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OPINION ARTICLE

# Drug Survival in Biologic Therapy. Do We Know What it Means? Can We Calculate it?☆

## Supervivencia en terapia biológica. ¿Sabemos a qué nos referimos? ¿ Podemos usarla?

**J.M. Carrascosa,[a,*] J. Notario[b]**

[a] *Servicio de Dermatología, Hospital Universitari GermansTrias i Pujol, Universitat Autònoma de Barcelona, Badalona, Spain*
[b] *Servicio de Dermatología, Hospital Universitari de Bellvitge, Universitat de Barcelona, Barcelona, Spain*

Now that biologic therapy has been used for some years in the treatment of psoriasis and we anticipate short and medium term outcomes consistent with the results of the pivotal clinical trials, the objective of the dermatologist with experience in managing this condition has changed. We now look beyond the predicted response to weigh up the likelihood that a given drug which achieves a satisfactory response during the initial months of therapy will continue to be a suitable option in the long term.

What is considered to be a suitable option and the basis on which such a decision is made will depend largely on the requirements and expectations of both patient and physician. The decision will be based not only on objective considerations but also on the patients' prior treatment history, their experience with other drugs and, therefore, the chances that a satisfactory response will be achieved with acceptable safety and tolerance.

We should start by defining the concept referred to in the title of this article. While the meaning of the term *drug survival* is taken for granted by most dermatologists with expertise in the management of biologic therapy, there is no recognized uniform definition in the literature. Here it may be sufficient to define drug survival as the period during which a given drug continues to be an adequate treatment for a specific patient. It will therefore be determined by whether the patient continues the regimen or discontinues the therapy, usually because of safety issues or lack of effectiveness. Currently available data indicates that, at least during the initial phase of treatment, biologic agents have a favorable safety profile that is even better than that of the classical therapies.[1,2] If we accept that withdrawal of biologic therapy in psoriasis is, in most cases, not motivated by safety concerns, then the effectiveness of treatment or clinical response is the main factor we should analyze.

The biologic agents currently available for the treatment of psoriasis have been approved for continuous and, in principle, indefinite use. Moreover, it should be remembered that a drug may still be a good choice for a patient even when it is not actually being administered; that is, when it induces a prolonged period of remission and allows the patient to suspend treatment or use an intermittent therapeutic strategy. Thus one of the key considerations is the survival of patient response, that is, the survival of the response in the patient obtained by the drug.

The survival of biologic therapy—as distinct from the limits that we might wish to establish or should be

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* Corresponding author.
*E-mail address:* jmcarrascosac@hotmail.com (J.M. Carrascosa).

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established—is a key element in any evaluation of the performance of the different drugs available. We should bear in mind that in most patients with moderate to severe psoriasis, adequate control of the condition will require indefinite continuous treatment with an appropriate therapeutic modality.[3] Thus, our overall evaluation of the clinical effectiveness of a drug with a very high chance of a successful response will be considerably lower if a high percentage of patients are obliged to discontinue treatment after 1 or 2 years due to safety issues or loss of the initial response. It is important to consider the negative impact of such withdrawal on the quality of life of both the patient, who is once again faced with a problem he or she thought had been resolved, and the clinician, who is once more faced with the challenge of obtaining a satisfactory response. We must also take into account the cost implications of discontinuing a biologic therapy. We know that the failure of one biologic agent often leads to a switch to another, which involves an induction regimen that is significantly more expensive than a maintenance regimen.[4]

Now that we have defined the concept—albeit with intrinsic limitations that are hard to overcome—our next task is to ascertain what data is available on drug survival for the biologic agents currently on the market. And, to go one step further, to find out whether the results for different agents can be compared and to include drug survival as just one more variable in the decision about which biologic therapy to use in psoriasis.

The following aspects should be included in any evaluation of studies assessing the outcomes achieved and the survival of treatment over time for a specific drug: a) the type of study (clinical trial or case series); b) the objective or primary outcome measure used to define a response as adequate; c) the measure used to define loss of response, which is a very important aspect that warrants consideration in greater depth (see below); d) the percentage of patients who discontinued treatment owing to safety issues; e) the constraints imposed by the protocol, such as whether only naive patients were included or whether the design permitted combination therapy or dosages not specified in the Summary of Product Characteristics (SPC), that is, strategies that involve increasing or reducing the intensity of the regimen; and f) consideration of whether treatment was discontinued by the patient for reasons unrelated to efficacy or safety.

The implications of heterogeneity in the design and objectives of the studies included in the assessment is very important. It should be remembered that clinical trials and open label extension studies generally only report the results for patients who fulfil a certain objective response criteria—for example, maintenance of a 75% improvement in the Psoriasis Area Severity Index (PASI) score (a PASI 75 response) obtained during the initial phase of treatment. However, the outcome measures used in case series are much more diverse; the authors may accept moderately good responses, such as a PASI 50-75 response, or use relative PASI criteria (for example, PASI < 3 or > 5), quality-of-life scores (Dermatology Life Quality Index < 5) or, in even less rigorous but perhaps more realistic series, a response may be deemed to be adequate if it satisfies both the patient and the clinician. Drug survival data may be influenced by the desired or expected level of response, that is, by a predefined expectation or objective; the reported drug survival rate will be lower if the predefined outcome measure is an improvement greater than PASI 75 than it would be if a PASI 50 response was deemed to be satisfactory response.

Strictly speaking, the survival of a drug-related response is a similar concept to the non-responder imputation (NRI) approach used in the analysis of clinical trial results. In other words, it reflects the percentage of patients who maintain a response that fulfils a minimum criterion for the specific period of time studied. As well as discounting the patients who fail to sustain a response that fulfils the predefined efficacy measure, it also discounts all those in whom the drug was withdrawn due to safety issues or any other reason. NRI may be considered to be an excessively demanding model because it underestimates the performance of the drug in that all patients who leave the study are classified as non-responders, irrespective of whether the reason for discontinuation was actually related to efficacy. Moderately conservative methods—such as the last observation carried forward (LOCF) model, in which the last recorded values for each patient are carried forward to the date the assessment is completed—are generally not used in clinical series and may give a somewhat distorted impression of drug survival. Another less demanding strategy is the as-treated (AT) model, in which only the response values for patients who remain in the study are used.[5] This model is not useful here because it fails to reflect all the patients who abandon treatment owing to safety issues or a clearly inadequate clinical response.

Infliximab, a molecule widely used in inflammatory conditions, was one of the first biologic drugs approved for the management of moderate to severe psoriasis. However, in the clinical trials for this agent, follow-up in pivotal studies was limited to 50 weeks. In one pivotal study, of the 301 patients who were treated from the outset with infliximab, only 236 completed treatment at week 50 (78%) and treatment was discontinued due to adverse effects in 27 (9%). At the end of the evaluation period, taking into account all the patients who could be evaluated from the beginning (i.e., using intention to treat analysis), 61% sustained a PASI 75 response and 69% a PASI 50 response.[6] Of note is the fact that no further data is reported for the patients included in this series relating to open label extension studies and we know nothing of other patients recruited for the treatment of moderate to severe psoriasis in other clinical trials with this drug. Perhaps the consideration of long-term maintenance, which later emerged as an important consideration, was not seen as a priority in those early studies, in which the central focus was on demonstrating the efficacy of biologic therapy in psoriasis.

Etanercept was also one of the first biologics used to treat moderate to severe psoriasis. Of the 311 patients who received etanercept in a study by Tyring et al.,[7] 233 (76.6%) completed 96 weeks of treatment. Of those who abandoned, 16 (5% of all the patients in the study) did so because of adverse effects. The PASI 50 and PASI 75 response rates were 82.6% and 51.1%, respectively, of all of the patients who started the study. It should be taken into account that a sizeable proportion of patients treated with etanercept received doses of 100 mg/wk (double the approved dose specified in the SPC for use after the first 12 weeks of treatment). In a post hoc study, Papp et al.[8] found that in a

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