Patients with psoriatic arthritis who are not eligible for randomised controlled trials for TNF inhibitors have treatment response and drug survival similar to those who are eligible

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ABSTRACT

Objectives To determine in a retrospective cohort whether patients with psoriatic arthritis (PsA) who would not have fulfilled the inclusion criteria for randomised controlled trials (RCTs) for the TNF inhibitor (TNFi) chosen for their treatment (excl) have similar benefits and drug survival as those patients who would have (incl).

Methods All patients with rheumatic disorders who are treated with biological disease-modifying antirheumatic drugs in Iceland are registered in ICEBIO. On 1 February 2016, 329 individuals with PsA were registered in ICEBIO, of whom 231 had data available for their first start of TNFi and could be evaluated according to the inclusion criteria of the respective RCTs. Disease activity was collected at baseline using Visual Analogue Scale (pain, fatigue and global (patient and physician) assessments), swollen joint count (SJc) and tender joint count (TJc), Disease Activity Score 28-joint count C reactive protein (DAS28-CRP) and Health Assessment Questionnaire (HAQ). Treatment response was measured at 6 and 18 months according to American College of Rheumatology response criteria, DAS28-CRP and Disease Activity Score in Psoriatic Arthritis for 28 joints. Drug survival rate was also analysed.

Results The demographics of these two groups were similar at baseline, although the incl group had higher SJc (5.5 vs 3.8) and subsequently higher DAS28- CRP (4.6 vs 4.2). While a larger change in disease activity was observed in the incl group with respect to HAQ and SJc, both groups had similar disease activity at follow-up. Drug survival was similar in both groups.

Conclusions Patients with PsA who would not have fulfilled the inclusion criteria in RCTs reach similar disease activity scores at follow-up of 6 and 18 months and have similar drug survival as those patients who would have been included in RCTs.

INTRODUCTION

Psoriatic arthritis (PsA) is a seronegative chronic inflammatory arthritis affecting individuals with psoriasis. Psoriasis has a variable prevalence, depending on geographical area and the method of study and affects around 3%–6% of the population, of whom 18.5%–20.9% also have PsA, according to a recent large meta-analysis.1–4 The global prevalence of PsA is 133 per 100 000, and in Iceland, the prevalence of PsA is estimated to be 139 per 100 000.2 PsA is a heterogenic disease, the most common form being an oligoarticular or polyarticular pattern of peripheral arthritis. However, PsA may present with axial involvement, with swelling of entire digits, that is, dactylitis, or with enthesitis.5 PsA often debuts in younger adults and may cause severe destruction of joints and significant disability. There are effective treatment modalities; however, no cure exists for PsA,
and the main goals of treatment are to reduce pain and stiffness and to preserve joint function and health-related quality of life in the long term.6 Most patients require therapy with disease-modifying antirheumatic drugs (DMARDs), for example, methotrexate, with or without intra-articular steroid injections, although up to over 40% require treatment with biological disease-modifying antirheumatic drugs (bDMARDs).7 TNF alpha inhibitors are most commonly used, while more recently, specific cytokine inhibitors, for example, targeting interleukin (IL)-17 or IL-12/23, along with non-biological small molecules such as phosphodiesterase 4 (PDE4) and Janus kinase (JAK) inhibitors, have become available.6 TNF inhibitors (TNFi’s) have dramatically altered the disease course and improved the quality of life of patients with PsA in recent decades. Treatment with TNFi is costly and requires resources for close follow-up for efficacy and adverse events; however, it is socioeconomically beneficial to provide treatment with TNFi to individuals with active PsA.1,9

Randomised controlled trials (RCTs) are a powerful tool to evaluate new therapies in comparison with placebo or current best practice as RCTs eliminate physician and patient biases in the most effective possible way. Despite this, it may be unclear whether the results from RCTs can be generalised to the group of patients seen in daily clinical practice.10 11 When conducting RCTs for bDMARDs, patients are recruited using strict entry criteria, presumably to ensure the correct diagnosis for the tested population and to reduce confounding when trying to demonstrate treatment superiority.10 We have recently reported that two-thirds of patients requiring treatment with TNFi for PsA in Iceland would not have been eligible for RCTs performed leading up to the approval of the respective pharmaceutical products.12 The most common reason for exclusion in the study is an insufficient number of swollen joints (45%) and various comorbidities (16%), which is particularly interesting, considering the heterogeneity of PsA discussed earlier. The main purpose of that study was to examine eligibility for RCTs, and reasons for exclusions were not discussed in further detail. Fairly limited data exist on inclusion or exclusion rates into RCTs in rheumatology. Aside from our previous study, we have not encountered other studies examining the eligibility of patients with PsA to clinical trials, although more has been published on the trial eligibility and treatment efficacy of bDMARDs among patients with rheumatoid arthritis.13–16 Inclusion criteria vary considerably between bDMARD trials in PsA. Some require a minimum of as many as six swollen joints, while others require active skin disease and no conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) except methotrexate. The studies also have strict rules regarding comorbidity and/or corticosteroid use. These are all important clinical factors that influence treatment decisions in daily clinical practice.17–23

In the present study, we aimed to determine on a nationwide basis whether patients with PsA, who would not have fulfilled the inclusion criteria for RCTs of the chosen TNFi, experience similar treatment benefits and have comparable drug survival as those patients who did fulfil the same inclusion criteria.

METHODS
All patients with rheumatic disorders who are treated with bDMARDs in Iceland are registered in ICEBIO, a nationwide database. ICEBIO is based on the Danish Registry for biological therapies in rheumatology or DANBIO and was adapted to Icelandic conditions in 2007.24 Currently, ICEBIO has comprehensive individual patient characteristics, along with long-term disease activity scores and information on treatment of >98% of all patients with PsA treated with bDMARDs in Iceland. When the treating rheumatologist deems the use of TNFi is indicated, he applies for a drug licence to the Medicine Committee at the University Hospital as these drugs are almost fully reimbursed in Iceland. The Committee has published treatment guidelines that are very similar to those published by EULAR (only published in Icelandic). An entry into ICEBIO is also required prior to initiation of therapy, and generally, a prior csDMARD treatment failure is required.

The present study includes all patients with PsA registered in ICEBIO who received either adalimumab, etanercept, golimumab or infliximab as their first biological treatment during the period from January 2000 to February 2016. This same group of patients has previously been studied with regard to infliximab dosing regimens and on the influence of obesity on TNFi therapy.25–27 In our previous study, this patient population was classified according to the inclusion criteria of respective pharmaceutical RCTs, that is, whether they would have been included (incl) or excluded (excl) from the RCT performed, leading up to market approval of each respective biological therapy.22 For example, patients receiving golimumab were classified according to inclusion criteria to the GO-REVEAL trial. We refer to those publications for details about the classification process.12 17–25

Information on disease activity, including patient Visual Analogue Scale (VAS) for pain, fatigue and global assessment, physician VAS global assessment, swollen joint count (SJC) and tender joint count (TJC), Disease Activity Score 28-joint count C reactive protein (DAS28-CRP) and Health Assessment Questionnaire (HAQ) scores were extracted from ICEBIO at baseline (last visit before starting TNFi), 6 months (nearest visit to 180 days (90–210)) and 18 months (540 days (211–570)). We also collected standard demographic data at the time of start of the TNFi treatment. Times for treatment response evaluation were chosen with respect to Icelandic biological drug regulations, which require a clinical evaluation of efficacy and registration into ICEBIO within 7 months of initiation of bDMARDs and then annually for renewal of treatment licence. The large time frame around each visit was chosen as available visits...
in ICEBIO were more sporadic so long after initiation of TNFi therapy.

American College of Rheumatology (ACR) response was calculated, and patients achieving improvement by 20% (ACR20) or higher compared with the baseline visit were considered to be responding. We calculated the Disease Activity Score in Psoriatic Arthritis for 28 joints (DAPSA28) and considered a decrease by one or more disease categories to be a response to therapy (cut-off values for remission (≤4), low (>4 to ≤14), moderate (>14 to ≤28) and high (>28) disease activities). DAPSA28 is the following summation: (SJC+TJC)×1.6+patient global (0–10 VAS)+pain (0–10 VAS)+C reactive protein (CRP) (mg/dL). Additionally, we considered DAS28-CRP with a decrease by one or more disease activity categories as response, for example, moderate DAS28-CRP score (3.2–5.2) to low (2.6–3.1). DAS28-CRP and DAPSA28 were chosen because of availability; we have 66/68 joint examinations entered into our database in only a minority of patients, so calculations would be unreliable. Furthermore, we analysed the drug survival rate over the first 2 years of treatment.

All data were anonymised before analysis. Statistical analysis was performed in R V.3.4.2 (R Project for Statistical Computing, Vienna, Austria) and data manipulation in Microsoft Excel V.1805. χ² test was used for comparison between responders and non-responders, and drug survival was demonstrated using a Kaplan-Meier curve, along with a log-rank test between the curves. To account for missing data in the response criteria, we employed the LUNDEX method, an integration of clinical response and adherence to therapy in a composite value, the multiplication of the proportion of patients adhering to therapy by the proportion fulfilling the response criteria. The groups were further subdivided by subtypes of TNFi and log-rank tests performed between each pair of drug survival curves. Unpaired t-tests were used for comparison of disease activity indicators and composite scores.

**RESULTS**

**Patients**

On 1 February 2016, 1058 individuals were registered in ICEBIO, of whom 329 had been diagnosed with PsA. Of these, 274 patients initiated their first-ever treatment with a TNFi, of whom 226 could be classified using available data according to the inclusion criteria for the RCTs of adalimumab, etanercept, golimumab or infliximab. This group represents the study population, and within this group, 74 patients would have fulfilled the inclusion criteria (incl), and 152 patients would not have (excl). In the incl group, the most commonly used TNFi was etanercept (38%), while the most used TNFi in the excl group was infliximab (63%). Details on the TNFi used are shown in table 1.

### Table 1 Baseline characteristics of the two study groups, that is, those who met inclusion criteria for randomised controlled trial (incl) and those who did not (excl)

<table>
<thead>
<tr>
<th>Met inclusion criteria</th>
<th>Did not meet inclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total, n</td>
<td>74</td>
</tr>
<tr>
<td>Age (years)</td>
<td>49±13</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>45 (61%)</td>
</tr>
<tr>
<td>Disease duration at start (years) (n=246)</td>
<td>7.3±7.0</td>
</tr>
<tr>
<td>Weight (kg) (n=178)</td>
<td>92±20</td>
</tr>
<tr>
<td>Height (cm) (n=105)</td>
<td>174±9</td>
</tr>
<tr>
<td>BMI (n=105)</td>
<td>30±6</td>
</tr>
<tr>
<td>TNFi inhibitor type, n (%)</td>
<td>Infliximab (23 (31%))</td>
</tr>
<tr>
<td></td>
<td>Etanercept (28 (38%))</td>
</tr>
<tr>
<td></td>
<td>Golimumab (11 (15%))</td>
</tr>
<tr>
<td></td>
<td>Adalimumab (9 (12%))</td>
</tr>
</tbody>
</table>

Demographic data and disease activity at entry of the study

The two groups were similar at baseline with respect to age, sex, disease duration, weight, height, body mass index, CRP, patient global VAS and physician global VAS, as shown in tables 1 and 2. The incl group had a higher mean SJC (5.5±3.3 vs 3.8±3.6, p=0.003), and subsequently, they had a higher DAS28-CRP score (4.6±0.8 vs 4.2±0.9, p=0.01; table 2). Ankylosing Spondylitis Disease Activity Score (ASDAS), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI) scores were available for <10% of patients and were not further analysed.

**Disease activity at 6 and 18 months**

No difference was noted in patient-reported outcomes and disease activity indicators at either 6 or 18 months in any of our indicators (DAPSA28, DAS28-CRP, VAS pain, VAS fatigue, VAS global patient, VAS global physician, TJC or SJC). The excl group had a higher mean CRP of 6.1±9.6 at 18 months compared with the incl group mean of 3.1±2.5, although there was no difference between the groups at baseline or at 6 months. Further results are shown in table 2.

**Response to therapy**

Treatment response is outlined in table 3. No difference in response was seen between the two groups with respect to VAS scores for pain, fatigue, patient global or physician global assessment. The incl group had a statistically significantly better response in HAQ (−0.8±0.7 vs excl.
Table 2  Baseline disease activity indicators with response after initiation of first-line TNFα inhibitors, mean values±SD.

<table>
<thead>
<tr>
<th>Score</th>
<th>At baseline</th>
<th>At 6 months</th>
<th>At 18 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incl</td>
<td>Excl</td>
<td>Incl</td>
</tr>
<tr>
<td>VAS pain</td>
<td>65±17</td>
<td>64±22</td>
<td>30±23</td>
</tr>
<tr>
<td>VAS fatigue</td>
<td>68±24</td>
<td>66±24</td>
<td>29±25</td>
</tr>
<tr>
<td>VAS global</td>
<td>71±21</td>
<td>66±24</td>
<td>31±23</td>
</tr>
<tr>
<td>VAS physician</td>
<td>57±16</td>
<td>53±18</td>
<td>28±18</td>
</tr>
<tr>
<td>CRP</td>
<td>11±11</td>
<td>12±20</td>
<td>5.1±6.4</td>
</tr>
<tr>
<td>HAQ</td>
<td>1.2±0.7</td>
<td>1.0±0.7</td>
<td>0.6±0.6</td>
</tr>
<tr>
<td>SJC</td>
<td>5.5±3.3*</td>
<td>3.8±3.6*</td>
<td>1.5±1.8</td>
</tr>
<tr>
<td>TJC</td>
<td>6.3±3.8</td>
<td>5.4±4.4</td>
<td>2.0±3.1</td>
</tr>
<tr>
<td>DAPSA28</td>
<td>45±18</td>
<td>39±24</td>
<td>18±16</td>
</tr>
<tr>
<td>DAS28-CRP</td>
<td>4.6±0.8*</td>
<td>4.2±0.9*</td>
<td>2.8±1.1</td>
</tr>
</tbody>
</table>

*Denotes a p value of <0.05 by unpaired t-test on testing for the statistical difference between incl and excl groups (both columns designated *).

CRP, C-reactive protein; DAPSA28, Disease Activity Score in Psoriatic Arthritis for 28 joints; DAS28-CRP, Disease Activity Score 28-joint count C reactive protein; HAQ, Health Assessment Questionnaire; SJC, swollen joint count; VAS, Visual Analogue Scale.

−0.3±0.6, p=0.008) at 6 months, but this difference did not reach statistical significance at 18 months (−0.6±0.7 vs −0.3±0.6, p=0.051). The incl group also showed a larger change in the SJC at 6 months (−4.3±2.7 vs −2.2±2.7, p=0.001), and this remained statistically significant at 18 months (−4.4±3.4 vs −2.2±3.6, p=0.007). No response difference between the groups in TJC was noted.

We had sufficient data to calculate treatment responses based on ACR criteria and movement between DAS28-CRP and DAPSA28 response groups for 75 patients in our study group, 26 in the incl group and 49 in excl group (table 4). There were no statistically significant differences in response between the groups with regard to ACR20 at 6 months (77% vs 60%, p=0.207) or 18 months (69% vs 59%, p=0.545). There was a numerical but not statistically significant difference in the proportion of patients achieving American College of Rheumatology response criteria, improvement by 50% (ACR50) at 6 months, but by 18 months, this difference had reached statistical significance (65% vs 34%, p=0.034). There were no differences noted between the groups in achieving American College of Rheumatology response criteria, improvement by 70% (ACR70). There were no statistically significant differences in the proportion of patients showing response between the groups as measured by DAS28-CRP or DAPSA28 at 6 or 18 months.

Since we had a significant number of patients without available response data, we performed an evaluation of our data correcting for dropouts using the LUNDEX method. This revealed no statistically significant differences at either 6 or 18 months in any of the composite disease activity scores, although the numerical difference remained in ACR50 at both 6 and 18 months. The response rates according to this method for the incl and excl groups, respectively, were DAS28-CRP 66% to 64% at 6 months and 49% to 45% at 18 months; DAPSA28 71% to 63% at 6 months and 45% to 45% at 18 months; ACR20 66% to 54% at 6 months and 42% to 40% at 18 months; ACR50 49% to 36% at 6 months and 39% to 25% at 18 months; and finally, ACR70 29% to 21% at 6 months.

Table 3  Response to first TNFα inhibitors, mean values±SD unless otherwise indicated

<table>
<thead>
<tr>
<th>Improvement in clinical parameters</th>
<th>6 months</th>
<th>18 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incl</td>
<td>Excl</td>
</tr>
<tr>
<td>VAS pain</td>
<td>−34±30</td>
<td>−29±28</td>
</tr>
<tr>
<td>VAS fatigue</td>
<td>−35±33</td>
<td>−24±29</td>
</tr>
<tr>
<td>VAS patient global</td>
<td>−41±38</td>
<td>−28±30</td>
</tr>
<tr>
<td>VAS physician global</td>
<td>−34±19</td>
<td>−32±19</td>
</tr>
<tr>
<td>HAQ</td>
<td>−0.8±0.7</td>
<td>−0.3±0.6</td>
</tr>
<tr>
<td>SJC</td>
<td>−4.3±2.7</td>
<td>−2.2±2.7</td>
</tr>
<tr>
<td>TJC</td>
<td>−4.2±3.8</td>
<td>−2.8±5.1</td>
</tr>
</tbody>
</table>

*Denotes a p value of <0.05 by unpaired t-test.

DAPSA28, Disease Activity Score in Psoriatic Arthritis for 28 joints; HAQ, Health Assessment Questionnaire; SJC, swollen joint count; TJC, tender joint count; VAS, Visual Analogue Scale.
and 30% to 19% at 18 months. The group of patients who had no response measures available at either time point did have a numerically longer disease duration (6.7 to 8.1 years) and higher joint counts (SJC 4.0 to 4.8, TJC 5.2 to 6.3; p<0.05).

**Drug survival**

The groups had similar 2-year drug survival (figure 1), with 46% of the patients having discontinued therapy before the end of the second year in the incl group (n=114) and 44% in the excl group (n=152). There were no statistically significant differences in drug survival noted between the two groups when the four types of TNFi (adalimumab, etanercept, golimumab or infliximab) were analysed separately (data not shown).

Reasons for discontinuing therapy were similarly distributed between the two groups, with 41% of incl and 42% of excl discontinuing for lack of drug response. Adverse events, including various side effects and infections, were the reason for discontinuation in 38% of those discontinuing in the incl group and 29% in the excl group.

**DISCUSSION**

In the present study, we have demonstrated that patients with PsA who would not have fulfilled the inclusion criteria for the RCTs performed prior to the approval of the TNFi did benefit from treatment with TNFi, achieving similar levels of disease activity, largely a similar response rate and similar drug survival as those who would have fulfilled the inclusion criteria in the same RCTs. This study addresses a well-known and common problem in all fields of medicine. Study populations are included in RCTs based on strict entry criteria, and as a result, clinical decision-making is often based on evidence from trials that do not include the typical patient populations present in daily clinical practice. Patients with PsA are such a heterogenic population that it is urgent to confirm that the part of the patient population that would not have been eligible for these pharmaceutical trials enjoys similar benefits from treatment as those who did. With databases for long-term bDMARD therapy follow-up such as ICEBIO, it is possible to perform observational studies on this important issue. The added information from the present study on this population of patients with PsA less active than those typically included in trials will also help guide future research in this population, which in this study comprised two-thirds of the entire population of patients with PsA available for analysis.

The strict inclusion criteria of RCTs are likely chosen to ensure the correct diagnosis and to reduce confounding when trying to demonstrate superiority of the treatment. This approach is common and we are not suggesting changes in this research practice but rather stress the...
importance of being aware of this disparity when making clinical decisions based on data from RCTs.

Disease activity measures are comparable to previous publications from Nordic countries. In our study, the two groups are similar at baseline except for two important factors. First, the incl group has a more severe disease at baseline, with higher SJC and subsequently a higher DAS28-CRP, reflecting their eligibility for clinical trials. Second, the groups differ in choice of TNFi, where the excl group receives infliximab in two-thirds of cases and the incl group in only a third of cases, with etanercept being the most commonly used TNFi. During the study period, no patients were treated with certolizumab since it is not marketed in Iceland. Furthermore, although the SJC and HAQ response effects are larger in the incl group, both groups converge at a similar disease activity level after 6 and 18 months of treatment. We conclude that the different effect size is mostly due to more baseline disease activity in the incl group.

Drug survival is an indirect marker of treatment efficacy and it is similar between the groups. Around 45% of each group had discontinued treatment after 2 years, which is common in bDMARD treatment trials, and the reasons for discontinuation were similarly distributed between the two groups. There was no obvious difference in drug survival between different TNFi’s in either group, although small group sizes do not allow for a detailed analysis.

The strength of this study is that it is a population-wide study using a data source that contains information on more than 98% of all patients receiving biologics in Iceland. Additionally, 84% of patients studied for eligibility in our previous publication could be classified according to inclusion and exclusion criteria despite the retrospective manner of data collection and the requirement of 66/68 joint counts in all the TNFi RCTs. However, the patients who could not be classified according to RCT criteria had a longer disease duration and overall more disease activity at baseline. The study is limited by the size of the study population since full data for calculating clinical response are only available in a third of the patients, reducing statistical power. Furthermore, only 28 joints are included in the assessment in most of the ICEBIO data with only a few 66/68 joint counts recorded, therefore limiting our analysis to 28 joint counts. ICEBIO data do not specify which domain of PsA is being treated, and although we extracted disease activity markers for axial disease, they were documented in <10% of patients, too few to allow for any conclusions to be drawn; the same applies for enthesitis and dactylitis. Although no difference is found based on trial eligibility among these 226 patients, we were only able to calculate response rates in one-third of patients. At some time points, we observed numerical differences, where the incl group responded more frequently to therapy, but this was not statistically significant except in the case of ACR50 response at 18 months. After correction for missing data with the LUNDEX method, this difference was only numerically but not statistically significant. Thus, a clinically relevant effect may not have reached statistical significance due to small sample sizes in our study, or alternatively, this could be an artefact related to multiple testing. We therefore recommend that our work be repeated in another registry of patients on biological treatment with a larger sample group to achieve more statistical power and to enable further subgroup analysis.

Patients with PsA who would not have fulfilled the inclusion criteria in RCTs have similar disease activity scores at follow-up and similar drug survival as those patients who would have been included in RCTs. Their treatment effect size is smaller on some measures, but both groups arrive at a similar absolute disease activity, with the difference in effect size being potentially explained by more severe disease at baseline in the incl group. Thus, treatment outcomes for bDMARD treatment in PsA from RCTs may likely be applied to daily clinical practice, irrespective of whether patients would have fulfilled RCT criteria or not. However, more detailed studies are needed on this issue.

**Contributors** Conception or design of the work: OP, PSG, EER, AIG and BG. Data collection: NSK, OP and BG. Data analysis and interpretation: OP, TJL, AIG and BG. Drafting the article: OP and BG. Critical revision of the article: OP, TJL, AIG and BG. Final approval of the version to be published: OP, TJL, AIG, PSS, EER, NSK and BG.

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**Competing interests** BG reports speaker’s bureau from Amgen, Novartis and Pfizer, outside the submitted work. TJL reports personal fees from Celsgene, outside the submitted work. The other authors have no competing interests to declare.

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**Ethics approval** The study protocol was approved by the National Bioethics Committee and the Icelandic Data Protection Authority (VSNb 2015120017/03.03).

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Our data can be made available to other researchers if the research protocol is approved by the National Bioethics Committee and the Icelandic Data Protection Authority. However, due to our nation’s small population, the data would be identifiable if released in its entirety.

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