New Data and Hot Topics in Rheumatoid Arthritis: Highlights From the European League Against Rheumatism (EULAR) Congress 2016
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Guidelines for Early Rheumatoid Arthritis (ERA): 2016 Update of EULAR Recommendations

- Overarching Principles
  - Shared decision making
  - Rheumatologists should treat ERA
  - Diagnosis should be confirmed after careful history taking, examination, and appropriate laboratory studies

EULAR ERA Guidelines

• Recommendations
  – Rheumatologist should be seen no later than 6 weeks after symptoms start
  – Physical examination is best for detecting arthritis; may have to be confirmed with ultrasonography
    ▪ No MRI (change from 2007 guidelines)
    ▪ Further studies on sonography and MRI, especially in relation to important long-term outcomes, need to be awaited
  – If no definite diagnosis is made, risk factors for persistent and/or erosive disease should be considered

MRI=Magnetic resonance imaging
• **Recommendations**
  – Patients at risk of persistent arthritis should start DMARDs within 3 months, even if classification criteria are not fulfilled
  – Methotrexate is the preferred first DMARD

DMARD=Disease-modifying antirheumatic drug
EULAR ERA Guidelines

- Oral corticosteroids can be added early at the lowest dose and tapered within 6 months
- Aim for remission with regular monitoring of disease activity, 1 to 3 months
- Monitoring should include patient/physician global assessment, SJC/TJC, ESR/CRP, composite index
  - Imaging and functional assessment can complement these

SJC=swollen joint count; TJC=tender joint count
ESR=erythrocyte sedimentation rate; CRP=C-reactive protein
EULAR ERA Guidelines

• Nonpharmacologic interventions should be used, including physical and occupational therapy
• NSAIDs should be used for the shortest duration and at the lowest dose for symptom control
• Smoking cessation, dental care, weight control, and vaccination status should be assessed
• Patients should be educated about their disease
Strategies for Mitigating Cardiovascular (CV) Risk

• EULAR 2015 recommendations for CV risk management propose supra-aortic vessel ultrasound for atheromatous plaque detection and CV risk estimation

• In practical terms, this means performing carotid ultrasound

EULAR 2015 recommendations also suggest that global cardiovascular risk factors calculated by other metrics, such as the Framingham Risk Score, be multiplied by a factor of 1.5 for all RA patients.

In this study, 157 patients with RA (mean age of 61 ±11 years) underwent total CV risk estimation. In these patients, application of 2010 EULAR recommendations would lead to an immediate statin prescription in 28% of patients.

Cardiovascular Risk

• Application of EULAR 2015 recommendations (use of carotid ultrasound to estimate total CV risk) would lead to a statin prescription in 61% of patients.

• Updating recommendations increases the population of patients who are deemed to be at high risk and who need risk mitigation through statins.

RA-specific Risk Factor Calculators

- Are RA-specific CV risk factor calculators superior or inferior to those used for the general population?
- Seven RA cohorts from the United Kingdom, Norway, the Netherlands, United States, South Africa, Canada, and Mexico were combined

RA-specific Risk Factor Calculators

- The performance of QRISK2, EULAR multiplier, and ERS-RA were compared with risk calculators developed for the general population.
- The QRISK2, EULAR multiplier, and ERS-RA algorithms did not predict CVD risk more accurately in patients with RA than did CVD risk calculators developed for the general population.

QRISK2: https://www.qrisk.org/
European League Against Rheumatism, EULAR
Extended Risk Score – Rheumatoid Arthritis, ERS-RA
Biologic Safety in the Elderly

- Interim analysis of a single-arm, non-interventional study (ICHIBAN; a prospective German registry of 902 RA patients treated with IV tocilizumab) evaluated safety and efficacy of long-term IV administered tocilizumab in patients with moderate-to-severe RA based on age (<50, 50 to 65, >65 years)

Biologic Safety in the Elderly

• IV tocilizumab treatment resulted in improvement in disease activity and reduction in steroid use
• RA patients >65 years benefited as much as younger patients without increased risk of infection despite greater disease severity, duration of disease, and comorbidities

Biologic Safety in the Elderly

- AEs and SAEs were slightly higher for the elderly, but rate of infections, serious infections, and tocilizumab discontinuation due to AEs did not increase with age.
- There were 2 intestinal perforations: 1 in the <50 age group and 1 in the 50 to 65 age group.

Incidence of Herpes Zoster

- Twelve-year analysis of the Canadian RHUMDATA registry examined the incidence rates of herpes zoster (HZ) in patients with RA, ankylosing spondylitis (AS), or psoriatic arthritis (PsA)
- Rates of HZ were estimated in patients who received biologics and patients who did not
- Use of biologic agents doubled the risk of herpes zoster in RA and AS/PsA patients
- Significant predictors of herpes zoster among RA patients included age and use of biologics

Risk of Herpes Zoster in Patients with RA

- Retrospective, longitudinal population-based study using a Japanese health insurance database compared the incidence rate of HZ in people with and without RA.
- HZ was increased in RA (14.1/1000 pt years)
  - Non-RA group (8.3/1,000 pt years)
- Increased risk was augmented by renal disease, diabetes, and steroid use, but not by biologics or methotrexate.

Comparative Risk of Herpes Zoster (HZ) in Tofacitinib and Other Biologic-treated Patients

- Using health plan data, RA patients without a history of HZ or HSV, who initiated tofacitinib or biologics from 2010 to 2013, were identified.
- A total of 1746 patients initiating tofacitinib were compared with patients who initiated anti-TNFs, abatacept, rituximab, or tocilizumab.
- The risk for zoster associated with tofacitinib was approximately double that observed in patients using other biologics.

HSV=herpes simplex virus; anti-TNF=anti-tumor necrosis factor
Duration of Vaccination Protection

- Evaluation of the duration of HZ vaccine effectiveness among older patients with autoimmune diseases
- A total of 59,627 vaccinated Medicare patients with auto-immune or inflammatory diseases were compared with 119,254 unvaccinated matched patients
- Vaccinated patients had a significantly lower risk of HZ compared with unvaccinated patients through 5 years but not beyond

Discussion

- Ultrasound as an early assessment tool
- Markers of poor prognosis
- The challenge of access to rheumatologists
- Drilling down on the term “remission”
- Questions about the ICHIBAN trial
PRAIRI Study

- A total of 81 participants with arthralgia who tested positive for ACPA and rheumatoid factor. Patients also had CRP levels of at least 3 mg/L or signs of subclinical synovitis on ultrasound or MRI of hands.
- A total of 41 patients received a single infusion of 1000 mg of rituximab; 40 received a placebo infusion.
- All were treated with 100 mg of methylprednisolone to prevent infusion reactions.

ACPA= Anti-citrullinated protein antibody
PRAIRI Study

- At median follow-up of 27 months, 30/81 patients developed arthritis:
  - 16 in placebo group (40%) after a median of 11.5 months
  - 14 in rituximab group (34%) after a median of 16.5 months

PRAIRI Study

- Those who received rituximab and went on to develop RA did so at 24 months, compared with 12 months for placebo.
- Assuming a 40% background incidence in RA in this cohort, rituximab reduced risk of developing RA by 55% at 12 months.

Baricitinib Safety

• Assess safety of baricitinib across 8 completed studies and 1 ongoing long-term extension study

## Safety Profile of Baricitinib in Patients With Active RA: an Integrated Analysis

<table>
<thead>
<tr>
<th>Study Set</th>
<th>Death</th>
<th>Malignancy ex. NMSC</th>
<th>MACE</th>
<th>Serious Infection</th>
<th>Herpes Zoster</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>6-study Data Set, Wks 0 to 24</strong></td>
<td></td>
<td></td>
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<tr>
<td>PBO (N=1070)</td>
<td>2 (0.5)</td>
<td>2 (0.5)</td>
<td>2 (0.5)</td>
<td>17 (4.2)</td>
<td>4 (1.0)</td>
</tr>
<tr>
<td>Bari 4 mg (N=997)</td>
<td>3 (0.7)</td>
<td>2 (0.5)</td>
<td>2 (0.5)</td>
<td>16 (3.8)</td>
<td>18 (4.3)</td>
</tr>
<tr>
<td><strong>4-study Data Set, Wks 0 to 24</strong></td>
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<tr>
<td>PBO (N=551)</td>
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<td>2 (1.2)</td>
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<tr>
<td>Bari 2 mg (N=479)</td>
<td>0</td>
<td>1 (0.5)</td>
<td>0</td>
<td>8 (4.2)</td>
<td>6 (3.1)</td>
</tr>
<tr>
<td>Bari 4 mg (N=479)</td>
<td>1 (0.5)</td>
<td>0</td>
<td>2 (1.1)</td>
<td>11 (5.7)</td>
<td>10 (5.2)</td>
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<tr>
<td><strong>RA-BEGIN (DMARD naïve), Wks 0 to 52</strong></td>
<td></td>
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<tr>
<td>MTX (N=210)</td>
<td>3 (1.7)</td>
<td>1 (0.6)</td>
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<td>8 (4.6)</td>
<td>2 (1.1)</td>
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<td>Bari 4 mg (N=159)</td>
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<td>Bari 4 mg + MTX (N=215)</td>
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<td>5 (2.6)</td>
<td>5 (2.6)</td>
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<tr>
<td><strong>RA-BEAM (MTX-IR), Wks 0 to 24</strong></td>
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<tr>
<td>PBO (N=488)</td>
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<td>7 (3.5)</td>
<td>2 (1.0)</td>
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<tr>
<td>Bari 4 mg (N=487)</td>
<td>2 (0.9)</td>
<td>2 (0.9)</td>
<td>1 (0.5)</td>
<td>5 (2.3)</td>
<td>7 (3.2)</td>
</tr>
<tr>
<td>Adalimumab (N=330)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (1.4)</td>
<td>4 (2.8)</td>
</tr>
<tr>
<td><strong>RA-BEAM (MTX-IR), Wks 0 to 52</strong></td>
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<td>1 (0.4)</td>
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<td>1 (0.4)</td>
<td>5 (1.8)</td>
<td>5 (1.8)</td>
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<td><strong>All Bari RA</strong></td>
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<tr>
<td>Phases 1 to 3 (N=3464)</td>
<td>13 (0.3)</td>
<td>29 (0.7)</td>
<td>16 (0.5)</td>
<td>137 (3.2)</td>
<td>143 (3.4)</td>
</tr>
</tbody>
</table>

ex. = excluding; IR = incidence rate/100 PY; MACE = major adverse cardiovascular event; NMSC = non-melanoma skin cancer; perm DC = permanent discontinuation of study drug. With the exception of AE leading to perm DC, analyses include follow-up observation. *Significantly different vs comparator (95% CI: 2.6, 6.8).

Conclusion: Baricitinib had an acceptable safety profile in patients with moderate-to-severe RA

Objective: To assess whether baseline ACPA status is associated with response to abatacept or anti-TNF therapy in patients with RA

Using Corrona RA registry, 566 patients who started abatacept and 1715 patients who started a TNF inhibitor were enrolled between June 2002 to January 2015

Primary outcomes measure: mean change in CDAI after 6 months

CDAI=Clinical Disease Activity Index
<table>
<thead>
<tr>
<th>Initiator</th>
<th>Group</th>
<th>Change in CDAI (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abatacept</td>
<td>Double+</td>
<td>-8.55 (-10.00, -7.10)**</td>
</tr>
<tr>
<td></td>
<td>Single+</td>
<td>-7.39 (-9.19, -5.59)**</td>
</tr>
<tr>
<td></td>
<td>Double-</td>
<td>-3.82 (-5.64, -2.00)</td>
</tr>
<tr>
<td>Anti-TNF</td>
<td>Double+</td>
<td>-7.18 (-7.94, -6.42)</td>
</tr>
<tr>
<td></td>
<td>Single+</td>
<td>-7.58 (-8.58, -6.58)</td>
</tr>
<tr>
<td></td>
<td>Double-</td>
<td>-6.40 (-7.40, -5.40)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Initiator</th>
<th>Outcome</th>
<th>Group</th>
<th>Odds ratios (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abatacept</td>
<td>LDA</td>
<td>Double+ vs Double-</td>
<td>2.39 (1.45, 3.94)**</td>
</tr>
<tr>
<td></td>
<td>LDA</td>
<td>Single+ vs Double-</td>
<td>1.34 (0.76, 2.38)</td>
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<tr>
<td></td>
<td>Remission</td>
<td>Double+ vs Double-</td>
<td>3.93 (1.67, 9.24)**</td>
</tr>
<tr>
<td></td>
<td>Remission</td>
<td>Single+ vs Double-</td>
<td>2.68 (1.07, 6.71)</td>
</tr>
<tr>
<td>Anti-TNF</td>
<td>LDA</td>
<td>Double+ vs Double-</td>
<td>1.14 (0.86, 1.52)</td>
</tr>
<tr>
<td></td>
<td>LDA</td>
<td>Single+ vs Double-</td>
<td>1.18 (0.86, 1.63)</td>
</tr>
<tr>
<td></td>
<td>Remission</td>
<td>Double+ vs Double-</td>
<td>1.17 (0.83, 1.66)</td>
</tr>
<tr>
<td></td>
<td>Remission</td>
<td>Single+ vs Double-</td>
<td>0.94 (0.63, 1.40)</td>
</tr>
</tbody>
</table>

*ps<0.05, **ps<0.01, ***ps<0.001
Discussion

PRAIRI Study
  – Were these patients really pre-RA?

Is herpes zoster a pan-JAK concern?
Biosimilars: Real-world Experience

- A 2015 change in Danish national guidelines mandated a nonmedical switch from originator infliximab to a biosimilar for patients with rheumatoid disease.
- Objective: To investigate 3-month clinical outcomes in patients with RA, psoriatic arthritis, and spondyloarthitis who switched and were monitored prospectively in the DANBIO registry.
Biosimilars: Real-world Experience

- Patients had been treated for 6.7 years with infliximab (4.1 to 9.4 years) when they switched
- More than two-thirds of patients with RA or PsA were also taking methotrexate during the study period
- For 77% of patients, infliximab was the first biological treatment

Conclusion: In 647 patients treated with infliximab for >4 years, disease activity was largely unaffected in the majority of patients 3 months after a switch to the biosimilar.

Approximately 6% stopped treatment due to loss of efficacy or an AE.

In a subcohort analysis, the switch did not have an impact on serum infliximab levels or anti-drug antibodies 2 to 4 months after the switch.

Biosimilars

- Objective: To determine if antibodies to infliximab innovator-treated patients cross react with the biosimilar CT-P13.
- First study that demonstrated cross-immunogenicity between infliximab innovator and a biosimilar molecule in patients with rheumatic diseases.

Closing Discussion

- Biosimilar “buzz”
- Questions about durability of response
- Non-ubiquity of mechanisms of action across diseases
- Economic and social questions
- Diminishing R&D?
Thank You