JIDOpen

# Differential Drug Survival of Second-Line Biologic Therapies in Patients with Psoriasis: Observational Cohort Study from the British Association of Dermatologists Biologic Interventions Register (BADBIR)

Ireny Y.K. Iskandar[1], Richard B. Warren[2,3], Mark Lunt[4], Kayleigh J. Mason[3], Ian Evans[4], Kathleen McElhone[3], Catherine H. Smith[5], Nick J. Reynolds[6,7], Darren M. Ashcroft[1,8] and Christopher E.M. Griffiths[2,3,8], the BADBIR Study Group

Little is known about the drug survival of second-line biologic therapies for psoriasis in routine clinical practice. We assessed drug survival of second-line biologic therapies and estimated the risk of recurrent discontinuation due to adverse events or ineffectiveness in psoriasis patients who had failed a first biologic and switched to a second in a large, multicenter pharmacovigilance registry (n = 1,239; adalimumab, n = 538; etanercept, n = 104; ustekinumab, n = 597). The overall drug survival rate in the first year after switching was 77% (95% confidence interval = 74–79%), falling to 58% (55–61%) in the third year. Female sex, multiple comorbidities, concomitant therapy with cyclosporine, and a high Psoriasis Area and Severity Index at switching to the second-line biologic were predictors of overall discontinuation (multivariable Cox proportional hazard model). Compared to adalimumab, patients receiving etanercept were more likely to discontinue therapy (hazard ratio = 1.95, 95% confidence interval = 1.46–2.59), whereas patients receiving ustekinumab were more likely to persist (hazard ratio = 0.46; 95% confidence interval = 0.37–0.58). Discontinuation of the first biologic because of adverse events was associated with an increased rate of second drug discontinuation because of adverse events (hazard ratio = 2.48; 95% confidence interval = 1.48–4.16). In conclusion, drug survival rates differed among biologics and decreased over time; second-line discontinuation because of adverse events was more common among those who discontinued first-line treatment for this reason. The results of this study should support clinical decision making when choosing second-line biologic therapy for patients with psoriasis.

*Journal of Investigative Dermatology* (2017) ■, ■–■; doi:10.1016/j.jid.2017.09.044

## INTRODUCTION

Biologic therapies have markedly improved the management of moderate to severe psoriasis. The efficacy of these therapies has been established in large randomized clinical trials, with up to 88% of patients achieving at least a 75% improvement in the Psoriasis Area Severity Index (Nast et al., 2015; Reich et al., 2012). In addition, several prospective cohort studies have also shown the effectiveness of these therapies in routine clinical practice (Iskandar et al., 2017b; Norlin et al., 2012; Strober et al., 2016; Zweegers et al., 2016a).

Despite these impressive findings, approximately 11–35% of patients fail their first biologic therapy during the first year of treatment, either because of ineffectiveness or following the development of adverse events (AEs) (Warren et al., 2015). Switching biologic therapies on treatment failure is common (Iskandar et al., 2017a; Leman and Burden, 2012; Norlin et al., 2012), with several studies suggesting that

[1]*Centre for Pharmacoepidemiology and Drug Safety, Division of Pharmacy and Optometry, School of Health Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, UK;* [2]*Dermatology Centre, Salford Royal NHS Foundation Trust, The University of Manchester, Manchester Academic Health Science Centre, Manchester, UK;* [3]*Arthritis Research UK Epidemiology Unit, Centre for Musculoskeletal Research, Manchester Academic Health Science Centre, The University of Manchester, Manchester, UK;* [4]*Division of Musculoskeletal and Dermatological Sciences, School of Biological Sciences and NIHR Manchester Biomedical Research Centre, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, UK;* [5]*St. John's Institute of Dermatology, Guy's and St Thomas' NHS Foundation Trust, London, UK;* [6]*Institute of Cellular Medicine, Medical School, Newcastle University, NIHR Newcastle Biomedical Research Centre Newcastle upon Tyne, UK; and* [7]*Department of Dermatology, Royal Victoria Infirmary, Newcastle Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK*

[8]*These authors contributed equally to this work as senior authors.*

*Correspondence: Christopher E.M. Griffiths, The Dermatology Centre, Barnes Building, Salford Royal NHS Foundation Trust, Manchester, M6 8HD, UK. E-mail: christopher.griffiths@manchester.ac.uk or Ireny Y.K. Iskandar, Centre for Pharmacoepidemiology and Drug Safety, Division of Pharmacy and Optometry, The University of Manchester, Room 1.134, 1st Floor, Stopford Building, Oxford Road, Manchester, M13 9PT, UK. E-mail: ireny.iskandar@manchester.ac.uk*

*Abbreviations: AE, adverse event; BADBIR, British Association of Dermatologists Biologic Interventions Register; CI, confidence interval; HR, hazard ratio; PASI, Psoriasis Area and Severity Index; TNFI, tumor necrosis factor inhibitors*

*Received 14 April 2017; revised 31 August 2017; accepted 22 September 2017; accepted manuscript published online XXX; corrected proof published online XXX*







FLA 5.5.0 DTD ■ JID1131_proof ■ 16 November 2017 ■ 11:33 am ■ ce

initiating therapy with a second biologic is beneficial (Clemmensen et al., 2011; Downs, 2010; Gottlieb et al., 2012; Lecluse et al., 2009; Mazzotta et al., 2009; Ortonne et al., 2011; Van Lümig et al., 2010). However, to date, these studies have included relatively small numbers of patients (range = 10–282 patients), which makes it difficult to establish a substantive estimate of the risk of recurrent discontinuation because of AEs or ineffectiveness. Furthermore, the optimal choice of the subsequent treatment in those patients who fail or who are intolerant of the first-line biologic treatment is not established (Mauskopf et al., 2014).

Drug survival is a comprehensive measure of drug effectiveness, safety, and real-world utility (van den Reek et al., 2015a). Several studies reported on drug survival with biologic therapies among patients previously exposed to biologic therapies. Four of these studies have reported only on drug survival with tumor necrosis factor inhibitors (TNFIs) (Brunasso et al., 2012; Gniadecki et al., 2011; Inzinger et al., 2016; Menting et al., 2014), two studies involved the Danish National Psoriasis Biologic Safety Registry Data (Gniadecki et al., 2011, 2015), one study involved the PSOriasis Longitudinal Assessment and Registry (Menter et al., 2016), and the other studies reported data from either a single or a limited number of dermatology centers (López-Ferrer et al., 2013; Umezawa et al., 2013; van den Reek et al., 2015b; van den Reek et al., 2014a; Zweegers et al., 2016b). The findings from these studies differ markedly; for instance, Menting et al. (2014) reported that drug survival did not differ significantly between biologic therapies among patients previously exposed to biologics, whereas Gniadecki et al. (2015) found that the survival of ustekinumab was equal to that of adalimumab and infliximab but superior to that of etanercept. More recently, Menter et al. (2016) found that ustekinumab had superior drug survival compared with infliximab, adalimumab, and etanercept. Moreover, none of these studies took into consideration that the threshold for drug discontinuation may change over time (Dávila-Seijo et al., 2016) or investigated whether the reason for failing the first-line biologic therapy is predictive of the clinical outcome in patients receiving a second biologic. Furthermore, Menter et al. (2016) included that patients who could have discontinued their previous biologic therapy before enrollment into the register; this has the potential to introduce a source of bias due to left censorship.

Therefore, a number of clinically important questions remain unanswered. First, drug survival with second-line biologic therapies in routine clinical practice needs further exploration. In doing so, the effect of the increasing number of biologics available to treat psoriasis in recent years and their effect on the threshold for drug discontinuation need to be considered (Dávila-Seijo et al., 2016). In addition, the risk of recurrent discontinuation because of AEs or ineffectiveness and whether the reason for failing a first biologic is predictive of failure of a second is unknown and warrants investigation.

The British Association of Dermatologists Biologic Interventions Register (BADBIR) is a UK and Republic of Ireland prospective, longitudinal pharmacovigilance register. This represents an ideal resource to assess real-world drug survival with second-line biologic therapies for psoriasis because of its large size, a rigorous data collection process, inclusion of clinically relevant covariates, and high external validity through participation of 153 dermatology centers (Burden et al., 2012). In this cohort study, we examined the comparative drug survival with second-line use of adalimumab, etanercept, and ustekinumab and identified clinically relevant risk factors for drug discontinuation. We also estimated the risk of recurrent discontinuation because of AEs or ineffectiveness.

## RESULTS

From a prospective cohort of 6,109 biologic-naïve patients with psoriasis, we identified a total of 1,239 (adalimumab, n = 538; etanercept, n = 104; ustekinumab, n = 597) who failed their first biologic therapy and were switched to a second while under follow-up in the BADBIR (Figure 1). Overall, 1,181 (95%) of these patients failed first-line TNFIs, and 47 (4%) and 11 (1%) patients failed first-line ustekinumab or other biologics, respectively (see Supplementary Table S1 online). Patients who failed first-line TNFIs were switched to second-line ustekinumab (50%), adalimumab (42%), and etanercept (8%); 89% and 46% of patients failing first-line ustekinumab and other biologics were switched to second-line adalimumab and etanercept, respectively (see Supplementary Table S1). In total, 941 (76%) of those patients who were switched to second-line biologics discontinued the first biologic because of ineffectiveness, whereas 154 (12%) and 144 (12%) patients discontinued the first biologic because of the development of AEs or for other reasons, respectively (see Supplementary Table S2 online).

At the time of switching to a second biologic, the mean ± standard deviation age of patients was 46.3 ± 12.8 years, with 42% female. The mean PASI and Dermatology Life Quality Index were 12.4 ± 9.8 and 13.3 ± 13.7, respectively. Overall, 285 (23%) patients reported having psoriatic arthritis (PsA), and 70% reported having one or more comorbidities other than PsA. Baseline (at the time of switching) demographic and disease characteristics are summarized in Table 1.

### Drug survival with second-line biologic therapies

Drug survival data for second-line biologic therapies were available for a mean ± standard deviation, total follow-up, and range of follow-up time of 2.7 ± 1.6; 2,405.7; and 0.5–7.8 person-years, respectively, with a mean ± standard deviation follow-up time for patients receiving adalimumab of 3.2 ± 1.7 years, those receiving etanercept of 2.7 ± 1.6 years, and those receiving ustekinumab of 2.3±1.3 years. Over the time frame of the study, 457 of 1,239 patients (37%) discontinued their second biologic therapy.

Kaplan-Meier survival analyses (Table 2) found an overall survival rate of 77% (95% confidence interval [CI] = 74–79%) one year after switching, falling to 58% (55–61%) at 3 years. For individual biologics, the 1-year survival rate for ustekinumab was 85% (82–87%), for adalimumab was 74% (70–77%), and for etanercept was 49% (39–58%), falling to 73% (68–77%), 50% (46–55%), and 25% (14–37%), respectively, at 3 years (Figure 2a). One year after starting therapy with second-line biologics, 15% (13–17%) of patients discontinued therapy because of ineffectiveness, 5% (4–7%) because of AEs, and 3% (2–4%) for





FLA 5.5.0 DTD ■ JID1131_proof ■ 16 November 2017 ■ 11:33 am ■ ce