HEPATIC SAFETY IN PATIENTS WITH RHEUMATOID ARTHRITIS WHO RECEIVED IMASONIDE FOR LATE TUBERCULOSIS: POST-HOC ANALYSIS FROM PHASE 3 BARICITINIB STUDIES

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Background: Baricitinib (BARI) is an oral selective Janus kinase (JAK 1/2) inhibitor approved in the EU, Japan, and other countries for treatment (tx) of moderately to severely active rheumatoid arthritis (RA) in adults. RA therapies may increase risk of tuberculosis (TB). The use of isoniazid (INH) plays a vital role to control TB. However, INH may result in hepatic adverse events (AEs). Limited data exist on hepatic safety in TB patients (pts) with RA treated with JAK inhibitors and INH.

Objectives: To evaluate the hepatic safety in pts with RA, who were receiving INH for latent TB (LTBI) in BARI phase 3 trials.

Methods: This is a descriptive post-hoc analysis of three phase 3 studies: BARI-RA-BUILD, BARI-RA-BEACON. All pts were screened for LTBI prior to randomisation. Pts with untreated LTBI and without documentation of prior completed tx, received INH at least for 4 weeks (wk) prior to randomisation and during the clinical trial period. Changes in ALT levels (≥1X, ≥3X, ≥5X, and >10X of ULN) from baseline up to 24 wk were analysed by tx groups (BARI 4 mg, BARI 2 mg, adalimumab [ADA], and placebo [PBO]).


Disclosure of Interest: None declared

LIVER ENZYME ABNORMALITIES AFTER TOFACITINIB TREATMENT IN PATIENTS WITH HEPATIC STEATOSIS FROM THE RHEUMATOID ARTHRITIS, PSORIASIS ARTHRITIS AND PSORIASIS CLINICAL PROGRAMMES


Background: Non-alcoholic fatty liver disease, characterised by hepatic steatosis (HS), is a major cause of chronic liver disease in many countries. Limited data are available on liver enzyme elevation in patients (pts) with HS who are receiving medications for inflammatory conditions, such as rheumatoid arthritis (RA), psoriatic arthritis (PsA) and psoriasis (PsO). Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA and PsA, and has also been studied in PsO.

Objectives: To describe baseline characteristics and liver enzyme abnormalities in pts from the tofacitinib RA, PsA and PsO clinical programmes with/without HS at baseline.

Methods: Pts randomised to the tofacitinib (5 or 10 mg twice daily; doses pooled) and placebo arms of 25 studies in the RA, PsA and PsO programmes were...
included in this pooled post hoc analysis. Most studies allowed or mandated concomitant treatment with disease-modifying antirheumatic drugs. HS was determined in all investigations and captured per the Medical Dictionary for Regulatory Activities term at baseline. Baseline characteristics, incidence of elevated total bilirubin, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) >1 and 3 x the upper limit of normal (ULN) up to Month (M) 3, and change from baseline in C-reactive protein (CRP) at M3—all by HS at baseline—are reported.

Results: A total of 10 212 pts were included in the analysis. The prevalence of HS was 1.6% across indications (RA: 87/6729 [1.3%]; PsA: 27710 [2.8%]; PsO: 456773 [1.6%]). Baseline characteristics were generally similar in pts with or without HS (table 1). However, baseline obesity, diabetes, triglycerides and liver enzymes were numerically higher, and CRP was numerically lower, in pts with HS than in those without HS (table 1). In both tofacitinib- and placebo-treated pts, incidence of elevated total bilirubin, AST and ALT >3 ULN up to M3 was higher in pts with HS than in those without HS, across indications (table 1). Incidence of elevated total bilirubin, AST and ALT >3 ULN up to M3 was low across indications, irrespective of HS (table 1). Among tofacitinib-treated pts, CRP was reduced at M3 in pts with or without HS, but to a lesser extent in those with HS, across indications. Among placebo-treated pts, changes in CRP were small, irrespective of HS (table 1).

Abstract FR00999 – Table 1. Baseline characteristics and liver function up to Month 3, by HS at baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>With HS (n=160)</th>
<th>Without HS (n=10072)</th>
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<tbody>
<tr>
<td>Age (yrs)</td>
<td>64.6±15.5</td>
<td>65.3±11.8</td>
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<tr>
<td>Female (%)</td>
<td>58.1</td>
<td>52.1</td>
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<tr>
<td>Mean CRP (mg/L)</td>
<td>3.9±1.8</td>
<td>3.5±1.1</td>
</tr>
<tr>
<td>Baseline ALT (U/L)</td>
<td>17.9±17.3</td>
<td>17.4±14.9</td>
</tr>
<tr>
<td>Baseline AST (U/L)</td>
<td>32.0±31.6</td>
<td>29.3±24.1</td>
</tr>
<tr>
<td>Baseline total bilirubin (mg/dL)</td>
<td>0.9±0.6</td>
<td>0.8±0.5</td>
</tr>
<tr>
<td>Baseline ALK (U/L)</td>
<td>59.6±37.4</td>
<td>57.5±30.1</td>
</tr>
<tr>
<td>End of treatment ALT (U/L)</td>
<td>13.6±12.5</td>
<td>13.3±11.3</td>
</tr>
<tr>
<td>End of treatment AST (U/L)</td>
<td>19.5±17.5</td>
<td>19.1±14.7</td>
</tr>
<tr>
<td>End of treatment total bilirubin (mg/dL)</td>
<td>0.8±0.5</td>
<td>0.8±0.5</td>
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</table>

Conclusions: In this exploratory analysis, prevalence of HS at baseline was 1.6% across the tofacitinib RA, PsA and PsO programmes. After up to 3 months of tofacitinib treatment, incidence of mildly elevated liver enzymes was higher in pts with HS than in those without HS. Incidence of severely elevated liver enzymes was low overall, and similar in pts with or without HS. Further studies are needed to evaluate the effects of tofacitinib on CRP and liver enzymes, and the potential impact on clinical response, in pts with RA, PsA or PsO who have comorbid HS.

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FR01001

UMMET NEEDS IN THE TREATMENT OF RHEUMATOID ARTHRITIS. AN OBSERVATIONAL STUDY AND A REAL-LIFE EXPERIENCE FROM A SINGLE UNIVERSITY CENTRE

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Background: Despite the progress in the treatment of rheumatoid arthritis (RA), a significant number of patients does not achieve low disease activity (LDA).

Objectives: The purpose of this study was to estimate the size of unmet needs in the treatment of RA, using all the conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) and/or biological DMARDs (bDMARDs) in a long-term observational study.

Methods: Between January 2006 and December 2017, 538 patients with early RA were followed up in the outpatient rheumatology clinic. All patients fulfilled the 2010 ACR/EULAR classification criteria, had disease duration less than 1 year and were csDMARDs and bDMARDs naïve. The patients were treated according to EULAR and ACR recommendations and strategies for RA. The following

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MULTI-OMICS ANALYSIS IDENTIFIES A GENE SIGNATURE ASSOCIATED WITH THE CLINICAL RESPONSE TO ANTI-TNF THERAPY IN RHEUMATOID ARTHRITIS


Background: Tumour Necrosis Factor (TNF) inhibitors have improved the management of many patients with rheumatoid arthritis (RA). However, ~30% of anti-TNF treated patients do not show a significant clinical improvement. To date, little is known on the biological mechanisms underlying the differential response to anti-TNF agents.

Objectives: We sought to identify genetic variation associated with the anti-TNF response in RA using a sequential multi-omics approach.

Methods: First, we aimed to identify gene coexpression modules (GCMs) associated with anti-TNF response. For this objective, we extracted the RNA from synovial biopsies of 13 RA patients starting anti-TNF therapy and determined the expression profiles using illumina microarrays. GCMs were identified using the WGCNA approach. The association between GCMs and anti-TNF response was performed using the eigengene of each GCM. Clinical response was defined using the EULAR criteria at week 14. To analyse the association of GCMs with anti-TNF response at the genetic level, we used 348 anti-TNF treated RA patients from Spain. The statistical analysis was performed using GWAS data and the set-based test in PLINK. The GCMs that were significantly associated with anti-TNF response were subsequently tested for validation in an independent cohort of 2706 anti-TNF treated RA patients. The functional implication of the validated GCMs was studied via pathway and cell type epigenetic enrichment analyses.

Results: We identified 148 GCMs in the RA synovium. From these, 15 GCMs were found to be associated with anti-TNF response (p<0.05). At the genetic level, we found two of the 15 GCMs to be associated with the adalimumab (ADL) and infliximab response (p<0.05) in the Spain cohort. In the independent cohort, we replicated the association of the GCM associated with ADL response (p=0.01). The validated GCM was found to be enriched in genes that participate in the nucleotides metabolism (p=2.41e-5). The epigenetic analysis revealed that ADL-associated variants are enriched in epigenetic marks from immune cell types like Tregs (p=0.04).

Conclusions: Our study shows the existence of a drug-specific genetic basis for the anti-TNF response. Therefore, this molecular diversity should be considered for biomarker research in RA.

Disclosure of Interest: None declared