POST 023

A NEWLY DEVELOPED SMALL MOLECULE CD38 INHIBITOR EXERTS THERAPEUTIC EFFECTS IN A COLLAGEN-INDUCED ARTHRITIS MOUSE MODEL

Keywords: Disease-modifying drugs (DMARDs), Rheumatoid arthritis, Animal models

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Background: CD38 is a NAD+ consuming enzyme ubiquitously expressed on immune cells and its expression increases in several pathological conditions, including Rheumatoid Arthritis (RA) [1, 2]. Pre-clinical studies in CD38 knock-out models have demonstrated that CD38 deficient animals develop an attenuated form of Collagen-induced-Arthritis (CIA) characterized by reduced inflammation and damage at the joint level suggesting a causal role of CD38 in the pathogenesis of CIA and, potentially, RA [3-5].

Objectives: This study investigated the efficacy of NTX-748, a newly developed, potent and orally available small molecule inhibiting the enzymatic activity of CD38, in reducing the inflammation, cartilage destruction, pannus formation, and bone resorption associated with developing CIA in mice, a well-established animal model for the study of RA.

Methods: Mice were injected intra-dermally (ID) with Freund's complete adjuvant (CFA) containing bovine type II collagen to induce arthritis on study days 0 and 21.

Results: Treatment with NTX-748 at 10 and 30mg/kg showed a statistically significant dose-dependent beneficial effect reducing day 36 CAS by 37% and 50% respectively relative to vehicle (p=0.13 and p=0.047), without showing any toxicity, including body and spleen weights. Histopathology analysis of paws and spleen confirmed NTX-748 efficacy. Strikingly, NTX-748 reduces incidence of CAS up to 50% in a dose-dependent manner (p = 0.0015). Plasma concentrations of NTX-748 increased approximately in proportion to dose. Mass Spectrometry-based tissue metabolic analysis (liver and spleen) confirmed target engagement with dose dependent increases of NAD+ levels, the main substrate of CD38-mediated NAD+ hydrolysis, and decreases of NAM and ADPR, both concentrations of NTX-748 increased approximately in proportion to dose. Mass Spectrometry-based tissue metabolic analysis (liver and spleen) confirmed target engagement with dose dependent increases of NAD+ levels, the main substrate of CD38-mediated NAD+ hydrolysis, and decreases of NAM and ADPR, both products of the same enzymatic reaction. Metathreonate 1mg/kg also demonstrated efficacy (98% reduction in CAS) however significant splenomegaly (3-fold increase) indicated toxicity at this dose.

Conclusion: Our results demonstrated that NTX-748, a small molecule inhibiting the NADase enzymatic activity of CD38, is efficacious in the mouse CIA model, and thus potentially RA. These data confirm the potential of CD38 as druggable target in the treatment of inflammation-driven autoimmune diseases such as RA.

REFERENCES:

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Objectives: To evaluate the effect of tofacitinib on muscle mass of collagen-induced arthritic (CIA) mice.

Methods: CIA was induced in male DBA/1J mice. Animals were randomized into 5 groups: I) CIA; II) tofacitinib (CIA-TOF; n=10); II) CIA + vehicle (CIA-VEH; n=10); III) healthy controls (CO; n=9). Vehicle (PBS) or tofacitinib 15mg/kg were administered twice a day, between days 18 and 45 after the disease induction. Clinical score, edema and body weight were evaluated during the experimental period. After euthanasia, tibio-tarsal joints were collected for assessment of disease histopathological score, and tibialis anterior (TA) and gastrocnemius (GA) muscles were weighed to assess muscle mass. Muscle atrophy was evaluated by measurement of TA myofiber cross-sectional area (CSA). Expression of proteins related to muscle regeneration or catabolism (Pax7, MyoD, myogenin and Murt-1) were evaluated by western blot in GA homogenates. Serum inflammatory markers (TNF and IL-6) were evaluated by ELISA. Statistical analysis included ANOVA followed by Tukey’s or with Kruskal-Wallis. The statistical difference was assumed for p<0.05.

Results: As expected, tofacitinib treatment decreased arthritis severity by reducing clinical score (p=0.03) and hind paw edema (p=0.04) in comparison with CIA-VEH group. CIA-TOF showed weight gain (p=0.02), higher TA (p=0.009) and GA (p=0.02) weights, and increased CSA compared to CIA-VEH group (p=0.01). On day 45, CIA-TOF presented increased muscle strength compared to CIA-VEH group (p=0.006), however, no difference was found in the fatigue parameter among groups (p=0.05). The expression of Pax7 was unchanged (p=0.07), while MyoD expression showed an increase trend, and myogenin expression was significantly increased in CIA-TOF compared to CIA-VEH (p=0.04) and CO groups (p=0.02). The treatment did not significantly modify Murt-1 expression. Compared to CIA-VEH group, CIA-TOF mice showed decreased serum levels of TNF (p=0.04), and no difference in IL-6 serum levels (p=0.08).

Conclusion: Tofacitinib attenuated muscle loss in arthritic mice, as increased muscle weight and muscle CSA were detected in treated mice. Additionally, an increased activation of satellite cells regeneration, based on the expression of myogenin, is a potential mechanism involved in tofacitinib-protection against muscle loss.

REFERENCES:

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