Clinical and scientific aspects related to biosimilars in inflammatory bowel diseases (IBD): position document of the Belgian IBD Research Group (BIRD)

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1. Introduction

The management of chronic inflammatory disorders including inflammatory bowel diseases has been revolutionized by the entrance of biological agents now almost 20 years ago. Over 350 million of people have been treated worldwide with biologicals. In Belgium, biologicals represent 26% of the total Belgian pharmaceutical budget both in the ambulatory settings and in the hospitals (53% are used in hospitals). In inflammatory bowel diseases (IBD), biological agents directed against TNF alpha are mainstay treatments for inducing and maintaining remission in moderate to severe Crohn's disease and ulcerative colitis. Three anti-TNF agents have been approved by EMA for use in Crohn's disease (infliximab and adalimumab) or ulcerative colitis (infliximab, adalimumab and golimumab). Eighteen years after the finalization of the pivotal trials, the patent for infliximab was the first to expire. Hence, biosimilare to infliximab are emerging on the market including for the treatment of IBD. Biosimilars are biological drugs which are similar to the authorized biologics ("reference product") but not identical. Recently EMA has approved 2 biosimilars to infliximab on the basis of two trials in rheumatology. Notwithstanding the potential economic benefits the extrapolation across indications has caused concern about their efficacy and safety with physicians. Within the Belgian IBD Research group (BIRD), a discussion was held and the summary is reflected in this position document.

2. Biosimilars of anti-TNF: overview and EMA regulation

According to the European Medicines Agency (EMA), a biosimilar is a biological medicinal product claimed to be similar to an approved reference biological medicinal product. The evaluation process for the registration of a biosimilar within EMA is focusing on proving the similarity between the

reference product and the biosimilar. Both quality, safety and effectiveness are studied under strict criteria. So far, 21 biosimilars have been approved in Europe as of September 2014, of which 2 anti-TNF biosimilars, namely Remsima® and Inflectra®. It is important to emphasize that a biosimilar of a biologic agent is similar but not identical to its reference product and therefore not the same as a generic of a small molecule. Biological agents are manufactured from living systems including organisms, cells or tissue cultures. The production of recombinant proteins starts with cell expansion and cell production in bioreactors, after which they are recovered through filtration or centrifugation and subsequently purified by chromatography. Each of these processes has product-specific characteristics: the type of cell line used, the media in which the cells grow, the methods of expansion, the conditions in the bioreactors, binding and elution conditions for the purification process etcetera. A small molecule is chemically synthesized, has a defined structure, is 100% reproducible, stable, will not induce an immunogenic response and is not or much less sensitive to process changes. Biological drugs in contrast are large complex instable molecules, grown from cells with a heterogeneous structure, are immunogenic and sensitive to changes in the manufacturing process. In fact, also the original molecule infliximab (Remicade®) has undergone several (probably subtle) changes over the past decades including changes in cell line and strictly taken, infliximab of today could be seen as its own biosimilar compared to the infliximab generated in 1995.

3. Biosimilar development- EMA regulatory approval process

For all these reasons the process of development of biosimilars is tightly regulated by the regulatory authorities (EMA and FDA). First, the quality control of the drug needs to follow the same procedures as for an original compound but includes for a biosimilar also an analytical comparison with the reference product. Proving similar to a reference product requires often multiple iterations of process change and physicochemical characterization. A number of functional activities need to be demonstrated: binding to the target (antigen binding (Fab) portion) and to its receptors (constant domain (Fc fraction): Fcgamma receptor RI to RIII, neonatal Brambell receptor (FcRn essential salvage from clearance of monoclonal antibodies) and complement factors (e.g. C1Q). Next to binding capacities functional properties need to be demonstrated including Fab-associated functions such as neutralization and activation and Fc-associated functions as ADCC and CDC with complement activation. In turn and specific for biologic agents a number of preclinical studies such as pharmacokinetics and toxicologic studies are not mandatory. The validation process includes preclinical and PK/PD studies to confirm the biosimilarity and clinical efficacy trials. For the latter, 2 trials are required, one studying the pharmacology and pharmacokinetics using a single dose and a

second pivotal study on efficacy and safety in 1 indication. This indication remains to be chosen by the manufacturer. The EMA guideline in this states that in general, the most sensitive patient.

4. Clinical comparability studies in rheumatology

Remicade® has approved indications in Crohn's disease, ulcerative colitis, rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis and psoriasis. The biosimilar performed a Phase 1 pharmacokinetic study in patients with AS. This study, called Planetas, was performed in 250 patients. The large equivalence study (Planetra) was done on 606 RA patients. With these 2 studies, Remsima and Inflectra automatically got all the Remicade-approved indications from EMA. However clinicians from different fields lack important data e.g. for IBD no information on mucosal healing, corticosteroid-free remission or immunogenicity and loss of response in CD or UC patients is available.

5. Can the clinical efficacy from other diseases be extrapolated?

Within the BIRD group, the position of biosimilars and reference drugs in the management of IBD patients was carefully examined and discussed and some important remarks were made. We feel that extrapolation from the Planetra and Planetas studies to Crohn's disease and/or ulcerative colitis cannot be done. Besides the above-mentioned reasons of lack of data, an additional reason is that the mode of action of infliximab may be different in the different diseases. We know that in RA, AS and psoriasis, mainly binding to soluble TNF-alpha is required whereas in IBD, binding to membrane-bound TNF and inhibition of cytokine production seem to be more important. The results of etanercept in RA as compared to CD are a well-known example of the difference in efficacy between the diseases. Therefore, the group felt unanimously that clinical efficacy studies in IBD are needed. In this respect, a large randomized double-blind comparative study in active CD is about to start. This study will randomize patients to Remicade or Remsima and study response, remission and healing rates and immunogenicity. There is a cross-over after 6 months to the other arm. Only this type of studies will give more solid conclusions in IBD. Also, pediatric patients have not been exposed to biosimilars yet. It is nevertheless anticipated that biosimilars will also gradually be used in children under the age of 18. The BIRD group felt that the same statements made for adult patients should apply also to pediatric patients. Studies specifically looking at some pediatric outcomes such as growth and development are therefore welcomed.

6. Biosimilarity and interchangebility

Governments and health authorities are under considerable financial pressure. Financial advantages may therefore stimulate governments to impose these biosimilars. We feel it is important that physicians maintain control over prescribing these products and financial pressure alone should never become the driver for the decision. It is anticipated that biosimilars will lead to a cost reduction of 20 to 30%. During the life cycle of biologicals, there are already a number of reductions in their price. Eighteen years after their introduction, a biological drug has decreased with 25% of its price as compared to the original level. The development of a biosimilar is significantly more expensive than the development of a generic drug. The anticipated reduction in cost will therefore be less as compared to the reduction for generic drugs. The above remarks and comments on efficacy also apply to safety. It is anticipated that the profile of side effects and complications will overlap with the safety profile of the reference drugs, but new side effects related to the preparation of the biosimilar (i.e. purification) may be reported. Biosimilarity does not imply that the drugs are interchangeable. Furthermore, there is so-called divergence over time and this may go in opposite directions for the reference product and the biosimilar. Additional safety factors should also be considered such as previous exposure to anti-TNFs. These concerns raised by the BIRD Group are shared with IBD specialists from all over the world. For example, Health Canada decided to approve the biosimilar-infliximab only for RA, AS, PsA and Pso. Because of the lack of convincing safety and efficacy data, adult and pediatric IBD are currently not withheld as extrapolated indications.

7. Safety

As for all medicinal products a risk management plan is developed and an adequate pharmacovigilance is set up to ensure permanent follow-up of the safety of the medicinal product after market authorization. Additional risk minimization activities are treated national by the FAGG/AFMPS. As mentioned above specific for biologicals is their ability to cause immunogenicity. This is very important as it may affect safety and efficacy. Immunogenicity can not be predicted by preclinical studies. Testing immunogenicity requires specific longitudinal tests such as detailed pharmacokinetics studies including testing for anti drug antibodies. Extrapolation of the safety data from the reference product is therefore impossible.

8. Conclusion

BIRD welcomes the advent of biosimilars agent if this can alleviate the financial burden for our patients and society. However it is important to realize that biosimilars are similar but not identical to the reference product. Therefore as physicians we have concerns about the efficacy and safety of the biosimilars. There is still very limited clinical experience with anti-TNF biosimilars and future studies are therefore needed. Therefore BIRD specifically feels as a group that direct evidence of safety and benefit from clinical trials in IBD is needed before we can advocate the use of biosimilars in IBD. Meanwhile, we recommend not to switch a patient who has a durable response on infliximab to the biosimilar-infliximab. It is likely that anti-TNF naïve patients will benefit equally from infliximab or infliximab-biosmilar but a large international study is underway to hopefully show this. There are no data about cross-linking anti drug antibodies, therefore one cannot advise on the safety of starting biosimilars in patients with prior use of infliximab or in patients with infusion reaction to infliximab.

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