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Abbreviations used in this issue:

- CD = Crohn’s disease
- CRP = C-reactive protein
- DMARD = Disease-modifying anti-rheumatic drug
- HBI = Harvey-Bradshaw Index
- IBD = Inflammatory bowel disease
- RA = Rheumatoid arthritis
- TNF = Tumour necrosis factor
- UC = Ulcerative colitis

Welcome to the fourth issue of Biologics Research Review.

In this issue we have focused on treatments for IBD, psoriatic arthritis and rheumatoid arthritis and begin with an interesting study of early versus late anti-TNF induction for mild-to-moderate UC. Also for the treatment of UC, we have included a first-in-human study of an oral anti-TNF agent, AVX-470. While the number of patients in this study was small, the agent shows promise and further studies are awaited with interest.

We hope you find our selection for Biologics Research Review stimulating reading and we welcome your feedback. Furthermore, if you have discovered or been involved with what you think is significant global research, please let us know and we will consider it for inclusion next time.

Kind Regards,

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Similar clinical and surgical outcomes achieved with early compared to late anti–TNF induction in mild-to-moderate ulcerative colitis: A retrospective cohort study

Authors: Ma C et al.

Summary: This Canadian retrospective, single centre, cohort study used data from 115 ulcerative colitis (UC) patients receiving infliximab (n = 78) or adalimumab (n = 37) from 2003 to 2014 to determine whether earlier initiation (within three years of diagnosis) alters clinical and surgical outcomes. During a median follow-up of 175.6 weeks, 57 (49.6%) patients received early anti-TNF initiation (median time to initiation 38.1 weeks) versus 58 in the late initiator cohort (414.0 weeks). Early initiators had more severe endoscopic disease at induction (mean Mayo endoscopy sub-score 2.46 vs 1.86; p < 0.001). Multivariate regression analysis suggested that early initiation was not associated with colectomy (HR 2.02; 95% CI 0.57-7.20), hospitalisation (HR 1.66; 95% CI 0.84-3.30), or secondary loss of response (HR 0.86; 95% CI 0.52-1.42).

Comment: There is evidence from randomised trials that initiation of biologic therapy early in a CD patient’s disease course may improve treatment response. It is not clear as to whether these observations can be extended to include individuals with UC. The current retrospective cohort study investigated the relationship between response and disease duration in 115 patients with UC with respect to initiation of either infliximab or adalimumab. Early treatment initiation was defined as ≤3 years from diagnosis. Infliximab was more commonly used as the anti-TNF of choice. The “early initiation” patients had more active disease based upon their Mayo endoscopic scores and their CRPs at baseline (both p < 0.001). Surprisingly this was not reflected in their prior exposure to immunomodulators. There were no significant differences across the primary outcome measures. This was likely driven at least in part by the design of the study, emphasising the importance of prospective studies to further address this question of risk stratification and top-down therapy for UC patients.


Abstract
AVX-470, an orally delivered anti-tumour necrosis factor antibody for treatment of active ulcerative colitis: Results of a first-in-human trial

Authors: Harris MS et al.

Summary: This double-blind, placebo-controlled, first-in-human trial examined the safety, pharmacokinetics, immunogenicity and preliminary efficacy of 4 weeks of AVX-470 (an oral, polyclonal bovine-derived anti-TNF) antibody 0.2, 1.6 or 3.5 g/day versus placebo in 36 patients with active UC. Treatment and follow-up was completed by 33 (92%) patients and the incidence of adverse events did not differ between treatments. There were no allergic reactions or opportunistic infections reported and AVX-470 did not induce human anti-bovine antibody formation. Bovine immunoglobulin levels in serum were low and bovine immunoglobulin with TNF binding capacity was detected in stools. In total, 25.9% of AVX-470 recipients achieved a clinical response versus 11.1% of placebo recipients across all AVX-470 dosages. The greatest improvements occurred with the 3.5 g/day dosage and were associated with improvements in proximal colon endoscopy and serum CRP and IL-6 reduction.

Comment: Anti-TNF strategies are now established in the treatment of IBD. However, thus far, these agents are given systemically with the subsequent concerns around safety and immunogenicity. The current first-in-human study describes an oral anti-TNF agent, AVX-470, in the treatment of patients with UC. AVX-470 is derived from bovine colostrum. Importantly the majority of the healthy population is constantly exposed to bovine immunoglobulin through the ingestion of milk and beef. In total 33 of 37 subjects with moderately to severely active UC (Mayo score 5-12) completed the study at three dose regimes (0.2, 1.6, 3.5 g/day) versus placebo over 4 weeks. There were no adverse events or opportunistic infections reported and AVX-470 recipients achieved a clinical response versus 11.1% of placebo recipients. The greatest improvements occurred with the 3.5 g/day dosage and were associated with improvements in proximal colon endoscopy and serum CRP and IL-6 reduction.


Brief report: Secukinumab provides significant and sustained inhibition of joint structural damage in a phase III study of active psoriatic arthritis

Authors: van der Heijde D et al.

Summary: In a phase III, double-blind, placebo-controlled study, 606 patients with active psoriatic arthritis received secukinumab (10 mg/kg) in weeks 0, 2 and 4 followed by subcutaneous secukinumab 150 mg or 75 mg; n = 404 or placebo (n = 202; non-responders at 24 weeks were re-randomised to secukinumab 150 mg or 75 mg) to determine the effect on sustained inhibition of radiographic progression. Overall, secukinumab inhibited radiographic progression through 52 weeks (primary endpoint); with reductions in both erosion and joint space narrowing scores and in patients who switched from placebo to secukinumab after week 24. Subgroup analyses suggested that secukinumab reduced radiographic progression at week 24, irrespective of previous anti-TNF exposure. In anti-TNF-naive patients (71% of patients), mean changes in modified total Sharp/van der Heijde scores were 0.05 with secukinumab versus 0.57 with placebo after 24 weeks, while in those with an inadequate response or intolerance to anti-TNF treatment the mean changes were 0.16 versus 0.58. Through 52 weeks, anti-TNF-naive patients had negligible progression. Structural damage was inhibited through week 52, regardless of methotrexate use. The majority of secukinumab recipients had no progression to 24 weeks (82.3% of 150 mg and 92.3% of 75 mg recipients) and from 24 to 52 weeks (85.7% of 150 mg and 85.8% of 75 mg recipients).

Comment: This was part of the FUTURE 1 phase III study of secukinumab in active psoriatic arthritis patients, focussing on the radiography results of the program. Secukinumab is a fully humanized IgG1 monoclonal antibody that selectively binds and neutralises IL-17A. We have recently covered a similar study in patients with ankylosing spondylitis and the FUTURE1 dosing regime was identical to this. A total of 606 subjects were randomised, 404 to one of two active arms and 202 to the placebo arm. Those in the placebo group were classified as responders or non-responders at week 16, with the latter re-randomised to active drug from that time point and responders re-randomised to active drug from week 24. Secukinumab inhibited radiographic disease progression through to week 52 as compared to placebo, and for both erosion and joint space narrowing scores. Although anti-TNF status did not impact on these results to week 24, the anti-TNF naive subgroup demonstrated superior response from weeks 24 to 52 as compared to those with a previous inadequate response to anti-TNF. This requires further studies given the small numbers in relevant subgroups. Concomitant methotrexate did not augment response as compared to secukinumab monotherapy. However, patient selection was based upon ongoing active disease despite methotrexate therapy and hence, further comparator studies will be required to establish the role of concomitant immunomodulator treatment.


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Effect of adalimumab on the work-related outcomes scores in patients with early rheumatoid arthritis receiving methotrexate

Authors: Emery P et al.

Summary: A post hoc analysis of data from the Optimal Protocol for Treatment Initiation with Methotrexate and Adalimumab (OPTIMA) and PRevention Of Work Disability (PROWD) trials was conducted to assess the effect of adalimumab plus methotrexate (ADA + MTX) on work-related outcomes in early rheumatoid arthritis (RA) patients at increased risk of loss of employment (RA Work Instability Scale [RA-WIS] score >10, indicating medium to high risk for job loss). In OPTIMA, work instability was better in ADA + MTX versus MTX plus placebo recipients based on changes in RA-WIS scores (mean change -7.22 vs -5.23). More ADA + MTX recipients also experienced improvements in one or more risk categories (58% vs 47%) and increases of ≥5 (55% vs 43%), ≥7 (47% vs 35%) or ≥9 (42% vs 26%) points in RA-WIS score. Changes observed in PROWD were not significant. In OPTIMA, ADA + MTX recipients also demonstrated greater improvements in activity impairment (-27.3 vs -18.3), presenteeism (-24.6 vs -17.1) and overall work impairment (-27.3 vs -18.3).

Comment: The disabilities associated with RA can have a significant impact both in the short and long term in terms of employment and productivity. Studies indicate that 20-30% of subjects with early RA become disabled within 10 years. The current study by Emery and colleagues investigated the potential benefits of combination therapy using a DMARD (methotrexate) with a biological DMARD (adalimumab) over monotherapy with methotrexate in the context of two existing trials, OPTIMA and PROWD. The mean age across the two studies ranged between 45-47 years, 53-70% of participants were female, and mean disease duration ranged between 4 and 9 months, with PROWD patients having longer duration compared to OPTIMA. Using validated measures of work instability and work productivity, the investigators demonstrated significant improvements in work instability scores in the OPTIMA cohort (n = 320) and in work productivity. These measures did not achieve significance in the PROWD cohort (n = 124). These results are important for individuals with chronic inflammatory disorders. Further studies over longer periods of observation are required in RA and other related auto-inflammatory disorders to investigate the impacts of biologic drugs on indirect costs.


Subcutaneous ustekinumab provides clinical benefit for two-thirds of patients with Crohn's disease refractory to anti-tumor necrosis factor agents

Authors: Wils P et al.

Summary: This retrospective observational study, based on the Groupe d’Etude Thérapeutique des Affections Inflammatoires du tube Digestif study, used data from 122 anti-TNF therapy refractory CD patients to examine the effects of subcutaneous ustekinumab. A clinical benefit was observed in 79 (65%) patients within 3 months of ustekinumab initiation. The odds of a clinical benefit were increased in patients receiving concomitant immunosuppressant therapy at study inclusion (OR 5.43; 95% CI 1.14-25.77; p = 0.03). The cumulative probability of maintenance of clinical benefit for 6 months was 93% and for 12 months was 68%.

Comment: Individuals within the Australian and New Zealand health care systems with active CD are typically treated with corticosteroids to induce response or remission, together with a thiopurine as maintenance therapy. Patients refractory or intolerant to this combination can benefit from anti-TNF therapy through government schemes. These schemes have been in place for over 8 years and in that time a proportion of CD patients have either lost response or developed intolerances or idiosyncratic reactions to anti-TNFs. Thus, alternative (biologic) therapies are required to optimise disease control. Ustekinumab may be a future option for these patients, given that it is already on the PBS scheme in Australia for refractory plaque psoriasis. Ustekinumab is a monoclonal antibody against the p40 subunit of IL-12 and IL-23, thus targeting the T helper 1 and T helper 17 pathways. A phase II study has demonstrated efficacy (clinical response) and safety in a subgroup of CD patients refractory or intolerant to anti-TNFs following IV induction with ustekinumab followed by subcutaneous maintenance therapy up to 36 weeks. The current study by Wils and colleagues examined the efficacy and safety of ustekinumab in a real life CD cohort from centres in France and Switzerland. This was a retrospective cohort study, which included 122 patients between 2011 and 2014. The primary outcome was the percentage of patients who demonstrated clinical benefit from ustekinumab. This was defined as a significant improvement in CD symptoms and objective tests that resulted in continued ustekinumab therapy and tapering of corticosteroids (if taken at baseline) without the need for surgery or commencement of an immunomodulator. The majority of patients had received treatment with an immunomodulator (98%) and/or an anti-TNF (100%). 79 patients (65%) achieved the primary endpoint at 3 months. The most common protocol used was ustekinumab 90 mg every 8 weeks (49%). There was evidence of sustained benefit in responders at 6 (93%) and 9 (68%) months with only 4 of 122 patients requiring discontinuation of the medication due to adverse events (severe infection, myalgia, intolerance). These real life data are most encouraging for patients with refractory CD and for their treating clinicians given the limited number of accessible biologic options as compared to subjects with inflammatory arthritis.

**Vedolizumab induction therapy for inflammatory bowel disease in clinical practice – a nationwide consecutive German cohort study**

**Authors:** Baumgart DC et al.

**Summary:** Adult IBD patients (n = 212) with active CD (Harvey-Bradshaw Index [HBI] >7) or UC (partial Mayo >4) receiving vedolizumab were examined to determine real-world efficacy. Most patients had extensive mucosal involvement (Montreal L3 69.1%/E3 53.9%) and few were anti-TNF-α naive (6.2% CD; 24.3% UC). After 14 weeks, 23.7% of CD patients and 23.5% of UC patients achieved clinical remission (HBI ≤4, partial Mayo ≤1; primary endpoint). In addition, 19.1% CD and 19.1% UC patients were in steroid-free remission and 60.8% and 57.4% had a clinical response (HBI/partial Mayo score drop ≥3). In CD patients, week 14 clinical remission was associated with an absence of prior extra-intestinal manifestations (p = 0.019), previous adalimumab use (p = 0.011), and a low HBI (p = 0.02). In UC patients, clinical remission was associated with active (p = 0.044) or previous smoking (p = 0.028) and no prior use of anti-TNF-α (p = 0.023). The most common adverse events were joint pain, acne and nasopharyngitis.

**Comment:** The introduction of vedolizumab, a gut-focussed anti-integrin targeting α4β7, to the Australian PBS scheme has improved therapeutic options for patients with refractory CD and UC. Following large-scale registration studies, additional data from real life cohorts will be valuable in determining the role of concomitant immunomodulators, the use of therapeutic drug monitoring and ongoing analysis of safety. Baumgart and colleagues describe an observational cohort study that included 97 patients with active CD (median Harvey-Bradshaw index 11) and 115 patients with active UC (median partial Mayo 6). The primary endpoint of clinical remission at week 14 was achieved in just under a quarter of patients in each disease group while clinical response was reached in 57-60% of cases. While faecal calprotectin levels dropped significantly between baseline and week 14 for both CD and UC (p = 0.003 and p < 0.0001), CRP levels only showed trends. Some of these outcome results are similar to the limited real-life data thus far published, specifically the response and remission rates seen in the CD subgroup. Predictors of both week 14 and 12-month remission included features often associated with a milder disease course, including an absence of extraintestinal manifestations, no hospitalisations, no anti-TNF exposure, and lower baseline clinical activity scores. In terms of safety, the commonest adverse events recorded were arthralgia, acne, and arthritis. These extraintestinal events may be related to the mechanism of action of vedolizumab. Prospective registry studies will be most effective at further investigating these points.

**Reference:** Aliment Pharmacol Ther. 2016;43(10):1090-102

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