



HAL
open science

Evolution of Drug Survival with Biological Agents and Apremilast Between 2012 and 2018 in Patients with Psoriasis from the PsoBioTeq Cohort

T. Bettuzzi, H. Bachelez, M. Beylot-Barry, H. Arlégui, C. Paul, M. Viguier, E. Mahé, N. Beneton, D. Jullien, M.-A. Richard, et al.

► To cite this version:

T. Bettuzzi, H. Bachelez, M. Beylot-Barry, H. Arlégui, C. Paul, et al.. Evolution of Drug Survival with Biological Agents and Apremilast Between 2012 and 2018 in Patients with Psoriasis from the PsoBioTeq Cohort. *Acta Dermato-Venereologica*, 2022, 102, pp.adv00665. 10.2340/actadv.v101.566 . hal-03660920

HAL Id: hal-03660920

<https://hal.science/hal-03660920>

Submitted on 31 May 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

Evolution of Drug Survival with Biological Agents and Apremilast Between 2012 and 2018 in Patients with Psoriasis from the PsoBioTeq Cohort

Thomas BETTUZZI^{1,2}, Hervé BACHELEZ³, Marie BEYLOT-BARRY⁴, Hugo ARLÉGUI⁵, Carle PAUL⁶, Manuelle VIGUIER⁷, Emmanuel MAHÉ⁸, Nathalie BENETON⁹, Denis JULLIEN¹⁰, Marie-Aleth RICHARD¹¹, Pascal JOLY¹², Florence TUBACH⁵, Alain DUPUY¹³, Emilie SBIDIAN^{1,2,14#}, Olivier CHOSIDOW^{1,15#} and the PsoBioTeq study group

¹Créteil Medical School and Dermatology Department, Assistance Publique-Hôpitaux de Paris, Henri-Mondor Hospital, Paris-Est Créteil University, ²EpiDermE, Paris Est Créteil University, Créteil, ³SorbonneParis Cité Paris Diderot University; Dermatology Department, Assistance Publique-Hôpitaux de Paris, Saint-Louis Hospital, INSERM UMR 1163, Institut Imagine, Paris, ⁴Dermatology Department, Saint-André Hospital, INSERM U1053, Bordeaux University, Bordeaux, ⁵Sorbonne University, INSERM, Pierre Louis Institute of Epidemiology and Public Health, Assistance Publique-Hôpitaux de Paris, Sorbonne University, Pitié Salpêtrière Hospital, Public Health Department, Centre de Pharmacopépidémiologie (Cephepi), CIC-1422, Paris, ⁶Dermatology Department, Toulouse University Hospital; Paul Sabatier University, UMR INSERM 1056, Toulouse, ⁷Dermatology Department, Robert Debré University Hospital, Reims, ⁸Dermatology Department, Victor Dupouy Hospital, Argenteuil, ⁹Dermatology Department, Le Mans Hospital, Le Mans, ¹⁰Dermatology Department, HCL, Lyon University Hospital, Edouard Herriot Hospital, Lyon, ¹¹Dermatology Department, University Hospital, La Timone Hospital, Marseille, ¹²Department of Dermatology, Rouen University Hospital, Normandie University, INSERM U 1234, ¹³Dermatology Department, Rennes University Hospital, Hôpital Pontchaillou; Inserm CIC 1414, Rennes 1 University, Rennes, ¹⁴INSERM, Centre d'Investigation Clinique 1430, Créteil, and ¹⁵Research Group Dynamic, EA7380, Créteil Medical School, National Veterinary School of Alfort, USC ANSES, Paris-Est Créteil University, Créteil, France

#These 2 authors contributed equally and should be considered as co-last authors.

Drug survival reflects treatment effectiveness and safety in real life. There is limited data on the variation of drug survival with the availability of systemic treatments with additional biological disease-modifying antirheumatic drugs (bDMARDs) or synthetic disease-modifying antirheumatic drugs (sDMARDs). The aim of this study was to determine whether the increasing number of available systemic treatments for psoriasis affects drug survival over time. Patients were selected from the PsoBioTeq cohort, a French prospective observational cohort enrolling patients with moderate to severe psoriasis. All patients initiating a first bDMARD or sDMARD were included. The primary outcome was comparison of drug survival over time. A multivariate Cox proportional hazard ratio model was computed. A total of 1,866 patients were included; 739 females (39%), median age 47 years. In the multivariate Cox model, no association was found between the calendar year of initiation and drug survival (hazard ratio) overlapping from 0.80 (0.42–1.52) to 1.17 (0.64–2.17), $p=0.633$). In conclusion, drug survival in psoriasis is not affected by the year of initiation.

Key words: psoriasis; drug survival; treatment; biologic; apremilast.

Accepted Nov 22, 2021; Epub ahead of print Nov 22, 2021

Acta Derm Venereol 2022; 102: adv00665.

DOI: 10.2340/actadv.v101.566

Corr: Emilie Sbidian, Hôpital Henri Mondor, 51 avenue du Maréchal de Lattre de Tassigny, FR-94010 Créteil, France. E-mail: emilie.sbidian@aphp.fr

Psoriasis is a chronic inflammatory skin disease with a prevalence ranging from 0.9% to 8.5% of the population in Europe (1, 2), and an incidence ranging from 78.9/100,000 to 230/100,000 (1, 2). The last 2 decades have witnessed the approval of numerous biological

SIGNIFICANCE

Drug survival is thought to represent a balance between effectiveness and safety in real life. Nevertheless, there is limited data on the variation of drug survival with the availability of additional biological or synthetic systemic treatments. This study found that drug survival in psoriasis is not affected by the year of initiation, suggesting that drug survival of patients with moderate to severe psoriasis is not sensitive to the increasing therapeutic armamentarium, and therefore strengthens its use to estimate balance between treatment effectiveness and adverse reactions over years.

agents, i.e. tumour necrosis factor (TNF) inhibitors, interleukin (IL)-12–23 inhibitors, IL-17 inhibitors, IL-23 inhibitor and/or apremilast, creating a wide therapeutic armamentarium (3). Most randomized clinical trials (4) include short-term evaluation of efficacy and safety (4). In a real-life setting, due to a loss of effectiveness, or to adverse events, some patients may discontinue or switch treatment, potentially leading to diseases flares and/or a reduced quality of life. To further evaluate and compare treatments, drug survival through time, also called “persistence” is frequently used (5–7). Drug survival is a surrogate criterion representing a good balance between effectiveness and safety in a real-life setting (5).

Several studies have evaluated drug survival in patients with moderate to severe psoriasis. Variations in drug survival were observed between cohorts with up to 79% retention rates at 1 year from 2008 to 2013 in the Spanish BIOBADADERM cohort (8), 77% from 2007 to 2014 in the British BADBIR cohort (6), and only 62% according to the French healthcare system between 2009 and 2016 (9). An Israeli cohort reported that the calendar year of initiation could be associated with a significant variation

in drug survival over time, patients initiating a systemic treatment more recently having shorter drug survival (10). In France, drug approval was granted in 2005 for etanercept and infliximab, 2008 for adalimumab, 2010 for ustekinumab, 2016 for ixekizumab, secukinumab, and apremilast. This widening of the armamentarium of psoriasis treatments may have promoted a reduction in drug survival, by giving patients and physicians additional options in case of suboptimal effectiveness and safety. Hence, it was hypothesized that the increasing number of available treatments would shorten the drug survival over the years. The objective of this study was to assess the evolution of drug survival according to the calendar year of initiation in patients with moderate to severe psoriasis.

PATIENTS AND METHODS

Overview and data source

The PsoBioTeq cohort is a French prospective observational cohort that enrolls and follows prospectively adult patients (aged > 18 years) with moderate to severe psoriasis. The objectives of PsoBioTeq are to describe the use, benefit and risks of systemic treatments with conventional, synthetic disease-modifying antirheumatic drugs (sDMARDs) and biological disease-modifying antirheumatic drugs (bDMARDs) in a real-life setting. The choice of treatment is left to the clinicians and is not influenced by participation in the cohort. PsoBioTeq is currently recruiting patients from 41 departments of dermatology across France. Several ancillary studies have already been published with the PsoBioTeq study (11, 12). The study protocol was approved by the "Comité d'Evaluation de l'Ethique des projets de Recherche Biomédicale (CEERB) du GHU Nord" (authorization number JMD/MDM/177-11). The ClinicalTrials.gov identifier is NCT01617018. Written informed consent was obtained from all patients before study inclusion.

Population and data collection

All patients initiating a first therapeutic line of biological disease-modifying antirheumatic drugs (bDMARDs) or a synthetic disease-modifying antirheumatic drugs (sDMARD) between 1 July 2012 and 31 December 2018 were included in the analysis. Patients treated only with methotrexate (MTX), acitretin and cyclosporine were not included. Also excluded were patients treated with brodalumab, certolizumab pegol and guselkumab, given their late French approval, occurring after 2018. Patients with only 1 inclusion visit were also excluded. The follow-up was conducted until 31 December 2019.

Demographic variables, including age and sex, were assessed. The study also assessed previous treatments including previous cyclosporine use, previous MTX use and previous phototherapy, concomitant MTX treatment at baseline, body mass index (BMI), main comorbidities (including chronic human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV) infections, psoriatic arthritis (PsA), intestinal bowel disease (IBD), uveitis, diabetes, history of major adverse cardiovascular event (MACE), history of diabetes, dyslipidaemia, chronic obstructive pulmonary disease (COPD), chronic renal failure and positive tuberculous screening), and baseline disease severity according to Psoriasis Area and Severity Index (PASI).

The primary outcome was the rate of drug survival at 1 year, defined by evidence of a switch of treatment, or a discontinuation

of more than 180 days. The covariate of interest was the calendar year of initiation. All patients were censored at 1 year if they had not stopped the treatment. The study also evaluated factors associated with drug survival as exploratory outcomes.

Statistical analysis

Descriptive statistics. Quantitative variables are presented as median (interquartile range; IQR) or mean \pm standard deviation (SD), and categorical variables are presented as absolute values (percentage). The Kaplan–Meier method was used to display the rate of drug survival at 1 year with its 95% confidence interval (95% CI). To avoid informative censorship over time and biased estimators due to discrepancies in the follow-up between the different years of initiation, the study analysed only 1-year drug survival.

Inference. To determine whether the calendar year of initiation would impact the rate of drug survival at 1 year, 2 different models were used (see below). All tests were 2-tailed and p -value < 0.05 were considered significant. All statistics were performed with R software (R CRAN 3.6.2 (R foundation for statistical computing, Vienna, Austria)).

Survival model. Using Kaplan–Meier's method, the crude drug survival rates were calculated for all the treatments during the all-study period (from 2012 to 2018), then per year of initiation. Hazard ratios (HRs) and their 95% confidence interval (95% CI) were then computed using a Cox proportional HR model. The multivariate analysis included the calendar year of initiation and the variables with a known effect on drug survival in the medical literature (6–8), including treatments, previous treatment history, age, sex, body mass index, concomitant MTX, the presence of comorbidities, and PASI at baseline. It was decided not to impute missing data. Interactions were tested. The assumption of proportionality was assessed by visualizing the Schoenfeld residuals and the assumption of log-linearity by visualizing the Martingale residuals.

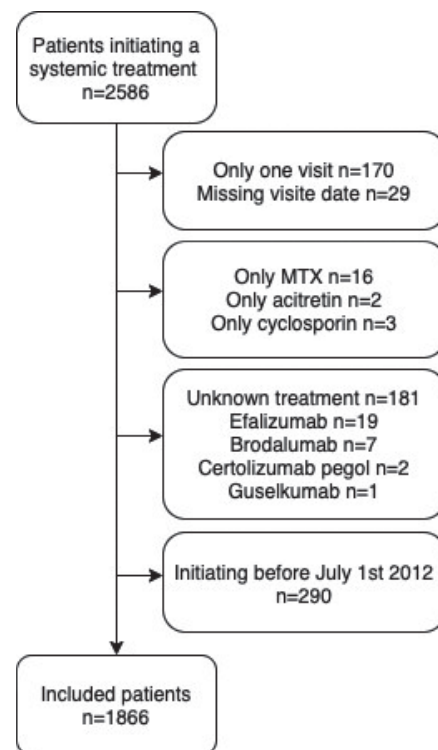


Fig. 1. Flow chart of the included population.

Table I. Characteristics of the included population

| | Overall (n = 1,866) | TNF-inhibitors (n = 1,106) | Ustekinumab (n = 518) | IL17-inhibitors (n = 80) | Apremilast (n = 162) |
|------------------------------------------------------------------|------------------------|-------------------------------|--------------------------|-----------------------------|-------------------------|
| Females, n (%) | 739 (39) | 432 (39) | 200 (39) | 38 (47) | 70 (43) |
| Age, years, median (IQR) | 47 (36–57) | 48 (36–58) | 44.0 (33.3–54.7) | 43.8 (34.2–55.0) | 50.5 (41.3–60.7) |
| BMI, kg/m ² , median (IQR) | 26.7 (23.4–30.8) | 27.0 (23.4–31.1) | 26.0 (23.2–30.1) | 26.8 (24.2–30.8) | 26.7 (23.9–30.5) |
| PASI at baseline (median, IQR) | 9.6 (4.5–15.6) | 10.2 (5.2–16.1) | 8.9 (3.7–15.0) | 9.0 (4.0–19.3) | 7.4 (3.2–13.2) |
| Psoriasis arthritis, n (%) | 343 (19) | 258 (23) | 56 (11) | 8 (10) | 21 (13) |
| Intestinal bowel disease, n (%) | 7 (0.5) | 5 (0.5) | 2 (0.4) | 0 (0) | 0 (0) |
| Uveitis, n (%) | 3 (0.1) | 2 (0.2) | 1 (0.2) | 0 (0) | 0 (0) |
| HIV, n (%) | 7 (0.4) | 3 (0) | 4 (1) | 0 (0) | 0 (0) |
| Hepatitis B virus, n (%) | 20 (1) | 13 (1) | 5 (1) | 0 (0) | 2 (1) |
| Hepatitis C virus, n (%) | 19 (1) | 12 (1) | 4 (1) | 0 (0) | 3 (2) |
| Diabetes, n (%) | 207 (11) | 136 (12) | 46 (9) | 6 (7) | 19 (11) |
| History of MACE, n (%) | 61 (3) | 47 (4) | 6 (1) | 2 (2) | 6 (4) |
| Dyslipidaemia, n (%) | 282 (15) | 186 (17) | 62 (12) | 10 (12) | 24 (15) |
| COPD, n (%) | 66 (4) | 41 (4) | 14 (3) | 1 (1) | 10 (6) |
| Cirrhosis, n (%) | 35 (2) | 28 (3) | 2 (0.4) | 0 (0) | 5 (3) |
| Chronic renal failure, n (%) | 30 (2) | 23 (2) | 5 (1) | 1 (1) | 1 (1) |
| History of tuberculosis, n (%) | 4 (0.2) | 1 (0) | 2 (0.4) | 1 (1) | 0 (0) |
| Positive tuberculosis screening (IFN gamma release assay, n (%)) | 112 (6) | 68 (6) | 33 (6) | 4 (4) | 7 (4) |
| Concomitant MTX at baseline, n (%) | 221 (12) | 145 (13) | 43 (8) | 5 (6) | 28 (17) |
| Previous MTX use, n (%) | 1,113 (59) | 718 (65) | 288 (56) | 35 (44) | 72 (44) |
| Previous cyclosporine use, n (%) | 251 (13) | 154 (14) | 83 (16) | 5 (4) | 9 (6) |
| Previous PUVA therapy, n (%) | 1245 (67) | 752 (68) | 354 (68) | 52 (65) | 87 (54) |

IQR: interquartile range; TNF: tumour necrosis factor; IL: interleukin; BMI: body mass index; PASI: Psoriasis Area and Severity Index; MACE: major adverse cardiovascular event; COPD: chronic obstructive pulmonary disease; IFN: interferon; MTX: methotrexate, PUVA: psoralen plus ultraviolet A.

Subgroup analyses were conducted considering each drug separately (9). For IL-17 inhibitors and apremilast, the study period was from 2016 (date of the first commercialization in France) to 2018. Multivariate analyses could not be performed with IL-17 inhibitors due to small sample sizes.

Time series analysis. Secondly, a linear model was used to determine whether the calendar semesters would impact the rate of drug survival at 1 year. Compared with other former treatments, 2 highly effective bDMARDs treatments were marketed in 2016 (ixekizumab and secukinumab) (4). Thus, 2016 was considered as an intervention date, with a pre-period (from 2012 to 2015) and post-period (from 2016 to 2018). The dependent variable was the drug survival rate at 1 year computed from the Kaplan–Meier representation. The independent variable was the calendar semester of initiation. In case of no change in baseline level nor in trend between the 2 periods, a more parsimonious model was computed, i.e. a simple linear regression with estimation of the trend across the study period. The results are expressed as an estimate coefficient \pm standard error (SE) and its 95% CI. Subgroup analyses were also realized, considering ustekinumab, etanercept and adalimumab separately. Such analyses were not performed for IL-17 inhibitors and apremilast related to the date of the first commercialization (2016).

RESULTS

Population

A total of 1,866 patients were included (**Fig. 1**); 739 females (39%) with a median age of 47 years (IQR 36–57 years). Their characteristics are presented in **Table I**. PsA was found in 343 (19%) patients, and the overall median PASI at baseline was 9.6 (4.5–15.6). Regarding first-line therapy, 1,106 patients (59%) were initially treated with TNF inhibitors, including 665 receiving adalimumab, 389 etanercept and 52 infliximab. A total of 518 patients (28%) received ustekinumab, 80 patients (4%) received an IL-17 inhibitor, including 44 treated with secukinumab

and 36 with ixekizumab. A total of 162 patients (9%) received apremilast. The numbers of patients initiating a first biologic per year and per drug are available in the **Table SI**. A total of 579 patients discontinued their treatment within the first year, indicating a global drug survival rate of 0.67 (95% CI 0.65–0.69) according to the Kaplan–Meier representation. The drug survival of the different treatments is shown in **Fig. S1**. During the study period (2012 to 2018), the crude drug survival rates at 1 year were 0.65 (95% CI 0.62–0.68) for TNF inhibitors, including 0.60 (0.55–0.65) for etanercept, 0.56 (0.44–0.72) for infliximab and 0.69 (0.65–0.72) for adalimumab. The crude drug survival rate at 1 year were 0.84 (95% CI 0.80–0.87), 0.77 (95% CI 0.70–0.86) for ustekinumab and IL17 inhibitors respectively, but only 0.23 (0.17–0.31) for apremilast.

Inference

Regarding the primary outcome, the Kaplan–Meier representation of drug survival according to the calendar year of initiation is shown in **Fig. 2**, indicating no difference according to the year of initiation. The calendar year of initiation was not associated with a reduction in 1-year drug survival over time in multivariate analysis, with HR overlapping from 0.80 (0.42–1.52) to 1.17 (0.64–2.17), and a global *p*-value of 0.63 (**Table II**).

The subgroup analyses considering biological treatments 1 by 1 showed results consistent with the primary analysis (**Fig. 2** and **Table SII**), with HR overlapping from 0.52 (0.22–1.25) to 0.67 (0.28–1.59) for adalimumab, 0.37 (0.12–1.16) to 0.59 (0.10–1.74) for ustekinumab and 0.68 (0.19–2.48) to 1.71 (0.82–3.57) for etanercept. The yearly causes of discontinuation are shown in **Table SII**. Discontinuation because of ineffectiveness appeared

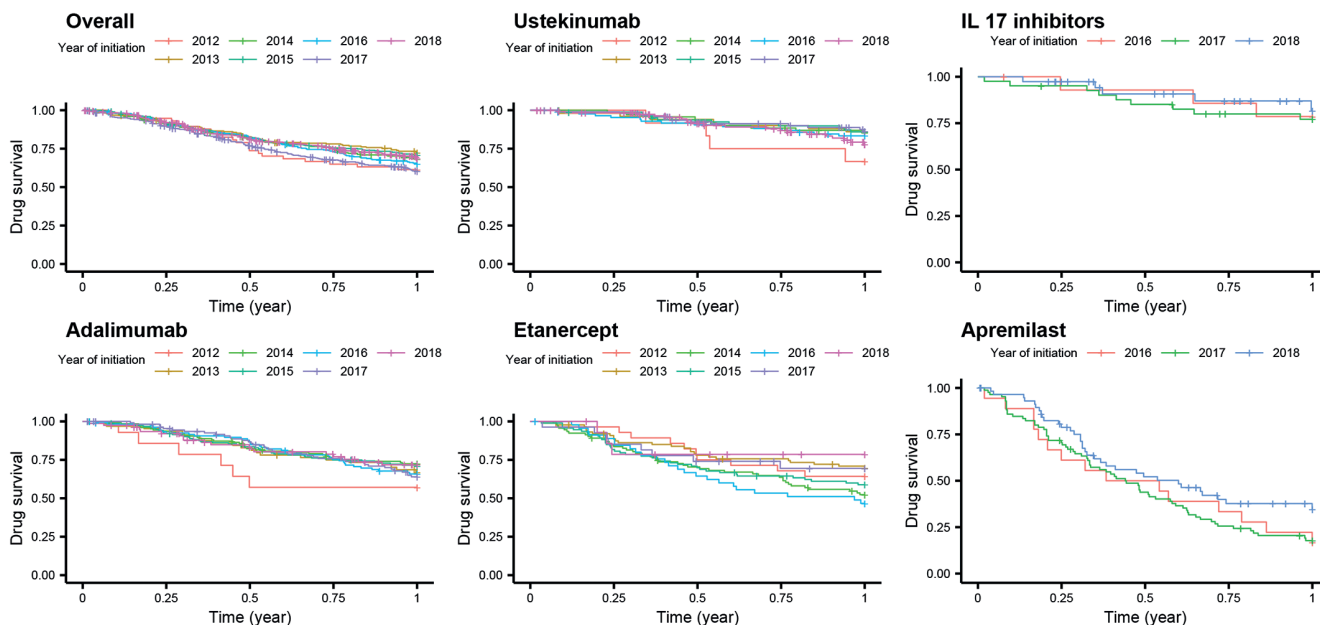


Fig. 2. Kaplan–Meier of drug survival according the calendar year of initiation including overall treatments, ustekinumab interleukin (IL)-17 inhibitors, adalimumab, etanercept and apremilast.

to decrease slightly over time (from 77% in 2012 to 51% in 2018).

The segmented linear regression is represented in **Fig. 3** and **Table III**. Regarding all treatment, there was no significant effect of 2016 on the change in mean drug survival rate at 1 year ($-0.047 \pm 0.063\%$, $p=0.47$), or on

the time trend ($-0.0004 \pm 0.017\%$ per semester, $p=0.98$). A simple linear regression was thus computed, which showed similar results, with a global stability and a trend of $-0.006 \pm 0.004\%$ per semester, $p=0.13$. Subgroup analyses considering ustekinumab, etanercept and adalimumab showed consistent results, with no significant effect of 2016 and a stability over years, except for etanercept with a higher survival drug after 2016 (Fig. 3 and Tables SII–SIV).

Table II. Hazards ratio obtained from Cox model

| | Crude HR (95% CI) | p-value | Adjusted HR (95% CI) | p-value |
|------------------------------------------|----------------------|-----------------------------|-------------------------|-----------------------------|
| Treatment | | < 10⁻⁴ | | < 10⁻⁴ |
| TNF inhibitors | Ref | Ref | Ref | Ref |
| Ustekinumab | 0.40 (0.32–0.51) | < 10⁻⁴ | 0.42 (0.32–0.56) | < 10⁻⁴ |
| IL17 inhibitors | 0.47 (0.27–0.83) | 0.009 | 0.36 (0.18–0.71) | 0.004 |
| Apremilast | 3.42 (2.77–4.21) | < 10⁻⁴ | 3.60 (2.67–4.83) | < 10⁻⁴ |
| Year of initiation | | 0.06 | | 0.63 |
| 2012 | Ref | | Ref | |
| 2013 | 0.67 (0.41–1.09) | | 0.80 (0.42–1.52) | |
| 2014 | 0.79 (0.49–1.25) | | 1.03 (0.56–1.90) | |
| 2015 | 0.71 (0.45–1.13) | | 0.98 (0.53–1.81) | |
| 2016 | 0.88 (0.55–1.40) | | 1.17 (0.64–2.17) | |
| 2017 | 1.02 (0.65–1.60) | | 1.04 (0.56–1.94) | |
| 2018 | 0.78 (0.48–1.24) | | 0.97 (0.51–1.83) | |
| Sex (Female) | 1.51 (1.28–1.78) | < 10⁻⁴ | 1.31 (1.08–1.58) | 0.007 |
| PsA | 1.09 (0.89–1.34) | 0.39 | 0.92 (0.72–1.18) | 0.50 |
| Age, years | 1.01 (1.00–1.02) | 0.007 | 1.00 (0.99–1.01) | 0.35 |
| Body mass index, kg/m² | | 0.003 | | 0.036 |
| < 25 | Ref | Ref | Ref | Ref |
| 25–30 | 1.22 (0.98–1.51) | 0.07 | 1.22 (0.96–1.54) | 0.10 |
| > 30 | 1.45 (1.17–1.79) | 0.0006 | 1.36 (1.07–1.73) | 0.011 |
| Comorbidities | | | | |
| 0 | Ref | Ref | Ref | Ref |
| 1+ | 1.18 (0.99–1.41) | 0.07 | 1.11 (0.89–1.38) | 0.33 |
| Positive TB screening | 0.74 (0.51–1.08) | 0.12 | 0.72 (0.46–1.12) | 0.15 |
| Concomitant MTX at baseline | 1.43 (1.14–1.79) | 0.002 | 1.25 (0.94–1.66) | 0.12 |
| Previous MTX use | 1.17 (0.99–1.39) | 0.06 | 1.10 (0.90–1.35) | 0.34 |
| Previous cyclosporine use | 1.14 (0.90–1.43) | 0.26 | 1.20 (0.91–1.58) | 0.19 |
| Previous PUVA therapy | 0.90 (0.76–1.06) | 0.22 | 1.08 (0.88–1.33) | 0.52 |
| PASI at baseline | 1.00 (0.99–1.01) | 0.26 | 1.01 (0.99–1.02) | 0.15 |

HR: hazard ratio; MTX: methotrexate; PsA: psoriasis arthritis; PUVA: psoralen plus ultraviolet A; TNF: tumour necrosis factor; IL-17: interleukin-17; TB: tuberculosis; PASI: Psoriasis Area and Severity Index. Bold: p-value < 0.05.

Factors associated with drug survival during the study period

Regarding treatments, ustekinumab and IL-17 inhibitors were associated with a decreased risk of discontinuation compared with TNF inhibitors with HR of 0.42 (0.32–0.56), $p < 10^{-4}$ and 0.36 (0.18–0.71), $p=0.004$, respectively. In contrast, apremilast was associated with an increased risk of discontinuation, with an HR of 3.60 (2.67–4.83), $p < 10^{-4}$. Regarding clinical factors associated with drug survival, female sex and BMI > 30 kg/m² were associated with an increased risk of discontinuation with respective HR of 1.31 (1.08–1.58), $p=0.007$ and 1.36 (1.07–1.73), $p=0.011$ in multivariate analysis.

DISCUSSION

This large real-life setting study, did not find any association between calendar year of initiation and drug survival among patients with moderate to severe psoriasis conducting a multivariate Cox model and a segmented linear regression.

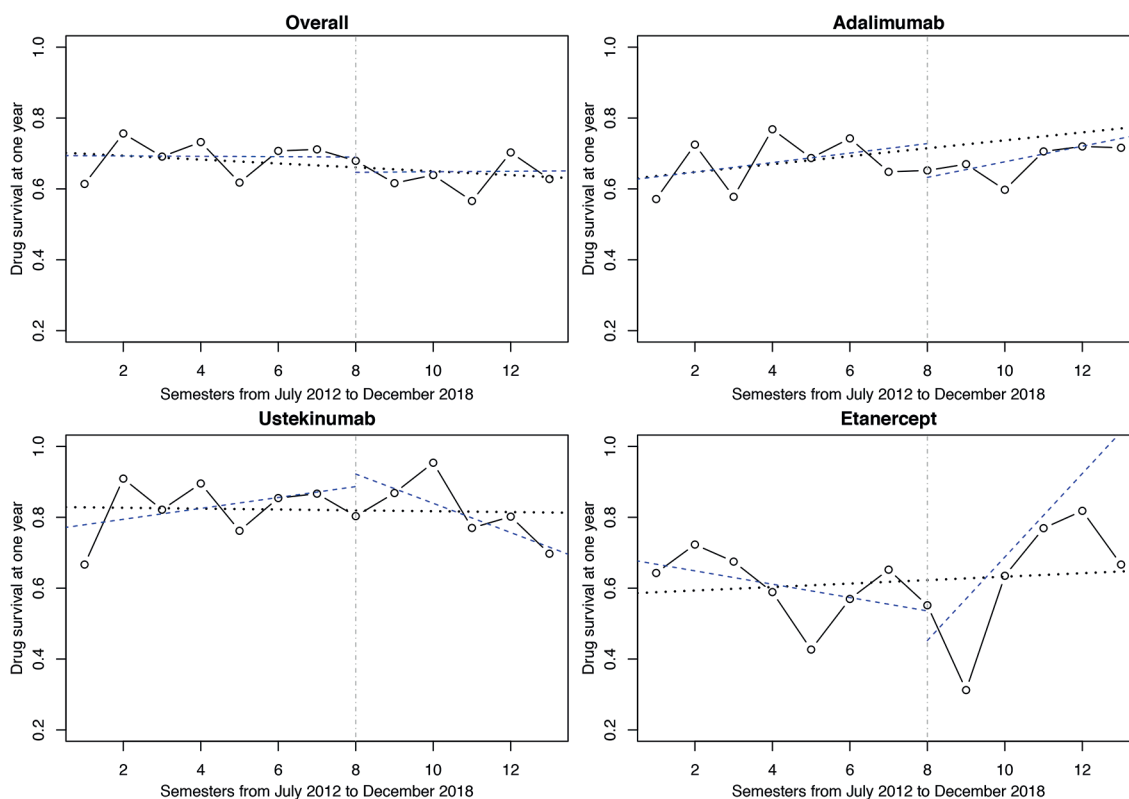


Fig. 3. Drug survival rate at 1 year according to the calendar semester of initiation including overall treatments, adalimumab, ustekinumab and etanercept. Blue dotted line: segmented linear regression. Black dotted line: simple linear regression.

Regarding precisely the risk of drug discontinuation over time, the results of this study seem to be at variance with those of Shalom et al. (10) and Graier et al. (13), who reported that the calendar year of initiation was associated with an increased risk of discontinuation, particularly after the marketing of IL-17 inhibitors, using a Cox model and a Kaplan–Meier representation (10, 13). In this study, the authors assessed the drug survival for patients with psoriasis treated with biologics, irrespective of the number of treatment lines already received. To take into account time-period effects from the release of new drugs, they defined 2 periods; before and after 2016. Biologics’ drug survival decreased over time at an overall relative HR of 1.5 for the time-period (before and after 2016). However, interdependence analysis on drug survival using Cox regression revealed no treatment-independent effects of time-period. Such results were consistent with the current analyses. Moreover, contrary to Graier et al. (13),

we adjusted for many confounders in order to assess the effect of the calendar year of initiation. The current results were also confirmed when we replicated the analyses for each biological agent. Therefore, the current findings suggest that, against the odds, drug survival of patients with moderate to severe psoriasis is not sensitive to the increasing therapeutic armamentarium, and that patients do not discontinue their treatments due to a high number of alternatives, but mostly in case of a suboptimal effectiveness/adverse reactions balance. Nevertheless, regarding etanercept specifically and contrary to expectations, an increasing survival rate was found after 2016. This may be explained by a sampling fluctuation in line with the decreasing number of patients treated with etanercept over years, making its drug survival less robust/precise than other treatments.

Moreover, contrary to Graier et al. (13), we adjusted for many confounders in order to assess the effect of the calendar year of initiation. The current results were also confirmed when we replicated the analyses for each biological agent. Therefore, these findings suggest that, against the odds, drug survival of patients with moderate to severe psoriasis is not sensitive to the increasing therapeutic armamentarium, and that patients do not discontinue their treatments due to a high number of

Table III. Segmented linear regression regarding overall treatments

| Rate of drug survival | Coefficient | SE | (95% CI) | p-value |
|--------------------------------------------------------|-------------|-------|---------------|----------------------------|
| Full model: segmented linear regression (2012 to 2018) | | | | |
| Baseline level, β_0 | 0.69 | 0.05 | (0.59–0.80) | <10⁻⁴ |
| Baseline trend, β_1 | -0.0005 | 0.01 | (-0.02–0.02) | 0.96 |
| Change in level after 2016, β_2 | -0.05 | 0.06 | (-0.19–0.09) | 0.47 |
| Change in trend after 2016, β_3 | -0.0004 | 0.02 | (-0.04–0.04) | 0.98 |
| Final model*: simple linear regression (2001 to 2019) | -0.006 | 0.004 | (-0.01–0.002) | 0.13 |
| Trend | | | | |

SE: standard error; 95% CI: 95% confidence interval. Significant value is given in bold.

alternatives, but mostly in case of a suboptimal effectiveness/adverse reactions balance. Nevertheless, regarding etanercept specifically, and contrary to expectations, the results showed an increasing survival rate after 2016. This may be explained by a sampling fluctuation in line with the decreasing number of patients treated with etanercept over years, making its drug survival less precise than other treatments.

This study confirms the good and similar drug survival of IL-17 inhibitors and ustekinumab (14). It also confirms the poor drug survival of apremilast, already observed by Sbidian et al. (15) compared with methotrexate. Here, the results are unambiguous compared with biologics, indicating its difficult placing in the increasing therapeutic armamentarium. These observations may be in line with the lower efficacy compared with biologics and with the higher rate of adverse events, with 79% of patients presenting at least one adverse event in the ESTEEM-1 trial (16).

Regarding age, sex and prevalence of PsA, the current results were similar to those of other cohorts (6–8). Nonetheless, in the current study, the overall mean retention rate is 0.67 at 1 year, which is lower than the 2 drug survival studies of the BADBIR cohort, with 0.77 and 0.79 retention rates at 1 year (6, 7), and the BIOBADADERM cohort, with 0.79 drug survival at 1 year (8). This difference is partially explained by the inclusion of apremilast and etanercept in the current model, which are likely to be associated with a decreased survival compared with other systemic treatments (15, 18). Nonetheless, taking separately, the mean retention rate at 1 year of adalimumab, ustekinumab or IL17 inhibitors are still lower than the BADBIR study, with 0.78 (0.77–0.79), 0.88 (0.87–0.89) and 0.88 (0.86–0.91), respectively. Hence, this difference might also be explained by a lower overall drug survival in France compared with other European countries, potentially associated with the particularities of the French health system (9).

Strengths

This study has several strengths. The first is its prospective large scale, associated with the real-life setting, as well as the capture of many clinical parameters, which are relevant in order to investigate drug survival. Moreover, the use of 2 different statistical models and sensitivity analyses, resulting in no effect of the calendar year of initiation on drug survival, strengthens these findings.

Limitations

This study also has several limitations. The first is a potential lack of power, mostly for subgroup analyses, due to scarce number of patients. Moreover, we cannot exclude that the profile of patients receiving bDMARDs and sDMARDs has changed over the years. Nevertheless, the analyses were adjusted on potential confounders, but

could not include the Dermatology Life Quality Index (DLQI) because of too many missing values. Moreover, this study does not capture pharmacokinetics/pharmacodynamics parameters that could be relevant for drug discontinuation, especially the drug concentrations, such as the presence of antibodies. In addition, the study considered only first-line therapies in the analyses, but no second- or third-line therapies, whereas refractory patients with many previous therapeutic failures may be maintained on their treatment due to a lack of alternatives, and be switched to better ones after their approval. Last, but not least, it cannot be excluded that the length of study is insufficient over years, and that drug survival would decrease for patients initiating a treatment after 2018, e.g. in 2019 or 2020 and subsequent years, or after 1 year of follow-up, mainly because of the marketing of IL23p19 inhibitors.

Conclusion

Despite the increasing therapeutic armamentarium over the years, the calendar year of initiation does not seem to have any impact on drug survival in patients with moderate to severe psoriasis, which seems more linked to treatment, sex, or obesity. This finding suggests that drug survival of patients with moderate to severe psoriasis is not sensitive to this increasing armamentarium, and therefore strengthens its use to estimate balance between treatment effectiveness and adverse reactions over time. Nonetheless, they require confirmation on larger cohorts or databases with an extended follow-up.

ACKNOWLEDGEMENTS

This work was supported by unrestricted research grants from the French Ministry of Health (PHRC AOM 09 195), the French National Agency for the Safety of Medicines and Health Products (ANSM), Abbvie, Janssen, Pfizer, MSD France, Lilly France, Novartis Pharma, Celgene, Leo Pharma and Amgen. None of the private funders had any role in the design of this ancillary study, data management, analysis and interpretation of the data, preparation or approval of this manuscript or decision to submit this manuscript for publication. They received the manuscript before submission for information purposes. The study was sponsored by the Département a la Recherche Clinique et au Développement (DRCD – Department for Clinical Research and Development), Assistance Publique–Hopitaux de Paris (Paris Hospitals). This study has been supported by the French Society of Dermatology and its Psoriasis Research Group. The study protocol was approved by the "Comite d'Evaluation de l'Ethique des Projets de Recherche Biomedicale (CEERB) du GHU Nord" [Institutional Review Board (IRB) of Paris North Hospitals, Paris 7 University, AP-HP], (authorization number JMD/MDM/177-11) registered on ClinicalTrials.gov under the reference NCT01617018. The authors acknowledge Nessima Yelles, Sarra Pochon, Hadia Hafirassou, from the centre de pharmaco-épidémiologie de l'AP-HP for the implementation, management and monitoring of the study, and Yann De Rycke for data management and statistical analysis coordination.

Conflicts of interest: CP has been an investigator and consultant for AbbVie, Amgen, Boehringer Ingelheim, Celgene, GSK, Janssen,

LEO Pharma, Lilly, Novartis and Pfizer. HB has undertaken activities as a paid consultant, advisor or speaker for Abbvie, Ammirall, Amgen, Baxalta, Biogen, Boehringer Ingelheim, Celgene, Janssen, Leo Pharma, Lilly, Novartis, Pfizer, UCB and Sun Pharmaceuticals. He has also received grant funding from Pfizer; MB-B offers a consultancy service and is an investigator for Abbvie, Amgen, Celgene, Janssen, Leo Pharma, Lilly, MSD, Novartis and Pfizer; MV has undertaken activities as a paid consultant, advisor or speaker for Janssen, Abbvie, MSD, Pfizer, Leo Pharma, Medac, Boehringer Ingelheim, Novartis, Lilly and Arrow. EM is a consultant for Novartis, Abbvie, Pfizer and Janssen, has also been an investigator for Leo Pharma, Amgen, AstraZeneca, Abbvie, Novartis and Pfizer, and has received speaker remuneration from Abbvie, Janssen, Novartis and Pfizer. NB has been an investigator for Pfizer and Novartis. She is a consultant for Janssen and has received speaker remuneration from Janssen. DDJ is a consultant for MEDAC UCB Fresenius Kabi, Biogen, Abbvie, Celgen, Novartis, Lilly, Janssen, Pfizer and MSD. MAR is a consultant for Pfizer, Leo Pharma, Janssen, Galderma, Abbvie, Novartis, Pierre Fabre, Merck and BMS. PJ is a consultant for Roche, GSK, Lilly, Principabio and Sanofi Aventis. FT is Head of the Clinical Research Unit at Pitie-Salpetrière Hospital and the Centre de Pharmacologie epidemiologie (Cephepi) (Pharmaco-epidemiology Centre) of the Assistance Publique – Hôpitaux de Paris (Paris Hospitals). She has received research funding, grants and fees for consultancy activities from a large number of pharmaceutical companies that have contributed to employee salaries. FT is not employed by these structures and did not receive any personal remuneration from these companies. OC is a member of the PsoBioTeq cohort scientific committee, OC is the principal investigator. The PsoBioTeq cohort is supported by unrestricted research grants from the French Ministry of Health (PHRC AOM 09 195), the French agency for drugs (ANSM), Abbvie, Janssen, Pfizer, and MSD France. The PsoBioTeq cohort study is part of its pharmaceutical industry partners, on the request of the Haute Autorité de Santé. The sponsor is the Département à la Recherche Clinique et au Développement (DRCD), Assistance Publique–Hôpitaux de Paris. The PsoBioTeq cohort stands under the umbrella of the French Society of Dermatology and its Groupe de Recherche sur le Psoriasis. *The other authors have no funding or conflicts of interest to declare.*

REFERENCES

- Grodner C, Sbidian E, Weill A, Mezzarobba M. Epidemiologic study in a real-world analysis of patients with treatment for psoriasis in the French national health insurance database. *J Eur Acad Dermatol Venereol* 2021; 35: 411–416.
- Parisi R, Symmons DPM, Griffiths CEM, Ashcroft DM, Identification and management of psoriasis and associated Comorbidity (IMPACT) project team. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. *J Invest Dermatol* 2013; 133: 377–385.
- Sbidian E, Le Cleach L, Trinquart L, Do G, Hughes C, Naldi L, et al. Systemic pharmacological treatments for chronic plaque psoriasis. *Cochrane Skin Group*, editor. *Cochrane Database Syst Rev* 2015 Feb 16 [cited 2020 Nov 1]; Available from: <http://doi.wiley.com/10.1002/14651858.CD011535>.
- Sbidian E, Chaimani A, Afach S, Doney L, Dressler C, Hua C, et al. Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis. *Cochrane Database Syst Rev* 2020; 1: CD011535.
- Lin P-T, Wang S-H, Chi C-C. Drug survival of biologics in treating psoriasis: a meta-analysis of real-world evidence. *Sci Rep* 2018; 8: 16068.
- Warren RB, Smith CH, Yiu ZZN, Ashcroft DM, Barker JNWN, Burden AD, et al. 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). *J Invest Dermatol* 2015; 135: 2632–4260.
- Yiu ZZN, Mason KJ, Hampton PJ, Reynolds NJ, Smith CH, Lunt M, et al. Drug survival of adalimumab, ustekinumab and secukinumab in patients with psoriasis: a prospective cohort study from the British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR). *Br J Dermatol* 2020; 183: 294–302.
- Dávila-Seijo P, Dauden E, Carretero G, Ferrandiz C, Vanaclocha F, Gómez-García F-J, et al. Survival of classic and biological systemic drugs in psoriasis: results of the BIOBADADERM registry and critical analysis. *J Eur Acad Dermatol Venereol* 2016; 30: 1942–1950.
- Sbidian E, Mezzarobba M, Weill A, Coste J, Rudant J. Persistence of treatment with biologics for patients with psoriasis: a real-world analysis of 16 545 biologic-naïve patients from the French National Health Insurance database (SNIIRAM). *Br J Dermatol*. 2019; 180: 86–93.
- Shalom G, Cohen AD, Feldhamer I, Comaneshter D, Freud T, Pavlovsky L. Drug survival in patients with psoriasis is associated with the availability of biologic medications. *J Eur Acad Dermatol Venereol* 2020; 34: 1524–1528.
- Masson Regnault M, Castañeda-Sanabria J, Diep Tran MHT, Beylot-Barry M, Bachelez H, Beneton N, et al. Users of biologics in clinical practice: would they be eligible for phase III clinical studies? Cohort Study in the French Psoriasis Registry PSOBIOIOTEQ. *J Eur Acad Dermatol Venereol* 2020; 34: 293–300.
- Sbidian E, Giboin C, Bachelez H, Paul C, Beylot-Barry M, Dupuy A, et al. Factors associated with the choice of the first biologic in psoriasis: real-life analysis from the PsoBioTeq cohort. *J Eur Acad Dermatol Venereol* 2017; 31: 2046–2054.
- Graier T, Salmhofer W, Jonak C, Weger W, Kölli C, Gruber B, et al. Biologic drug survival rates in the era of anti-IL-17 antibodies: a time period-adjusted registry analysis. *Br J Dermatol* 2021; 184: 1094–1105.
- Phan C, Beauchet A, Burztejn A-C, Severino-Freire M, Barbarot S, Girard C, et al. Biological treatments for paediatric psoriasis: a retrospective observational study on biological drug survival in daily practice in childhood psoriasis. *J Eur Acad Dermatol Venereol* 2019; 33: 1984–1992.
- Sbidian E, Billionnet C, Weill A, Maura G, Mezzarobba M. Persistence of apremilast in moderate-to-severe psoriasis: a real-world analysis of 14 147 apremilast- and methotrexate-naïve patients in the French National Health Insurance database. *Br J Dermatol* 2020; 182: 690–697.
- Papp K, Reich K, Leonardi CL, Kircik L, Chimenti S, Langley RGB, et al. Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, in patients with moderate to severe plaque psoriasis: Results of a phase III, randomized, controlled trial (Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis [ESTEEM] 1). *J Am Acad Dermatol* 2015; 73: 37–49.
- Carrascosa JM, Vilavella M, Garcia-Doval I, Carretero G, Vanaclocha F, Daudén E, et al. Body mass index in patients with moderate-to-severe psoriasis in Spain and its impact as an independent risk factor for therapy withdrawal: results of the Biobadaderm Registry. *J Eur Acad Dermatol Venereol* 2014; 28: 907–914.
- Egeberg A, Ottosen MB, Gniadecki R, Broesby-Olsen S, Dam TN, Bryld LE, et al. Safety, efficacy and drug survival of biologics and biosimilars for moderate-to-severe plaque psoriasis. *Br J Dermatol* 2018; 178: 509–519.