analesdepediatría

www.analesdepediatria.org

EDITORIAL

Medicines of high health and economic impact: The required balance between innovation and sustainability☆

Medicamentos de alto impacto sanitario y económico: el necesario equilibrio entre innovación y sostenibilidad

Francisco J. Morales-Olivas

Departamento de Farmacología, Facultad de Medicina y Odontología, Universitat de València, Valencia, Spain

The use of medicines in children involves peculiarities due to the lower knowledge of their effects in this population and the methodological and ethical limitations that affect clinical research in paediatrics. In addition, most rare diseases manifest during childhood, and the availability of drugs to treat them ranges from low to non-existent. To these challenges we must add the concern voiced by some authors that medicines with a high economic impact (an euphemism for ''very expensive'') threaten the sustainability of the health care system. The picture may appear bleak, but an adequate analysis of the current situation allows us to hope for a future with more and better drugs for paediatric patients.

This issue of *Anales de Pediatría* includes two articles that contribute to our understanding of the use of new medicines in everyday clinical practice. One[1] describes the real-world effectiveness of ivacaftor, a drug that potentiates the cystic fibrosis transmembrane conductance regulator, which has been found to improve nutritional status and lung function in clinical trials. The study includes 4 children aged 6 to 14 years with cystic fibrosis and the F508del/G551D mutation that were followed up for a median of 24 months of treatment with ivacaftor. The aim was to assess whether the benefits observed in the carefully selected patients in clinical trials would extend to real-world patients that do not meet the inclusion criteria for trials. The article described the outcomes in each individual patient, and all of them improved. None experienced adverse events. The authors discuss the results thoroughly and remark on the usefulness of these studies to assess the effectiveness of drugs that have proven efficacious under experimental conditions. We ought to highlight that one of the patients had to wait to be 6 years of age to receive treatment. The reason was that the drug was not formulated in a way that would allow appropriate dosing in children with weights of less than 25 kg and is only approved for use in patients aged 6 years with weights of at least 25 kg.

It is remarkable that there are no formulations for young children of a medicine designed to treat a disease that is usually diagnosed in the first years of life, despite the economic advantages that come with its classification as an orphan drug.

It may seem that the publication of the outcomes of 4 patients of heterogeneous characteristics is of little scientific interest, but given the difficulty of conducting

☆ Please cite this article as: Morales-Olivas FJ. Medicamentos de alto impacto sanitario y económico: el necesario equilibrio entre innovación y sostenibilidad. An Pediatr (Barc). 2019;90:139–140.

E-mail address: Francisco.Morales@uv.es

clinical trials in this age group, a register of data of treated patients may be very useful to document and analyse the effects of new drugs after authorization to confirm or refute their usefulness in real-world practice. A study that was recently conducted in Ireland[2] by reviewing data from a register of patients with cystic fibrosis and which followed up treatment with ivacaftor over 36 months obtained results similar to those reported by Gómez-Cámara et al, and concluded that ivacaftor not only improved clinical outcomes, but also reduced health care costs in the management of these patients.

This aspect, the reduction of health care costs besides the cost of the drugs themselves, is an important factor to consider in the accurate assessment of the impact of expensive drugs on the sustainability of the health care system. We must not forget that the cost of drugs is not the greatest contributor to health care expenditure, and that at least 30% of the pharmacy bill corresponds to brand-name medicines protected by a patent. Should the sustainability of the system be truly threatened, some experts propose solutions such as fixing drug prices based on the actual value of drugs, capping total expenditure per product, making payments per cured patient, decreasing drug prices based on the number of treated patients or a combination of all of the above so that economic risk would be shared by health care systems and pharmaceutical companies. Price should not be a limitation if a drug truly resolves a problem for which there is no efficacious treatment.

The other such study in the current issue[3] analysed the use of a combination of ledipasvir/sofosbuvir for treatment of children with hepatitis C virus infection. This combination has been authorised since 2014 for patients aged more than 12 years, but according to the authors, it was not at the time they conducted the study, which included 9 patients, 2 of them younger than 10 years, who were treated with half of the habitual dose used in adults (45/200 mg versus 90/400 mg). To date, there is only one published clinical trial in children, and it only included children aged more than 12 years. The characteristics of the patients were not homogeneous and individual outcomes were not described for each patient, and therefore, although the authors concluded that treatment was effective, with a reduction in viral load at 12 weeks of treatment and only 3 patients experiencing adverse effects that were mild, it would not be possible to enter its effects on children aged less than 12 years to a hypothetical database. The authors noted that in the younger children the combination was given as off-label treatment, but we need to keep in mind that the enactment of Royal Decree RD 1015/2009, which regulates the use of medicines under special conditions, has simplified the off-label use of authorised drugs under conditions other than those stipulated in the summary of product characteristics, for which the previously required official authorization is no longer needed. At present, all that is needed is informing the patient on the associated risks and benefits, documenting it in the health records and obtaining a signed written informed consent. Compassionate use is currently restricted to drugs undergoing clinical trials for their use outside the context of such trials.

Whereas in the past they used to say that children needed to be protected from clinical research, today we can assert that the best way to protect them is to have them partake in ethical and high-quality clinical research, which is not limited to clinical trials. Individual patient data from appropriately documented case series can obviate the need to perform complex trials. This possibility is illustrated by the application of article 45 of the European Paediatric Regulation (1091/2006), which requires pharmaceutical companies to submit all the data available from paediatric studies to update the information on drugs for which research had been conducted and perhaps even published, but is not reflected in the corresponding summary of product characteristics. After 7 years of work, many of these summaries have been modified, including further clarification about paediatric use, specific safety aspects and even new indications.[4] The recurrent claim that there is a dearth of paediatric data is not entirely true; instead, there seems to be a considerable amount of scattered data that could be very useful if analysed as a whole. All the data collected through the enactment of article 45 is entered in an open-access database.[5]

The conditions under which drugs are used in the management of paediatric patients have improved in recent years, but off-label use continues to be too frequent. The development of new drugs that are effective, but at a very high price tag, demands that we collect and analyse all the available information to determine as soon as possible whether or not they are of high therapeutic value. Given the difficulties involved in conducting clinical trials in children, the establishment of registers of data published in studies like the ones discussed here could contribute to a better use of medicines.

References

1. Gomez-Pastrana D, Nwokoro C, McLean M, Brown S, Christiansen N, Pao CS. Efectividad de ivacaftor en vida real en niños con fibrosis quística y mutación G551D. An Pediatr (Barc). 2019;90:148–56.
2. Kirwan L, Fletcher G, Harrington M, Jeleniewska P, Zhou S, Casserly B, et al. Longitudinal trends in real-world outcomes following initiation of ivacaftor: a cohort study from the cystic fibrosis registry of Ireland. Ann Am Thorac Soc. 2018, http://dx.doi.org/10.1513/AnnalsATS.201802-149OC [Electronic publication].
3. Quintero J, Juampérez J, Julio E, Cabello V, Mercadal-Hally M, Soler-Palacín P, et al. Combinación de ledipasvir/sofosbuvir como tratamiento de la infección crónica por hepatitis. An Pediatr (Barc). 2018, http://dx.doi.org/10.1016/j.anpedi.2018.07.007.
4. Saint-Raymond A, Pelle B, Zaccaria C, Sennwitz M, Branch S. Usage of unpublished paediatric data. Arch Dis Child. 2016;101:81–4.
5. EMA List of recommended changes to product information for nationally-approved medicines. Available from: http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/Paediatric_Regulation/Article_45_and_previous_Worksharing/CMDh-124-2008-Rev4.xls [accessed 26.12.18].