948;2.042)</td>
<td>0.0919</td>
</tr>
<tr>
<td>LN</td>
<td>(+)</td>
<td>28 (66.67)</td>
<td>0.316</td>
</tr>
<tr>
<td></td>
<td>(-)</td>
<td>38 (86.36)</td>
<td>0.108 (0.924)</td>
</tr>
</tbody>
</table>

Evaluating Antirheumatic Treatment Using Synovial Biopsy: a Guideline for Standardisation to Be Used in Clinical Trials

Marleen G.H. van de Sande¹, Danielle M. Gerlag¹, Beatrijs M. Lodde¹, Lisa G.M. van Baarsen¹, Stefano Alivernini² Veronica Codullo³, Ioana Felea⁴, Elsa C.V. de Sousa⁵, Richard Reece⁶, Carlomaurizio Montecucco³, Doug J. Veale⁷, Costantino Pitzalis⁸, Paul Emery⁶, Lars Klareskog⁹, Iain B. McInnes¹⁰, Paul P. Tak¹ EULAR Synovitis Study Group – AutoCure Project

- Arthroscopy
- US-guided
Immunohistological assessment of the synovial tissue in small joints in rheumatoid arthritis: validation of a minimally invasive ultrasound-guided synovial biopsy procedure

Carlo Alberto Scirè¹, Oscar Epis¹, Veronica Codullo¹, Frances Humby², Patrizia Morbini³, Antonio Manzo², Roberto Caporali¹, Costantino Pitzalis² and Carlomaurozio Montecucco¹

Histological patterns of synovial inflammation

CD20+ B cell aggregational score

- score 0
- score 1
- score 2
- score 3

CD68+ sublining macrophage score

- score 1
- score 2
- score 3

ESR

- p < 0.0001

CRP

DAS

Lymphoid pattern is strongly associated with CXCL13 expression

Bugatti S et al. Rheumatology 2014..
Serum CXCL13 is increased in patients with RA and reflects synovial synthesis.
Different response rates to TNF inhibitors and tocilizumab based on myeloid and lymphoid biomarkers

Next stage of RA treatment: is TNF inhibitor-free remission a possible treatment goal?

A ‘treatment holiday’ of biological agents is possible in patients with early RA.

Discontinuation of biological agents during treatment of RA has become an important area of investigation in rheumatology patients and governments from the risk-benefit viewpoint including health economic considerations.

Guidelines on biologic withdrawal in case of clinical response are still lacking.
Heterogeneity exists across studies, particularly in study design and target population. Study enrolment based on disease activity lower than a given threshold, that differed across studies.

Concomitant non-biologic treatment at discontinuation and treatment changes after discontinuation were not sufficiently reported in most of the studies.
# The role of low-dose glucocorticoids for rheumatoid arthritis in the biologic era

R. Caporali¹, C.A. Scirè², M. Todoerti¹, C. Montecucco¹

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Drug</th>
<th>Number</th>
<th>Design</th>
<th>Duration of biologic use</th>
<th>Discontinuation criterion</th>
<th>Concurrent DMARD</th>
<th>Concurrent GC (PND)</th>
<th>GC</th>
<th>GC dose</th>
<th>Outcome (failure)</th>
<th>Time</th>
<th>Absence of failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aguilar-Lozano et al. (34)</td>
<td>2013</td>
<td>TCZ</td>
<td>45</td>
<td>LTE</td>
<td>5 years</td>
<td>DAS28&lt;2.6 SJC28=0</td>
<td>Cross sectional</td>
<td>100%</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>SJC28=0</td>
<td>12 months</td>
</tr>
<tr>
<td>DREAM (33)</td>
<td>2013</td>
<td>TCZ</td>
<td>187</td>
<td>LTE</td>
<td>Median 7.8 years</td>
<td>DAS28&lt;3.2</td>
<td>Cross sectional</td>
<td>100%</td>
<td>Y (stable &lt;10mg/d)</td>
<td>34.2%</td>
<td>2.8mg/d</td>
<td>DAS28 ≥3.2 drug-free</td>
<td>At 52 wks</td>
</tr>
<tr>
<td>PRESERVE (35)</td>
<td>2013</td>
<td>ETN</td>
<td>200</td>
<td>RCT</td>
<td>8 months</td>
<td>DAS28&lt;3.2</td>
<td>Cross sectional</td>
<td>100%</td>
<td>Y (stable &lt;10mg/d)</td>
<td>61%</td>
<td>?</td>
<td>DAS28 ≥3.2</td>
<td>At 52 wks</td>
</tr>
<tr>
<td>CERTAIN (36)</td>
<td>2013</td>
<td>CZP</td>
<td>17</td>
<td>LTE</td>
<td>6 months</td>
<td>CDAI ≥2.8</td>
<td>Cross sectional</td>
<td>100%</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>CDAI &gt;2.8</td>
<td>28 weeks</td>
</tr>
<tr>
<td>HIT HARD (37)</td>
<td>2013</td>
<td>ADA</td>
<td>87</td>
<td>LTE</td>
<td>6 months</td>
<td>N/A</td>
<td>N/A</td>
<td>100%</td>
<td>Y (&lt;10mg/d)</td>
<td>?</td>
<td>?</td>
<td>DAS28 ≥2.6</td>
<td>24 wks</td>
</tr>
<tr>
<td>ADMIRE (38)</td>
<td>2012</td>
<td>ADA</td>
<td>15</td>
<td>RCT</td>
<td>Median 43.3 months</td>
<td>DAS28 &lt;2.6</td>
<td>≥3 months</td>
<td>100%</td>
<td>Y (stable &lt;10mg/d)</td>
<td>?</td>
<td>?</td>
<td>DAS28 ≥2.6</td>
<td>At 28 wk</td>
</tr>
<tr>
<td>BRIGHT (31)</td>
<td>2012</td>
<td>ADA</td>
<td>22</td>
<td>LTE</td>
<td>Mean 45.8 months</td>
<td>DAS28 &lt;2.7</td>
<td>Cross sectional</td>
<td>13.6%</td>
<td>Y</td>
<td>40%</td>
<td>3.7mg/d</td>
<td>DAS28 ≥2.7</td>
<td>52 wks</td>
</tr>
<tr>
<td>DOSERA (39)</td>
<td>2012</td>
<td>ETN</td>
<td>23</td>
<td>RCT</td>
<td>Mean 25.3 months</td>
<td>DAS28 &lt;3.2</td>
<td>11 months</td>
<td>100%</td>
<td>Y (≥7.5mg)</td>
<td>?</td>
<td>?</td>
<td>DAS28 ≥3.2 and A ≥0.6</td>
<td>48 wks</td>
</tr>
<tr>
<td>HONOR (40)</td>
<td>2012</td>
<td>ADA</td>
<td>51</td>
<td>SA</td>
<td>Mean 16.6 months</td>
<td>DAS28 &lt;2.6</td>
<td>6 months</td>
<td>100%</td>
<td>N</td>
<td>6%</td>
<td>0</td>
<td>DAS28 ≥2.6</td>
<td>12 months</td>
</tr>
<tr>
<td>Van der Maas et al. (41)</td>
<td>2012</td>
<td>IFX</td>
<td>51</td>
<td>SA</td>
<td>Mean 67.2 months</td>
<td>DAS28 &lt;3.2</td>
<td>6 months</td>
<td>100%</td>
<td>Y</td>
<td>4%</td>
<td>?</td>
<td>Stopping/low-duration</td>
<td>54 wks</td>
</tr>
<tr>
<td>OPTIMA (32)</td>
<td>2012</td>
<td>ADA</td>
<td>102</td>
<td>RCT</td>
<td>26wks</td>
<td>DAS28 &lt;3.2</td>
<td>4 wks</td>
<td>100%</td>
<td>Y?</td>
<td>?</td>
<td>?</td>
<td>DAS28 ≥2.6</td>
<td>At 52 wks</td>
</tr>
<tr>
<td>BeSt (42)</td>
<td>2011</td>
<td>IFX</td>
<td>104</td>
<td>LTE</td>
<td>Median 11 months</td>
<td>DAS ≥2.4</td>
<td>6 months</td>
<td>100%</td>
<td>N</td>
<td>6%</td>
<td>0</td>
<td>DAS2 ≥2.4</td>
<td>12 months</td>
</tr>
<tr>
<td>ALLOW (43)</td>
<td>2011</td>
<td>ABA</td>
<td>80</td>
<td>RCT</td>
<td>12 wks</td>
<td>DAS responders</td>
<td>Cross sectional</td>
<td>100%</td>
<td>Y (stable &lt;10mg/d)</td>
<td>55%</td>
<td>3.8mg/d</td>
<td>DAS28 ≥2.6</td>
<td>At 12 wks</td>
</tr>
<tr>
<td>Saleem et al. (44)</td>
<td>2010</td>
<td>ADA</td>
<td>47</td>
<td>SA</td>
<td>19mo (27) 120mo (20)</td>
<td>DAS28 &lt;2.6</td>
<td>≥6 months</td>
<td>100%</td>
<td>N</td>
<td>0</td>
<td>0</td>
<td>DAS28 ≥2.6 or A&gt;1.2</td>
<td>24 months</td>
</tr>
<tr>
<td>RRR (30)</td>
<td>2010</td>
<td>IFX</td>
<td>102</td>
<td>SA</td>
<td>?</td>
<td>DAS28 &lt;3.2</td>
<td>24 weeks</td>
<td>100%</td>
<td>Y (&lt;5mg/d)</td>
<td>?</td>
<td>2.5mg/d</td>
<td>DAS28 ≥3.2</td>
<td>12 months</td>
</tr>
<tr>
<td>Brocq et al. (44)</td>
<td>2009</td>
<td>ADA</td>
<td>21</td>
<td>SA</td>
<td>Mean 40.3 months</td>
<td>DAS28 &lt;2.6</td>
<td>6 months</td>
<td>66.7%</td>
<td>Y (≥5mg/d)</td>
<td>14.3%</td>
<td>2.7mg/d</td>
<td>DAS28 ≥3.2</td>
<td>12 months</td>
</tr>
<tr>
<td>Quina et al. (46)</td>
<td>2005</td>
<td>IFX</td>
<td>10</td>
<td>LTE</td>
<td>12months</td>
<td>N/A</td>
<td>N/A</td>
<td>100%</td>
<td>Y</td>
<td>?</td>
<td>?</td>
<td>DAS28</td>
<td>58 wks</td>
</tr>
<tr>
<td>ATTRACT (47)</td>
<td>2004</td>
<td>IFX</td>
<td>17</td>
<td>LTE</td>
<td>24 months</td>
<td>N/A</td>
<td>Cross sectional</td>
<td>100%</td>
<td>Y</td>
<td>?</td>
<td>?</td>
<td>Loss of ACR20</td>
<td>15 wks</td>
</tr>
</tbody>
</table>

TCZ: tocilizumab; ABA: abatacept; ETA: etanercept; ADA: adalimumab; CZP: certolizumab pegol; INF: infliximab; PND: prednisone equivalent; LTE: long-term extension trial; RCT: randomised controlled trial; SA: single arm trial; DAS: disease activity score; CDAI: clinical disease activity index; N/A: not available or applicable.
Maintenance, reduction, or withdrawal of etanercept after treatment with etanercept and methotrexate in patients with moderate rheumatoid arthritis (PRESERVE): a randomised controlled trial

Josef S Smolen, Peter Nash, Patrick Durez, Stephen Hall, Elena Ilivanova, Fedra Irazoque-Palazuelos, Pedro Miranda, Min-Chan Par, Karel Pavelka, Ronald Pedersen, Annette Szumski, Constance Hammond, Andrew S Koenig, Bonnie Vlahos

Open label period: over 36 weeks, all patients were given 50 mg etanercept plus methotrexate every week.

Double-blind phase: participants in sustained low disease activity were followed for 52 weeks more.

PRESERVE was the only study powered to determine differences between continuation of ETA 50 mg or 25 mg/week versus discontinuation of ETA, although it was not powered to determine differences between the 2 ETA dose groups.
The proportion of patients with remission (defined by several indices) fell rapidly after week 36 in the group given placebo.

The difference between proportions of patients in remission in the 50 mg or 25 mg etanercept groups and the placebo group grew with time.
Significantly more patients in etanercept achieved a radiographic progression rate of the smallest detectable difference or less at week 88 than in the placebo.

The change in mTSS from week 36 to week 88 in the group given 50 mg etanercept was significantly different from the group given placebo, but the change in the group given 25 mg etanercept was not.
The proportion of patients who sustained DAS28-ESR <2.6 (48%) and DAS28-ESR <3.2 (62%) for 1 year were significantly lower in the ADA discontinuation vs ADA continuation group.

However, in patients with deeper remission (DAS28-ESR ≤1.98), identified by ROC analysis, these rates increased to 68% and 79%, respectively, with no significant difference between both groups.
ACR/EULAR definition of remission identifies patients with persistent absence of functional disability and suppression of ultrasonographic synovitis

Ultrasonographic evaluation of joint involvement in early rheumatoid arthritis in clinical remission: power Doppler signal predicts short-term relapse

Carlo A. Scirè¹, Carlomauroirio Montecucco¹, Veronica Codullo¹, Oscar Epis¹, Monica Todoerti¹ and Roberto Caporali¹

PD-positive synovial hypertrophy identifies an ongoing inflammation even during remission and predicts short-term relapse.
In this study, total US scores for synovial inflammation were identified as statistically significant predictors of relapse within 6 months after discontinuation of bDMARD in RA patients, whereas other baseline clinical measures, including the DAS28, were not.
Factors associated with continued LDA after TCZ cessation at a) univariate and b) multivariate analysis.

Multivariate Cox regression analysis identified low serum IL-6 and normalisation of MMP-3 levels at cessation of TCZ as independent predictive markers for longer duration of LDA.
Predictive factors

Varially defined across studies for:

- Deeper clinical remission state at enrollment
- Shorter disease duration
- RF negativity, ACPA negativity
- Lab parameters (MMP, IL6, …)
- Better US disease activity control

SUBSET OF SUITABLE PATIENTS
Personalized medicine in rheumatoid arthritis: is the glass half full or half empty

Huizinga TW. J Intern Med 2014
Unità di Reumatologia
Università di Pavia
Fondazione IRCCS Policlinico S.Matteo

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Monica Todoerti, M.D.
Elena Prisco, MD
Blerina Xoxi, MD
Silvia Balduzzi, MD