Differential Drug Survival of Biologic Therapies for the Treatment of Psoriasis: A Prospective Observational Cohort Study from the British Association of Dermatologists Biologic Interventions Register (BADBIR)

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Drug survival reflects a drug's effectiveness, safety, and tolerability. We assessed the drug survival of biologics used to treat psoriasis in a prospective national pharmacovigilance cohort (British Association of Dermatologists Biologic Interventions Register (BADBIR)). The survival rates of the first course of biologics for 3,523 biologic-naive patients with chronic plaque psoriasis were compared using survival analysis techniques and predictors of discontinuation analyzed using a multivariate Cox proportional hazards model. Data for patients on adalimumab ($n=1,879$), etanercept ($n=1,098$), infliximab ($n=96$), and ustekinumab ($n=450$) were available. The overall survival rate in the first year was 77%, falling to 53% in the third year. Multivariate analysis showed that female gender (hazard ratio (HR) 1.22; 95% confidence interval (CI): 1.09–1.37), being a current smoker (HR 1.19; 95% CI: 1.03–1.38), and a higher baseline dermatology life quality index (HR 1.01; 95% CI: 1.00–1.02) were predictors of discontinuation. Presence of psoriatic arthritis (HR 0.82; 95% CI: 0.71–0.96) was a predictor for drug survival. As compared with adalimumab, patients on etanercept (HR 1.63; 95% CI: 1.45–1.84) or infliximab (HR 1.56; 95% CI: 1.16–2.09) were more likely to discontinue therapy, whereas patients on ustekinumab were more likely to persist (HR 0.48; 95% CI: 0.37–0.62). After accounting for relevant covariates, ustekinumab had the highest first-course drug survival. The results of this study will aid clinical decision making when choosing biologic therapy for psoriasis patients.

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INTRODUCTION

Biologic therapies have revolutionized the treatment of severe psoriasis. Biologics currently licensed for psoriasis include the tumor necrosis factor inhibitors (TNFIs)—adalimumab, etanercept, and infliximab—and an IL-12/IL-23 inhibitor—ustekinumab. It has been established, however, that as a general rule biologic therapies lose effectiveness over time (Carrascosa *et al.*, 2014a). There is a lack of clinical trial data on the comparative effectiveness of the aforementioned biologics. Moreover, the long-term safety and "real-world" utility profile of these novel drugs cannot be adequately assessed in clinical trials, as trials are restricted by their

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Abbreviations: AE, adverse event; BADBIR, British Association of Dermatologists Biologic Interventions Register; BMI, body mass index; CI, confidence interval; DLQI, dermatology life quality index; HR, hazard ratio; PASI, psoriasis area and severity index; PsA, psoriatic arthritis; TNFI, tumor necrosis factor inhibitor

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inclusion criteria and size, being powered for primary efficacy outcomes, resulting in a low external validity for the "real-world" psoriasis population (Garcia-Doval *et al.*, 2012). The clinical factors that influence the safety and effectiveness of these novel agents are largely unknown.

Drug survival acts as a proxy marker of drug effectiveness, safety, and real-world utility (Saad *et al.*, 2009). An accurate assessment of drug survival in the clinical setting will help physicians choose the right drug, first time for patients, and thereby help health-care systems to be more cost effective. Large-scale cohorts are required to fully understand the factors influencing survival with these novel drugs.

To date, seven studies have reported on the comparative drug survival with biologics for psoriasis based on observational registries. Three of these studies have only reported on drug survival with TNFIs (Gniadecki *et al.*, 2011; Brunasso *et al.*, 2012; Esposito *et al.*, 2013), whereas two involved the same Danish national psoriasis biologic safety registry data DERMBIO (Gniadecki *et al.*, 2011, 2014), with the other centers reporting data from either a single or a limited number of centers (Umezawa *et al.*, 2013; Menting *et al.*, 2014; van den Reek *et al.*, 2014c). The British Association of Dermatologists Biologic Interventions Register (BADBIR) is a UK and Republic of Ireland prospective, longitudinal pharmacovigilance register which represents an ideal resource to assess real-world drug survival with biologics for psoriasis due to its size, which allows for analysis of both TNFIs and ustekinumab, a rigorous data collection process, independent data analysis, inclusion of important covariates, and high external validity through participation of multiple dermatology centers (Burden *et al.*, 2012). The aims of this study were to establish which biologic is most likely to persist in biologic-naive patients with psoriasis and to identify clinically relevant risk factors for drug discontinuation.

RESULTS

Baseline demographics and disease characteristics

A total of 3,523 biologic-naive patients with at least 6 months of follow-up data after initiation of biologic therapy were included in the study from a data cut in August 2014 (Table 1). The mean (standard deviation (SD)) age of patients, disease duration, and age of onset were 45.3 (12.8) years, 22.0 (12.4) years, and 23.3 (12.9) years, respectively, with 39.7% female. The mean (SD) body mass index (BMI) was 31.1 $kg\,m^{-2}$ (7.3), with 50% having a BMI $>30\,kg\,m^{-2}$. Overall, 60.9% of patients had one or more comorbidities, with hypertension (27.7%), depression (23.3%), and psoriatic arthritis (PsA; 20.1%) being the most common. The most common prescribed biologic was adalimumab: 1,879 (53.3%) patients. As expected, a higher proportion of patients with PsA were on TNFIs as compared with ustekinumab (Table 1).

Mean (SD) Psoriasis Area and Severity Index (PASI) and Dermatology Life Quality Index (DLQI) scores at registration were 15.9 (8.5) and 14.3 (8.9), respectively, with 13.7% suffering from unstable psoriasis. The median, mean, and range of the number of previous conventional systemic therapies used for psoriasis were 2, 2.13, and 0–5, respectively.

Drug survival with first course of biologic therapy

Drug survival data for the first course of biologic therapy were available for a median (interquartile range), total follow-up, and range of follow-up time of 1.4 (1.7), 5,955, and 0.5–6.9 person-years, respectively, with the median (interquartile range) follow-up of patients receiving adalimumab being 1.3 (1.6) years, etanercept 1.5 (2.0), infliximab 1.2 (1.6), and ustekinumab 1.2 (0.9). There were 1,315 discontinuations of treatment. Dosing data were investigated for adalimumab, etanercept, and ustekinumab but not for the infliximab cohort, as the number of subjects ($n=96$) was low. The standard licensed dosing regimen for the above biologics are as follows: 40 mg every other week for adalimumab; 25 mg twice weekly or 50 mg once weekly for etanercept; and 45 mg 12 weekly for ustekinumab if the patient's weight is ≤ 100 kg and 90 mg 12 weekly if the patient's weight is >100 kg. In all, 14% ($n=147$) of patients on etanercept, 5.5% ($n=99$) on adalimumab, and 10.6% ($n=46$) on ustekinumab had a starting dose or dosing interval that was either higher or shorter, respectively, than the standard licensed regimen or had experienced an escalation in dose and/or reduction in dosing interval during follow-up. The effect of dose escalation was investigated through a sensitivity analysis as detailed below.

Kaplan–Meier survival analyses (Table 2) Figure 1 revealed an overall survival rate in the first year of 77%, second year of 63%, and third year of 53%. In the first year of therapy, 13% of patients discontinued therapy due to ineffectiveness, 6% due to adverse events (AEs), and 4% due to other reasons (Table 2). Regarding the individual biologics, the first year survival rate for ustekinumab was 89%, adalimumab 79%, etanercept 70%, and infliximab 65%. The distribution of AEs associated with drug discontinuation overall and for the individual biologic therapies is shown in Table 3, with infection being the most common AE experienced.

Predictors of drug survival with the first course of biologic therapy

Adalimumab was considered as the reference standard to which the other biologic therapies were compared with because it was the most commonly prescribed biologic in the registry. The results from the univariate analysis are presented in Table 4. The multivariate Cox model met the assumption of proportionality globally. The overall multivariate model showed that female gender (hazard ratio (HR) 1.22; 95% confidence interval (CI): 1.09–1.37), being a current smoker (HR 1.19; 95% CI: 1.03–1.38), having a higher baseline DLQI (HR 1.01; 95% CI: 1.00–1.02), and being on etanercept (HR 1.63; 95% CI: 1.45–1.84) or infliximab (HR 1.56; 95% CI: 1.16–2.09) were predictors of discontinuation, whereas PsA (HR 0.82; 95% CI: 0.71–0.96) and being on ustekinumab (HR 0.48; 95% CI: 0.37–0.62) were predictors of drug survival (Table 4). For the model for discontinuation due to ineffectiveness, BMI $\geq 35\,kg\,m^{-2}$ as compared with a normal-range BMI, being a current smoker (HR 1.25; 95% CI: 1.02–1.54),

Table 1. The baseline demographic and disease characteristics of the study cohort

Demographic and disease characteristics						
Characteristic	**First biologic cohort (*n* = 3,523)**	**Etanercept (*n* = 1,098, 31.2%)**	**Infliximab (*n* = 96, 2.7%)**	**Adalimumab (*n* = 1,879, 53.3%)**	**Ustekinumab (*n* = 450, 12.8%)**	***P*-value**
Demographic (mean, SD for continuous variables; n, % cohort for categorical variables)						
Age (years)	45.3 (12.8)	45.5 (13.0)	47.1 (12.9)	44.9 (12.6)	46.0 (13.0)	0.126
Female	1,400 (39.7%)	453 (41.3%)	30 (31.3%)	745 (39.7%)	172 (38.2%)	0.220
BMI category (kg m^{-2})						
Underweight (<18.5)	32 (1.0%)	14 (1.4%)	1 (1.2%)	13 (0.8%)	4 (1.0%)	
Normal (18.5–24.99)	559 (17.4%)	186 (18.8%)	16 (18.8%)	292 (16.9%)	65 (15.9%)	
Overweight (25–29.99)	1,024 (31.9%)	316 (31.9%)	18 (21.2%)	568 (32.9%)	122 (29.8%)	
Obese I (30–34.99)	788 (24.5%)	238 (24.0%)	18 (21.2%)	437 (25.3%)	95 (23.2%)	
Obese II (35–39.99)	464 (14.4%)	154 (15.5%)	14 (16.5%)	238 (13.8%)	58 (14.2%)	
Obese III (>40)	346 (10.8%)	84 (8.5%)	18 (21.2%)	179 (10.4%)	65 (15.9%)	**0.002**
Current smoker	894 (30.0%)	252 (29.5%)	35 (41.7%)	485 (29.7%)	122 (30.1%)	**0.018**
Psoriatic arthritis	694 (20.1%)	216 (20.2%)	18 (19.2%)	401 (21.7%)	59 (13.3%)	**0.001**
No comorbidity[1]	1377 (39.1%)	412 (37.5%)	31 (32.3%)	768 (40.9%)	166 (36.9%)	
1–2 Comorbidities[1]	1638 (46.5%)	536 (48.8%)	47 (49.0%)	855 (45.5%)	200 (44.4%)	
3–4 Comorbidities[1]	436 (12.4%)	127 (11.6%)	15 (15.6%)	225 (12.0%)	69 (15.3%)	
≥5 Comorbidities[1]	72 (2.0%)	23 (2.1%)	3 (3.1%)	31 (1.7%)	15 (3.3%)	0.056
Disease						
Disease duration	22.0 (12.4)	22.3 (12.4)	21.6 (13.3)	21.7 (12.2)	22.2 (12.9)	0.577
Early onset (<40)	3,063 (87.6%)	949 (86.8%)	81 (84.4%)	1,642 (88.2%)	391 (87.5%)	0.713
Registration PASI	15.9 (8.5)	15.4 (7.9)	25.6 (11.7)	15.7 (8.3)	15.6 (8.9)	**<0.001**
Registration DLQI	14.3 (8.9)	15.1 (8.4)	16.8 (10.1)	14.1 (9.0)	13.1 (9.1)	**<0.001**
Unstable psoriasis	484 (13.7%)	142 (12.9%)	33 (34.4%)	245 (13.0%)	64 (14.2%)	**<0.001**
Medication history						
Baseline concomitant methotrexate	327 (9.3%)	93 (8.5%)	17 (17.7%)	184 (9.8%)	33 (7.3%)	**0.009**
Baseline concomitant ciclosporin	129 (3.7%)	49 (4.5%)	5 (5.2%)	59 (3.1%)	16 (3.6%)	0.250

Abbreviations: BMI, body mass index; DLQI, dermatology life quality index; PASI, psoriasis severity and area index.
P-value tests for significant differences among the four biologic cohorts.
[1]Includes any of hypertension, angina, ischemic heart disease, stroke, pulmonary fibrosis, asthma, chronic obstructive pulmonary disease, diabetes, thyroid disease, peptic ulcers, hepatic disease, renal disease, demyelinating disease, epilepsy, depression, tuberculosis, and cancer. Bold: $P<0.05$.

and being on etanercept (HR 2.28; 95% CI: 1.93–2.69) were predictors of discontinuation, whereas ustekinumab (HR 0.37; 95% CI: 0.25–0.57) was a predictor for drug survival. For the model for discontinuation due to AEs, female gender (HR 1.79; 95% CI: 1.40–2.28) and being on infliximab (HR 2.82; 95% CI: 1.79–4.45) were predictors for discontinuation, whereas being on ustekinumab (HR 0.60; 95% CI: 0.39–0.92) was a predictor for drug survival (Figure 2).

Sensitivity analysis was performed investigating the effects of dose escalation. We stratified for the group of patients with a standard licensed dosing regimen to investigate whether dose escalation affected differential biologic drug survival in our patient cohort. We did not find a difference in either the Kaplan–Meier plot or the multivariate regression analysis between the overall patient population and the patient population on standard licensed dosing with no dose escalation, indicating that dose escalation did not alter the differential individual biologic survival (Supplementary Figure S1 and Supplementary Table S1 online). Another sensitivity analysis investigated the impact of PsA with the exclusion of the cohort of patients with concomitant PsA, showing the same relative biologic drug survival as the overall patient cohort. Other sensitivity analyses to investigate the impact of missing dates of PASI and DLQI and the method of missing data analysis were conducted to add robustness to the results, with the differential overall drug survival with the individual biologic therapies similar in all sensitivity analyses models.

Table 2. The overall and differential biologic survival functions, stratified by reason for drug discontinuation, at years 1, 2, and 3

Reasons for drug discontinuation	First biologic (*n* = 3,523)	Etanercept (*n* = 1,098)	Infliximab (*n* = 96)	Adalimumab (*n* = 1,879)	Ustekinumab (*n* = 450)
All reasons					
Year 1	0.77 (0.76–0.79)	0.70 (0.67–0.73)	0.65 (0.54–0.74)	0.79 (0.77–0.81)	0.89 (0.86–0.92)
Year 2	0.63 (0.61–0.65)	0.51 (0.48–0.54)	0.50 (0.39–0.60)	0.67 (0.65–0.70)	0.82 (0.76 –0.86)
Year 3	0.53 (0.51–0.55)	0.40 (0.37–0.44)	0.35 (0.24–0.47)	0.59 (0.56–0.62)	0.75 (0.68–0.81)
Ineffectiveness					
Year 1	0.87 (0.86–0.88)	0.80 (0.77–0.82)	0.86 (0.76–0.92)	0.90 (0.88–0.91)	0.96 (0.93–0.97)
Year 2	0.78 (0.76–0.79)	0.65 (0.62–0.68)	0.79 (0.66–0.87)	0.83 (0.81–0.85)	0.93 (0.89–0.95)
Year 3	0.71 (0.69–0.73)	0.55 (0.52–0.59)	0.76 (0.63–0.85)	0.79 (0.76–0.82)	0.89 (0.82–0.93)
Adverse events					
Year 1	0.94 (0.93–0.94)	0.94 (0.93–0.96)	0.84 (0.74–0.90)	0.93 (0.92–0.94)	0.96 (0.93–0.98)
Year 2	0.90 (0.89–0.92)	0.91 (0.89–0.93)	0.74 (0.62–0.83)	0.90 (0.88–0.92)	0.93 (0.90–0.96)
Year 3	0.88 (0.86–0.89)	0.90 (0.87–0.92)	0.59 (0.43–0.72)	0.87 (0.85–0.89)	0.91 (0.86–0.95)

Data presented as mean (95% confidence interval).

Table 3. Adverse events leading to patient withdrawal by individual biologic therapy

	Patient withdrawal due to adverse events			
Adverse event leading to withdrawal (MedDRA system organ classification)	**Etanercept (*n* = 1,098)**	**Infliximab (*n* = 96)**	**Adalimumab (*n* = 1,879)**	**Ustekinumab (*n* = 450)**
Blood and lymphatic system disorders	0	0	2 (0.1%)	0
Cardiac disorders	0	0	3 (0.2%)	0
Ear and labyrinth disorders	0	0	0	0
Endocrine disorders	1 (0.1%)	0	0	0
Eye disorders	2 (0.2%)	0	1 (0.1%)	0
Gastrointestinal disorders	2 (0.2%)	2 (2.1%)	8 (0.4%)	4 (0.9%)
General disorders and administration site conditions	5 (0.5%)	3 (3.1%)	14 (0.7%)	1 (0.2%)
Hepatobiliary disorders	1 (0.1%)	2 (2.1%)	2 (0.1%0	0
Immune system disorders	2 (0.2%)	1 (1.0%)	0	0
Infections and infestations	10 (0.9%)	3 (3.1%)	25 (1.3%)	6 (1.3%)
Injury, poisoning, and procedural complications	0	3 (3.1%)	1 (0.1%)	0
Investigations	2 (0.2%)	2 (2.1%)	8 (0.4%)	1 (0.2%)
Metabolism and nutrition disorders	1 (0.1%)	0	0	0
Musculoskeletal and connective tissue disorders	1 (0.1%)	2 (2.1%)	9 (0.5%)	1 (0.2%)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	4 (0.4%)	0	4 (0.2%)	1 (0.2%)
Nervous system disorders	4 (0.4%)	0	7 (0.4%)	2 (0.4%)
Psychiatric disorders	1 (0.1%)	1 (1.0%)	1 (0.1%)	2 (0.4%)
Renal and urinary disorders	1 (0.1%)	0	2 (0.1%)	0
Reproductive system and breast disorders	1 (0.1%)	0	0	1 (0.2%)
Respiratory, thoracic, and mediastinal disorders	5 (0.5%)	3 (3.1%)	3 (0.2%)	0
Skin and subcutaneous tissue disorders	5 (0.5%)	1 (1.0%)	9 (0.5%)	2 (0.4%)
Vascular disorders	0	0	0	0
Total	48	23	99	21

Abbreviation: MedDRA, Medical Dictionary for Regulatory Activities.
Data presented as *n* (% of all patients in the biologic group).

Table 4. The univariate and multivariate Cox proportional hazard analysis for drug discontinuation, presented by reason for withdrawal

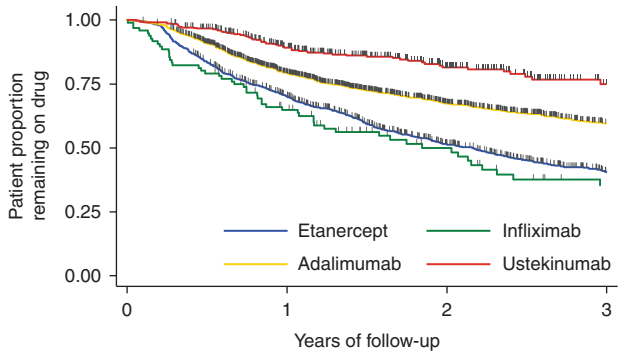
Univariate and multivariate Cox proportional hazard analysis for drug discontinuation						
Variable	**Overall withdrawal**		**Withdrawal due to ineffectiveness**		**Withdrawal due to adverse events**	
	Univariate	**Multivariate**	**Univariate**	**Multivariate**	**Univariate**	**Multivariate**
Demographics						
Age	1.00 (0.99–1.00)	1.00 (0.99–1.01)	**0.99* (0.98–1.00)**	1.00 (0.99–1.01)	**1.01* (1.00–1.02)**	1.01 (1.00–1.03)
Female	**1.28* (1.15–1.43)**	**1.22* (1.09–1.37)**	1.11 (0.96–1.29)	1.02 (0.87–1.20)	**1.74* (1.38–2.19)**	**1.79* (1.40–2.28)**
BMI category (kg m^{-2})[1]						
Underweight (<18.5)	1.61 (1.00–2.61)	1.30 (0.80–2.11)	1.59 (0.79–3.22)	1.27 (0.63–2.55)	1.00 (0.31–3.21)	0.69 (0.21–2.27)
Overweight (25–29.9)	0.90 (0.76–1.07)	0.98 (0.82–1.17)	1.03 (0.81–1.31)	1.13 (0.89–1.44)	0.82 (0.58–1.17)	0.86 (0.60–1.24)
Obese I (30–34.99)	0.92 (0.77–1.10)	1.01 (0.84–1.21)	1.12 (0.87–1.44)	1.23 (0.97–1.59)	**0.66* (0.45–0.96)**	0.67 (0.46–1.00)
Obese II (35–39.99)	1.07 (0.88–1.30)	1.12 (0.92–1.37)	**1.34* (1.02–1.75)**	**1.44* (1.09–1.90)**	0.82 (0.55–1.24)	0.79 (0.52–1.21)
Obese III (>40)	1.07 (0.86–1.32)	1.15 (0.92–1.43)	1.22 (0.90–1.65)	**1.48* (1.09–2.02)**	0.89 (0.56–1.40)	0.76 (0.47–1.22)
Smoking status[2]						
Ex-smoker	1.04 (0.89–1.20)	1.08 (0.93–1.26)	1.04 (0.85–1.28)	1.12 (0.91–1.39)	1.03 (0.75–1.43)	1.00 (0.72–1.38)
Current smoker	**1.23* (1.06–1.42)**	**1.19* (1.03–1.38)**	**1.24* (1.02–1.51)**	**1.25* (1.02–1.54)**	1.28 (0.94–1.76)	1.15 (0.83–1.59)
Comorbidities[3]						
Psoriatic arthritis	0.87 [0.75–1.00)	**0.82* [0.71–0.96)**	0.87 [0.72–1.06)	0.83 (0.68–1.02)	1.04 (0.77–1.39)	1.02 (0.75–1.39)
1–2 Comorbidities	1.01 (0.90–1.13)	0.97 (0.86–1.10)	0.93 (0.79–1.09)	0.87 (0.74–1.03)	1.10 (0.85–1.42)	1.03 (0.79–1.34)
3–4 Comorbidities	1.07 (0.89–1.27)	1.09 (0.90–1.31)	1.01 (0.79–1.28)	1.01 (0.78–1.31)	1.18 (0.81–1.71)	1.04 (0.69–1.55)
≥5 Comorbidities	1.16 (0.80–1.69)	1.33 (0.90–1.96)	0.91 (0.52–1.59)	1.02 (0.57–1.82)	1.53 (0.75–3.15)	1.37 (0.65–2.90)
Disease						
Disease duration	**0.99* (0.99–1.00)**	0.99 (0.99–1.00)	**0.99* (0.98–1.00)**	0.99 (0.98–1.00)	1.00 (0.99–1.01)	1.00 (0.98–1.01)
Early-onset disease (<40 years)	0.87 (0.72–1.06)	0.94 (0.74–1.21)	0.85 (0.65–1.11)	0.91 (0.65–1.27)	0.81 (0.54–1.21)	0.90 (0.54–1.51)
Registration PASI	**1.01* (1.00–1.02)**	1.01 (1.00–1.01)	**1.01* (1.00–1.02)**	1.01 (1.00–1.02)	**1.02* (1.01–1.03)**	1.01 (1.00–1.03)
Registration DLQI	**1.02* (1.01–1.02)**	**1.01* (1.00–1.02)**	**1.02* (1.01–1.02)**	1.01 (1.00–1.02)	**1.02* (1.00–1.03)**	1.01 (0.99–1.02)
Unstable psoriasis	**1.19* (1.03–1.38)**	1.13 (0.97–1.31)	**1.18* (0.97–1.44)**	1.19 (0.97–1.47)	1.27 (0.93–1.73)	1.03 (0.75–1.42)
Concomitant[4] methotrexate	**1.41* (1.20– 1.65)**	**1.33* (1.13– 1.57)**	**1.54* (1.25– 1.90)**	**1.49* (1.18– 1.88}**	1.03 (0.71– 1.49)	0.94 (0.62– 1.43)
Concomitant[4] ciclosporin	**2.90* (2.41– 3.50)**	**2.60* (2.15– 3.15)**	**3.42* (2.70– 4.34)**	**3.08* (2.37– 4.00)**	**1.71* (1.06– 2.76)**	**1.66* (1.00– 2.75)**
Biologic therapy[5]						
Etanercept	**1.74* (1.55–1.95)**	**1.63* (1.45–1.84)**	**2.43* (2.08–2.84)**	**2.28* (1.93–2.69)**	0.79 (0.60–1.03)	0.77 (0.58–1.02)
Infliximab	**1.97* (1.49–2.61)**	**1.56* (1.16–2.09)**	1.17 (0.70–1.97)	0.86 (0.51–1.47)	**3.26* (2.14–4.97)**	**2.82* (1.79–4.45)**
Ustekinumab	**0.48* (0.38–0.62)**	**0.48* (0.37–0.62)**	**0.37* (0.25–0.56)**	**0.37* (0.25–0.57)**	**0.60* (0.39–0.92)**	**0.60* (0.39–0.92)**

Abbreviations: BMI, body mass index; DLQI, dermatology life quality index; PASI, psoriasis severity and area index.
Data presented as hazard ratio (95% confidence interval).
Drug year is adjusted for in the multivariate analysis.
*$P<0.05$, shown in bold.
[1]Reference category: normal BMI 18.5–24.9.
[2]Reference category: never smoked.
[3]Reference category: no comorbidities (excluding psoriatic arthritis); includes any of hypertension, ischemic heart disease, stroke, pulmonary fibrosis, asthma, chronic obstructive pulmonary disease, diabetes, thyroid disease, peptic ulcers, hepatic disease, renal disease, demyelinating disease, epilepsy, depression, tuberculosis, and cancer.
[4]Time-varying covariates.
[5]Reference category: adalimumab.

DISCUSSION

Current findings

This study represents the largest observational real-world cohort study assessing the drug survival with biologics in psoriasis to date. Our study focuses on biologic-naive patients and shows that the survival with biologic therapies decreases over time, from 77% in the first year to 53% in the third year. One of the most notable findings is that ustekinumab had a significantly higher survival rate than TNFIs, and this difference persisted after controlling for clinical factors likely



Number at risk

Etanercept	1,098	718	418	225
Infliximab	96	55	30	15
Adalimumab	1,879	1,175	596	277
Ustekinumab	450	307	120	40

Figure 1. Crude drug survival of the first biologic course showing disaggregated biologic data (Kaplan–Meier survival curve).

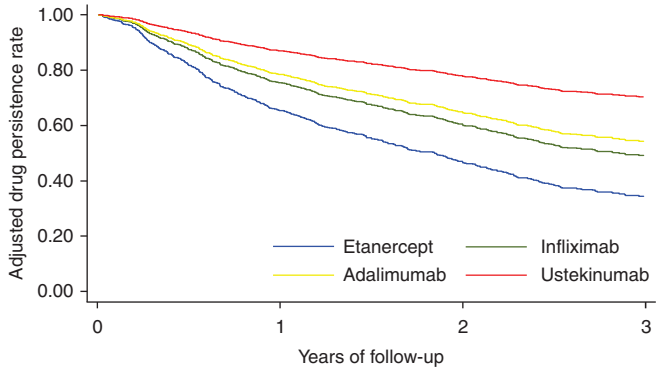


Figure 2. Adjusted drug survival curves using disaggregated data based on the overall multivariate Cox proportional hazard model in Table 4.

to cause systematic bias in biologic-naive patients. Of the TNFIs, adalimumab had the highest survival rate in biologic-naive patients. Important predictors for drug failure included female gender, a higher registration DLQI, and current smoking status, whereas patients with PsA persist with biologic therapy longer than those without. As compared with adalimumab, infliximab was a predictor for discontinuation overall and due to AEs, whereas etanercept was a predictor for discontinuation both overall and due to ineffectiveness.

Comparisons with current literature

The results of our study are broadly consistent with the comparable published studies that considered drug survival with both TNFI and ustekinumab in psoriasis. An updated study from DERMBIO involving 1,277 psoriasis patients treated with biologic therapy found that ustekinumab had the highest survival rate with 81.9% at 4 years (Gniadecki *et al.*, 2014). A Dutch study from 8 regional centers of 213 patients found the 1-year survival rate of 85% for ustekinumab, 74% for adalimumab, and 68% for etanercept, with a multivariate analysis showing that ustekinumab had a significantly higher drug survival than etanercept but not adalimumab (van den Reek *et al.*, 2014c).

Due to the size and quality of baseline covariate data in our study, we were able to robustly test whether the finding of ustekinumab as the biologic therapy with the highest drug survival represented a true finding or was a result of systematic bias in the population. We studied a large biologic-naive population, which negated any systematic effect of prior biologic exposure on individual biologic drug survival. We controlled for likely clinical factors that could exert a confounding effect on the result, e.g., channeling bias (the confounding effect of assigning certain treatments to specific subgroups) through the concomitant prescription of methotrexate and ciclosporin using a time-dependent method. As drug survival with biologic therapy may also be influenced by its dual efficacy on psoriasis and PsA, we explored the effect of PsA on the individual biologic survival. A sensitivity analysis, using separate models with and without the cohort with PsA, did not reveal a substantial change in the differential individual biologic survival results. In addition, the stratified model for the group of patients with a standard licensed dosing regimen and no dose escalation against the whole patient population also did not reveal a significant change to the differential biologic survival results (Supplementary Figure S1, and Supplementary Table S1 online). The low number of patients with dose escalation is likely to relate to the system of public funding for these medications in the United Kingdom, where applications for up-titration are often not accepted.

The ustekinumab cohort in our study was twice the size of the largest published study to date for the first ($n = 450$) course of therapy in biologic-naive patients, thereby giving the study more power for the investigation of comparative biologic survival. In addition, we included clinically relevant *a priori* covariates for the multivariate analysis, whereas both Gniadecki *et al.* (2014) and van den Reek *et al.* (2014c) included only variables that were significant in the univariate analysis. This approach has the potential to miss important effects of factors such as concomitant ciclosporin, smoking status, and so on that, in combination with the lower study numbers, may have accounted for the lack of significant difference found between ustekinumab and adalimumab in the Dutch study. Importantly, Gniadecki *et al.* (2014) showed in their study that the prevalence of PsA was higher in the TNFI group as compared with the ustekinumab group, but this was neither adjusted nor accounted for. Thus, the current report represents the analysis of the largest cohort study assessing biologic survival in biologic-naive psoriasis patients to date, taking into account the effects of important clinically relevant covariates.

Probable factors accounting for survival with biologics

Biologic survival reflects various factors including primary or secondary drug effectiveness, drug safety and AE profile, and tolerability. Through our sensitivity analyses, we are confident that the differences between the drug survival of the biologics used to treat psoriasis are not explained by potential

confounders such as differential dosing escalation strategies or difference in drug survival in the patients with concomitant PsA. Possible reasons contributing to the higher drug survival shown by ustekinumab as compared with the TNFIs, based on the literature and known licensing information, are high effectiveness (Griffiths *et al.*, 2010), lower immunogenicity (Carrascosa *et al.*, 2014a), lower drug discontinuation due to AEs (Table 4), dosing regimen, and method of administration.

Differences in the immunogenicity of the biologics may affect survival rates, especially for withdrawals due to ineffectiveness. A recent systematic review (Carrascosa *et al.*, 2014a) describes that antidrug antibodies are found in 4–46% patients on adalimumab, 1.1–18.3% on etanercept, 19.5–51.5% on infliximab, and 3.8–5.1% in ustekinumab. In addition, it has been shown that antidrug antibodies and trough drug levels for adalimumab correlate with drug effectiveness (Lecluse *et al.*, 2010). The comparatively lower proportion of antidrug antibodies seen in studies on ustekinumab may partly explain the higher drug survival with this biologic in this study, although it should be noted that variations in reported antidrug antibody levels may partly reflect the sensitivity of the different detection assays used.

A study into self-reported adherence to self-injectable TNFIs in rheumatoid arthritis patients found that 27% of patients had not taken the drug on the scheduled date on at least one occasion in the first 6 months of therapy (Bluett *et al.*, 2014). Crucially, this was associated with a lower measured response following 6 months of therapy, suggesting that nonadherence may have a role in the loss of effectiveness of biologic therapies. The fact that ustekinumab is a 12-weekly nurse-administered injection in most centers as compared with the more frequent self-injection regimens for other biologics may contribute to better drug adherence.

Consistent with the findings of our study, female gender has been reported previously as a predictor of discontinuation of biologics (Gniadecki *et al.*, 2011, 2014; Esposito *et al.*, 2013; van den Reek *et al.*, 2014a, b). Female gender is a predictor for drug discontinuation in other conditions, such as hypertension and postmyocardial infarction treatments (Franconi and Campesi, 2014; Manteuffel *et al.*, 2014), whereas women with rheumatoid arthritis have lower remission rates for treatment with TNFI therapy (Barnabe *et al.*, 2014; Couderc *et al.*, 2014). Women also have a higher rate of severe AEs (Davies *et al.*, 2009; Pirmohamed *et al.*, 2004).

We have shown that PsA is a predictor for overall drug survival. Psoriatic arthritis has been found to be a predictor for drug survival with TNFIs in one other observational study that did not examine survival with ustekinumab (Brunasso *et al.*, 2012). As the severity of PsA and its response to treatment were not captured in this study, this may represent a confounding effect of the effectiveness of the biologic on PsA. Although the sensitivity analysis for models with patients with and without PsA showed that the HRs were similar, further PsA-focused studies are needed before it could be regarded as a genuine predictor for drug survival with biologic therapies in psoriasis patients.

Our study reports that a BMI of $>35\,kg\,m^{-2}$ significantly predicted for drug discontinuation due to ineffectiveness. A high BMI is a known predictor for discontinuation of biologics (Naldi *et al.*, 2008; Di Lernia *et al.*, 2012; Edson-Heredia *et al.*, 2014; Carrascosa *et al.*, 2014b). Ustekinumab is used in two doses, 45 mg in patients weighing ≤ 100 kg and 90 mg in those >100 kg, whereas adalimumab and etanercept are used as fixed doses irrespective of body weight. However, the differential biologic survival did not change when the analysis was restricted to patients <100 kgs (results not shown). Consistent with previous studies showing poor treatment response for TNFIs in psoriasis patients who were smokers, we found that being a current smoker was a predictor for overall discontinuation and for discontinuation due to ineffectiveness (Di Lernia *et al.*, 2014), whereas being an ex-smoker did not predict for discontinuation, suggesting that an active smoking status could affect the effectiveness of a biologic therapy.

Strengths and limitations

The major strengths of this study are the prospective real-world cohort study design, the sample size, detailed data capture allowing numerous covariates to be analyzed, fully independent data analysis, and the multiple centers in the UK and Republic of Ireland that, together, are unparalleled in studies published to date. The wide inclusion criteria and the participation of numerous centers across the UK and Republic of Ireland (151 dermatology centers as of August 2014) ensure high external validity. As BADBIR is constructed primarily as a pharmacovigilance register, limitations to studying effectiveness are inherent to the study design; e.g., the intention behind concomitant medication, i.e., overlap, rescue, or long term.

The accuracy of delineating the reason for drug withdrawal is dependent on information from the recruiting dermatology center. Recall and reporting bias may occur with patient-reported characteristics. An inherent limitation in an observational study is nonrandomization that may introduce selection bias, and although this is partially negated by adjustment for clinically relevant covariables, the presence of unmeasured confounders cannot be ruled out. Patient adherence was not measured as part of this study. The infliximab cohort is small because of the stricter prescription criteria of this drug in most of the United Kingdom, and hence the power of this cohort for analysis is a particular concern. However, the infliximab cohort was recruited from 47 centers, with no concentration at any one center and no specific concentration across a particular region; hence, this cohort is likely to have high external validity. Future analyses when BADBIR has matured further may yield important data on second and subsequent courses of biologics.

Summary

In summary, we have shown that biologics in clinical practice have a good overall survival rate in psoriasis patients but decrease over time, with loss of response being the main determinant of discontinuation. After accounting for relevant covariates, ustekinumab had the highest first-course drug survival in biologic-naive patients. Of the TNFIs, adalimumab showed the highest survival rate in biologic-naive patients.

The results of this study will aid clinical decision making when choosing biologic therapy for psoriasis patients.

MATERIALS AND METHODS

Subjects were selected in a data snapshot from August 2014. BADBIR, established in September 2007, compares a cohort of psoriasis patients on biologics to a similar cohort on conventional systemic therapies. A detailed report of the design of BADBIR has been published previously (Burden *et al.*, 2012). Of relevance to this study, the NICE (National Institute for Health and Care Excellence), a national guidance body, guidelines for the specific biologics include the criteria of PASI ≥ 20 and DLQI >18 for the prescription of infliximab, and PASI ≥ 10 and DLQI >10 for the other biologics. Guidelines in Scotland and the Republic of Ireland are similar.

Baseline assessment

Baseline data are collected with patient consent before or during the initial 6 months of treatment. The classifications of disease characteristics were determined by the treatment center physician. Registration PASI and DLQI scores were taken at the time the patient started the biologic therapy. The date of scoring was collected following a protocol amendment in 2011.

Follow-up assessments

Data from patients are collected 6-monthly in the first 3 years and then annually thereafter. Details of the biologic therapies are recorded, including any change in dose or therapy, gaps in treatment, start and stop dates, and reasons for discontinuation. Patient questionnaires are recorded to monitor for any hospital admissions, new concomitant medications, and DLQI, whereas start and stop dates of concomitant medications are recorded. Details of the AEs were classified using the MedDRA (Medical Dictionary for Regulatory Activities) system (Bousquet *et al.*, 2005).

Data analysis

Drug survival was defined as the length of time from initiation to discontinuation of therapy (Cramer *et al.*, 2008). Discontinuation of therapy was defined as any gap in treatment for more than 90 days, to disregard temporary or intermittent treatment due to clinical reasons, e.g., infections or surgery, and takes into account the early UK licensing prescription of etanercept in an intermittent regimen with gaps of <90 days. The discontinuation date includes the earliest date of any switchers to different biologics or death while registered on BADBIR. This definition is in accordance with other drug survival studies in psoriasis and psoriatic arthritis (Saad *et al.*, 2009; Gniadecki *et al.*, 2011; Esposito *et al.*, 2013; van den Reek *et al.*, 2014b).

The study inclusion criteria are biologic-naive patients with chronic plaque psoriasis and at least one dermatologist's follow-up questionnaire, i.e., with follow-up data of ≥ 6 months, in the biologics cohort. Differences in baseline characteristics between the biologics were analyzed using analysis of variance for continuous variables and the χ^2 test for categorical variables (Table 1). Drug survival was examined using Kaplan–Meier survival analysis, with censorship occurring at the last available follow-up date. Reasons for withdrawal, classified as due to ineffectiveness, AEs, and others, were noted. AEs that were considered attributable to the drug by the treatment center have been presented. For analysis of drug dosing regimen, the standard licensed dosing regimens for the biologics that were investigated were as follows: 40 mg every other week for adalimumab; 25 mg twice weekly or 50 mg once weekly for etanercept; and 45 mg 12 weekly for ustekinumab if the patient's weight is ≤ 100 kg and 90 mg 12 weekly if the patient's weight is >100 kg. Any increase in the prescribed dose or decrease in the dosing interval was considered to be dose escalations.

An *a priori* list of covariates was determined to address potential predictors of discontinuation and as adjusters of potential confounding (Table 4). BMI, derived from baseline measurements for height and weight, was categorized according to the World Health Organization classification to maximize interpretability. The baseline comorbidities were taken from a prespecified list and a free-text section. Concomitant methotrexate and ciclosporin were analyzed as time-varying covariates throughout the period of follow-up. The covariates were entered for adjustment in the multivariate model but not discussed because of the risk of channeling bias. The year of biologic prescription was included for adjustment.

Multivariate Cox proportional hazard models were used to ascertain predictive factors for the first biologic course discontinuation. The proportional hazard assumption was tested formally using Schoenfeld residuals. Separate models were developed to analyze overall discontinuation, discontinuation due to ineffectiveness, and AEs. Patients were categorized as having an AE if they either stopped therapy due to an AE or due to both an AE and ineffectiveness.

A multiple imputation model of 20 cycles was performed to account for missing data, the details of which are listed in Supplementary Table S3 online. Sensitivity analyses that were performed to add robustness to the results include a complete case analysis model, a multiple-imputed model without the cohort with PsA (Supplementary Table S1 online), a multiple-imputed multivariate model using the data of PASI and DLQI scores with a valid date (post-2011 protocol modification, Supplementary Table S2 online), and a multiple-imputed model with a cohort on a standard dosing regimen and no dose escalation. Analyses were performed using STATA version 13 (StataCorp, College Station, TX).

Ethical approval

This study was approved in March 2007 by NHS Research Ethics Committee North West England, reference 07/MRE08/9. All subjects gave written consent for their participation in the registry.

CONFLICT OF INTEREST

RBW has acted as a consultant and/or speaker and/or received research grants for Abbvie, Amgen, Celgene, Eli Lilly, Pfizer, Novartis, and Janssen, all of whom manufacture biologic therapies. DMA has received grant funding from the National Institute for Health Research (NIHR) and grant funding from Abbvie and served on advisory boards for Pfizer and GSK. JNWNB reported receiving grant support from Schering Plough and Abbvie, consulting fees from Abbvie and Wyeth, and lecture fees from Schering-Plough, Janssen-Cilag, Abbvie, and Wyeth. ADB has acted as lecturer, consultant, and researcher for Abbvie, Janssen, Leo, MSD, Novartis, and Pfizer. ADO has lectured for or received travel assistance from Janssen, Abbvie, and Pfizer, has participated in advisory boards for MSD and Abbvie, and his department has received research funding from Abbvie, Janssen, Pfizer, Novartis, and MSD. CEMG has received honoraria and/or research grants from Abbvie, Actelion, Amgen, Celgene, Lilly, GSK-Stiefel, Janssen, MSD, Novartis, Pfizer, and Sandoz. CEMG is a National Institute for Health Research Senior Investigator. NJR has received honoraria, travel support, consulting income, and research grants

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SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/jid

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