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 (CRPBH). 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 CRPBH 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 CRPBH RA patients.
# Table of Contents

Declaration ...................................................................................................................... I

Abstract ........................................................................................................................... II

Acknowledgements .......................................................................................................... III

List of Figures .................................................................................................................. VIII

List of Tables ................................................................................................................... XI

List of Abbreviation ......................................................................................................... XII

Chapter 1  Introduction ................................................................................................. 1
  1.1 Brief Introduction of Combination Therapeutics .................................................... 1
  1.2 Drug Selection in Combination Therapeutics ........................................................ 9
  1.3 The Mechanisms of Combination Therapeutics ................................................... 13
  1.4 The Challenges in Combination Therapeutics ...................................................... 20
  1.5 Computational Approaches in the Discovery of Combination Therapeutics .......... 22
  1.6 Conclusions .......................................................................................................... 25

Chapter 2  High Baseline Serum CRP Level (CRP^{BH}) in RA Patients Predicts the Failure of Leflunomide in Attenuating the Progressive Bone Erosion (PBE+) .................................................................................................................. 28
  2.1 Introduction ............................................................................................................. 28
  2.2 Materials and Methods ......................................................................................... 29
    2.2.1 Study Design .................................................................................................. 29
    2.2.2 Patients .......................................................................................................... 31
    2.2.3 Radiological Evaluation by Modified Sharp Score ........................................ 32
    2.2.4 Human Serum Assay ...................................................................................... 33
    2.2.5 Animal Handling ............................................................................................ 34
    2.2.6 Collagen-induced Arthritis Rats ..................................................................... 34
    2.2.7 MicroCT Analysis .......................................................................................... 36
    2.2.8 Bone Histomorphometric Analysis ............................................................... 37
    2.2.9 Tartrate-Resistant Acid Phosphatase (TRAP) Staining .................................... 38
Chapter 6  A combination of Ligustrazine and Leflunomide decreased serum CRP level and attenuated bone erosion in RA patients with high serum CRP at baseline (CRP_{BH}).

6.1  Introduction

6.2  Materials and Methods

6.3  Results

Chapter 7  Discussion

References

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