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THU0199

PHARMACOKINETICS, SAFETY AND TOLERABILITY OF SINGLE- AND MULTIPLE- DOSE ONCE-DAILY BARICITINIB IN CHINESE HEALTHY VOLUNTEERS – A RANDOMIZED PLACEBO-CONTROLLED STUDY

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Background: Baricitinib, an oral selective inhibitor of JAK1 and JAK2, is efficacious in patients with moderately to severely active rheumatoid arthritis and an inadequate response to methotrexate.

Objectives: To evaluate the pharmacokinetics (PK), safety and tolerability of baricitinib when given orally as single and multiple doses in healthy Chinese subjects.

Methods: This was a single-site, subject- and investigator-blinded, randomized, and placebo-controlled study (NCT02758613) conducted from 04 May 2016 to 25 July 2016. Eligible subjects were healthy Chinese adults (≥ 18 years) with a body mass index of 19.0 to 24.0 kg/m² (inclusive). Subjects received a once daily dose (QD) of baricitinib 2, 4 or 10 mg or placebo on Day 1 (single dose) and Days 4 through 10 for 7 consecutive days (multiple dose). Safety assessments were performed throughout the treatment period. Plasma PK samples were collected up to 48 hours after dosing on Days 1 and 10, with predose samples collected prior to dosing on Day 1 and Days 4 through 10. PK parameters were calculated using noncompartmental analysis.

Results: A total of 33 healthy volunteers were randomized and received at least 1 dose of study drug (placebo, n=8; baricitinib 2 mg, n=8; baricitinib 4 mg, n=9; baricitinib 10 mg, n=8). All subjects were male and the mean age was 27.8 years. After both single- and multiple-dose administration, baricitinib 2 to 10 mg was rapidly absorbed, reaching peak plasma concentrations within 0.5 to 1 hour (median). Plasma concentrations declined rapidly following attainment of peak concentrations, with a mean terminal half-life of 5.7 to 7.3 hours. Steady state plasma concentrations of baricitinib were achieved after the second day of QD dosing, with minimal accumulation of baricitinib in plasma (up to 10%) during 7 days of QD oral doses of 2 to 10 mg baricitinib. Single- and multiple-dose mean values for AUC_(0-∞) and C_{max} appeared to increase in an approximately dose-proportional manner across the dose range. Overall incidence of treatment-emergent AEs (TEAEs) is 33.3%. All TEAEs reported were mild in severity, with no serious AEs reported and no subjects were withdrawn due to AEs. Although there was an apparent increase in the incidence of drug-related TEAEs over the 2 to 10 mg dose range, the incidence of drug-related TEAEs at the 10 mg dose was comparable to placebo.

Conclusion: The PK of baricitinib in Chinese healthy subjects were characterized by rapid absorption and elimination following single and multiple oral doses of up to 10 mg. Systemic exposure to baricitinib increased in an approximately dose-proportional manner following single and multiple doses. Single and multiple oral doses of daily-administered baricitinib up to 10 mg were well tolerated by healthy Chinese subjects.

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THU0200

DRUG UTILISATION IN PEOPLE WITH EARLY RHEUMATOID ARTHRITIS IN THE UNITED KINGDOM

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Background: Despite a growing body of evidence in the pharmacological management of people with early rheumatoid arthritis (RA), there is still uncertainty concerning the most effective treatment regimen. Until 2018, guidance for England and Wales stated that everyone with early RA should receive combination therapy with 2 or more conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) in parallel. However, from epidemiological studies and anecdotal information, we know that this has not been the case in practice.

Objectives: (i) To determine the proportion of patients with new onset RA who start methotrexate (MTX) either alone or in combination with another csDMARD (ii) to describe which combinations are currently being prescribed and (iii) to describe the characteristics associated with the choice of initial RA treatment strategy

Methods: Consecutive patients with RA participating in the Rheumatoid Arthritis Medication Study (RAMS), a large UK study recruiting patients starting MTX for the first time, were eligible. Data on demographics, disease activity, comorbidity and all RA treatments are captured at baseline, 6 and 12 months following start of MTX. Analysis was limited to patients starting MTX within the first 2 years of symptom onset as part of their first treatment regimen for RA. Prevalent users of alternative csDMARDs, defined as use > 6 weeks prior to MTX start, were excluded. Participants were categorised as either starting MTX monotherapy or MTX in combination with another csDMARD (defined as started $\pm$ 6 weeks of MTX start date). Baseline characteristics were compared between monotherapy and combination therapy groups using descriptive statistics.

Results: 1,374 patients with a mean (SD) age of 58 (14) years were included in this study; 64% were female. At baseline, 996 (76%) started MTX monotherapy and 316 (24%) started MTX/csDMARD combination therapy (84% with hydroxychloroquine and 16% with sulphasalazine). Patients starting combination therapy were younger ($p<0.005$), with higher DAS28 scores ($p<0.005$), higher HAQ scores ($p<0.05$), lower MTX starting doses ($p<0.005$), and shorter symptom duration ($p<0.05$) compared with the monotherapy group.

Conclusion: These data show that despite national guidelines recommending combination csDMARD therapy in all patients diagnosed with RA, over three quarters of patients still started MTX monotherapy. People who were prescribed combination therapy had more severe disease suggesting that prescribers do consider prognosis in their treatment decisions. A majority of patients starting combination therapy did so with hydroxychloroquine, despite a lack of evidence for the benefits of this particular combination in clinical practice.

Table 1. Baseline characteristics of the monotherapy and combination therapy groups

Characteristic	Monotherapy (n=1,034)	Combination therapy (n=340)	P value
Age (years)	61 (50, 70)	57 (46, 67)	0.001
Female sex	655 (63)	223 (66)	0.455
Symptom duration (months)	6.3 (3.7, 11.0)	5.8 (3.4, 9.0)	0.020
HAQ score	1.0 (0.4, 1.5)	1.13 (0.5, 1.6)	0.015
DAS28	4.1 (3.2, 5.1)	4.5 (3.5, 5.5)	0.002
Co-morbidities: ≥ 1	468 (45)	130 (38)	0.023
MTX starting dose (mg/ week)	15 (10, 15)	10 (10, 12.5)	0.000

Values are frequency (%) or median (IQR)

Abbreviations: HAQ, health assessment questionnaire; DAS, disease activity score; MTX, methotrexate