Small Molecule Drugs in Osteoporosis

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Abstract

Objectives: Using receptor activator of NF-κB ligand (RANKL) induced osteoclast differentiation on RAW264.7 as a screening tool; we synthesize and identify small-molecule inhibitors preserving immunomodulatory effects as therapeutics for rheumatoid arthritis.

Methods: Differentiation into osteoclast-like cells was examined by tartrate-resistant acid phosphatase (TRAP) staining and expression of osteoclast differentiation markers. Collageninduced arthritis (CIA) mice were administered test articles by gavages to assess its efficacy. Then clinical, histological, and biochemical parameters were assessed to determine the effects of N-(4-chloro-2-fluorophenyl)-2-hydroxybenzamide (NDMC101) on synovial inflammation and bone erosion by hematoxlin and eosin staining and Enzyme-linked immunosorbent assay (ELISA).

Results: NDMC101 markedly inhibited RANKL-induced formation of TRAP+ multinucleated cells in RAW264.7 and bone marrow macrophage cells (BMMs). Moreover, pit formation assay showed that NDMC101 significantly reduced the bone-resorbing activity of mature osteoclasts. In CIA mice, oral administration of NDMC101 reduced arthritic index and mitigated bone erosion. Serum TNF-α and IL-1β concentrations in these mice were decreased significantly at the higher dose of 62.5 mg/kg.

Conclusions: Screening of our chemical library, our findings suggest that NDMC101 inhibits osteoclastogenesis which also ameliorates paw swelling and inflammatory bone destruction. Its efficacy is associated with the inhibition of such transcription factors as NF-κB and NFATc1 as well as multiple protein kinases, including p38, ERK, and JNK. There results guarantee further clinical tests of NDMC101 for its therapeutic potential in the treatment of inflammationinduced bone diseases.

Keywords Collagen-induced arthritis . osteoclast . NFATc1 . salicylic acid