Colchicine and Bortezomib co-administration reduce the NF-κB and MMP13 expression as markers for osteoarthritis-associated inflammation: an experimental study

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INTRODUCTION:

Osteoarthritis (OA), a leading cause of disability worldwide, is characterized by articular cartilage degeneration, angiogenesis, subchondral bone sclerosis, and synovitis. Both cartilage and surrounding soft tissues may contribute to the pathogenesis of OA. Catabolic factors, including immune cells, proteases, and pro-inflammatory cytokines, have been detected in the synovium and are believed to play a pivotal role in cartilage degeneration through OA. Despite recent investigations, many gaps remain in understanding the biological mechanisms involved in the pathogenesis of OA.

Colchicine, an alkaloid extracted from autumn crocus plants, is believed to possess anti-inflammatory/fibrotic activity with a well-documented therapeutic effect against gout. On the other hand, bortezomib is a proteasome inhibitor routinely employed to treat multiple myeloma. It also inhibits T cells associated with pro-inflammatory cytokines in patients with rheumatoid arthritis (RA) and bone erosion/joint inflammation in adjuvant-induced RA mice models (Figure 5). Inhibition of NF-κB and MMP13 secretion by colchicine and bortezomib can be associated with improving OA symptoms. OA is a highly debilitating disease with no known effective treatment; hence, there is a need to identify more effective treatments for OA. No prior study has investigated the simultaneous effect of colchicine and bortezomib in the treatment of OA. Given the significant role of the nuclear factor-kappaB (NF-κB) in the regulation of pro-inflammatory mediators in arthritis, we aimed to evaluate the anti-inflammatory effects of two drugs (colchicine and bortezomib) through the inhibition of NF-κB.

METHODS:

OA was induced in thirty-six male Sprague-Dawley rats by anterior cruciate ligament transection with medial meniscus resection in week eight. Using a random table of numbers, animals were then randomly allocated to four treatments in the 12th week: 1) colchicine, 2) bortezomib, 3) a combination of colchicine and bortezomib, and 4) saline (control group) (Figure 1). The first group received 0.5 mg/ml intraarticular colchicine twice weekly for three consecutive weeks (6 injections). The second group received 0.25 mg/ml intraarticular bortezomib twice weekly for three consecutive weeks (6 injections). The third group received both medications intraarticularly. The fourth group, the control group, was subjected to normal saline injections with the same protocol. All rats were sacrificed by intraperitoneal injection of pentobarbital sodium (390 mg/mL). The tissues were evaluated using the Osteoarthritis Cartilage Histopathology Assessment (OARSI) score, the Mankin cartilage histopathology assessment system, and the Krenn criteria for graded synovitis (Figure 2). NF-κB and matrix metallopeptidase 13 (MMP13) expression levels were measured.

SPSS version 29 software and GraphPad Prism 9 were used for data analysis. The chi-square or Fisher's exact test was applied to compare qualitative variables. Independent one-way ANOVA and the Kruskal-Wallis test were employed to analyze variables with and without normal distribution, respectively. Pearson or Spearman tests were used to evaluate the correlation between continuous variables. A Bonferroni-adjusted p-value of less than 0.05 was defined as significant.

RESULTS: The group that received a combination of colchicine and bortezomib showed better outcomes on both OARSI and Mankin assessments than the control group (p-value = 0.005). The synovial membrane inflammation score did not differ between the groups (p-value = 0.322). Compared to the control group, OARSI was significantly lower for the bortezomib + colchicine group (p-value = 0.035) (Figure 3). Co-administration of the drugs significantly lowered the NF-κB levels compared to the control and colchicine groups (p-value = 0.017). Compared to the control group, the MMP13 levels were lower in the combination group (0.67 ± 0.11 versus 1.03 ± 0.11, p-value = 0.044) (Figure 4). There was a significant correlation between MMP13 and NF-kB levels (r = 0.587, p-value = 0.045).

DISCUSSION AND CONCLUSION: Co-administration of colchicine and bortezomib is a promising treatment method for OA that lowers the expression levels of MMP13 and NF-κB and reduces the resultant cartilage degradation.

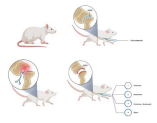

Figure 1. Osteoarthritis induction and treatment groups (Created with BioRender.com)

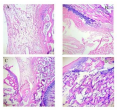

Figure 2. Histopathology of all 4 groups shows that the Colchicine + Bortezomib group has rare inflammatory cell inflammation (D). In contrast, in the control group, the inflammatory cells are evident (A), and also, in the colchicine group (B) and bortezomib group (C), the inflammation has been reduced but not as much as in the main group.

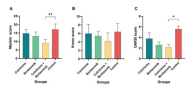

Figure 3. Differences in Mankin, Krenn, and OARSI scores between 4 groups

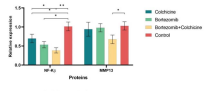

Figure 4. MMP13 levels between the four groups

Figure 5. Effects of Bortezomib and Colchicine on the inflammatory pathways in osteoarthritis. (Created with BioRender.com)