Effects of Zeel T (Ze14) on knee osteoarthritis at a molecular level

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The full title of the original publication is:
Reduction of Matrix Metallopeptidase 13 and Promotion of Chondrogenesis by Zeel T in Primary Human Osteoarthritic Chondrocytes (2021)

Key findings

- Experiments on knee cartilage cells (chondrocytes) derived from patients with osteoarthritis (OA) demonstrated that Zeel T **reduces several characteristics of OA** in a multitarget way:
  - Zeel T **supports cartilage matrix formation (chondrogenesis)** by increasing the synthesis of type II collagen, one of the main components of articular cartilage
  - At the same time, Zeel T possibly reduces MMP-13 which is central to type II collagen breakdown and thereby **may prevent cartilage degradation**.

What did the study look at?

- **Osteoarthritis (OA)** is a disease that affects all the tissues of the joint, including the cartilage, bone, ligaments, synovium, and muscles. The disease is complex and driven by an imbalance between the formation and breakdown of cartilage components. Enzymes such as matrix metalloproteinases (MMPs) and aggrecanases are more abundant or become overactive in OA, breaking down collagen and other cartilage components. Over time, this results in abnormal anatomic and/or physiologic changes to the joint, such as the breakdown of cartilage, joint inflammation, bone thickening, and the appearance of osteophytes, leading to the loss of normal joint function. This causes joint pain, stiffness, and swelling.

- **Cartilage** homeostasis is maintained by chondrocytes, the unique cells of cartilage. Especially the degradation of cartilage is central to the pathological process of OA. Some important components of the cartilage and their roles in OA are the following:
  - **Aggrecan** is the main proteoglycan of articular cartilage.
  - **Type II collagen** is one of the main components of healthy cartilage and can be broken down by an enzyme called matrix-metallopeptidase-13 (MMP-13).
  - **Matrix-metallopeptidase-13 (MMP-13)** is a specific enzyme central to cartilage breakdown. It is a major enzyme involved in the degradation of type II collagen and is significantly more present in the articular cartilage of OA patients.

- **Cellular communication network factor 1 (CCN1)** is a protein involved in type II collagen and aggrecan production and also inhibits the enzyme A Disintegrin And Metalloproteinase with ThromboSpondin motifs (ADAMTS-4).
- **ADAMTS-4** is an important enzyme involved in aggrecan breakdown.

- **Zeel T (Ze14)** is a medicinal product made from 14 natural ingredients and is used for the treatment of arthrosis/OA, and/or rheumatic joint disease and for the relief of symptoms such as joint pain and stiffness.
- **The goal** of the study was to gain more insights into Ze14's mode of action in OA by identifying changes in the transcriptomic profile of human OA chondrocytes treated with Ze14. These changes could explain on a molecular level how Ze14 reduces the characteristics of OA. Protein expression of affected key genes was analyzed as well.

How was the study conducted?

- Samples of cartilage were taken from the knees of 19 patients with severe knee OA undergoing total knee joint replacement surgery.
- The collected samples were kept in the form of chondrocyte cultures.
- These chondrocyte cultures were treated with either Ze14 or placebo (saline).
- The effects of Ze14 on the transcriptomic profile and protein levels of affected key genes of the osteoarthritic chondrocytes were then studied and compared to placebo.

What were the results of the study and how can they be interpreted?

- In comparison to the placebo treatment, treatment with Ze14 was found to significantly modulate the expression of 13 genes in cultured chondrocytes from the knees of patients with severe OA.
- Importantly, Ze14 treatment changed the mRNA expression of several MMP-13 pathway mediators in a way that could lead to reduced MMP-13 activation and levels.
- The expression of the MMP13 gene itself was also reduced.
- Supporting data confirmed that production of pro-MMP-13 protein (the inactive precursor of MMP-13 protein) was also reduced.
- Overall, this suggests a downregulation of MMP-13 protein expression, central to type II collagen and thus cartilage degradation. Ze14 may thereby limit cartilage degradation.
- At the same time, Ze14 also has pro-anabolic properties on OA cartilage as it increased cartilage matrix formation (chondrogenesis) via CCN1:
  - CCN1 was significantly increased by Ze14 treatment. CCN1 promotes the synthesis of type II collagen and aggrecan, two main components of the cartilage matrix, and prevents aggrecan degradation.
  - Indeed, Ze14 significantly increased type II collagen production.

Why are these study findings important?

- Currently, the main treatments for OA are analgesics and anti-inflammatories e.g., non-steroidal anti-inflammatory drugs (NSAIDs). Unfortunately, long-term use of NSAIDs can cause side effects, so there is a need for new treatments to be developed that improve symptoms and stop the progression of OA and/or reverse damage that has already occurred.
- Ze14 works on multiple targets which could improve OA on a molecular level. This multitarget feature could be beneficial in a complex disease such as OA.
- The findings of this *in vitro* study may explain some beneficial effects seen in previous clinical observational studies.
- These results are encouraging and support further research into the effects of Ze14.

Further information

- You can find the full article for free here: *https://www.frontiersin.org/articles/10.3389/fphar.2021.635034/full*
- The study included several additional analyses not covered in this summary.
- All patients have signed the informed patient consent, and the ethical committee of the Catholic University of Louvain approved the protocol.
- This plain language summary was prepared by: Ms Mebruka Mohammed, Dr James Mason, and Dr Steven Walker on behalf of Heel GmbH. The original authors were involved in preparing this summary. This summary was not peer-reviewed.