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Welcome to the third 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 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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Cost-effectiveness of routine measuring of serum drug concentrations and anti-drug antibodies in treatment of rheumatoid arthritis patients with TNF-α blockers

Authors: Laine J et al.

Summary: This study of data from Finish RA patients receiving adalimumab and infliximab modelled the cost-effectiveness and estimated the probability of optimal or non-optimal treatment decisions based on drug trough level (DTL; n samples = 486) and anti-drug antibody (ADA; n samples = 1137) monitoring. 42% of adalimumab and 50.4% of infliximab recipients had a DTL within the target range and ADAs were found in 20% of adalimumab and 13.5% of infliximab samples. ADAs occurred in 52.3% of those with a low adalimumab DTL and 41.3% of those with a low infliximab DTL. A short-term (3-6 months) clinical decision-making model found the combined measurement of DTL and ADA was cost saving versus non-testing when monitoring results altered treatment in at least 2-5% of patients, a proportion exceeded in real-life clinical practice.

Comment: There remains some debate and controversy regarding the value and cost-effectiveness of therapeutic drug monitoring (TDM) for biologic drugs, including the anti-TNF agents. Studies in patients with inflammatory bowel disease have demonstrated the value of TDM including the measurement of ADAs in terms of defining “loss of response” more precisely, specifically as to whether this relates to a genuine lack of response in the face of therapeutic drug levels, or a lack of response due to inadequate drug levels, or undetectable drug level due to high titres of ADA. This additional information allows clinicians to optimise treatment decisions in terms of staying within drug class or choosing an alternative therapy. The study by Laine et al. uses real-life data from a Finish population of RA patients to demonstrate that routine TDM is cost-beneficial in this subgroup. Importantly, cost savings require that a minimum of 2-5 per 100 patients demonstrate TDM results that affect treatment decisions, a range well below that observed in day-to-day clinical practice.


Abbreviations used in this issue:

ADA = anti-drug antibody
CCP = cyclic citrullinated peptide
CRP = C-reactive protein
DAS28 = 28-joint Disease Activity Score
DMARD = disease-modifying anti-rheumatic drug
DTL = drug trough level
ESR = erythrocyte sedimentation rate
hs = high-sensitivity
RA = rheumatoid arthritis
RF = rheumatoid factor
SEER = Surveillance, Epidemiology and End Results
TDM = therapeutic drug monitoring
TNF = tumour necrosis factor

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**Tocilizumab in refractory rheumatoid arthritis: long-term efficacy, safety, and tolerability beyond 2 years**

**Authors:** Farah Z et al.

**Summary:** A UK retrospective single-centre study in 22 patients with RA examined long-term efficacy and safety of tocilizumab in patients refractory to synthetic DMARDs, anti-TNF agents, and B-cell depletion therapy with rituximab. In total, 15 patients completed the study, all of whom exhibited an improvement in disease activity markers over a mean of 35 months. Among 17 patients who failed to respond to rituximab, 12 remained on tocilizumab. Adverse events occurred in eight patients, five discontinued tocilizumab. Tocilizumab did not result in long-term deterioration in lipid profile from initiation to follow-up (total cholesterol 5.25 to 5.28 mmol/L, HDL-cholesterol 1.72 to 1.67 mmol/L, LDL-cholesterol 3.05 to 2.98 mmol/L; cholesterol to HDL-cholesterol ratio 3.41 to 3.40).

**Comment:** Tocilizumab is a humanised monoclonal antibody targeting the IL-6 receptor. It has demonstrated efficacy in RA patients who have previously failed to make an adequate response to synthetic DMARDs such as methotrexate and biologic DMARDs such as the anti-TNF agents. However, further long-term efficacy and safety data are warranted given the potential side effects of tocilizumab including infection (related to neutropenia) and negative effects of lipid profiles (related to hepatic LDL-receptor expression). The current single centre study, analyses the course of all patients with RA who had received tocilizumab up to May 2015. In total, there were 22 patients (20 female), mean age 62 years, 20 seropositive, and 14 with erosive disease on their most recent radiography. The majority of patients (17/22) had failed anti-TNF and rituximab. Median disease duration was 15 years, and median follow-up after first dose of tocilizumab was 28 months (mean 35 months). In total, 15 patients remained on tocilizumab at the end of the study, with significant improvements in 28-joint count, ESR-based disease activity score (DAS28-ESR). Four of nine patients on corticosteroids at baseline were able to cease these. There were three episodes of sepsis, two of significant neutropenia, one disease flare, one anaphylaxis and one case of shingles. Lipid profiles did not show any adverse changes over 36 months.

**Reference:** Biologics 2016;10:59-66

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**Correlations between immunogenicity, drug levels, and disease activity in an Italian cohort of rheumatoid arthritis patients treated with tocilizumab**

**Authors:** Benucci M et al.

**Summary:** This retrospective Italian study examined the real-life ADA immunogenicity, drug levels, and disease activity in 126 RA patients with an inadequate 12-week response to any synthetic or biological DMARDs, who received tocilizumab monotherapy (n = 13), or tocilizumab plus methotrexate (mean dose 12.6 mg/week; n = 107), or leflunomide 20 mg/day plus tocilizumab (n = 6). After 6 months, one patient had ADAs (84 ng/mL) for tocilizumab. Comparing 84 patients with tocilizumab drug levels <10 µg/mL versus 42 patients with tocilizumab drug levels of >10 µg/mL, mean DAS28 was 3.09 vs 2.78 (p = 0.0005), mean ESR was 27 vs 14 mm/hour (p = 0.0001) and mean CRP was 1.47 vs 0.65 mg/dL (p = 0.0086).

**Comment:** The current real-life RA study evaluates immunogenicity, tocilizumab levels, and disease activity in 126 patients who had made an inadequate response to synthetic and biological DMARDs. The majority of patients were treated with combination therapy (tocilizumab and methotrexate, n=107), and all patients were on prednisolone (mean dose 6.4 mg/day). Baseline and 6-month data were collected: DAS28; RF IgM, IgA, and IgG; anti-CCP; TNF-α; IL-6; ESR; CRP; and, both tocilizumab levels and anti-tocilizumab antibodies (Lisa Tacker Duo). Only one patient developed anti-tocilizumab antibodies. Using a cut-off tocilizumab level of 10 µg/mL, patients with levels <10 µg/mL (n = 84) demonstrated significantly higher DAS28, ESR and CRP scores at 6 months as compared to the 42 patients with a tocilizumab level >10 µg/mL. There were no further differences in the other biomarkers tested (RF IgM, IgA, IgG, anti-CCP, TNF-α, IL-6, tocilizumab levels and anti-tocilizumab antibodies) and no differences between seropositive as compared to seronegative cases. The study confirms the low frequency of anti-tocilizumab antibodies, but was limited by short follow-up time.

**Reference:** Biologics 2016;10:53-8

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**Rhoma is Resilient**

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 every 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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The majority of patients do not store their biologic disease-modifying antirheumatic drugs within the recommended temperature range

Authors: Vlieland ND et al.

Summary: In a Dutch observational study, 255 adult patients from eight pharmacies received a validated temperature logger with their biologic DMARDs prescription to be stored with packages according to standard label instructions (2-8°C). Only 17 (6.7%) patients stored the medication within the recommended temperature range, while 24.3% stored the medication for more than 2 hours below 0°C (median 3.7 hours) and 2% stored it above 25°C for more than 2 hours (median 11.8 hours).

Comment: This is an important practical study assessing the behaviour of adult patients on biologic DMARDs with respect to storage of their medication under appropriate conditions. Biologic DMARDs are protein-based drugs and hence may be more susceptible to external factors including extreme temperature conditions. This prospective study investigates home storage temperatures across eight Dutch pharmacies in patients receiving treatment with one of the following: etanercept, adalimumab, golimumab, certolizumab, or abatacept. Patients were provided with both verbal and written information and each prescription was provided in a closed sealed bag including a temperature logger. All the temperature data were securely stored in an online database. The primary outcome was the proportion of patients storing biologic DMARDs within the recommended storage range (2-8°C). 255 patients (of 293, 87%) completed the study, mean age 53.2 years, 51.4% female, and the majority (95.3%) were prescribed either etanercept or adalimumab. The mean temperature monitoring time was 105.7 days. Only 6.7% of patients stored all biologic DMARDs within the defined temperature range. 26.3% of patients stored their medication either below 0°C or above 25°C for longer than two consecutive hours. Age and gender did not influence “drug storage behaviour”. This study provides much longer-term data on storage of biologic DMARDs as compared to previously published work. However, the study does not address the potential effects of moderate- or extreme-temperature deviations on product quality, efficacy and the occurrence of medication side effects.


Abstract

Hidradenitis suppurativa (HS): An unrecognized paradoxical effect of biologic agents (BA) used in chronic inflammatory diseases

Authors: Faiwe C et al.

Summary: A European multicentre retrospective study was conducted to determine the clinical characteristics and outcome in 25 patients developing paradoxical hidradenitis suppurativa (HS) induced by biologic agents (adalimumab, infliximab, etanercept, rituximab, tocilizumab). The median biologic agent exposure duration before HS onset was 12 months; most patients were Hurley stage I (n = 13) or II (n = 11). In 11 patients, additional inflammatory diseases developed at the same time or within 1 year of developing HS; these included paradoxical reactions (psoriasis, Crohn’s disease, alopecia areata, erythema elevatum diutinum). Complete improvement of HS occurred more frequently after biologic agent discontinuation or a switch (60%) rather than with maintenance (7%); and reintroducing of the same biologic agents resulted in a relapse in three of three patients.

Comment: Paradoxical skin reactions can occur in patients receiving biologic agents for chronic inflammatory disorders. The most widely reported of these is psoriasis. HS is a chronic, painful, inflammatory skin disorder characterised by abscesses, fistulas, purulent discharge and subsequent scarring of the affected skin. The condition typically involves the intertriginous apocrine gland-bearing areas. The current study was a nationwide retrospective investigation of HS in patients treated with biologic agents including 11 centres in France and one in Belgium. All cases of HS, confirmed by a dermatologist, and occurring after the commencement of a biologic agent, were reported to a central location. Over 11 years, 25 patients (20 female) developed HS while receiving biologic therapy. 52% were smokers and the majority were either overweight (60%) or obese (36%), features shared with sporadic HS. An anti-TNF agent was the most commonly involved biologic agent (18 patients). Mean age at onset of the HS was 35.6 years and the mean delay in onset of HS from start of biologic therapy was 25.2 months (range 1-120). Eleven patients developed other inflammatory disorders either at the time of the HS or within one year. Resolution of the HS was most frequently achieved with either complete discontinuation of the biologic agent or switching to an alternative agent.


Abstract

Tofacitinib, an oral Janus kinase inhibitor: analysis of malignancies across the rheumatoid arthritis clinical development programme

Authors: Curtis JR et al.

Summary: This analysis of data (n = 5671) from the clinical development programme (six phase II, six phase III and two long-term extension studies) of the oral Janus kinase inhibitor tofacitinib was conducted to determine the role of Janus kinase inhibition on development of malignancies. Excluding non-melanoma skin cancer, a total of 107 tofacitinib recipients developed malignancies. These included 24 patients with lung cancer, 19 with breast cancer, 10 with lymphoma and six with gastric cancer. The malignancy rate remained stable over time and standardised incidence ratios (versus SEER data) for all malignancies and for lung, breast, lymphoma and non-melanoma skin cancer were within the expected range.

Comment: The assessment of any new treatment in chronic disease includes long-term safety analysis. This is complex in chronic inflammatory disorders where there is interplay between the underlying disease, lifestyle factors and treatment effects. This is particularly pertinent to malignancy risk. The current study focuses on the potential of the Janus kinase inhibitor, tofacitinib, to play a role in the development of malignancies when used in the treatment of RA. Patients from phase II, III, and long-term extension studies were included, receiving doses of either 5 or 10 mg twice daily as monotherapy. In total, there were 5671 patients who received tofacitinib and who had no history or existing malignancy at baseline (other than non-metastatic basal or squamous skin cancer or cervical carcinoma in situ). Incidence rates (IRs) and standard incidence ratios (SIRs) were calculated for all malignancies, lung cancer, breast cancer, lymphoma, and non-melanoma skin cancer. The IRs and SIRs observed in the tofacitinib program were stable over time and with increasing drug exposure. The SIRs for lung cancer and lymphoma were 2.19 and 2.64, respectively. All lung cancers occurred in current or ex-smokers while the lymphoma risk in this study is similar to that found in other RA populations, likely influenced by immunosuppressive therapy and disease severity. Although the study relies on clinical trial data, it indicates that there is no increased malignancy risk that directly relates to tofacitinib.


Abstract
Effectiveness and safety of vedolizumab induction therapy for patients with inflammatory bowel disease

Authors: Amit A et al.

Summary: Data from a multicentre, nominative, compassionate, early access program was analysed to ascertain the effectiveness and safety of the integrin α4β7 binding agent vedolizumab in 173 patients with Crohn’s disease and 121 patients with ulcerative colitis who failed anti-TNF therapy. After a 14-week induction phase, 276 patients remained, with 18 discontinuations because of a lack of response (n = 14), infusion-related reaction (n = 2) or infection (n = 2). Steroid-free clinical remission was observed in 31% of Crohn’s disease patients and 36% of ulcerative colitis patients with a response in 51% of Crohn’s disease patients and 50% of ulcerative colitis patients. Severe adverse events occurred in 24 (8.2%) patients, including 15 (5.1%) leading to vedolizumab discontinuation (one pulmonary tuberculosis; one rectal adenocarcinoma).

Comment: Vedolizumab is a humanised monoclonal antibody that specifically binds to and blocks the α4β7 integrin on circulating T lymphocytes, thus preventing the circulation of these cells into the gut via the ligand MadCAM-1. It is the first biological agent targeting the integrin receptor and is now approved for the treatment of Crohn’s disease and ulcerative colitis. The current French study is based upon an early compassionate access program for patients with Crohn’s disease or ulcerative colitis refractory to conventional therapy including at least one anti-TNF agent. Inclusion criteria included a baseline Harvey-Bradshaw index (HBI) >4 or a Mayo score >6. All patients received induction at weeks 0, 2 and 6 followed by 8 weekly infusions. The primary outcome was steroid-free remission at week 14 (HBI ≤4) or a partial Mayo score ≤3. 294 patients were enrolled in the study (173 Crohn’s disease, 121 ulcerative colitis). Crohn’s disease patients were younger (37.3 vs 42.8 years) and less often male (37% vs 55%). The majority of patients had received at least one anti-TNF (99-99%) and/or an immunosuppressant (95-97%). At week 6, 33 (19%) of Crohn’s disease and 26 (21%) of ulcerative colitis patients were in steroid-free clinical remission. By week 14, 53 Crohn’s disease (31%) and 43 ulcerative colitis (36%) patients were in steroid-free remission. Almost two-thirds of patients demonstrated a clinical response. These results are not directly comparable with the GEMINI trials given that their primary endpoints differ, weeks 6 and 10 versus week 14. However, the results in this refractory population of anti-TNF-experienced patients are encouraging, as was the safety profile. The study also identified potential predictors of steroid-free remission, including clinical response at week 6 (+), low clinical activity score (+), use of concomitant steroids (+), and CRP >20 (+). There was no benefit seen from the use of a concomitant immunomodulator.

Reference: Clin Gastroenterol Hepatol. 2016;Feb 22 [Epub ahead of print]

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