

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

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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.

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

2.2.10	Statistical Analysis.....	39
2.3	Results	40
Chapter 3	Ligustrazine Postulated by Bioinformatics as The Candidate Drug Combined with Leflunomide to Inhibit CRP-Related Events.....	53
3.1	Introduction	53
3.2	Materials and Methods	55
3.2.1	Study Design	55
3.2.2	CRP Transcriptional Regulatory Network.	55
3.2.3	CRP-related Osteoclastic Signaling Network.....	56
3.2.4	RA Drugs and Drug Targets.....	57
3.2.5	Combined Drug Effects on CRP Production.	57
3.2.6	Combined Drug Effects on CRP-related Osteoclastic Signaling.....	58
3.2.7	Safety Estimation of Combined Drugs	59
3.3	Results	60
Chapter 4	A combination of Leflunomide and Ligustrazine decreased CRP production in Hep3B cells and blocked CRP-related osteoclastic signaling pathway in osteoclasts.	65
4.1	Introduction	65
4.2	Materials and Methods	66
4.2.1	Study Design	66
4.2.2	Cell Culture.....	67
4.2.3	Q-PCR Analysis.....	68
4.2.4	Western Blot Analysis	70
4.3	Results	70
Chapter 5	A combination of Leflunomide and Ligustrazine decreased serum CRP level and attenuated bone erosion in CIA rats with high serum CRP level at baseline (CRP ^{BH}).....	76
5.1	Introduction	76
5.2	Materials and Methods	77

5.2.1 Study Design	77
5.2.2 Animal Handling	78
5.2.3 Collagen-induced Arthritis Rats	78
5.2.4 MicroCT Analysis	80
5.2.5 Tartrate-Resistant Acid Phosphatase (TRAP) Staining	81
5.2.6 Bone Histomorphometric Analysis Related to Bone Resorption	82
5.2.7 Statistical Analysis	83
5.3 Results	83
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})	93
6.1 Introduction	93
6.2 Materials and Methods	94
6.2.1 Study Design	94
6.2.2 Sample Size Determination	97
6.2.3 Radiological Evaluation by Modified Sharp Score	98
6.2.4 Human Serum Assay	98
6.2.5 Statistical Analysis	100
6.3 Results	104
Chapter 7 Discussion	113
References	115
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