Biosimilars-induced Adverse Drug Reactions. Analysis of the Italian Pharmacovigilance Database

G. Stoppa[1], S. Opri[1], L. Sottosanti[2], U. Moretti[1], M. Pagliarini[1], A. Conforti[1]

[1]Dept. of Public Health and Community Medicine, Section of Pharmacology, University of Verona, Italy
[2]Italian Medicines Agency, Pharmacovigilance Office, Rome, Italy

Since 2006, the expiration of the patent covering the first generation of biotech drugs has allowed the marketing of biosimilars in Italy. Unfortunately, the medical community has concerns about the potential toxicity of biosimilars. By the end of 2014, three biosimilars (epoetin alfa or zeta, filgrastim, and somatropin), were marketed in Italy. Pharmacovigilance could help to clarify doubts about the safety and their risk/benefit profile. In Italy the national network of pharmacovigilance, RNF, has been active since 2001 and ensures the collection, management and analysis of spontaneous reports of suspected adverse drug reactions, ADRs. We searched the ADR reports from 2001 to 2014 for epoetin and filgrastim to test whether the RNF can extract useful information on their safety profiles. We excluded from the analysis somatropin because in the RNF there are too few ADR reports for biosimilars. Recombinant human erythropoietin (epoetin) is approved for the treatment of anemia secondary to renal diseases and to chemotherapy treatment. Total epoetin reports over the period are 84 for originator drug (Eprex®) out of which 51% serious, and 128 for biosimilars (Binocrit® and Retacrit®) of which 30% serious. We detected interregional differences, particularly the large number of biosimilars' reports collected in Sicily. This may be related to regulatory measures which made the prescription of the originator possible only if a patient experienced ADR from biosimilars. The most frequently reported serious originator drug ADRs are anemia, pure red cell aplasia and bone marrow failure, and for biosimilars is the lack of therapeutic response.

Filgrastim is a glycoprotein which regulates the production and release of functional neutrophils from the bone marrow. We found a total of 49 reports for originator (Granulokine®) out of which 43% serious, and 145 for biosimilars (Ratiograstim®, Tevagrastim®, Zarzio® and Nivestim®) of which 33% serious. The most frequently reported serious originator drug ADRs affect the skin (rash, dermatitis, erythema) and for biosimilars are the lack of therapeutic response, neutropenia and chest pain. Our analysis suggests the difficulty of comparing the safety profiles of originators with biosimilars, due to multiple confounders in pharmacovigilance system. Some of the confounders identified were: i) the different dates of marketing authorization of originators and biosimilars with different reporting rates of ADRs in Italy in the considered years. For example in 2001 the Italian reporting rate was 131 reports/million inhabitants (one of the lowest in Europe) while in 2014 was 858 (one of the highest in the world); ii) the distrust of biosimilars by the medical profession may have led to the phenomenon of "selective reporting", because clinicians focused on biosimilars ADRs; iii) regional regulatory measures may also have contributed to a certain distortion, as underlined by the AIFA. On the other hand, our analysis showed that the reports involving biosimilars are mainly not serious. Studies of active surveillance may be more appropriate instrument to counteract an inadequacy of the pharmacovigilance system to provide reliable information.