Preclinical Efficacy of an Oxazolopyridine IRAK4 Inhibitor in Rodent Models of Inflammation

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory auto-immune disease manifesting with joint pain and tissue destruction which can lead to permanent disability. Despite recent advances in the treatment of RA, many patients are still unable to reach sustainable remission. Interleukin-1 receptor-associated kinase 4 (IRAK4), a serine-threonine kinase, plays a key role in inflammatory signaling via regulation of the expression of proinflammatory cytokines through MYD88-dependent pathway in immune cells. The interaction of IRAK4 and IRAK2 with MYD88 leads to phosphorylation of IRAK1 and interaction with TNF receptor-associated factor 6 (TRAF-6) [1]. TRAF-6 activates the transcription factors nuclear factor-kappa of B cells (NF-κB) [1], which initiates the production of the inflammatory cytokines TNF-α and IL-6, playing a central role in RA pathogenesis through the mediation of bone remodeling, induction of inflammatory cytokines and stimulation of both adaptive and innate immune cells. Inhibition of IRAK4 could block the expression of inflammatory cytokines and the development of specific IRAK4 inhibitors represents one of the novel strategies for the treatment of RA. CA-4948 is a member of the oxazolopyridine class of IRAK4 inhibitors and has been shown to suppress TLR agonist-induced NF-κB activation, TNF-α and IL-1β expression in the THP-1 monocytic cell line.

OBJECTIVE

Our objective was to determine whether a highly potent and selective oxazolopyridine IRAK4 inhibitor CA-4948 demonstrates efficacy in mouse models of arthritis and systemic inflammation; compared to an isoquinoline inhibitor PF-06650833.

METHODS

The protocol and procedures involving the care and use of the animals in this study were reviewed and approved by CR-MTL Institutional Animal Care and Use Committee (IACUC). The study was performed using the mouse model of collagen induced arthritis (CIA) and lipopolysaccharide (LPS)-induced cytokine release mouse model of systemic inflammation. To induce CIA model, all animals received intradermal injections of bovine type II collagen. Once the disease was established, mice were treated daily for 20 days with vehicle, CA-4948, PF-06650833 or dexamethasone by oral gavage. In the CIA mouse model, disease activity was determined by measuring inflammation swelling in the affected joints (paw volume) and clinical score over time. Histopathological evaluation was performed on two hind limbs for all animals in CIA study. A single oral dose of IRAK4 inhibitor was administered to CD-1 mice followed by intraperitoneal administration of LPS at 3 hours. ELISA kits were used to evaluate cytokine levels in mouse serum samples at 1 and 3 hours after LPS challenge. Statistical analysis was performed with either one-way ANOVA followed by Dunnett's multiple comparison test or Student's t-test for unpaired comparisons using GraphPad Prism 8 software. Values of $p < 0.05$ were considered significant.

RESULTS

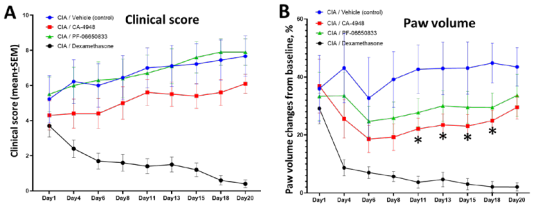

Figure 1. Treatment with CA-4948 alleviates CIA disease severity. All treatments were started on Day 1. (A) Group mean values (Day 1-20) for clinical score (sum of four paws). (B) Percent changes (Day 1-20) of paw volume from baseline (sum of hindpaws). (C) Group mean values for body weight (Day 1-20). *, $p<0.05$

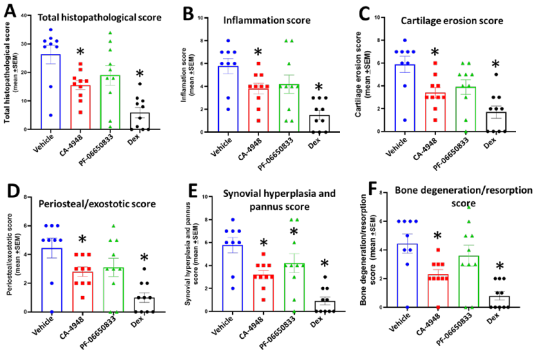

Figure 2. CA-4948 decreased the score of all histopathological parameters (sum of left and right hindpaws) including (A) total histopathological score, (B) inflammation score, (C) cartilage erosion score, (D) periosteal/exostotic score, (E) synovial hyperplasia and pannus score, (F) bone degeneration/resorption score.*, $p<0.05$

RESULTS

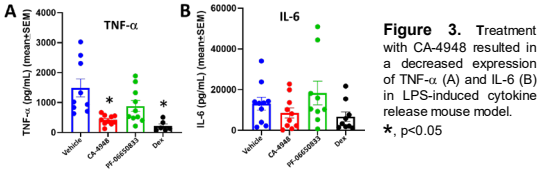

Figure 3. Treatment with CA-4948 resulted in a decreased expression of TNF-α (A) and IL-6 (B) in LPS-induced cytokine release mouse model. *, $p<0.05$

Treatment with CA-4948 or PF-06650833 resulted in inhibition of arthritis severity in the CIA mouse model (Fig. 1, 2) and a decreased expression of proinflammatory cytokines as measured in mouse blood after LPS challenge (Fig. 3). Treatment with CA-4948 resulted in decreases (up to 50%) in paw volume compared to vehicle control, with differences attaining statistical significance at days 11-18 (Fig. 1B). Consistent with CIA in-life data, treatment with CA-4948 decreased the score of all histopathological parameters (inflammation, cartilage erosion, synovial hyperplasia and pannus, bone degeneration/resorption, periosteal/exostotic changes) when compared to vehicle control and the differences attained statistical significance for all histopathological parameters (Fig. 2). Treatment with CA-4948 resulted in a significant reduction of cytokine levels by 72% for TNF-alpha and 35% for IL-6 in LPS-induced cytokine release mouse model (Fig. 3).

CONCLUSIONS

A highly selective oxazolopyridine IRAK4 inhibitor, CA-4948, demonstrated potent therapeutic efficacy in mouse models of arthritis and systemic inflammation.

REFERENCES

1. De Nardo D, Balka KR, Gloria YC, et al. Interleukin-1 receptor-associated kinase 4 (IRAK4) plays a dual role in myddosome formation and Toll-like receptor signaling. J Biol Chem, 2018:293 (39):15195-15207.

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