The risk of serious infections in patients receiving anakinra for rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register

Sin, Anakinra (ANA) is an IL-1 receptor antagonist, which is licensed for the treatment of resistant RA. The use of ANA in the context of RA has never gained popularity but ANA has become an increasingly attractive agent in the treatment of a number of other diseases. Early studies in patients with systemic-onset JIA [2] and adult onset Still’s disease [3] (AOSD) have shown very promising results, while interest has developed in the effectiveness of ANA in much more prevalent diseases including Type II diabetes [4] and OA [5]. A major question surrounding the use of biologic therapies concerns safety. A recent Cochrane review of trials of ANA in RA identified no significant difference in serious infection (SI) rates compared with placebo [1]. Given the growing use of ANA in other fields, we felt it was important to share our experience within the British Society for Rheumatology (BSR) Biologics Register (BSRBR), a prospective cohort study set up in 2001 to monitor the safety of biologic therapies in RA in the UK.

Full details of the BSRBR methodology have been published previously [6]. For this analysis all patients had a diagnosis of RA and were recruited between October 2001 and May 2008. Patients receiving either ANA or non-biologic (nb) DMARDs were followed up for 5 years, until December 2008, or death, whichever came first. SI was defined as an infection requiring hospitalization, i.e. antibiotics or resulting in death. SI was attributed to ANA if it was diagnosed while on drug or within 30 days of the last dose. The analysis was limited to patients starting ANA as their first biologic therapy for RA following failure of traditional nbDMARDs. We compared the rates of SI between the two cohorts using a Cox proportional hazards model. Adjustment for baseline confounders (age, gender, disease severity, disease duration, comorbidty, year of entry into the study and baseline steroid exposure) was performed using matched propensity scores. Where patients had multiple infections during follow-up, only the first event was considered in the analysis. Missing baseline data were replaced using multiple imputations. Full details of the statistical methodology are available as supplementary data (at Rheumatology Online). Ethics approval for the study was obtained in December 2000 from the Multicentre Research Ethics Committee (MREC) for the Northwest of England.

ANA was prescribed to 111 RA patients as their initial biologic. One hundred and five were recruited prior to 2004 and none has been recruited since 31 December 2007. Patients prescribed ANA were younger, had more severe disease, longer disease duration and higher exposure to steroids than the comparison cohort (Table 1). Drug survival on ANA was short [median (IQR) survival: 5 months (IQR 3–12 months)] and 93 (84%) of patients later switched to another biologic agent during follow-up. The reasons for discontinuation of ANA were inefficacy (70%), adverse event (20%) and unrecorded/unknown (10%). Fifteen SIs occurred in 10 patients on ANA, with the most common sites being respiratory (n = 4) and skin/soft tissue (n = 4). Three ANA-treated RA patients died from SIs that developed while receiving the drug (one septic arthritis, one urinary sepsis and one necrotizing fasciitis). The crude rate of first SI was 92/1000 patient-years (95% CI 44, 170) in the ANA cohort compared with 34/1000 patient-years (95% CI 30, 38) in the nbDMARD cohort. The unadjusted hazard ratio (HR) for first SI was 2.8 (95% CI 1.5, 5.3) in the ANA cohort. After adjusting for confounders, there remained a tendency towards increased infection rates, although this was no longer significant [HR 1.58 (95% CI 0.92, 2.74)].

The patients treated with ANA within the BSRBR had higher rates of SI than the nbDMARD comparison population. This likely reflects a combination of the characteristics of patients chosen to receive ANA and an effect of the drug itself. In order to separate out these effects, a fully adjusted analysis was performed but unmeasured confounding remains possible. In addition, the small number of patients in the ANA cohort and short duration of follow-up (due to high rates of drug discontinuation) limit the power of the study to detect a difference.

Acknowledging these limitations, the results presented here from real-world data suggest a trend towards an increased infection rate with ANA in patients with RA. To put these results in context, we have reported increased SI rates with anti-TNF therapy that are of a similar order of magnitude during the first 6 months of therapy [7]. Our findings should encourage clinicians to remain vigilant for SI in patients prescribed ANA. The growing use of ANA in other conditions should be accompanied by further research to evaluate fully the safety profile in other diseases.

Rheumatology key message

- ANA was associated with a trend towards increased infection risk in patients with RA.

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Supplementary data

Supplementary data are available at Rheumatology Online.

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References


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A case of Behcêt’s disease associated with myelodysplastic syndrome involving trisomy 8 and a gain-of-function mutation in SHP-2

Sir, Behcêt’s disease (BD) has been reported to involve a variety of immunological abnormalities [1,2]. However, it remains to be determined whether these abnormalities are primary or secondary events in the development of BD. BD has recently been linked to a group of autoinflammatory diseases that are associated with an inability to control inflammation caused by primary dysfunction of members of the innate immune system, such as neutrophils and monocytes/macrophages, without evidence of adaptive immune dysregulation [3]. Recently, there have been sporadic case reports of BD associated with myelodysplastic syndrome (MDS)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ANA (n = 111)</th>
<th>DMARD (n = 3515)</th>
<th>P-value</th>
<th>Matched DMARD patients (n = 333)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up time, years</td>
<td>108</td>
<td>3515</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (s.d.), years</td>
<td>56 (11)</td>
<td>60 (12)</td>
<td>&lt;0.001</td>
<td>57 (12)</td>
</tr>
<tr>
<td>Gender: female, %</td>
<td>75</td>
<td>72</td>
<td>0.575</td>
<td>74</td>
</tr>
<tr>
<td>Disease duration, years, median (IQR)</td>
<td>13 (6–20)</td>
<td>6 (1–15)</td>
<td>&lt;0.001</td>
<td>8 (1–18)</td>
</tr>
<tr>
<td>DAS-28 score, mean (s.d.)</td>
<td>6.4 (1.0)</td>
<td>5.1 (1.3)</td>
<td>&lt;0.001</td>
<td>5.8 (1.3)</td>
</tr>
<tr>
<td>HAQ, mean (s.d.)</td>
<td>2.0 (0.6)</td>
<td>1.5 (0.8)</td>
<td>&lt;0.001</td>
<td>1.9 (0.7)</td>
</tr>
<tr>
<td>Steroid at baseline, %</td>
<td>50</td>
<td>23</td>
<td>&lt;0.001</td>
<td>25</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>20</td>
<td>24</td>
<td>0.495</td>
<td>26</td>
</tr>
<tr>
<td>Ex-smoker, %</td>
<td>39</td>
<td>40</td>
<td>0.495</td>
<td>32</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>5</td>
<td>7</td>
<td>0.617</td>
<td>5</td>
</tr>
<tr>
<td>COPD, %</td>
<td>11</td>
<td>10</td>
<td>0.445</td>
<td>10</td>
</tr>
<tr>
<td>Prior cancer, %</td>
<td>3</td>
<td>7</td>
<td>0.087</td>
<td>5</td>
</tr>
</tbody>
</table>

with trisomy 8 and a gain-of-function mutation in SHP-2. We describe here a new case of BD associated with myelodysplastic syndrome involving trisomy 8 and a gain-of-function mutation in SHP-2. The patient was a 45-year-old male who presented with BD symptoms at the age of 18 years. He was treated with methotrexate, azathioprine, and ciclosporin. At the age of 35 years, he was diagnosed with myelodysplastic syndrome involving trisomy 8 and a gain-of-function mutation in SHP-2. He was treated with lenalidomide and subsequently with ibrutinib. The patient is currently in complete remission of BD and myelodysplastic syndrome. This case highlights the potential role of autoinflammatory diseases in the development of BD.