BIOLOGIC THERAPIES: FROM COMPLEXITY TO CLINICAL PRACTICE IN A CHANGING ENVIRONMENT

This symposium took place on 27th October 2015 as part of the United European Gastroenterology (UEG) Week 2015 in Barcelona, Spain

Chairperson

Remo Panaccione[1]

Speakers

Remo Panaccione,[1] Geert D'Haens,[2] Brian Feagan[3]

1. Department of Medicine, University of Calgary, Calgary, Alberta, Canada

2. Inflammatory Bowel Disease Center, Academic Medical Center, Amsterdam, Netherlands

3. Robarts Research Institute, University of Western Ontario, University Hospital, London, Ontario, Canada

Disclosure: Remo Panaccione has been a consultant for Abbvie/Abbott, Amgen, Aptalis, AstraZeneca, Baxter, BMS, Celgene, Cubist, Eisai, Ferring, Gilead, Janssen, Merck, Robarts, Salix, Samsung, Shire, Centocor, Elan, GlaxoSmithKline, UCB, Pfizer, and Takeda. He has participated in speaker's bureaux for Abbvie, Abbott, Aptalis, AstraZeneca, Ferring, Janssen, Merck, Prometheus, Shire, and Takeda; and advisory boards for Abbvie, Abbott, Amgen, Aptalis, AstraZeneca, Baxter, Eisai, Ferring, Genentech, Jansen, Merck, Schering-Plough, Shire, Centocor, Elan, GlaxoSmithKline, UCB, Pfizer, Bristol-Myers Squibb, Takeda, Cubist, Celgene, and Salix. He has received research/educational support from Abbvie, Abbott, Ferring, Janssen, and Takeda. Geert D'Haens has served as advisor for Abbvie, Ablynx, Actogenix, Amakem, Amgen, AM Pharma, AstraZeneca, Avaxia, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Celltrion, Cosmo, Covidien, Elan, Ferring, DrFALK Pharma, Centocor/Jansen Biologics, Engene, Ferring, Galapagos, Gilead, GlaxoSmithKline, Hospira, Medimetrics, Millenium/Takeda, Mitsubishi Pharma, Merck Sharp & Dohme, Mundipharma, Novo Nordisk, Otsuka, Pfizer, Protein Design Laboratories, Prometheus laboratories/ Nestlé, Receptos, Robarts Clinical Trials, Salix, Sandoz, Setpoint, Shire, Teva, Tigenix, Tillotts, Topivert, UCB, Versant, and Vifor; and received speaker fees from Abbvie, Ferring, Jansen Biologics, Merck Sharp & Dohme, Mundipharma, Norgine, Shire, Takeda, Tillotts, UCB, and Vifor. Brian Feagan has been a consultant for Abbott/AbbVie, Actogenix, Akros, Albireo Pharma, Amgen, AstraZeneca, Avaxia Biologics Inc., Avir Pharma, Axcan, Baxter Healthcare Corp., Biogen Idec, Boehringer Ingelheim, Bristol-Myers Squibb, Calypso Biotech, Celgene, Elan/Biogen, EnGene, Ferring Pharma, Roche/Genentech, GiCare Pharma, Gilead, Given Imaging Inc., GlaxoSmithKline, Ironwood Pharma, Janssen Biotech (Centocor), Johnson & Johnson/ Janssen, Kyowa Kakko Kirin Co Ltd., Lexicon, Lilly, Lycera BioTech, Merck, Mesoblast Pharma, Millennium, Nektar, Nestlé, Novo Nordisk, Pfizer, Prometheus Therapeutics and Diagnostics, Protagonist, Receptos, Salix Pharma, Serono, Shire, Sigmoid Pharma, Synergy Pharma Inc., Takeda, Teva Pharma, TiGenix, Tillotts, UCB Pharma, Vertex Pharma, VHsquared Ltd., Warner-Chilcott, Wyeth, Zealand, and Zyngenia. He has participated in speaker's bureaux for Abbott/AbbVie, Johnson & Johnson /Janssen, Takeda, Warner-Chilcott, and UCB Pharma; and advisory boards for Abbott/AbbVie, Amgen, AstraZeneca, Avaxia Biologics Inc., Bristol-Myers Squibb, Celgene, Centocor Inc., Elan/Biogen, Ferring, Johnson & Johnson /Janssen, Merck, Nestlé, Novartis, Novo Nordisk, Pfizer, Prometheus Laboratories, Protagonist, Salix Pharma, Takeda, Teva, TiGenix, Tillotts Pharma AG, and UCB Pharma. He has received grants/research support from Abbott/ AbbVie, Amgen, AstraZeneca, Bristol-Myers Squibb (BMS), Janssen Biotech (Centocor), Johnson & Johnson /Janssen, Roche/Genentech, Millennium, Pfizer, Receptos, Santarus, Sanofi, Tillotts, and UCB Pharma.
Acknowledgements: Writing assistance was provided by Dr Vanessa Lane, Medical Writing Limited.
Support: The symposium was jointly organised and funded by Abbvie. All authors received honoraria for preparation and delivery of their presentations. The publication of this article was funded by Abbvie. The paper is an interpretation of the views of the speakers, but is not written by them. The views and opinions expressed are those of the authors and not necessarily those of Abbvie.
Citation: EMJ Gastroenterol. 2015;4[1]:50-57.

MEETING SUMMARY

This symposium provided an opportunity for global experts to discuss the challenges posed by the introduction of biosimilars. The impact of the manufacturing process on clinical outcomes, maintaining

treatment responses over the long term, and issues surrounding patient management in a changing environment were addressed.

The symposium was opened by Prof Panaccione describing the evolution of inflammatory bowel disease (IBD) treatment in the last 20 years and how biologics have improved outcomes. Prof D'Haens provided an explanation of the complexity surrounding biologic drug development and the hurdles facing drug manufacturers when ensuring high quality and consistently performing products over time. Prof Panaccione discussed the clinical challenges in balancing the transition from induction to maintenance therapy in order to provide a clinically relevant and sustained response to therapy. He also discussed the evidence for long-term outcomes with adalimumab for IBD. Prof Feagan highlighted the issues faced by clinicians treating patients with biologics, including the ability to switch between biologics without loss of efficacy or impact on safety, and the need to consider interchangeability between biologic therapies and the potential risk and impact of immunogenicity.

Evolution of Therapeutic Progress in Inflammatory Bowel Disease

Professor Remo Panaccione

Biologics have had a significant impact on the treatment of many serious inflammatory diseases, including Crohn's disease (CD) and ulcerative colitis (UC). Their use has resulted in significant improvements in outcomes, including patient quality of life (QoL), and has enabled self-care and the ability to return to work for many patients.

CD and UC significantly affect patient health and QoL. Before the advent of anti-tumour necrosis factor treatments (anti-TNFs), patients were typically chronically hospitalised with a stoma and required total parenteral nutrition. Patients themselves often expressed that they felt ashamed, afraid, and had a lack of control of their disease, and some became very desperate and without hope.

Treatment goals have been redefined with the advent of biologic therapies such as recombinant receptor–Fc fusion proteins, e.g. abatacept and etanercept; monoclonal anti-TNFs, including chimeric, humanised, and human forms; and the pegylated Fab fragment, e.g. certolizumab pegol.[1] These drugs are clinically effective and have a rapid onset of action, and lead to improvements in QoL.[2-8] In patients with IBD, new treatment targets now include mucosal healing: the ability to induce and maintain clinical remission and improvements in serum or faecal biomarkers, such as C-reactive protein and faecal calprotectin.[9]

The therapeutic pipeline includes several biologic therapies outside the anti-TNF class, including interleukin inhibitors, cell adhesion molecule inhibitors, JAK3 inhibitors, chemokine receptors, immunomodulators, and stem cell therapies.[10] In the next 3–5 years, at least two or three new classes of biologics are expected to become available, as well as biosimilars of current reference products. These new drugs bring their own challenges in terms of their ability not only to demonstrate efficacy, safety, and tolerability, but also to address the complex and robust manufacturing and production processes required for biologics.

Biologic Therapy Complexity and Insights Into Manufacturing

Professor Geert D'Haens

When developing a biosimilar, comparable quality, safety, and efficacy to the reference product needs to be demonstrated. The European Medicines Agency (EMA) has stated that a biosimilar sponsor *"is to generate evidence substantiating the similar nature, in terms of quality, safety, and efficacy, of the new similar biological medicinal product and the chosen reference medicinal product authorised in the community."*[11] Equally, the US Food and Drug Administration (FDA) stated that a *"biologic product is highly similar to the reference product, notwithstanding minor differences in clinically inactive components"* and *"No clinically meaningful differences exist between the biologic product and the reference product in terms of the safety, purity, and potency."*[12]

It is important to recognise that biosimilars are similar to the reference product, but are not necessarily the same. The challenge is to establish if minor differences between biosimilars and reference products could lead to changes in clinical or pharmacological effects. Regulators very closely monitor the manufacturing processes of all biologics, which is a very delicate and complex

procedure and is affected by many factors, including the duration of cell culture, pH, temperature, and culture media, as well as how much oxygen and how many nutrients are added to the culture.[13,14] Other factors that influence the properties of the product include how much host-cell DNA is removed in the process and immunogenic influences. This complexity means that drugs are produced in batches, with the goal of ensuring homogeneity within a batch and consistency between batches.

Not surprisingly, the biologics that have been on the market the longest have had the greatest number of changes over time. Remicade® (infliximab) has had more than 35 manufacturing changes in its lifetime, including new purification methods and setting up of a new manufacturing site, which can affect the manufacturing technique, cell culture medium, and where cells are grown.[15,16] Enbrel® (etanercept; not licensed for IBD) has also undergone changes in its manufacturing procedures over time, with a resulting modification in the number of basic versus acidic variants, which can impact efficacy and antigenicity.[15]

To determine whether changes incurred in the manufacturing process affect the efficacy of a biologic, it is important to understand how the drug acts. This can be challenging because the mechanism of action of anti-TNFs is not fully understood. Within the structure of a therapeutic antibody, the Fab fragment is the most active component. It is known to bind soluble TNF that is freely circulating in the body and mucosae, but there can be differences between anti-TNFs with regard to the avidity and affinity of binding.[16] Anti-TNFs also bind to cells on which TNF is exposed on the cell membrane, and this binding induces cell apoptosis.[17-19] Antibodies also have an Fc 'tail', which may have biologic effects and can have a significant impact on the elimination and half-life of the molecule. The Fc tail is typically where sugars adhere to, but it may also bind to other cells. Experimentally, adalimumab and infliximab, which have an Fc tail, stimulate the conversion of monocytes into macrophages, which themselves decrease lymphocyte proliferation (Figure 1).[20]

This does not occur with certolizumab, which does not have an Fc tail and lacks this activity. However, when a version of certolizumab with an Fc tail was tested, it had a similar effect on lymphocyte proliferation to that seen for adalimumab and infliximab.[20] Post-translational modifications, e.g. glycosylation resulting in folding of the molecule, can also occur.[20] These modifications can lead to changes in the sugars and lysine groups, which in turn can alter the efficacy and safety of the biologic. Adalimumab is a recombinant IgG1 glycoprotein containing 1,330 amino acids, and which has high specificity for human TNFα.[21] Adalimumab has been manufactured since 1997 and the number of indications for which it is used has increased over time. The manufacturing process has also changed as the scale of production increased.[22] To counter this, the robustness of the manufacturing process has become more stringent to ensure no differences occur in the batches produced over time and also between different factories.[22] The cell line, cell culture media, and the steps taken to purify the molecule have remained the same.[22]

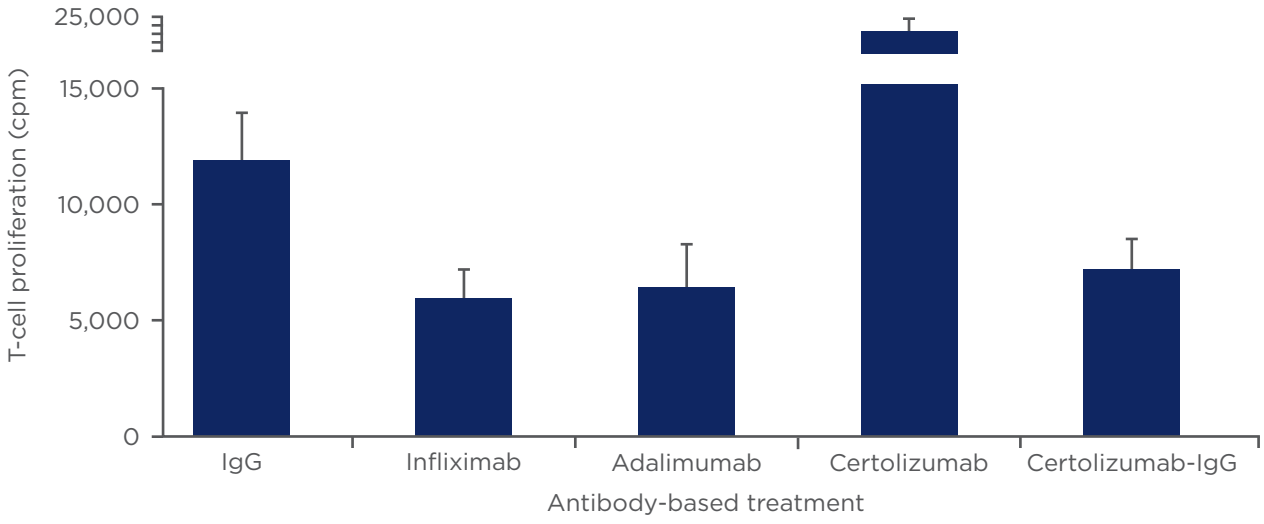

Figure 1: Effect of the Fc region on T lymphocyte cell proliferation.[20]

In summary, structure has an impact on function and is related to the post-translational modification of the protein. The production of biologics is complex: all biologics have inherent heterogeneity and can vary in terms of their immunogenic potential. In addition, some biologics may have significant batch variations. Any of these factors can impact on drug efficacy and safety if not carefully controlled.

Maintaining Sustained Inflammation Control in Inflammatory Bowel Disease

Professor Remo Panaccione

With the advent of anti-TNF therapies, treatment goals have evolved from simple response to remission, including clinical remission, mucosal healing and, possibly in UC, histological remission.[23] Regardless of the goals that are aspired to, what is truly needed is sustainability of treatment response. This is currently managed with induction therapy followed by a decrease in the dosage by either decreasing treatment intensity or increasing the interval between doses. One of the challenges is determining the length of the induction period, which is not necessarily addressed in clinical trials.

In the Phase III, randomised, double-blind, placebo-controlled CHARM (Crohn's trial of the fully Human antibody Adalimumab for Remission Maintenance) study, which investigated the efficacy of adalimumab maintenance therapy in patients with moderate-to-severe CD, patients received adalimumab induction therapy (80/40 mg) at Weeks 0 and 2 and were subsequently randomised to receive 40 mg every other week, 40 mg weekly, or placebo through Week 56.[24] The primary endpoint was the rate of randomised responders (defined as a CD activity index [CDAI] decrease ≥70 points at Week 4) who achieved clinical remission (CDAI <150 points) at Weeks 26 and 56. The percentage of randomised responders was 58% at Week 4, still leaving a substantial number of non-responders. However, if the induction period was increased to 12 weeks in the initial non-responders, 60% went on to achieve clinical remission,[25] which mimics what is seen in clinical practice. In terms of long-term maintenance of remission (4 years), this was achieved in 84% of observed patients, 80% using last observation carried forward (LOCF), and 54% using hybrid non-responder imputation analysis (Table 1).[26] Similar results were seen in a subset of patients who had fistulae at baseline.

Comparable results were reported in patients with active moderate-to-severe UC treated with adalimumab. In the ULTRA-3 open-label extension study, patients in remission at the end of the ULTRA-1 and ULTRA-2 studies were followed beyond Week 52.[27] In ULTRA-3, approximately 80% of patients continued to be in remission up to Week 156 and 82% maintained mucosal healing up to Week 144, according to LOCF analysis. In addition, approximately 60% of patients were steroid-free at Week 208, and hospitalisation and surgical rates decreased in Years 1, 2, and 3. These results demonstrated that remission and mucosal healing rates were maintained after 4 years of adalimumab therapy, and were associated with low colectomy and hospitalisation rates and improved QoL.

In terms of explaining the sustainability of the response to adalimumab therapy, pharmacokinetic studies have shown that the difference between peak and trough is extremely small and therefore the variability in the individual patient may be very low.[26] This contrasts with infliximab treatment every 8 weeks, which is associated with much more variability in the peak and trough levels;[28] the latter is thought to increase the risk of immunogenicity.

Table 1: Adalimumab long-term maintenance of remission in Crohn's disease.[26]

	Patients in remission, % (n)			
Weeks from baseline	**80**	**104**	**164**	**212**
hNRI analysis	77.2 (112/145)	77.2 (112/145)	64.8 (94/145)	53.8 (77/145)
LOCF analysis	82.1 (119/145)	86.2 (125/145)	82.8 (120/145)	80.0 (116/145)
As-observed analysis	83.0 (112/135)	86.8 (112/129)	84.7 (94/111)	83.8 (62/74)

hNRI: hybrid non-responder imputation; LOCF: last observation carried forward.

The ongoing MOSAIC study may provide more information regarding the relationship between the variability in peak and trough levels and possible subclinical inflammation in the near future.

As long-term use of anti-TNF therapies becomes accepted practice, risk assessment requires an understanding of their long-term safety. Analysis of long-term safety across a number of indications for adalimumab (almost 12 years of exposure) in over 23,000 patients demonstrated individual differences in rates according to disease populations.[29] However, no new safety signals were reported and the safety profile was consistent with what was already known regarding the anti-TNF class.

There have also been results from the ongoing, multi-centre, uncontrolled, 6-year, non-interventional Pyramid registry, which was designed to evaluate the long-term safety of adalimumab as it is used in routine clinical practice in patients with active moderate-to-severe CD.[30] The registry includes patients who participated in clinical trials, as well as patients prescribed adalimumab post-marketing. It includes 424 sites in 24 different countries and, as of December 2014, there were more than 5,000 registered patients, with a retention rate of approximately 60%. At the end of the study, 5–6 years of exposure data for more than 25,000 patients is expected. Thus far, only 14% of patients have withdrawn from the registry due to lack of efficacy and 7% have withdrawn due to adverse events. These results corroborate with observations in the pivotal studies.

In summary, adalimumab has been shown to have a sustained efficacy for up to 4 years in both CD and UC; it has been shown to be safe and well tolerated in both maintenance studies and safety registries. The small variability in peak and trough levels may be responsible for these results and are being explored further.

Patient Management: Strategies and Challenges in a Changing Environment

Professor Brian Feagan

Patient management faces the challenge of interchangeability, due to multiple non-medical switching by a pharmacist. The primary concerns for patients are efficacy and safety. This situation is a provocative manoeuvre for formation of anti-drug antibodies. Accordingly, a patient in stable remission is unlikely to want to switch to another product, no matter how similar it is, because of concerns over changes in efficacy and safety, and physicians share these concerns. The primary reason for switching to a biosimilar is cost savings to payers and society, which can create a tension between the individual's rights, expectations as a patient, and the broader societal need.

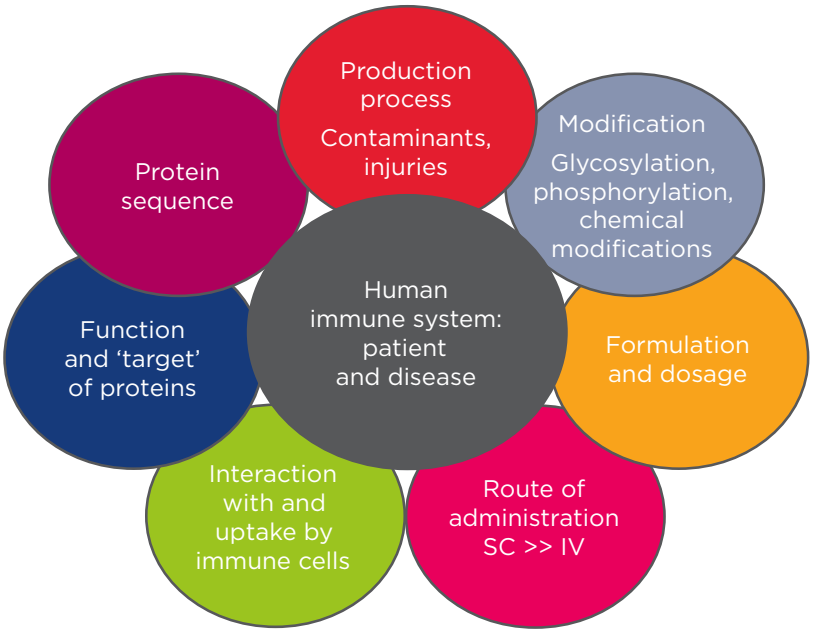

Figure 2: Product-related factors contribute to the immune response.[42,43]
IV: intravenous; SC: subcutaneous.

In terms of clinical evidence and durability of response, there is a wealth of data for reference drugs, which is reassuring for prescribers and physicians. This contrasts with biosimilars, which have little data on patient experience before they come to market.

There are two types of switching: (1) medically relevant switching due to lack of efficacy or because of adverse events. The challenge is establishing how to manage these patients; switching within a drug class or outside a drug class is often considered. Controlled data for current drugs is available to help decision-making,[31-34] but is often not available for biosimilars; (2) non-medical switching occurring because of preference issues for the patient, which have nothing to do with efficacy or safety, or because of the need for cost savings in the case of biosimilars. The lack of clinical data renders it difficult to assess the clinical and health economic consequences of this practice.[35]

In an assessment of 754 patients with CD, UC, ankylosing spondylitis, psoriasis, or psoriatic arthritis who underwent non-medical switching between different anti-TNFs, switchers were less well controlled than continuers (47% versus 88%).[36] Inpatient stays and emergency department visits were also greater in switchers versus continuers (5.0 versus 3.4 and 14.3 versus 4.2, respectively).[33]

In a different disease area, a systematic review of 58 clinical trials in which more than 12,000 patients were switched between classes of erythropoietin, growth hormone, or granulocyte-colony stimulating factor concluded that patients could be safely switched from one product to another.[37] However, most of the clinical trials were not designed to identify switch-related adverse events and some studies only followed up patients after they were switched in single-arm, open-label studies.

With regard to anti-TNF therapy and switching to biosimilars, the EMA, FDA, and Health Canada have all indicated that there is insufficient evidence to draw any conclusions regarding the safety of non-medical switching, but they also state that this issue is not within their jurisdiction. Ultimately, policy decisions will be made at a regional level, which is not ideal.

Immunogenicity is potentially the most serious consequence of multiple switching. All foreign proteins have the potential to be immunogenic.[38] The immune response is a complex, unpredictable process[39,40] that is governed by multiple factors (Figure 2).[41,42] Tertiary and quaternary protein structures govern whether T cells react, sensitise, or tolerise. This consideration has raised some concerns regarding the immunogenicity of biosimilars. At the last count there were nine biosimilar infliximab molecules under development. No high-quality clinical data are available to evaluate the consequences of interchangeability of these products.

The development of antibodies to a drug being administered is a concern because they can neutralise the biologic effect, impair drug pharmacokinetics, and cause hypersensitivity reactions. In patients who developed antibodies to infliximab, a shorter duration of therapeutic response was observed.[43] These patients were also more likely to develop hypersensitivity reactions and infusion reactions.[43] Sensitisation is also an issue for humanised anti-TNFs such as adalimumab, with approximately 20% of rheumatoid arthritis patients developing anti-drug antibodies.[44] In these patients, a high titre of antibodies was associated with low drug concentrations and reduced clinical efficacy.[45]

Changes in the manufacturing process can rarely result in autoimmunity. Cases of pure red-cell aplasia (PRCA) have been reported in patients treated with recombinant erythropoietin who developed anti-erythropoietin antibodies.[45] The cause was a change in the plasticiser present in syringe stoppers, which resulted in adjuvant activity and the formation of anti-erythropoietin antibodies.[46] More recently, multiple cases of PRCA have been reported in Thailand as a result of autoantibody development to biosimilar erythropoiesis-stimulating agents manufactured in India.[47]

The Phase IV NOR-SWITCH study, funded by the Norwegian government, has been designed to assess the efficacy and safety associated with non-medical switching between Remicade (infliximab) and the biosimilar Remsima™ (infliximab) in 18 hospitals.[48] The study has enrolled 500 patients with rheumatoid arthritis, spondyloarthritis, psoriatic arthritis, UC, CD, and chronic plaque psoriasis and will be completed in May 2016. Concerns regarding this study include the small patient numbers, which compromise the validity of the non-inferiority design, and the fact that the trial only assessed a simple substitution and not multiple switches between agents. In an ideal world, a study needs to address the impact of multiple switching to reflect what is likely to

happen in clinical practice when biosimilars become widely available.

In summary, the use of biosimilars is increasing but further data are needed to assess their efficacy and safety. The potential for immunogenicity should be considered when deciding upon the use of a biosimilar instead of its originator biologic or when switching between biosimilar products.

Q&A session

What kind of studies need to be done to address immunogenicity issues?

Prof Feagan stated that studies would need to include a sufficient numbers of switches (4 or 5) of sufficient duration (1–2 years) in the case of infliximab, where the half-life is 12–14 days, with switch intervals of around 4–6 months.

On what basis did Health Canada decide not to extrapolate into IBD for the infliximab biosimilar?

Prof Panaccione replied that the Health Canada position for not extrapolating into IBD was based on structure and function. There are data that suggest the Fc tail may be associated with antibody-dependent cytotoxicity which, in turn, may be associated with some therapeutic efficacy in CD and possibly in UC. They also cited a few safety concerns.

What kind of data, or how much data, would be required to recommend the use of a biosimilar in IBD?

Prof Feagan replied that he would accept index extrapolation in most situations. In order to extrapolate across indications, it is important to choose the indication that is most capable of differentiating between the biosimilar versus the reference product and to choose a sensitivity assay. In the case of the biosimilar infliximab, measurement of ACR20 scores in patients with rheumatoid arthritis was chosen, but Prof Feagan felt that this assay was not sensitive enough. Prof D'Haens added that there is currently only one biosimilar in Europe, Remsima (infliximab), and that the data, despite being limited, showed that it was equally as effective as Remicade (infliximab). In the future there could be ≥8 biosimilar infliximab molecules to choose from. If the choice is based only on cost, then every year a different company may win the tender and patients would have to be switched to a new infliximab without fully understanding the clinical and immunogenic consequences.

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