Welcome to the first issue of Biologics Research Review. This review is a unique Australian publication providing topical, relevant and accessible information for health professionals with an interest in the use of biologic therapies. In essence, the review is a summary of what we consider to be some of the most significant new studies in this area. For each paper we have provided commentary on why the findings are important and, where relevant, have suggested how they can potentially affect local practice.

We hope you find our inaugural 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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Clinical utility of random anti-tumor necrosis factor drug-level testing and measurement of antidrug antibodies on the long-term treatment response in rheumatoid arthritis

Authors: Jani M et al.

Summary: This study involving 331 patients with RA, 160 treated with adalimumab and 171 treated with etanercept, investigated whether antidrug antibodies and/or drug non-trough levels predict the long-term treatment response of such patients, and identified factors influencing antidrug antibody and drug levels in order to optimise future treatment decisions. At 12 months of follow up, antidrug antibodies were detected in 24.8% of those receiving adalimumab (31 of 125) and in none of those receiving etanercept. Low adalimumab level and antidrug antibody formation at 3 months were found to be significant predictors of non-response at 12 months according to EULAR criteria; area under the receiver operating characteristic curve 0.71 (95% CI 0.57-0.85); Furthermore, after adjustment for confounders, adalimumab level was the best predictor of change in the DAS28 at 12 months; regression coefficient 0.088 [95% CI 0.019-0.16], p = 0.012). Compared with antidrug antibody-negative patients, antidrug antibody-positive patients received lower median dosages of methotrexate (15 mg/week vs 20 mg/week; p = 0.01) and had longer disease duration (14.0 vs 7.7 years; p = 0.03). While etanercept levels were associated with the EULAR response at 12 months (regression coefficient 0.088 [95% CI 0.019-0.16], p = 0.012), after adjustment, this difference was not significant. Both poor adherence and a BMI ≥30 kg/m² were associated with lower drug levels.

Comment: This well-powered prospective study once again illustrates the potential significance of therapeutic drug monitoring in the biologic era, and using non-trough levels for adalimumab. Some important observations here include the association between drug levels and change in disease activity, and between concomitant immunomodulator dose and likelihood of antidrug antibody formation. The 3-month combination of low adalimumab level and antidrug antibody status was a significant predictor of non-response (AUC 0.71). The risk of antidrug antibody formation in patients with auto-inflammatory disorders such as RA remains a major clinical challenge, limiting the therapeutic shelf life for many patients. Strategies to mitigate against this including appropriate dosing with immunomodulators seem reasonable.


Abstract

Independent commentary by Dr Graham Radford-Smith.

Graham Radford-Smith is a full time clinician and Head of the Inflammatory Bowel Disease service for the Royal Brisbane Hospital and the Metro North Health Service. His clinical team also provides an extensive outreach service, including IBD Telehealth, to the regional areas of Wide Bay and Central Queensland. Graham completed his medical degree at Oxford. He trained in London and Oxford before moving to Brisbane in 1994. He was appointed as a staff specialist in Gastroenterology at the Royal Brisbane in 1997. He was appointed as a visiting scientist at QIMR Berghofer in 2006 and an Honorary Group Leader in 2012. He is Past-President, GE Society of Queensland, past member of the AIBDA and GESA research committees, a founding member of the International IBD Genetics Consortium, and founder of the ANZ IBD Consortium, a collaborative of 16 IBD centres across our region.
Efficacy and safety of secukinumab in the treatment of moderate to severe plaque psoriasis: a meta-analysis of randomized controlled trials

Authors: Xiong HZ et al.

Summary: This meta-analysis of eight RCTs involving a total of 3213 patients investigated the use of secukinumab 150 mg versus placebo for moderate-to-severe plaque psoriasis. Overall efficacy favoured secukinumab, based on PASI 75 score (fixed-effects OR 49.25; 95% CI 33.67-72.06; p < 0.00001), PASI 90 score (OR 44.92; 95% CI 24.72-81.62; p < 0.00001) and the Investigator’s Global Assessment scale (OR 22.25; 95% CI 7.83-64.84; p < 0.00001). There were no significant adverse effects in secukinumab recipients.

Comment: This meta-analysis provides further evidence for the dramatic efficacy of secukinumab on psoriasis, backed up by a solid safety profile. Secukinumab also has proven efficacy in the inflammatory arthropathies including ankylosing spondylitis, RA and psoriatic arthritis. Recent studies have also demonstrated superiority in clinical efficacy over ustekinumab in plaque psoriasis. However, this drug failed in Crohn’s disease as did abatacept, indicating that the biologics armamentarium for intestinal inflammatory disorders trails well behind other auto-inflammatory disorders.


Abstract

Differential drug survival of biologic therapies for the treatment of psoriasis: A prospective observational cohort study from the British Association of Dermatologists Biologic Interventions Register (BADBIR)

Authors: Warren RB et al.

Summary: This analysis of data from a prospective national pharmacovigilance observational cohort study (British Association of Dermatologists Biologic Interventions Register [BADBIR]), assessed the survival rates of the first biologic course, adalimumab (n = 1879), etanercept (n = 1098), infliximab (n = 96), and ustekinumab (n = 450), in biologic-naive patients with chronic plaque psoriasis. Overall survival rate was 77% in the first year declining to 53% by the third year. Multivariate analysis indicated that predictors of discontinuation were female gender (HR 1.22; 95% CI 1.09-1.37), current smoking (HR 1.19; 95% CI 1.03-1.38), and higher baseline Dermatology Life Quality Index (HR 1.01; 95% CI 1.00-1.02). The presence of psoriatic arthritis (HR 0.82; 95% CI 0.71-0.96) predicted drug survival. When compared with adalimumab, etanercept (HR 1.63; 95% CI 1.45-1.84) and infliximab (HR 1.56; 95% CI 1.16-2.09) recipients were more likely to discontinue therapy, whereas ustekinumab recipients were more likely to persist (HR 0.48; 95% CI 0.37-0.62).

Comment: Real-life clinical data is essential in assessing long-term drug safety and efficacy. This is a well powered, prospective cohort study comparing three anti-TNF strategies and ustekinumab in a UK psoriasis population. The study confirms gradual loss of response to the biologics over time, with 77% survival at 1 year and 53% by the third year. Ustekinumab outperformed the anti-TNFs, while female gender, obesity and active smoking were predictors of discontinuation. The real-world application of these drugs cannot be adequately determined from clinical trial data; hence the ongoing need for large cohort studies and well run registries such as this.


Abstract

Twelve years of living with Crohn's disease has taught Rhoma the power of resilience. She knows life is precious, and obstacles won't stand in her way. With maintenance treatment infusions eight weeks apart, Rhoma has the freedom to travel. Something she's done plenty of in the ten years she's been treated with REMICADE.

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**Prospective evaluation of the achievement of mucosal healing with anti-TNF-α therapy in a paediatric Crohn’s disease cohort**

**Authors:** Nuti F et al.

**Summary:** This prospective study tested the effect of biologics in stimulating mucosal healing in 37 biologic-naïve paediatric (mean age 12.3 years; disease duration 13.0 months) Crohn’s disease patients. After 9–12 months of follow-up, Paediatric Crohn’s Disease Activity Index and Simple Endoscopic Score for Crohn’s Disease were significantly lower than at baseline (p < 0.01). There was no difference in mucosal healing frequency between early and late introduction of anti-TNF-α treatment. Combination therapy with immunomodulators versus biologics alone was superior in producing complete plus partial mucosal healing (p < 0.01). One year after the second endoscopy, all patients with complete mucosal healing and 75% of those with partial mucosal healing were still in clinical remission. After 2 years, 79% of patients with complete mucosal healing and 67% of those with partial mucosal healing remained in clinical remission.

**Comment:** This prospective, paediatric study provides additional evidence and support for the use of concomitant immunomodulator therapy in Crohn’s disease. This is particularly relevant to this age group given the concerns around safety and the need for drug therapy over a prolonged period. The study has limited statistical power and thus further messages from the study need to be interpreted with caution. Specifically disease duration did not influence rates of mucosal healing, but biologic therapy was in general commenced relatively early. Further, less invasive methods to assess mucosal healing are required including the correlation between faecal calprotectin and histological improvement or healing.

**Reference:** J Crohn’s Colitis 2015;Jul 17 [Epub ahead of print]

**Abstract**

**Efficacy and safety of certolizumab pegol for Crohn’s disease in clinical practice**

**Authors:** Moon W et al.

**Summary:** The efficacy, safety and predictors of response to certolizumab pegol for Crohn’s disease were assessed in 358 patients treated at a tertiary care center in the US in a 6-year period (between 2008 and 2013) since FDA approval of the agent. Medical records were retrospectively reviewed for steroid-free complete response, loss of response and safety. Certolizumab pegol was the second and third biological agent in 112 (31.3%) and 189 (52.8%) patients, respectively. At 26 weeks, the probability of a steroid-free complete response was 19.9% (95% CI 15.9-24.5) and a steroid-free survival free of loss of response at 2 years was 46.7% (95% CI 32.5-59.5). Age of >40 years at Crohn’s disease diagnosis was a predictor of steroid-free complete response; HR relative to those <17 years of age 4.69 (95% CI 1.75-12.61), while negative predictors were current perianal fistula (HR 0.39; 95% CI 0.16-0.98) and prior primary non-response to adalimumab (HR relative to secondary loss of response 0.18; 95% CI 0.04-0.76). Serious adverse events were experienced by 23 (6.4%) patient and 19 (5.3%) discontinued certolizumab due to adverse events.

**Comment:** There are limited published “real world” studies that document the efficacy and safety of certolizumab pegol for patients with Crohn’s disease. It is currently not on the Pharmaceutical Benefits Scheme for Crohn’s disease in Australia. The association between response and age at diagnosis may be confounded by other factors including disease location and smoking behaviour. The population was characterised by a low rate of concomitant immunomodulator use and there are limited details on the characteristics of previous anti-TNF- failure(s) in these patients. Thus, the rates of sustained clinical response and survival free of loss of response may have been influenced by improved understanding of anti-TNF therapy and treatment optimisation across the disease course for each case.

**Reference:** Aliment Pharmacol Ther. 2015;42(4):428-40

**Abstract**

**Proteolytic cleavage and loss of function of biologic agents that neutralize tumor necrosis factor in the mucosa of patients with inflammatory bowel disease**

**Authors:** Biancheri P et al.

**Summary:** This in vitro laboratory investigation examined the effect of activated matrix metalloproteinase 3 (MMP3) and MMP12, and mucosal proteins from Crohn’s disease, 8 ulcerative colitis and 8 healthy control patient biopsies, along with sera from 29 Crohn’s disease patients and 33 ulcerative colitis patients with active disease, on immunoblots or in luciferase reporter assays measuring the TNF activity of anti-TNF agents infliximab, adalimumab, and etanercept. Infliximab, adalimumab, and etanercept were cleaved by both MMP3 and MMP12 generating a 32-kDa Fc monomer. Thereafter, cleaved infliximab and adalimumab acted as F(ab’)2 fragments, while the etanercept derivative no longer neutralised TNF. Proteins derived from the monomer. Thereafter, cleaved infliximab and adalimumab acted as F(ab’)2 fragments, while the etanercept derivative no longer neutralised TNF. Proteins derived from the mucosa of patients with inflammatory bowel disease, on immunoblots or in luciferase reporter assays measuring the TNF activity of anti-TNF agents, including non-specific protease activity. Given the transmural nature of inflammatory bowel disease, this protease activity may be of greater relevance to this form of disease as compared to ulcerative colitis. An MMP9 monoclonal antibody is currently under investigation for the treatment of Crohn’s disease and ulcerative colitis.

**Comment:** A novel and well designed study, which explores additional mechanisms by which IBD patients may lose response to anti-TNF drugs. Patients with higher levels of disease activity, or patients who are anti-TNF experienced, but may not have received concomitant immunomodulators, may be expected to have higher levels of circulating IgG. For example, multiple patients treated with these agents develop a variable titre of anti-nuclear antibody but only rarely drug-induced lupus. Similarly, chronic inflammatory disease may generate tissue inhibitors of anti-TNF agents, including non-specific protease activity. Given the transmural nature of Crohn’s disease, this protease activity may be of greater relevance to this form of IBD as compared to ulcerative colitis. An MMP9 monoclonal antibody is currently under investigation for the treatment of Crohn’s disease and ulcerative colitis.

**Reference:** Gastroenterology 2015;149(6):1564-74

**Abstract**

**Risk of lymphoma, colorectal and skin cancer in patients with IBD treated with immunomodulators and biologics: a Quebec claims database study**

**Authors:** Kopylov U et al.

**Summary:** The risk of colorectal cancer, melanoma, non-melanoma skin cancer and lymphoma associated with immunomodulators and biologics in patients with IBD was assessed in this Canadian nested case-control study using the provincial health insurance database of Quebec (RAMQ/MedECHO). A total of 19,582 patients were included in the analysis, which revealed that >5 years treatment with thiopurine was associated with a significantly increased risk of non-melanoma skin cancer (OR 1.78; 95% CI 1.25-2.54), while negative predictors were current perianal fistula (HR 0.39; 95% CI 0.16-0.98) and prior primary non-response to adalimumab (HR relative to secondary loss of response 0.18; 95% CI 0.04-0.76). No increased risk of non-Hodgkin’s lymphoma was seen with immunomodulator use (OR 0.87; 95% CI 0.53-1.41). Neither anti-TNF-α agents nor immunomodulators were associated with an increased risk of melanoma or colorectal cancer.

**Comment:** The study draws on administrative data to investigate the associations between immunomodulator or anti-TNF therapy and the risk of neoplasias that have previously been linked to these therapies. Although potentially reassuring, these results are in contrast to multiple other studies demonstrating increased risk of lymphoma in patients exposed to immunomodulator and/or anti-TNF therapy. Confounders may include duration of therapy and patient age. However, the authors discuss the variability in results across studies, and some of the key issues around case ascertainment, including their own. These issues underline the potential benefits of nationwide registries for IBD patients, similar to that developed in Japan.

**Reference:** Inflamm Bowel Dis. 2015;21(8):1847-53

**Abstract**
Comparative risk of hospitalized infection associated with biologic agents in rheumatoid arthritis patients enrolled in Medicare

Authors: Yun H et al.

Summary: This retrospective cohort study used Medicare data from 2006-2011 to identify 31,801 new treatment episodes of etanercept, adalimumab, certolizumab, golimumab, infliximab, abatacept, rituximab and tocilizumab in RA patients and compared the risks of hospitalised infections associated these agents. All patients had previously used another biologic agent (etanercept 12%, adalimumab 15.2%, certolizumab 5.9%, golimumab 4.4%, infliximab 12.4%, abatacept 28.9%, rituximab 14.8% and tocilizumab 6.3%) and were followed up from the initiation date of the new biologic agent until the earliest date of the following: hospitalised infection, 12 months, >30 days exposure gap, death or loss of Medicare coverage. A total of 2530 hospitalised infections were identified during follow-up; incidence rates ranged from 13.1 (abatacept) to 18.7 (rituximab) per 100 person years. After adjustment, significantly higher HRs of hospitalised infection were seen with etanercept (HR 1.24; 95% CI 1.07-1.45), infliximab (HR 1.39; 95% CI 1.21-1.60) and rituximab (HR 1.36; 95% CI 1.21-1.53) compared with abatacept.

Comment: Large, well-designed study using a US claims database to determine risks of severe infection requiring hospitalisation in a rheumatoid population. The study population were required to have received at least one prior biologic agent and the investigators utilised an infection risk score based upon established and potential infection-related confounding factors such as age, prior infection, and comorbidities. After adjustment, the risk of hospitalised infection was lowest for abatacept, which also contained the oldest subgroup of treated patients. The relative risk differences between biologics was as high as 40%. As in previous studies the risk of serious infection is highest in the first 12 months of treatment, underlining the importance of adequate screening of patients prior to commencement of biologic therapy. However, as with similar administrative datasets, the study lacked clinical data including disease severity and smoking status that may have differed between groups.

Reference: Arthritis Rheumatol. 2015;Aug 28 [Epub ahead of print]