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 2 phase 2 and 3 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 deucanotinib). 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 event such as a fatal, life threatening, or requiring hospitalisation.

Results: Thirty-one trials were analysed, reporting data on 13,495 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% to 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 had higher rates of malignancies, compared with methotrexate between 12 and 24 weeks before the treatment was implemented, but the difference did not reach statistical significance (odds ratio (OR) 2.48, 95% confidence interval (CI) 0.76 to 8.13 and 0.39, 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 availableRCTs, 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.


METHODS:

In this exploratory, post hoc analysis, data were pooled from 2 open-label LTE studies (NCT00413699 [ongoing; database not locked at date of data cut-off]; NCT00681661) of pts with RA who had participated in Phase (P) 1/2 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/change 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=851); 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 ACRO20 response, and sub-groups for the Step-down and Remain 10 groups were defined based on initial ACRO50 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 ACRO20 response, and sub-groups for the Step-down and Remain 10 groups were defined based on initial ACRO50 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.

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

Methods: 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.

REFERENCE:

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