Impact of Conventional Antirheumatic Treatment on Cardiovascular Risk in Patients with Rheumatoid Arthritis

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Background: Cardiovascular diseases (CVD) are the most common and socially significant comorbidities and the main cause of premature mortality in rheumatoid arthritis (RA). Appropriate RA therapy should not only suppress RA activity, but also reduce CVD risk.

Objectives: To evaluate CVD risk and analyze its association with the use of conventional therapy in RA patients (pts).

Methods: The study included 100 pts with RA (92 women and 8 men) aged 30 to 60 without established CVD. The median age was 49.5 [44.5;53] years. Duration of RA was 144 [60;240] months, DSAS was 4.4 [3;5.3] points. Eighty-six RA pts (86%) treated with disease-modifying antirheumatic drugs (DMARDs) (methotrexate, n=55; sulfasalazine, n=11), including 33 pts (33%) in combination with glucocorticoids (GCs). Fourteen pts (14%) received monotherapy with GCs.

Results: No differences were found between the groups when calculating CVD risk using ASSIGN (table 1). Estimated CVD risk by GRISK3 was lower in DMARDs group (4.9 [3.0;7.7]) than in DMARDs+GCs group (7.1 [4.4;13.6], p<0.05). High CVD risk on the ERS-RA scale was determined less frequently (13%) and median CVD risk was lower in DMARDs group (4.2 [2.2;5.4]) than in GCs group (5.7% [8.9;4.8;11.7], p=0.01) and DMARDs+GCs group (9.9% [6.8;3.9], p=0.05, respectively). In DMARDs group, significant differences in CVD risk by ERS-RA were found in pts treated with hydroxychloroquine (2 [1.4;5.8]) and leflunomide (6.2 [2.8;12.3], p<0.05).

Conclusion: RA pts treated with DMARDs have a reduced risk for CVD than pts treated with GCs or a combination of DMARDs and GCs. GCs significantly increase CVD risk. To clarify the impact of hydroxychloroquine and leflunomide on CVD risk, a study on a larger number of pts is required.

Table 1. The impact of conventional antirheumatic therapy on CVD risk.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ASSIGN</th>
<th>GRISK3</th>
<th>ERS-RA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High CVD risk, %</td>
<td>median [25-75 percentiles]</td>
<td>High CVD risk, %</td>
</tr>
<tr>
<td>DMARDs, n=53</td>
<td>6</td>
<td>11 [6.5;14]</td>
<td>2</td>
</tr>
<tr>
<td>GCs, n=14</td>
<td>7</td>
<td>9.5 [7.13]</td>
<td>7</td>
</tr>
<tr>
<td>DMARDs+GCs, n=33</td>
<td>15</td>
<td>10 [5.13]</td>
<td>9</td>
</tr>
</tbody>
</table>

Note: *p<0.05; **p<0.001 between pts receiving DMARDs and GCs; ***p<0.005 between pts receiving DMARDs and DMARDs+GCs.

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Evaluation of the Effect of Filgotinib on the Pharmacokinetics of Rosuvastatin, Atorvastatin, and Prazastatin

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Background: Filgotinib is an orally administered small molecule that preferentially inhibits Janus kinase 1 and is approved for use in Europe and Japan in adult patients with rheumatoid arthritis (RA) who have had an inadequate response to conventional therapies. Patients with RA are at a higher risk of cardiovascular morbidity and mortality relative to the general population. Thus, it is important to understand potential drug-drug interactions of filgotinib with lipid-lowering agents such as statins. Based on in vitro studies, filgotinib is not expected to significantly increase exposure of statins via inhibition of the organic anion transporting peptide (OATP) at clinically relevant exposures. Hence, in Phase 2 and Phase 3 clinical studies, statins were allowed for use with filgotinib. A post-hoc analysis showed no increase in statin-induced AEs such as muscle or liver toxicities when statins were coadministered with filgotinib (‘Concomitant Use of Statins in Filgotinib-Treated Patients with Rheumatoid Arthritis: A Post Hoc Analysis’; submitted to EULAR 2021).

Objectives: The objectives of this study (NCT04608344) were to evaluate the effect of filgotinib on the pharmacokinetics of atorvastatin, pravastatin, and rosuvastatin, which are sensitive substrates for the OATP1B1/1B3, and the short-term safety of administering filgotinib with or without statins.

Methods: This was an open-label, randomized, two-way, crossover study in healthy adult volunteers (n=27). Study participants received a single dose of atorvastatin (ATV 40 mg) and a single dose of a cocktail of pravastatin (PRA 40 mg) and rosuvastatin (ROS 10 mg), on two different occasions with washout in between, alone or in combination with filgotinib (200 mg QD for 11 days). Serial pharmacokinetic sampling was performed and pharmacokinetic parameters for each statin were calculated. Safety was assessed throughout the study. An analysis of variance using a mixed-effects model was applied to the natural log-transformed pharmacokinetic parameters (Cmin, Cmax and AUC0-t) for ATV, 2-OH-ATV (active metabolite of ATV), PRA, and ROS. Geometric least-squares means (GLSM) ratios and 90% confidence intervals (90% CI) of pharmacokinetic parameters were estimated for each analyte and were compared against pre-specified lack of pharmacokinetic alteration boundaries of 70 to 143%.

Results: Of the 27 enrolled participants, 25 participants completed all study treatments. A total of 215 AEs and 32 serious adverse events were reported. None of the 215 AEs was considered related to filgotinib. One participant discontinued due to a Grade 3 increase in creatinine kinase and 1 participant discontinued due to difficulty in blood draws. Following coadministration of filgotinib with ATV, relative to ATV alone, ATV AUCinapp was unaffected.