Exploring Talarozole as a Novel Therapeutic Approach for Osteoarthritis: Insights From Experimental Studies

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Clinical Medicine Insights: Arthritis and Musculoskeletal Disorders
Volume 17: 1–2

DOI: 10.1177/11795441231222494

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ABSTRACT: Osteoarthritis (OA) is a prevalent degenerative joint disease characterized by the slow degeneration of joint components that primarily affects the elderly. There is currently no cure for OA; thus, treatment focuses on symptom reduction. This article investigates the potential of talarozole, a retinoic acid metabolism-blocking agent (RAMBA), as a new treatment for hand OA. Talarozole showed promising results by inhibiting retinoic acid degradation and increasing its levels in the body. Six hours after destabilization of the medial meniscus, talarozole significantly reduced inflammation in mice's cartilage. The findings underscore the importance of the protein encoded by the ALDH1A2 gene in retinoic acid metabolism, shedding light on its potential implications for the management of OA. Maintaining adequate retinoic acid levels may help to reduce mechano-inflammatory gene regulation. Furthermore, RAMBAs like talarozole may emerge as disease-modifying OA therapies, promising improved symptom control and slower disease progression. In conclusion, this research provides critical genetic insights into severe hand OA and promotes talarozole as a prospective therapy option. These findings pave the door for additional research that could revolutionize OA treatment by targeting retinoic acid metabolism to reduce symptoms and slow disease progression.

KEYWORDS: Osteoarthritis, talarozole, RAMBA, ALDH1A2 gene

RECEIVED: July 18, 2023. **ACCEPTED:** December 7, 2023.

TYPE: Correspondence

FUNDING: The author(s) received no financial support for the research, authorship, and/or publication of this article.

COMPETING INTERESTS: The author(s) declare that there is no conflict of interest.

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The most common type of arthritis, osteoarthritis (OA), primarily affects the elderly. While joint soreness and stiffness are common symptoms, understanding of its course has progressed beyond a simple linear decline.[1] Osteoarthritis is increasingly recognized as a multidimensional disorder characterized by complicated alterations in joint tissues, rather than being only the result of wear and strain.[1] Osteoarthritis development is complicated by a number of factors, including aging, obesity, prior joint injuries or operations, repetitive motions, joint anatomical abnormalities, and genetic predisposition.[1] Osteoarthritis typically affects the hands, hips, and knees, and forecasts show that the incidence of knee OA will raise globally, affecting an estimated 250 million people.[2,3] According to the Centers for Disease Control and Prevention (CDC), approximately 32 million people in the United States with OA, with the hands being among the most commonly affected body parts. Despite not being weight-bearing joints, hand OA affects about 27% of the population and can affect up to 80% of older persons. Due to pain and a lack of hand function, the illness causes severe impairment.[4] Osteoarthritis symptoms frequently appear nonlinearly, affecting one or more joints. While joint soreness may lessen with rest, it might worsen at night, and people typically have morning stiffness that lasts less than 30 minutes. Osteoarthritis can cause limited joint motion, structural changes, localized edema, and a general sensation of joint instability.[1]

Osteoarthritis currently has no known cure; thus, treatment focuses on symptomatic management. Increased physical activity, physical therapy with exercises to strengthen the muscles, weight loss if necessary, medication like painkillers, and the use of crutches or canes are some of the therapies used by doctors.[2] When all other forms of treatment fail, surgery is considered. Self-management techniques are essential for lowering OA-related pain and disability.[2] Given the limited number of available treatments, efforts are being made to identify novel therapeutic strategies. For hand OA, researchers are investigating new treatments, like the medication talarozole (TLZ).[4]

The foundation of their exploration into the genetic underpinnings of severe hand OA was rooted in the findings of a groundbreaking Icelandic study in 2014. The investigation discovered a key relationship between polymorphic ALDH1A2 gene variations and an increased risk of severe hand OA. The researchers performed a genome-wide association analysis (GWAS) using 623 Icelanders with severe hand OA as cases and 69 153 people as population controls to further understand the genetic components linked to severe hand OA.[5] They discovered 34.2 million sequence variants by whole-genome sequencing 2230 Icelanders, and they subsequently evaluated these variants for associations with severe hand OA.[5] The common variant at 15q22, represented by rs12907038[G], and the rare variant at 1p31, both of which are situated in the same linkage disequilibrium (LD) block as the ALDH1A2 gene, were found to have the strongest connections.[5] The research team at the University of Oxford in the United Kingdom began their investigation by using information from the UK Biobank and validating earlier findings from the aforementioned Icelandic study.[4]

Zhu et al investigated TLZ, a retinoic acid metabolism-blocking agent (RAMBA), in light of these genetic findings. Talarozole functions by inhibiting the breakdown of retinoic acid and elevating its levels within the body. This is significant because the protein encoded by the ALDH1A2 gene is in

charge of turning retinaldehyde into all-trans retinoic acid (atRA). A careful balance between production and degradation allows for the maintenance of this active vitamin A metabolite at low quantities. All-trans retinoic acid is eliminated via hydroxylation by the (Cytochrome P450) CYP26 enzymes, specifically CYP26A1, CYP26B1, and CYP26C.[4]

In a sizable UK cohort, the prevalence of ALDH1A2 allelic variants—first identified in the Icelandic population—has been linked to hand OA.[4] Furthermore, based on ALDH1A2 genotype and gene dosage classification, RNA sequencing of hand OA cartilage has shown differential regulation of cellular networks and called attention to atRA as a possible anti-inflammatory molecule in articular cartilage.[4] These findings show that by inhibiting atRA cellular metabolism with drugs like TLZ during cartilage injury, one can minimize mechano-inflammatory gene regulation. In addition, in vivo research done on mice with surgically induced OA has shown that limiting atRA metabolism involves modulating (Peroxisome proliferator-activated receptors) PPARγ, a mechanism that controls inflammation, in addition to preventing structural joint deterioration.[4]

The scientists investigated the anti-inflammatory effects of TLZ in a surgical-induced OA model in mice and ex vivo pig cartilage injury. The medicine considerably decreased inflammation in mice's knee joints within 6 hours after destabilization of the medial meniscus (DMM), and it also significantly reduced osteophyte development and cartilage degeneration 26 days after DMM. Due to its capacity to raise retinoic acid levels and reduce inflammation, TLZ—which had previously passed clinical testing for treating psoriasis and a rare congenital skin condition—showed from early experimental evidence that there is a potential for additional exploration in the setting of hand OA.[4] These results open the door to more investigation and new therapeutic approaches for those with hand OA.

According to the research, retinoic acid likely plays a significant role in how different tissues respond to damage. RAMBAs offer promise as possible disease-modifying drugs for the treatment of OA, since preliminary research suggests that boosting atRA levels may have the capacity to reduce mechanoinflammation in articular cartilage, both in vitro and in vivo.[4] It is important to highlight, however, that more research is needed before contemplating this treatment for OA in human patients. These findings pave the way for further research and the development of therapy options focused at targeting atRA metabolism to address the signs and symptoms of OA and potentially decrease its progression.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Acknowledgements
None.

Author Contributions
Laraib Iqbal: Investigation; Writing—original draft.**Ushna Zameer**: Conceptualization; Data curation.**Maheen Iqbal Malick**: Writing—original draft; Writing—review & editing.

Availability of data and materials
Not applicable.

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