INHIBITION OF OSTEOLYSIS BY BISPHOSPHONATES IN A CONTINUOUS PARTICLE INFUSION MODEL

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Introduction:

Many total joint replacements are performed in the world these days. While they have contributed to the treatment of arthritis for release of agony and deformation, revision arthroplasties are increasing because of the osteolysis and the aseptic loosening which are the leading causes for the late failure of joint replacements. It appeared that the prostheses after arthroplasties have finite life spans and eventually fail. The bone-resorbing cytokines released from the macrophages that phagocytosed polyethylene wear particles from the bearing surface stimulate osteoclastic bone resorption, and the inflammatory foreign body reaction leads to peri-implant osteolysis and eventually to loosening of the components.

It is reasonable that the development of inhibition of osteolysis and aseptic loosening makes not only the release of patient’s agony from multiple operations but also economizing a large amount of medical expenses.

Our present study aimed to examine the inhibitory effect of novel bisphosphonates, TRK-530 and Incadronate (YM-175), on the bone resorption in a rat osteolysis model given the continuous infusion of high-density polyethylene (HDPE) particles in the knee joint, and the differences of effect among no-medication, preventive medication, and treatment medication.

Method:

Experimental procedure: Fifty-five female Wistar rats at 10 weeks of age were used. We treated the animals in a humane manner and the investigation was approved by the institutional animal care committee. The animals were randomized into a vehicle group, TRK-530 group, or Incadronate group. In addition, the TRK-530 group and Incadronate group were separated into prevention groups or treatment groups. In the treatment groups, we started to administer from the fifth week, because we have noticed that the osteolysis on radiograph in this model appeared after four weeks of the operation in a previous study (1), and we thought it clinical timing to begin medication generally. In each rat, a cement implant was placed in the distal part of the right femur, and HDPE particles (mean diameter of 2±1µm) were continuously infused into the knee joint through an implantable pump. The osmotic pump was filled with 200µl of rat serum containing 0.1mg of polyethylene particles (1.33×10^5 particles), and was implanted subcutaneously in the back of a rat. The infusion rate was already set for 0.5µl/h.

On the day after the operation, the animals were subcutaneously injected with saline for eight weeks (vehicle group), 1 mg/kg of TRK-530 or 0.1 mg/kg Incadronate for eight weeks at three times a week (prevention group), or saline for first four weeks and same quantity of TRK-530/Incadronate from the fifth week through the eighth week (treatment group). The rats were euthanized at eight weeks after the operation. The right hind femurs were removed en bloc, and the soft tissues were removed.

Radiological examination: Anteroposterior (AP) radiograph was taken of each treated femur at the time of sacrifice, and was examined for the evidence of endosteal erosion, focal bone lysis, and trabecular bone loss. We defined the presence of osteolysis on the basis of these findings. They were also examined for the evidence of sclerosis of the periprosthetic bone. The radiographs were compared for osteolysis by three independent observers who were blind to the animal group.

Histomorphometric analysis: After fixation and demineralization, the dehydrated specimens were embedded in paraffin, and the horizontal cross sections were cut at a uniform depth of 3 mm proximal to the articular surface of the femur. They were stained with hematoxylin and eosin. The percentage of bone area around the cement implant was measured using computer image analysis. Then the average bone stock was calculated for each group. Addition to that, the ratio of surrounding length of reactive thick membrane to circumference around the cement implant was compared to investigate growth of inflammatory reaction.

Results: Radiographic study: At the time of sacrifice, focal osteolysis, endosteal erosion, or trabecular bone loss were observed in 83.3% of the vehicle group examined after 8 weeks. On the other hand, the cases with such changes were few in both of the treatment groups, TRK-530 and Incadronate. In the prevention groups, osteolysis was still less than the treatment groups, especially, there was no case with osteolysis in Incadronate group (Fig.1).

While the sclerosis of the periprosthetic bone was observed in none of the vehicle group, such change was observed in some of the treatment groups. In the prevention group, it was estimated that much more cases showed bone sclerosis around prosthesis (Fig.2).

Histomorphometric study: The average of the bone area in the vehicle group around the cement implant was 11.53%. The average of the periprosthetic bone increased slightly in the treatment groups. On the other hand, the prevention groups had distinct differences in the periprosthetic bone volume. The bone volume around the implant was significantly more in the prevention groups compared with the vehicle group (TRK-530:p<0.002 / Incadronate:p<0.0001) and the treatment groups (TRK-530:p=0.02 / Incadronate:p<0.0001) (Fig.3).

In the vehicle group, we observed the increase of fibrous membranes with infiltration by inflammatory cells between the trabecular bone and the cement implant. The periprosthetic bone was infiltrated by a fibrous membrane and destroyed. On the histological studies, the inflammatory response and osteolysis were recovered slightly in the treatment groups and the prevention groups. We could not find significance among them, however, the interface membrane around the implant was most in the vehicle group in those groups, and tended to be more in the treatment groups than the prevention groups.

Discussion:

The characteristic of this in vivo model is that the animal is supplied with the continuous infusion of polyethylene particles into the joint (1). Adopting this model, we have already reported that TRK-530-treated rats, which are equivalent for the prevention group in the present study, showed significantly less osteolysis and less growth of inflammatory membranes compared with the vehicle rats in the previous study (2). The radiographs and the histological results obtained in the present study demonstrated that the preventive rats by bisphosphonates showed less osteolysis when compared with the vehicle group and the treatment groups. The growth of inflammatory reaction tended to be less in the prevention groups than the vehicle group and the treatment groups.

These results showed that the medication by these bisphosphonates is effective for the formation of inflammatory periprosthetic osteolysis induced by particles, and they may be more useful in the preventing administration from the operation than the treatment one after appearing of osteolysis.

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References