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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?

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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

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

group of 506 patients coming from Phase III clinical trials who were treated for up to 4 years with varying dosages of up to 100 mg/wk, 307 (60.07%) could be evaluated for at least 24 months. Among those who did not continue, adverse effects were cited as the reason in 18 (3%), but there is no way to rule out the possibility that adverse effects were also the reason in other cases in which no motive was specified. In the AT analysis, 28.6% sustained a complete or almost complete response (Psoriasis Global Assessment [PGA], 0/1) at 24 months; this percentage remained almost unchanged at 36 and 48 months (29.2% and 27.8%, respectively). While these results may appear modest, we must take into account that the PGA 0/1 criterion is not comparable to the PASI 75 response and is closer to a PASI 90. Finally, it should be added that the survival of treatment in this study was 48 months for 27.8% of the patients, a figure very close to the 28.6% reported at 24 months. However, this reading may be somewhat misleading since only the patients who remained in the study were included in the analysis, which explains why the response is apparently better at 36 months than at 24 months. If a more conservative analytical approach is used (modified imputation), these percentages are reduced to more modest numbers: 23.3% at 24 months and 19.4% at 48 months. In other words, from an only moderately conservative perspective, one out of every 4 to 5 patients had a very good response after 3 or 4 years of treatment. As the patients were taking part in clinical trials with diverse criteria, the dermatologist was not always able to tailor the dosage to the course of the disease, a course of action that would have favored both drug survival and patient response.

Evaluations of small clinical series should be interpreted with extreme caution for all the reasons cited above (differences in the primary outcome assessed, dosage regimens other than those approved by the SPC, off-label use of combination therapy), and they will only be mentioned here briefly. However, it is worth making the point that in some of these series the use of the AT model—an overly tolerant analytical strategy in our opinion because it omits from the denominator all the patients who abandon treatment for any reason—gives rise to obviously optimistic and even paradoxical results. For example, drug survival increases as treatment duration lengthens,[9] a logical outcome when this model is used because a patient only remains in the AT group so long as he or she responds to treatment and experiences no unacceptable adverse effects. In such cases, careful reading of the article—paying particular attention to the sections on materials and methods and the interpretation of results, and often disregarding the abstract—allows us to identify the limitations that make it impossible to compare such results with other studies in which a more rigorous analytical approach was used.[10]

In the case of adalimumab, data on drug survival from clinical trials can be found in a subanalysis of the pivotal REVEAL trial.[11] In that study, Gordon et al. assessed 345 patients treated with adalimumab at the dosage specified in the SPC from week 16 for up to 3 years without interruption. Although the author of that article reports that the response was very satisfactory, with PASI 75 being attained by 89% of the patients, only 43% (160) of the patients who started the study were assessed at week 144. Of the patients who started the study, the regimen was escalated to 40 mg weekly in 113 (33%). Overall, 74 (21%) patients

abandoned the study and the reason given for withdrawal was adverse events in 14 (4%) and insufficient clinical response in 15 (4.4%). However, the criteria used were more stringent than those required in standard practice, both in terms of response and management: the minimum criteria for response was PASI 75, the possibility of combination therapy was excluded, and patients who required dosage escalation were not classified as responders. In that study, there might have been some difference between the percentage of patients who fulfilled the requirements and objectives of the study and those who might have fulfilled them if, for example, patients who required dosage escalation had been considered valid responders. Overall, in the group assessed according to the protocol from the start, 53% of patients sustained a PASI 75, 33% a PASI 90, and 19% a PASI 100 response. The analytical strategy used in this case was only moderately conservative (LOCF). It is worth noting that the percentage of patients who achieved a PASI 90 or PASI 100 response remained very consistent throughout the 3-year study. These results appear to indicate that there is a subgroup of patients who could be considered elite responders and who exhibit an excellent response from the start of treatment and have good prospects of sustaining this response over time.

One example of the differences in the results obtained using different analytical strategies to assess the data can be seen in the study by van Lümig et al.[12] In that paper, which deals with a clinical series of patients treated with adalimumab between 2007 and 2011, drug survival was assessed using both a conservative method (NRI) and a much more tolerant model (AT). The mean duration of treatment was 1.4 years. The PASI 75 response obtained at 132 weeks was 35% to 40% using NRI and 45% to 55% using AT. The corresponding results for PASI 50 were 65% (NRI) and 65% to 85% (AT).

Ustekinumab is the biologic drug most recently added to the therapeutic arsenal for the management of moderate to severe psoriasis. In the pivotal clinical trials for ustekinumab, greater attention has been paid to assessing the maintenance of response over time, perhaps because of the deficits in this respect observed in the trials of other biologic agents. Of the 753 patients who received at least one dose of ustekinumab, 517 (68.7%) completed treatment through week 244.[13] Overall, independent of dosage, 8% discontinued treatment because of problems related to safety or efficacy. When the results of the open-label extension Phoenix studies are analyzed using conservative criteria (NRI), 63% (for a 45 mg dose) and 72% (for a 90 mg dose) of the patients achieved and maintained a PASI 75 response after 5 years of continuous treatment.[13] This represents the longest follow-up period to date in a clinical trial studying the treatment of psoriasis with a biologic drug. Any appraisal of these results should take into account that in 26% of the patients the regimen was intensified by reducing the dosing interval from 12 to 8 weeks. The fact that many of the patients in whom treatment was intensified had achieved a PASI 75 response or better leads us to pose the question of whether the response criteria considered adequate for approval of the drug actually represent an acceptable therapeutic outcome for patients and clinicians. In this case, the maintenance of the drug-related response takes precedence over the protocol for the use of the drug. However, there is a higher cost associated with the strategies used to optimize

response and/or increase drug survival, such as increasing the dose or frequency of administration.[1]

Today, the closest we can come to a comparison of the different biologic treatments available is to compare the results reported in patient registries. However, we must be extremely cautious when making such comparisons because of the differences that may exist between the groups of patients receiving each treatment; for example, a particular treatment might be chosen for patients with more severe disease or the results obtained in a particular clinic may be affected by the practices and habits of the center.

We must also be careful when evaluating registry-based studies reported in articles because such studies are often affected by the tendency of registries to record more data on the withdrawal or substitution of treatment than on changes in dosage, the use of therapeutic combinations, or the clinical course of the disease. Well known as one of the first to reflect this bias was the study by Gniadecki et al.[14] based on data from the Danish DERMBIO database. Using an intention-to-treat approach, the authors analyzed drug survival at 4 years for 882 treatment series with various anti-TNF agents. The response criterion used—at least PASI 50—was consistent with clinical practice. In most cases drug withdrawals were due to a lack of efficacy (183, 20%) and in only 30 cases (3%) by problems relating to safety. After 4 years, 474 patients were still being treated with the same drug. The drug survival rate for infliximab (70%) was higher than that achieved by etanercept and adalimumab (40% in both cases). The most common reasons for discontinuing treatment were loss of efficacy (75%) and adverse effects (12%).

In addition to the drug used, a history of prior failure to respond to biologic therapy was also a risk factor for discontinuation of treatment. It is possible that the use of individualized dosing in infliximab—in almost one-third of patients the dosage had been modified to an interval of under 8 weeks—influenced the better results obtained in this group, although the additional cost of dose escalation should also be evaluated. Using the same database and similar assessment criteria, Clemmensen et al. found differences in drug survival between a group of anti-TNF agents and ustekinumab. Only 3 out of 71 patients (4.2%) on ustekinumab discontinued treatment during a total follow-up of 321 days (although with an average treatment duration of between 140 and 170 days) compared to 29 out of 108 of patients treated with adalimumab or etanercept—21 (19%) due to lack of efficacy and 5 (4%) due to adverse effects. The conclusions that can be drawn are limited by the one-year maximum follow-up and the lack of subsequent monitoring of these patients.[15]

Using data from a registry combining cases from 3 Italian hospitals, Esposito et al.[16] described a series of 650 patients treated for over 6 months with etanercept, infliximab, or adalimumab between 2007 and 2011. Overall drug survival was 72.6% (NRI) with noticeable differences between drugs (80.7%, 61.9%, and 58.8% respectively for etanercept, infliximab, and adalimumab). Most of the patients who discontinued therapy did so owing to problems related to efficacy (primary or secondary treatment failure) and 29 withdrew because of adverse events. Although the response rate criterion (a minimum of PASI 50) was reasonably comparable to those used in clinical practice, the conditions were not so comparable in other ways because the study evaluated only anti-TNF agent-naive patients treated according to the SPC. Those criteria were excessively rigorous and excluded the sizable group of patients in whom strategies involving escalation and subsequent reduction of the dosage regimen or combination therapy were used and also patients who had a history of failure to respond to biologic therapy, a situation that is becoming increasingly more common. In other words, the study excluded the strategies that could enhance the survival of response to treatment.

Now that, after several years of experience with different biologic agents in the treatment of psoriasis, we are conversant with the short and medium term prospects for response and the safety profile for each agent, what is emerging as one of the most important tasks is to improve the data available on drug survival, and in particular on the survival of treatment associated with a drug-related response—the really important criterion in clinical practice. Data on increased drug survival will provide information concerning the maintenance of an adequate therapeutic target (largely determined by how demanding a response criterion we use), the presence or absence of adverse events that lead to withdrawal of treatment, and the possibility of achieving long-term disease control. Prolonged drug survival for a given therapy is not only associated with greater satisfaction on the part of both patients and clinicians, but also implies greater efficiency because it avoids or reduces switching of biologic therapy and the additional cost involved in such a change.

An overall view of the data presented suggests that patients who achieve a better response may also be able to sustain the response for a longer period. On the other hand, individualized therapy, with dosage adjustments based on the course of the disease, is another strategy that can be used to improve the survival of the response, although the efficiency of this strategy must be assessed and compared with the possibility of switching to an alternative biologic agent when response to the current agent administered at the approved dose is inadequate. Another factor that should be taken into account in the concept of drug survival associated with a drug-related response is the period of time the patient is without psoriasis or has only minimal disease during long periods of remission after withdrawal or with only intermittent treatment.

In summary, and in answer to the questions posed at the beginning of this article, we may say that, although we do know what we mean when we talk about drug survival, the problem may lie in the multiplicity of nuances and considerations involved in this concept. In this respect, comparisons between studies of different types and designs must be made with extreme caution if we are to avoid errors. Since drug survival is a priority target in clinical practice, we should undoubtedly also prioritize the search for and adoption of standardized measures for its evaluation that will result in this variable becoming a useful and measurable parameter for clinical decision making.

Conflicts of Interest

companies: Merck-Serono, Pfizer, MSD, Abbvie, Centocor, Janssen-Cilag, Novartis, Lilly, and Amgen.

J. Notario reports receiving honoraria for speaking at events, collaboration and participation in clinical trials, or consultancy work from the following companies: Abbvie, Pfizer, Janssen, and MSD.

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