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

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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 patients 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 (CD) and ulcerative colitis (UC). 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, biosimilars 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 a rigorous and extensive comparability exercise in all characteristics via a development programme that included quality, nonclinical and clinical data including two clinical trials in rheumatology (ankylosing spondylitis and rheumatoid arthritis) (1).

Notwithstanding the potential economic benefits, the extrapolation across indications has caused concern about their efficacy and safety. Within the Belgian IBD Research & Development group (BIRD), a discussion was held and the summary is reflected in this position document.

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 highly similar to an approved reference biological medicinal product. The evaluation process for the registration of a biosimilar within EMA is focused on proving a high degree of similarity between the variability of a reference biologic product on structural and functional attributes and the variability of the biosimilar on the same attributes. Quality, safety and effectiveness attributes are studied under strict criteria, similar to those required by EMA after manufacturing changes for reference biologics. So far, 21 biosimilars have been approved in Europe as of September 2013, of which 2 are 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, which is chemically synthesized (2). Because all biological agents are manufactured from living systems including organisms, cells or tissue cultures, they all exhibit inherent variability, and therefore non-identicality is the norm. 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

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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. In contrast, a small molecule is chemically synthesized, has a defined structure, is 100% reproducible, rarely immunogenic, and is much less sensitive to process change. Biological drugs are large complex molecules, grown from cells with a heterogeneous structure, are often immunogenic and sensitive to changes in the manufacturing process. It is well-known that reference biologics also demonstrate batch-to- batch variability and that multiple versions may be in the market at the same time. In fact, the originator biologic, Remicade® (infliximab), has undergone more than 40 (minor and major) manufacturing changes over the past decades including the introduction of a new manufacturing plant (Malvern, PA, US). Strictly taken, the Remicade® of today could be seen as its own "biosimilar" compared to the Remicade® initially manufactured in 1995. For each manufacturing change, the company must demonstrate similarity to the original version through analytic structural and functional comparability exercises.

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 extensive comparability exercise with the reference product, via state-of-the art analytical techniques to assess non-clinical structural and functional data. 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 Antibody Dependent Cellular cytotoxicity (ADCC) and Complement-Dependent Cytotoxicity (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 must include PK/PD equivalence studies to confirm biosimilarity as well as therapeutic equivalence trials which assess comparative immunogenicity, safety and efficacy in the most sensitive patient population(s). The indication(s) for therapeutic equivalence is chosen by the manufacturer, but approved by CHMP prior to study.

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 was studied in a Phase 1 pharmacokinetic study in patients with AS. This study, called PLANETAS, was performed in 250 patients and conducted for 54 weeks (3). The large equivalence study (PLANETRA) was performed in 606 RA patients and also conducted for 54 weeks (4). With these 2 studies and after assessing the totality of the data, Remsima® and Inflectra® received all the Remicade-approved indications from EMA.

The assessment of extrapolation for each indication is a case-by-case evaluation based on sound and objective scientific criteria. 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.

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.

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 its introduction, infliximab 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 known 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 as demonstrated in PLANETRA and PLANETAS, but new side effects of the biosimilar may be reported. The risk management plan (RMP) for biosimilars will be the same as that required for the originator biologic. In some cases, depending on the timing of the initial approval of the reference biologic, the RMP may be more extensive for a biosimilar. Biosimilarity does not imply that the drugs are interchangeable. 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 (5-8). For example, Health Canada decided to approve the biosimilar-infliximab only for RA, AS, and the extrapolated indications PsA and Pso (8). Because of a difference in an *in vitro* ADCC assay and because it was concluded that ADCC cannot be ruled out as an important mechanism of action in IBD, adult and pediatric IBD are currently not withheld as extrapolated indications. No differences were noted in ADCC assays that were conducted ex vivo, which was a more physiologic environment. The EMA felt that the ex vivo results overrode the in vitro results, and therefore did not feel that the in vitro result would result in a clinically meaningful difference between Remicade® and Inflectra®. Based on the ex vivo results, as well as a strong degree of similarity on all other Fab and Fc related functions and other mechanisms of action potentially important in IBD, EMA approved Inflectra® for the IBD indications.

Safety

As for all medicinal products a risk management plan is developed and adequate pharmacovigilance is set up to ensure quick identification and permanent follow-up of the safety of the medicinal product after market authorization. Additional risk minimization activities are treated nationally in Belgium by the FAGG/AFMPS (1). As mentioned above specific for biologicals is their ability to cause immunogenicity. This is very important as it may affect safety and efficacy. Immunogenicity cannot be predicted by preclinical studies. Testing immunogenicity requires specific longitudinal tests such as detailed pharmacokinetics studies including testing for anti-drug antibodies. Even though the results of the two clinical trials showed highly comparable pharmacokinetics and immunogenicity for both arms (Remicade® and biosimilar-infliximab) with different dosages and settings (monotherapy and combination therapy), the BIRD felt that extrapolation of the safety data from the reference product was impossible. The weighing of benefits and risks of a medicinal product as the time of approval will always include some uncertainty which, however, is anticipated to be less for biosimilars than for new innovative products.

Conclusion

BIRD welcomes the advent of biosimilar agents if this can alleviate the financial burden for our patients and society. However it is important to realize that biosimilars have a proven similarity without being identical to the reference product. Therefore as physicians we have concerns about the efficacy and safety of the biosimilars. Even though the EMA procedure is very rigorous, 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 fully can advocate the use of biosimilars in IBD. More specifically, as there are no data yet about cross-linking anti-drug antibodies, one cannot advise on the safety of starting biosimilars in IBD patients with prior use of infliximab or in patients with infusion reactions to infliximab.

Meanwhile, we recommend to start with naïve patients but 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 investigate this.

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