

'Old but Gold' – Insights About Anti-TNF- α Therapy in the Treatment of Inflammatory Bowel Disease

These interviews took place in October 2019 at the 27th United European Gastroenterology (UEG) Week in Barcelona, Spain

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Interview Summary

In these interviews, the experts clearly highlighted four key messages:

- 1) Too few patients with inflammatory bowel disease (IBD) are being treated with biologics, including anti-TNF- α therapies.
- 2) Some patients may also be receiving this treatment too late in the disease course, when structural damages have already occurred. This may be due to the high cost of originator biologics or a lack of awareness among physicians of the proven benefits of early anti-TNF- α therapy introduction. These therapies have been shown to decrease complications and disease progression.
- 3) The development of affordable anti-TNF- α biosimilars can facilitate greater access to these therapies and could extend their early use to more patients, with no detected safety issues in switched patients discerned to date.
- 4) Newer therapeutic options with other mechanisms of action are available, but for now at least, anti-TNF- α therapies are seen as 'old but gold'.

Professor Remo Panaccione

Prof Panaccione believed that biologic therapies are generally underutilised in patients with IBD; they are started too late and prescribed to too few patients. Some physicians still prefer conventional therapy and a slow step up to biologics; this means by the time their patients are started on biologic therapy, the biologic efficacy has been compromised.¹ However, he did acknowledge the challenges faced by doctors looking to treat IBD patients earlier with biologics. These include limited accessibility on the grounds of cost, as well as a lack of awareness among these physicians about the benefits of early intervention.¹ According to Prof Panaccione, there is also a lack of awareness among IBD patients about the benefits, and established safety profile, of the anti-TNF- α antibodies in particular. There are now two decades of experience supporting these benefits. Some physicians and patients also do not understand the severity of the disease and its progressive nature. Peoples' feelings towards their IBD and its severity not only relate to their symptoms but also the overall disease burden and the risk factors that predict poor outcomes.

Drawing on his extensive clinical experience, Prof Panaccione believed that all patients could benefit from early intervention with biologic therapy, particularly the paediatric population due to the associated growth problems.² In young patients, a 'top-down' strategy should be increasingly used to induce deep remission as an attempt to

modify the clinical course of the disease.^{1,2} He is also of the opinion that biologic treatment is most effectively used in early, uncomplicated disease.

Prof Panaccione was clear in his beliefs: "Shifting to these drugs earlier is associated with better outcomes, fewer complications, and slower disease progression." On the other hand, he also recognised that, in a real-world setting, limited access to these treatments means clinicians should focus on patients with a significant disease burden and unfavourable risk factors. These patients should be treated early, with clinicians adopting a pragmatic top-down approach.¹ He emphasised that newer modes of action (MoA) have yet to demonstrate the same benefit to IBD patients; currently the best outcomes from early treatment all point to anti-TNF administration.^{1,3}

Professor Thomas Ochsenkühn

Prof Ochsenkühn focussed on long-term experience with anti-TNF. In his opinion, anti-TNF remain first-line biologics with a central role in the treatment of IBD; they are fast, effective, and have a low incidence of side effects. He recognised that anti-TNF- α biosimilars are driving down the cost of access and creating the opportunity for more patients to be treated with these therapies, even though newer MoA are available. For him, anti-TNF occupy a huge space in IBD treatment and will be used even more in the future.

Quoting 2016 data from German insurance companies, he pointed out that 6% of ulcerative colitis and 9% of Crohn's disease patients were treated with antibodies. He describes this as "a dramatic underuse of these drugs." Looking ahead, he expects this situation to change, affordable anti-TNF- α biosimilars being the catalyst.

According to Prof Ochsenkühn, anti-TNF are the first choice when immunomodulation becomes necessary. He bases this on their proven efficacy over 20 years, the speed of onset of action, their use in pregnancy, their postoperative impact, their low rates of side effects, and affordability. According to him, immunomodulators with other MoA can be used as a second-line treatment when anti-TNF- α therapies fail, if patients experience intolerance, or when side effects present following anti-TNF- α treatment.

Prof Ochsenkühn also believed that anti-TNF should be used early in the management of patients with high-risk factors for an aggressive course of IBD. These high-risk factors include severe flares, high inflammatory burden, long segment involvement in Crohn's disease, pancolitis in ulcerative colitis, fistulising disease, stricturing disease, and a high or ongoing need for steroids.

He stressed that anti-TNF have a preventive action which newer MoAs,¹ such as the anti-integrins (e.g., vedolizumab), ustekinumab (an antagonist of the p40 subunit of IL-12 and IL-23), and JAK-inhibitors (e.g., tofacitinib), have yet to demonstrate. And until more data are available, his view was that anti-TNF will remain the first-line biologic to prevent structural damage and functional losses in the long term. To date this preventive action has not been shown with newer MoA,¹ and hence the key player is anti-TNF therapy for most IBD patients.

Professor Stefan Schreiber

Prof Schreiber described the efficacy of anti-TNF therapies and how the introduction of biosimilars has changed the IBD landscape. He remarked that there is substantial evidence to show that higher dosages and early intervention with anti-TNF- α therapies improve outcomes in patients with IBD. He commented that affordable biosimilars will

be an option for increasing access, permitting higher doses, and allowing earlier treatment. In addition, these cheaper biosimilars keep spending constant.

However, despite this body of evidence, he echoed the sentiment of Prof Panaccione and described an unmet need for the continuous medical education of some healthcare professionals, especially those not practising in specialist IBD centres, or those who are seeing more patients but not prescribing anti-TNF optimally in-line with the latest algorithms.

Asked whether he feels confident about using biosimilars, Prof Schreiber asserted: "I am confident to use biosimilars [...] At the moment we have an extremely high production quality for the biosimilars we are using. We have companies that are open to research and invest in data generation to support the best practice use of established molecules."

In this context, Prof Schreiber described the value of GIANT, the first prospective, global, noninterventional study to evaluate the effectiveness, safety, and cost-effectiveness of adalimumab and infliximab in Crohn's disease under real-world conditions.

GIANT is a large observational study that bridges the evidence gap between a controlled study and the observation of clinical practice. Although it regards real-world patient access, GIANT is constructed in such a way as to generate prospective data that are quality-controlled and reusable for therapy optimisation, as well as for patient outcome improvement.

Prof Schreiber emphasised that GIANT will help to answer open scientific questions and increasing knowledge surrounding the effectiveness of adalimumab and infliximab in routine clinical care and will additionally evaluate the newly introduced IBD disease severity index under real-world conditions. Data on best practice usage with these established drugs are needed, stated Prof Schreiber: "I would foresee that in the next years anti-TNF therapy gets even stronger and will be the entry-level drug for most of our patients."

In a similar vein, Prof Schreiber contrasted the earlier placebo-controlled approval study of adalimumab, ULTRA, with the results derived from

the recently published head-to-head VARSITY study. Here, the efficacy and safety of adalimumab was assessed versus an active comparator (vedolizumab) in patients with moderate-to-severe ulcerative colitis. One important result is that, when compared with an active comparator, adalimumab showed greater efficacy than revealed through ULTRA, with high response rates and no attenuation.⁴ This was explained by Prof Schreiber who believes we get both closer to the real world and discover better data about established drugs from an active comparator rather than placebo-controlled trials. In his opinion, the latter are typically not representative of real-world practice due to issues concerning patient extraction.

Professor Jonas Halfvarson

Prof Halfvarson from Sweden was asked to share his experience about biosimilar usage in Nordic countries. These countries have already amassed considerable experience of switching. Patients have been switched from an originator to a biosimilar and also between biosimilars, as well as from an originator to a first biosimilar and then to another second biosimilar. His reply couldn't have been clearer: "In Nordic countries, we haven't experienced any safety issues after switching patients from originator to biosimilar or from one biosimilar to another biosimilar." His conclusion

was based on extensive clinical experience and the patient data routinely collected and included at a national level in the Swedish Quality Registry (SWIBREG) for IBD. SWIBREG was launched in 2005 and, as of April 2019, includes 46,400 patients with IBD.⁵

When it comes to managing a patient's move to biosimilars, Prof Halfvarson emphasised the importance of good communication. His advice is to implement a standardised switching regimen and let patients know the reasons for switching and exactly how the switch will be performed. It is also necessary to communicate with colleagues and nurses about the need and rationale for switching, and to let the patient organisation know. Beyond the switch, he advised tight monitoring of anti-TNF patients for proactive treatment adaptations.

Closing Remarks

Those expecting leaders in the field to be moving IBD patients to newer therapeutic options may have to wait, at least until further data are published. For now, it seems to our interviewees that biosimilars may extend, widen, and enable the early use of anti-TNF in the treatment of IBD and in doing so help improve patient outcomes. With no safety-related issues in switched patients to date, old is indeed gold.

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