Response to the Comment by Van den Reek et al. on *Drug Survival Analysis is Not a Good Method for Assessing the Safety or Effectiveness of Systemic Therapies in Psoriasis*☆

Respuesta a la réplica de Van den Reek et al. 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 thank Van den Reek et al. for their comments and the opportunity they provide for further discussion of the limitations of drug survival analysis. While we concur with their enumeration of the problematic aspects of such analysis, we do not agree with their assessment of the importance of those difficulties.

Imagine that you are ill and your doctor tells you: ''If you start taking this drug you have an 80% possibility of still being on the same treatment in twelve months''. Would you be happy with that information? Or would you prefer to know more about the possibilities of being free of lesions in a year's time and whether the drug will cause adverse effects? In our opinion, drug survival is a proxy measure that does not facilitate decision making. This would be less important if the results of drug survival analysis and the results of more useful proxy measures were similar; however, at least on some occasions, they do not coincide. Analysis of data on safety has revealed discrepancies between the results of drug survival analysis and the adverse event rate.[1] Unfortunately, we do not have sufficient comparisons between treatments of efficacy or effectiveness to check whether such discrepancies also exist between the data on drug survival and the results of clinical trials and registry studies.

To illustrate the significant limitations of drug survival analysis, we will comment on the results of some of the articles cited by Van den Reek et al.,[2–6] which are probably the most cited articles on drug survival in psoriasis in the literature. While those articles and the letter of comment from Van den Reek et al. propose solutions to the difficulties involved in drug survival analyses, the problems inherent in such analyses persist.

With respect to how withdrawal of treatment is defined, 2 of the studies (references 4 and 5 in the article by Van den Reek et al.)[3,4] consider that treatment has been discontinued if the patient has not received a dose for more than 90 days. This means that a course of treatment with ciclosporin or methotrexate that is suspended for 2 months and then restarted does not count as withdrawal of treatment, but a delay of 15 days in the administration of a dose of ustekinumab represents cessation of treatment. The authors propose the use of sensitivity analysis to assess the effect of this decision in the case of ustekinumab, but this solution does not address the difficulties that arise in the case of other drugs. The problem of the definition used does not disappear with the application of this arbitrary criterion. In 2 of the references (6 and 7 in the article by Van den Reek et al.),[5,6] no explanation whatsoever is given concerning the definition of discontinuation of treatment.

Surprisingly, none of the 4 articles cited (4 to 7 in the article by Van den Reek et al.)[3–6] include the possibility of withdrawal due to a good outcome in their results. In our analysis of the Biobadaderm registry,[1] remission of psoriasis was the motive for discontinuation in 27% of patients and the motive cited in a further 15% of cases was ''other''. Given that these studies are based on registry data and, therefore, represent routine clinical practice, such a large discrepancy (27% in Biobadaderm vs 0% in the other registries) is difficult to explain. In the article cited by reference 4, the authors recognize another aspect of the problem of positive and negative outcomes in studies of drug survival.[3] They introduce the concept of *happy survival* for patients who continue on the treatment and have a Dermatology Life Quality Index score of 5 or less. This proxy represents drug survival associated with a positive outcome, in effect reflecting the survival of treatment due to remission. However, once again, the solution highlights the fact that the problem persists: in 28% of the patients still on treatment after 9 months and in 21% after 1 year, the outcome is *unhappy survival*. How is this reflected in the overall data on drug survival? Is *unhappy survival* a good or a bad outcome?

They also point to the importance of controlling for confounding variables, that is, external factors associated with the drug and the duration of treatment. Three such factors are the interval between doses of the drug, pricing, and drug prescription behavior. However, all the methods we use to control confounding variables in observational studies (restriction, stratification, multivariate analysis) are only useful if the confounders can be measured and when they affect different drugs. In drug survival analysis, some of the confounding variables fail to meet those requirements: there may be no overlap across different treatments of factors related to pricing and the interval between doses; and clinicians prescription habits are difficult to measure. This makes it impossible to control for these confounding factors.

With respect to intermittent therapy, the limitation is that most of the published articles, including those cited, only consider one cycle of treatment per patient in each analysis and this failure to consider the data as a whole distances the authors from their ultimate goal of reflecting the real situation in clinical practice.

We agree with you that drug survival analysis is a composite measure of many factors, but in our opinion it includes so many different factors that the result is fuzzy and difficult to interpret. As a patient, I would want to know whether my condition will improve and whether I will experience adverse events; the survival of the treatment is of very little importance to me. Whether I will still be receiving the same treatment in a year's time is of interest only

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to the people selling the drug and those who are paying for it.

Conflict of Interests

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

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