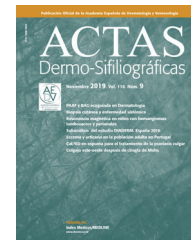




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OPINION ARTICLE

Treatment Appraisal Reports: Usefulness and Transparency[☆]



Informes de posicionamiento terapéutico: utilidad y transparencia

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The assessment and authorization of new drugs, following their approval by the European Medicines Agency (EMA), is the first step in the process of deciding on their pricing and reimbursement within the National Health System in Spain and their eventual use in medical practice in this country. This process involves several assessment bodies, including those of the Spanish Agency of Medicines and Medical Devices (AEMPS), the Directorate-General for National Health System Basic Services Portfolio and Pharmacy (DGCBSF), and their counterparts in the autonomous communities that will eventually fund the therapies. These successive evaluations can be redundant, consume resources, and in some cases lead to inequitable situations. To address those problems, in 2013 the main bodies involved in the process reached an agreement to create a coordinated and collaborative network for the elaboration of treatment appraisal reports (TARs) in Spain: the Treatment Appraisal Coordination Group (GCPT).¹ The aim of this initiative, in

addition to facilitating the authorization of new drugs, was to provide relevant data and an evidence-based appraisal of the new drug (or new indication) and its possible uses compared to other available treatments. The reports are prepared by an Appraisal Working Group made up of representatives of AEMPS and 2 Autonomous Communities. This group drafts the final report, which is then sent to the DGCBSF, where it informs the decision on pricing and funding, which also takes into account the comparative economic assessment and budgetary impact.

TARs "shall include, in the initial phase, a comparative assessment of the efficacy and safety of the treatment, as well as the criteria regulating its use and subsequent monitoring. Optionally, at the discretion of the GCPT, the report may also include an economic evaluation. In the second phase, after the pricing and funding process, an economic analysis and budgetary impact assessment shall be incorporated".¹

It is interesting to compare this centralized model including the participation of the Autonomous Communities with those of the countries which, by and large, serve as a reference for these processes within Europe.

The National Institute of Clinical Excellence (NICE) was set up in England in 1999 as a special health body in order to reduce the variability in the availability and quality of

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treatments provided by the National Health Service across different areas of the country.² The NICE process follows a clearly defined protocol and involves the participation of the pharmaceutical companies, which contribute data for the assessment.³ The appraisals are based on both clinical evidence and economic data. Approval of a drug may also be conditioned by confidential agreements between the pharmaceutical company and the NHS on a discounted price. The existence of such an agreement is explicitly stated in the public report and in most cases purchases are centralized.

In Germany, since 1 January 2011, 2 bodies—the Federal Joint Committee (Gemensamer Bundesausschuss, G-BA) and the Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, IQWiG)—have been responsible for assessing the benefit of newly licensed drugs and regulating their pricing and reimbursement by health insurance providers.⁴ Pharmaceutical companies are obliged to submit a detailed dossier on the efficacy of the drug and pharmacoeconomic assessments. These are then evaluated in a highly transparent process.⁵ Once the drug has been assessed, a reference price is assigned and this is re-evaluated approximately 1 year later. Dermatologists can prescribe biologic agents with dermatological indications and these drugs are dispensed by main street pharmacies, unlike the situation in Spain, where biologic drugs are classified as outpatient medications and can only be dispensed by a hospital pharmacy. In general, when comparing effectiveness, the G-BA tends to apply more stringent criteria than NICE.⁶

Owing to their evidence-based content and rigorous overall analyses, the Spanish TARs have been seen as useful reference documents for both medical professionals and the departments in the health ministries of the Spanish Autonomous Communities responsible for health technology assessment. Pharmacoeconomic and cost-benefit references have generally been scarce. This is not surprising given the decentralized model used in Spain for the acquisition and reimbursement of health technologies.

However, the most recent TARs on biologic agents with dermatological indications have included final conclusions that appear contradictory in light of the content of the reports. These considerations are included directly in the conclusions section but are unsupported by any analysis, reasoned justification, or bibliographic references in the report. This discrepancy is important because these final conclusions restrict the use of the drug and have important implications for the bodies that manage available resources and for the patients receiving these treatments.¹

A clear example of this new tendency can be found in the TAR on guselkumab,⁷ the biologic agent most recently evaluated for the treatment of psoriasis; although the same anomaly can also be found in the TAR on dupilumab,⁸ the first biologic drug indicated for the treatment of moderate to severe atopic dermatitis, and in the report written on the approval of ixekizumab, an interleukin (IL) 17 inhibitor for use in patients with psoriatic arthropathy.

Guselkumab (Tremfya®) is the first biologic agent in a therapeutic class of monoclonal antibodies designed to bind to the p19 subunit of IL-23. In November 2017, it was approved by the EMA for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.⁹

The TAR, prepared by the AEMPS and representatives of the Autonomous Communities of Galicia and Castile-La Mancha, includes final remarks indicating that the use of guselkumab should be restricted “to the treatment of moderate to severe plaque psoriasis in adults who have not responded to conventional systemic therapy and who have previously been treated with a biologic TNF inhibitor”.⁷ This is an unprecedented restriction for a biologic therapy for psoriasis in Spain.

Elsewhere, the report states that “guselkumab is highly effective in clearing skin lesions in the treatment of moderate to severe plaque psoriasis and has a safety profile similar to that of other biologic agents and a relatively low immunogenicity profile. Guselkumab is an alternative to other biologic agents for second-line therapy in patients with moderate to severe plaque psoriasis in the case of inadequate response, contraindication, or intolerance to conventional systemic treatments and PUVA. In patients with extensive, severe, and disabling psoriasis who require biologic therapy from the outset, guselkumab could be an appropriate treatment option.”⁷

This wording is almost identical to that of the final considerations in the TARs of other IL-17 inhibitors, including secukinumab (Cosentyx®) and ixekizumab (Taltz®), and of the report on the IL-17 receptor antagonist brodalumab (Kyntheum®), which were approved in July 2015, July 2016, and August 2018, respectively.¹ All of these TARs conclude with the following statement: “In the selection of x (secukinumab, ixekizumab, brodalumab, guselkumab) or other drugs that have shown high efficacy for this indication, criteria related to efficiency must also be taken into account”. In other words, by not including a cost-effectiveness or pharmacoeconomic analysis in the TAR, the authors leave in the hands of the health technology assessment bodies of the Autonomous Communities the final appraisal, which will depend on pricing variations, thereby allowing reasonable flexibility.

The new criteria introduced in the guselkumab TAR leads the report’s target audience—whether the Autonomous Community agency or the health professionals involved in the care of the patient—to wonder what the reason or justification is for the restrictive limitation applied to this IL-23 inhibitor.

The same shift in the appraisal criteria has also been observed in other cases, for instance in the TAR published after ixekizumab (Taltz®) was approved for use in psoriatic arthritis (January 2019).¹⁰ The final considerations of the GCPT in that report state that “funding conditions have restricted the use of ixekizumab to patients who have previously been treated with a TNF inhibitor”. However, as in the case described above, this restriction was not applied to secukinumab (Cosentyx®), another IL-17 inhibitor, in the TAR (April 2016) relating to its use in psoriatic arthritis.¹¹ That report stated that “the choice of drug will be based primarily on efficiency criteria since no clinically relevant differences have been found between the efficacy and safety of this biologic agent and the alternative available biologic therapies, all of which are funded for patients with psoriatic arthritis who have not responded to conventional systemic therapy”.

In summary, the restrictions imposed by the most recent TARs discriminate without justification between certain

biologic agents despite very similar conclusions in the assessment of the evidence on their efficacy and safety and without the support of any pharmacoeconomic study that can be contrasted or reviewed.

In both cases, it appears clear that the intention is to restrict the use of these drugs (and other future biologic agents) in psoriasis and psoriatic arthritis to patients who have been treated with anti-TNF biosimilars.

The establishment as a first line of treatment for psoriasis and psoriatic arthritis of biosimilars—which do not offer better performance than the original agents but may cost less and, therefore, offer improved cost-effectiveness—is important and desirable for the sustainability of the system. However, the choice should always be based on efficiency criteria and justified by cost-effectiveness and in a transparent way. Given the lack of any efficiency study, the first paragraph of the GCPT's final considerations in the TAR on guselkumab is not supported by the available scientific evidence and is not even consistent with the text of the report itself. Guselkumab has been shown to be more effective than all the TNF inhibitors and, in general, also has a more favorable safety and immunogenicity profile.^{12–14}

Taking the Psoriasis Area and Severity Index (PASI) 90 response at endpoint as a reference, indirect and direct comparisons indicate that, among the biologics administered subcutaneously, secukinumab, ixekizumab, brodalumab, and guselkumab are the most effective, followed by ustekinumab and adalimumab, with etanercept in last place.^{15–17} Cost-per-respondent analyses are consistent with this classification.¹⁸

Application of the TAR restriction to those on second-line treatment would create a situation of inequity because a patient who has previously been exposed to or has failed to respond to treatment with any biologic agent other than a TNF blocker could start second-line treatment with any biologic except guselkumab, which must be preceded by an TNF inhibitor.

Furthermore, as the restriction specifies TNF inhibitors in general rather than explicitly specifying biosimilars, the future introduction of certolizumab pegol—a TNF inhibitor with no biosimilar—would invalidate any possible justification based on the possible pharmacoeconomic benefit of limiting guselkumab to use as a second-line biologic following treatment with a TNF inhibitor.

This is not the only disconcerting situation arising from TAR appraisals in dermatology. In the case of dupilumab (Dupixent®), approved by the EMA in September 2017 for the treatment of moderate to severe atopic dermatitis in adult patients who are candidates for systemic treatment,¹⁹ the resolution of the DCGBSF in the final considerations of the GCPT is that the treatment will not be funded. Once again, the decision is at odds with the conclusions of the report itself, which asserts the superiority of dupilumab over placebo, assigns the drug a favorable safety profile, and indicates its suitability in the treatment of patients who have an inadequate response, contraindication, or intolerance to ciclosporin and of patients presenting extensive, severe, or incapacitating atopic dermatitis in whom the continuation of treatment with ciclosporin would be inadvisable.⁸ In fact, this is precisely the situation of some of the patients who were included in the clinical trials or who have already begun off-label treatment or treatment with dupilumab as

an imported drug. In these patients, most of whom have no other reasonable alternatives, the continuation of their therapy has now fallen into an administrative limbo. This is another decision that has not been justified by any pharmacoeconomic study or cost-efficiency criteria that could serve as a basis for negotiation and it will leave a group of patients who have an incapacitating disease without funding and place them in an inequitable position with respect to patients in other European countries. The same thing also occurred in the case of NICE.²⁰

In conclusion, as dermatologists specialized in the treatment of psoriasis and as members of the Psoriasis Group of the Spanish Academy of Dermatology and Venereology, we wish to express with this statement our perplexity and disagreement with the unjustified restrictive conclusions in the TARs mentioned above.

Furthermore, we want to underscore the need for greater independence, transparency, consistency, and pharmacoeconomic documentation (incremental cost per respondent, modeling with time horizons) in the development of TARs, all of which are essential if we are to create a system comparable with those of European references, such as NICE or G-BA.

Conflicts of interest

L. Puig has received fees as a speaker and/or consultant and/or has participated in clinical trials and studies sponsored by Abbvie, Amgen, Baxalta, Biogen, Boehringer Ingelheim, Celgene, Gebro, Janssen, Leo-Pharma, Lilly, Merck-Serono, MSD, Mylan, Novartis, Pfizer, Regeneron, Roche, Samsung-Bioepis, Sandoz, Sanofi, and UCB.

J.M. Carrascosa has received fees as a speaker and/or consultant and/or has participated in trials or studies as a PI/SI for AbbVie, Amgen, Biogen Amgen, Celgene, Janssen Pharmaceuticals Inc, Leo-Pharma, Lilly, MSD, Novartis, and Pfizer-Wyeth.

J. Notario has received fees as a speaker and/or consultant and/or has participated in clinical trials or studies sponsored by AbbVie, Amgen, Biogen Amgen, Celgene, Gebro, Janssen, LeoPharma, Lilly, MSD, Novartis, and Pfizer.

I. Belinchón has received fees as a speaker and/or consultant and/or has participated as a PI/SI for AbbVie in trials or studies sponsored by Amgen, Biogen Amgen, Celgene, Janssen Pharmaceuticals Inc, Leo-Pharma, Lilly, MSD, Novartis, and Pfizer-Wyeth.

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