Adverse reactions to biological medicinal products: analysis from the Italian spontaneous reporting system

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Introduction

Biological therapies (i.e. biologicals) have revolutionized the pharmacological treatment of important chronic diseases. Compared with the traditional small molecule drugs, biologicals have specific characteristics, which might also influence their safety profile. Increased risk of infection, malignancy, or administration reactions has been described for most of these compounds. Other adverse effects have been specifically reported in association with individual biologicals, as a result of the exerted action on selected targets. Furthermore, animated debate exists about both effectiveness and safety of biosimilars. In this context, comparative safety evaluation of biologicals and biosimilars in clinical practice is warranted.
The aim of this study is to analyze adverse reactions regarding biologicals and biosimilars received from the Italian spontaneous reporting system (SRS).

Methods

We performed an analysis on the Italian SRS database from 2001 to 2012. We selected all the adverse drug reaction (ADR) reports attributed to biologicals, classified in the following mechanistic classes: a) monoclonal antibodies and fusion proteins; b) cytokines and antagonists; c) enzymes; d) recombinant hormones; and e) others. Vaccines, toxins, blood derivatives, and radiopharmaceuticals were excluded from the analysis. Frequency analyses for biologicals and, separately, for biosimilars have been conducted.

Results

Overall 165,310 ADR reports have been collected and, of these, 9,196 (5.6%) were related to biologicals. The mean age of patients with biological-related ADR was 58 years (female/male= 1.2). Serious ADRs, including 148 fatal cases, accounted for 38.7% (N=3,563) of total reports. Regarding specific mechanistic classes, 6,339 reports (68.9%) were associated with monoclonal antibodies and fusion proteins, 1,493 (16.2%) with cytokines and antagonists, 1,213 (13.2%) with recombinant hormones, 167 (1.8%) with enzymes, and 76 (0.8%) with others. Concerning therapeutic classes, two-thirds of all ADR reports involved anticancer monoclonal antibodies (n=3,562; 38.7%), TNF-alpha Inhibitors (n=1,876; 20.4%) and interferons (n=1,052; 11.4%). The most frequently implicated individual biological agents were: bevacizumab (12.1%), cetuximab (11.2%), rituximab (9.7%), and infliximab (8.8%). Reported ADRs were more frequently 'skin and appendages disorders' (17.0%), 'general disorders' (14.1%), and 'gastro-intestinal system disorders' (11.3%). Moreover, 265 (1.8%) cases of cancer were reported.
As regard biosimilars, 138 reports (1.5% of total reports for biopharmaceuticals) were identified. Among these, 62 (44.9%) were related to filgrastrim, 42 (30.4%) to somatotropin, and 34 (24.6%) to epoetins. Overall, 20 (14.5%) reports concerned drug ineffectiveness, which were almost equally distributed between epoetins (N=11) and filgrastrim (N=9).

Conclusions

Based on these results, most of the ADR attributed to biologicals seems to be immune system-related. Several reports of cancer have been described, which requires further investigation. With respect to the specific therapeutic classes, monoclonal antibodies are the most frequently implicated biologicals. This finding may be due to the fact that the registry-based monitoring existing for these and other biopharmaceuticals in Italy may facilitate ADR reporting. A low proportion of biological-related ADR reports concern biosimilars and a relevant proportion of them indicate drug ineffectiveness.