Effects of IL6 inhibitors on the incidence of major adverse cardiovascular events in rheumatoid arthritis patients: a systematic review with meta-analysis

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Background: Rheumatoid arthritis (RA) is associated with a 2-fold increased risk of cardiovascular events (CVE) and mortality when compared to the general population. The systemic inflammation in RA seems to play a pivotal role by creating endothelial dysfunction and thus accelerating atherosclerosis. This long-lasting inflammatory process potentiates the effects of additional classical cardiovascular risk factors. Since the 2000s, numerous therapeutic advances, in particular biologics, allow better control of this inflammation. Among these, IL6 inhibitors (IL6i) are known to provide rapid and sustained improvements in clinical, biological and radiographic outcomes. However, an increase in circulating lipid concentrations in patients treated with IL6i is usual. This raises the question of the risk-to-benefit ratio of IL6i.

Objectives: The purpose of this systematic literature review and meta-analysis was to evaluate the impact of IL6i on the incidence of major adverse cardiovascular events in RA patients in comparison with TNFalpha inhibitors (TNFi), non TNFi bDMARDs or csDMARDs.

Methods: A systematic literature search of MEDLINE (via PubMed), EMBASE and the Cochrane Library databases until February 2019 was performed. Included studies were observational studies or randomized controlled trials having reported relevant confirmed CVEs (death from CVE, myocardial infarction, heart failure and stroke) in patients with RA compared to patients with IL6i compared to patients in the control groups was performed. A random effect model was applied in case of substantial heterogeneity.

Results: Of 6869 studies, 23 randomized controlled trials and 6 controlled cohorts could be included. IL6i were significantly associated with a reduction in the risk of myocardial infarction in comparison with IL6i (OR, 0.73; 95% CI [0.56 to 0.96]). No other significant effects were observed with regard to the risks of stroke, heart failure (HF), and death from CVE in comparison with csDMARDs, TNFi, or non-TNFi bDMARDs (table 1).

Table 1. Pooled relative risks of cardiovascular events in RA patients treated with IL-6 inhibitors and respective control groups

<table>
<thead>
<tr>
<th></th>
<th>Cs DMARDS</th>
<th>TNFi</th>
<th>Non TNFi bDMARDs</th>
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<tbody>
<tr>
<td>Myocardial infarction</td>
<td>1.44 (0.50-4.17)</td>
<td>0.73 [0.56; 0.96]</td>
<td>0.81 [0.48; 1.36]</td>
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<tr>
<td>Stroke</td>
<td>1.08 (0.40-2.91)</td>
<td>1.20 [0.82; 1.77]</td>
<td>0.73 [0.39; 1.37]</td>
</tr>
<tr>
<td>Heart failure</td>
<td>0.17 (0.01-4.08)</td>
<td>1.51 [0.61; 3.70]</td>
<td>1.19 [0.71; 1.98]</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>1.59 (0.62-4.11)</td>
<td>1.13 [0.72; 1.78]</td>
<td>NA</td>
</tr>
</tbody>
</table>

Our findings of a potentially protective effect of IL6i use on the risk of MI are reassuring. Although several beneficial effects might be involved, like the effective control of systemic inflammation, the anti-arrhythmia effect or the improvement of endothelial and left ventricle dysfunction, a potential indication bias with a decreased likelihood to prescribe these drugs in patients with high cardiovascular risk cannot be excluded.

Conclusion: This review of the literature with meta-analysis provides reassuring results about the association between use of IL6i and CVE in RA patients. Data from long-term observational studies is however needed to confirm and ascertain this result.

Disclosure of Interests: None declared

Introduction: The rate of cardiovascular (CV) events is higher in patients with rheumatoid arthritis (RA) as compared to the general population. IL6 inhibitors (IL6i) have a role in preventing CV events. However, the incidence of CV events after IL6i initiation is increased. The aim of this study was to determine if the CV event rate after IL6i initiation is increased.

Methods: This was a single-center, retrospective, observational study. All patients with RA treated with IL6i from 2017 to 2019 were included. The primary outcome was CV events (death from CVE, MI, stroke, heart failure) within 1 year or 24 hours. The secondary outcome was CV events (death from CVE, MI, stroke, heart failure) within 1 year or 24 hours after the first dose of IL6i.

Results: There were 76 patients included. The primary outcome was CV events within 1 year or 24 hours after the first dose of IL6i in 37 patients (49%). The secondary outcome was CV events within 1 year or 24 hours after the first dose of IL6i in 54 patients (72%). The CV event rate within 1 year or 24 hours was significantly higher in the secondary outcome compared to the primary outcome (29% vs 14%, p = 0.04).

Conclusion: The CV event rate within 1 year or 24 hours after the first dose of IL6i is increased. However, the CV event rate within 1 year or 24 hours after the first dose of IL6i is significantly lower than the CV event rate within 1 year or 24 hours after the first dose of non-TNF inhibitors.

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