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New treatment strategies for growth failure caused by chronic inflammation in children

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ABSTRACT

Chronic inflammation during childhood often leads to impaired bone growth and reduced height in adulthood. Interleukin-1 β (IL-1 β), interleukin-6 (IL-6) and the tumour necrosis factor- α (TNF- α) are pro-inflammatory cytokines up-regulated during chronic inflammation. At the same time, experimental studies indicate that those cytokines affect growth by interfering with the Growth Hormone (GH)/Insulin-like Growth Factor I (IGF-I) axis. Moreover, IL-1 β and TNF- α decrease murine bone growth in vitro by acting at the growth plate level.

To counteract growth retardation in children with severe forms of JIA, GH therapy has been used, with beneficial effects on growth and final height in some patients. On the other hand, the introduction of biologic agents has revolutionized the treatment of rheumatoid arthritis in children and adults. Anti-TNF therapy not only decreases disease activity but may also improve growth in some juvenile idiopathic arthritis (JIA) patients. However, there is still a group of children in which the GH or anti-TNF therapy does not affect growth positively. For this reason, it is necessary to investigate new treatment strategies to prevent and/or treat growth failure in those patients.

First, the effects of TNF- α antagonism on longitudinal growth in paediatric JIA patients were studied, differentiating any response from the normal pubertal growth spurt. From this study it can be concluded that TNF inhibition with etanercept (TNF soluble receptor) improves growth in a majority of JIA patients independent of puberty. Nevertheless, there are still patients who do not respond to TNF-inhibition and therefore are in need of alternative treatment modalities to optimize their growth.

In the second study, it was hypothesized that biologic agents may rescue foetal rat metatarsal bones from cytokine-induced growth impairment and that IGF-I may potentiate such an effect. Indeed, both anakinra (IL-1 receptor antagonist) and etanercept efficiently and dose-dependently prevent cytokine-induced bone growth impairment in cultured bones. Combinations of anakinra or etanercept with IGF-I further improved bone growth.

In the third study, it was found that IL-1 β and TNF- α are produced by growth plate chondrocytes and that both cytokine antagonists improve growth of cultured foetal rat metatarsal bones suggesting that these cytokines play a physiological role in the normal regulation of longitudinal bone growth.

In the fourth study, the local effects of IL-6 on growth plate chondrocytes of foetal rat metatarsal bones were studied. It was found that in the presence of its receptor, IL-6 decreases in vitro bone growth and it further suppresses growth when combined with IL-1 β or TNF- α . Furthermore, IL-6 is produced by growth plate chondrocytes in vitro after stimulation with IL-1 β +TNF- α , which may partially explain the synergistic inhibitory effect of those cytokines on murine bone growth.

In conclusion, pro-inflammatory cytokines, normally up-regulated in children suffering from chronic inflammatory diseases, act in a synergistic way targeting growth plate chondrocytes and thereby decrease longitudinal bone growth. Biological agents blocking the actions of pro-inflammatory cytokines may improve bone growth.