Welcome to the second 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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Characteristics of skin lesions associated with anti-tumor necrosis factor therapy in patients with inflammatory bowel disease: A cohort study

Authors: Cleynen I et al.

Summary: In a large, single centre, retrospective cohort study, researchers examined the characteristics associated with the development of skin lesions in 917 IBD patients receiving anti-TNF antibodies. Over a median follow-up of 3.5 years, skin lesions developed in 264 (29%; 31% of women and 26% of men) patients (30.6% psoriasisform eczema; 23.5% eczema; 10.6% xerosis cutis; 5.3% palmoplantar pustulosis; 3.8% psoriasis; 26.1% other lesions). These lesions typically occurred in flexural regions, genitalia and the scalp, particularly the psoriasisform lesions. There were no differences in infliximab median cumulative dose (2864 vs 2927 mg/y) or trough level (4.2 vs 4.0 µg/mL) between those with and without lesions. In all but 28 (11%) cases, the lesions were managed by therapy interruption.

Comment: This is a large retrospective cohort study from one of Europe’s foremost IBD centres. Psoriasiform eczema is the predominant lesion in this population of patients. Interestingly, the frequency of psoriasis in the current study (3.8%) of patients who have received anti-TNF is lower than rates in historical IBD cohorts (9-11% in CD, 5-6% in UC, and 2-3% in controls) prior to the introduction of anti-TNF therapies, underlining the importance of a matched anti-TNF naive control group for studies such as this. Recent results from a large German cohort of 434 IBD patients identified 21 subjects (4.8%) who developed psoriasisform skin lesions, with the more severe cases responding well to ustekinumab. The results of the current study remain reassuring for clinicians and underline the importance of early referral to a dermatologist to make an accurate diagnosis and instigate appropriate therapy.


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.
 Secukinumab, an interleukin-17A inhibitor, in ankylosing spondylitis

Authors: Baeten D et al.

Summary: Two randomised, double-blind, placebo-controlled phase III trials (MEASURE 1, n = 371; MEASURE 2, n = 219) studied the use of the anti-interleukin-17A monoclonal antibody in patients with active ankylosing spondylitis (AS). Spondyloarthritis International Society (ASAS20) response rates (primary endpoint) at week 16 of MEASURE 1 (subcutaneous secukinumab 150 or 75 mg every four weeks after intravenous loading dose 10 mg/kg at weeks 0, 2 and 4) were 61% for secukinumab 150 mg, 60% for secukinumab 75 mg and 29% for placebo (p < 0.001 for both doses vs placebo). In MEASURE 2 (subcutaneous secukinumab 150 or 75 mg every four weeks from baseline), the ASAS20 response rates were 28% with placebo versus 61% (p < 0.001) for the 150 mg dose and 41% (p = 0.1) for the 75 mg dose. Across both trials, secukinumab 75 mg was effective only after a high intravenous loading dose. Infections, including candidiasis, were more common with secukinumab during the placebo-controlled phase of MEASURE 1 (in both trials, placebo recipients were randomised to secukinumab 150 or 75 mg at week 16). Clinical responses at week 16 were maintained through 52 weeks of treatment among patients receiving secukinumab from baseline. In secukinumab-treated patients, the pooled exposure-adjusted incidence rates per 100 patient-years were 0.7 for grade 3 or 4 neutropenia, 0.9 for candida infections, and 0.7 for CD over 52 weeks.

Comment: This study incorporated the results of two phase III randomised, placebo-controlled trials in patients with AS. The majority of the patients were Caucasian (55-96%), male (64-76%), and HLA-B27 positive (69-80%) across the four active and two placebo groups. A minority were on concomitant immunomodulators (methotrexate, 11-18%) and 61-74% were anti-TNF naïve. The primary endpoint, the ASAS20 response, was met in all the active treatment arms, as was the ASAS40 response. There were also significant reductions in the hsCRP and the BASDAI score from baseline, and significant improvements in QoL scores. The response rates for secukinumab were similar to anti-TNF agents (58-64% at weeks 12 to 24) and included patients previously refractory to anti-TNF. The infection rate was higher in the active treatment groups. Specifically, six cases of candidiasis resolved spontaneously or responded to standard antifungal treatment.


Abstract

Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments: a randomised, placebo-controlled, dose-ranging phase 2b trial

Authors: Thaçi D et al.

Summary: In this randomised, placebo-controlled, multinational, dose-ranging, 16 week phase IIb trial, different dose regimens (300 mg once a week [qw], 300 mg q2w, 200 mg q2w, 300 mg q4w, 100 mg q4w or placebo qw) of the interleukin (IL)-4 and IL-13 fully-human monoclonal antibody dupilumab were tested in 380 adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments. Eczema Area and Severity Index (EASI) score improvements were significant (p < 0.0001) for all dupilumab dose-regimens versus placebo (300 mg qw -74%, 300 mg q2w -68%, 200 mg q2w -65%, 300 mg q4w -64%, 100 mg q4w -45%, placebo -18%). 258 (81%) of dupilumab and 49 (80%) of placebo recipients experienced treatment-emergent adverse events with nasopharyngitis the most common (28% and 26%, respectively).

Comment: Atopic dermatitis is often a lifelong condition with a relative minority of patients being diagnosed in adulthood. There is a significant unmet need with topical corticosteroids being the mainstay of treatment and ciclosporin used for more refractory cases. Dupilumab, a fully human monoclonal antibody directed against the IL-4 receptor subunit (which blocks both IL-4 and IL-13 signalling), has successfully undergone phase I and phase II trials in atopic dermatitis. The current phase IIb study demonstrated clinical efficacy across a range of doses including 300 mg qw, and a favourable safety profile. For all subjects in the active treatment arms (n = 318), the mean age was 37 years, 61% were male, disease duration of 27.6 years. There were highly significant improvements across multiple endpoints including percent body surface area involvement and weekly pruritus scores, as early as week 1. None of the toxic effects were dose limiting with the commonest adverse event being upper respiratory tract infection. These results are highly encouraging for a condition with significant morbidity and negative impacts on quality of life.

Reference: Lancet 2015;387(10013):40-52

Abstract
Consensus decision models for biologics in rheumatoid and psoriatic arthritis: Recommendations of a multidisciplinary working party

Authors: Madan J et al.

Summary: This Consensus Working Party composed of clinical specialists, modellers, and policy makers, have recommendations on model structure, assumptions, and appropriate data sources and approaches to development of health economic models for biologic therapies. Four primary areas of consensus were achieved, these were initial treatment response, long-term disease progression, lifetime benefits and costs and model structure. Other key parameters identified include outcome measure choice, methods for data extrapolation and treatment switching. The group also identified a research agenda to support further consensus.

Variability in golimumab exposure: A ‘real-life’ observational study in active ulcerative colitis

Authors: Detrez I et al.

Summary: In this study, serum samples from 21 UC patients receiving 14 weeks of golimumab therapy were analysed to determine whether low golimumab serum concentration and/or a positive anti-golimumab antibody status reduced drug efficacy. In total, 10 (48%) patients had a partial clinical response by week 14. The median serum golimumab level was higher in partial- than in non-responders (10.0 vs 7.4 µg/mL at week 2, p = 0.035; and 5.1 vs 2.1 µg/mL at week 6, p = 0.037). Anti-golimumab antibodies developed in four patients of whom three had experienced a partial clinical response. Clinical non-responders had more severe collitis (higher endoscopic Mayo score at baseline) than partial-responders (p = 0.048).

Analysis of inflammatory and anemia-related biomarkers in a randomized, double-blind, placebo-controlled study of siltuximab (anti-IL6 monoclonal antibody) in patients with multicentric Castleman disease

Authors: Casper C et al.

Summary: This placebo-controlled study examined the effect of suppression of IL-6 by the anti-IL-6 monoclonal antibody siltuximab (11 mg/kg q3w until treatment failure) on inflammation in 79 patients with multicentric Castleman disease (MCD). Levels of IL-6 and C-reactive protein (CRP) were found to be highly correlated at baseline (r = 0.708; p < 0.0001). The CRP level decreased by a median of 92% by cycle 1 day 8 and remained suppressed throughout siltuximab treatment (n = 49), but was unchanged in placebo recipients (n = 26). There was no correlation between response parameters and baseline CRP or IL-6, MCD symptom burden, histologic subtype, ethnicity or maximum CRP decrease. Haemoglobin response (change ≥ 15 g/L at week 13) occurred in siltuximab recipients (61%; p = 0.0067), along with changes in total iron-binding capacity (r = -0.354; p = 0.01694) and ferritin (r = 0.599; p = 0.0001). Changes from baseline in ferritin, haemoglobin, and total iron-binding capacity were greater in anaemic siltuximab recipients.

Reference: Clin Cancer Res. 2015;21(19):4294-304

Abstract

Comment: This paper provides a useful account of the current challenges facing the health industry, including “purchasers” and “providers” with respect to the role of biologic drugs in the management of chronic inflammatory disorders. With the increasing number of biologics available for the chronic inflammatory arthritides, it is essential to have consensus on the “best” clinical and economic models for the use of these drugs in optimising patients’ treatment. This includes: validated indices; mapping between one index and another; definitions of short and long-term responses; effect of concomitant treatments; and stopping rules. A key feature of this consensus paper relates to the complimentary skill sets of the panel, which included both clinical and modelling experts, thus maximising the credibility of future models in day-to-day clinical practice.

Reference: Rheumatol Ther. 2015;2(2):113-25

Abstract

Reference: J Crohns Colitis 2016;Jan 6 [Epub ahead of print]

Abstract

Comparative effects of biologics on cardiovascular risk among older patients with rheumatoid arthritis

Authors: Zhang J et al.

Summary: This retrospective cohort study compared coronary heart disease risk (acute myocardial infarction [MI] and a composite outcome of acute MI or coronary revascularisation) among 47,183 patients (mean age 64 years; 85% women) with rheumatoid arthritis initiating biologic disease-modifying anti-rheumatic drugs. Crude incidence rates for acute MI ranged from 5.7 to 8.8 cases/1000 person-years. The risk for acute MI was elevated among anti-TNF-α monoclonal antibody, golimumab. The study is small, but with detailed longitudinal data up to week 14 at which point clinical response, mucosal healing, golimumab levels and anti-drug antibodies were analysed. Not surprisingly, based on extensive experience with infliximab and adalimumab, response appears to correlate with drug levels. More significant disease at baseline favoured a negative response to treatment. These data question the current induction and maintenance regimes for golimumab in refractory UC patients, and support a more “personalised” approach to treatment, potentially including a more detailed biomarker evaluation at baseline in combination with therapeutic drug monitoring.


Abstract

Comment: This is an early report investigating the lower than expected response rates in medically refractory UC patients who receive treatment with the subcutaneously administered, humanised anti-TNF-α monoclonal antibody, golimumab. The study is small, but with detailed longitudinal data up to week 14 at which point clinical response, mucosal healing, golimumab levels and anti-drug antibodies were analysed. Not surprisingly, based on extensive experience with infliximab and adalimumab, response appears to correlate with drug levels. More significant disease at baseline favoured a negative response to treatment. These data question the current induction and maintenance regimes for golimumab in refractory UC patients, and support a more “personalised” approach to treatment, potentially including a more detailed biomarker evaluation at baseline in combination with therapeutic drug monitoring.
Treatment persistence among patients with immune-mediated rheumatic disease newly treated with subcutaneous TNF-α inhibitors and costs associated with non-persistence

Authors: Dalén J et al.

Summary: This Swedish study aimed to describe real-world treatment persistence with subcutaneous TNF-α inhibitors (adalimumab, etanercept, certolizumab pegol, golimumab) in 4903 patients with immune-mediated rheumatic disease (AS, PsA or RA). Over 3 years golimumab had higher persistence than adalimumab (p = 0.022) and etanercept (p = 0.004). Non-biologic health care resource utilisation costs differed between persistent and non-persistent patients and the difference was greater after biologic therapy. Subcutaneous TNF-α immune-mediated rheumatic disease patients receiving golimumab had higher persistence rates than those receiving adalimumab or etanercept. Overall persistence rates in this study were lower than those in clinical trials.

Comment: There are limited data on the costs associated with non-persistence of biologic therapy for immune-mediated disorders, including the inflammatory arthropathies. This retrospective observational study used a combination of national registers to obtain treatment data and healthcare resource utilisation on 4903 adult patients who fulfilled the study criteria, including treatment-naive status to subcutaneous anti-TNF-α biologics. The mean age of the total treated population was 50.3 years, 62.3% were female, and the major indication was rheumatoid arthritis (52.3%). Median survival (persistence) time ranged between 15.1 (etanercept) and 18.1 (golimumab) months. Golimumab demonstrated the highest level of persistence both in unadjusted and in propensity scoring analyses. Inpatient, outpatient, and non-DMARD drug costs were significantly lower in the persistent patients as compared to the non-persistent, both before initiation and during the 12 months post-initiation of biologic therapy.

Reference: Rheumatol Int. 2016; Jan 16 [Epub ahead of print]

Abstract

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†Cumulative exposure estimates for approved indications, August 2015‡

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