Ten years with biologics: to whom do data on effectiveness and safety apply?

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Abstract

Objectives. During the past decade, the position of biologics in the therapeutic armamentarium, the number of approved indications and the number of available biologics have changed. Available data on (long-term) safety might thus pertain to patient populations not comparable with contemporary patients. The aim of this study was to assess the extent to which contemporary patients who start or switch biologic therapies are comparable with those patients who gave rise to the currently available data on effectiveness and safety.

Methods. We identified all adult patients with RA (n = 9612), PsA (n = 1417) and other SpA (n = 1652) initiating a first biologic therapy between 1 January 1999 and 31 December 2008, registered in the Swedish Biologics Register (ARTIS), including information on demographics, disease characteristics and 1-year risk of first-line treatment discontinuation.

Results. Over calendar time, measures of disease activity at start declined substantially for all indications, and diminished between first-, second- and third-line therapy starts. One-year risks of first-line therapy discontinuation increased. Switchers to anti-TNF and non-TNF biologics had different comorbidities. Despite <50% drug retention at 5 years, most patients remained exposed to some biologic.

Conclusions. The trends in baseline characteristics and drug retention underscores that any effects of biologics, including comparison between different biologics, must be interpreted in light of the characteristics of the population treated. The observed differences further call for continued vigilance to properly evaluate the safety profiles of biologic treatments as they are currently used. Exposure to multiple biologics presents a challenge for attribution of long-term effects.

Key words: Biologics, Rheumatoid arthritis, Anti-tumour necrosis factor, Psoriatic arthritis, Spondylarthritides.

Introduction

Since their introduction in 1999, the therapeutic position of biologic drugs has changed from a last chance in long-standing refractory RA to an earlier therapeutic option, in several rheumatic diseases, and with several different biologics available. As the threshold for treatment initiation has changed, the characteristics of patients initiating, receiving or switching biologic treatment today may be different from those in whom these treatments were initially evaluated and indicated. They may also be different from those patients whose treatment experiences have so far been reported in observational studies. This is especially true for long-term safety (which, by necessity,
reflect patients who started treatment long ago) and for patients with PsA or other SpA (many of the available safety data pertain to patients with RA). Safety data pertaining to switchers (who may represent a selected group particularly prone to non-response or adverse drug reactions), and safety comparisons between established and more recently introduced biologics may also be different.

To better understand the generalizability of available or emerging data on treatment outcomes and short- and long-term safety of biologics, the aim of the present study was to compare demographics, disease activity and comorbid conditions between (i) patients starting a first biologic therapy 10 years ago vs more recently; (ii) patients starting their first biologic drug vs switching to a second or third biologic, including switching to non-TNF biologics; and (iii) patients with RA, PsA or SpA. To do this, we used data from the Swedish biologics register anti-rheumatic therapy in Sweden (ARTIS), in which nationwide data on patients prescribed biologic therapies for the treatment of rheumatic disease in Sweden have been collected since they were first available in clinical practice (1999).

Methods
Setting and study population
The Swedish health-care system and medical treatment are public and tax funded. Treatment (biologic or non-biologic DMARDs) of rheumatic diseases is primarily administered by rheumatologists. Although treatment guidelines provide recommendations for the use of biologics, the ultimate treatment decision resides in the hands of the treating rheumatologists. Estimates suggest that as of 1 January 2008, between 15 and 18% (22–27%, aged 16–59 years) of all patients with RA in Sweden were receiving a biologic therapy, depending upon RA criteria.

ARTIS was established in conjunction with the introduction of the first biologic therapies. The register is overseen by the Swedish Rheumatology Association and is a research database extracted from the Swedish Rheumatology Quality register that is integrated into clinical practice rather than conducted as a separate trial. At start of a biologic, the rheumatologist enters core information on the treated disease. At regular follow-ups, information on disease activity and treatment is also reported. Adverse events reporting into the database is facilitated by a web-based reporting tool. Though initially approved for RA, new indications for biologics in other rheumatic diagnoses have led to the addition of patients with PsA and SpA. Estimates suggest that ARTIS covers between 87 and 92% of all patients with RA treated with biologic therapies [2]; however, at this time, it is not known whether this can be extrapolated also to SpA or PsA. For this study, all patients, at least 16 years of age at first presentation, initiating a biologic therapy between 1999 and 2008 for either RA (n=9612), SpA (n=1652) or PsA (n=1417), were identified (total n=12681). Informed consent was collected and the study was approved by the Ethics Committee at Karolinska Institute.

Additional data and covariates
For each patient in ARTIS, information on all biologic therapies started (restricted to first, second and third starts) was collected. Data on sex, disease duration, age, measures of disease activity [28-joint DAS (DAS-28), CRP in mg/l, swollen and tender joint counts, ESR in mm/h and patient’s global health and pain both measured by visual analogue scale (VAS) score], functional status (HAQ) and biologic drug was collected. For SpA and PsA, only time trends in CRP, HAQ and pain VAS are presented because the registration of pertinent indices of disease activity (e.g. BASDAI) has changed during the study period. For each biologic treatment, any date of discontinuation was also collected, including reported reason of treatment termination or pause.

Using the personal identification numbers issued to all Swedish residents alive in 1947 or born/emigrated thereafter, information from ARTIS was linked to other data sources. In the Swedish National Patient Register, data on hospital discharges (diagnoses according to International Classification of Diseases codes [ICD], versions 7 through 10) since 1964 (nationwide since 1987), and data on outpatient non-primary care visits since 2001, have been recorded.

Characteristics at treatment start
We calculated summary statistics for each of the three indications (RA, SpA and PsA), describing disease characteristics at treatment start by calendar period and by the first, second and third time starting a biologic. Hospitalizations with comorbid conditions according to the National Patient Register were also included. The Wald test was used to evaluate whether there were significant linear trends over time by year of biologic therapy initiation from linear regression models [3]. Among RA patients who were first prescribed an anti-TNF biologic, we also examined how these characteristics differed by choice of second-line therapy class (anti-TNF vs non-TNF biologic).

Adherence to therapy
One-year risks of discontinuing first biologic treatment, along with the proportion reporting stopping due to adverse event or due to lack or loss of efficacy (referred to as ineffectiveness), were calculated. Kaplan-Meier curves were plotted for time on first biologic therapy by year of treatment initiation. Individuals were considered on first treatment until the first of the following: reported discontinuation, end of follow-up (31 December 2008), emigration, death or 450 days since last ARTIS visit for individuals who were lost to follow-up. Treatments with rituximab (Mabthera) were excluded from these analyses because the dosing schedule is irregular and discontinuation may be indistinguishable from a long delay between infusions. In these analyses, we also excluded biologic...
initiators in 2008 because a full calendar year had not yet accrued in the data at the time of this analysis.

For patients with RA, we also plotted the distribution of their biologics-exposed person-time using start of first biologic as the origin. This figure showed the proportion of person-time during follow-up that a patient is either on their first, second or third anti-TNF treatment, non-TNF biologic or no biologic drug but still in the study. On a secondary axis in the same figure, we plotted the number of participants contributing to each 6-month period.

Results

Distribution of treated diagnoses, and biologic drugs, among first-time initiators of biologic therapies 1999–2008

In total, 12,681 patients started their first biologic between 1999 and 2008 for RA, SpA or PsA (Table 1). RA was the most common diagnosis, but the proportions of patients with SpA and PsA increased with time (Table 1). The class of anti-TNF drug represented by far the largest proportion of patients in this register. A total of 313 (310 RA, 1 SpA, 2 PsA) patients were registered with a non-TNF biologic as their first treatment. While the annual number of first-time treatment starts was nearly constant for RA (disregarding the reduced market availability of etanercept between 2000 and 2002), the annual number of first-time biologic initiators increased during the study period for both SpA and PsA. The internal distribution of individual biologic drugs was similar for RA, SpA and PsA.

Demographic, disease and comorbidity characteristics among first-time initiators of biologic therapies 1999–2008

Among the 9,912 patients with RA, the median age was 57 years, 76% were female, and the median disease duration was 8.4 years. During the study period, median disease duration at biologic start decreased with time, while median age at initiation increased (Table 1). Objective measures of disease activity and inflammation at biologic start declined significantly over time; swollen joint count, HAQ, DAS-28, CRP and ESR were all lower at treatment initiation for more recent starters as compared with biologic initiators in the earlier years (Table 2). A similar decline was also seen for more subjective markers of disease severity, including tender joint count, pain and global health. Despite the declines, the mean DAS-28 among patients starting treatment in 2008 was 5.0 and 44% of these patients had EULAR high disease activity (DAS-28 ≥ 5.2). There was no clear pattern over time of concomitant MTX, other DMARD, NSAIDs or CSs use at biologic initiation (data not shown). There was no trend in history of comorbidity at initiation with the exception of history of joint surgery, the prevalence of which declined over time (Table 2).

Among the 1,652 patients with SpA first starting a biologic therapy, the median age was > 10 years younger (43 years) than the RA group, and two-thirds were male.
The median disease duration was 12.2 years, though shorter in more recent years. None of these characteristics displayed any major trend during the study period (Table 1). Similar to RA, inflammatory markers declined during the study period but remained elevated among patients starting treatment in 2008 (e.g. mean CRP = 19).

The proportion of patients with SpA reporting use of NSAIDs, MTX, any DMARD or CSs decreased by calendar year of biologic treatment initiation (data not shown). As in RA, there was no trend in comorbidity for first biologic initiators except for joint surgery (though numbers were small, data not shown).

Among the 1417 PsA patients first starting a biologic therapy, the median age was 48 years, about half were female and the median disease duration (8.8 years) was similar to that of RA. Median disease duration appeared to decline during the study period (Table 1). Inflammatory markers not only declined during the study period for PsA first biologic initiators, but also remained elevated among patients starting treatment in 2008 (e.g. mean CRP = 14). In PsA, there was no clear trend in reported use of MTX or any DMARDs at biologic start, though the proportion of patients reporting use of CS and NSAIDs were lower in recent calendar periods compared with the earlier initiators (data not shown). Comorbidity at first-line initiation was similar to patients with SpA (data not shown).

Adherence to therapy
Figure 1 displays survival on first biologic by treatment indication and calendar period of treatment start (overall curves, and curves for starters in 2000, 2003 and 2006 are presented for simplicity). Survival of first biologic appears to be similar across years in RA and PsA, whereas in SpA survival is higher earlier on in 2000 compared with starters in 2003 and 2006 (presumably related to the small sample size of SpA starters in 2003, n = 31).

Overall, between one-quarter and one-third of all patients discontinued their first biologic treatment within 1 year of treatment start between 1999 and 2007. Inefficacy and adverse events accounted for the majority of discontinuations. Reported inefficacy increased with calendar time, while adverse events as cause of discontinuation reported in ARTIS decreased (Table 3).

Although we found that <25% of patients first starting a biologic therapy in 2000 (RA, SpA and PsA) remained on their first therapy in 2008, Fig. 2 shows that discontinuation of one biologic does not mean that the patient halts treatment with biologic drugs. Roughly 40% of the person-time still under observation up to 6 years after first biologic therapy was attributed to patients with RA still taking their first anti-TNF biologic, >20% to a second anti-TNF, and overall, 82% of the accrued person-time during the first 6 years reflected time spent on active biologic therapy (first, second or third biologic, Fig. 2).

Demographic, disease and comorbidity characteristics among switchers, 1999–2008
A total of 3121 patients with RA, 385 with SpA and 371 with PsA started treatment with a second or third biologic during the study period. The median age was relatively

<table>
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<th>Table 2</th>
<th>Disease activity and characteristics by calendar year of first biologics initiation in patients with RA in Sweden</th>
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<tbody>
<tr>
<td>Year of initiation of biologic therapy</td>
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<tr>
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<tr>
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<tr>
<td>Sedimentation rate*</td>
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<tr>
<td>DAS-28*</td>
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<tr>
<td>HAQ*</td>
<td>1.7</td>
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<td>Prosthetic joint surgery</td>
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<td>Malignancy</td>
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*P for trend <0.05.
unchanged for first, second and third starters with RA, but the proportion of female patients was higher for second- and third-line biologic initiators (79 and 80%, respectively). The proportion of switchers starting their second biologic with a reported adverse event on their first decreased with calendar year; however, no obvious pattern was observed for reported inefficacy over time. The same was generally true for third-line biologic therapy.

FIG. 1 Overall time on first biologic by calendar year (all years, 2000, 2003, 2006) of biologic therapy initiation (for each of the three indications separately).
**TABLE 3** Discontinuation of first biologic within 1 year of initiation by treatment indication (RA, SpA and PsA) and year

<table>
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<tr>
<th></th>
<th>Year</th>
<th>1999</th>
<th>2000</th>
<th>2001</th>
<th>2002</th>
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<td>205</td>
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<td>320</td>
<td>301</td>
<td>263</td>
<td>319</td>
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<td>First starts, %</td>
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<tr>
<td></td>
<td>Ineffective, %</td>
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<td>24</td>
<td>26</td>
<td>37</td>
<td>37</td>
<td>44</td>
<td>46</td>
<td>47</td>
<td>38</td>
<td>82</td>
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<td>42</td>
<td>36</td>
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<td>10</td>
<td>29</td>
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<tr>
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<td>Ineffective, %</td>
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<td>18</td>
<td>50</td>
<td>34</td>
<td>40</td>
<td>43</td>
<td>39</td>
<td>52</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>Adverse event, %</td>
<td>0</td>
<td>0</td>
<td>64</td>
<td>40</td>
<td>48</td>
<td>43</td>
<td>38</td>
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<tr>
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<td>Discontinued, n</td>
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<td>7</td>
<td>10</td>
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**FIG. 2** Distribution of person-time and people since first biologic therapy in patients with RA. The bars and primary vertical axis (proportion of observed person-time) represent the proportion of person-time during follow-up that a patient is either on their first, second or third anti-TNF treatment, non-TNF biologic, or no biologic drug but still in the study (with start of first biologic therapy as the point of origin). On a secondary vertical axis, we plotted the number of participants contributing to each 6-month follow-up period, as presented by the grey line. The horizontal axis represents the 6-month person-time observation periods since first biologic treatment, 1 is the first 6 months of follow-up, 2 is the second half-year and so on. Approximately 40% of the person-time still under observation up to 6 years (12 6-month periods) after first biologic therapy was attributed to patients still taking their first anti-TNF biologic, and overall, 82% of the accrued person-time during the first 6 years reflected time spent on active biologic therapy (first, second or third biologic).
starters, though less pronounced for adverse events (data not shown).

Disease activity at treatment initiation, as measured by DAS-28, declined by calendar time among second and third biologic therapy starts with RA. Furthermore, the DAS-28 appeared slightly higher for second- and third-line starters overall, but despite more inflammation and disease activity among early vs more recent switchers, there appeared to be no clinically meaningful differences in pain, CRP or HAQ among initiators of a first, second or third biologic drug in 2008 (Fig. 3A–C). The same was generally true for initiators of second and third biologic treatments for SpA and PsA.

The overall proportion of patients with RA with a history of hospitalization with infection increased from 12% at first start to 20 and 24% at second and third biologic

treatment start, respectively. Although the other comorbid conditions were less common, the proportions increased with number of previous biologic therapy treatments (data not shown). For second- and third-line biologic users there were no trends by calendar time in comorbidity with the exception of a decreasing prevalence of hospitalization for joint surgery over time.

There were a number of differences among patients with RA who were initially treated with an anti-TNF biologic therapy who switched to either another anti-TNF biologic or a non-TNF treatment as their second biologic. Switchers to non-TNF biologics had slightly higher levels of inflammation at second-line treatment start (mean ESR: 38 vs 35), as well as higher DAS-28 (5.5 vs 5.1) and HAQ (1.4 vs 1.3) scores. The prevalence of comorbid conditions among switchers was similar for cancer, joint surgery, diabetes and chronic obstructive pulmonary disease for those starting a second anti-TNF treatment and those switching to a non-TNF biologic therapy. However, history of infection at second treatment start was greater among those who switched to a non-TNF regimen compared with those initiating a second anti-TNF therapy (32 vs 18%). Results were nearly identical when we restricted to second-line therapy initiators from 2005 onwards (non-TNF, n = 242; anti-TNF, n = 1548) to account for differences in drug availability in the earlier calendar period (but the gap for history of infection widened, 36 vs 19%).

Discussion

Examining one decade of clinical experience with biologics in Sweden, we found several and marked temporal trends. Among those starting a first biologic in 2008, the disease activity at treatment initiation remained high and the median disease duration at first biologic use was ≥8 years (RA and PsA) and 12.2 years (SpA). In RA, declines of measures of disease activity at treatment start were noted with calendar time for first-time biologic users and switchers. However, this difference in disease activity between first, second and third treatment starters diminished in recent years. The frequency of previous joint replacement surgery at treatment start declined over time. We found that increasing 1-year discontinuation risks of first biologic were accompanied by a rise in reported inefficacy.

Some degree of declining disease activity at first biologic therapy for RA is expected, given the transition of biologic therapeutics from last resort to a mainstream treatment for patients not responding to, or with contra-indications to, MTX. Consistent with our findings, the South Swedish Arthritis Treatment Group (SSATG) showed that among 1839 biologic initiators between 1999 and 2006 (these patients are also in our nationwide assessment), baseline HAQ, DAS-28 and inflammatory markers at start decreased with calendar time [4]. The nationwide registry of biological therapies in Denmark (DANBIO) found decreasing baseline disease activity from 2000 to 2005 [5]. An earlier study combining DANBIO and the Norwegian NOR-DMARD showed that the prescribing patterns of anti-TNF treatments had become less strict over the 4 years of observation (2000–2003) [6].

Interestingly, in the present study, the annual number of first-time biologic initiators with RA remained relatively stable and disease activity was high, even in new starters in 2008, suggesting that biologics are still preferred for a select group. For PsA and SpA, the annual number of new starts steadily increased following the approvals of these indications by the European Medicines Agency and was paralleled by a decline in measures such as CRP. One study showed a decline in baseline characteristics of patients with AS initiating anti-TNF drugs with calendar year of initiation, including previous DMARD use, disease duration and CRP [7]. Although our SpA patient population includes both patients with AS and other SpAs, the baseline characteristics at first biologic use in the present study were similar to those from a recent British study of 261 patients with AS starting their first biologic therapy between 2002 and 2006 [8].

We showed that CRP, ESR, joint counts, disease activity measures and history of joint surgery were lower in biologic starters in 2005 compared with 2000, and even lower in 2008. In addition to laboratory markers of inflammation and number of swollen joints, subjective measures also showed a decline with calendar time; trends were seen for both patient- and physician-driven measures of global assessment, as well as patients’ perceived pain. Measures of disease activity more specific to PsA and SpA were not available in the present study. However, available covariates for these diseases showed similar trends consistent with previous and current findings in RA [4, 7]. Although not routinely registered as part of the disease activity in all PsA and SpA patients, we also found that mean swollen joint count decreased significantly with time (1999: 4.8 in SpA and 9.0 in PsA; 2008: 1.3 in SpA and 4.4 in PsA). With respect to our observation of increasing discontinuation rates driven by increasing inefficacy as the reported reason for discontinuation, we also found a simultaneous declining proportion of discontinuations related to reported adverse events. Over time, additional biological therapeutics have become available, perhaps lowering patient or physician thresholds to wait for an improvement or treatment response. As we showed in Fig. 1, only one-quarter of initiators in 2000 remained on their first therapy after 8 years. Together, these results call for more detailed assessments of time trends, not only of patient characteristics but also of effectiveness and response to biologics.

In a recent systematic review of 29 randomized controlled trials (RCTs) of anti-TNF treatment in RA, over 40% of the studies followed participants for ≤14 weeks [9]. Being underpowered for outcomes such as serious infection or malignancy, in combination with the more stringent inclusion criteria in most, but not all RCTs, raises the question of whether safety data in these studies generalize to patients starting biologics. Although in the context of clinical trials such events may be well documented, and further supported by extensive post-marketing surveillance periods, our observation that disease activity at
treatment start may be declining, necessitates updated evaluations. The generalizability of previously published relative risks [10–13] may also be limited in these new patient populations, as well as among switchers.

We found that switchers with RA initiating a non-TNF biologic second treatment were different from those initiating a second anti-TNF therapy with regard to disease activity and comorbidity at second treatment start. Furthermore, as expected, age ($P=0.004$) and calendar year ($P<0.001$) were inversely associated with switching to a second anti-TNF therapy compared with switching to a non-TNF biologic. Nevertheless, the marked differences in patient characteristics at treatment start (including the calendar period trends among patients starting TNF-inhibitors) highlight some of the challenges inherent in comparing the performance of TNF vs non-TNF biologics, or biologics introduced at different time points. Similarly, the high proportion of person-time (following discontinuation of first biologics) that still represents biologics exposure highlights the increasing challenges in attributing risks for long-term outcomes to individual biologics.

Apart from the previously mentioned limited statistical power for some analyses, the present study is not without limitations. We relied upon register linkage for identification of comorbid conditions, but the determination of rheumatic disease diagnosis and indices of disease activity were made by the patient’s treating rheumatologist. The ARTIS register is a detailed data source following biologic initiators regularly; the completeness of the data and register have been described elsewhere in detail [14]. It is important to note, however, that the granularity of the data did not allow us to look at subtypes of SpA or PsA; diagnoses which themselves are heterogeneous.

This study describes patients with adult-onset RA, SpA and PsA for whom rheumatologists made the decision to initiate therapy with a biologic drug. Misclassification of rheumatic disease is not of great concern as these are clinically characterized patients receiving ongoing care from a rheumatologist and not identified through claims or other common registry data sources. The emphasis of this study is on treatment initiation, patient and disease characteristics, and physician reports within ARTIS at treatment start. Therefore, misclassification associated with treatment compliance is not a large concern in the present study because the intention to treat has been captured by the reported therapy initiation.

Strengths include the nationwide coverage, the large number of patients, and the capture of data on treatment starts (rather than ongoing treatments) from the very time point when biologics were first available. As well as presenting data on anti-TNF therapies, the present study includes other biologic therapies used in treating rheumatic diseases including anakinra, rituximab and abatacept. In addition, we could compare anti-TNF with non-TNF biologics, switchers and three different population-based samples of patients diagnosed with rheumatic diseases initiating biologic therapy. It should be noted that while these data were available, >90% of biologic starts were anti-TNF therapies.

During the last 10 years, the clinical characteristics of patients starting biologic therapy have changed considerably, including a decline in inflammatory markers and measures of disease activity and severity, as represented by history of prosthetic joint surgery, in initiators. Furthermore, differences in characteristics of patients switching to another anti-TNF drug vs a non-TNF biologic may have implications for the interpretation of risk levels associated with the latter drug and must be further examined. These changes in patient characteristics warrant continued safety vigilance in order to properly evaluate the safety profile of biologic treatment. Lastly, limited comparability with respect to risk levels between RA, PsA and SpA, together with the overall limited safety data regarding the two latter diseases, calls for safety studies specifically in non-RA biologic-treated populations.

**Rheumatology key messages**

- Disease activity and inflammation in biologic initiators have declined over the past decade, although still elevated.
- Continued vigilance and assessments of safety in contemporary biologic users are needed, in RA and non-RA biologics-treated populations.

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