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The importance of being able to compare: methodologies that result in the best decisions

La relevancia de poder comparar: metodologías que ayudan a tomar las mejores decisiones

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In this issue of the *Revista* we are publishing an interesting article by Martínez-Sesmero *et al.*[1] that analyzes the use of matching-adjusted indirect comparisons, a kind of indirect comparison method employed by several drug regulatory agencies when evaluating drugs for cancer indications. The article invites the reader to reflect on the current situation in the field of oncology, where there is a growing influx of drugs targeted at the same indication and at similar group of patients. The authors underscore the need to develop a robust methodology to evaluate and position newly approved medicines and suggest that the advent of new medications entails a unique opportunity at a healthcare and hospital management level.

The last few years have seen an acceleration in the number of cancer medications approved by regulatory agencies, prompted partly by the continuing lack of treatment options for different types of cancer, and partly by the growing understanding of the molecular basis of cancer and of the role of the immune system in fighting the disease. The increase in the number of approved medications[2], as well their impact on public budgets, are likely to remain a reality in the years to come[3]. When they offer a genuine clinical advantage and add value to patients lacking appropriate treatment alternatives, these new drugs may constitute a great opportunity. In order to determine whether the contribution of these medicines is decisive or marginal, it is essential to possess a powerful assessment and therapeutic positioning tool[4].

Against this backdrop, it has become fairly usual to see how several drugs targeted at a similar therapeutic niche receive regulatory approval with very little time separation between them. Examples include immune therapy medications for lung cancer, CDK inhibitors for breast cancer, or androgen receptor antagonists for prostate cancer, among others. This could be interpreted as a waste of research resources which, instead of being directed at exploring new therapeutic areas, are systematically spent on the same conditions. Conversely, one could see it as an opportunity to encourage competition in areas where certain drugs are protected by exclusive marketing rights and/or where drugs are associated with a high economic or budgetary impact.

The gold standard for comparing efficacy and safety across different health interventions is the randomized clinical trial. However, randomized clinical trials comparing cancer drugs head-to-head are extremely rare and the few that exist do not include medium- or long-term follow-ups. In the absence of head-to-head comparisons, what is needed is a sound methodology which, short of a randomized study, may be of help in evaluating and comparing the risks and benefits of the different therapeutic alternatives. Such methodologies include indirect comparisons (ICs), which can be made by comparing the relative effects of treatments against a common comparator, or by combining a variety of comparisons that, taken together, form one or more chains linking the treatments of interest (these are variously referred to as mixed treatment comparisons or network meta-analyses[5]).

As described by Veer *et al.*, the last decade saw a rapid increase in the number of ICs performed in the realm of anti-cancer drugs[6]. These authors carried out an interesting analysis of the assumptions made by ICs in the field of oncology and of the risks of using the IC methodology with respect to anti-neoplastic medications. They came to the interesting conclusion that the level of evidence of a matching-adjusted indirect comparison is similar to that of an observational study. They also pointed out that, although the results of those comparisons must always be taken cautiously, they are invariably more reliable than those presented by "naïve" or non-adjusted comparisons.

We believe, however, that rather than on the number of articles published on ICs, one should focus on analyzing how such comparisons are used by regulatory agencies, such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA)[7] and by technology assessment agencies[8]. Although the National Institute for Health and Care Excellence (NICE) (England and Wales), the Scottish Medicines Consortium (SMC) (Scotland), the Haute Autorité de Santé (France), and the Institute for Quality and Efficiency in Health Care (IQWIG) (Germany) have all used the IC methodology for cases where head-to-head comparisons were not available, the individual studies of these agencies are difficult to compare because of the specific requirements established and the approach emplo-

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yed by each of them[8]. Although the requirement to submit matching-adjusted ICs is similar across all agencies, IQWIG is reluctant to accept new methods such as network meta-analysis, which is nevertheless accepted by HAS or NICE. It would therefore be advisable to develop a consensus and a set of guidelines common to all the different agencies, at least at the European level. Reaching that consensus would enhance transparency and comparability in the use of the methodology and, more importantly, it would improve the way ICs are used in decision-making.

At a European level, the Magnitude of Clinical Benefit Scale of the European Society of Medical Oncology (MCBS-ESMO) is a useful tool for analyzing cancer medications[9]. However, in areas where several drugs complete within the same therapeutic niche, and in the absence of head-to-head comparisons between them, the value of the MCBS-ESMO scale is relative. Indeed, the scale only analyzes published trials based on the main variable in each study, without regard to their internal or external validity. Moreover, as far as applicability is concerned, it does not analyze whether the comparator used in the most suitable one or whether there is a therapeutic option with which the medication of interest has not been compared. This means that the MCBS-ESMO scale is not well-suited to make decisions in these specific scenarios.

At the level of the methodological advances of therapeutic positioning reports, the latest version of the "Standardized procedure for clinical evaluation, economic evaluation and therapeutic positioning"[10] states that meta-analyses, network meta-analyses or ICs will be added when the indirect comparisons included in the drug's core dossier are considered inappropriate. It is however specified that the analyses will only be attached when certain requirements are met: the variable must be a significant one, comparisons must be based on high-quality trials, and they must comply with the basic assumptions behind matching-adjusted ICs (homogeneity, transitivity, and consistency).

The methodology used by the Drug Evaluation Working Group (GENESIS) of the Spanish Society of Hospital Pharmacists (SEFH) under the MADRE method[11], designed to assist SEFH members in drafting evaluation reports, contains a specific section on ICs. The section discusses both the performance of self-prepared ICs and the review of already published ICs, including guidance on how to interpret the results with a view to evaluating the validity and applicability of the IC through an internal validity and applicability checklist.

Some methodologies can be applied to reduce the potential bias associated to the performance of an IC in the absence of overall clinical similarities between the patients included in the studies. The use of such methodologies is contingent on the availability of individual data on the patients or, at least, some of the studies to be compared. Such methodologies include matching-adjusted ICs, with recourse to propensity-score weighting, the use of which has been analyzed by Martínez Sesmero *et al.*[1]. However, for an IC that uses this method to be valid and helpful for decision-making, it must comply with all the requirements applicable to ICs mentioned on the GENESIS working group's checklist[12], as well as a series of other criteria. Some scenarios must also be accepted[13]. When interpreting the results, it must be taken into account that the planned analysis of the trial has been altered, considering the consequences that such an alteration could involve.

We share the belief that if these tools are used with care, transparency, and critical judgement they can be of great help in making the best decisions on the basis of the available information, and in estimating the uncertainty that may exist concerning those decisions. However, they must not be used to avoid employing more appropriate methods when these are available. Key aspects such as selection of the comparator, transparency, avoidance of bias, etc., should always play a key role in the decision-making process.

The foregoing experiences and analyses suggest that, for cases where different drugs compete for similar populations in very similar therapeutic niches, different methodological tools can be used, which need to be fully understood, specifically in terms of their validity and applicability. Nonetheless, hospital pharmacists must go beyond the merely methodological considerations. As mentioned in an editorial recently published in the *Revista*[14], the contribution of hospital pharmacists to therapeutic decision-making is of high value, and well recognized by their fellow clinical team members. It is precisely in these situations, where hospital pharmacists are challenged to evaluate the comparative effectiveness of anti-cancer drugs, that their contribution can, and must, be considered an opportunity. The lack of a comparative effectiveness evaluation makes it impossible to apply management tools, hence the importance of performing ICs. Carrying them out whenever possible, provided that it is done with due consideration for the patients' safety, will allow a more efficient management of anti-cancer drugs, which comprise a class of high-impact medications targeted at a group of conditions where better solutions are still required to achieve better outcomes for our patients, who should remain the focus of all our efforts.

Bibliography

1. Martínez-Sesmero JM, De Castro-Carpeño J, López-de las Heras A, Fernández-Nistal A, Parrondo-García FJ. Metodología de la comparación indirecta ajustada con emparejamiento en la evaluación de fármacos hematooncológicos. Farm Hosp. 2021;45(2):55-60.
2. Hilal T, González-Velez M, Prasad V. Limitations in Clinical Trials Leading to Anticancer Drug Approvals by the US Food and Drug Administration. JAMA Intern Med. 2020;180:1108-15.
3. DeMartino PC, Miljković MD, Prasad V. Potential Cost Implications for All US Food and Drug Administration Oncology Drug Approvals in 2018. JAMA Intern Med. 2021;181:162-7.
4. Vivot A, Jacot J, Zeitoun JD, Ravaud P, Crequit P, Porcher R. Clinical benefit, price and approval characteristics of FDA-approved new drugs for treating advanced solid cancer, 2000-2015. Ann Oncol. 2017;28:1111-6.
5. Hawkins N, Scott DA, Woods BS, Thatcher N. No study left behind: a network meta-analysis in non-small-cell lung cancer demonstrating the importance of considering all relevant data. Value Health. 2009;12:996-1003.
6. Ter Veer E, van Oijen MGH, van Laarhoven HWM. The Use of (Network) Meta-Analysis in Clinical Oncology. Front Oncol. 2019;9:822.
7. Ollendorf DA, Kim E, Bridger N, Naci H The Supercar Stays in the Garage: Factors Preventing Indirect Comparisons of Novel Medicines Targeting the Same Condition. J Manag Care Spec Pharm. 2020;26:333-4.
8. Lebioda A, Gasche D, Dippel FW, Theobald K, Plantör S. Relevance of indirect comparisons in the German early benefit assessment and in comparison to HTA processes in England, France and Scotland. Health Econ Rev. 2014;4:31.
9. ESMO. Magnitude of Clinical Benefit Scale (ESMO-MCBS). [Internet] [accessed 02/2021]. Available at: https://www.esmo.org/guidelines/esmo-mcbs
10. Ministerio de Sanidad. Comisión Permanente de Farmacia. Procedimiento Normalizado de Trabajo de evaluación clínica, evaluación económica y posicionamiento terapéutico para la redacción de informes de posicionamiento terapéutico de medicamentos en el sistema nacional de salud. [Internet] [accessed 02/2021]. Available at: https://www.mscbs.gob.es/profesionales/farmacia/IPT/docs/20200708.PNT_elaboracion_IPT_CPF8Julio.pdf
11. Marín R, Puigventós F, Fraga MD, Ortega A, López-*Briz* E, Arocas V, *et al.* Grupo de Evaluación de Novedades y Estandarización e Investigación en Selección de Medicamentos (GENESIS) de la Sociedad Española de Farmacia Hospitalaria (SEFH). Método de Ayuda para la toma de Decisiones y la Realización de Evaluaciones de medicamentos (MADRE). [Internet] Versión 4.0. Madrid: SEFH; 2013 [accessed 02/2021]. Available at: http://gruposdetrabajo.sefh.es/genesis/genesis/basesmetodologicas/programamadre/index.html
12. Ortega A, Fraga MD, Alegre-Del-Rey EJ, Puigventos-Latorre F, Porta A, Ventayol P, *et al.* A checklist for critical appraisal of indirect comparisons. Int J Clin Pract. 2014;68:1181-9.
13. Philippo DM, Ades AE, Dias S, Palmer S, Abrams KR, Welton NJ. NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submission to NICE [Internet]. NICE; 2016 [accedes 02/2021]. Available at: http://nicedsu.org.uk/wp-content/uploads/2018/08/Population-adjustment-TSD-FINAL-ref-rerun.pdf. Acceso 15/02/2021
14. López-Briz E, Fraga-Fuentes MD, Clopés-Estela A, Ortega-Eslava A, Alegre-Del Rey EJ. Drug evaluation is also a clinical activity. Farm Hosp. 2020;45:45-7.