obtained. Furthermore, by using individual patient data (IPD), outcome definitions and methods can be harmonized for a valid combined analysis.

Objectives: To determine the effectiveness of treatment with TCZ on radiographic progression compared to MTX in RA patients over two years.

Methods: Randomized controlled trials in RA patients using TCZ as one of the treatment arms with radiographic damage assessed on radiographs at baseline and after two years were identified and IPD obtained.

The primary endpoint was defined as any radiographic progression over two years. Secondary endpoint was the amount of joint damage progression (points per time unit, expressed as incidence rate). Analyses were performed on total scores and for erosions and joint space narrowing (JSN) separately. TCZ strategies were compared with the control strategies. Within the TCZ strategies, a comparison between monotherapy and the combination with MTX was made.

A two-step IPD meta-analysis was performed. In the first step, data of the individual trials were analysed using logistic regression and zero-inflated Poisson models. In the second step association measures (odds ratio's (OR) and incidence rate ratio's (IRR)) of individual trials were pooled using random effect models in Review Manager¹. A subgroup analysis was performed on early versus established RA. All analyses were adjusted for baseline DAS28 and Sharp van der Heijde (SvdH) score to provide a more precise treatment effect estimate.

Results: Five trials were identified, one trial² using a tight-control treat-to-target approach, and the four other RCTs³⁻⁶ allowed the control group to start TCZ after 6 months or 1 year when the treatment target was not reached. Two trials were performed in early RA¹⁻². The dose of TCZ was tapered down in two studies^{2,6}. IPD of 4 trials could be obtained and were included (n=2439 randomized to TCZ arm and n=791 to control arm, MTX in all cases)²⁻⁵.

The radiographs, performed at baseline and after two years, were all assessed with the SvdH method. Due to missing radiographic data, 1766 patients were evaluated in the TCZ arms and 543 patients in MTX arms. Patient characteristics are shown in Table 1. The occurrence of any radiographic progression was statistically significantly less in the TCZ arms compared to MTX arms (pooled OR 0.76 [95%CI 0.67 to 0.86]). The effect for erosions (OR 0.77 [95%CI 0.67 to 0.88]) was stronger than for JSN (OR 0.88 [95%CI 0.78 to 0.98]) with both being in favour of TCZ. No clear differences between early and established RA were observed for any progression. Any radiographic progression did not occur statistically significantly more often in the TCZ monotherapy group compared to the combination group. No statistically significant difference were observed for the amount of radiographic progression.

Conclusion: Based on this individual patient data meta-analysis, radiographic progression was less common in TCZ-treated patients compared to MTX-treated patients in RCTs, possibly more for progression of erosions. No difference was observed between TCZ used as monotherapy or in combination with MTX.

REFERENCE:

[1] Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Disclosure of Interests: Maxime Verhoeven: None declared, Janneke Tekstra: None declared, Johannes H. G. Jacobs Grant/research support from: Roche, Consultant for: Roche, Jacob M. van Laar Grant/research support from: Genentech, Consultant for: F. Hoffmann-La Roche, Johannes WJ Bijlsma Grant/research support from: The department of the author who included patients (JWJB) in the U-Act-Early trial received reimbursements from Roche Nederland BV. JWJB reported grants and fees from Roche, AbbVie, Bristol-Myers Squibb, Merck Sharp & Dohme, Pfizer, and UCB

Table 1 Patient characteristics per individual trial

Trial	Act-Ray ³ n= 417	Function ⁵ n= 857	Lithe ⁴ n= 803	U-Act-Early ² n= 232
Female, n (%)	345 (83)	677 (79)	667 (83)	161 (69)
Age (years), mean (SD)	52.8 (12.1)	50.0 (13.0)	52.0 (11.9)	53.9 (12.4)
BMI (kg/m ²), mean (SD)	26.2 (5.1)	27.5 (6.2)	27.4 (5.9)	26.0 (4.4)
Duration RA (months), mean (SD)	96 (93)	6 (6)	116 (97)	1 (1)
Baseline DAS28, mean (SD)	6.3 (1.0)	6.7 (1.1)	6.3 (1.3)	5.1 (1.1)
RF positive, n (%)	-	776 (91)	658 (82)	166 (72)
Baseline SvdH score, median (IQR)	29 (17.5-50.5)	1.5 (0.5-5.5)	19.5 (8-44)	0 (0-1)
Baseline Erosion SvdH score, median (IQR)	15.5 (10-24)	1 (0-3.5)	14 (6-26.5)	0 (0-0)
Baseline JSN SvdH score, median (IQR)	13.5 (7-27)	0 (0-1.5)	5.5 (1-16.5)	0 (0-0)
Initial treatment strategies, n (%)				
- MTX monotherapy	-	211 (25)	258 (32)	74 (32)
- TCZ+MTX 8mg/kg	215 (52)	220 (25)	272 (34)	78 (34)
- TCZ+MTX 4mg/kg	-	211 (25)	273 (34)	-
- TCZ monotherapy 8mg/kg	202 (48)	215 (25)	-	80 (34)

n=number of patients, SD= standard deviation, BMI= body mass index, RA= rheumatoid arthritis, DAS28= disease activity score assessing 28 joints, RF= rheumatoid factor, SvdH= Sharp van der Heijde, JSN= joint space narrowing, MTX= methotrexate, TCZ= tocilizumab.

Table 1 Number of patients with any radiographic progression per treatment over 2 years and ratio of any radiographic progression or amount of joint damage between TCZ treatment and MTX treatment over 2 years, pooled outcomes

TCZ vs. MTX	TCZ	MTX	OR	95% CI	OR	95% CI
Total score	507/1766 (28)	262/543 (48)	0.76 (0.67 to 0.86)		0.76 (0.67 to 0.86)	
- Early RA	36/104 (34)	13/280 (5)	0.88 (0.64 to 1.20)		0.88 (0.64 to 1.20)	
- Established RA	406/1662 (24)	249/263 (95)	0.79 (0.55 to 0.89)		0.79 (0.55 to 0.89)	
Erosions	49/1766 (3)	23/543 (4)	0.77 (0.53 to 0.88)		0.77 (0.53 to 0.88)	
- Early RA	13/104 (12)	3/280 (1)	0.83 (0.48 to 0.97)		0.83 (0.48 to 0.97)	
- Established RA	36/1662 (2)	20/263 (8)	0.75 (0.50 to 0.86)		0.75 (0.50 to 0.86)	
JSN	50/1766 (3)	24/543 (4)	0.88 (0.78 to 0.98)		0.88 (0.78 to 0.98)	
- Early RA	10/104 (10)	4/280 (1)	0.88 (0.48 to 1.13)		0.88 (0.48 to 1.13)	
- Established RA	40/1662 (2)	20/263 (8)	0.85 (0.68 to 0.96)		0.85 (0.68 to 0.96)	

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developing IRR (OR 2.5, 95% CI 1.3-4.7, $p=0.006$). Seventy (78.7%) of the patients with SjS had positive anti-SSA antibody, but the presence of anti-SSA antibody was not a significant risk for IRR after controlling for the diagnosis of SjS. The IRR per infusion was not related to the RTX dose. The IRR in an infusion did not lead to stopping of the therapy, although infusion rate and premedication can be adjusted in the following therapies. Only 39.6% of the patients with an IRR had suffer from more IRR in the following infusions. Besides, male gender and the increasing cycles were associated with less IRR ($p=0.029$ and 0.007 , respectively). In the 100 patients received more than 4 cycles, the rate of IRR decreased along with the cycles. No life-threatening IRR happened in the 1893 infusions.

Conclusion: Our study had found that patients with SjS had higher IRR compared to other diseases. Female had more frequent IRR might due to the sexual distribution of these diseases.

Acknowledgement: NA

Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2019-eular.2326

FRI0127

IMPACT OF JANUS KINASE INHIBITORS ON RISK OF CARDIOVASCULAR EVENTS IN PATIENTS WITH RHEUMATOID ARTHRITIS: SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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Background: Janus kinase inhibitors (JAKis) are emerging as novel therapies for patients with rheumatoid arthritis (RA). Two JAK inhibitors have been approved and more pipeline products are ongoing to be launched, but their safety profiles of cardiovascular events (CVEs) have not been fully-established yet.

Objectives: To identify the association between CVEs and JAKis therapies in adult patients with RA via a meta-analysis of randomized controlled trials (RCTs).

Methods: RCTs reporting safety issues in RA patients treated with JAKis were reviewed in PubMed, Embase, and Cochrane Library (from inception to October 2018). CINAHL and the major relevant congress (2016-2018) were searched for additional reports. Mantel-Haenszel fixed-effects method with odds ratios (ORs) and 95% confidence intervals (CIs) were performed on extracted data.

Results: Out of 405 references screened, 26 RCTs involving 11 800 patients were included. No statistically significant difference was observed in risk of CVEs associated with the use of JAKis in general (OR 1.04, 95% CI 0.61-1.76, $p=0.89$), tofacitinib (OR 0.63, 95% CI 0.26-1.54, $p=0.31$), baricitinib (OR 1.21, 95% CI 0.51-2.83, $p=0.66$), upadacitinib (OR 3.29, 95% CI 0.59-18.44, $p=0.18$), peficitinib (OR 0.43, 95% CI 0.07-2.54, $p=0.35$), decernotinib (OR 1.12, 95% CI 0.13-10.11, $p=0.92$) (Figure 1). Regarding frequently-used dosage, dose-ranging impact of JAKis on the risk of CVEs was not observed in tofacitinib (5mg vs. 10mg, twice daily), upadacitinib (15mg vs. 30mg, once daily), while baricitinib at 2mg once daily was found to be safer than 4mg (OR 0.19, 95% CI 0.04-0.88, $p=0.03$) (Figure 2).

Conclusion: The existing evidence from RCTs indicated that JAKis-based therapies are not related to statistically significant risk of CVEs in RA patients during the limited randomized controlled periods. However, a special focus on baricitinib 4mg once daily is needed concerning the cardiovascular safety in the future.

Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2019-eular.472

Figure 1. Odds ratio (OR) of cardiovascular events (CVEs) in patients treated with JAKis compared with placebo in randomized controlled trials using Mantel-Haenszel fixed-effects method. JAKis, janus kinase inhibitors; P-Y: person-year; CI: confidence interval; df, degrees of freedom

Figure 2. Odds ratio (OR) of cardiovascular events (CVEs) in patients treated with different dosages of JAKis compared with placebo in randomized controlled trials using Mantel-Haenszel fixed-effects method. JAKis, janus kinase inhibitors; P-Y: person-year; CI: confidence interval; df, degrees of freedom