AMINO BISPHOSPHONATE (YM175) SUPPRESSES JOINT INFLAMMATION AND BONE DESTRUCTION IN RAT ADJUVANT ARTHRITIS.

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Introduction:
Rheumatoid arthritis (RA) is a chronic inflammatory disorder characterized by joint swelling, synovial inflammation and joint destruction. Currently, there is little evidence that anti-rheumatic drugs such as gold, sulphasalazine and methotrexate can change the long-term disease outcome with regard to joint destruction. It is therefore necessary to develop new agents that are effective for preventing joint destruction as well as synovial inflammation in RA. Many bisphosphonates have been developed as promising agents for the therapeutic correction of enhanced bone resorption seen in miscellaneous bone disease, such as Paget’s disease, tumoural osteolysis, tumoural hypercalcaemia and osteoporosis. Several papers have reported that pamidronate lessened the development of periarticular erosions in RA (1). Some non-amino bisphosphonates, such as etidronate, clodronate, tildronate and risedronate, have been shown to inhibit bone destruction in rat adjuvant arthritis (AA), an animal model of rheumatoid arthritis. Bisphosphonates may be effective for prevention of the progressive bone destruction seen in cases of RA.

Disodium dihydrogen (cyclohexylamino) methylene-1, 1-bisphosphate monohydrate (YM175) is one of a new generation of bisphosphonates, in which a portion of the amino group in the side chain is substituted by a heptacyclic side chain. It has been reported that the inhibitory effect of YM175 on bone resorption in rat hypercalcemia models is stronger than that of pamidronate or alendronate. To our knowledge, however, there have been no reports concerning the effect of YM175 in rat adjuvant arthritis (AA), an animal model of rheumatoid arthritis. Bisphosphonates may be effective for prevention of the progressive bone destruction seen in cases of RA. The present study was designed to investigate the effects of YM175 on arthritis-related bone resorption in rat AA. This study may also provide some clarification with regard to the mechanism of bisphosphonate action.

Methods:
Thirty-five female Lewis rats, 7 weeks of age, were randomly allocated into 5 groups (7 rats/group). Four groups were given an intradermal injection of heat-killed Mycobacterium butyricum for induction of AA. In the three YM175-treated (0.01, 0.1 and 1 mg/kg/day) AA groups, YM175 was injected subcutaneously every day from day 0 (day of immunization with the adjuvant) to day 42 (end of the experiment). The effects of YM175 in AA rats were evaluated according to the arthritis score, hind paw volume, radiological index and histological examinations. All measurements are shown as mean±SEM. The Mann-Whitney U-test was used to analyse each set of variables. Differences were considered significant when p<0.05. This experiment was reviewed by the Committee of the Ethics on Animal Experiment in Graduate School of Medical Sciences, Kyushu University.

Results:
YM175 suppressed the joint inflammation and bone destruction in rat AA in a dose-dependent manner. YM175 at doses of 0.01, 0.1 and 1 mg/kg inhibited the hind paw volume by 27%, 34% and 39% on day 26 (The hind paw volume of the positive control peaked on day 26), the radiological index by 31%, 52% and 79% on day 42, respectively, compared to that of the positive control (p<0.01, n=14). The histopathological changes in rat AA were also prevented by YM175 in a dose-dependent manner. The number of TRAP-positive cells (osteoclasts and preosteoclasts/osteoclast precursors) in bone marrow spaces and granulation tissue in the YM175-treated groups was reduced, dose-dependently.

Discussion:
The present study demonstrated that YM175 suppressed not only bone destruction, but also joint inflammation in rat AA. However, other studies have demonstrated that amino bisphosphonates, including pamidronate, alendronate and YM175, are ineffective against inflammation in collagen-induced arthritis in the rat or mouse (2, 3). These contrasting findings could be attributable to differences in the structure of the agents, the method of administration or the animal models used. The precise mechanism behind the anti-inflammatory effect of YM175, has not yet been fully clarified.

On the other hand, we found that YM175 reduced the number of TRAP-positive cells (as a marker of osteoclasts and preosteoclasts/osteoclast precursors) in a dose-dependent manner in AA rats. As far as we are aware, this is the first report to demonstrate that bisphosphonates inhibit osteoclastic formation in vivo either directly or indirectly. This finding is consistent with other studies that YM175 inhibited multinuclear TRAP-positive cell formation in mouse bone marrow cultures (4). We obtained similar result in rat bone marrow culture system. We propose that the inhibition of osteoclastic formation could be one of the mechanisms of suppressed bone resorption by bisphosphonates. In contrast, other investigators have reported that alendronate, an amino bisphosphonate, increased both the number and the size of osteoclasts in the tibiae of normal mice, although bone resorption was inhibited by this bisphosphonate (5). The discrepancy in the effects of these two bisphosphonates on osteoclastic formation may be due to differences in the structure of the agents, the method of administration or the animal models used, although YM175 shares an amino residue with alendronate.

In summary, the present study demonstrated that YM175 suppressed not only bone destruction by inhibiting osteoclastic formation either directly or indirectly, but also joint inflammation in rat AA. On the basis of these results, we propose that the ability of YM175 to ameliorate the pathological changes of AA in rats warrants further evaluation with regard to the treatment of various arthritic conditions, including human RA. YM175 could be a potentially useful drug for the treatment of rheumatoid arthritis.

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References: