IMMUNOMODULATORS FOR MS: GENERICS VS. ETHICAL DRUGS
ETHICAL DRUGS

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As intellectual property protections are beginning to expire after more than 20 years of treatment with immunomodulatory drugs, cheaper follow-on biologics (FOB) or biosimilars (meaning - biological products which are similar, but not identical, to reference products) for interferon-beta (IFN-β) and follow-on for the nonbiologic complex drug (NBCD) glatiramer acetate (GA) are entering the vibrant market of multiple sclerosis (MS) therapies. In contrast to generics for small molecule drugs, the greater complexity of biologics or NBCD and the possibility of differences in bioavailability and immunogenicity introduced by manufacturing differences make their comparability to their innovator products more difficult, and may result in unpredictable differences in efficacy or safety.

Small molecule drugs are generally organic chemicals of 300-1000 Da in size, with a limited number of functional chemical groups. The requirements for demonstrating therapeutic equivalence of their generics to the innovators are quite simple and consist of demonstrating pharmaceutical equivalence (i.e. identical active substances) and bioequivalence (i.e. comparable pharmacokinetics) in a cross over volunteer study, in addition to structural identity. No further clinical trials are required. On the other hand, biologics and NBCD show greater chemical and structural complexity:

Biologics contain many more functional groups in a chain of tens to hundreds amino acids, typically 10,000 to 30,000 Da in size (or as large as 150,000 Da for monoclonal antibodies), and may contain secondary, tertiary and quaternary structural features. Proteinaceous biologics may also have post-translational modifications such as fatty acylation(s) and multiple phosphorylation and glycosylation sites required for biologic activity. Therapeutic protein preparations are produced by living cells and may be lacking terminal amino acids or contain process related impurities like host cell proteins, and their storage may result in other modifications such as aggregation and oxidation. The dose–response curve of biologics is often non-linear, bell shaped and/or protracted, and the predictive value of PK studies for the clinical activity of biologics has not been established. Some of these products may be metabolized at the injection site or enter the lymph system directly from the injection site without entering the circulation, and the presence of the endogenous homolog or neutralizing antibodies may alter the pharmacokinetic behavior of the exogenously administered biologic, decrease its efficacy or induce side effects. These complexities may have major impacts on bioequivalence and therapeutic equivalence and can affect immunogenicity and adverse event profiles with even minor differences in manufacturing conditions or by using different cell-lines or bioreactors in the manufacturing process. What is purported to be the "same" product may have different biologic behavior even when made by a single manufacturer in different locations. Thus, it is likely that the structure and function of a biologic and its biosimilar may differ greatly. An FOB is expected to be comparable to its innovator and show therapeutic equivalence: equally safe, comparably effective, and substitutable. Therefore, strict evaluation of comparability between FOBs and their innovators is essential. This requires strict regulation over their development and approval, including the need for additional preclinical testing and properly conducted clinical trials before the marketing approval of an FOB. Even after approval, long-term monitoring of safety is essential to uncover unexpected differences resulting from changes in manufacturing, handling, or use practices. Guidelines on similar biological medicinal products containing IFN-β issued by the EMA include both preclinical (comparative in vitro bioassays, e.g. receptor binding, anti-viral, anti-proliferative and immunomodulatory activitie) and clinical (crossover comparative PK/PD study and comparative efficacy/safety clinical trial of at least 12 months duratin with a placebo arm for a short period and MRI endpoints) development. These complexities and the lack of appropriate regulation in some parts of the world may explain why several IFN-β biosimilars have failed to show therapeutic or biological equivalence to their innovator products.

NBCD may present even greater degree of complexity than biologics produced by recombinant DNA technology:

Glatiramer acetate (GA, Copaxone®, Teva Pharmaceuticals, Israel) is the prototype and the only approved member of the Glatiramoid class, a family of complex heterogeneous mixture of synthetic polypeptides composed of the L-isomer of glutamate, lysine, alanine and tyrosine

in a pre-defined molar ratio and an averaged molecular weight of 5,000-9,000 Da. The random polymerization of these 4 amino acids may result in $>10^{29}$ possible theoretical sequences.

As GA is not a single molecular entity but rather a heterogeneous mixture of potentially millions of distinct, synthetic polypeptides of varying lengths, no two glatiramoid mixtures prepared by different manufacturers can be shown to be "identical". The consistency of polypeptide sequences within GA is dependent on a well-controlled proprietary manufacturing process. The complexity of glatiramer acetate is amplified by the fact that its exact mechanism of action is unknown, and the specific amino acid sequences (epitopes) responsible for efficacy and safety cannot be identified. Furthermore, bioequivalence cannot be established by pharmacokinetic ("PK") or pharmacodynamic ("PD") testing due to the rapid hydrolysis of glatiramer acetate at the site of injection and its uptake by local antigen presenting cells, and the lack of validated PD markers of glatiramer acetate activity. A series of well-controlled manufacturing processes and rigorous testing procedures developed specifically for GA analysis were designed and implemented to ensure the batch-to-batch consistency, safety and efficacy. Minor differences in the manufacturing process of the glatiramoids can produce altered polypeptide sequences, which are likely to affect the safety and efficacy of the product. A single change introduced in the manufacturing process of GA resulted in a new glatiramoid product (denoted TV-5010 or protiramer) that caused significant toxic effects in animals, especially in long- term, repeat-dose studies. Therefore, it is not possible to predict the toxicity of a glatiramoid from its structural characteristics or bridging, shorter-term toxicity studies. TV-5010 also shows increased immunogenicity profile than GA, suggesting that the structural differences may affect the immune response. Thus, a complete analysis of the immunogenicity profile as well as a detailed physical and chemical, biological and immunological characterization of any glatiramoid should be performed as part of the non-clinical and clinical studies. Since neither PK analysis nor validated pharmacodynamic markers for clinical efficacy are available, clinical efficacy and safety of glatiramoid similars should be established, preferably in a three arm clinical trial in MS patients.

Different lots of Copaxone demonstrate structural, biological, clinical and safety similarities and consistencies. However, when compared with another 3 glatiramoids – Glatimer (Natco, India), Probioglat (Probiomed, Mexico), and Escadra (Raffo, Argentina), substantial differences in their physico-chemical properties, immunogenicity, gene expression, impact on biological pathways, safety profiles and most importantly – clinical efficacy, have been shown. These differences should preclude their use as "generics" for GA, and call for more stringent regulations and carefully designed, comparative clinical trials to ensure the efficacy and safety of follow-on glatiramoids.