



# ACTAS Derma-Sifiliográficas

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## LETTERS TO THE EDITOR

### Comment on “Drug survival analysis is not a good method for assessing the safety or effectiveness of systemic therapies in psoriasis”



### Réplica a: “El análisis de supervivencia no es un buen método para evaluar la seguridad o la efectividad de los tratamientos sistémicos en psoriasis”

Dear Editor,

We read with great interest the article “Drug survival analysis is not a good method for assessing the safety or effectiveness of systemic therapies in psoriasis” by Davila-Seijo and Garcia-Doval.<sup>1</sup> In the article, the authors explain that drug survival studies are not a good way to evaluate the safety or effectiveness of psoriasis treatments because biases can seriously affect the interpretation of drug survival data. We agree with this statement but would like to add that drug survival should be regarded as a different entity than a mere effectiveness or safety outcome, and that it should be complementary to those outcomes. Drug survival is a comprehensive measure that incorporates effectiveness and safety as well as the preferences of both patients and doctors. Drug survival data can easily be split for the reason for the discontinuation (e.g., ineffectiveness or adverse effects) to provide more detailed information.<sup>2</sup> This does not mean that drug survival directly measures the rate of adverse effects or the precise effectiveness of a drug. However, it does provide important information, including the following: (1) which adverse effects or level of ineffectiveness are considered unacceptable by the doctor and patient; (2) when do adverse effects or (in)effectiveness occur; and (3) which variables predict a sustained and successful response to a drug.

One of the author’s main points is that drug survival is particularly inappropriate for the comparison of drugs. However, we would like to point out that, irrespective of the outcome (drug survival or disease activity), a control group is actually needed for comparative effectiveness studies. In an observational setting, confounding by (contra)indication often plays a role in this context and is indeed problematic. We believe that the real problem in these comparative effectiveness studies the authors are referring to is not the use of drug survival as an outcome, but the lack of a control

group or the lack of confounder correction in observational studies.

The authors also describe certain biases that may occur in drug survival studies. Fortunately, there are solutions that minimize the impact of most biases, as we have described in the *Journal of Investigative Dermatology*.<sup>3</sup> Dávila-Seijo and García-Doval mention that the authors of many studies fail to report how the end of treatment was defined, and that defining withdrawal on the basis of the loss of one or several doses could lead to problems when studying drugs with long dosing intervals. This problem can be solved in part by defining discontinuation as withdrawal of the treatment for a period of more than 90 days; this is an arbitrary but widely accepted threshold.<sup>2</sup> The statement that ustekinumab should be stopped 24 weeks before it can be considered to have been discontinued does not seem valid to us. We dealt with this problem differently, analyzing cases of ustekinumab in which therapy had been stopped for more than 90 days with sensitivity analyses, considering the last injection date as well as the last injection date plus the specific treatment interval for each case (often 12 weeks) as the possible dates of discontinuation.<sup>3,4</sup> The authors state that intermittent therapy poses a problem in drug survival. We, however, think that patients on intermittent therapy should not be investigated using this method because the research question in drug survival studies refers to long-term use of treatment for chronic disease. To our knowledge, hardly any articles on drug survival focus on intermittent therapy. Analyzing positive events, such as disease remission, is also considered a problem. Positive events can be analyzed when the distinction between negative and positive events is maintained at all times and the reader is made aware of this important distinction.<sup>3</sup> If a drug can be discontinued due to both positive (e.g. remission) and negative (e.g. ineffectiveness) events, one can censor the positive events when one is only interested in the negative events and vice versa.

We agree that drug survival can be influenced by external factors, such as changes in reimbursement criteria or the introduction of new biologics. One solution to this problem is to restrict analyses to specific time periods.<sup>3</sup> For instance, in a drug survival study (adalimumab, etanercept, ustekinumab), we chose to analyze only treatment episodes that started after the introduction of ustekinumab, thereby minimizing the competing risks.<sup>4</sup> Events that lead to withdrawal of an agent do indeed differ between prescribers and patients. Therefore, a large, heterogeneous group of prescribers and patients should be evaluated; offering a general view of what patients and doctors accept from a drug in terms of safety issues and ineffectiveness. It has

been shown that large psoriasis drug survival studies with a heterogeneous group of patients and prescribers reported similar findings overall.<sup>5-7</sup>

To answer the question asked by these authors—“Is it really important which treatments survive longer?”—we do think that drug survival is a suitable measure for analyzing the performance of a drug in daily practice, provided the necessary steps are taken to minimize bias.<sup>3</sup> However, drug survival should not be regarded as a sole outcome measure for effectiveness or safety. It is important to use a combination of several different outcomes, each one with its specific biases, to fully judge the performance of a drug.

### Conflict of interest

J.M.P.A. van den Reek performed clinical trials for AbbVie and Janssen. J.M.P.A. van den Reek has received speaking fees from AbbVie and Eli Lilly and reimbursement for attending a symposium from Janssen, Pfizer, and AbbVie. Fees were paid directly to the institution.

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