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OPINION ARTICLE

Intermittent Treatment Regimens and the Rational (Efficient) Use of Biologic Agents in Psoriasis

Uso racional (eficiente) de biológicos y terapia intermitente en psoriasis

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The World Health Organization (WHO) defines the rational use of medication as the situation in which “patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community” (WHO, 1985).¹ While the main purpose of the WHO’s strategic approach is to guarantee the proper supply, distribution, and consumption of essential medication for diseases prevalent in developing countries, there can be no doubt of its current relevance to clinical practice in developed countries. Indeed, in our immediate context, Spanish Law 29/2006 concerning the guarantees and rational use of medications included in its statement of rationale that the law deals with “the set of actions whose goal is that patients receive them (drugs) and use them in a way that is appropriate to their clinical needs, at the correct dose according to their individual requirements, for an appropriate period of time, with information for their correct use and at the lowest possible cost.”²

It thus appears legitimate for physicians to be concerned not only with the efficacy and safety of drugs, but also with their efficient use, understood as giving the most benefit at the least possible cost. To illustrate the need to take this approach, we present some figures that show what

the prescription of biologic agents represents in economic terms (apart from the significant gain in quality of life that these drugs have offered patients with moderate to severe psoriasis). Biologic agents currently represent as much as 90% of the total cost of medications used in reference hospitals with units dedicated specifically to the treatment of psoriasis in dermatology departments; they may represent on average between 25% and 30% of the total budget, including all cost-generating activities (hospitalization, surgery, outpatient clinics, medical day hospitals, etc) and budgeted items (personnel, services, drugs, disposable material, etc). In addition, the current expenditure on biologic agents for a reference hospital’s dermatology department can be as high as 75% to 95% of personnel expenditure.³ A comparison with personnel costs shows that annual spending of the Spanish national health system on biologics for 4 patients in continuous treatment is about the same as the annual total cost (and not the salary alone) of a dermatologist.

These data suggest a point that deserves mention: with the dermatology departments of reference hospitals spending between €1 million and €3 million on biologic agents, it is difficult to argue that it is not a physician or department head’s place to be concerned with questions of efficiency. Furthermore, simply being aware of what efficiency consists of can give us the background knowledge we need to define strategies that would allow greater access to treatment and a better distribution of resources

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which, in view of the current economic structure (and not merely the economic situation), are far from unlimited.

In the context of prospective budgets for health care institutions and dermatology departments and units, the efficient use of biologic agents should be seen as a redistribution issue—a matter of efficiency, in fact—rather than one of rationing or savings in absolute terms. The following lines will allow us to clarify this dichotomy.

More than 5 years' experience with biologic agents for the routine treatment of psoriasis has enabled us to define a series of prescription strategies that can improve the efficiency of their use. While the direct objective of some of these strategies is to improve the efficacy and safety of treatment, both of these are a prerequisite for efficiency and can therefore also be considered strategies to improve the efficient use of biologics. These strategies include the following: use of these drugs following the indications stipulated in the prescribing information and according to consensus papers published by scientific societies; appropriate selection of patients and biologic agents; addressing comorbidities, such as obesity (in this regard, recent studies have shown the negative effect of weight on efficacy of treatment⁴); minimizing adverse events, which generate indirect costs (hospitalization, medical leave, other drugs, etc) on top of the cost of the biologic treatment itself; related to these last 2 strategies, the acquisition of a firm commitment on the part of the patient to improve comorbidities (obesity, alcoholism, etc), to adhere to the recommendations for follow-up (visits, blood tests, early reporting of adverse events, etc), as well as to appropriately store and use the medication; combination therapy (especially with topical drugs, phototherapy, methotrexate, or acitretin) as an alternative before suspending or switching biologic agent and as a way to lengthen survival of the treatment; finally, intermittent treatment regimens, in which, once a complete or submaximal therapeutic response (Physician Global Assessment [PGA] score, 0-1⁵ or at least a 75% improvement in the Psoriasis Area and Severity Index [PASI 75]⁶) has been achieved and stabilized, the biologic agent is temporarily discontinued (off periods) until recurrence of symptoms.

Despite its potential impact on efficiency, there are arguments both for and against the use of intermittent treatment regimens. One argument against off periods relates to the absence of cumulative toxicity with biologic agents, as opposed to traditional systemic drugs such as methotrexate or cyclosporine. There is consequently no need to suspend biologic treatment in order to avoid long-term cumulative toxicity. However, biologics, like traditional systemics, are associated with an expected noncumulative toxicity, which, although infrequent, can be severe. This is the reason patients are monitored during treatment. From the point of view of toxicity, the off periods represent intervals without exposure to the medication and, therefore, to its possible adverse effects. The quality of life of the patients in treatment is another argument against the suspension of biologic therapy; it must be remembered, however, that the highest level of quality of life for a patient is the absence of disease without the need for treatment. Moreover, in a chronic disease characterized by flare-ups, there is always the

possibility that the patient may be receiving treatment when the disease is in a remission phase, when the drug is unnecessary. The possibility of a rebound effect following suspension of treatment, an argument against intermittent treatment regimens, has not in fact been observed to a significant extent in patients previously treated with etanercept, adalimumab, or ustekinumab. The loss of efficacy or absence of a complete response to retreatment is another argument against intermittent treatment; early resumption of treatment before the appearance of the first signs of recurrence (for example, PGA 1-2) may help the patient achieve the initial therapeutic response. Finally, the argument most cited against intermittent treatment regimens equates them with a mere cost savings maneuver; again, the economic benefit of such regimens should be understood as a powerful strategy for the redistribution of resources, making access to treatment possible for the greatest number of patients within a fixed budget.

Two studies of intermittent treatment with etanercept and adalimumab, respectively, have provided data for estimating savings and drawing conclusions about the efficiency of this approach. In a recent study of Papp et al,⁵ treatment with adalimumab was discontinued and then resumed on recurrence of symptoms. The results of this study suggest that patients with a maximal or submaximal response to initial treatment and stable control of symptoms may be considered potential candidates for intermittent treatment if they have an off period without recurrence of more than 20 weeks. Applying these criteria, of the 862 patients in this study who completed treatment with adalimumab, up to 23% were appropriate candidates for intermittent treatment. Furthermore, 12.5% (n=107) in this study had not experienced a relapse after 40 weeks off treatment. On the basis of these data, what would the economic impact of intermittent treatment regimens in approximately a quarter of the respondents be? A simple calculation using the unit cost of medication during the off periods in the series of Papp et al shows that the total savings would be €1.7 million, the equivalent of the annual cost of continuous treatment with adalimumab for 119 patients. This amount would make it possible to provide treatment for another 14% of the 862 patients who completed treatment with adalimumab at the same total cost. It is precisely to this possibility of making the most of the available resources that we should refer when we consider intermittent treatment regimens as a strategy for the efficient use of biologic agents.

In another study on the treatment of psoriasis with etanercept in routine clinical practice, off periods were scheduled periodically for patients meeting the clinical response criteria (response in week 24, \geq PASI 75); this withdrawal phase was applied to 78% of the 85 patients initially treated with etanercept.⁶ Treatment was subsequently resumed in the event of recurrence of symptoms or loss of response indicated by a PASI score of \geq 10. The mean duration of time off treatment was 174 days for those patients who were assigned an alternative treatment (usually a topical one) and 117 days for those assigned to use no treatment at all. Making the same calculations as for the previous study, we can see that

the off periods freed up sufficient resources to treat an additional 15% of patients with continuous therapy, according to the most conservative estimates.

Thus, the real quantifiable impact of intermittent treatment regimens in terms of the number of additional patients who could be treated at no cost can be calculated by using simulation models incorporating different off periods (12, 16, 20, and 24 weeks) and applying the annual cost per unit of biologic therapy. According to these models, for off periods longer than 20 weeks—a realistic interval according to the above-mentioned studies on etanercept and adalimumab—the number of patients needed to treat (a well-known measure) with intermittent regimens to allow 1 additional patient to be given continuous treatment ranges from 3 to 4 patients for both etanercept and adalimumab.

Appropriate intermittent treatment regimens remain to be established, however, both with regard to the moment the biologic therapy should be discontinued and the moment it should be resumed. In any event, whether the treatment intervals are predetermined or self-managed by the patients, the decision to incorporate periods off treatment depends not only on clinical criteria (complete response, stable response, etc), but also on organizational factors (accessibility of a dermatology department), and on the patient's own preferences and commitment (in terms of seeking early medical attention in case of recurrence, ability to identify loss of response, etc).

Evidence of this inevitable trend towards efficiency can be found in the fact that the pharmaceutical industry is moving in the same direction. The publication of industry-sponsored studies on cost effectiveness and on the use of their drugs in routine clinical practice, with specific results for intermittent treatment regimens, combined therapy, etc, is part of a strategic shift that, while originally designed to avoid missing potential market niches, is already providing information of interest on the efficient use of their products.^{7,8}

In conclusion, all the stakeholders involved—patients, dermatologists, health care institutions, and the pharmaceutical industry—seem to agree that efficiency, seen as an issue of redistribution rather than rationing, must come into our clinical decision-making process. This must be done, of course, without compromising the quality of health care or the ethical principles of beneficence and fairness that guide our actions. Intermittent treatment regimens with biologic agents in patients with moderate to severe psoriasis can be a good example of this.

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