A187 CLASS EFFECTS OF TYROSINE KINASE INHIBITORS ON OSTEOCLASTOGENESIS IN VITRO

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Background/objectives Bone destruction in rheumatoid arthritis (RA) is mediated by osteoclasts (OCs). Imatinib, a tyrosine kinase inhibitor (TKI), has been shown to exert an inhibitory effect on osteoclastogenesis. The aim of this study was to investigate the effects of novel TKIs other than imatinib, namely dasatinib, inno 406 and sunitinib on osteoclastogenesis including the generation of OC precursors (pOCs) and the fusion of pOCs into mature OCs. The authors also wished to assess, whether TKIs also affect the bone resorbing capacity of mature OCs.

Material and methods The impact of TKIs on in vitro OC formation was assessed, including the number of OCs, generation of pOCs and the number of OC nuclei. Apoptosis of pOCs was measured by annexin V staining. The influence of TKIs on the mRNA expression of OC effector molecules was investigated by quantitative PCR. The effect of TKIs was also assessed in pit resorption assays.

Results The authors demonstrate that all four TKIs (imatinib, dasatinib, inno 406, sunitinib) have a pronounced inhibitory effect on the formation of pOCs. Moreover, all of them show a dose-dependent inhibition of OC numbers at clinically relevant concentrations. Furthermore, TKIs inhibit the bone resorbing capacity of OCs. Annexin V labelling has demonstrated that TKIs do not induce apoptosis in pOCs. In addition, imatinib and inno 406 also reduce the mRNA levels of OC effector molecules cathepsin K and matrix metalloproteinase 9, which are important for extracellular matrix degradation.

Conclusions These data show that various TKIs potentially inhibit osteoclastogenesis and therefore might be able to prevent joint destruction in patients with RA or other diseases associated with increased bone loss, such as osteoporosis.