Survival of Second-Line Biologics in Psoriasis: The British BADBIR Registry Data Informs Daily Practice

Alexander A. Navarini¹,² and Lars E. French¹,²

Psoriasis is one of the most chronic diseases in dermatology. Only a small percentage of patients ever experience relapse-free survival. The constant presence of plaques and comorbidities that affect the cardiovascular system, joints, and other organs greatly impair patients’ quality of life. In addition, the life expectancy of psoriatic patients is shortened by several years. Hence, long-term and ideally systemic treatment with minimal adverse effects may be warranted.

The advent of biologics has transformed the treatment of psoriasis. Drugs that are suitable for long-term treatment are now available. In the initial years of biologic treatment, scientific and clinical interest focused mostly on short-term efficacy and safety. In the meantime, the number of biologics and targeted therapies for psoriasis therapy has greatly increased, and all have achieved the basic premises of adequate efficacy and safety. Etanercept, the oldest biologic for psoriasis on the market, achieves a reported 75% reduction of psoriasis activity and severity (PASI75) in 38% of patients within 12 weeks (Van De Kerkhof et al., 2008). In contrast, ixekizumab and secukinumab, the “new biologics on the block,” achieve the PASI75 threshold in 80–90% of patients (Gordon et al., 2016; Langley et al., 2014).

Even though short-term PASI reduction is easy to measure and has become our criterion standard for assessing the efficacy of psoriasis drugs, it may not be the most relevant measure of efficacy for patients. Indeed, the MAPP study (Lebwohl et al., 2014) has indicated that other factors are crucial from a patient’s perspective, including long-term safety and efficacy. A large percentage of patients who suffer from psoriasis and psoriatic arthritis are dissatisfied with the long-term safety of not only conventional oral therapy (34–50%) but also modern biologic therapy (32–53%) (Lebwohl et al., 2014, 2016; van de Kerkhof et al., 2015).

Classical randomized controlled clinical trials offer limited information on long-term effects of drugs because of study design and demographics of the study populations. To answer these questions, high-quality prospective patient registries are of great utility. Fortunately, registries are now components of national psoriasis care efforts in many countries (Maul et al., 2016). The British Association of Dermatologists Biologic Interventions Register (BADBIR) registry is one such registry, and it is one of the largest worldwide. Because of its size and structure, BADBIR provides the statistical power to study events that do not occur in all patients, including rare and/or delayed adverse effects, and the treatment outcomes of patients switched from one biologic treatment to another. BADBIR currently includes data from more than 9,000 patients treated at more than 100 centers in the United Kingdom. BADBIR, in conjunction with the German psoriasis registry PsoBest (n = 7,000) (Reich et al., 2015) and other European registries, has provided evidence in recent years that the safety of biologics is at least comparable to that of conventional therapies with respect to serious infections (Yiu et al., 2017), although combinations of biologics with methotrexate further increase the risk of infections (Davila-Seijo et al., 2017).

Comparative long-term efficacy in the real life situation is also best depicted by prospective registries. Analysis of the length of time from initiation to discontinuation of a therapy, also known as drug survival, is an interesting way to express the practical long-term effectiveness, tolerability, and safety of drugs (van den Reek et al., 2015). Drug survival describes how long a selected drug is administered continuously to a given patient within a registry, assuming (but not actually measuring) successful control of psoriasis. Drug discontinuation is defined as withdrawal of the treatment for a period of more than 90 days (Glintborg et al., 2013). Drug survival is a comprehensive measure that provides an indication of efficacy and safety and, in addition, some indication of the preferences of physicians and patients.

In 2015, BADBIR investigators reported drug survival in biologics-naïve patients (Warren et al., 2015) and provided real life evidence that overall drug survival of biologics in psoriasis decreases from 77% in the first year to 53% in the third year. Ustekinumab’s survival was higher than any of the tumor necrosis factor antagonists, even after correction for clinical factors that may have potentially contributed to bias. This effect was also confirmed in other patient registry studies (Gniadecki et al., 2015; van den Reek et al., 2015).

Regardless of the drug, these studies indicate that survival with biological drugs, despite their interesting efficacy and safety profiles, is not unlimited. Up to one third of patients interrupt therapy with their first biologic within the first year of treatment. When should these...
Clinical Implications

- Ustekinumab has a longer drug survival rate than tumor necrosis factor antagonists when given as a first and as a second biologic treatment.
- The survival rates of biologics are similar when the drugs are used as first or second biologics.
- Treatment with biologics is discontinued more often because of loss of efficacy than because of an adverse event.
- Patients who discontinue an initial biologic because of an adverse event are likely to discontinue a second biologic because of an adverse event.

Patients be transitioned to a second biologic, and what is the expected outcome? Do patients experiencing a failure of the first biologic also have a high chance of failing the second, that is, because of rapid production of product antibodies or other resistance mechanisms? Do all biologics given in second instances perform similarly?

In this issue, Iskandar and colleagues (2018) of the BADBIR study group provide data addressing these questions. They studied drug survival of biologics in chronic plaque-type psoriasis patients who experienced failure of their first-line biologic drug by analyzing data collected within the multicenter UL pharmacovigilance register BADBIR. Included in the analysis were more than 1,239 psoriasis patients (43.4% receiving adalimumab, 8.4% receiving etanercept, and 48.2% receiving ustekinumab) for whom the first biologic had failed and who had switched to a second-line biologic. Overall, 76% of these individuals had discontinued the first biologic because of inefficacy and 12% as the consequence of an adverse event.

The overall drug survival rate within this cohort of 1,239 patients receiving second-line biologics at the end of the first year was shown to be 77% (95% confidence interval = 74–79%) and 58% (55–61%) at the end of the third year. The first year data, although not directly comparable, are in line with previous BADBIR drug survival analysis data published for first-line biologics patients described earlier (Warren et al., 2015). Thus, and importantly from a practical perspective, although drug survival decreases over time, drug survival rates appear to be similar at 1 year in patients receiving their first or second biologic.

Iskandar et al. (2018) also searched the BADBIR registry data for factors that may be predictors of drug discontinuation in the described patient cohort. Females and patients with multiple (3–4) comorbidities, concomitant therapy with cyclosporine, and a high PASI at the time of switching to the second biologic drug had lower drug survival, and these were considered to be predictors of overall discontinuation.

Drug-related differences in drug survival in the context of second-line biologic therapy were also analyzed, and when compared with adalimumab, patients receiving ustekinumab were more likely to continue therapy (longer drug survival), whereas those receiving etanercept were less likely to continue therapy (shorter drug survival). For individual biologics, the 1-year survival rate for ustekinumab was 85%, followed by adalimumab at 74% and etanercept at 49%. In addition, when the first biologic had been discontinued because of an adverse event, the likelihood for the second biologic to be discontinued because of an adverse event was 2.5 times higher.

These and other data suggest that anti-drug antibodies are most probably not the only factor shortening drug survival. Etanercept has previously been thought to be “resistant” (Anderson, 2005; Bartelds, 2011; Bendtzen et al., 2006; Dore et al., 2007; Garcés et al., 2012; Moots et al., 2017; Pascual-Salcedo et al., 2011; Radstake et al., 2008; van Schouvenburg et al., 2013) to anti-product antibodies, although this concept has become controversial. Because etanercept has by far the shortest drug survival rate in all studies, it follows that either as yet undetectable drug antibodies are responsible for this effect or, more likely, that other mechanisms (including clinical efficacy levels) have adverse effects on drug survival.

In this context, it must be acknowledged that the value of drug survival as a proxy measure of drug efficacy and safety is not unconditionally accepted. Dávila-Seijo and García-Doval (2017) recently proposed that drug survival used as a proxy indicator of safety can be misleading because factors other than loss of efficacy or appearance of adverse effects can justify interrupting treatment and thus can affect drug survival.

Despite this note of caution, drug survival studies provide important information on questions that are otherwise difficult to address, namely current real-life practice; the time at which loss of efficacy, adverse effects, and other factors determining treatment continuation occur; the variables that can predict (or not) sustained and successful responses to drugs; and most importantly, the levels of efficacy and safety that are no longer perceived as acceptable by physicians and patients (van den Reek et al., 2015). Furthermore, drug survival studies have significant utility, in our opinion, not only for clinical but also financial reasons. It has been shown that patients who switch biologics generate higher costs than non-switchers (Meissner et al., 2014), and thus it is relevant also from a financial point of view to investigate the drug survival rate of biologics.

In aggregate, the data of Iskandar et al. (2018) inform and reassure clinicians that a second biologic has the same chance of succeeding as when it is given as a first treatment. However, when a patient interrupts the first biologic because of an adverse event, the clinician must be prepared for more frequent occurrence of an adverse event with a second-line biologic. These data are helpful for the management of patients with plaque-type psoriasis, but extrapolation to other, rarer forms of psoriasis such as pustular psoriasis requires further investigation (Navarini et al., 2017).
COMMENTS

CONFLICT OF INTEREST

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