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Biologic drug survival rates in the era of anti-interleukin-17 antibodies: a time-period-adjusted registry analysis*

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Conflicts of interest
Full details are given in the Appendix.

*Plain language summary available online

Summary

Background Drug survival rates reflect efficacy and safety and may be influenced by the availability of alternative treatment options. Little is known about time-dependent drug survival in psoriasis and the effect of increasing numbers of biologic treatment options.

Objectives To determine whether drug survival is influenced by the availability of treatment options and by factors such as gender, psoriatic arthritis or previous biologic treatment.

Methods This observational, retrospective, multicentre cohort study analysed data from patients registered in the Austrian Psoriasis Registry (PsoRA) who were treated with biologics between 1 January 2015 and 30 November 2019.

Results A total of 1572 patients who received 1848 treatment cycles were included in this analysis. The highest long-term Psoriasis Area and Severity Index improvement was observed after treatment with ixekizumab, followed by ustekinumab and secukinumab, adalimumab and etanercept. Overall, ustekinumab surpassed all other biologics in drug survival up to 48 months. However, when adjusted for biologic naïvety, its superiority vanished and drug survival rates were similar for ixekizumab (91·6%), secukinumab (90·2%) and ustekinumab (92·8%), all of them superior to adalimumab (76·5%) and etanercept (71·9%) at 12 months and beyond. Besides biologic non-naïvety (2·10, $P < 0·001$), the introduction of a new drug such as secukinumab or ixekizumab (relative hazard ratio 1·6, $P = 0·001$) and female gender (1·50, $P = 0·019$) increased the risk of treatment discontinuation overall, whereas psoriatic arthritis did not (1·12, $P = 0·21$).

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Conclusions The time-dependent availability of drugs should be considered when analysing and comparing drug survival. Previous biologic exposure significantly influences drug survival. Women are more likely to stop treatment.

What is already known about this topic?

- Female gender and previous biologic exposure have been discussed as predictors for decreased drug survival in patients with psoriasis, but it remains unknown whether a time-dependent increased availability of treatment options alters biologic drug survival.

What does this study add?

- The increased availability of alternative biologic treatments over time leads to an elevated risk for treatment discontinuation overall; therefore, drug survival analysis has to be time adjusted.
- Moreover, the study reveals that the impact of previous biologic treatment on drug survival is tremendous and confirms worse drug survival in female patients.

Biologics have revolutionized the treatment of psoriatic disease. In clinical trials, the latest classes of biologics [targeting interleukin (IL)-17 and IL-23] have proved to be effective antipsoriatics, promising complete clearance of plaques for a large number of patients.[1–5] However, their effectiveness, safety and drug persistence in real-life settings may not match those in clinical trials. Recent registry studies suggest that between 14·6% and 58·6% of patients with psoriasis on biologics would not have been eligible for a clinical trial and that safety and efficacy – but not risk of treatment discontinuation – would have been worse.[6,7]

Drug persistence is considered to be an indirect predictor of efficacy and safety,[8,9] and in general, dermatologists consider prolonged drug survival a favourable goal of systemic antipsoriatic treatment both clinically and economically.[10,11] However, this cannot automatically be applied to biologic treatment. A drug may be discontinued for many reasons (both related and unrelated to the drug's performance). These include safety reasons (i.e. adverse events),[12,13] pregnancy, complete remission or lack of improvement, denial of reimbursement, availability of alternative treatment options, and increasing expectations of physicians and patients or unconsidered patient needs[14–16] as more and more drugs become available. This is best reflected in drug survival, which encompasses all these reasons and factors. Indeed, in rheumatology, prolonged drug survival has been associated with the insufficient availability of effective alternative treatments.[17,18] Therefore, it is not surprising that recent studies have aimed at identifying patient characteristics that can predict drug survival.

So far, female gender and obesity have been identified as factors in decreased persistence of biologic therapy, while psoriatic arthritis is a factor associated with prolonged persistence in patients receiving antitumour necrosis factor-α or anti-IL-12/23 treatment.[12,19] Biologic non-naïvety is another well-known factor influencing drug persistence and it even seems that persistence is getting worse with the number of biologics that patients have received previously.[20,21] Whereas the impact of gender and concomitant psoriatic arthritis on biologic-specific drug survival has already been studied for adalimumab, etanercept and ustekinumab,[12,21–27] it has not been studied for the IL-17 inhibitors secukinumab and ixekizumab.

Therefore, we aimed to investigate the time-dependent drug survival rates of biologics, taking into account that they may be influenced by the overall number of available biologics, and then determine drug survival rates in the era of anti-IL-17 antibodies. Additionally, we aimed to determine whether the introduction of new biologics such as secukinumab and more recently ixekizumab have independently lowered drug survival rates for the remaining biologics.

Methods

Study design

This was an observational retrospective multicentre analysis of clinical data extracted from the Psoriasis Registry Austria (PsoRA). The design of this registry has been described in previous studies.[28–32] This nationwide Austrian database contains data on treatment cycles from patients with psoriasis treated under real-life conditions at six university dermatology departments, eight non-university dermatology departments and 12 dermatology practices. A list of all PsoRA centres is available at www.psoriasisregistry.at.

In the registry, treatment cycle is defined as the time period after a patient's allocation, followed by at least one visit, until last observation or discontinuation of treatment. Continuous prescription of a drug has to be confirmed for every visit recorded in the registry. End of treatment is defined as end of a biologic treatment cycle, which has to be entered in the

database along with the reason for treatment discontinuation. Interrupting a biologic treatment for longer than 12 weeks after the regular drug application interval is considered treatment discontinuation, and restarting thereafter on the same biologic is considered a new treatment cycle (for ustekinumab 24 weeks after last administration). The registry has been approved by the ethics committee of the Medical University of Graz (application number 21-094 ex 09/10), and the present analysis was conducted in accordance with the principles of the Declaration of Helsinki.

Data analysis and statistics

The study population included patients older than 18 years of age who had chronic plaque psoriasis, started a biologic therapy (adalimumab, etanercept, ustekinumab, secukinumab or ixekizumab) after January 2015 (after the introduction of secukinumab into clinical practice), and continued therapy until November 2019, and had at least one follow-up visit with the same treatment, irrespective of previous systemic treatment, psoriatic arthritis or any comorbidities. In addition, data from patients who received ustekinumab before 2015 were analysed to study its drug survival over time. Drug survival for each biologic treatment was calculated using Kaplan–Meier estimates. Treatment cycles for which no end of treatment was recorded were censored. Cox regression analysis was used to test for treatment effects, risk factors and interaction. The relative hazard ratio (HR) for gender, concomitant psoriatic arthritis, biologic naïvety and introduction of new treatments was calculated. Patients in whom the presence of concomitant arthritis was unknown were considered not to have psoriatic arthritis for the purposes of this analysis. To detect time-period effects from the release of new drugs, observation times were divided into the time at risk spent before the release of a new drug (period 1, January 2015 to July 2016) and after the release of the new drug (period 2, July 2016 to November 2019). A cycle extending over both periods was censored at the end of period 1 and considered to have entered period 2 not at time zero but at the time from the beginning of treatment (i.e. the time at which it was censored for period 1) and continuing in period 2 until end of treatment or censoring. Additionally, drug survival of ustekinumab was calculated for the time periods before and after the introduction of secukinumab (19 March 2015) as well as after the initiation of the first ixekizumab treatment (13 July 2016), to determine differences in the drug's survival in the presence of more available treatment options. Survival rates of all available biologics were calculated for the period before and the period after the first patient with ixekizumab treatment had been entered into the registry. The effectiveness of treatment was evaluated in terms of monitoring absolute Psoriasis Area and Severity Index (PASI) values with regard to values reported at each visit (as observed) and per last observation carried forward (LOCF). The chi-squared test was used to determine treatment allocation concerning gender, psoriatic arthritis and biologic naïvety. Calculations were performed by R 3·6·2 (www.r-project.org) using the package 'survival 3·1-8'.

Results

General patient characteristics

At the time of data extraction (30 November 2019), the PsoRA contained data on 4348 patients who had undergone a total of 7002 systemic treatment cycles. Of these, 1572 patients [573 (36·5%) women and 999 (63·5%) men] who had undergone a total of 1848 cycles of biologic treatment beginning after 1 January 2015 were eligible for the current analysis (Table S1; see Supporting Information). Overall, 547 (34·8%) patients had concomitant psoriatic arthritis (Table S1); for 80 patients (84 cycles) the presence of arthritis was unknown. Concomitant arthritis was significantly more frequent in women than men (38·2% vs. 32·8%, $P = 0·035$) (Table S1). The total number of treatment cycles for each biologic is depicted in Table 1, ranging from 96 cycles for etanercept to 662 cycles for ustekinumab. The mean (SD) age at the start of the treatment for a specific cycle in those patients was 45·6 (14·7) years (Table 1). Other patient characteristics at the start of the treatment cycle such as disease duration, weight, body mass index, presence of arthritis and biologic naïvety are also shown in Table 1. Furthermore, differences in treatment allocation dependent on whether a patient had concomitant arthritis or not were observed, with patients with arthritis receiving adalimumab, etanercept, ixekizumab and secukinumab much more frequently than ustekinumab (40·6–57·3% vs. 18·0%) ($P < 0·001$) (Table S2; see Supporting Information). Comorbidity rates among patients treated with ixekizumab or secukinumab were similar, except for hyperlipidaemia (14·3% vs. 20·3%) and obesity (18·5% vs. 12·1%) (Table S3; see Supporting Information). There was no statistically significant difference in treatment allocation for a specific drug between women and men (Tables S4, S5; see Supporting Information). A total of 1028 (55·6%) of the treatment cycles in this study were received by biologic-naïve patients and 820 (44·4%) cycles were administered to patients who had already been treated with at least one biologic (Table S6; see Supporting Information). The IL-17 inhibitors secukinumab and ixekizumab were more frequently administered to biologic non-naïve patients than were adalimumab, etanercept and ustekinumab (62·3% and 52·2% vs. 30·6%, 40·6% and 35·6%, respectively; overall P-value < 0·001) (Table S6).

Drug effectiveness

PASI values at treatment start were documented for 1126 (60·9%) treatment cycles. There were differences in PASI values at treatment start, with patients taking ixekizumab (mean 9·65) and secukinumab (9·60) having the highest PASI followed by ustekinumab (8·20), adalimumab (7·23) and etanercept (6·07) ($P = 0·028$) (Figure 1 and Table S7; see Supporting Information). Ixekizumab showed the highest PASI

Table 1 Characteristics of treated patients (n = 1572) with regard to initiation of a cycle (n = 1848)

Treatment cycles and characteristics	Adalimumab	Etanercept	Ixekizumab	Secukinumab	Ustekinumab	All treatment cycles
Total number of treatment cycles	294	96	406	390	662	1848
Characteristic at start of treatment cycle						
Number (%) of treatment cycles in male patients	189 (64·3)	56 (58·3)	277 (68·2)	229 (58·7)	407 (61·5)	1158 (62·7)
Mean age (SD), years	44·8 (14)	47·5 (14·8)	45·2 (13·7)	47·5 (14·7)	44·7 (15·3)	45·6 (14·7)
Mean PASI (SD) in biologic-naïve patients	7·6 (6·5)	7·2 (8·5)	9·87 (7·33)	9·95 (8·9)	8·47 (6·4)	8·9 (7·3)
Mean PASI (SD) in biologic-non-naïve patients	6·8 (6·7)	7·9 (11·4)	9·6 (6·7)	8·6 (7·9)	9·3 (7·3)	8·95 (7·4)
Number (%) of cycles in patients with arthritis	149 (50·7)	55 (57·3)	165 (40·6)	164 (42·1)	119 (18·0)	652 (35·3)
Mean years (SD) of disease duration	16·5 (12·6)	21 (15·7)	16·4 (11·1)	16·7 (12·2)	16·2 (12·5)	16·6 (12·4)
Mean weight in kg (SD)	85·9 (21·6)	80·1 (22·5)	91·3 (21·1)	84·2 (17·5)	85·8 (20)	86·1 (20·2)
Mean BMI (SD)	28·4 (6·4)	27·9 (8·6)	28·9 (6·1)	27·5 (5·2)	27·5 (6·2)	27·9 (6·1)

PASI, Psoriasis Area and Severity Index; BMI, body mass index.

improvement 3 months after treatment start in patients analysed as observed or with LOCF. The highest long-term PASI improvement (at least until 24 months) was also observed for treatment with ixekizumab, followed by ustekinumab and secukinumab, adalimumab and etanercept (Figure 1 and Table S7).

Drug survival

There were significant differences in drug survival for the different biologics ($P < 0·001$). Overall, the drug survival rate was highest for ustekinumab (Figure 2 and Tables S8, S9; see Supporting Information). In fact, drug survival at 12 months in patients treated with ustekinumab was 89·0%, compared with 86·0% for ixekizumab, 78·1% for secukinumab, 76·5% for adalimumab and 66·0% for etanercept (Table S8). The differences were statistically significant (Table S9) and were sustained or increased up to 48 months (Figure 2). The median survival rate of 50% was reached for etanercept at 27·0 months, for adalimumab at 30·8 months, and for secukinumab at 34·3 months (Figure 2), but not for ixekizumab at its maximum follow-up of 36 months or for ustekinumab at its maximum follow-up of more than 48 months. Of note, the dosage regimen was reported for 599 treatment cycles (32·4%) (Table S10; see Supporting Information). While most of those cycles were initiated with in-label dosage, irrespective of treatment allocation, off-label dosage change was most frequently observed in patients treated with ustekinumab (14·1%) (higher dosage of 90 mg vs. 45 mg subcutaneously and/or shorter administration intervals) (Table S10). Furthermore, when adjusted for time period in the overall cohort, the superiority of ustekinumab vs. ixekizumab vanished

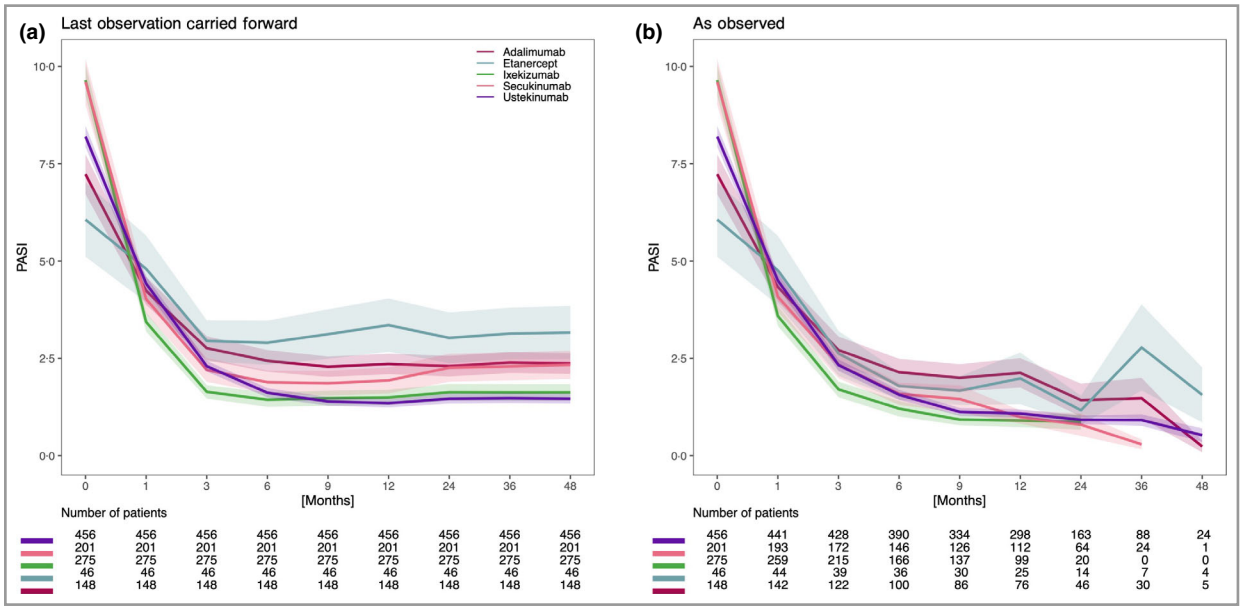

Figure 1 Effectiveness of biologics. Psoriasis Area and Severity Index (PASI) values and 95% confidence interval (see Table S7; Supporting Information) for treatment cycles analysed as last observation carried forward (a) and as observed (b).

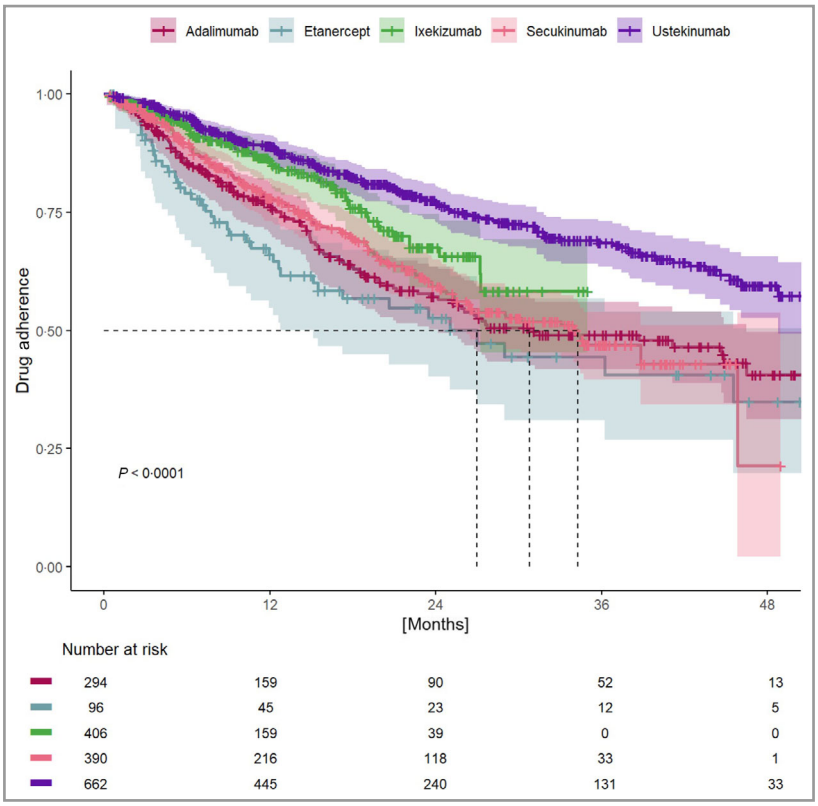

Figure 2 General drug survival rates. Relative drug survival rates (± 95% confidence intervals) of a specific biologic with regard to treatment cycles (n = 1848) using Kaplan–Meier estimates and log-rank tests. Dotted lines indicate timepoints at which 50% of cycles have been stopped for a respective biologic. The dotted lines indicate timepoints at which half of the patients have discontinued a respective treatment.

statistically (P = 0·075) (Figure S1; see Supporting Information). Indeed, ustekinumab's drug survival continuously declined over time (when comparing the periods before secukinumab initiation and before and after ixekizumab initiation) (Figures 3 and 4). Similar declines in drug survival over time were observed for adalimumab, etanercept and secukinumab (Figure 3 and Table S11; see Supporting Information). Overall, the probability that a treatment was discontinued significantly increased after the initiation of ixekizumab (relative HR 1·6, P = 0·001), irrespective of the treatment that had been administered (P = 0·858) (Table S12; see Supporting Information). Analysing drug survival with regard to gender revealed a treatment-independent (P = 0·392) increased risk (relative HR 1·50, P = 0·019) for drug discontinuation in women in overall (Figure 5). Previous biologic treatment also significantly increased the risk for treatment discontinuation (relative HR 2·10, P < 0·001), irrespective of the drug administered (P = 0·367) (Figure 6 and Table S12). After adjustment for biologic naïvety, the gap in drug survival between secukinumab (90·2%) and both ixekizumab (91·6%) and ustekinumab (92·8%) closed at 12 months and beyond (Table S8). The presence of psoriatic arthritis did not significantly influence the risk of treatment discontinuation in patients treated with biologics (P = 0·261) (relative HR 1.12, P = 0·21) (Figure S2 and Table S12; see Supporting Information). The drugs that were administered after initial treatment was stopped are listed in Table S13 (see Supporting Information). Of note, there were a substantial number of intraclass switches in anti-IL-17 drug from secukinumab to ixekizumab, as well as a number of switches to a new class of anti-IL-23-p19 antibodies (guselkumab, risankizumab and tildrakizumab) (Table S13). However, intraclass switching in IL-17 inhibitors is not uncommon, as it may restore clinical efficacy.[33] Overall, the rate at which a previously administered drug was restarted (after an interval of at least 12 weeks after the regularly scheduled administration as defined in the methods) ranged from 2·6% to 19·0% for etanercept, adalimumab, secukinumab, ustekinumab and ixekizumab (Table S13).

Reasons for treatment discontinuation

In total, 544 (29·4%) of 1848 treatment cycles were discontinued. The main reasons for discontinuation were no remission (20·0%) or partial remission (10·3%) (i.e. primary therapeutic failure), loss of efficacy (26·1%) and side-effects (17·3%) in the overall cohort (Table S14; see Supporting Information). However, there were differences in drug discontinuation in the drug-specific analysis (Table S15; see Supporting Information). The treatment stopped most frequently for primary treatment failure (with regard to total cycle number) was etanercept (18·8%), followed by secukinumab (10·8%), adalimumab (10·5%), ustekinumab (9·1%) and

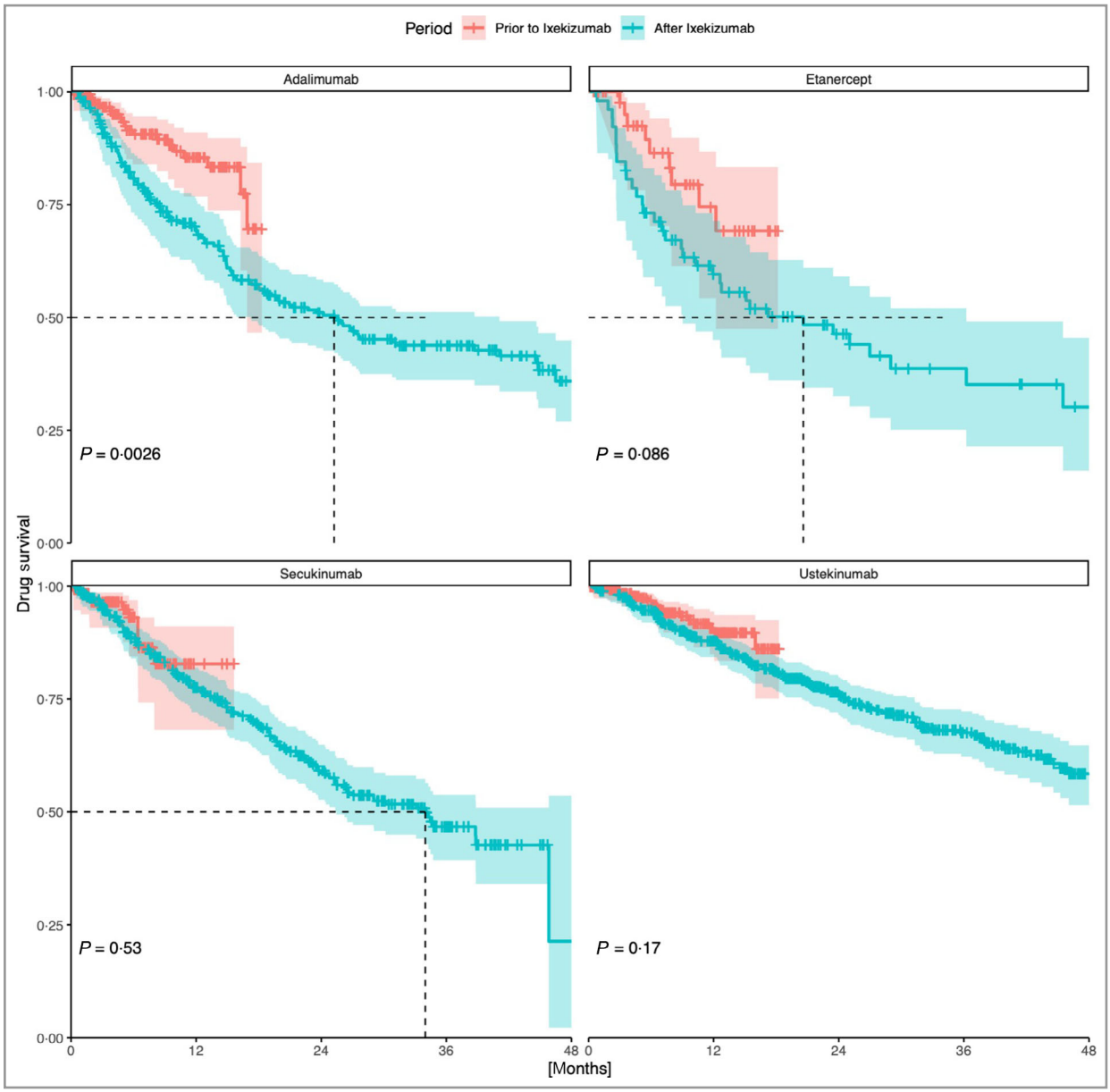

Figure 3 Drug survival prior to and after release of ixekizumab. Relative drug survival rates [± 95% confidence intervals (CIs)] of a specific biologic with regard to treatment cycles that were started prior to or after the initiation of ixekizumab in Austria (13 July 2016) and reported to PsoRA, using Kaplan–Meier estimates and log-rank tests. The red line and its CI represent treatment cyclesin patients in whom treatment was started, administered and stopped between 1 January 2015 and 13 July 2016. The blue line and its CI represent treatment cycles in patients in whom treatment was started any time after 1 January 2015, and continued or stopped after 13 July 2016. Respective P-values are plotted in the graphs. For number of treatment cycles with a specific biologic see Table S11 (Supporting Information). The dotted lines indicate timepoints at which half of the patients have discontinued a respective treatment.

ixekizumab (3·4%) (Table S15). The treatment stopped most frequently for loss of efficacy (with regard to total cycle number) was adalimumab (12·9%); the one stopped least frequently for the same reason was ixekizumab (3·9%) (Table S15). The treatment stopped most frequently because of side-effects (with regard to total cycle number) was secukinumab (6·9%), followed by adalimumab (6·5%), etanercept (5·2%), ixekizumab (4·9%) and ustekinumab (3·5%) (Table S15). The side-effects leading to discontinuation that were reported most frequently were infections, ranging from 0·6% for ustekinumab to 3·1% for secukinumab (Table S16; see Supporting Information). These infections included candida infection in 1·0% of ixekizumab cycles and 0·3% of secukinumab cycles. From a relative point of view, infections were also the most common cause for stopping treatment, ranging from 17·4% for ustekinumab to 45·0% for ixekizumab considering the discontinued cycles per drug only (Table S17; see Supporting Information).

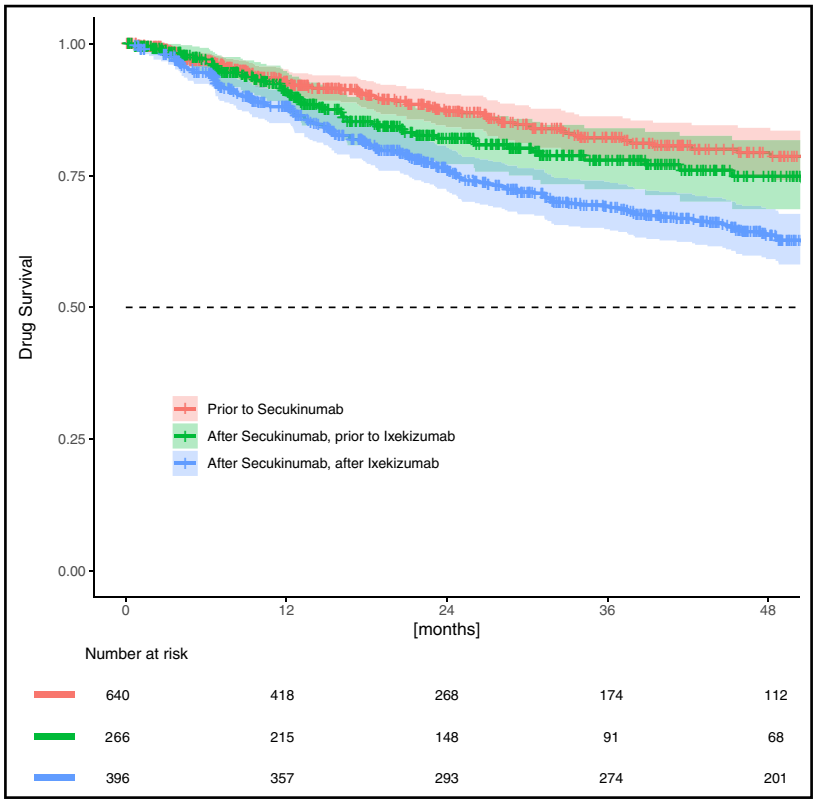

Figure 4 Drug survival of ustekinumab over time. Relative drug survival rates (± 95% confidence intervals) of ustekinumab (n = 1302) with regard to treatment cycles that were started prior to or after the first treatment initiation with secukinumab (19 March 2015) or ixekizumab (13 July 2016) reported in the Austrian Psoriasis Registry (PsoRA), using Kaplan–Meier estimates and log-rank tests. The drug survival rate for ustekinumab was significantly lower (P = 0·006) for the time period after ixekizumab introduction (blue) compared with the time periods prior to ixekizumab (green) and secukinumab (red) introduction (P = 0·305). Note that this analysis contains, besides the 662 ustekinumab cycles administered since January 2015, an additional 640 ustekinumab treatment cycles initiated prior to January 2015, resulting in a total of 1302 cycles. The dotted lines indicate timepoints at which half of the patients had discontinued a respective treatment.

Discussion

This study of 1572 patients and 1848 treatment cycles is one of the larger registry studies that have examined the effect of gender, psoriatic arthritis and biologic naïvety on biologic drug survival, especially with regard to the IL-17 inhibitors.[21,22,24–27,34] It is also one of the largest registry studies so far to compare drug survival for ixekizumab, secukinumab and ustekinumab head to head. Our analysis unambiguously indicates that the time-dependent availability of drugs must be considered when analysing drug survival. When taking into account the IL-17 inhibitor era (i.e. the timespan since the clinical introduction of secukinumab), ustekinumab apparently surpassed all other biologics in drug survival (Figure 2). However, most of the off-label dosage changes were reported for ustekinumab (14·1%). Furthermore, when comparing drug survival rates before and after the release of ixekizumab, the superiority of ustekinumab vanished (Figure S1), well in line with the general decline in drug survival rates of ustekinumab since its introduction in 2009 (Figure 4). Similarly, drug survival rates of adalimumab, etanercept and secukinumab also declined over time at an overall relative HR of 1·60 (P = 0·001) (Figure 3 and Table S12). In agreement with these findings, the drug survival rates of adalimumab and etanercept after the release of ixekizumab that we noted in the present study appeared to be slightly lower than in one of our previous studies for the period between 2004 and 2013·[29] After adjustment for biologic naïvety, the drug survival rates for ustekinumab (92·8%), ixekizumab (91·6%) and secukinumab (90·2%) were closer at 12 months and beyond in biologic-naïve patients.

Overall, the drug-specific survival rates for ustekinumab, adalimumab and etanercept that we have observed in this study compare favourably with previously reported findings.[12,24–27,34] However, the rates for ixekizumab and secukinumab in this study (Table S8) appear to be higher.[20,35,36] Notably, comorbidity rates among patients treated with ixekizumab or secukinumab were similar, except for hyperlipidaemia (14·3% vs. 20·3%) and obesity (18·5% vs. 12·1%) (Table S3). Compared with our findings, a recent Swedish registry study observed a similar median drug survival rate for adalimumab but a worse median discontinuation rate for etanercept (17·5 months vs. 27·0 months).[37] A recent analysis of a smaller dataset from the Slovenian psoriasis registry (with

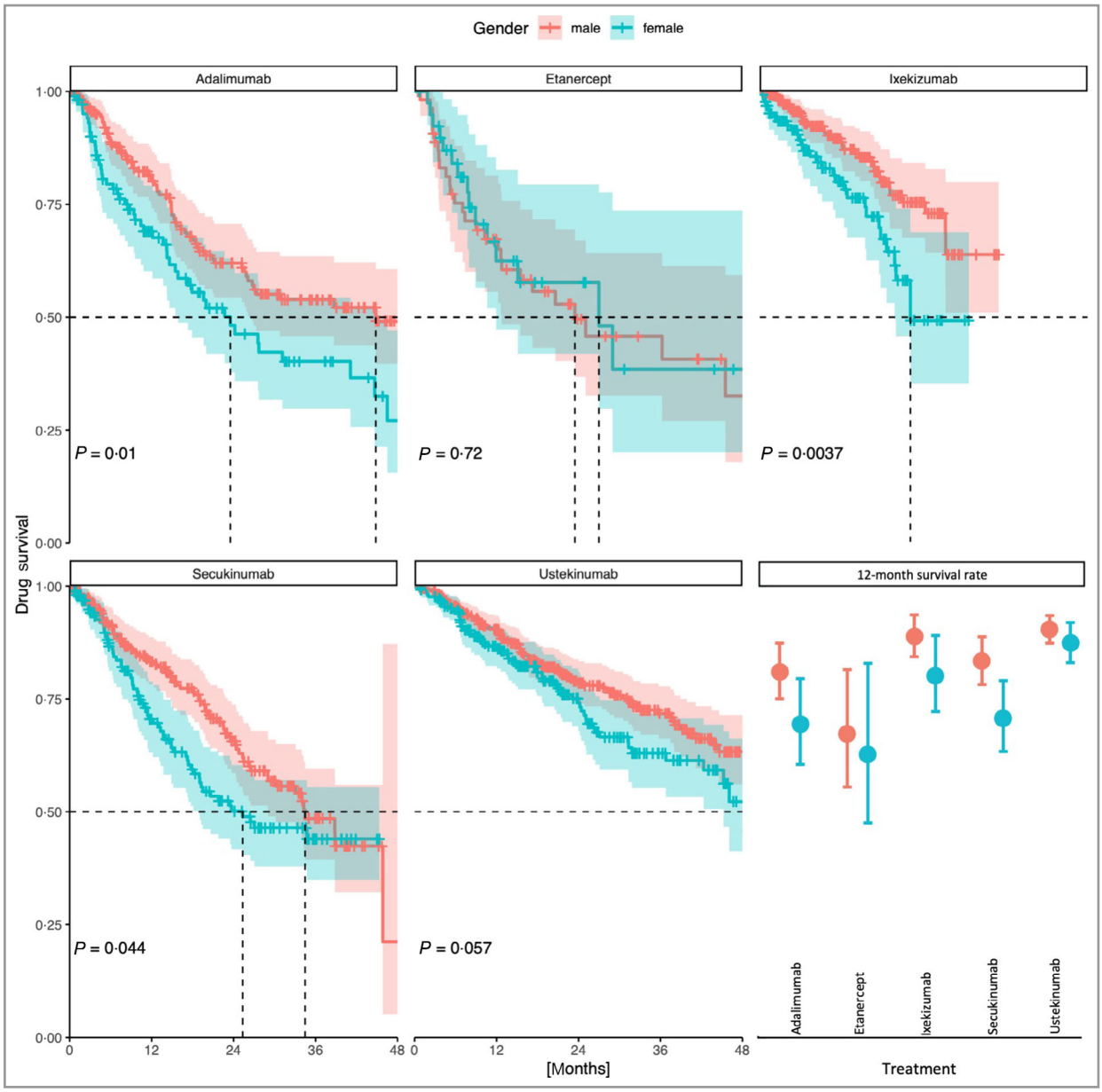

Figure 5 Drug survival rates regarding gender. Relative drug survival rates (± 95% confidence intervals) of a specific biologic with regard to treatment cycles (n = 1848) comparing women and men using Kaplan–Meier estimates and log-rank tests. Respective P-values are plotted in the graphs. Interdependence analysis revealed that the significant influence of gender on drug survival was independent from the administered biologic (see Table S12; Supporting Information). The dotted lines indicate timepoints at which half of patients have discontinued a respective treatment.

regard to IL-17 inhibitors) also found a similar drug survival rate for ustekinumab but lower rates for ixekizumab and secukinumab.[38] Likewise, a recent Italian study found a relatively high survival rate of ustekinumab,[39] similar to the rate for secukinumab, but much higher than the rates for adalimumab, infliximab and etanercept (ixekizumab was not included in the study). Overall, our findings are also consistent with those of a US study (which did not take into consideration time period of application) in which the drug survival rate was higher for ixekizumab than for secukinumab, but in which the rates for both were lower than in our study.[35] Similar results were obtained in a smaller Danish cohort with relatively short follow-up times of 12 months.[20]

According to a recent meta-analysis, previous studies have already identified female gender as an independent risk factor for stopping biologic treatment in psoriasis,[12,19,21,22,27,40] with HRs of 1·22 overall, 1·53 for adalimumab and 1·56 for etanercept.[19] In comparison, the gender HR in our present study was 1·50 (P = 0·019), indicating that women were more likely than men to discontinue biologic treatment. We

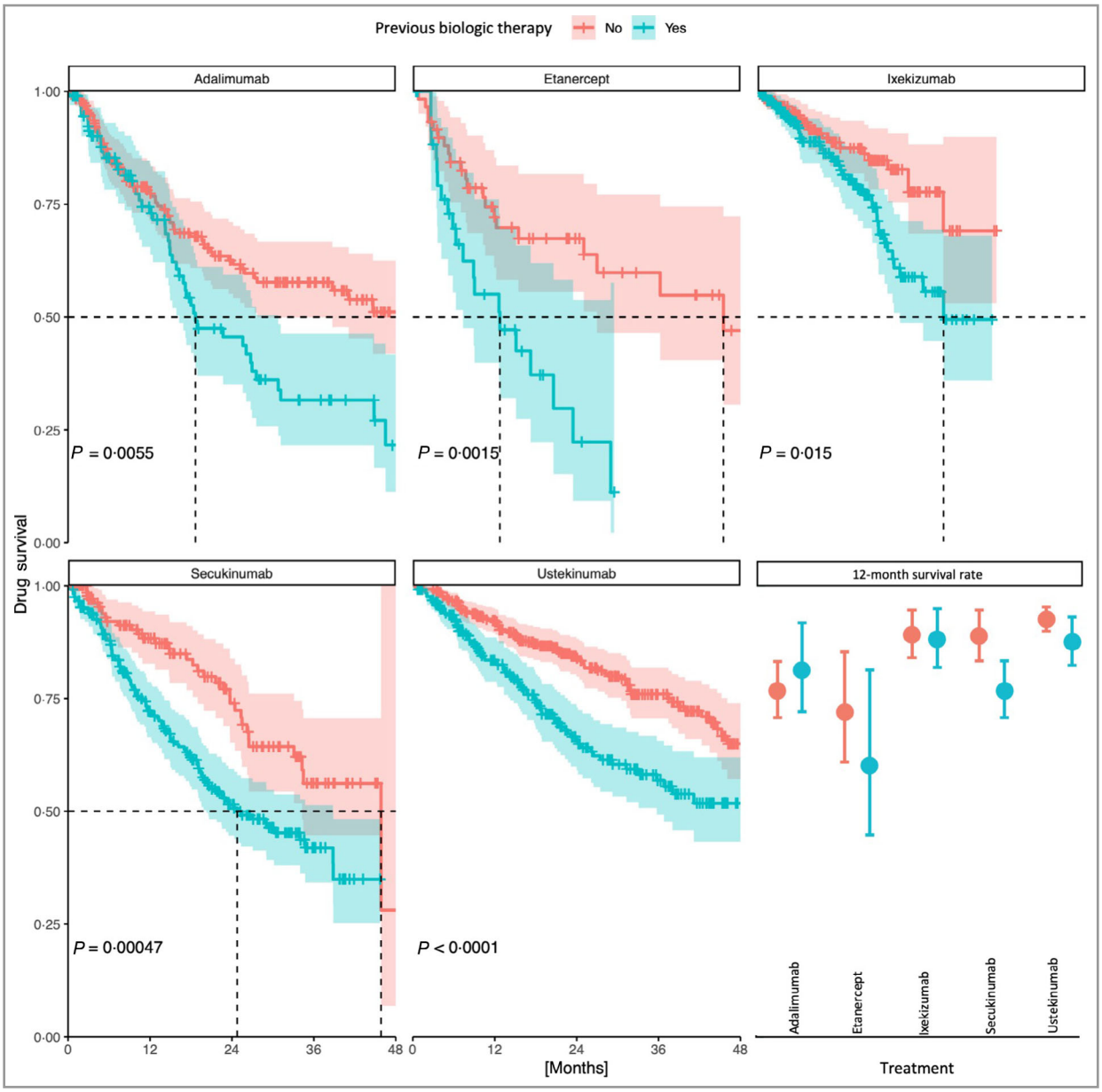

Figure 6 Drug survival rates regarding previous biologic treatment. Relative drug survival rates (± 95% confidence intervals) of a specific biologic with regard to treatment cycles (n = 1848) comparing naïve and non-naïve patients using Kaplan–Meier estimates and log-rank tests. Respective P-values are plotted in the graphs. Note the relative drug survival rate at 12 months for patients entering a cycle naïvely was 76·7% for adalimumab, 72·1% for etanercept, 89·1% for ixekizumab, 88·8% for secukinumab and 92·5% for ustekinumab, respectively (see also Table S8; Supporting Information). The dotted lines indicate timepoints at which half of patients have discontinued a respective treatment.

also observed a slightly increased HR of 1·12 for stopping treatment in patients with psoriatic arthritis; however, this was not statistically significant (Figure S2 and Table S12).[19,41]

Previous biologic treatment is a well-known risk factor for drug discontinuation[42] and appears to be increasing the rate of drug discontinuation as patients receive more and more drugs.[20] For instance, a study from 2015 revealed an increased HR of 1·24 for biologic-naïve patients remaining on biologic treatment.[42] However, in a recent British registry analysis, previous biologic treatment strongly influenced drug survival. While previous exposure to a biologic predicted discontinuation in secukinumab- and ustekinumab-treated patients, it was linked to increased drug survival in adalimumab-treated patients.[41] In comparison, the risk of treatment discontinuation after previous biologic exposure in our present study was 2·10 ($P < 0·001$), irrespective of the treatment given (Figure 6 and Table S12).

Therefore, it is very likely that the relatively worse drug survival rate for secukinumab overall seen in our study (Figure 1) was due to the high percentage (62·3%) of non-naïve patients being treated with it (compared with 30·6% receiving adalimumab, 35·6% receiving ustekinumab, 40·6% receiving

etanercept, and 52.2% receiving ixekizumab) (Table S6). Consistent with this notion, the loss of efficacy rate for secukinumab was 10·2% compared with 3·9% for ixekizumab (Table S15). The similar drug survival rates for secukinumab and ustekinumab seen in our study compare favourably with those reported in a British study (72·9% biologic-naïve treatment cycles of secukinumab and 74·8% of ustekinumab).[41]

The main reasons for treatment discontinuation in the present study were primary treatment failure, secondary loss of efficacy, side-effects and patient request. However, the frequency of those reasons for treatment discontinuation differed slightly depending on the drug used. The rate of primary treatment failure was highest for etanercept (18·8%); that of secondary loss of efficacy, highest for adalimumab (12·9%); and that of side-effects, highest for secukinumab (6·9%) (Table S15). A recent meta-analysis revealed worse tolerability of ixekizumab compared with secukinumab.[43] Analysis of confounding factors in our study revealed hardly any differences among patient characteristics; however, treatment discontinuation due to side-effects was relatively low across all drugs (Table S15). Overall, the most common side-effect was infection (0·6% for ustekinumab, 1·0% for etanercept, 2·0% for adalimumab, 2·2% for ixekizumab and 3·1% for secukinumab) (Table S16).

Regarding study limitations, beside the registry's retrospective design, most of the data reported to PsoRA come from tertiary treatment centres caring for patients with moderate-to-severe psoriasis. Thus, drug survival among patients with psoriasis in Austria might differ slightly. Because this analysis included data from patients treated through November 2019, it is possible that IL-23p19 inhibitors, clinically introduced in Austria in early 2019, may have influenced drug survival rates. However, this was not taken into consideration in this analysis. This may have some implications for our analysis of ixekizumab drug survival rates as IL-23p19 inhibitors are the most common drugs administered in patients failing ixekizumab (32·8%), while ixekizumab was the most frequently prescribed drug after failing adalimumab (25·7%), ustekinumab (28·4%) and secukinumab (41·1%) (Table S13).

In conclusion, this study contributes to the understanding of biologic drug survival in psoriasis. In Austria, biologics approved as first-line therapy for moderate-to-severe psoriasis are usually reimbursed only after conventional (systemic) treatments have been tried. However, until very recently, there have been no economic restrictions on the selection of biologic drug once the decision is made to move from conventional to biologic antipsoriatic treatment. Because this may not be the case in other countries,[44] our results offer a nonbiased, real-world analysis of outcome and the persistence of biologic treatments independent of insurance guidelines. The fact that gender and biologic non-naïvety affects drug survival rates in a similar fashion for all biologic treatments (independent of the type of drug) may help both patients and clinicians in treatment decision-making. Most importantly, because the availability of alternative treatment options strongly affects drug survival rates of biologics, the timepoints at which newer biologics become available must be considered when analysing and comparing drug survival rates.

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Appendix Conflicts of Interest

T.G. has received a travel grant from Novartis. W.S. has received speaker and consulting honoraria from Abbvie, Almirall and Novartis. C.J. has received research grants, speaker and/or consulting honoraria, and/or travel refunds from AbbVie, Almirall, Celgene, Eli Lilly, Janssen, Leo Pharma, Mallinckrodt/Therakos, Novartis, Pfizer and 4SC. W.W. has received research grants, speaker and/or consulting honoraria and/or travel refunds from AbbVie, Almirall, Amgen, Celgene, Eli Lilly, Galderma, Janssen, Leo Pharma, Merck Sharp & Dohme, Novartis, Pelpharma, Pfizer, Sandoz and UCB. C.K. has received travel refunds from Almirall, Celgene, Janssen and Pelpharma and consulting honoraria from Lilly and Novartis. P.G.S. has received research grants, speaker and/or consulting honoraria and/or travel refunds from AbbVie, Actelion, ALK, Almirall, Amgen, Celgene, Eli Lilly, Galderma, Gilead, Janssen, Leo Pharma, Maruho, Merck Sharp & Dohme, Novartis, Pfizer, Sandoz and UCB. K.P. has received speaker and consulting honoraria from AbbVie, Eli Lilly, Janssen and Novartis; and travel refunds from AbbVie, Almirall, Celgene, Eli Lilly, Janssen, Leo Pharma and Novartis. A.M. has received research grants, speaker and/or consulting honoraria and/or travel refunds from AbbVie, Almirall, Amgen GmbH, Celgene, Eli Lilly, Janssen, Leo Pharma, Novartis and Pfizer. M.S.-B. has received speaker and consulting honoraria from AbbVie, Celgene, Lilly, Janssen and Novartis. L.R. has received speaker and/or consulting honoraria from AbbVie, Almirall, Janssen, Leo Pharma, Lilly, MSD, Novartis and Pfizer. G.R. reports personal fees from AbbVie, Eli Lilly, Janssen, Novartis and Pfizer, and grants and personal fees from Leo Pharma, all during the conduct of the study as well as outside the submitted work. K.W.-S. received speaker and/or consulting honoraria and/or travel refunds from AbbVie, Amgen GmbH, Eli Lilly, Janssen, Leo Pharma, Novartis and Pfizer. H.S. received honoraria/travel refunds as speaker/consultant from AbbVie, Almirall, Celgene, Janssen, Leo, Lilly, Novartis, Pfizer and UCB. M.I. has received speaker and consulting honoraria and travel refunds from AbbVie, Eli Lilly, Janssen, Novartis and Pfizer. B.L.-A. reports personal fees for advisory board meetings from AbbVie, Eli Lilly, Leo and Novartis, outside the submitted work. I.V. has received research grants, speaker and/or consulting honoraria and/or travel refunds from AbbVie, Almirall, Amgen GmbH, Celgene, Eli Lilly, Janssen, Leo Pharma, Merck Sharp & Dohme, Novartis, Pfizer and Sandoz. W.H. has received research grants, speaker and consulting honoraria from AbbVie, Almirall, Amgen GmbH, Bencard, Celgene, Eli Lilly, Janssen, Leo Pharma and Novartis. F.T. reports personal fees from AbbVie, Almirall, Amgen, Eli Lilly, Janssen-Cilag, Leo Pharma and Novartis, from outside the submitted work. W.S. reports personal fees from AbbVie, Almirall and Novartis. P.W. has received research grants, speaker and/or consulting honoraria and/or travel refunds from AbbVie, Almirall, Amgen GmbH, Celgene, Eli Lilly, Janssen, Leo Pharma, Merck Sharp & Dohme, Novartis, Pfizer and Sandoz. The remaining authors have nothing to disclose.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Table S1 Gender prevalence of psoriatic arthritis.

Table S2 Treatment allocation in patients with psoriatic arthritis.

Table S3 Comorbidities in treatment cycles with interleukin (IL)-17 inhibitors.

Table S4 Treatment allocation regarding gender.

Table S5 Gender allocation regarding treatment.

Table S6 Treatment allocation regarding biologic naïvety status.

Table S7 Treatment effectiveness.

Table S8 Drug survival at 12 months with regard to different characteristics.

Table S9 Statistical comparison of drug survival.

Table S10 Dosage regimen of biologic treatments.

Table S11 Treatment cycles prior to and after ixekizumab initiation.

Table S12 Interdependence analysis of prescribed biologics.

Table S13 Treatment after stop of initial therapy.

Table S14 Drug-specific reason for drug discontinuation.

Table S15 Reason for drug discontinuation.

Table S16 Reason for treatment discontinuation due to side-effect.

Table S17 Drug-specific reason for treatment discontinuation due to side-effect.

Figure S1 Drug survival of ixekizumab and ustekinumab.

Figure S2 Drug survival regarding concomitant psoriatic arthritis.