Box S1 | **Pharmacovigilance and the role of regulators**

Pharmacovigilance is an essential instrument in recognizing and acting upon the emergence of adverse reactions. This becomes critical for adverse reactions that are not identified in either preclinical tests or clinical trials. For example, serious infections associated with efalizumab therapy were only identified in the post-marketing phase leading to its withdrawal from the market. Another immunomodulatory biologic, alefacept which targets CD2, a human T-lymphocyte molecule, was shown to be relatively safe with respect to infections in clinical trials[1,2]. However, reports of serious infections have been documented after approval. Pharmacovigilance registers can be a key resource in quantifying the nature and magnitude of risks associated with immunomodulatory biologic therapy. European registries such as the British Society for Rheumatology Biologics Register (BSRBR), Rheumatoid Arthritis-Observation of Biologic Therapy (RABBIT), anti-rheumatic therapy in Sweden (ARTIS), Dutch Rheumatoid Arthritis Monitoring (DREAM) and British Association of Dermatologists Biologic Interventions Register (BADBIR) are active in this regard. A global pharmacovigilance register specifically for biologics does not exist but the World Health Organisation's (WHO) VigiBase and EMA's EudraVigilance collect data on adverse events associated with all drugs including biologics. The role of regulators in strengthening pharmacovigilance is well recognised. European regulators have protocols in place for intensive monitoring of newly licensed therapeutics (soon to be introduced throughout the EU) and this enhances the degree of pharmacovigilance and enables rapid regulatory response when adverse reactions arise. Regulatory bodies thus play a key and essential role in the mitigation and prevention of biologics-induced adverse reactions. The complexity of this area has been further increased by the arrival of biosimilars with differences in opinions as to how these should be regulated. The FDA has recently developed guidance in this area in 2012, whilst the European Union has had guidance in place since 2005. The regulatory bodies been at the forefront of efforts aimed at the construction of a systematic framework for ensuring the safety of biosimilars[3-6]. Filgrastim (G-CSF) is currently the only immunomodulatory biosimilar approved by the EMA. Other biosimilars at various stages of development include mAbs (e.g. trastuzumab and rituximab) and interferons[7]. Thus far, the EMA experience of biosimilar drug safety has been encouraging. The current regulatory focus on assuring safety of biosimilars is on instituting robust pharmacovigilance measures. However, EMA guidelines do take into account biophysical properties, preclinical data and clinical trial data for all biosimilar products. That such approaches can be effective is exemplified in the case of the biosimilar Alpheon (interferon-α) whose authorisation was refused by the EMA on the grounds of safety concerns and decreased efficacy compared to its reference product Roferon-A[8]. It has been have suggested that an important point to consider with biosimilars is the potential for immunogenicity[6]. Some minor differences in certain parameters such as variation in post-translational modifications are currently allowed as long as they do not impact the pharmacokinetics, efficacy and safety of the biosimilar. This is done on a case by case basis, as some of the post-translational modifications can influence immunogenic responses more than others. Since, immunogenicity of biosimilars cannot be fully predicted by preclinical tests, the current regulatory practice is to present clinical trial data, apply post-approval pharmacovigilance procedures through risk management plans and act on any reports of emerging adverse reactions. Regulators therefore can, by setting the right terms of reference, influence how the pharmaceutical industry develops biologics which have a reduced risk of developing unwanted effects.

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