**Welcome** to the seventh issue of Biologics Research Review.

Switching from originator to biosimilar infliximab appears to be a safe and effective option for patients with immune-mediated diseases, according to the NOR-SWITCH study. Following on, we look at an interesting meta-analysis comparing the efficacy of different biologic agents for mucosal healing in Crohn’s disease (CD). Other topics covered in this issue are the influence of pregnancy on the pharmacokinetics of infliximab in inflammatory bowel disease (IBD), the response to ustekinumab in patients with medically refractory CD, infliximab and malignancy in paediatric IBD, tofacitinib for induction and maintenance of CD, and peficitinib in rheumatoid arthritis.

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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**Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial**

Authors: Jørgensen KK et al.

**Summary:** The NOR-SWITCH study, a randomised, non-inferiority, double-blind, phase IV trial with 52 weeks of follow-up examined the efficacy, safety, and immunogenicity of switching from originator infliximab [Remicade®] to the less expensive biosimilar CT-P13. Between Oct 24, 2014, and July 8, 2015, 482 adult patients on stable treatment with infliximab originator treated in a hospital setting for at least 6 months were selected for participation; 408 were included in the per-protocol analysis. Among the cohort, 32% had CD, 19% had UC, 19% had SpA, 16% had rheumatoid arthritis, 6% had psoriatic arthritis and 7% had chronic plaque psoriasis.

Data collected at infusion visits in 40 Norwegian study centres revealed disease worsening in 53 (25%) patients in the infliximab originator group versus 61 (30%) patients in the CT-P13 group (per-protocol set; adjusted treatment difference -4.4%; 95% CI -12.7 to 3.9). According to the prespecified non-inferiority margin of 15%, switching from infliximab originator to CT-P13 was not inferior to continued treatment with infliximab originator. The two groups demonstrated a similar frequency of adverse events; serious adverse events 10% for infliximab originator vs 9% for CT-P13, overall adverse events 70% vs 68%, and adverse events leading to discontinuation 4% vs 5%, respectively.

**Comment:** The NOR-SWITCH study is well known to most readers. The study is a 52-week randomised, double-blind, non-inferiority phase IV switch trial in patients with a range of autoimmune conditions including IBD, CD, SpA, rheumatoid arthritis, psoriatic arthritis and plaque psoriasis. The originator infliximab was initially undertaken as therapy and this study investigated the efficacy, safety and immunogenicity in a group of inflammatory disease states treated with continuous infliximab versus patients switched to CT-P13 (a biosimilar infliximab – Remsima). Switching was non-inferior across all groups, in a large sample. The study was not powered to assess non-inferiority in specific disease states, but nonetheless a very reassuring paper.

Reference: Lancet 2017;389(10086):2304-16

Abstract
Systematic review with meta-analysis: comparative efficacy of biologics for induction and maintenance of mucosal healing in Crohn’s disease and ulcerative colitis controlled trials

Authors: Cholapranee A et al.

Summary: This systematic review and meta-analysis included 12 RCTs examining mucosal healing as an endpoint of immunosuppressive agents, anti-TNF-α or anti-integrin monoclonal antibody therapy for moderate-to-severe CD (2 induction, 4 maintenance trials) or UC (8 induction, 5 maintenance trials). Mucosal healing induction and maintenance were assessed at 6-12 weeks and 32-54 weeks, respectively, and pooled effect sizes calculated and pairwise treatment comparisons evaluated using a Bayesian network meta-analysis. Anti-TNFs were more effective than placebo for maintaining mucosal healing (28% vs 1%; OR19.71; 95% CI 3.51-110.84) in CD, while in UC, both anti-TNFs and anti-integrins were more effective than placebo for inducing (45% vs 30%) and maintaining mucosal healing (33% vs 18%). Adalimumab was found to be inferior to infliximab and combination infliximab/azathioprine for inducing mucosal healing (OR 0.45; 95% credible interval [CrI] 0.25-0.82 and OR 0.32; 95% CrI 0.12-0.84, respectively). No statistically significant pairwise difference between vedolizumab and anti-TNF agents in UC was observed.

Comment: One of the immunologic processes in pathogenesis of IBD is the interaction between integrins on the surface of leukocytes. The α4β7 integrin expressing T-cell is involved in pathogenesis and represents a new drug target for the treatment of IBD. Vedolizumab is a humanised monoclonal antibody, which acts against α4β7 integrin heterodimer and blocks the interaction of α4β7 integrin with MAdCAM-1. Vedolizumab safety issues include slightly higher risk of infections, headache and nasopharyngitis as compared to placebo. A definite endpoint (in this case mucosal healing) is a firm outcome measure, and this meta-analysis confirms the efficacy of adalimumab and infliximab in achieving this goal. The most interesting point is the comparable efficacy with anti-TNF agents. Recent studies have demonstrated clinical benefit of vedolizumab on articular manifestations in patients with active spondyloarthritis associated with inflammatory bowel disease (Orlando et al., 2016). Further large studies are required, but this represents a further possible therapeutic avenue in spondyloarthropathy.

Reference: Aliment Pharmacol Ther. 2017;45(10):1291-1302

The effects of pregnancy on the pharmacokinetics of infliximab and adalimumab in inflammatory bowel disease

Authors: Seow CH et al.

Summary: The influence of pregnancy on the pharmacokinetics of anti-TNF agents in women with IBD (median disease duration 9.2 years) was investigated in this prospective study involving 25 women (median age 29.6 years) from the University of Calgary IBD pregnancy clinic receiving maintenance infliximab (15 women; 8 CD and 7 UC) or adalimumab (10 women, 11 pregnancies). Serum bio-banking was undertaken each trimester and ANSER infliximab and adalimumab assays were employed to determine infliximab trough and adalimumab steady-state levels. During trimesters one, two and three, median trough infliximab concentrations were 8.50 μg/mL (IQR 7.23-10.07 μg/mL), 10.31 μg/mL (IQR 7.66-15.63 μg/mL) and 21.02 μg/mL (IQR 16.01-26.70 μg/mL), respectively. Adjusting for albumin, CRP and BMI, infliximab trough levels increased by 4.2 μg/mL per trimester (p = 0.02), but adalimumab drug levels remained stable (p > 0.05). The authors concluded that therapeutic drug monitoring in the second trimester might be useful in guiding dosing in the third trimester.

Comment: Certainly informative data but the clinical relevance is the key question. The important notion is whether the increased levels led to any effect on maternal or baby outcomes. An interesting step in the right direction, but longer follow up is required.


Clinical, endoscopic and radiographic outcomes with ustekinumab in medicinally-refractory Crohn’s disease: real world experience from a multicentre cohort

Authors: Ma C et al.

Summary: This retrospective multicentre cohort study involving 167 medicinally-refractory CD patients receiving ustekinumab (95.2% had previously failed anti-TNF therapy) between 2011 and 2016 assessed real-world clinical, endoscopic and radiographic response and remission outcomes. At 3- and 6-month’s follow-up, clinical response was achieved by 38.9% and 60.3% of patients and remission by 15.0% and 25.2% of patients, respectively. At 12 months, 59.5% achieved clinical response and 27.9% remission. At 6 and 12 months, endoscopic or radiographic response was demonstrated in 54.5% and 55.8% of patients, respectively.

Comment: The conclusion of this study is strongly positive, but caution needs to be exercised. This study is a retrospective cohort study with clinical response and remission recorded as outcome measures. Note that only a relatively small proportion of subjects achieved remission at 6 months (25%) and at 12 months (27%). Further study is required.

Reference: Aliment Pharmacol Ther. 2017;45(9):1232-43

Infliximab is not associated with increased risk of malignancy or hemophagocytic lymphohistiocytosis in pediatric patients with inflammatory bowel disease

Authors: Hyams JS et al.

Summary: These authors calculated standardised incidence ratios (SIRs) for malignancy and hemophagocytic lymphohistiocytosis (HLH) in paediatric patients receiving infliximab therapy for IBD by comparing unadjusted incidence rates of malignancy and HLH in paediatric patients with IBD exposed to this agent and patients not exposed to biologics. Data from 5766 patients (≤17 years) who had CD, UC, or IBD-unclassified with 24,543.0 patient-years of follow-up were analysed. Unadjusted incidence rates demonstrated no increased risk of malignancy (0.46/1000 patient-years) or HLH (0.01/1000 patient-years) in patients exposed to infliximab compared to biologic-naïve patients (malignancy 1.12/1000 patient-years; HLH 0.56/1000 patient-years). Compared to patients not exposed to infliximab, those exposed to the agent did not demonstrate an increased risk of malignancy; SIR 2.17; 95% CI 0.59-5.56 vs SIR 1.69; 95% CI 0.46-4.32, respectively.

Comment: Very reassuring data from a large long-term cohort. This cohort is unique in size, duration of therapy and low rate of malignancies overall in the patients treated with infliximab. Interestingly, thiopurine exposure appeared to be a more important factor in subsequent malignancy development but infliximab exposure, after adjustment for age, gender and race, was not associated with an increased risk.

Reference: Gastroenterology 2017;152(8):1901-14
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‡52 weeks after induction, 53.1% of 128 STELARA patients were in clinical remission (CDAI score <150 points) with 8-weekly maintenance doses vs 35.9% of 131 placebo (induction dose only) patients (p=0.005).¹

CDAI, Crohn’s Disease Activity Index; IV, intravenous; TNF, tumour necrosis factor.

³In UNITI-2, 68.6% of STELARA patients (n=209) were TNF inhibitor-naïve. The remaining population was previously exposed to, but did not fail, treatment with TNF inhibitors. All patients in the study had failed conventional treatment (e.g. azathioprine, 6-mercaptourine, methotrexate, or corticosteroids).³

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Tofacitinib for induction and maintenance therapy of Crohn’s disease: results of two phase IIb randomised placebo-controlled trials

Authors: Panés J et al.

Summary: In two randomised, double-blind, placebo-controlled, multicentre phase IIb studies, these authors evaluated the efficacy and safety of tofacitinib for induction and maintenance treatment in adult patients with moderate-to-severe CD. Patients received either induction treatment with placebo or tofacitinib 5 or 10 mg twice daily for 8 weeks and those with a clinical response (decrease in CDAI score at week 8 of ≥100 points from baseline) were re-randomised to maintenance treatment with placebo, tofacitinib 5 or 10 mg twice daily for 26 weeks. A total of 180/280 patients who had been randomised in the induction study were enrolled in the maintenance study. Clinical remission (CDAI <150 points) at week 8 was achieved by 43.5% of the 5 mg twice daily recipients (p = 0.325 vs placebo) and 43.0% of the 10 mg twice daily recipients (p = 0.392 vs placebo), compared with 36.7% of placebo recipients. During the maintenance phase, at week 26, 55.8% of tofacitinib 10 mg twice daily recipients (p = 0.130 vs placebo) and 39.5% of tofacitinib 5 mg twice daily recipients exhibited a clinical response compared with 38.1% of placebo recipients. Following both induction and maintenance treatments, the change in CRP from baseline was statistically significant (p < 0.0001) with 10 mg twice daily compared with placebo.

Comment: The Janus kinase (JAK) proteins are well known to readers. A family of non-receptor tyrosine kinases, they possess a highly conserved kinase domain responsible for enzymatic activity. The family consists of JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2). Tofacitinib interferes with the JAK-STAT signalling by competing with ATP for binding to the kinase domain of JAKs and inhibits JAK1, JAK2, and JAK3. In vitro studies, however, demonstrate preferential inhibition of JAK1 and JAK3 with less effect on JAK2. These results show that tofacitinib was statistically no more effective than placebo in induction or maintenance of remission in CD. It is important to recognise that the study participants were highly treatment-refractory; many of the patients had failed TNF-blocker therapy, and all had failed conventional therapies. Nonetheless the future of JAK blockade in CD is uncertain based on these results. The situation is different in UC, where JAK inhibition appears to lead to more positive results, underscoring the different pathophysiological mechanisms driving these diseases with similar phenotypes.


Abstract

Indepedent commentary by Associate Professor Paul Bird
FRACP, PhD, Grad Dip MRI

Paul Bird is a rheumatologist in private practice and a Conjoint A/Professor at the University of New South Wales. In addition to his clinical duties, he is the Director of Optimus Clinical Research, a clinical research centre undertaking phase II, III and IV trials of novel agents for the treatment of rheumatic diseases.

He has completed a Post Graduate Diploma in Magnetic Resonance Imaging (RMIT University) and his PhD thesis (University of NSW) examined the feasibility, reliability and validity of MRI as an outcome measure in patients with rheumatoid arthritis (RA). He maintains ongoing participation in research projects examining the application of Magnetic Resonance Imaging (MRI) in inflammatory arthritis and is an active core member of the OMERACT international MRI imaging group. In addition, he is a current member of GRAPPA (Group for Research and Assessment of Psoriasis and Psoriatic Arthritis).

A/Professor Bird is actively involved in undergraduate education, as a lecturer and examiner for students undertaking a medical degree at UNSW. He is a co-supervisor for postgraduates, including national and international PhD candidates. Within the Australian Rheumatology Association, he has been a member of the Education Committee and Chair of the Professional Affairs Committee from 2003-2007. He is a past member of the Scientific Committee. In addition, he has been involved in education of Physician Trainees, holding the post of Director of Physician Training for the St George Physician Training Network from 2002-2005. He is an active reviewer for the Arthritis and Rheumatology, Annals of Rheumatic Diseases, Journal of Rheumatology, Rheumatology (Oxford), Arthritis Care and Research, Seminars in Arthritis and Rheumatism journals.

His current research interests are the use of MRI in rheumatoid and psoriatic arthritis, and the development of automated computerised techniques for measurement of activity and damage progression in RA.

Peficitinib, a JAK inhibitor, in combination with limited conventional synthetic disease-modifying antirheumatic drugs in the treatment of moderate-to-severe rheumatoid arthritis

Authors: Genovese MC et al.

Summary: In this randomised, double-blind, phase IIb trial, these authors evaluated the efficacy and safety of orally administered once-daily peficitinib in combination with limited conventional synthetic DMARDs in 289 patients with moderate-to-severe rheumatoid arthritis receiving peficitinib 25 mg, 50 mg, 100 mg,150 mg or matching placebo once daily for 12 weeks. At week 12, an ACR20 response (primary endpoint) was achieved by 22.0%, 36.8%, 48.3% (p < 0.05), 56.3% (p < 0.01), and 29.4% of peficitinib 25 mg, 50 mg, 100 mg, 150 mg, and placebo recipients, respectively. Compared with those in the placebo group, peficitinib 100 mg and 150 mg recipients achieved a rapid and statistically significant (p < 0.05) ACR20 response by week 2. The overall incidence of adverse events did not significantly differ between peficitinib and placebo recipients; the most frequent adverse events were upper respiratory tract infection (5%), nausea (4%) and urinary tract infection (4%). None of the patients experienced grade 2 or higher neutropenia or lymphopenia.

Comment: Peficitinib (ASP015K) is an orally bioavailable JAK inhibitor for the treatment of rheumatoid arthritis. Peficitinib inhibits JAK1, JAK2, JAK3 and TYK2 enzyme activities and has moderate selectivity for JAK3 inhibition. The other JAK inhibitors, tofacitinib or baricitinib, selectively suppress JAK3 or JAK1/2, respectively. Milder inhibition of JAK2 by peficitinib may contribute to the mitigation of effects on red blood cells and platelets, reported to be caused by JAK2 inhibition. In this phase II trial, the drug appears effective, with the ACR20 results showing a dose response. Safety outcomes were similar to the known side effects of the JAK inhibitors, but importantly neutropenia and lymphopenia were mild. A phase III multicentre randomised, placebo-controlled, double-blind, parallel-group, confirmatory study to evaluate the efficacy and safety of peficitinib alone or in combination with DMARDs in patients with RA who had an inadequate response to DMARDs is underway (NCT02308163). Etanercept will also be administered as the reference drug in this trial in an open-label manner. This will be an interesting drug to watch as the JAK family evolves.


Abstract