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Selective Inhibition of the MK2 Pathway: Data From a Phase IIa Randomized Clinical Trial in Rheumatoid Arthritis

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Objective. The study objective was to evaluate the safety, tolerability, pharmacodynamics, and preliminary efficacy of ATI-450 with methotrexate in patients with rheumatoid arthritis (RA).

Methods. A parallel-assignment, placebo-controlled, investigator-blinded/patient-blinded multicenter study evaluated patients with moderate-to-severe RA aged 18 to 70 years. Eligible patients were randomized (1:1) to ATI-450 50-mg oral tablets twice daily or placebo with a stable weekly dose of methotrexate for 12 weeks. The primary objective was to assess ATI-450 safety and tolerability. The secondary objectives were to assess the median percentage change from baseline high-sensitivity C-reactive protein (hs-CRP) levels, the mean change from baseline in Disease Activity Score in 28 joints based on CRP level (DAS28-CRP) and Rheumatoid Arthritis Magnetic Resonance Imaging Score hand-wrist assessments of synovitis or bone erosion at week 12, and the proportion of patients with American College of Rheumatology 20/50/70 (ACR 20/50/70) and with DAS28-CRP scores of less than 2.6. The exploratory outcomes were change from baseline in endogenous and ex vivo–stimulated cytokine levels.

Results. ATI-450 was well tolerated with no severe adverse events reported. ATI-450 reduced median hs-CRP levels by 42% or more at all posttreatment timepoints. In the ATI-450 group, a mean (median) decrease in DAS28-CRP score of 2.0 (2.1) was observed at week 12; proportions of patients with an ACR 20/50/70 response in the per-protocol population were 60%, 33%, and 20%, respectively, at week 12. Endogenous plasma levels of key inflammatory cytokines (tumor necrosis factor α, macrophage inflammatory protein 1β, interleukin 6, interleukin 8) were reduced across the 12 treatment weeks.

Conclusion. This is the first clinical study demonstrating that selective mitogen-activated protein kinase (MAPK)–activated protein kinase 2 (MK2) pathway blockade leads to a sustained antiinflammatory effect. This suggests that targeting the MK2 pathway mitigates the tachyphylaxis observed with p38 MAPK inhibitors in RA and supports further exploration.

INTRODUCTION

The p38 mitogen-activated protein kinase (p38 MAPK) signaling pathway has long been a focus of immunoinflammatory research and a therapeutic target for the treatment of inflammatory diseases owing to its involvement in the regulation and expression of the inflammatory cytokines tumor necrosis factor α (TNF-α), interleukin (IL) 1β, IL-6, and other inflammatory signals (1–3). Unfortunately, the inhibition of p38 MAPK has resulted in underwhelming efficacy in diseases such as rheumatoid arthritis (RA). Understanding the reasons for the failure of p38 MAPK inhibitors may lead to the development of therapies that optimally target the pathway and lead to new therapeutic approaches to treat inflammatory diseases (4,5).

Clinical studies of p38 MAPK inhibitors resulted in a tachyphylaxis-like, transient initial reduction in C-reactive protein

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(CRP) levels followed by a return to baseline within 4 to 8 weeks in RA. In addition to blocking proinflammatory cytokines, p38 MAPK regulates more than 60 substrates, many of which are associated with normal cell physiology, negative feedback loops, and the upregulation of antiinflammatory pathways (6). The leading mechanistic hypotheses for the transient changes in CRP levels observed with p38 MAPK inhibitors are (a) inhibition of negative feedback loops resulting in hyperactivation of proinflammatory pathways and/or (b) inhibition of antiinflammatory downstream p38 MAPK substrates, thereby dampening the desired response (7–10). Global blockade of this kinase could therefore be counterproductive in delivering antiinflammatory efficacy.

Inflammation driven by p38 MAPK is specifically mediated by the downstream serine and threonine kinase, MAPK-activated protein kinase 2 (MK2) (6,11). MK2 is the key substrate of p38 MAPK that regulates TNF-α, IL-1β, IL-6, and IL-8 production and is an alternative target in this signaling pathway (6,12–17). Moving downstream to MK2 uncouples the antiinflammatory and negative feedback axes from the proinflammatory axis, and inhibitors of this kinase should exhibit durable efficacy while limiting toxicities. Unfortunately, the development of ATP-competitive inhibitors of MK2 has been unsuccessful, resulting in compounds with limited potency (18) and selectivity and poor biochemical efficiency (19).

ATI-450 (also known as CDD-450) is a selective, orally available MK2 pathway inhibitor with a novel mode of inhibition, as it targets the interface formed on the high-affinity docking of p38 MAPK and MK2 (13). Through binding to this bimolecular-complex interface in a substrate-selective manner, ATI-450 inhibits MK2 phosphorylation by p38 MAPK and locks the kinase in an inactive conformation, thereby blocking the downstream pathway function (5,13). ATI-450 was generally safe and well tolerated in healthy participants over a range of single doses (≤100 mg) and multiple doses (≤50 mg twice daily [BID] for 7 days) in a phase I trial (5).

A phase IIa trial was conducted in patients with RA to evaluate whether blockade of the MK2 pathway with ATI-450 could overcome the key issues associated with p38 MAPK inhibition, namely tachyphylaxis and tolerability concerns. We hypothesized that, by targeting the MK2 pathway, ATI-450 would selectively inhibit proinflammatory pathways without impacting antiinflammatory pathways and negative feedback loops, thereby enhancing efficacy and avoiding tachyphylaxis, as demonstrated by a sustained reduction in CRP. A median reduction in CRP from baseline of at least 25% at day 7, with a subsequently sustained reduction of at least 25% at each study visit out to week 12, was considered sufficient to demonstrate an effect that was demonstrably different from the p38 MAPK inhibitors and provide evidence to discharge the risk of tachyphylaxis. The duration of the study was 12 weeks, thereby providing an efficient model to test the potential of downstream MK2 pathway inhibition to avoid tachyphylaxis.

The primary objective of this phase IIa trial was to evaluate the safety and tolerability of ATI-450. The secondary objectives were to assess the pharmacodynamics and preliminary efficacy of ATI-450 in combination with methotrexate (MTX) in patients with moderate-to-severe RA.

PATIENTS AND METHODS

Trial oversight. This 12-week, randomized, placebo-controlled phase IIa study, conducted from March 2020 through February 2021 at study sites in the United States, was blinded to the investigators, patients, site personnel, and Aclaris clinical monitors. The Aclaris statistician and the safety monitor were unblinded to treatment assignments. Prior to study initiation, investigators received written and dated approval from the institutional review board and/or independent ethics committee at each study site. The study was conducted in accordance with the International Council for Harmonisation E6 (R2) Good Clinical Practice Guideline, Declaration of Helsinki guidelines, and all applicable regulatory requirements. All patients provided written informed consent before study participation. The trial is registered at www.Clinicaltrials.gov (identifier NCT04247815).

Patients. Eligible patients were 18 to 70 years of age and met the following criteria: had a diagnosis of adult-onset RA as defined by the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism classification criteria; had moderate-to-severe disease, defined by a Disease Activity Score in 28 joints based on CRP level (DAS28-CRP) of 3.2 or greater; had at least 4 tender joints of 28 total and 4 swollen joints of 28 total; had a high-sensitivity CRP (hs-CRP) level of at least 5 mg/L at screening (upper limit of normal for hs-CRP was 3 mg/L); had definitive intra-articular synovitis or osteitis, defined by a score of 1 or greater on hand-wrist magnetic resonance imaging (MRI) as assessed by a central imaging reader; and received a stable MTX dose (between 7.5 and 25 mg/wk) and a stable dose of folic/folinic acid (≥5 mg/wk) for at least 4 weeks prior to screening. Patients could have received previous biological antiinflammatory drugs or Janus kinase inhibitors, but a washout period was required prior to study entry.

Randomization. The safety, pharmacokinetics, and pharmacodynamics data from the phase I study supported the 50-mg BID dose level as the most appropriate for this study (5). Patients were randomly assigned (3:1) to receive ATI-450 (50 mg BID) plus a stable dose of MTX (7.5-25 mg/wk) or to receive matching placebo plus MTX, all administered orally.

Patients visited the clinic on screening and days 1, 7, 14, 28, 42, 56, and 84 for safety, efficacy, and pharmacodynamic assessments, with the morning dose of study medication administered in the clinic on each study visit day. Treatment period was

up to day 84 (week 12), with a safety follow-up visit occurring 30 days after the last dose of study medication.

Outcomes. The primary outcome was safety and tolerability as measured by the number and percentage of treatment-emergent adverse events (TEAEs) and serious adverse events (serious AEs). Reports of AEs were collected from administration of the first dose of study medication through the end-of-study visit or 30 days after the last study drug administration, whichever was later. AEs were coded using the Medical Dictionary for Regulatory Activities, version 23.0.

Secondary outcomes were the median percentage change from baseline in hs-CRP levels over time, ACR 20/50/70 responders, the mean change from baseline in DAS28-CRP score over time, the proportion of patients with a DAS28-CRP score of less than 2.6, and the mean change from baseline to week 12 in the Rheumatoid Arthritis Magnetic Resonance Imaging Score hand-wrist assessments of synovitis (score range, 0-3) or bone erosion (0-10). A post hoc analysis was conducted in the per-protocol (PP) population to evaluate mean and median values for the Clinical Disease Activity Index (CDAI) in the ATI-450 and placebo treatment groups.

Exploratory outcomes were the mean and median change in ex vivo cytokine production and endogenous cytokine levels relative to baseline (day 1 before dose), respectively. For ex vivo–stimulated cytokine analysis, patient whole blood samples were incubated with 100 ng/mL of lipopolysaccharide for 5 hours at 37°C. Plasma cytokine concentrations were determined using Meso Scale technology (Meso Scale Diagnostics). For the measurement of endogenous cytokine levels, patient plasma samples were isolated at the clinical sites within 30 minutes of the draw, frozen at −70°C, and (at the end of the study) analyzed using Meso Scale technology. Healthy donor plasma samples used in the endogenous cytokine analysis were provided through the Confluence Discovery Technologies blood donor program and were processed similarly.

Statistical analysis. Sample size was based on numbers required to gain insight into the tachyphylaxis potential based on hs-CRP pharmacodynamics and to provide safety information. Approximately 25 patients were planned for enrollment with the expectation that at least 15 patients would complete the 12 weeks of treatment.

Simulations were conducted to determine the study's ability to detect a sustained reduction in hs-CRP (a secondary endpoint); the probability of observing a sustained reduction in hs-CRP (a median reduction of ≥25% at each visit from day 14 to day 84) was 76.4%. The probability of observing a sustained reduction of 25% from baseline hs-CRP with tachyphylaxis occurring was only 3.6%. The probability of observing a sustained reduction in hs-CRP using simulations that assume no treatment effect was 0.7%. All simulations assumed that hs-CRP is log-normally distributed with a baseline central value of 6 mg/L, a coefficient of variation in hs-CRP of 1.1, and a within-patient correlation in the log(hs-CRP) of 0.75.

Imputation using a multiple imputation model was used for efficacy analyses conducted on the intent-to-treat (ITT) population. Efficacy was evaluated in the ITT population (all patients who were assigned a randomization number) and the PP population (all patients who completed their week 12 visit and had valid hs-CRP values for at least six of the seven scheduled data collection times). For efficacy summaries in the ITT population, a model-based multiple imputation procedure was used to impute missing data, where appropriate. Missing data were not imputed for the safety and efficacy summaries in the PP population.

RESULTS

Patients. From May 28, 2020, to November 5, 2020, 19 patients were enrolled at five US centers (ATI-450, n = 16; placebo, n = 3; Supplementary Figure 1). Recruitment was stopped when low rates of discontinuation suggested that 15 patients would complete treatment to week 12 without the need for fully enrolling 25 patients. The ITT population included all 19 patients, and the PP population included 17 patients who completed 12 weeks of treatment (ATI-450, n = 15; placebo, n = 2). Two patients from the ATI-450 group discontinued before study completion; one patient discontinued due to an AE during the treatment period and a second patient discontinued during the 4-week follow-up period (after completing all treatment visits; this patient is included in the PP analysis). One patient in the placebo group discontinued during the treatment period after taking a prohibited medication. The female-to-male ratio of the enrolled patients was 74% female (14 patients) to 26% male (5 patients), and the overall mean age was approximately 56 years. Baseline mean (SD) [median] DAS28-CRP scores were 5.7 (0.9) [5.7] and 5.8 (0.8) [5.3] in the ATI-450 and placebo groups, respectively, with the mean (SD) [median] hs-CRP level in the ATI-450 group being 13.7 (9.1) [11.7] mg/L versus 21.7 (9.3) [21.3] mg/L in the placebo group (Supplementary Table 1).

Safety. In the safety population (patients who received at least one dose of study treatment; N = 19), 10 patients (53%) experienced at least 1 TEAE (ATI-450, n = 8 [50.0%]; placebo, n = 2 [66.7%]). A total of 27 TEAEs were reported, including 25 in the ATI-450 group and 2 in the placebo group. All TEAEs were mild (3 patients; 16%) or moderate (7 patients; 37%); no patient reported a severe TEAE (Table 1). Treatment-related AEs were reported by three patients (19%) in the ATI-450 group: mouth ulceration, urinary tract infection, blood creatine phosphokinase (increased to three to four times the upper limit of normal). No treatment-related events were reported in the placebo group. One patient in the ATI-450 group experienced a serious AE of COVID-19 pneumonia after completing treatment during the

Table 1. Summary of TEAEs by preferred term and severity

Preferred term	ATI-450 50 mg BID + MTX (n = 16)		Placebo + MTX (n = 3)	
	Mild, No. (%)	Moderate, No. (%)	Mild, No. (%)	Moderate, No. (%)
Blood cholesterol increased	1 (6.3)	—	—	—
Blood creatine phosphokinase increased	—	1 (6.3)	—	—
Blood pressure increased	—	1 (6.3)	—	—
Constipation	1 (6.3)	—	—	—
COVID-19 pneumonia	—	1 (6.3)	—	—
Dental caries	1 (6.3)	—	1 (33)	—
Ear infection	1 (6.3)	—	—	—
Electrocardiogram abnormal	1 (6.3)	—	—	—
Essential hypertension	—	1 (6.3)	—	—
Hypokalemia	—	1 (6.3)	—	—
Ligament sprain	1 (6.3)	—	—	—
Low-density lipoprotein increased	1 (6.3)	—	—	—
Mouth ulceration	1 (6.3)	—	—	—
Muscle strain	—	—	—	1 (33)
Palpitations	1 (6.3)	—	—	—
Rash, erythematous	1 (6.3)	—	—	—
Sinusitis	—	1 (6.3)	—	—
Skin abrasion	1 (6.3)	—	—	—
Urinary tract infection	—	2 (13)	—	—
Ventricular extrasystoles	1 (6.3)	—	—	—
White blood cell count increased	1 (6.3)	—	—	—

Abbreviations: BID, twice daily; MTX, methotrexate; TEAE, treatment-emergent adverse event.

follow-up period; this patient withdrew from the study and did not attend the follow-up visit. No other serious AEs were reported.

Pharmacodynamics and efficacy. In the PP population, a median decrease of 42% or more in hs-CRP was maintained through day 84 in the ATI-450 group. A sustained reduction was not observed in the placebo group (Figure 1A). At the follow-up visit, 4 weeks after stopping the drug, hs-CRP had returned to baseline in patients stopping ATI-450 (15.6% median reduction vs. baseline). A decrease in DAS28-CRP was observed throughout the study in both the ITT and PP populations of the ATI-450 group (mean [median] decrease of 2.0 [2.1] in both analysis populations at week 12), whereas a mean [median] increase of 0.35 [0.35] was observed in both populations of the placebo group (Figure 1B shows PP results). At the 4-week follow-up visit, the mean [median] decrease in DAS28-CRP from baseline was only 1.54 [1.70]. In the ATI-450 treatment group at week 12, the mean [median] percentage decrease from baseline swollen joint count was 55.7% [75.0%], and tender joint count decreased by a mean [median] of 70.9% [87.0%] in the PP population (Figures 1C and 1D); the ITT population followed similar patterns. The proportion of patients with an ACR 20/50/70 response increased in the ATI-450 group PP population, with 60%, 33.3%, and 20%, respectively, at week 12 (Figure 2A; Supplementary Table 2). There were no ACR responders in the placebo group during the treatment period, but one patient in the placebo group, who received a prohibited methylprednisolone infusion 4 days prior to the week 12 visit, achieved ACR20 at the 4-week

follow-up visit. Median percentage changes, mean percentage changes, and mean changes in patient and physician visual analog scale scores are reported in Supplementary Figure 2 and Supplementary Table 3.

The proportion of patients with a DAS28-CRP score of less than 2.6 and the proportion with a DAS28-CRP score of less than or equal to 3.2 (indicating low disease severity) were 20% and 40%, respectively, in the ATI-450 group at week 12 (Figure 2B). No patient in the placebo group achieved a DAS28-CRP score of less than or equal to 3.2 at week 12. In the post hoc analysis evaluating CDAI in the PP population, the mean (median) CDAI decreased from 39.73 (40.90) to 5.73 (5.90) in the ATI-450 treatment group; the mean (median) CDAI decrease in the placebo group was 38.95 (38.95) to 14.65 (14.65). A total of 12 patients (80%) in the ATI-450 group achieved remission or low disease activity at week 12 based on the CDAI; no patient in the placebo group achieved remission or low disease activity at week 12.

MRI results in the PP population, including erosion and synovitis scores at baseline and week 12, are summarized in Supplementary Table 4. Over 12 weeks, the erosion and synovitis scores remained relatively stable in the ATI-450 group (mean [median] increases of 0.2 [0.0] and 0.1 [0.3], respectively) and worsened in the placebo group (mean [median] increases of 0.8 [0.8] and 1.5 [1.5], respectively).

A sustained, ATI-450–dependent, mean inhibition of ex vivo lipopolysaccharide–stimulated TNF-α and IL-1β production was observed from day 1 to day 84 (Figure 3). By contrast, no substantial modulation of these ex vivo–stimulated cytokines was
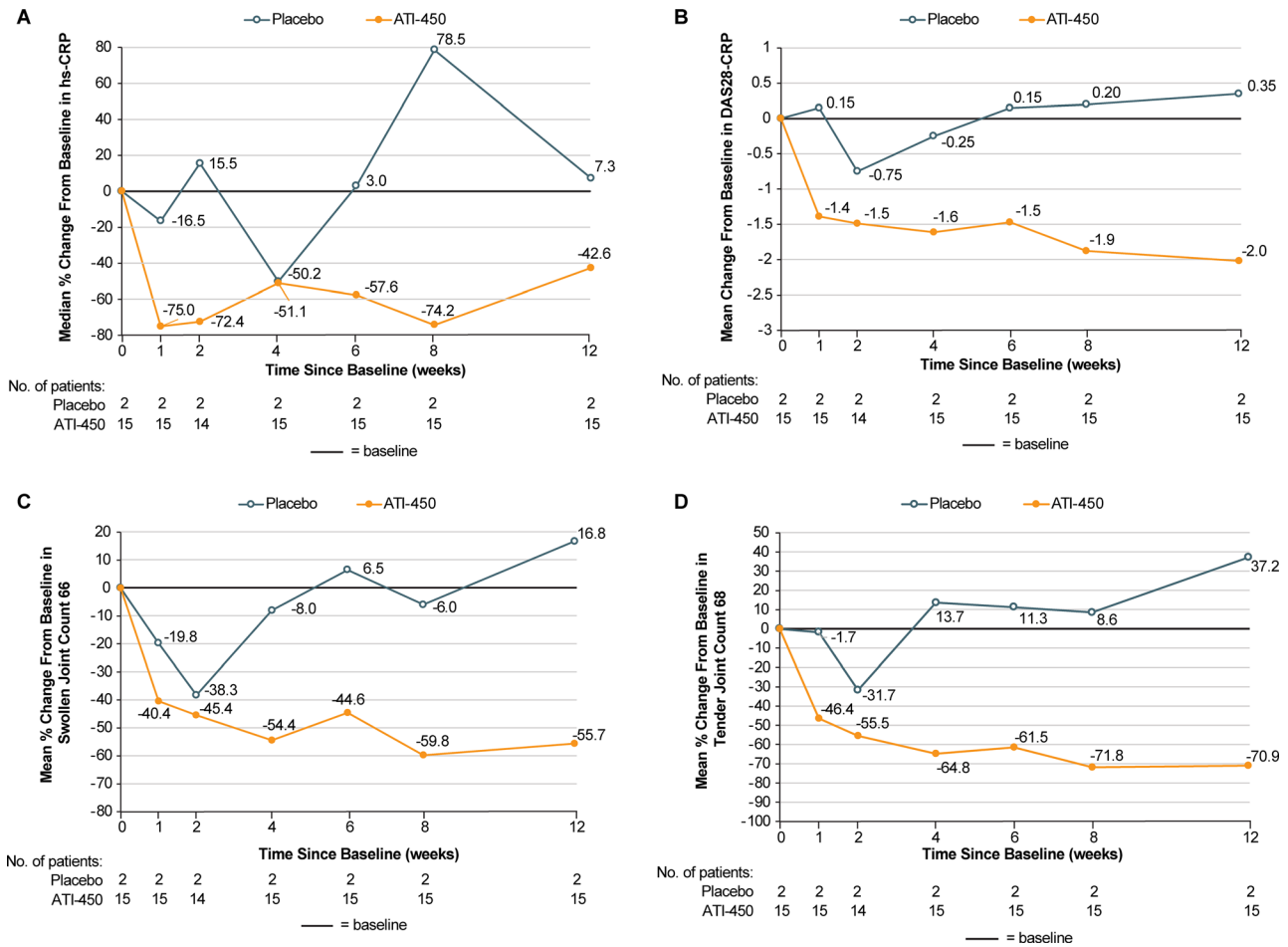
Figure 1. Changes from baseline over time in the per-protocol population with ATI-450 and placebo. (**A**) Median percentage change from baseline in hs-CRP. (**B**) Mean change from baseline in DAS28-CRP. (**C**) Mean percentage change from baseline in swollen joint count. (**D**) Mean percentage change from baseline in tender joint count. DAS28-CRP, Disease Activity Score in 28 joints based on C-reactive protein level; hs-CRP, high-sensitivity C-reactive protein assessment.
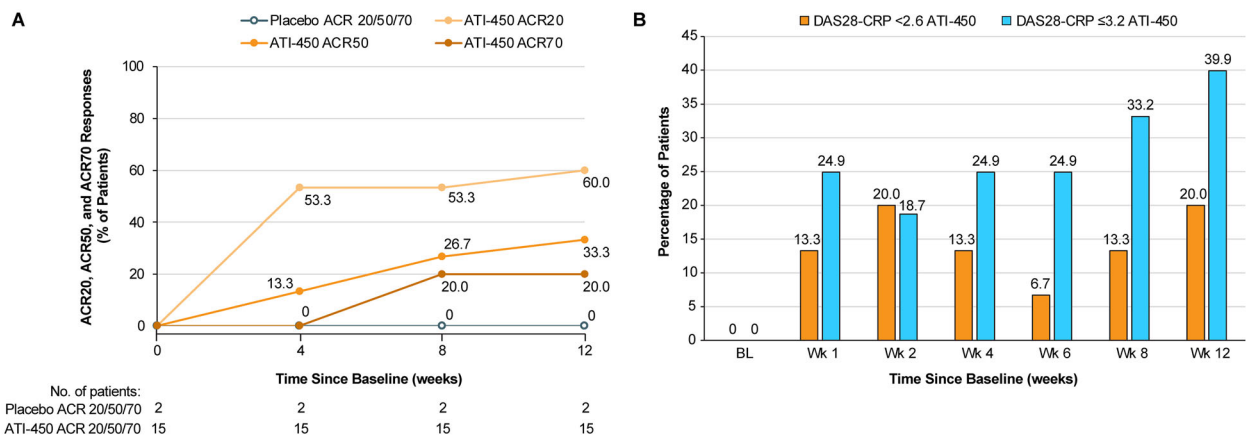

Figure 2. Proportion of ACR 20/50/70 (**A**) and DAS28-CRP (**B**) responders from baseline through day 84. Results are shown for the per-protocol population. Baseline values for ATI-450 and placebo groups are 0. Placebo group values at weeks 1, 2, 4, 6, 8, and 12 are all 0 and so are not shown in the graph. ACR, American College of Rheumatology; ACR 20/50/70, patients with ≥20% (or ≥50% or ≥70%) improvement in the number of swollen and tender joints (based on assessment of 66 and 68 joints, respectively) and ≥20% (or ≥50% or ≥70%) improvement in three or more ACR core measures; BL, baseline; DAS28-CRP, Disease Activity Score in 28 joints based on C-reactive protein level.
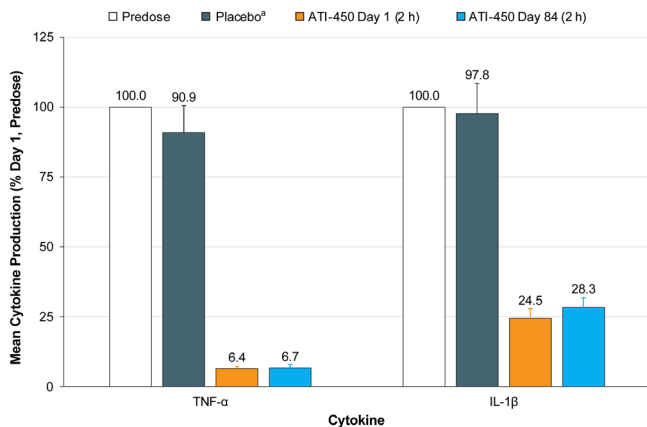
Figure 3. Ex vivo cytokine production in the placebo and ATI-450 treatment groups across the trial. ATI-450 treatment sustained modulation across the trial, and no substantial modulation was observed in the placebo-treated patients. [a]Placebo value equals the average of all six placebo values (two day-1 baseline, two day-1 after dose, and two day-84 after dose). Mean values with error bars representing standard error of the mean. IL, interleukin; LPS, lipopolysaccharide; TNF, tumor necrosis factor.

observed in placebo-treated patients. Similarly, endogenous proinflammatory cytokines/chemokines TNF-α, IL-8, macrophage inflammatory protein (MIP)-1β, and IL-6 elevated in patients with RA showed sustained ATI-450–dependent median reductions across the treatment period to levels at or near those in healthy blood donors (Figure 4). No impact of ATI-450 was observed on the antiinflammatory cytokine IL-1 receptor antagonist or on monocyte chemoattractant protein 1, a chemokine not elevated in patients with RA relative to healthy donors.

DISCUSSION

This study investigated the safety and efficacy of the MK2 pathway inhibitor ATI-450 in patients with moderate-to-severe RA. ATI-450, a mechanistically novel compound that targets the p38 MAPK/MK2 complex and selectively inhibits the proinflammatory MK2 pathway, was well tolerated in this study, although numbers of subjects were small. Tachyphylaxis was not observed over 12 weeks of treatment with ATI-450 as evidenced by durable decreases in hs-CRP and endogenous proinflammatory cytokines and chemokines (TNF-α, IL-6, IL-8, and MIP-1β) levels, along with sustained improvements in efficacy assessments (ie, DAS28-CRP, CDAI, proportion of ACR 20/50/70 responders). Based on simulations used to design the trial, the sustained reduction in hs-CRP observed in this study would be highly unlikely if ATI-450 had the same level of tachyphylaxis that is associated with p38 MAPK inhibitors.

Furthermore, the sustained inhibition of endogenous cytokines (TNF-α, IL-6, IL-8, and MIP-1β) and ex vivo–lipopolysaccharide-stimulated TNF-α and IL-1β by ATI-450 from day 1 to day 84

supports the hypothesis that moving downstream of p38 MAPK via MK2 pathway targeting overcomes the development-limiting tachyphylaxis observed with p38 MAPK inhibitors and supports MK2 as an optimal target in this key pathway. These exploratory pharmacodynamic findings contrast with the hypothesized p38 MAPK inhibitor–induced reprogramming of the signal transduction networks resulting in pathway-independent cytokine production as a mechanism of tachyphylaxis. The totality of these data support a differentiated and improved antiinflammatory profile for ATI-450 compared with p38 MAPK inhibitors, providing evidence that MK2 pathway inhibition may be the optimal approach for targeting this pathway to treat autoimmune diseases.

This was a small but adequately sized study to explore the pharmacodynamics of ATI-450 based on hs-CRP reduction over time and effect on cytokine levels. The study was not powered for a placebo comparison, and the purpose of the placebo group was to allow for blinded efficacy and safety assessments. Although the study was clearly not powered for efficacy outcomes, the placebo group did provide some reference, and it is encouraging to observe differences between the study arms in DAS28-CRP changes and ACR responder proportions. The MRI data indicate that patients had relatively advanced disease (more erosions relative to synovitis), which may explain a limited placebo response. In addition, the mean synovitis score at baseline in the ATI-450 group was low (5.0), which did not allow much room for improvement. Also, 87.5% of joints scored for synovitis in total had a baseline score of 1 or less (ie, 87.5% of joints contributing to the overall synovitis score had a score of 1 or less); in studies of other disease-modifying antirheumatic drugs, low baseline synovitis scores are often associated with lack of improvement in synovitis during treatment with otherwise effective therapies (20–22).

ATI-450 appeared to be well tolerated in patients with RA, with only one participant withdrawing because of an AE, elevated creatine phosphokinase. The elevation was approximately three to four times the upper limit of normal and not associated with signs or symptoms of muscle toxicity. Asymptomatic elevations in creatine phosphokinase have been observed with other antiinflammatory drugs, including infliximab (23) and upadacitinib (24).

This study was limited by the small sample size, especially in the placebo group (three patients). Although baseline disease characteristics were unbalanced based on mean hs-CRP levels, other baseline disease characteristics were similar among patients in each treatment group. Both of these limitations could be overcome by conducting a larger study of patients with moderate-to-severe RA. Even with these limitations, the results are encouraging and suggest that MK2 pathway inhibition may be a viable way to treat inflammatory diseases. This study supports progression to more definitive trials.
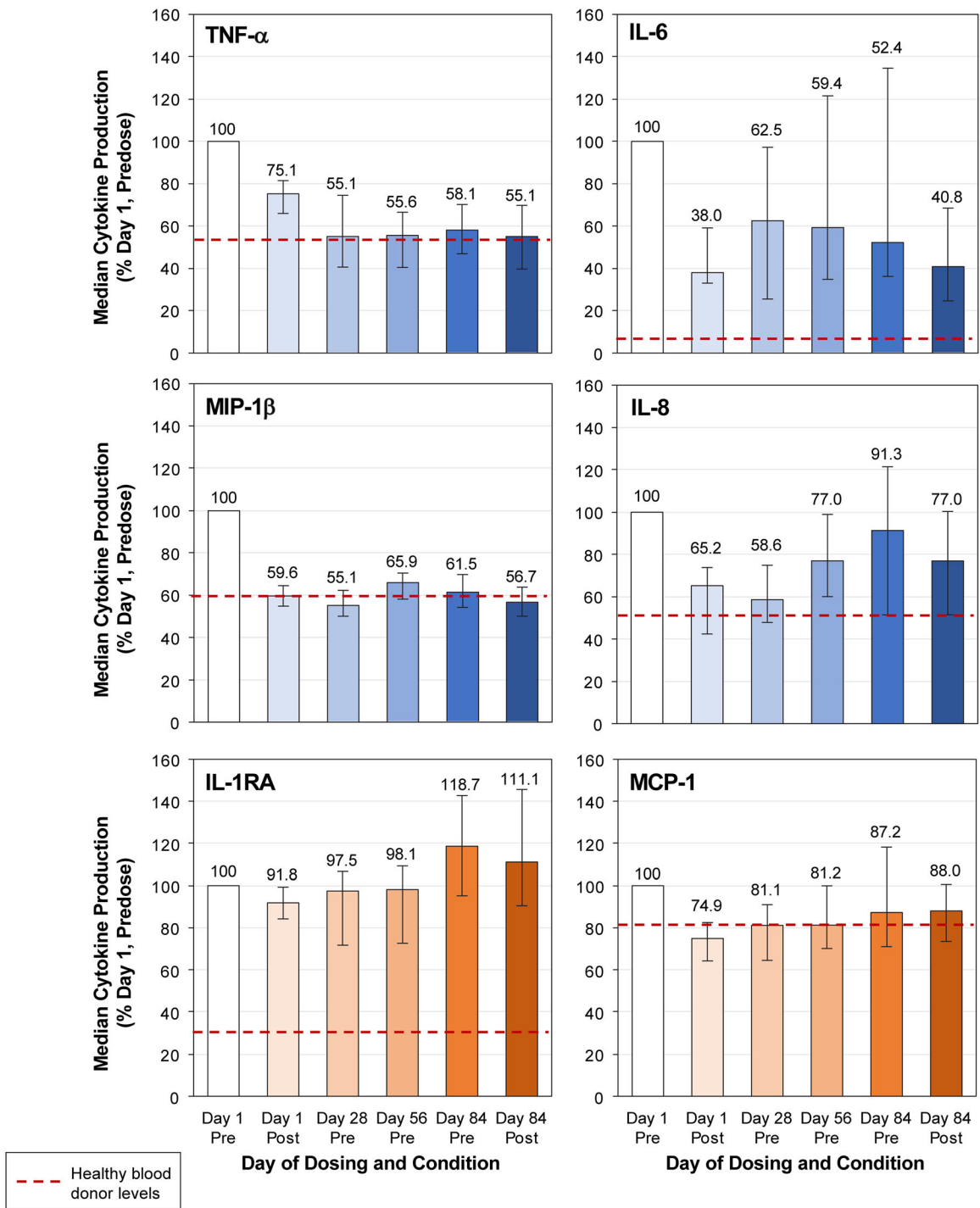
Figure 4. Modulation of endogenous, disease-elevated, proinflammatory cytokine and chemokine levels in the ATI-450 treatment group across the trial. Disease-elevated, proinflammatory TNF-α, IL-6, MIP-1β, and IL-8 (shown in blue) were reduced by ATI-450 treatment; antiinflammatory, disease-independent IL-1RA and MCP-1 (shown in orange) were unaffected. Median values with error bars representing the interquartile range (Q1, minus value; Q3, plus value) are shown. IL, interleukin; IL-1RA, interleukin 1 receptor antagonist; MCP, monocyte chemoattractant protein; MIP, macrophage inflammatory protein; post, after dose; pre, before dose; TNF, tumor necrosis factor.

The first-in-class MK2 pathway inhibitor ATI-450 was well tolerated in this study and induced sustained antiinflammatory efficacy over 12 weeks in patients with moderate-to-severe RA. Although the study was not powered to make placebo comparisons, initial efficacy and pharmacodynamic data in patients who received ATI-450 suggest that MK2 pathway inhibition can lead to durable antiinflammatory responses. Additional definitive and dose-range–finding trials are warranted to further establish the safety and efficacy of ATI-450.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Gordon had full access to all of the data in the study and takes full responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Gordon, Burt, Hope, Monahan.
Acquisition of data. Kivitz, Singhal, Bangs, Huff, Hope.
Analysis and interpretation of data. Gordon, Burt, Hope, Monahan.

ROLE OF THE STUDY SPONSOR

Employees of the funding source(s) contributed to the study design, to the collection, analysis, and interpretation of the data, to the writing of the manuscript, and to the decision to submit the manuscript for publication. Publication of this article was not contingent upon approval by the funding sources.

REFERENCES

1. Saklatvala J. The p38 MAP kinase pathway as a therapeutic target in inflammatory disease. Curr Opin Pharmacol 2004;4:372–7.

2. Schett G, Zwerina J, Firestein G. The p38 mitogen-activated protein kinase (MAPK) pathway in rheumatoid arthritis. Ann Rheum Dis 2008;67:909–16.

3. Burnette BL, Selness S, Devraj R, et al. SD0006: a potent, selective and orally available inhibitor of p38 kinase. Pharmacology 2009;84: 42–60.

4. Genovese MC. Inhibition of p38: has the fat lady sung? Arthritis Rheum 2009;60:317–20.

5. Gordon D, Hellriegel ET, Hope HR, et al. Safety, tolerability, pharmacokinetics, and pharmacodynamics of the MK2 inhibitor ATI-450 in healthy subjects: a placebo-controlled, randomized phase 1 study. Clin Pharmacol 2021;2021:123–34.

6. Singh RK, Najmi AK, Dastidar SG. Biological functions and role of mitogen-activated protein kinase activated protein kinase 2 (MK2) in inflammatory diseases. Pharmacol Rep 2017;69:746–56.

7. Genovese MC, Cohen SB, Wofsy D, et al. A 24-week, randomized, double-blind, placebo-controlled, parallel group study of the efficacy of oral SCIO-469, a p38 mitogen-activated protein kinase inhibitor, in patients with active rheumatoid arthritis. J Rheumatol 2011;38: 846–54.

8. Alten RE, Zerbini C, Jeka S, et al. Efficacy and safety of pamapimod in patients with active rheumatoid arthritis receiving stable methotrexate therapy. Ann Rheum Dis 2010;69:364–7.

9. Cohen SB, Cheng TT, Chindalore V, et al. Evaluation of the efficacy and safety of pamapimod, a p38 MAP kinase inhibitor, in a double-blind, methotrexate-controlled study of patients with active rheumatoid arthritis. Arthritis Rheum 2009;60:335–44.

10. Damjanov N, Kauffman RS, Spencer-Green GT. Efficacy, pharmacodynamics, and safety of VX-702, a novel p38 MAPK inhibitor, in rheumatoid arthritis: results of two randomized, double-blind, placebo-controlled clinical studies. Arthritis Rheum 2009;60: 1232–41.

11. Jones DS, Jenney AP, Joughin BA, et al. Inflammatory but not mitogenic contexts prime synovial fibroblasts for compensatory signaling responses to p38 inhibition. Sci Signal 2018;11.

12. Kotlyarov A, Neininger A, Schubert C, et al. MAPKAP kinase 2 is essential for LPS-induced TNF-alpha biosynthesis. Nat Cell Biol 1999;1:94–7.

13. Wang C, Hockerman S, Jacobsen EJ, et al. Selective inhibition of the p38α MAPK-MK2 axis inhibits inflammatory cues including inflammasome priming signals. J Exp Med 2018;215:1315–25.

14. Muniyappa H, Das KC. Activation of c-Jun N-terminal kinase (JNK) by widely used specific p38 MAPK inhibitors SB202190 and SB203580: a MLK-3-MKK7-dependent mechanism. Cell Signal 2008;20: 675–83.

15. Ma W, Lim W, Gee K, et al. The p38 mitogen-activated kinase pathway regulates the human interleukin-10 promoter via the activation of Sp1 transcription factor in lipopolysaccharide-stimulated human macrophages. J Biol Chem 2001;276:13664–74.

16. Waugh DJ, Wilson C. The interleukin-8 pathway in cancer. Clin Cancer Res 2008;14:6735–41.

17. Murphy C, McGurk M, Pettigrew J, et al. Nonapical and cytoplasmic expression of interleukin-8, CXCR1, and CXCR2 correlates with cell proliferation and microvessel density in prostate cancer. Clin Cancer Res 2005;11:4117–27.

18. Anderson DR, Meyers MJ, Vernier WF, et al. Pyrrolopyridine inhibitors of mitogen-activated protein kinase-activated protein kinase 2 (MK-2). J Med Chem 2007;50:2647–54.

19. Mourey RJ, Burnette BL, Brustkern SJ, et al. A benzothiophene inhibitor of mitogen-activated protein kinase-activated protein kinase 2 inhibits tumor necrosis factor alpha production and has oral anti-inflammatory efficacy in acute and chronic models of inflammation. J Pharmacol Exp Ther 2010;333:797–807.

20. Conaghan PG, Durez P, Alten RE, et al. Impact of intravenous abatacept on synovitis, osteitis and structural damage in patients with rheumatoid arthritis and an inadequate response to methotrexate: the ASSET randomised controlled trial. Ann Rheum Dis 2013;72: 1287–94.

21. Conaghan PG, Peterfy C, Olech E, et al. The effects of tocilizumab on osteitis, synovitis and erosion progression in rheumatoid arthritis: results from the ACT-RAY MRI substudy. Ann Rheum Dis 2014;73: 810–6.

22. Conaghan PG, Østergaard M, Bowes MA, et al. Comparing the effects of tofacitinib, methotrexate and the combination, on bone marrow oedema, synovitis and bone erosion in methotrexate-naïve, early active rheumatoid arthritis: results of an exploratory randomised MRI study incorporating semiquantitative and quantitative techniques. Ann Rheum Dis 2016;75:1024–33.

23. Theodoraki E, Orfanoudaki E, Foteinogiannopoulou K, et al. Asymptomatic hyperCKemia during infliximab therapy in patients with inflammatory bowel disease. Inflamm Bowel Dis 2018;24:1266–71.

24. Queeney K, Housley W, Sokolov J, et al. Elucidating the mechanism underlying creatine phosphokinase upregulation with upadacitinib [abstract FRI0131]. Ann Rheum Dis 2019;78:734–5.