Biologics Research Review™

Making Education Easy

Issue 15 - 2019

In this issue:

Abbreviations used in this issue:

CCR = continuous clinical response
CD = Crohn's disease
CDAI = Crohn's Disease Activity Index
CI = confidence interval
DAS28 = Disease Activity Score in 28 joints
ECOG = Eastern Cooperative Oncology Group
EIM = extraintestinal manifestation
IBD = inflammatory bowel disease
OR = odds ratio
PGA = Physician's Global Assessment
PFS = progression-free survival
QoL = quality of life
RA = rheumatoid arthritis
TNF = tumour necrosis factor
UC = ulcerative colitis
VEGF = vascular endothelial growth factor

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Welcome to Issue 15 of Biologics Research Review.

According to the findings of post hoc analyses of the GEMINI trials, vedolizumab therapy is associated with a reduced likelihood of new/worsening arthritis/arthralgia in CD and no increased incidence of such events in UC. Following on, we discover that RA patients who did not respond to an initial 3 mg/kg dose of infliximab exhibited improved clinical responses and radiographic assessment after a dose adjustment, without an increased risk of serious adverse events. Other studies included in this issue cover the topics of vedolizumab for IBD and pregnancy outcomes, switching from remicade to biosimilar CT-P13 in IBD, continuous clinical response (CCR) and disease course in UC treated with golimumab, tofacitinib induction and rapid onset of effect in UC, rapid response to vedolizumab in biologic-naive IBD patients, elemental diet with maintenance anti-TNF-α therapy in CD, BEVZ92 versus bevacizumab for metastatic colorectal cancer, and the long-term safety and tolerability of tofacitinib in CD

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,

Dr Ian Kronborg

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Incidence of arthritis/arthralgia in inflammatory bowel disease with long-term vedolizumab treatment: Post hoc analyses of the GEMINI trials

Authors: Feagan BG et al.

Summary: These post hoc analyses of data from the GEMINI studies evaluated the effect of vedolizumab (a gut-selective anti-trafficking agent) on arthritis/arthralgia, extraintestinal manifestations (EIMs) associated with IBD. In patients with CD, the incidence of sustained resolution of arthritis/arthralgia was similar with vedolizumab and placebo; however, vedolizumab was significantly less likely than placebo to be associated with new/worsening arthritis/arthralgia (HR 0.63; 95% CI 0.44-0.89). Among CD patients receiving corticosteroids at baseline, the risk of new/worsening arthritis/arthralgia was increased when the dose of corticosteroids was decreased (OR 7.49; 95% CI 3.50-15.97), regardless of treatment. Among those achieving a corticosteroid-free status, arthritis/arthralgia was less likely with vedolizumab than with placebo (HR 0.14; 95% CI 0.05-0.35). A similar incidence of new/worsening of arthritis/arthralgia was seen between vedolizumab and placebo in patients with UC. Among UC patients receiving corticosteroids at baseline, the risk of arthritis/arthralgia was greater in those achieving corticosteroid-free status than in those continuing corticosteroids (HR 2.63; 95% CI 1.13-6.11). In UC patients achieving corticosteroid-free status, the incidence of arthritis/arthralgia was similar with vedolizumab and placebo. The study authors concluded that vedolizumab therapy was associated with a reduced likelihood of new/worsening arthritis/arthralgia in CD and no increased incidence of such events in UC.

Comment: EIMs of IBD are common in both UC and CD, but their response to biologic therapies has been variable. With TNF antagonists, many don't respond and there is often relapse after an initial response. The introduction of vedolizumab has the possibility to give us some insight as it is a gut-specific agent and may help to sort if EIMs are due to an immune response to antigens released from the gut or migration of pro-inflammatory leucocytes from the gut to target organs. This study looked at these EIMs in patients in the GEMINI studies; arthritis/arthralgia, aphthous stomatitis, erythema nodosum, iritis/uveitis and pyoderma gangrenosum. The results are intriguing; in CD there is less worsening in arthritis/arthralgia but similar rates of improvement compared to placebo. In UC there are no clear effects on EIMs. Reducing the dose of steroids was not unexpectedly associated with an increased chance of flare of arthritic symptoms in both UC and CD. Patients with CD who were on steroids at baseline had the best response in terms of arthritis/arthralgias, but this was not seen in UC patients. I think the study strongly refutes reports of an increased incidence of EIMs with vedolizumab and suggests there is a subgroup of patients with CD who may obtain significant benefit in terms of their EIMs.

Reference: J Crohns Colitis. 2019;13(1):50-7

Abstract

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Infliximab dose adjustment can improve the clinical and radiographic outcomes of rheumatoid arthritis patients: REVIVE study results

Authors: Nozaki Y et al.

Summary: The clinical responses and radiographic outcomes of 90 patients (aged 21-81 years) with RA undergoing continuous (3 mg/kg; n = 50) or dose-adjusted (escalation and de-escalation based on DAS28 from week 14 to 3, 6, and 10 mg/kg; n = 40) infliximab treatment in the REVIVE study were investigated. At 104 weeks, patients treated continuously exhibited retention and low disease activity (DAS28) rates of 56.8% and 39.1%, while corresponding rates in the dose-adjusted group were 66.7% and 66.7%, respectively. The dose-adjusted group also exhibited significantly increased remission based on the DAS28 and the American College of Rheumatology (ACR)/European League against Rheumatism (EULAR) Boolean-based criteria. Radiographic assessment also showed a significant reduction in the mean changes in total Sharp score. Comparison of the two groups did not exhibit any significant difference in the cumulative rates of any adverse effects

Comment: This study examines the outcome as assessed by radiologic examination of dose escalation of infliximab on the course of RA. The strength of this study is the use of an objective measure to assess the outcome, but the weakness is that it is a retrospective non-randomised study. The outcomes are quite clear in that escalating the dose leads to increased retention in treatment (72.5% vs 54%) for a stable dose and improved clinical (87.5% vs 43.6%) and radiological response. There was no safety signal with the dose increase. Interestingly, the study was impacted by the fact that in the Japanese healthcare system the younger patients have to pay a higher percentage of the drug cost and some had to stop therapy. The cost implications need to be worked out; if an aggressive early treatment leads to remissions and less long-term complications the higher initial cost will need to be outweighed by longer-term economic gains.

Reference: Biologics 2018;12:171-82
Abstract

Outcome of pregnancies in female patients with inflammatory bowel diseases treated with vedolizumab

Authors: Moens A et al.

Summary: This retrospective, multicentre Belgian observational study evaluated pregnancy outcomes in 24 vedolizumab-treated female IBD patients (five had active disease at conception and one had disease flare during pregnancy). Two of the patients continued vedolizumab throughout pregnancy, while five stopped the agent in the 1st trimester and 16 in the 2nd trimester. There were 23 live births and complications including premature rupture of membranes, pre-eclampsia, miscarriage, elective termination and stillbirth, were observed in 25% of the pregnancies. In 35% of the infants, prematurity, intra-uterine growth retardation, small for gestational age and congenital malformations including hip dysplasia, pulmonary valve stenosis and Hirschprung's disease were identified. The median gestational age, weight and Apgar score 5 min after birth were 39 weeks, 3270 gm and 10, respectively. The authors concluded that no firm conclusions could be drawn from their study regarding the safety of vedolizumab use during pregnancy, and that until the findings of prospective and controlled registries are known, vigilance and strict follow-up of pregnant patients treated with the agent should be mandatory.

Comment: The current view is that the use of TNF antagonists in pregnancy in patients with IBD is probably safe and may improve outcomes. There is little or no data published about vedolizumab in pregnancy and trials fail to give us any real information. In this study, the authors identified 24 pregnancies in Belgium where patients had received vedolizumab. The outcomes were not great; there were complications in 25% of patients and 35% of infants, although it is impossible to work out the relationship to the drug. The message is clear; at present the lack of data means vedolizumab should be avoided in pregnancy. This study reinforces the need for better postmarketing follow up with prospective and controlled registers, especially in pregnancy.

Reference: J Crohns Colitis 2019;13(1):12-18
Abstract

Drug survival and immunogenicity after switching from remicade to biosimilar CT-P13 in inflammatory bowel disease patients: Two-year follow-up of a prospective observational cohort study

Authors: Smits LJT et al.

Summary: This single-centre, prospective, observational cohort study investigated the long-term drug survival, immunogenicity, and pharmacokinetics after switching from remicade to CT-P13 in 83 patients with IBD (57 CD, 24 UC, 2 IBD-unclassified). At week 104, three patients had been lost to follow up, but 55 (66%) remained on CT-P13. Ten patients had discontinued CT-P13 due to loss of response, seven had discontinued the agent due to disease remission and eight due to adverse events. Overall, 5/83 patients at baseline (before switching) had exhibited antidrug antibodies, while two patients exhibited these before week 52, with no subsequent antidrug antibodies detected until week 104. There was no significant change in median trough levels and clinical and biochemical disease activity at baseline, week 16, week 52 and week 104.

Comment: The use of biosimilars is markedly increasing, driven by financial reasons predominantly, so data to support their effectiveness is important. This study is prospectively looking at switching between remicade and CT-P13 and following for 2 years. There were 83 patients with 57 of whom had CD. The clinical outcomes were consistent with continued therapy with the original agent and importantly there was no increase in drug antibody levels. There were no changes in trough levels and biochemical disease activity either. The results are consistent with other studies, but this extends over a longer period and supports both the efficiency and safety of switching.

Reference: Inflamm Bowel Dis. 2019;25(1):172-9
Abstract

Continuous clinical response is associated with a change of disease course in patients with moderate to severe ulcerative colitis treated with golimumab

Authors: Reinisch W et al.

Summary: This post hoc analysis of the PURSUIT-M trial examined the 1-year clinical, endoscopic, QoL and biomarker, and 4-year clinical outcomes of patients receiving golimumab therapy for UC. Among patients receiving golimumab maintenance, greater proportions of patients with versus without a continuous clinical response (CCR) at week 54 achieved clinical remission (67.1% vs 1.9%), endoscopic remission (Mayo endoscopy score 0 [47.9% vs 1.3%]), corticosteroid-free remission (61.6% vs 1.9%), and normal QoL (IBD questionnaire score ≥170 [75.0% vs 24.4%]). Normalised calprotectin levels during maintenance were observed in patients with a CCR but not those without. A greater proportion of patients with versus without CCR maintained a PGA score of 0 through week 216 (58% vs 42%) in the extension study. None of the patients (47 induction non-responders and 13 induction responders) going onto colectomy achieved a CCR through 54 weeks.

Comment: The treatment of IBD has significantly improved over the last 10 years, but we are still struggling to decide what is the best target for obtaining a long-term remission. Deep remission, mucosal healing and other targets have been proposed. CCR is a more recent suggestion and seems to be holding up as more practicable in clinical use. This study looked at CCR with golimumab in severe UC as a predictor of outcome. If patients had CCR at 54 weeks on golimumab maintenance, more achieved clinical remission (67.15% vs 1.95%), with similar results for steroid-free status, endoscopic Mayo score and QoL. Long-term results for golimumab show about 58% have long-term symptom control at 216 weeks. No patient who achieved CCR had a colectomy compared to 13 induction responders who didn't achieve CCR. This study supports CCR as a target and notes that probably the Mayo score can be replaced by patient symptoms.

Reference: Inflamm Bowel Dis. 2019;25(1):163-71
Abstract

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Tofacitinib induction therapy reduces symptoms within 3 days for patients with ulcerative colitis

Authors: Hanauer S et al.

Summary: The onset of symptom improvement in post hoc analyses of data from two phase 3 trials of induction therapy with tofacitinib in patients with moderate-to-severe active UC (OCTAVE Induction 1 and 2) was investigated. The patients were intolerant to, or had failed previous treatment with corticosteroids, thiopurines, and/or TNF antagonists. Patients were treated with tofacitinib 10 mg twice daily (n = 905) or placebo (n = 234) for 8 weeks. Patients receiving tofacitinib exhibited significantly greater mean changes in reductions from baseline stool frequency subscore (tofacitinib -0.27 vs placebo -0.11; $p < 0.01$), total number of daily bowel movements (-1.06 vs -0.27; $p < 0.0001$), and rectal bleeding subscore (-0.30 vs -0.14; $p < 0.01$) by day 3 compared with placebo recipients. More tofacitinib recipients exhibited reductions from baseline in stool frequency subscore by ≥1 point (28.8% vs 17.9%; $p < 0.01$) and rectal bleeding subscore by ≥1 point (32.0% vs 20.1%; $p < 0.01$) by day 3 compared with placebo recipients. When analysed by subgroup, including failure of prior anti-TNF therapy, baseline corticosteroid use, and baseline serum levels of C-reactive protein, the consistent effect of tofacitinib was still observed.

Comment: Tofacitinib is one of the new oral JAK inhibitors being trialled in IBD. These grouped studies found an increased response rate at 3 days of about 50% more than in the placebo group. The response rate was only about one-third of patients, but was consistent in all subgroups. The question is does this improvement occur with other therapies as we have all seen patients respond rapidly to biologics. The original studies for the biologics in general had 2 weeks as the first endpoint so they do not address this. The important fact is that this is an oral agent, which seems to act quickly and seems to be active in patients where other therapies have failed. Response at this time was also predictive of response up to 8 weeks. Some patients who did not respond quickly did improve later, so failure to respond quickly should not lead to cessation of therapy. The key question will be – Can this agent in the future allow us to avoid using steroids?

Reference: Clin Gastroenterol Hepatol. 2019;17(1):139-47
Abstract

Rapid response to vedolizumab therapy in biologic-naive patients with inflammatory bowel diseases

Authors: Feagan BG et al.

Summary: This post hoc analysis of data from phase 3, randomised, controlled trials of vedolizumab versus placebo in adult patients with UC (n = 374) or CD (n = 784) investigated the time course of clinical response to vedolizumab in patients who were and were not previously treated with TNF antagonists. Overall, a significantly higher percentage of patients with UC given vedolizumab achieved the predefined composite symptom score at 2, 4, and 6 weeks compared to those given placebo. A significantly greater percentage of TNF antagonist-naive CD patients given vedolizumab achieved the predefined score at weeks 2 and 4 compared to those given placebo. Among UC patients treated with vedolizumab, 19.1% (overall) and 22.3% (TNF antagonist-naive) achieved a composite score of rectal bleeding of 0 and stool frequency ≤1 at week 2 compared to 10% (overall) and 6.6% (TNF antagonist-naive) placebo recipients. Among CD patients who were TNF antagonist-naive, 15.0% given vedolizumab achieved an average daily composite score of abdominal pain ≤1 and loose stool frequency ≤3 at week 2 (compared to 7.9% given placebo); 23.8% of vedolizumab recipients achieved these by week 4 (compared to 10.3% given placebo).

Comment: It has been thought that vedolizumab is effective, but the rate of onset is slow. This paper addresses that perception. The first observation is that there is no significant difference in response in biologic-experienced, to biologic-naive patients. Second is that in patients who respond, the difference in response rate increases till week 4 then stabilises. The importance of placebo control is again shown as the rate of placebo response in this study is half that in the tofacitinib study quoted above. One predictor of response seemed to be milder disease. Overall this study suggests there is an early response in vedolizumab therapy but that in some patient's therapy response is not seen until 14 weeks.

Reference: Clin Gastroenterol Hepatol. 2019;17(1):130-8
Abstract

Effect of a concomitant elemental diet with maintenance anti-tumor necrosis factor-α antibody therapy in patients with Crohn's disease: A multicenter, prospective cohort study

Authors: Hirai F et al.

Summary: These authors sought to clarify the additional effect of a concomitant elemental diet (ED) for patients with CD on maintenance anti-TNF therapy who had achieved clinical response (defined as delta CDAI >70 and CDAI <200) at 10-14 weeks after the start of infliximab or adalimumab. Patients underwent an ED tolerability test (900 kcal/day) for 3 days and if they chose to, received Elental 900 kcal/day or more (n = 37). Thirty-five patients were allocated to the non-ED group. The two groups showed no significant difference in cumulative remission rate at 2 years (60.9% vs 56.7%, p = 0.98). Adherence to the ED was relatively low, with only 11 patients maintaining treatment of 900 kcal/day.

Comment: Treatment of CD is evolving rapidly, but overall only 50-60% of patients have a long-term remission with significant cost and risk of side effects. Elemental diet has been proposed as adjuvant therapy and a meta-analysis suggested a 3-fold increase in obtaining remission. This study is an unblinded prospective multicentre cohort study to assess the benefit of ED in patients in remission with anti-TNF treatment. Patients had to be able to tolerate ED either orally or by tube before being entered into the study. Patients had to have responded to anti-TNF (delta CDAI >70) also to enter, and the endpoint was 2 years after induction. 72 patients were enrolled. Adherence to the ED had no clear effect on outcome and the only side effect noted was diarrhoea in two patients. There was no significant evidence of benefit. Another hopeful strategy bites the dust.

Reference: J Gastroenterol Hepatol. 2019;34(1):132-9
Abstract

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Independent commentary by Dr Ian Kronborg

After doing his medical training at Melbourne University Dr Ian Kronborg worked at the RMH and completed his gastroenterology fellowship. He then worked at The WEHI and went overseas to complete his training at the University of Southern California. He returned to Australia and worked at Western Health eventually becoming Head of Gastroenterology and Clinical Services Director for Medicine. He also established the Drug and Alcohol service and was lead clinician for IT in Western Health. He has published research in hepatology, IBD and addiction. Currently he continues an active research program and works in private practice.

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Bevacizumab biosimilar BEVZ92 versus reference bevacizumab in combination with FOLFOX or FOLFIRI as first-line treatment for metastatic colorectal cancer: a multicentre, open-label, randomised controlled trial

Authors: Romera A et al.

Summary: The pharmacokinetic profile, efficacy, safety, and immunogenicity of BEVZ92 (a proposed biosimilar to bevacizumab) with reference bevacizumab as a first-line treatment in patients (aged ≥18 years) with metastatic colorectal cancer was investigated in this randomised, open-label trial involving 15 centres in Argentina, Brazil, India, Spain, and Ukraine. All patients had metastatic colorectal cancer with ≥1 measurable non-irradiated lesion for which first-line chemotherapy was indicated and an ECOG performance status of ≤2. None of the patients had received treatment for advanced disease and all had bone marrow, renal, hepatic and coagulation markers within normal ranges. Patients received BEVZ92 (n = 71) or reference bevacizumab (5 mg/kg on day 1 of each cycle every 2 weeks; n = 71) plus fluorouracil, leucovorin, and irinotecan (FOLFIRI) or fluorouracil, leucovorin, and oxaliplatin (FOLFOX). Bioequivalence between the two agents was established if the 90% CIs for the ratio of BEVZ92 to reference bevacizumab of the geometric means for the area under the concentration-versus-time curve after a single infusion ($AUC_{0\text{-}336h}$) and the AUC at steady state (AUC_{ss}) at cycle 7 in the assessable population (all treated patients with serum concentration measurements during the first seven cycles) were within the acceptance interval of 80-125%. The geometric mean ratio of $AUC_{0\text{-}336h}$ in the BEVZ92 versus the control group was 99.4% (90% CI 90.5-109.0) and the AUCss was 100.0% (90.2-112.0). Secondary endpoints including objective response rates (49% vs 56%), clinical benefit (87% vs 92%), and PFS (median 10.8 months vs 11.1 months) were similar between the BEVZ92 and reference bevacizumab groups. There were no significant differences in safety profiles between the two agents, nor were there significant differences in the occurrence of anti-drug antibodies (two patients in the BEVZ92 group and one in the reference bevacizumab group). Neutropaenia was the most common grade 3 or 4 adverse event reported in the BEVZ92 (20%) and reference bevacizumab (27%) groups. 28% of BEVZ92 recipients and 30% of reference bevacizumab recipients experienced serious adverse events and two patients died from bevacizumab-related serious adverse events (one in each group).

Comment: Biosimilars are making rapid inroads in clinical practice due to significant cost savings. Bevacizumab used in oncology has been around since 2005 and this study is the first to show the equivalence of a biosimilar in the treatment of patients with metastatic cancer. This randomised, open-label study could find no evidence of different pharmacokinetics, efficacy, immunogenicity or safety in patients with metastatic colon cancer. The expected side effects of VEGF inhibitors were present, but at usual rates. Discontinuation was higher in the BEVZ92 group, but seemed to be related more to the chemotherapy or change in disease status. The availability of this agent could mean significant cost savings allowing the treatment of more patients.

Reference: Lancet Gastroenterol Hepatol. 2018;3(12):845-55
Abstract

Long-term safety and tolerability of oral tofacitinib in patients with Crohn's disease: Results from a phase 2, open-label, 48-week extension study

Authors: Panés J et al.

Summary: These authors report on the findings of their 48-week open-label extension study which investigated the long-term safety of oral tofacitinib 5 and 10 mg twice daily, and secondarily investigated the agents efficacy as maintenance therapy in patients with CD who had completed the phase 2b maintenance study, or withdrawn due to treatment failure. Tofacitinib 5 mg twice daily was administered to patients (n = 62) in remission (CDAI <150) at baseline, while tofacitinib 10 mg twice daily was administered to all others (n = 88). After 8 weeks of treatment, a single dose adjustment was allowed. Similar adverse event and serious infection rates were seen between the two groups, with CD worsening the most frequent adverse event for tofacitinib 5 (33.9%) and 10 mg (19.3%) recipients. The rates of serious adverse events were higher for patients not in remission at baseline receiving 10 mg than those receiving 5 mg (19.3% vs 8.1%) and discontinuation attributed to higher rates of insufficient clinical response (30.7% for 10 mg recipients vs 9.7% for 5 mg recipients). There were no new safety signals. Follow-up at 48 weeks revealed that in patients with baseline remission receiving 5 mg, 87.9% maintained remission and 75.0% sustained remission as observed (46.8% and 38.7%, respectively, by non-responder imputation).

Comment: Patients in this study to assess safety who were in remission received a lower dose, while treatment failures had the higher dose of 10 mg b.d. Previous studies have not shown a significant benefit for tofacitinib in induction of remission in moderate-to-severe CD and this open-label study was designed to look at safety primarily with some data on efficacy. 62 were in remission and 88 had active disease. In the group in remission, 69.4% completed treatment with treatment failure being the commonest reason to drop out compared to 51.1% in patients not in remission at baseline, with treatment failure the main reason. Rates of serious infections were 3.2% and 2.3%. Three cases of herpes zoster were reported and one skin BCC. Overall, the safety profile showed no new signals. Efficacy was unclear, but did not seem to be a loud signal. Overall this supports the suspicion that tofacitinib will be useful in UC, but not in CD.

Reference: Aliment Pharmacol Ther. 2019;49(3):265-76
Abstract

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