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SAT0143

A PHASE 1 STUDY IN HEALTHY VOLUNTEERS EXPLORING THE SAFETY, PHARMACOKINETICS AND PHARMACODYNAMICS OF ATI-450: A NOVEL ORAL MK2 INHIBITOR

J. Schnyder¹, J. Monahan¹, W. Smith¹, H. Hope¹, D. Kelly¹, D. Burt¹, E. Huff¹, A. Kaul¹, A. Hildebrand¹, B. Burnette¹, N. Klug¹, M. Bangs¹, D. Gordon¹. ¹Aclaris Therapeutics, Inc, Wayne, United States of America

Background: ATI-450, is an investigational small molecule inhibitor of the MAPK-activated protein kinase 2 (MK2) signaling pathway. This pathway drives the expression of multiple cytokines including TNF α , IL-1 α and β , and IL-6.

Objectives: We evaluated the safety and tolerability of ATI-450 in healthy volunteers as well as pharmacokinetics (PK) and pharmacodynamics (PD). Here we present data from single and multiple ascending dose cohorts. The aim was to select a dose for evaluation in phase 2 in patients with rheumatoid arthritis.

Methods: Safety, PK and PD were assessed in a randomized, observer-blind, placebo-controlled, phase 1 study in male and female healthy subjects aged 18-55 (n=77).

- Part A: Single Ascending Dose (SAD) (n=32, 8 subjects per dose cohort - 2 placebo, 6 active). A single dose of 10mg, 30mg, 50mg and 100mg was tested.
- Part B: Multiple Ascending Dose (MAD) (n=30, 10 subjects per dose cohort - 2 placebo, 8 active). 10mg BID, 30mg BID and 50mg BID doses were tested over 7 days of administration.

Safety and tolerability of ATI-450 was evaluated based on adverse events, clinical laboratory, vital signs, 12-lead ECG, Holter monitoring, and physical examination. Blood was drawn for PK analysis at 0.5, 1, 2, 4, 6, 8, 12 hours, 24, 36, and 48 hours post dose in the SAD cohort and on day 7 of the MAD cohort. PD of ATI-450 were explored by investigating the inhibition of a target biomarker, phospho-HSP27 (pHSP27) and proinflammatory cytokines, TNF α , IL1 β , IL6 and IL8 in ex-vivo LPS-stimulated blood samples collected 4 and 12 hours post dose on day 7 from subjects in the MAD cohorts.

Results: ATI-450 was generally well tolerated. No serious adverse events or severe adverse events were reported, and no adverse events led to discontinuation of the study medication. The most common adverse events (reported by 2 or more subjects who received ATI-450) observed during the trial were dizziness, headache, upper respiratory tract infection, constipation, nausea, and abdominal pain. All adverse events were mild. A trend of a decrease in absolute neutrophil count (ANC) was observed without correlated clinical sequelae.

ATI-450 had dose proportional PK with a terminal half-life ($t_{1/2}$) of 9-12 hours in the MAD cohort on day 7. A dose and concentration dependent inhibition of ex vivo stimulated cytokines and target biomarker was observed. On day 7, patients in the 50mg BID dose (the dose with the highest degree of inhibition) recorded mean trough drug levels (12 hours post dose) that were 1.4, 2.5, 2.5 and 2.4 times greater than the IC_{50} for TNF α , IL1 β , IL8 and pHSP27 respectively. Mean C_{max} drug levels (4 hours post dose) were 3.6, 6.4, 6.2 and 6.0 times greater than the IC_{50} for TNF α , IL1 β , IL8 and pHSP27 respectively. IL6 levels were inhibited by more than 50% for part of the dosing interval.

Conclusion: Oral ATI-450 was generally well tolerated at all doses with dose proportional PK. The $t_{1/2}$ suggests that once or twice daily oral dosing may be possible. At the 50mg BID dose, marked inhibition of TNF α , IL1 β and IL8, IL6 and pHSP27 was observed. ATI-450 has the potential to be an oral, small molecule drug which can target multiple cytokines. Exploration of its benefit to risk profile in patients with rheumatoid arthritis is warranted.

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DOES POLYPHARMACY IN RHEUMATOID ARTHRITIS PATIENTS AFFECT THE TREAT TO TARGET STRATEGY?

J. F. Jaramillo Gallego¹, J. Rosa¹, M. Scolnik¹, M. A. Tobar Jaramillo¹, L. Ferreyra¹, E. Soriano¹. ¹Hospital Italiano de Buenos Aires, Buenos Aires, Argentina

Background: Polypharmacy (PP) is an important risk factor for drug toxicity, delirium, falls, hospitalizations and death. Patients with rheumatoid arthritis (RA) often have comorbid conditions and have PP. Treat to target strategy (T2T) implies a drug escalation and rheumatologists may not apply it in patients with PP.

Objectives: Our objective was to analyze if PP affects T2T in a real-world scenario.

Methods: Observational, retrospective cohort study. Patients with a new RA diagnosis (ACR/EULAR 2010 criteria) after 2010, over 18 years old, belonging to a Health Management Organization (HMO) from a university tertiary hospital, with a minimum follow-up period of 2 years, were included. PP was defined as consumption greater than or equal to 5 medications at the time of RA diagnosis, regardless of the medication used for RA, administered for a minimum period of 6 months. T2T strategy was defined as accomplished if an escalation in treatment was done when the patient had moderate or high disease activity at medical visit (by DAS28 and/or CDAI), without a significant improvement with respect to the previous visit. Prevalence of PP at RA diagnosis was calculated and RA patients were divided in those with PP at RA diagnosis time and those without. The first 2 years of disease were analyzed and compare between both groups: clinical and demographic characteristics, percentage of visits where T2T was applied, treatments received during that period. A multivariate logistic regression analysis was performed in order to identify factors associated with no T2T compliance.

Results: 147 patients with RA were included, 86% women, with an average age at diagnosis of 60 years (SD: 15.8). The prevalence of PP at RA diagnosis was 12% (17 patients). Table 1 shows the comparison between patients with and without PP. Patients with PP showed a greater frequency of erosions at baseline and after 2 years of disease, a greater use of corticosteroids at 2 years, higher percentage of hospitalizations and a higher mortality. In the multivariate logistic regression analysis, no compliance of the T2T strategy was only associated with the consumption of corticosteroids at 2 years (OR: 0.36, CI95%: 0.15-0.85; p=0.019) and no association was found with PP at the beginning of the disease.

Table 1. Demographic and clinical characteristics in patients with and without polypharmacy.

	Patients without Polypharmacy (n= 127)	Patients with Polypharmacy (n= 17)	P
Male sex, n (%)	18 (13.8)	3 (17.6)	0.6
Mean age at diagnosis (SD)	58.5 (15.6)	70.6 (12.2)	0.9
Positive rheumatoid factor, n (%)	87 (66.9)	12 (70.5)	0.7
Positive anti CCP, n (%)	109 (85.8)	13 (81.2)	0.6
Erosions at baseline, n (%)	25 (19.2)	7 (41.1)	0.03
Active smoker, n (%)	28 (21.5)	3 (17.6)	0.2
Past smoker, n (%)	23 (17.6)	7 (35.2)	
Charlson score, median (IQR)	3 (1-4)	4 (4-5)	<0.0001
Polypharmacy at 2 years, n (%)	17 (13.0)	46.8 (88.2)	<0.0001
Rheumatological consultations in 2 years, mean (DE), (IC 95%)	8.6 (3.3) (8.0-9.2)	8.8 (3.1) (7.2-10.5)	0.6
Corticosteroid therapy at 2 years, n (%)	29 (22.3)	8 (47.0)	0.02
cDMARDs therapy at 2 years, n (%)	114 (87.6)	13 (76.4)	0.2
Biologic therapy at 2 years, n (%)	13 (10)	4 (23.5)	0.1
Erosions at 2 years, n (%)	29 (22.3)	9 (52.9)	0.007
No T2T compliance, n (%)	65 (50)	5 (29.4)	0.1
Hospitalizations, n (%)	12 (9.2)	7 (41.1)	<0.0001
Mortality, n (%)	2 (1.5)	2 (11.7)	0.01

Conclusion: The prevalence of PP in our patients with a new RA diagnosis was 12% and was associated with more baseline erosions, a higher consumption of steroids, and a higher frequency of hospitalizations and mortality during the first 2 years of the disease. No relationship between PP and adherence to the T2T strategy was demonstrated. In the multivariate logistic regression analysis, no compliance with the T2T strategy was only associated to the consumption of corticosteroids at 2 years, may be reflecting a poorer disease control.

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