[2] PIRRA patients have at least one clinically swollen joint, with objective evidence of active inflammation in power Doppler ultrasound (PDUS), often with elevated CRP levels, whilst NIRRA patients have apparent clinical swelling but absence of PDUS and often normal CRP levels. 

**Objectsives:** This study determined the prevalence of EULAR-defined refractory RA (D2T RA) in Leeds. Secondly, we established the prevalence of polyrefractory RA, i.e., patients that failed all available b/tsDMARD classes. Finally, we determined NIRRA/PIRRA phenotypes in refractory disease. 

**Methods:** 1591 RA patients receiving b/tsDMARD therapies between 2018-2022 were identified as part of a service evaluation, excluding those where DAS-28-CRP was unavailable. Patients fulfilling EULAR-ACR criteria for D2T RA, with DAS-28-CRP ≥ 3.2 and US imaging where available were evaluated. Patients were further divided into NIRRA and PIRRA, according to the presence/absence of signs of active synovitis as indicated by PDUS (Figure 1).

**Results:** 242/1591 (15.2%) met the EULAR D2T criteria of failing at least 2 b/tsDMARDs; 89/1591 (5.6%) failed 2 classes only, with a mean disease duration (mDD) of 11 years, 60/1591 (3.8%) failed 3 classes (mDD= 18) and 52/1591 (3.3%), 4 classes (mDD= 10.5). However, just 41/1591 (2.5%) had polyrefractory RA having failed all 5 classes (mDD= 21). Of them, 37/41 (90%) failed multiple drugs within each class. 4/41 (10%) polyrefractory and 45/242 (18.5%) of all EULAR D2T cases were seronegative. Regarding joint involvement patterns, most had typical small joint RA disease pattern but 26/242 (11%) had a predominant large joint pattern. 18/41 (43%) of the polyrefractory RA group had CRP levels within the normal ranges despite a DAS-28-CRP score above 3.2 (mean DAS-28-CRP of 5.3). 71 D2T RA patients had recent US of clinically involved joints, including 28 polyrefractory RA cases. 18/28 (64%) polyrefractory were above 3.2 (mean DAS-28-CRP of 5.3). 71 D2T RA patients had recent US of clinically involved joints. Specifically in the polyrefractory group, the CRP levels were within normal ranges in 6/10 (60%) NIRRA patients, while just 7/18 (39%) PIRRA cases had normal CRP levels.

**Conclusion:** Although 15.2% of Leeds RA patients met the EULAR criteria for D2T RA, real-world polyrefractory RA was present in only 2.5%. Almost half of the polyrefractory RA group, the CRP levels were within normal ranges in 6/10 (60%) NIRRA patients, while just 7/18 (39%) PIRRA cases had normal CRP levels.

**References:**


**Figure 1.** Flow-chart showing the prevalence of poly-refractory, PIRRA and NIRRA patients among Leeds RA patients.

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**Table 1.** Characteristics and incidence rates of demyelinating events in the included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Population</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lingyi 2022 (1)</td>
<td>Nested case-control</td>
<td>Canadian healthcare databases</td>
<td>Case = multiple sclerosis</td>
</tr>
<tr>
<td>Taylor 2021 (2) Prospective Cohort</td>
<td>Prospective Cohort</td>
<td>British Society for Rheumatology, Rheumatology Biologics Register</td>
<td>Incident (95% CI): 1.38 (0.96-1.92)</td>
</tr>
<tr>
<td>Kunchok 2020 (3)</td>
<td>Nested case-control</td>
<td>Mayo Clinic (USA)</td>
<td>Case = Any inflammatory CNS event</td>
</tr>
<tr>
<td>Koop 2020 (4)</td>
<td>Combined biologic registers in Sweden and Denmark</td>
<td>Incidence Rate: 0.37-0.39/1000 pt-yrs</td>
<td>p-yrs</td>
</tr>
<tr>
<td>Dreyer 2016 (5)</td>
<td>Register-based cohort study</td>
<td>DANBIO</td>
<td>RA: 0.65 (95% CI: 0.24-1.72)</td>
</tr>
<tr>
<td>Fernandez-Espartero 2011 (6)</td>
<td></td>
<td>BIOBADASER-Spain</td>
<td>Incident rate in RA: 0.69 (95% CI: 0.36-1.32)</td>
</tr>
<tr>
<td>Bernatsky 2010*</td>
<td>Nested case-control</td>
<td>Administrative data in Canada</td>
<td>Anakinra 0.80 (0.29 - 2.24) MTX 1.09 (0.83 - 1.89)</td>
</tr>
</tbody>
</table>

Abbreviations: RA, rheumatoid arthritis; SIR, standardized incidence rate; CI, confidence interval; CNS, central nervous system; HR, hazard ratio; OR, odds ratio; MTX, methotrexate; MS, multiple sclerosis; TNFi, tumour necrosis factor inhibitor.

Conclusion: No consistent and significant risk of demyelinating disease following TNFi treatment was found in RA patients. A marginal and slight increase of risk was found in male RA patients. The small number of events is reassuring when considering the use of TNFi.

**References:**


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The future perspectives in the treatment of SLE & Sjögren's__

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METABOLIC PROFILING IDENTIFIES METABOLITES LINKED TO KIDNEY DAMAGE WHICH ARE MODULATED BY ANIFROLUMAB IN A PHASE 2 TRIAL IN LUPUS NEPHRITIS

Keywords: -omics, Kidneys, Biomarkers

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Background: Lupus nephritis (LN) is one of the most common severe clinical manifestations of systemic lupus erythematosus (SLE), occurring in 21%–48% of SLE patients. The kidney is the major organ affected in SLE, with persistent inflammation leading to progressive loss of renal function and chronic kidney disease (CKD). The decline in kidney function level is associated with accumulation of uremic waste products normally cleared by the kidneys, known as uremic toxins. Uremic toxins negatively affect multiple organ systems, causing increased cardiovascular and kidney damage, among other effects. Given the clear link to kidney function, uremic toxins may serve as biomarkers of kidney damage and of treatment response. Anifrolumab, a monoclonal antibody that targets the type I interferon (IFN) receptor subunit 1, is approved for moderate to severe SLE treatment. The mechanism of action of anifrolumab in LN.

Objectives: In this study, we conducted unbiased metabolomic profiling to identify novel biomarkers of treatment response and provide insights into the mechanism of action of anifrolumab in LN.

Methods: In the 52-week phase 2 clinical trial TULIP-LN (NCT02547922), 147 patients with active LN were randomized 1:1:1 to receive intravenous anifrolumab every 4 weeks at standard SLE dosing (basic regimen [BR], 300 mg) or intensified dosing (intensified regimen [IR], 900 mg for the first 3 doses, 300 mg thereafter), or placebo in addition to standard therapy. Serum samples were obtained from 140 of these patients at baseline (BL) and Weeks 12, 24, and 52. Serum metabolites were analyzed using an unbiased liquid chromatography–mass spectrometry-based approach. Metabolites that were differentially modulated in the anifrolumab IR vs placebo group were identified using a mixed effects model evaluating the interaction of metabolite levels and treatment, adjusted for patients' IFN gene signature (IFNGS) status (high/low) and 24-hour urine protein–creatinine ratio (UPCR >3 or ≤3). Relationships between BL metabolite level and clinical characteristics of kidney damage were assessed by Spearman's correlation. Association of BL metabolite levels with complete renal response were evaluated by logistic regression, adjusted for IFNGS and UPCR status.

Results: Our unbiased metabolomic approach identified 2 metabolites significantly impacted by anifrolumab treatment compared with placebo (Figure 1). Cytosine (Cyt) and indoxyl sulfate (IS) levels were significantly reduced following anifrolumab IR treatment compared with placebo, while an intermediate, non-significant reduction was observed longitudinally with anifrolumab BR. Baseline Cyt and IS serum levels were positively correlated with serum creatinine and negatively correlated with estimated glomerular filtration rate. Baseline IS levels were also associated with complete renal response at Week 52. Compared to the trend observed in nonresponders, IS levels in responders were reduced from BL to Week 52. A trend in reduction of multiple uremic toxins not limited to IS was detected in the anifrolumab-treated group.

Conclusion: In patients with LN, anifrolumab treatment reduced levels of multiple circulating uremic toxins including IS, a known inductor of cardiovascular damage in CKD. Together, correlations with kidney damage measures at baseline and reductions in IS levels in responders vs nonresponders at Week 52 suggest improvements in kidney function following anifrolumab treatment. Overall, our results contribute to a deeper understanding of how inhibition of type I IFN affects renal disease in LN.

Disclosure of Interests: None Declared.

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