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Clinical Insight and Implications

FROM UEGW

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It's hard to miss the growing sense of optimism in the field of Inflammatory Bowel Disease (IBD), when the near future promises a multitude of therapeutic classes, each with several agents, for both Crohn's Disease (CD) and Ulcerative colitis (UC); attendees at UEG Week were presented with new data for all three of the emergent IL-23 p19 inhibitors, mirikizumab, guselkumab and rizankizumab; JAK inhibitors, filgotinib and upadacitinib; and also the two S1P1 receptor modulators, etrasimod and ozanimod. The luxury of choice may even facilitate therapeutic strategies yet to be fully exploited in IBD including intelligent advanced combination therapy and possibly in class, proactive 'cycling' of drugs, as is gaining traction within the field of rheumatology. The inevitable challenge moving forward will be choosing with, and for each patient, not only the optimal class, but also the optimal agent within that class and the most opportune moment to start that agent.

LUCID UEGW SUMMARY 2023

REAL-WORLD DATA ARE CONTINUING TO PROVIDE MORE INFORMATION TO **GUIDE CLINICAL DECISION-MAKING**

Fortunately, the Congress also saw a plethora of data, many real-world, that could assist in making such a decision. Dr Rofaida Desoki, on behalf of the UK BIORESOURCE group, presented a propensity score-matched (PSM) analysis from almost 13,000 patients evaluating the performance of first-line biologics (MP042). The impressive 4 years of follow-up used treatment persistence as a marker for efficacy. The timeframe necessarily limited the analysis to three anti-TNF agents (infliximab, adalimumab, golimumab) and anti-integrin vedolizumab. Concordant with the VARSITY study, vedolizumab came out on top over all anti-TNF agents for biologic-naïve UC. In biologic-naïve CD, the balancing for perianal disease between groups was suboptimal for analysis but, with perianal disease included, infliximab appeared to have an edge. This edge disappeared when perianal disease was excluded.

Infliximab was also favoured in a network meta-analysis of all Phase 3 randomised controlled trials published to date in CD which synthesised relative effect size versus placebo (MP046). The work, presented by Professor Stefan Schreiber, favoured subcutaneous infliximab among 8 comparator arms; intravenous delivery was in the middle of the field. However, the results may be vulnerable to bias, driven by the rapid drop in response rates for those randomised to placebo following intravenous induction in the subcutaneous infliximab trials.

In line with the suggested impact of perianal disease in CD another propensity score-adjusted analysis, presented by Dr Jeffrey McCurdy, was included from the BIORESOURCE data. The authors evaluated the comparative effectiveness of first-line biologics in preventing penetrating complications of CD (MP047). Over 40,000 patients without prior penetrating complications or biologic exposure were followed until a penetrating event or change in therapy, with over 8,500 penetrating complications identified. Anti-TNFs conferred a favourable hazards ratio when compared head-to-head with vedolizumab and ustekinumab in luminal penetrating disease; anti-TNFs lost their superiority over ustekinumab in perianal disease.

Also from the UK BIORESOURCE, Dr Christina Kapizioni presented another PSM analysis, this time of second-line biologic therapy after anti-TNF failure (MP045). Again, the analysis considered only anti-TNFs and vedolizumab. Understandably, the cohort was much smaller (3,410 patients) but, in UC, vedolizumab was superior to another anti-TNF in up to three years of follow-up. The only exception was in the setting of primary non-response (PNR) to adalimumab in which case there was no significant difference between those who received vedolizumab or infliximab second line. This of course would fit with the emerging data on the high drug levels required for efficacy of adalimumab in UC.
For CD perhaps surprisingly, staying in class seemed preferable in the case of PNR but switching class was superior in non-PNR as an approximation of secondary loss of response.

A facet specific to CD is that of post-operative recurrence and Dr Matthieu Allez presented prospective data from 192 patients from the REMIND group comparing the efficacy of ustekinumab and adalimumab in biologic-experienced individuals (OP067). Reassuringly, a PSM analysis found no differences between the two drugs in preventing early or severe recurrence; it is obviously reassuring to have data supporting multiple options in what can be quite a challenging clinical scenario.

Looking again at UC after anti-TNF failure, real-world data from 10 centres in France, presented by Dr Mathurin Fumery (MP041) found ustekinumab and vedolizumab to be comparable however ustekinumab had a slight edge in the hardest endpoints and after three prior biologic failures.

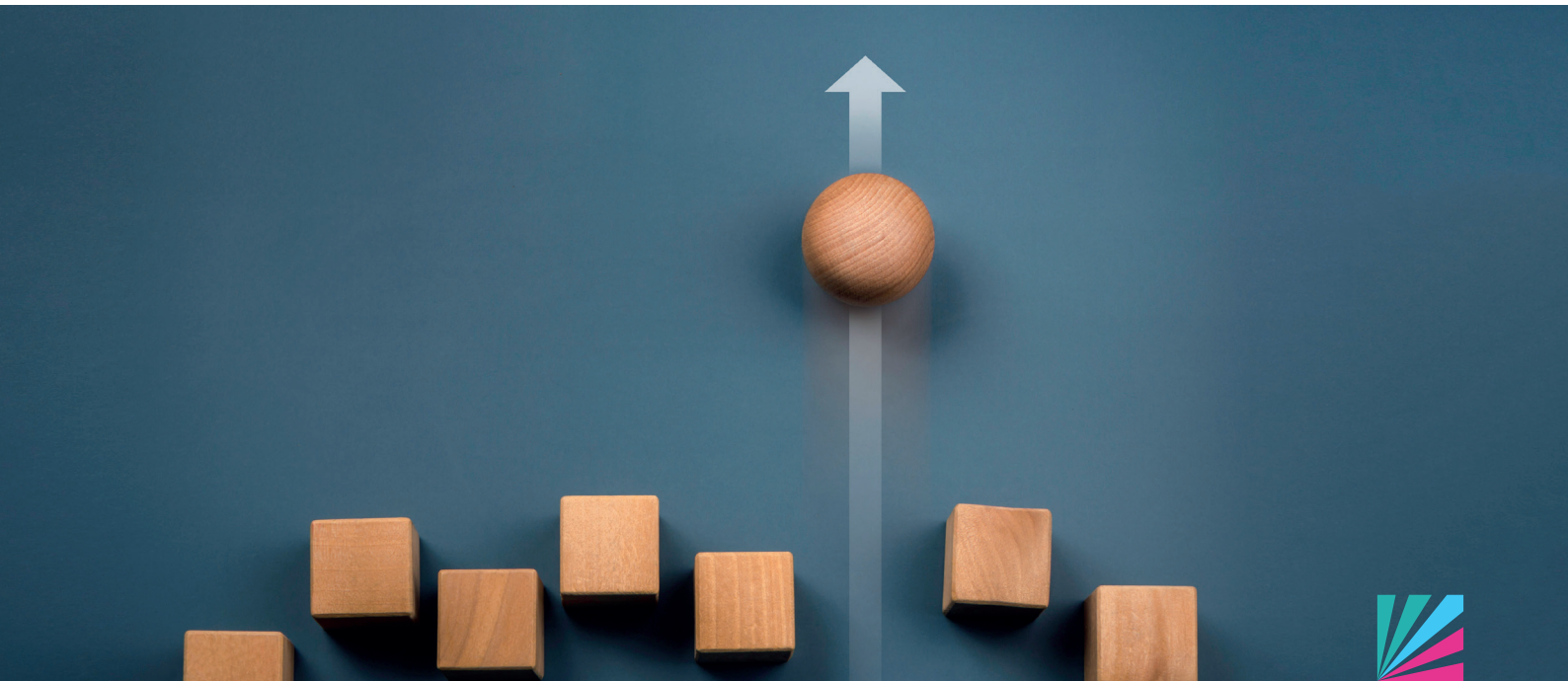
INCREASING INTEREST IN A MORE **TARGETED APPROACH TO IL-23**

Ustekinumab is of course an IL-23 p40 inhibitor targeting both IL-12 and IL-23; a theme from the conference was the evident superiority of a more specific anti-p19 strategy that only targets IL-23. This was exemplified in SEQUENCE (LB01), a head-to-head comparison of ustekinumab to risankizumab in moderate to severe CD with prior anti-TNF failure. The bias inherent in an open-label study notwithstanding, risankizumab was non-inferior to ustekinumab at inducing clinical remission (by CDAI) at Week 24 and superior at inducing endoscopic remission at Week 48. There is also a signal of reduced need to proceed to surgery in the risankizumab group. Taken together, these data may potentially claim risankizumab a slot ahead of ustekinumab in a treatment algorithm based on efficacy in anti-TNF-experienced CD. When ustekinumab comes off patent, cost, of course, will be an important consideration but the surgery data may well provide an intriguing caveat.

More exciting data on risankizumab came in the form of a post hoc, pooled analysis of the ADVANCE, MOTIVATE and FORTIFY studies in CD (OP037). Albeit with nominal p-values, risankizumab was effective at resolving baseline extra-intestinal manifestations (EIMs) although the higher maintenance dose of 360 mg was required to maintain said resolution. The EIMs driving the signal were predominantly anaemia, peripheral arthropathy and axial arthropathy, which is interesting as axial arthropathy is perhaps an area in which data on ustekinumab are less strong.

Ustekinumab also came up against another IL-23 p19 inhibitor in the form of guselkumab in the GALAXI long-term extension (LTE) data in CD (OP020) and, while ustekinumab featured as an important 'current practice' reference, the study was not powered to show superior clinical efficacy, Guselkumab did show numerical superiority in Patient Reported Outcomes (PROs) and endoscopic response across the time points.

We were given a closer look at the LUCENT 3 data for mirikizumab in UC and although the study included only responders from LUCENT 1 and 2, the lack of significant drop-off in delta over placebo for biologic-experienced



patients remained striking and certainly, by indirect comparison, seems more impressive than the more established therapies.

For both mirikizumab, in LUCENT (OP080), and guselkumab, in GALAXI (OP079), we saw the benefits of persisting with therapy and, in the case of mirikizumab, three additional intravenous induction doses for Week 12 non-responders. A significant proportion of clinical non-responders at Week 12 were able to achieve meaningful clinical benefit by the later time points of Week 40 and Week 52, respectively. While we may have some clues as to who the Week 12 non-responders might be (perhaps those with longer disease duration and those with ileal disease in CD) data is clearly lacking on how to discern who will remain resolute non-responders and who will get there with time (and/or extended induction). Similarly, for upadacitinib, we saw in the post hoc analysis of the U-EXCEED and U-EXCEI data (OP099) that early responders will do well at Week 12 and Week 52. Indeed, the U-ENDURE post hoc analysis (OP100) showed that this response is durable, albeit biologic-experienced patients likely need to stay on a 30 mg dose. However, once again, the characteristics of early responders are not adequately defined to allow identification of individuals likely to excel on the therapy. That said, it appears that early responders as a group may be enriched for colonic disease with less representation of ileal. This leads on to another interesting question; based on the repeated observation that a greater proportion of patients with ileal disease in a cohort correlates with a more difficult-to-treat group, should we begin to consider ileal disease as a separate entity with a unique treatment approach or separate experimental considerations?

Aside from the most obvious question of where to start when offered multiple excellent options in the same class, what many clinicians may find themselves asking (while also finding the current data lacking) is how, and even if, to use these new anti-IL-23 medications in patients who have already shown inadequate response to ustekinumab.

THE OPPORTUNITY REMAINS TO BETTER UNDERSTAND SEQUENCING AND COMBINATION OF TREATMENTS ACROSS AN INCREASING CHOICE OF AGENTS

On the matter of combining therapies, with the expansion in the number of available agents, the question remains as to what the optimal degree of overlap between mechanisms of action, if any, might be. We will also have more choice on how to sequence therapies, although this will likely remain a function of how rapid a response is required, balanced against comorbidities like established ischaemic heart disease and other susceptibilities to infection. That said, somewhat muddying the waters here is the emerging risk of serious infection posed by persistent active disease, particularly In CD.

The proliferation of therapeutic options was evident throughout UEG Week; there was plenty of promising data on agents in earlier phases of development, as well as novel surgical strategies. The choice will certainly bring possibilities, the application and exploration of new mechanisms of action will further our understanding of the underlying biology of disease and the potential for artificial intelligence to accelerate target selection and drug development is unknown but exciting!

Perhaps the most difficult challenge facing clinicians in the near future will be navigating the vast number of choices to ensure the best options are made for, and with, the patient sat in front of them.