Biologics (Rheumatology) Research Review™

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Issue 26 - 2020

In this issue:

Abbreviations used in this issue:

COPD = chronic obstructive pulmonary disease;
DAS28-ESR = 28-joint count Disease Activity Score calculated with erythrocyte sedimentation rate;
DMARD = disease-modifying antirheumatic drug;
LDL-C = low-density lipoprotein cholesterol;
HDL-C = high-density lipoprotein cholesterol; **HR** = hazard ratio;
MRI = magnetic resonance imaging; **PsA** = psoriatic arthritis;
RA = rheumatoid arthritis; **TLR** = Toll-like receptor;
TNF = tumour necrosis factor

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Welcome to Issue 26 of Biologics Research Review.

In this issue we have focused on the use of biologics in rheumatology. Secukinumab sustains improvement in the signs and symptoms of PsA, with consistent safety over 5 years according to the findings of the large international phase 3 FUTURE 2 trial. In patients with rheumatoid arthritis we discover that tofacitinib is associated with a 2-fold higher risk of herpes zoster versus 7 biologic DMARDs. Other topics covered in this issue include the discontinuation of methotrexate in RA patients treated with tocilizumab, cardiovascular safety of tocilizumab, the discontinuation of certolizumab pegol in early RA, and biologic versus conventional synthetic DMARDs in RA patients with COPD.

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,

Associate Professor Paul Bird

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Long-term efficacy and safety of secukinumab in patients with psoriatic arthritis: 5-year (end-of-study) results from the phase 3 FUTURE 2 study

Authors: McInnes IB et al.

Summary: The double-blind, placebo-controlled, phase 3 FUTURE 2 study examined the effect of secukinumab 75 mg, 150 mg or 300 mg in 397 patients (65% naive to TNF-inhibitors; 47% receiving concomitant methotrexate) with active psoriatic arthritis (PsA). In total, 248 (62%) patients completed 5 years of treatment, 64% of those initially receiving secukinumab 300 mg, 65% receiving secukinumab 150 mg, 60% receiving secukinumab 75 mg, and 61% receiving placebo; 52% of secukinumab recipients required dose escalation. American College of Rheumatology (ACR) responses at 5 years in secukinumab 300 mg recipients were ACR20 74%, ACR50 52% and ACR70 32%; among secukinumab 150 mg recipients the values were ACR20 70%, ACR50 43% and ACR70 29%. From 24-32 weeks and from 48-84 weeks after dose escalation from 150 mg to 300 mg doses of secukinumab, the number of ACR and Psoriasis Area and Severity Index (PASI) non-responders decreased and the number of ACR and PASI responders increased. Serious infection (exposure-adjusted incidence 1.7; 95% CI 1.1-2.5) was the most frequent treatment-emergent serious adverse event.

Comment: This is an important long-term safety study examining the 150 mg and 300 mg secukinumab dose in patients with PsA. It is interesting to observe that the percentage of patients completing 5-year follow up was equivalent in the 300/150/75 milligram groups, but importantly 52% of patients required dose escalation during the study, mirroring our clinical experience. Serious infection was noted to be higher in the secukinumab group, but no new or unexpected safety signals were otherwise recorded.

Reference: Lancet Rheum. 2020;2(4):E227-E235
Abstract

Biologics Research Review™

Independent commentary by Associate Professor Paul Bird

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Paul Bird is a Rheumatologist in private practice and 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 center undertaking Phase 2, 3 and 4 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. He maintains ongoing participation in research projects examining the application of Magnetic Resonance Imaging (MRI) in inflammatory arthritis and is co-chair of the OMERACT international MRI imaging group.

Assessment of the anti-CD40 antibody iscalimab in patients with primary Sjögren's syndrome: A multicentre, randomised, double-blind, placebo-controlled, proof-of-concept study

Authors: Fisher BA et al.

Summary: This multicentre, randomised, double-blind, placebo-controlled, proof-of-concept study tested a novel anti-CD40 monoclonal antibody, iscalimab (CFZ533; subcutaneous 3 mg/kg, intravenous 10 mg/kg) in 10 patients with primary Sjögren's syndrome. Adverse events did not differ between placebo and iscalimab recipients. Two serious adverse events (bacterial conjunctivitis and atrial fibrillation) occurred both of which were unrelated to iscalimab. European League Against Rheumatism Sjögren's syndrome disease activity index (ESSDAI) score was reduced by 21 points (95% CI 0.96-9.46; one-sided p = 0.0090) with intravenous iscalimab versus placebo, but there was no difference in ESSDAI score between subcutaneous iscalimab and placebo.

Comment: Iscalimab (CFZ533) is a novel monoclonal antibody that potently and selectively blocks CD40, a co-stimulatory pathway receptor important for germinal centre reactions and B cell activation. This proof of concept study explored 2 different doses of the compound in patients who fulfilled the 2002 American European consensus group diagnostic classification criteria for primary Sjögren's syndrome. In cohort 1, 12 patients were randomly assigned to receive either 3 mg/kg doses of iscalimab (n=8) or placebo (n=4), and in cohort 2, 32 patients were randomly assigned to receive either intravenous 10 mg/kg doses of iscalimab (n=21) or placebo (n=11). The primary objectives of the study were to assess the safety, tolerability, and efficacy of multiple doses of iscalimab in the two sequential dose cohorts, as measured by the change in European League Against Rheumatism Sjögren's syndrome disease activity index (ESSDAI) score after 12 weeks of treatment. The short duration of therapy and small numbers make the results difficult to interpret, but certainly worthy of further investigation.

Reference: Lancet Rheum. 2020;2(3):E142-E152
Abstract

Risk of admission to hospital for serious infection after initiating tofacitinib versus biologic DMARDs in patients with rheumatoid arthritis: A multidatabase cohort study

Authors: Pawar A et al.

Summary: This analysis of data from multiple databases (Medicare 20012-15; Optum Clinformatics 2012-18; IBM MarketScan® 2012-17) examined the risk of serious infection in 130,718 rheumatoid arthritis patients initiating tofacitinib, a targeted synthetic (ts)DMARD, compared with one of seven biologic DMARDs (bDMARDs). Over 100,790 person-years of follow-up, there were 3140 serious infections reported (crude incidence rate 3.12 per 100 person-years; 95% CI 3.01-3.23). The adjusted HR (aHR) for serious infection with tofacitinib was higher than with etanercept (aHR 1.41; 95% CI 1.15-1.73), abatacept (aHR 1.20; 95% CI 0.97-1.49), golimumab (aHR 1.23; 95% CI 0.94-1.62) and tocilizumab (aHR 1.17; 95% CI 0.89-1.53), did not differ from that with adalimumab (aHR 1.06; 95% CI 0.87-1.30) or certolizumab (aHR 1.02; 95% CI 0.80-1.29), and was lower than with infliximab (aHR 0.81; 95% CI 0.65-1.00). Tofacitinib had a 2-fold higher risk of herpes zoster versus all bDMARDs.

Comment: A large multi-database cohort study in patients with rheumatoid arthritis comparing the risk of serious infection with tofacitinib versus seven bDMARDs. The major finding, as expected, is that tofacitinib was associated with a 2-fold higher risk of herpes zoster versus all bDMARDs. Otherwise, the serious infection rate was similar between the groups.

Reference: Lancet Rheum. 2020;2(2):E84-E98
Abstract

Magnetic Resonance Imaging (MRI) results following discontinuation of methotrexate in rheumatoid arthritis treated with subcutaneous tocilizumab: The COMP-ACT MRI substudy

Authors: Peterfy C et al.

Summary: This substudy of the COMP-ACT trial examined differences in joint damage and inflammation using 1.5T MRI in 79 rheumatoid arthritis patients who achieved low disease activity (28-joint count Disease Activity Score calculated with erythrocyte sedimentation rate [DAS28-ESR] ≤3.2 at 24 weeks) and subsequently continued (n = 38) or discontinued methotrexate (n = 41). The results indicated that either treatment suppressed erosion progression, synovitis, osteitis and cartilage loss, and the proportion of patients with no progression in each outcome did not differ between groups (84.8-97.0% vs 92.3–100%).

Comment: This study used normal outcome measures in the form of MRI to assess differences in joint damage and inflammation using MRI between patients with rheumatoid arthritis who achieved low disease activity with tocilizumab plus methotrexate and subsequently continued or discontinued methotrexate. The study reports that in the subset of patients who achieved low disease activity, that the proportion of patients with erosion progression, residual synovitis, osteitis or cartilage loss was similar in patients who continued tocilizumab plus methotrexate, versus those who continued tocilizumab alone.

Reference: J Rheum. 2020;47(3):325-332
Abstract

Cardiovascular safety of tocilizumab versus etanercept in rheumatoid arthritis: A randomized controlled trial

Authors: Giles JT et al.

Summary: The objective of this randomised, open-label, parallel-group trial was to determine the risk of major adverse cardiovascular events (MACE) in rheumatoid arthritis patients treated with tocilizumab versus etanercept. After 4 weeks, tocilizumab recipients had higher serum LDL-C (median 11.1%), HDL-C (5.7%) and triglyceride (13.6%) levels than those receiving etanercept (all p < 0.001). Over a mean of 3.2 years of follow-up, tocilizumab recipients experienced 83 MACE versus 78 in the etanercept group (HR 1.05; 95% CI 0.77-1.43). Adverse events were more frequent in tocilizumab recipients, including serious infection and gastrointestinal perforation.

Comment: TNF-inhibitors have been associated with a reduction in MACE in patients with rheumatoid arthritis and this study seeks to explore whether the same principle is true for tocilizumab. The study utilises etanercept as the comparator, with a mean follow up of 3.2 years. The primary endpoint was comparison of time to first occurrence of MACE. During follow-up, 83 MACE occurred in the tocilizumab group compared to 78 MACE in the etanercept group.

Reference: Arthritis Rheumatol 2020;72(1):31-40
Abstract

Inhibition of radiographic progression across levels of composite index-defined disease activity in patients with active psoriatic arthritis treated with intravenous golimumab: Results from a phase-3, double-blind, placebo-controlled trial

Authors: Mease P et al.

Summary: This post-hoc analysis of data from the double-blind, placebo-controlled, phase III GO-VIBRANT trial (n = 480) of intravenous golimumab in PsA examined changes in total PsA-modified Sharp/van der Heijde scores (SHS) across different levels of disease activity. Across composite disease activity indices (minimal disease activity [MDA], very low disease activity [VLDA], Psoriatic ArthritiS Disease Activity Score [PASDAS], Disease Activity in Psoriatic Arthritis [DAPsA], Clinical Disease Activity Index [CDAI]), golimumab recipients had less radiographic progression than placebo recipients, regardless of the disease activity state reached under golimumab treatment (mean changes in PsA-modified SHS were -0.83 with golimumab vs 0.91 with placebo in patients achieving MDA, and -0.05 vs 1.49 in those not achieving MDA). Treatment differences at week 24 persisted through week 52. The patterns were consistent across VLDA, PASDAS, DAPsA, and CDAI composite endpoints.

Comment: This trial uses post hoc analyses to evaluate changes in total PsA-modified SHS across levels of composite index-defined disease activity following treatment in patients from the GO-VIBRANT trial of intravenous golimumab in PsA. In this phase 3, double-blind, placebo-controlled trial, 480 bio-naïve patients with active PsA randomly received intravenous golimumab 2 mg/kg (n = 241; week 0, week 4, every 8 weeks [q8w]) or placebo (n = 239; week 0, week 4, week 12, week 20) followed by golimumab (week 24, week 28, q8w) through week 52. The results suggest that golimumab-treated patients demonstrated less radiographic progression when compared to placebo-treated patients from week 0-24 and that the treatment differences observed at week 24 persisted through week 52. Post hoc analyses are useful, but must be interpreted with caution, particularly when the outcome measure used (in this case radiographs) has limited sensitivity to change.

Reference: Arthritis Res Ther. 2020;22:43
Abstract

Factors associated with successful discontinuation of certolizumab pegol in early rheumatoid arthritis

Authors: Tanaka Y et al.

Summary: This exploratory analysis of data from the double blind, placebo controlled Certolizumab–Optimal Prevention of joint damage for Early Rheumatoid Arthritis (C-OPERA) study in methotrexate-naive early rheumatoid arthritis patients aimed to identify factors associated with successful certolizumab pegol discontinuation after 1 year of combined certolizumab/methotrexate therapy. Over 104 weeks of follow-up, male sex and low baseline DAS28-ESR scores were associated with remission (simple disease activity index [SDAI)] score ≤3.3), while high baseline DAS28-ESR and modified total Sharp score (mTSS >3) were associated with radiographic progression. Low DAS28-ESR (<2.1) and rheumatoid factor (<74 IU/mL) at certolizumab discontinuation were associated with SDAI remission, which was achieved by 75.0% of low DAS28-ESR and rheumatoid factor patients versus 15.4% of patients with high DAS28-ESR and rheumatoid factor

Comment: Tapering and cessation of TNF inhibition in patients with rheumatoid arthritis remains an active area of research. In this study, the author's report the response in methotrexate-naive early rheumatoid arthritis patients with poor prognostic factors randomised to receive certolizumab/methotrexate or placebo and methotrexate. Those who completed the 1-year, double-blind period received methotrexate alone in year 2 (certolizumab + methotrexate → methotrexate, n = 108; placebo + methotrexate → methotrexate, n = 71). The results are not surprising, patients with low titre rheumatoid factor and low disease activity at certolizumab cessation were more likely to maintain remission with methotrexate as monotherapy.

Reference: Int J Rheum Dis. 2020;23(3):316-324
Abstract

GO-DACT: A phase 3b randomised, double-blind, placebo-controlled trial of GOlimumab plus methotrexate (MTX) versus placebo plus MTX in improving DACTylitis in MTX-naive patients with psoriatic arthritis

Authors: Vieira-Sousa E et al.

Summary: This Portuguese multicentre, randomised, double-blind, placebo-controlled, parallel-design, 24-week, phase IIIb trial tested the use of golimumab in combination with methotrexate (n = 21) versus methotrexate monotherapy (n = 23) in patients with PsA dactylitis. A favourable interim analysis led to discontinuation of enrolment at 50% planned recruitment. Median baseline Dactylitis Severity Score (DSS; primary endpoint) was 6 in both arms, but by week 24, golimumab plus methotrexate recipients had greater improvements in DSS than methotrexate monotherapy recipients (median change 5 vs 2 points; p = 0.026). In addition, greater proportions of golimumab plus methotrexate recipients than methotrexate monotherapy recipients achieved ≥50% or ≥70% improvement in DSS and ≥20%, ≥50% or ≥70% improvement in Leeds Dactylitis Index (LDI).

Comment: This study examines patients with PsA with dactylitis at baseline. The primary endpoint was DSS change from baseline to week 24. Key secondary endpoints included DSS and LDI response, and changes from baseline in the LDI and MRI dactylitis score. As expected, the combination of golimumab methotrexate as first-line therapy was superior to methotrexate in patients with PsA-related dactylitis.

Reference: Ann Rheum Dis. 2020;79(4):490-498
Abstract

Efficacy and safety of NI-0101, an anti-toll-like receptor 4 monoclonal antibody, in patients with rheumatoid arthritis after inadequate response to methotrexate: A phase II study

Authors: Monnet E et al.

Summary: This double-blind, randomised, placebo-controlled trial examined the use of a humanised monoclonal antibody blocking TLR4 (NI-0101 5 mg/kg, every 2 weeks for 12 weeks) versus placebo in 90 anti-citrullinated protein antibody (ACPA)-positive rheumatoid arthritis patients with an inadequate response to methotrexate. No between-group differences were observed for any of the efficacy endpoints (DAS28-CRP, European League Against Rheumatism (EULAR) good and moderate responses, ACR20, ACR50 and ACR70 responses) nor did subgroup analyses using baseline parameter covariants reveal any response differences. Treatment-emergent adverse events occurred in 51.7% of placebo versus 52.5% of NI-0101 recipients.

Comment: Toll-like receptors (TLR) are a family of transmembrane receptors that serve as signalling receptors in the innate immune system; their ligation by exogenous and possibly endogenous ligands triggers a pro-inflammatory signalling cascade in various cells linking innate immunity to inflammation. This study was designed to confirm preclinical investigations supporting a biomarker-driven approach for treatment of patients with rheumatoid arthritis who present positive for these immune complexes. The study enrolled ACPA-positive rheumatoid arthritis patients with an inadequate response to methotrexate. 86 patients completed the placebo-controlled study with no significant between-group difference observed for any of the efficacy endpoints. A negative study, reinforcing the redundancy within the immune pathways in rheumatoid arthritis and underscoring the need for affective biomarkers to coordinate effective, individualised, targeted therapy.

Reference: Ann Rheum Dis. 2020;79(3):316-323
Abstract

Comparative safety of biologic versus conventional synthetic DMARDs in rheumatoid arthritis with COPD: A real-world population study

Authors: Hudson M et al.

Summary: This study used data from the US-based MarketScan database to determine the risk of adverse respiratory events associated with biologics and targeted synthetic (ts)DMARDs in 7424 patients with rheumatoid arthritis and concomitant COPD compared with 7424 patients receiving conventional (c)DMARDs. The adjusted HR of hospitalised COPD exacerbation was 0.76 (95% CI 0.55-1.06) for biologic/tsDMARD versus cDMARD; for hospitalised pneumonia or influenza it was 1.02 (95% CI 0.82-1.27), for bronchitis it was 1.21 (95% CI 0.92-1.58) and for outpatient pneumonia or influenza it was 0.99 (95% CI 0.87-1.12). For a combined endpoint of COPD exacerbation, bronchitis and hospitalised pneumonia or influenza the HR was 1.04 (95% CI 0.89-1.21).

Comment: This large cohort study assessed the risk of adverse respiratory events associated with biologic and tsDMARDs compared with cDMARDs among rheumatoid arthritis patients with concomitant COPD in a large, real-world cohort. The cohort included 7424 patients initiating biologic/tsDMARDs and 7424 matched patients initiating cDMARDs. Primary outcome measures were adverse respiratory events including hospitalised COPD exacerbation, hospitalised pneumonia or influenza, and outpatient pneumonia or influenza. The study reports that biologic and targeted synthetic DMARDs were not associated with increased risk of adverse respiratory events when compared with conventional synthetic DMARDs in patients with rheumatoid arthritis and a background of COPD.

Reference: Rheumatol. 2020;59(4);820-827
Abstract