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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Objectives: 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 deoncitinib). 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 had higher rates of malignancies, compared with methotrexate between 12 and 24 weeks before the response 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: 0.7% to 2.0%, and 5.4%, respectively).

Methods: In this exploratory, post hoc analysis, data were pooled from 2 open-label LTE studies (NCT00413699 [ongoing; database not locked at data cut]; 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 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] vs 10 mg BID [LTE] (Step-up; n=833); 5 mg BID (index) vs 5 mg BID [LTE] (Remain 5; n=248)); 10 mg BID (index) vs 10 mg BID [LTE] (Remain 10; n=851); 10 mg BID index vs 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). 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) 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) 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

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REFERENCE:

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LONG-TERM EFFECTIVENESS OF THE COBRA SLIM REMISSION INDUCTION AND TREAT TO TARGET STRATEGY IN PATIENTS WITH EARLY RHEUMATOID ARTHRITIS LACKING CLASSICAL MARKERS OF POOR PROGNOSIS: 2 YEAR RESULTS OF THE CARERA TRIAL

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Background: EULAR guidelines recommend to treat all patients with early Rheumatoid Arthritis (eRA) with a combination of methotrexate (MTX) and a short-term course of Glucocorticoids (GC). The COBRA Slim strategy with MTX and a moderately dosed tapering down scheme of GC was effective, also in patients without classical markers of poor prognosis during the first year.

Objectives: To compare the outcomes of MTX with or without initial step-down GC in Low-Risk patients during the second year of the CareRA trial, in terms of disease control, safety and DMARD use.

Methods: CareRA is a two-year prospective investigator-initiated pragmatic multicenter RCT. DMARD naive eRA patients were stratified into a High- or Low-Risk group based on classical prognostic markers (presence of erosions, RF, anti-CCP and DAS28-CRP). Low-Risk patients (n=90) were randomised to either Taper Step Up (TSU) with MTX 15 mg weekly and prednisone tapering down scheme starting at 30 mg, tapered to 5 mg daily from w6 and stopped at w34. A treat-to-target approach was applied until year 1 and afterwards treatment was at the discretion of the rheumatologist. Proportions of DAS28-CRP remission at year 2 was a co-primary CareRA endpoint. Secondary outcomes were efficacy according to other remission criteria, EULAR/ACR response rates and functionality measured by HAQ (ITT analysis, last observation carried forward). Adverse events (AEs) and concomitant medication were registered.

Results: At year 2, 67.4% of Slim and 70.2% of TSU patients were in remission according to DAS28-CRP (p=0.777). Out of patients in DAS28CRP remission at year 1, 80.0% (24/30) in the Slim group, versus 69.0% (20/29) in the TSU group remained in remission at every three-monthly evaluation until year 2.Remission rates defined by Boolean criteria were higher in patients of the Slim (39.5%) versus TSU group (19.1%) (p=0.033). Functionality measured by mean area under the HAQ curve over 2 years was better in Slim patients (38.3±47.2) than in TSU patients (56.4±48.7) (p=0.025). Other secondary efficacy outcomes did not differ between the treatment arms. The total numbers of AEs reported as related to study therapy, were 69 in 34 TSU patients and 63 in 28 Slim patients. Biologics were started in 14 Low-Risk patients (15.6%), more specifically in 8 Slim and 6 TSU patients during the CareRA trial. At the year 2 visit 62.5% of Slim patients were on MTX monotherapy and 12.5% on a combination of csDMARDs.

Conclusions: In eRA patients lacking classical markers of poor prognosis COBRA Slim showed persistently high remission rates and good disease control 2 years after initiating therapy in a treat to target setting. COBRA slim seems to be slightly more effective than TSU according to the year 2 Boolean remission criteria and the 2 year functionality AUC but the CareRA study was not powered for this analysis.

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Background: Upadacitinib (UPA), an oral JAK inhibitor, showed efficacy in rheumatoid arthritis (RA) patients (pts) with an inadequate response to csDMARDs or bDMARDs on continuing stable csDMARD(s).1,2

Objectives: Safety and efficacy of switching to UPA 15 mg or 30 mg monotherapy versus continuing methotrexate (MTX) as a blinded study drug was evaluated in pts with inadequate response to MTX (MTX-IR).

Methods: Pts with active RA (TJC ≥ 6, SJC≥6, hsCRP ≥3 mg/L) on stable MTX were enrolled and randomised 1:1 in a double-blind manner to once-daily (QD) UPA 15 mg or 30 mg monotherapy or to continue MTX (cMTX) at their prior stable dose. At BL, all pts discontinued prior MTX without washout and received PBO (for pts on UPA) or MTX at prior dose (cMTX) as blinded study drug. The primary endpoints at Week (Wk) 14 were the proportion of pts achieving ACR20, and the proportion achieving DAS28-CRP<3.2 (NRI).

Results: 648 pts were randomised; all received study drug; 598 (92.3%) completed 14 wks. BL demographics and disease characteristics were generally similar across arms. Both primary endpoints were met (p<0.001); at Wk 14, a significantly greater proportion of pts receiving UPA monotherapy (15 mg and 30 mg) vs cMTX achieved ACR20 (67.7% and 71.2% vs 41.2%), and DAS28-CRP<3.2 (44.7% and 53.0% vs 19.4%) (table 1). All key secondary endpoints also showed UPA 15 and UPA 30 monotherapy to be superior to cMTX, including ACR50 (41.9% and 52.1% vs 15.3%), ACR70 (22.6% and 33.0% vs 2.8%), DAS28-2.6 (28.1% and 40.5% vs 8.3%), ΔHAQ-DI (−0.65 and −0.73 vs −0.32), ΔSF-36 PCS and ΔMorning Stiffness data are also shown (table 1). The proportion of pts achieving CDAI<10 was significantly greater with UPA 15 and 30 vs cMTX (34.6% and 46.3% vs 24.5%).

Adverse events (AEs) were reported at similar frequencies across arms; serious AEs were numerically higher in UPA 15 but similar between cMTX and UPA 30 (table 1). Numerically more infections were reported in cMTX and UPA 30 vs UPA 15. One serious infection each was reported in UPA 15 and cMTX, and none in UPA 30. Herpes zoster was more frequent in UPA 30 vs UPA 15 or cMTX. 3 malignancies (1 in cMTX and 2 in UPA 15) and 3 adjudicated MACE (1 in UPA 15 and 2 in UPA 30) were reported. One adjudicated pulmonary embolism was reported (UPA 15) in a pt with known risk factors (BMI 36; on oestrogen therapy). One death (haemorrhagic stroke due to ruptured aneurysm) was reported in UPA 15. No TB, renal dysfunction or Gl perforation was reported. Rates and types of laboratory abnormalities were consistent with prior UPA RA studies to date.