THU0211 META-ANALYSIS OF SERIOUS INFECTIONS WITH BARICITINIB, TOFACITINIB AND BIOLOGIC DMARDS IN RHEUMATOID ARTHRITIS

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Background: Tofacitinib is an oral Janus kinase (JAK) inhibitor for the treatment of rheumatoid arthritis (RA). Baricitinib is a JAK inhibitor being investigated for RA. Serious infection events (SIEs) have been reported in RA randomised controlled trials (RCTs) but limited head-to-head data are available to directly compare rates of these events for tofacitinib vs biologic (b)DMARDs and baricitinib.
Objectives: We present an updated meta-analysis of published RCTs and corresponding long-term extension (LTE) studies to contextualise the risk of SIEs[1] with tofacitinib and extend this work to include the JAK inhibitor baricitinib.
Methods: An initial systematic literature search (Medline, Embase, PubMed and regulatory submission documents) was conducted for SIEs with tofacitinib and bDMARDs (abatacept, adalimumab, certolizumab, etanercept, golimumab, infliximab, rituximab and tocilizumab).[1] A subsequent systematic literature review of RCTs was conducted using Medline, BIOSIS, Embase and conference abstracts to evaluate SIEs with baricitinib. Incidence rates (IRs; patients with events per 100 patient-years) were calculated for each agent, utilising a random effects meta-analytic model using R (version 2.15.2 for tofacitinib and bDMARDs; version 3.2.2 for baricitinib) with a Restricted Maximum Likelihood Estimator for between-study variances. Risk ratios and risk differences were calculated for each agent vs control across RCTs up to rescue of patients randomised to receive placebo using the random effects Mantel-Haenszel method.
Results: Six RCTs with baricitinib were included in this updated analysis. In the original analysis, 70 RCTs and 18 LTE studies met inclusion criteria for tofacitinib and bDMARDs. The table provides a summary of the meta-analyses conducted for SIE IRs (with and without LTE), risk ratios and risk differences relative to control. The IRs (95% confidence interval [CI]; heterogeneity [I^2]) for baricitinib were 4.75 (2.32, 9.74; I^2=19%) for 2 mg and 3.67 (2.33, 5.78; I^2=36%) for 4 mg. The analysis of risk ratios (p values 0.22 for 2 mg; 0.95 for 4 mg) and risk differences (p values 0.41 for 2 mg; 1.00 for 4 mg) did not reveal a significant difference from control for both doses of baricitinib, which is consistent with analyses of tofacitinib and bDMARDs. There were limited data to assess SIE incidence for baricitinib (4 mg) monotherapy vs in combination with methotrexate (MTX); the RA-BEGIN study showed IRs of 3.77 (1.7, 8.4) and 2.33 (0.97, 5.59), respectively. Pooled IR estimates for tofacitinib from the development programme were 1.70 (0.91, 2.92) and 1.79 (1.00, 2.95) for 5 and 10 mg BID monotherapy, respectively; when administered in combination with MTX, the IRs were 3.44 (2.41, 4.76) and 3.42 (2.42, 4.70) for 5 and 10 mg BID, respectively.

Table: Serious infection incidence rates, risk ratios and risk differences for tofacitinib vs biologic DMARDs and baricitinib[1]

Drug	Incidence rate (95% CI), per 100 pt-yr		Risk ratio (95% CI)	Risk difference (95% CI), %
	RCT+LTE	RCT	RCT	RCT
Abatacept	3.04 (2.49, 3.72)	2.97 (2.17, 4.07)	1.18 (0.45, 3.09)	0.4 (-0.72, 1.51)
Rituximab	3.72 (2.99, 4.62)	3.45 (2.73, 4.36)	1.01 (0.46, 2.22)	-0.42 (-1.63, 0.79)
Tocilizumab	5.45 (4.26, 6.96)	5.39 (4.05, 7.18)	1.82 (1.22, 2.73)	1.51 (0.68, 2.33)
Infliximab	6.11 (5.24, 7.12)	6.42 (5.50, 7.50)	0.83 (0.33, 2.06)	-0.52 (-3.56, 2.53)
Etanercept	4.06 (3.26, 5.08)	3.90 (2.76, 5.52)	1.00 (0.07, 15.24)	0.00 (-9.39, 9.39)
Certolizumab	7.59 (5.80, 9.94)	7.59 (5.80, 9.94)	2.18 (1.06, 4.50)	1.96 (0.8, 3.12)
Golimumab	5.31 (4.09, 6.89)	5.31 (4.09, 6.89)	1.3 (0.43, 3.90)	0.68 (-0.31, 1.67)
Adalimumab	5.04 (3.80, 6.69)	5.47 (3.92, 7.64)	2.27 (0.84, 6.13)	1.16 (-0.34, 2.67)
TNF inhibitors	4.90 (4.41, 5.44)	5.50 (4.86, 6.23)	1.50 (1, 2.25)	0.94 (0.25, 1.63)
Tofacitinib 5 mg, P2/P3	NA	2.71 (2.00, 3.58)[a] 2.35 (1.36, 4.06)[b]	1.34 (0.43, 4.15)	0.27 (-0.36, 0.9)
Tofacitinib 10 mg, P2/P3	NA	2.72 (2.04, 3.56)[a] 2.80 (1.95, 4.01)[b]	1.67 (0.60, 4.65)	0.42 (-0.22, 1.05)
Tofacitinib P123LTE (All doses)	2.74 (2.51, 2.99)[a]	NA	NA	NA
Baricitinib 2 mg	NA	4.75 (2.32, 9.74)	1.13 (0.24, 5.35)	-0.35 (-1.72, 1.02)
Baricitinib 4 mg	NA	3.67 (2.33, 5.78)	0.82 (0.34, 1.97)	-0.21 (-1.11, 0.69)

[a] Estimate from pooled patient-level data
[b] Estimate from random effects meta-analytic model

CI, confidence interval; DMARDs, disease-modifying antirheumatic drugs; JAK, Janus kinase; LTE, long-term extension; NA, not applicable; P2/P3, Phase 2 and Phase 3 studies; P123LTE, Phase 1, 2, 3 and LTE studies; pt-yr, patient year; RCT, randomised controlled trial; risk ratio, relative risk compared with placebo; risk difference, risk difference compared with placebo; TNF, tumour necrosis factor

Conclusions: The results from these meta-analyses suggest that the risk of SIEs (IRs, risk ratios and risk differences) with tofacitinib is comparable with published rates for bDMARDs and baricitinib in patients with moderate to severe RA.
References:
[1] Strand V et al. Arthritis Res Ther 2015; 17: 362.
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THU0212 THE IMPROVEMENT OF ULTRASONOGRAPHIC FINDINGS FOR 24 WEEKS MAY PREDICT REMISSION AT 52 WEEKS IN JAPANESE RHEUMATOID ARTHRITIS PATIENTS TREATED WITH IGURATIMOD THERAPY

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Background: Iguratimod (IGU) suppressed tumor necrosis factor-alpha-induced production of interleukin (IL)-6, IL-8, and monocyte chemoattractant protein 1 via inhibition of nuclear factor kappa B activation in cultured human synovial cells and human acute monocytic leukemia cells. We reported the clinical efficacy of IGU at ACR2014 and EULAR2015. However there is still few studies of improvement of ultrasonographic findings in rheumatoid arthritis (RA) treated with IGU.
Objectives: To evaluate the efficacy of IGU therapy in patients with RA using ultrasonography (US).
Methods: Participants comprised 54 Japanese RA patients who had recently received IGU. All patients with a diagnosis of RA according to the 2010 ACR/EULAR criteria. Patients underwent clinical and laboratory assessments from baseline to 52 weeks, and US assessments at baseline, 12 and 24 weeks. Gray scale (GS) and power doppler (PD) signals were scored using a semi-quantitative scale from 0 to 3 at 26 (0–78) synovial sites (22 joints) in the following joints: bilateral first to fifth metacarpopharangeal (MCP) joints (dorsal recess); first interphalangeal (IP) and second to fifth proximal interphalangeal (PIP) (dorsal recess) joints; and the wrists (dorsal radial, median and ulnar).
Results: The patients included 16 males and 38 females. The mean age was 65.4±11.6 years; the mean disease duration was 9.3±10.8 years; and the number of MTX combination, other DMARD excluded combination, IGU monotherapy and Biologics combination were each 32, 10, 8 and 4 cases.
Clinical findings related to RA were as follows: tender and swollen joint count, 4.2±2.9 and 3.2±2.1; patient's and physician's global assessment of disease activity, 40.2±24.0 and 40.2±19.9mm; CRP, 1.0±1.2 mg/dL; ESR, 31.2±18.2 mm/h; DAS28-ESR, 4.37±0.88 and SDAI, 16.4±7.0. The mean DAS28-ESR improved to 3.43±0.94 and 2.98±0.88 at Week 12 and 24 ($p<0.001$, $p<0.001$) and the mean SDAI improved to 8.8±6.1 and 6.3±5.2 at Week 12 and 24 ($p<0.001$, $p<0.001$) significantly. The mean GS score changed from 16.8±12.5 at baseline to 15.8±11.2 (p=0.458) and 14.8±10.3 (p=0.103) at week12 and 24. The mean PD score changed from 7.6±6.8 at baseline to 5.8±6.0 (p=0.053) and 5.3±5.4 (p=0.05) at week12 and 24. In the achieved remission for DAS28-ESR at Week52 (n=16) and not achieved or discontinued IGU patients (n=38), the respective changes in GS and PD scores from baseline to 12 or 24 weeks were as follows: ΔGS score: -3.7±0.8 vs 0.1±6.8 (p=0.068) at 12 weeks and -5.8±5.7 vs -0.4±9.8 (p=0.008) at 24 weeks; and ΔPD score: -3.4±5.6 vs -1.1±5.2 (p=0.065) at 12 weeks and -4.9±6.3 vs -1.2±6.1 (p=0.013) at 24 weeks (Fig.1). Areas under the receiver operating characteristic curves for the ΔGS and ΔPD score at each time point for remision achievement at 52 weeks were each 0.643 and 0.648 from week0 to 24 and 0.725 (cut-off index -3, odds ratio 5.60, sensitivity 0.74, specificity, 0.67) and 0.706 (cut-off index -1, odds ratio 4.71, sensitivity 0.63, specificity, 0.73) from week0 to 24 (Fig.2).

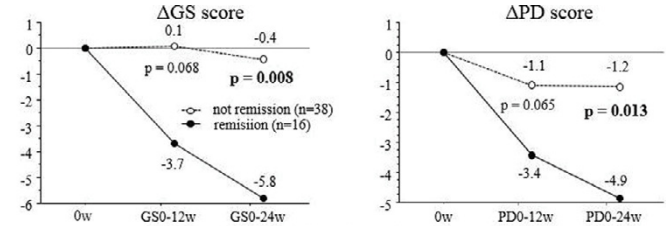

Figure 1 : Respective changes in ΔGS and ΔPD score from baseline to Week 24 in the achieved remission for DAS28-ESR at Week52 and not achieved or discontinued IGU patients

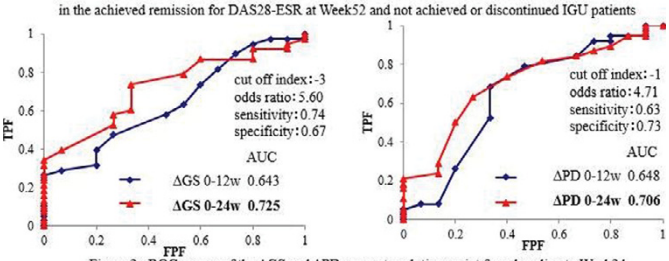

Figure 2 : ROC curves of the ΔGS and ΔPD score at each time point from baseline to Week24 for predicting the achieved remission at Week 52 after starting IGU therapy