DOCTORAL THESIS

Toward precision medicine: a combination of leflunomide and ligustrazine attenuates progressive bone erosion in rheumatoid arthritis patients with high baseline serum c-reactive protein level

He, Bing

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Abstract

Leflunomide is widely prescribed for Rheumatoid Arthritis (RA) patients in China. However, a number of RA patients still demonstrated progressive bone erosion (PBE+) after receiving Leflunomide in our clinical data. Moreover, the PBE+ is predicted by high baseline serum CRP level (CRP^{BH}). Further, the changes of serum bone resorption marker (Tartrate-resistant acid phosphatase 5b, TRAP5b) strongly correlated with those of CRP in PBE+ RA patients during Leflunomide treatment. Those were consistently observed in collagen-induced-arthritis (CIA) rats. To precisely address the issue, we screened a series of marketed drugs combined with Leflunomide to inhibit CRP production and CRP-related osteoclastic signaling pathway using bioinformatics analysis. Ligustrazine was postulated as an optimal candidate drug. *In vitro* studies demonstrated that the combination of Ligustrazine and Leflunomide not only suppressed hepatic CRP production, but also suppressed CRP-related osteoclastic signaling and osteoclast activities. *In vivo* studies showed that the combination attenuated bone erosion in CIA rats. Further, the randomized parallel controlled clinical trial in 120 CRP^{BH} RA patients showed that the combination therapy reduced serum CRP levels and attenuated bone erosion in those patients (ChiCTR-TRC-10001014). Together, this work presents a precision combination therapy for PBE+ in CRP^{BH} RA patients.

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