OP0032

MALIGNANCIES AND SERIOUS INFECTIONS IN RANDOMISED CONTROLLED TRIALS OF JANUS KINASE INHIBITORS IN PATIENTS WITH RHEUMATOID ARTHRITIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Two JAK inhibitors are currently approved by different agencies worldwide for their use in patients with rheumatoid arthritis. The safety profile of these agents has been of interest since the approval of the first JAK inhibitor, particularly the risk of developing malignancies or serious infections.

Objectives: We conducted a systematic review and meta-analysis of phase 2 and phase 3 trials to evaluate these two outcomes in patients receiving JAK inhibitors for rheumatoid arthritis.

Methods: We performed a search in 5 electronic databases and also searched clinicaltrials.gov, Food and Drug Administration, and European Medicines Agency. In addition, the bibliography list of included studies was also screened to search for further citations not retrieved from other sources. We included controlled trials evaluating the efficacy of a JAK inhibitor (i.e., tofacitinib baricitinib, filgotinib, peficitinib, ABT-494, or decenotinib). Two reviewers independently screened studies, evaluated their risk of bias, and extracted data. Primary outcome data included number and type of malignancies and infections and time point of occurrence when available. The reported publications was considered the primary source of data for all trials. Serious infections were defined as those meeting the criteria for a serious adverse events such as a fatal, life threatening, or leading to hospitalisation.

Results: Thirty-one trials were analysed, reporting data on 13 945 patients. Follow-up of the included trials ranged between 4 and 52 weeks with a median of 24 weeks. The risk of attrition bias was judged low for most studies. The reported rates of malignancies and serious infections across studies ranged from 0% and 0.7% to 2.0%, and 5.4%, respectively. Most commonly reported malignancies were lung cancer, melanoma, nonmelanoma skin cancer, basal cell and squamous cell carcinoma. Patients receiving the combination of JAK inhibitor plus methotrexate or JAK inhibitor monotherapy had higher rates of malignancies, compared with methotrexate between 12 and 24 weeks before the rescue treatment was implemented, but the difference did not reach statistical significance (odds ratio (OR) 2.48, 95% confidence interval (CI) 0.76 to 8.11 and 1.39, 95% CI: 0.21 to 9.11, respectively). Regarding serious infections, the JAK inhibitor groups had similar rates to those observed in the control groups (OR 0.90, 95% CI: 0.38 to 0.92, 95% CI: 0.35 to 2.43, respectively). However, there was a dose-response effect with higher rates of serious infections observed in those patients receiving higher doses of JAK inhibitors.

Conclusions: Although not reaching statistical significance, in the currently available RCTs, the rates of malignancy were higher in the JAK inhibitors groups compared to their controls. The rates of serious infections were similar between JAK inhibitor groups and their controls, but were dose-dependent. Future studies should aim to indirectly compare each JAK inhibitor to evaluate if these safety signals are also drug dependent and to assess risk per type of malignancy or infection.

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OP0033

EFFECT OF A STEP-UP OR STEP-DOWN IN TOFACITINIB DOSE ON EFFICACY AND SAFETY IN PATIENTS WITH RHEUMATOID ARTHRITIS IN LONG-TERM EXTENSION STUDIES

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Background: Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA). Efficacy and safety of tofacitinib 5 and 10 mg BID have been shown in long-term extension (LTE) studies up to 114 months.¹

Objectives: To assess the impact of tofacitinib dose changes on efficacy and safety in patients (pts) who increased (step-up) or who decreased (step-down) dose, vs pts who remained on the same dose when entering LTE studies.

Methods: In this exploratory, post hoc analysis, data were pooled from 2 open-label LTE studies (NCT00413699 [ongoing; database not locked at Jan 2016 data-cut]; NCT00661661) of pts with RA who had participated in Phase (P) 1/2/3 tofacitinib index studies and had ≥81 days of tofacitinib exposure (to allow ≥2 assessments) in each period (P1/2/3 index and LTE). Dose changes from index study dose were mandated by protocol (at LTE entry) or at the investigator's discretion (during LTE). This analysis only included pts who remained on their initial/changed dose in the LTE. Pts were analysed in 4 groups: 5 mg BID [index]→10 mg BID [LTE] (Step-up; n=833); 5 mg BID [index]→5 mg BID [LTE] (Remain 5; n=248); 10 mg BID [index]→10 mg BID [LTE] (Remain 10; n=951); 10 mg BID [index]→5 mg BID [LTE] (Step-down; n=234). To determine if initial efficacy (last index study assessment) affects response following dose change on LTE entry, sub-groups for the Step-up and Remain 5 groups were defined based on initial ACR20 response, and sub-groups for the Step-down and Remain 10 groups were defined based on initial ACR50 response. Efficacy was assessed up to Month 12 in the LTE based on ΔDAS28-4(ESR). Exposure-adjusted event rates (pts with events/100 pt-yrs) are presented for the most common adverse events (AEs) for the entire LTE study exposure.

Results: No statistically significant differences in ΔDAS28-4(ESR) were observed between the Step-up and Remain 5 groups (figure 1A), whether or not they had an initial ACR20 response (data not shown). In general, no significant differences in ΔDAS28-4(ESR) were observed between the Step-down and Remain 10 groups (figure 1B), whether or not they had an initial ACR50 response (data not shown). The rates and types of AEs were similar across all groups (table 1).

Abstract OP0033 – Table 1. Summary of AEs in the LTE study

	Step-up: 5 to 10 mg BID N=833	Remain on 5 mg BID N=248	Step-down: 10 to 5 mg BID N=234	Remain on 10 mg BID N=951
Total years of exposure	2726	907	822	3030
Discontinued due to AEs, n	207	53	48	221
Most common AE system organ classes, n (EAE): EAE>10.00 in any group				
Infections and infestations	578 (21.18)	171 (18.85)	141 (17.16)	663 (21.88)
Gastrointestinal disorders	257 (8.41)	93 (10.25)	83 (10.10)	266 (8.77)
Musculoskeletal and connective tissue disorders	323 (11.83)	78 (8.59)	56 (6.81)	366 (12.08)
Most common AE preferred terms, n (EAE): EAE>3.00 in any group				
Nasopharyngitis	101 (3.70)	70 (7.71)	63 (7.66)	146 (4.81)
Upper respiratory tract infection	130 (5.09)	37 (4.07)	33 (4.01)	170 (5.60)
Bronchitis	99 (3.82)	41 (4.51)	20 (2.43)	137 (4.52)
Urinary tract infection	121 (4.43)	12 (1.32)	18 (2.19)	115 (3.79)
Herpes zoster	94 (3.44)	34 (3.74)	18 (2.19)	95 (3.13)

EAE=pts with events/100 pt-yrs
 AE, adverse event; EAE, exposure-adjusted event rate; LTE, long-term extension; pt, patient

Abstract OP0033 – Figure 1. Mean ΔDAS28-4(ESR) over time for A) Step-up pts and those who remained on tofacitinib 5 mg BID and B) Step-down pts and those who remained on tofacitinib 10 mg BID

Conclusions: In pts with RA, the safety profile was similar regardless of dose change. Step-up from tofacitinib 5 to 10 mg BID, or step-down from 10 to 5 mg BID, did not affect efficacy over 12 months vs remaining on the same dose, and was not influenced by initial response. Conclusions were limited by small pt numbers in some groups, the open-label design and inclusion of pts in the LTE who showed tolerability for tofacitinib and drug retention.

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