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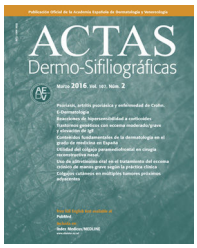

OPINION ARTICLE

Drug Survival Analysis Is Not a Good Method for Assessing the Safety or Effectiveness of Systemic Therapies in Psoriasis☆

El análisis de supervivencia no es un buen método para evaluar la seguridad o la efectividad de los tratamientos sistémicos en psoriasis

P. Dávila-Seijo,[a,b,*] I. García-Doval[b,c]

[a] *Servicio de Dermatología, Hospital Universitario de Umeå, Umeå, Suecia*
[b] *Unidad de Investigación, Fundación Academia Española de Dermatología y Venereología, Madrid, España*
[c] *Servicio de Dermatología, Complexo Hospitalario Universitario de Vigo, Vigo, Pontevedra, España*

Dermatology journals have recently published numerous articles using drug survival analysis, which assumes that a drug ''surviving'' longer in treatment will be one that is safer and/or more effective. Is this actually the case?

Survival analysis involves a series of statistical techniques to study time until the occurrence of an event of interest. Initially that event was death, hence the name, and death continues to be the endpoint in many studies. However, the application of survival analysis has broadened to make room for the study of time elapsing between many types of events.

One recent application is the study of drug survival, defined as the time a patient continues to take a medication. This concept has been used in various chronic diseases—rheumatoid arthritis for example—as a proxy for the overall effectiveness of a therapy, given survival's association with efficacy, side effects, and patient satisfaction.

We now have a growing number of publications describing the survival of systemic treatments for moderate to severe psoriasis.[1–8] Why has this type of analysis emerged in this setting?

In our opinion, 2 factors are mainly responsible for these studies. The first is the pressure to obtain real-life data on the treatment of psoriasis. The second is that survival analysis requires little information, merely the dates for starting and ending treatment and the reason for withdrawing the drug. There is no need for a control group or repeated measures of clinical variables. Many drug survival studies have no control groups and do not measure effectiveness, preventing them from using other approaches to obtain more significant results.

Because drug survival is associated with many variables, however, it is difficult to interpret. Comparisons between different studies or different drugs are generally impossible, and many discrepant findings are generated. We will discuss some of the problems these studies present.

Although defining the moment treatment stops may seem straightforward, in fact it is not. Some therapies are given intermittently, and some regimens include temporary interruptions. Many studies fail to state how the end of treatment is defined while others indicate that a treatment has stopped

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* Corresponding author.
E-mail address: pauladavilaseijo@gmail.com (P. Dávila-Seijo).

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after a fixed period off treatment or a certain number of lost doses. Using the loss of one or several doses as the definition of withdrawal of a drug means that it is much more difficult to study end of treatment with medications that have long dosing intervals (such as infliximab or ustekinumab, which are given at intervals of 8 and 12 weeks, respectively) than it is to study other biologics or traditional systemic medications. A patient would have to be off ustekinumab for 24 weeks before treatment could be said to have stopped. In contrast, withdrawal of treatment with acitretin could be recorded after 2 days off treatment. The period would be 2 weeks for methotrexate or etanercept.

Another important aspect to consider is that events (thresholds or marker cutoffs) that lead to suspending a treatment differ from one drug to another, between prescribers, between patients, and over time.

Thresholds differ from drug to drug because of intervals between doses and concerns about safety. Clinical practice routines also play a role. Suspension of treatment due to adverse effects is less likely to occur when there is a long interval between treatments. If the patient describes a problem with a drug whose next dose is to be administered months later, adverse effects that have long passed will probably not have much influence on the decision to suspend treatment or not. In contrast, decisions about whether or not to stop a drug like ciclosporin that is taken every 12 hours will have to be made daily, so adverse events are more likely to lead to suspension. These factors probably lead to longer survival times for ustekinumab and infliximab.

Another consideration is that traditional systemic treatments for psoriasis are used intermittently because of concerns about toxic effects on specific organs due to cumulative exposure. The best example of a drug prescribed for short periods of time is ciclosporin, as treatment lasting longer than a year increases the risk of adverse effects (nephrotoxicity). In comparison with traditional therapies, biologics do not seem to present a problem of toxicity over the long term, and current research suggests that continuous therapy improves disease control and quality of life.[9] When a patient is started on a biologic, long-term use is likely to be assumed.

Approaches to treatment are different in rheumatic diseases and psoriasis. Optimal control of inflammation through long-term therapy, in the interest of preventing sequelae, is the goal in rheumatic diseases. In psoriasis, there is insufficient evidence that preventing damage over the long term can be achieved through continuous treatment. This uncertainty, along with doubts about the long-term safety of biologics and concerns about their cost can lead some prescribers to prefer intermittent treatment whenever possible.

A randomized controlled trial showed that continuous therapy with some drugs—such as infliximab—is more effective, safer, and leads to fewer serious reactions related to the infusion.[10] This finding may explain why infliximab survives longer than other inhibitors of tumor necrosis factor (TNF) in some trials, especially when remission is the endpoint of interest.[10,11]

Criteria for interrupting treatment and withdrawing a drug can also vary between patients. Prior clinical history may be a factor in deciding to stop treatment. It seems reasonable that response to previous therapies or adverse effects would influence the survival of drugs tried later, especially if they share a chemical structure or their mechanisms of action target the same molecular pathway. For example, if a patient does not respond well to one anti-TNF agent, the prescriber may tend to stop another such agent tried at a later time if improvement fails to come as quickly as expected.[12]

The criteria for suspending treatment specified in a drug's summary of product characteristics (SPC) may also change over time. Etanercept was the first anti-TNF agent on the market and its SPC has changed since it was approved. The recommended dosage in 2006 was 25 mg twice weekly, and treatment was to continue until remission or up to 24 weeks. If retreatment with etanercept became necessary, the old recommendation called for applying the same criteria regarding duration of therapy.[13] However, since September 2009, the European Medicines Agency's label for etanercept recognizes the possibility of extending treatment beyond 24 weeks for some adults, and the decision to treat intermittently or continuously can be tailored to the individual if the physician considers it necessary.[14] Such differences appearing over time have the potential to influence etanercept's survival rates in comparison with other biologics that were recommended for continuous therapy from the start if researchers gather data from registries started before the SPC changes.

Another issue to consider is that more biologics have entered the market over time, raising expectations of effectiveness. This situation may be leading to more treatment suspensions in recent years, as patients are switched to another drug.

Drug costs also change over time, possibly affecting the survival of drugs used to treat psoriasis. Since the world economic crisis began in 2008, the Spanish national health service has tried to reduce spending on expensive therapies[15] through measures like requiring prescriptions, extending the time a patient is kept on certain drugs even if response is not optimal, or promoting intermittent use or switches to cheaper medications. All such changes distort drug survival analyses.

Yet another problem with drug survival studies is that the reasons for treatment interruption include both positive outcomes (such as remission) and negative ones (such as adverse events or lack of effectiveness). We also see a nonnegligible number of reasons for stopping treatment that do not fit into either of these categories and that are difficult to interpret. Some 15% of cases in the Biobadaderm registry involve such reasons.[16] Some drug survival studies group all reasons for suspension together, making their findings even more difficult to grasp and compare.

Finally, a more general criticism of drug survival analysis in psoriasis concerns the very research question being asked in these studies: Is it truly important for patients and clinicians to know which treatments survive longer? What is really important is which treatments are more effective or safer.

In summary, we believe that drug survival studies do not offer a good way to evaluate the safety or effectiveness of psoriasis treatments and that they are particularly inappropriate for comparing treatments. In a recent study utilizing Biobadaderm registry data we showed that drug survival used as a proxy indicator of safety was misleading.[16]

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The best way to measure safety, we think, is to publish the rates of adverse events in cohort studies. Effectiveness is best demonstrated through experimental or observational studies in which effectiveness is specified as the outcome measure. Drug survival analysis, with all its inherent problems, may be of interest mainly for generating models to assess treatment cost.

Conflicts of Interest

P. Dávila-Seijo has received grants from Pfizer and Janssen to attend conferences. I. García-Doval has received grants from Pfizer, Janssen, and Merck/Schering-Plough Pharmaceuticals to attend conferences.

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