Inhibition of HDAC Activity by ITF2357 Ameliorates Joint Inflammation and Prevents Cartilage and Bone Destruction in Experimental Arthritis

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Inhibition of histone deacetylases (HDAC) has been shown to modulate gene expression and cytokine production after stimulation with several stimuli. In the present study, the antiinflammatory effect of a potent HDACi, ITF2357, was explored in different experimental models of arthritis. In addition, the bone protective effect of ITF2357 was investigated in vitro. Treatment of acute arthritis (Streptococcus pyogenes cell wall (SCW) arthritis) with ITF2357 showed that joint swelling and cell influx into the joint cavity were reduced. Furthermore, the chondrocyte metabolic function was improved by treatment of ITF2357. The production of proinflammatory cytokines by synovial tissue was reduced after ITF2357 treatment. To examine the effect of HDAC inhibition on joint destruction, ITF2357 was applied to both rat adjuvant arthritis and mouse collagen type II arthritis. ITF2357 treatment both ameliorates the severity scores in arthritis models and prevents bone destruction. In an in vitro bone destruction assay, ITF2357 was highly effective at a dose of 100 nmol/L. In conclusion, inhibition of HDAC prevents joint inflammation and cartilage and bone destruction in experimental arthritis.

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antiinflammatory properties in models of disease in experimental animals (12,14).

In the present study, we have evaluated the effect of ITF2357 in several models of arthritis, ranging from acute to chronic models of arthritis. In addition, the effect of ITF2357 was studied on both TNF-α- and IL-1β-induced bone resorption.

**HDAC INHIBITORS DECREASE CYTOKINE PRODUCTION BY RA SYNOVIAL CELLS AND RA TISSUE EXPLANTS**

Recently, it was demonstrated that HDAC expression and activity in synovial tissue of RA patients correlates positively with the concentration of TNF-α (18). In addition, it was shown that HDAC in-

HDAC inhibitors suppress cytokine production by RA synovial tissue explants and that both TNF-α- and LPS-induced cytokine and chemokine production were decreased by inhibition of HDAC activity (19). However, HDAC inhibition did not influence the spontaneous cytokine production of RA synovial macrophages or intact synovial tissue explants. Interestingly, HDAC inhibited apoptosis in RA synovial macrophages by suppressing antiapoptotic Bcl-1 protein (19). It has been reported that HDACi activate either the extrinsic or the intrinsic death pathway or both of these pathways (20). In addition, it was demonstrated that HDACi induce growth arrest in RA synovial fibroblasts through induction of p21 and suppression of NF-κB nuclear accumulation (21). HDACi suppress cytokine production without an effect on cell death, which is of high interest. This indicates that it might be possible to uncouple inhibition of cytokine production and induction of apoptosis (14).

**INHIBITION OF HDAC ACTIVITY SUPPRESSES EXPERIMENTAL ARTHRITIS**

Since it was demonstrated that HDACi suppress the production of proinflammatory cytokines, several studies have been performed to investigate their antiinflammatory properties in models of arthritis. Anti-type II collagen antibody-induced arthritis (CAIA) is based on the formation of immune complexes in the joints of susceptible mice. The onset of this experimental model of arthritis is highly dependent on cytokines, such as TNF-α and IL-1. Both prophylactic and therapeutic treatment of CAIA with HDACi (TSA or FK228) suppressed arthritis severity (22,23) and reduced joint pathology. Of interest, enzymes that promote joint destruction such as matrix metalloproteinases (MMP)-3 and MMP-13 were reduced compared with vehicle. It is known that these MMPs are induced by TNF-α but predominantly IL-1β. HDAC inhibition will lead to suppression of these cytokines and the resultant reduction of MMP expression or activity can account for the benefit of HDACi in models of rheumatoid arthritis.
CARTILAGE CATABOLISM

ACUTE JOINT INFLAMMATION AND PROTECTIVE EFFECT OF ITF2357 ON IL-1

JOINT INFLAMMATION

...deficient mice. They revealed that IL-1...promotes cartilage destruction by upregulation of matrix MMPs. Irreversible cartilage damage elicited by MMPs is one of the hallmarks of joint destruction in inflammatory arthritis. The role of IL-1 was underlined further by elegant studies using IL-1 deficient mice. They revealed that IL-1β is the pivotal mediator that directs chronic joint inflammation, but both IL-1α and IL-1β promote cartilage damage (29,30).

PROTECTIVE EFFECT OF ITF2357 ON ACUTE JOINT INFLAMMATION AND CARTILAGE CATABOLISM

The effects of ITF2357 on cartilage catabolism were studied in a mouse model of Streptococcus pyogenes cell wall (SCW)-induced arthritis (31). This is a predominantly macrophage-driven arthritis model, initiated by TLR2 and NOD2 triggering (32). The study was performed in a prophylactic fashion in which the compound was administered orally before an intraarticular injection of 25 μg SCW fragments (30–32). ITF2357 was given orally at 1 and 10 mg/kg at -2 hours, 6 hours, day 1 and day 2. Treatment with 1 and 10 mg/kg ITF2357 mildly suppressed joint swelling as determined by tetroic uptake at days 1 and 2 (Figure 1A, B). Since inhibition of HDAC suppressed TNFα production in vitro as well as in vivo, it is likely that the reduced joint swelling seen after ITF2357 treatment is due to lower TNFα levels. Indeed, when the local cytokine production was determined, a 45% reduction of TNF production was seen in mice treated with 10 mg/kg ITF2357 (Table 1). In line with these findings, SCW-induced joint swelling is completely absent in TNFα gene deficient mice or mice treated with neutralizing anti-TNFα antibodies (28,30).

Reduction of SCW arthritis results in a dramatic suppression of chondrocyte metabolic function as measured by the incorporation of radiolabeled 35S-sulphate into the patellar cartilage. As an example, an inhibition of chondrocyte proteoglycan (PG)-synthesis of 44% is seen in Figure 1C. Oral treatment with 1 and 10 mg/kg ITF2357 dose dependently reduced the suppression of chondrocyte PG synthesis compared with the control group (27% and 13%, respectively, versus 44% in the control group). It is known that inhibition of chondrocyte PG synthesis due to joint inflammation, progressively leads to severe cartilage damage. IL-1β appears to be the most potent cytokine studied to date with respect to chondrocyte PG-synthesis. Overexpression of IL-1β results in irreversible cartilage destruction (27). It is likely that the same modulation of IL-1 by HDACi as seen in other models of inflammation accounts for the reduced inhibition of chondrocyte PG-synthesis seen here, and hence in a protective effect against cartilage catabolism during arthritis. This was confirmed by the finding that treatment with 1 mg/kg or 10 mg/kg ITF2357 produced less IL-1β, namely 17% and 62%, respectively, compared with SCW-control animals (Table 1). Interestingly, other proinflammatory cytokines (for example, IL-1α and IFNγ) including arthritogenic ones such as IL-6 and IL-12 or chemokines MIP-1α KC were dose dependently inhibited by ITF2357, suggesting a broad antiinflammatory effect for the drug (Table 1).

In SCW-induced arthritis, influx of predominantly PMNs can be noted in the joint cavity of inflamed joints (Figure 1D). Figure 1E shows the cellular influx at day 2 of SCW-induced arthritis and demonstrates that treatment with ITF2357 (10 mg/kg) reduces the number of inflammatory cells in the joint cavity. In contrast, no protective effect was noted on PG loss from the cartilage layers with either 1mg/kg or 10mg/kg ITF2357 as measured by Safranin O staining. However, since inhibition of HDAC activity results in protection against inhibition of chondrocyte PG synthesis, the overall effect on cartilage of ITF2357 is beneficial to the cartilage structure.

ITF2357 INHIBITS SEVERE BONE DESTRUCTION IN COLLAGEN-INDUCED ARTHRITIS AND ADJUVANT-INDUCED ARTHRITIS

Since inhibition of HDAC activity by ITF2357 resulted in amelioration of acute joint inflammation and cartilage damage (improved chondrocyte proteoglycan synthesis) the effect of the drug was stud-

### Table 1. Protective effect of ITF2357 on acute joint inflammation and cartilage catabolism.

| mg/kg | TNFα | IL-1β | IL-1α | IL-6 | IFNγ | IL-12 | MIP-1α | KC |
|-------|------|-------|-------|------|------|-------|--------|----|
| 1     | -11.8 | 16.7  | 36.7  | -9.3 | 4.8  | 0.5   | 0.7    | 17.4 |
| 5     | 17.5  | 30.1  | 35.2  | 14.3 | 42.1 | 23.8  | 17.2   | 32.0 |
| 10    | 45.3  | 61.7  | 66.3  | 39.3 | 59.1 | 64.2  | 51.9   | 25.8 |

Joint inflammation was induced by injection of 25 μg SCW fragments into the right knee joint of C57/B6 mice 2 h after ITF2357 had been supplied orally (n = 5 mice per group). After 4 h, patellae with surrounding synovial tissue were isolated and cultured for 1 h at RT in RPMI 1640 medium. Cytokines were determined by Luminex bead array system. Values represent the reduction in cytokine production compared with vehicle control. A negative value indicates induction of cytokines.
In arthritis models expressing severe joint destruction (bone and cartilage), namely murine type II collagen-induced arthritis (CIA) and rat adjuvant–induced arthritis (AA), joint destruction is the hallmark of RA and one of the main targets for targeted therapies in RA.

In the CIA model, ITF2357 was administered either immediately after immunization with CII/FCA (prophylactic treatment) or 22 days after the induction of arthritis (therapeutic treatment). As shown in Figure 2A, 10 mg/kg ITF2357 given prophylactically had a suppressive effect on arthritis development (macroscopic disease activity), when compared with vehicle. Interestingly, a virtually identical effect was seen when ITF2357 (10 mg/kg) was administered in the therapeutic regimen (Figure 2B). The beneficial effects of ITF2357 treatments were demonstrated further by histopathology analysis of the joint carried out on day 35. As seen in Table 2, both inflammatory cell influx and joint destruction were decreased dramatically after exposure to 10 mg/kg/day of ITF2357, irrespective of the treatment regimen.

Since rat AA displays more severe prominent bone destruction compared with murine CIA, rats with AA were treated with 5–50 mg/kg ITF2357. Prophylactic treatment with 50 mg/kg/day showed an optimal anti-inflammatory effect when compared with vehicle control (Figure 2C). This suppressive effect was almost similar to leflunomide treatment (positive control) and resulted in strong reduction of bone pathology (data not shown).

Several reports confirmed the above findings that inhibition of HDAC strongly reduced disease severity in models of experimental arthritis (25). In line with our results, prominent protection against bone destruction was seen after treatment with HDACi (33).

**BONE PROTECTIVE EFFECT OF ITF2357**

Several preclinical studies showed that HDACi, including ITF2357, protect against severe bone destruction. TNFα and IL-1 are important cytokines that drive bone erosion in arthritis as shown in transgenic mice overexpressing human TNFα, where bone destruction was a prominent feature, and by blocking IL-1 receptors with antibodies early in the disease, which prevented bone loss. Furthermore, massive bone destruction was strongly reduced in mice transgenic for human TNFα but deficient in IL-1 (34,35). The effect of ITF2357 on bone turnover was, therefore, studied in a bone assay where bone destruction is induced by either TNFα or IL-1β (36). Calcium release from 5-day-old mouse calvaria was measured 48 hours after addi-
Inflammatory cells to the inflamed joints and proteoglycan synthesis and the influx of swelling, the inhibition of chondrocyte in particular, suppressed both acute and antiinflammatory and antidestructive effects. The results on ITF2357 presented here demonstrate that HDACi have a strong activity on lymphocytes (9).

Table 2. Histopathology evaluation of the effect of givinostat administration (10 mg/kg) on joint inflammation and tissue damages in the CIA model at day 28.

| Treatment | Periarticular score | Bone and cartilage damage | Dilatation of joint cavity | Necrotic and inflammatory deposits in the joint cavity |
|-----------|---------------------|-----------------------------|---------------------------|-----------------------------------------------------|
| Vehicle   | 2.08                | 1.50                        | 1.25                      | 1.75                                                |
| Prophylactic | 0.75                | 0.67                        | 0.58                      | 0.58                                                |
| Therapeutic | 0.83                | 0.42                        | 0.33                      | 0.50                                                |

Collectively the data from the literature and the results on ITF2357 presented here demonstrate that HDACi have a strong antiinflammatory and antiderosive effect in several models of arthritis. ITF2357, in particular, suppressed both acute and chronic arthritis. In the SCW model, joint swelling, the inhibition of chondrocyte proteoglycan synthesis and the influx of inflammatory cells to the inflamed joints were suppressed dose dependently by oral treatment with the drug. TNFα and IL-1β in the joint cavity also were reduced by ITF2357. This is consistent with the role played by the two cytokines in this model where joint swelling and cell influx are driven by TNFα, and IL-1β is crucial in the inhibition of chondrocyte PG synthesis. Inhibition of TNFα and IL-1β is not the only mechanism by which ITF2357 exerts its protective effect in the SCW model; since other proinflammatory cytokines including arthritogenic IL6 and IL12 and chemokines were downmodulated equally by the drug (Table 1).

In addition to the suppressive effect in the acute model of arthritis, ITF2357 and other HDACi are protective in models of chronic arthritis. Remarkably, the efficacy seen upon administration of the drug before arthritis induction is comparable to that obtained when the treatment begins after the onset of the disease (25,33 and Figure 2). Furthermore, as with the SCW model, HDAC inhibition reduces bone destruction in these models of chronic arthritis (33 and Table 2; see Figure 2).

Inhibition of bone resorption also was observed in vitro where ITF2357 suppressed calcium release induced in mouse calvaria by IL-1β or TNFα or other stimuli (Figure 3). Thus, not only is HDAC inhibition able to downregulate the expression of proinflammatory cytokines, it also is repressing their destructive effects on the bone. This is consistent with the results from LPS-induced activation of human PBMC where ITF2357, vorinostat and other HDACi suppress monocyte/macrophage production of TNFα, IL12, IL-1β, etc. and their activity on lymphocytes (9).

One of the critical questions for the treatment of human arthritic conditions with HDACi is whether or not sufficient circulating concentrations can be achieved by safe doses of these drugs. Approximately 500 patients with different pathologies have been treated to date with ITF2357. Safe doses range from 1.4 to 2.1 mg/kg/day. Owing to differences in the metabolic and adsorption processes, the Cmax and AUC values of a dose of 1.0 mg/kg/day ITF2357 in humans (including children) corresponds to 25–30 and 40 mg/kg/day, respectively, in rodents. Therefore the efficacious doses of 10 or 50 mg/kg/day seen here in the var-

**Final Remarks**

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**Figure 3.** IL-1β- or TNFα-induced bone resorption is inhibited by ITF2357. (A) IL-1β-induced Ca-release using the standard mouse calvaria assay. Bone resorption assay (calcium release in 48 h) from 5-day-old mouse calvaria (n = 5 per group). ITF2357 was added in a dose-range from 0 up to 1 μM. PGE2 served as positive control. IL-1β at 5ng/mL. (B) Identical for TNFα-induced bone resorption. TNFα at 1 μg/mL. Mann-Whitney U test was used for statistical analysis. *P < 0.001.

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ious models of experimental arthritis are consistent with a human use. Indeed, in a clinical trial in juvenile idiopathic arthritis (JIA), givinostat (ITF2357) was given to children at 1.5 mg/kg (in two divided doses) for 12 weeks (5). The drug was well tolerated and the overall arthritis score was suppressed in these children.

DISCLOSURE
The authors declare that they have no competing interests as defined by Molecular Medicine, or other interests that might be perceived to influence the results and discussion reported in this paper.

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