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Assessment of drug use in special situations: evidence levels to guide off label prescribing

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Article 6 of directive 2001/83 /EC requires that medicinal products are authorised before they are marketed in the Community. Unauthorised medicinal products may be available through an approved clinical trial protocol. A treatment option for patients in European Union suffering from a disease for which no satisfactory authorised alternative therapy exists or who cannot enter a clinical trial, may be use of an unathorised medicinal product in a Compassionate Use Programme. On the other hand, although off-label prescribing (the prescription of a medication in a manner different from that approved by EMA) is common, it is often done in the absence of adequate supporting data. Off-label uses have not been formally evaluated. Spain has a new regulation regarding the use of drugs in special situations (Royal Decree 1015/2009).

Objectives: To describe the drugs required to be used in off-label (OL) and unlicensed (UL) situations, and the clinical indications for its use. To evaluate evidence level of the above prescriptions.

Methods: A cross-sectional study including all applications in 2010. Setting: University Hospital. Analysis: Review of SmPC and evidence according to the NICE. Descriptive analyisis.

Results: A total of 451 applications regarding off-label use of medication were submitted to the Standing Pharmacy Committee. Among them we identified 84 different indications or types of applications, mainly from Oncohaematology Service. Applications corresponded to a total of 41 drugs. The most frequently requested pharmacological groups (ATC) were: L (56%%), J (17%) and H (4.8%). However, taking into account the number of applications, was group A the most requested, due to the high rate of applications of misoprostol for labor induction due to fetal death (N=273, 60%). Some drugs were used for more than a different OL use (eg: rituximab for 9 indications, immunoglobulins and erythropoietin for 6, or bevacizumab for 5). 47% of the applications was not well supported (levels 2-3 according to NICE; eg: raltegravir in children, adalimumab for Birdshot retinopathy, or bevacizumab for prematurity retinopathy), while 53% was based on at least one clinical trial (eg: erythropoietin for anemia secondary to ribavirin, omalizumab for atopic dermatitis or Immunoglobulins for miastenia gravis). There were only two applications with very high level of evidence (botulinum toxin for neurogenic bladder and mycophenolate for lupus nephritis). There are drugs with different support depending on the disease: good evidence level for one (bevacizumab for neurovascular glaucoma) and bad for another (bevacizumab for glioblastoma multifome). A total of seven treatment protocols previously approved by the Spanish Medicines Agency are being used. Regarding the compassionate use, 35 applications were received, involving the following active principles: thalidomide, everolimus, vinflunine, teprostinil, ipilimumab, pazopanib, abiratenone, alitretinoin, stiripentol, fingolimod, glycopyrrone, idebenone, picibanil, plerixafor.

Conclusions: Our findings identified a high volume of OL prescribing in the absence of good evidence (suppositional or investigational, but not supported uses). Future research should focus on these drugs, particularly if are known to have safety issues, and/or are costly or being marketed heavily.