A183 IN VITRO ACTIVITY OF P38 MAPK INHIBITOR-LOADED PARTICLES FOR THE LONG TERM INTRA-ARTICULAR TREATMENT OF OSTEOARTHRITIS

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Background and objectives Osteoarthritis (OA) is the most frequent rheumatic disease and this chronic disease still represents a largely unmet medical challenge. Cartilage damage observed in OA is related to the presence of cytokines with pro-inflammatory and catabolic actions. Mitogen activated pathway kinases (MAPK) intervene in the regulation of cytokine expression and in the intracellular signals induced by cytokines. Thus, the intra-articular administration of MAPK inhibitors may be of interest for the treatment of OA and may also potentially reduce the risk of side effects related to the systemic administration of these drugs.
The purpose of this work was to formulate nanoparticles and microparticles loaded with VX-745 or SB203580 (two p38 MAPK inhibitors) exhibiting extended release properties and to test their activity on human fibroblast-like synoviocytes (FLS) in vitro.
Materials and methods *Formulation and characterisation of particles*: Poly(lactic-co-glycolic acid) biodegradable VX-745- or SB203580-loaded particles of three different sizes were produced by emulsification/evaporation. After preparation, particles were purified and freeze-dried. *In vitro studies*: In vitro activity was assessed on two human FLS lines. Cell viability was measured by MTT test and bioactivity evaluated by interleukin 6 (IL-6) production after IL-1β activation. Statistical analysis was performed using Student's t test.
Results Blank, VX-745- and SB203580-loaded particles ranging from 300 nm up to 30 µm were produced. FLS viability was not decreased by blank nanoparticles and microparticles, by VX-745 and by SB203580 solubilised in dimethyl sulfoxide or in loaded particle formulation.
IL-6 production by resting FLS was not induced by drug-free particles. For inhibition experiments, FLS were stimulated with IL-1 (1 ng/ml) and treated with control or VX-745 loaded particles. 100% theoretical release of the p38 inhibitor was used to determine particle loadings. IL-6 production was inhibited by VX-745-loaded particles in a dose-dependent and size-dependent pattern. For instance, at a drug concentration of 800 nM, VX-745-loaded particles significantly inhibited the IL-6 release down to 44%±2.1%, 58%±1.3% and 65%±4.1% of controls for 25-, 2.5 µm microparticles, and nanoparticles, respectively. The significantly higher inhibition obtained by the nanoparticles formulation compared to microparticles formulation reflected a more rapid release of the VX-745, reaching a higher effective concentration at 24 h. This suggests that the extended release of the inhibitor can be controlled by modulating particle size.
Conclusion Based on these in vitro studies, VX-745-loaded nanoparticles and microparticles display differential extended release properties. Further in vitro and in vivo experiments are ongoing to test these promising novel formulations in different models of rheumatic diseases.
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