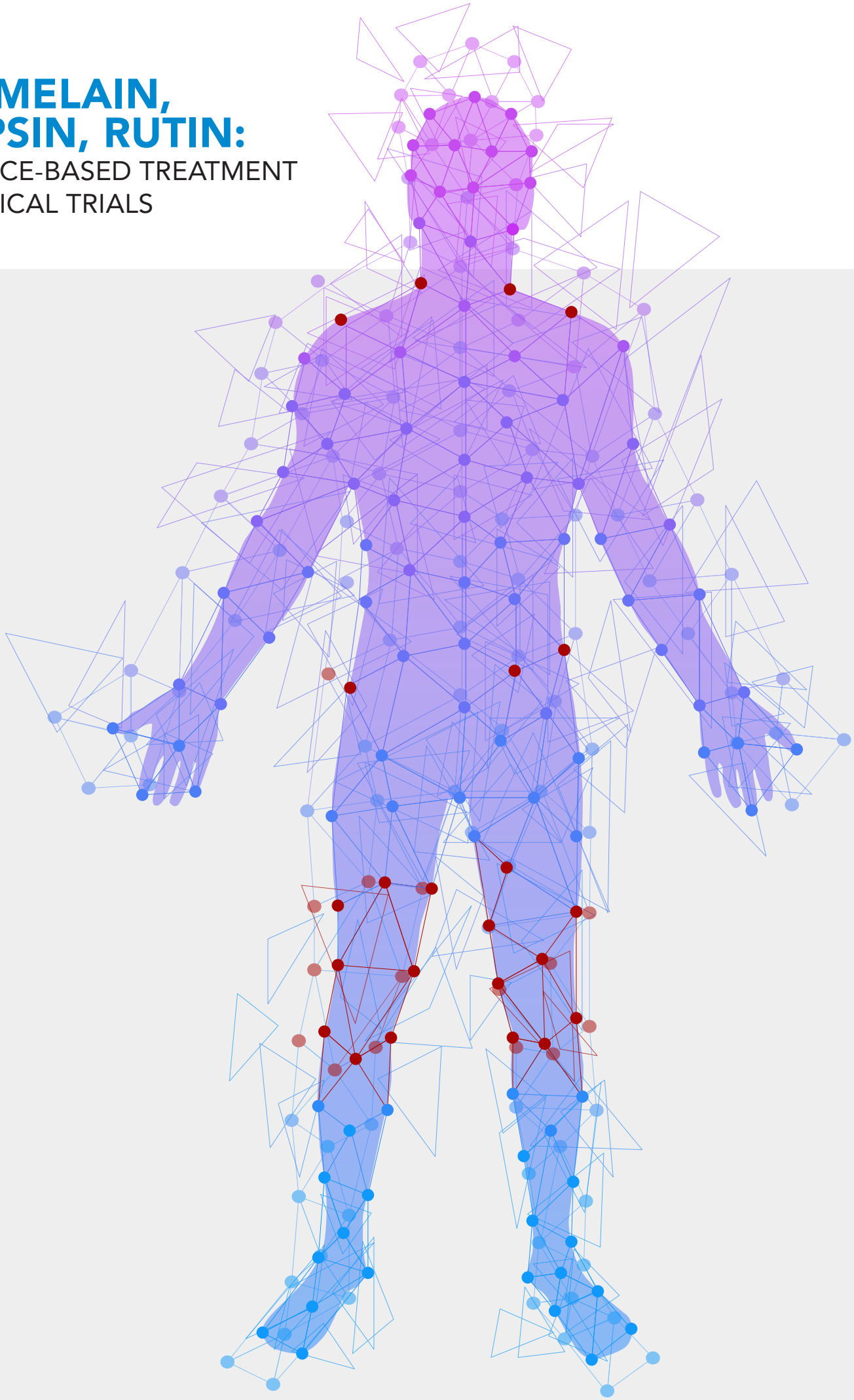
BROMELAIN, TRYPSIN, RUTIN:

EVIDENCE-BASED TREATMENT IN CLINICAL TRIALS



EDUCATIONAL INFORMATION FOR HEALTH CARE PRACTITIONERS ONLY

Introduction

Osteoarthritis is a leading cause of disability among elderly people[1]. Estimates of the prevalence in the literature range from 12.3% to 21.6%[2], and up to 34% in adults over 65 years[3]. Symptomatic knee OA is highly prevalent among people aged over 50 years, affecting more than 250 million people worldwide[4,5].

Patients with Osteoarthritis suffer from severe joint pain, which results in physical disability; the more severe the walking disability, the higher is the risk of death[6]. Global estimates indicate that among people with OA, 80% have limitations in movement, and 25% cannot perform their major daily activities of life[7].

The disease has a slow but continuous progression with inflammatory episodes. The principal symptoms are pain and loss of joint function. The standard therapy for moderate rheumatic pain is analgesic and antiphlogistic treatment with non-steroidal anti-inflammatory drugs (NSAIDs)[8].

NSAIDs improve pain relief but do not affect degenerative progression[9]. Moreover, NSAIDs are associated with several adverse effects and are contraindicated in people with comorbidities[10,11,12,13]. Therefore, doses should be as low as possible, and NSAID treatment should be continued for as short a time as possible[14] which is a problem in a condition such as OA that requires long-term management.

In light of these risks and the fact that osteoarthritis is a chronic disease without causal treatment, the search for an effective, safe, and well-tolerated anti-inflammatory treatment to slow down Osteoarthritis progression and improve symptoms is more important than ever. The search has involved numerous clinical trials comparing the effectiveness of systemic enzyme therapy with standard NSAID therapy.

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13: Bannuru, R.R., et al., OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. Osteoarthritis Cartilage, 2019. 27 (11): p. 1578-1589.
14: Kolasinski, S.L., et al., 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. Arthritis Care Res (Hoboken), 2020. 72 (2): p. 149-162.

Contents

Mode of Action

Better in combination – spectrum of proteolytic enzyme action
Primarily (clinically apparent) systemic enzyme therapy has an anti-edematous and anti-inflammatory action and therefore relieves pain. It can also improve blood flow. From a pharmacological and therapeutic perspective, combining different enzymes is useful since the individual enzymes act in different ways.

Cytokines: the immune system's messenger molecules
Inflammation is a healthy and crucial response of the immune system to potentially harmful stimuli. Cytokines play a fundamental role in controlling the progression and duration of inflammatory responses. Their influence on inflammatory processes can be broken down into two key modes of action: pro-inflammatory cytokines promote the inflammatory response, while anti-inflammatory cytokines inhibit the inflammatory response. The coordinated interplay of pro- and anti-inflammatory cytokines is a prerequisite for the normal progression of inflammations.

In the event of an acute immune response, pro-inflammatory cytokines predominate, while in the case of chronic inflammatory processes anti-inflammatory cytokines outweigh. Restoring the balance of the different cytokines in the body is vital in ensuring an immune response that results in healing.

Everything in balance – cytokine regulation by enzymes
Proteolytic enzymes have a role in reducing inflammation by helping to restore the balance between pro-inflammatory and anti-inflammatory cytokines. Following absorption through the intestinal mucosa, these enzymes bind to the antiprotease alpha-2-macroglobulin in the blood to activate it. Activated alpha-2-macroglobulin is then able to irreversibly bind to the excess cytokines and restore the balance necessary for reducing inflammatory responses.[1,2,3]

1: Cater, J.H., M.R. Wilson, and A.R. Wyatt, Alpha-2-Macroglobulin, a Hypochlorite-Regulated Chaperone and Immune System Modulator. Oxid Med Cell Longev, 2019. p. 5410657.
2: Lorkowski, G., Gastrointestinal absorption and biological activities of serine and cysteine proteases of animal and plant origin: review on absorption of serine and cysteine proteases. International journal of physiology, pathophysiology and pharmacology, 2012. 4 (1): p. 10.
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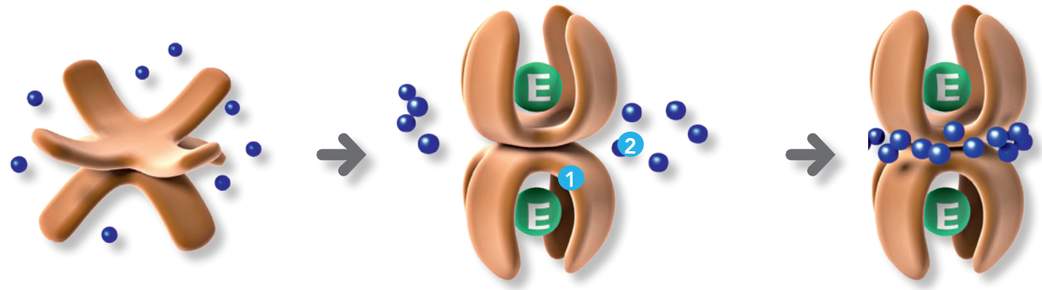
Mode of action of enzymes in inflammation[1]



Free alpha-2-macroglobulin surrounded by cytokines

Activated alpha-2-macroglobulin
1 Bound enzyme
2 Exposed cytokine binding site

Cytokines irreversibly bound to alpha-2-macroglobulin

Modulating inflammation by oral enzymes
Proteolytic enzymes, therefore, do not suppress the inflammatory response, but support it and actually accelerate the controlled physiological progression of the immune response and inflammatory processes. That is, they strengthen self-healing processes – and are better tolerated than NSAIDs. Enzyme preparations are, therefore, particularly suited to long-term therapy.

Total activity of the daily dose of oral enzymes used in the clinical trials described further is 2700 FIP-Units bromelain, 8640 FIP-Units trypsin (and 600 mg of the flavonoid rutoside, or rutine as it is also called). There are several methods to measure active enzymes, the Fédération internationale pharmaceutique recommends FIP-Units to be used[2].

1: Cater, J.H., M.R. Wilson, and A.R. Wyatt, Alpha-2-Macroglobulin, a Hypochlorite-Regulated Chaperone and Immune System Modulator. Oxid Med Cell Longev, 2019. p. 5410657.
2: Fédération internationale pharmaceutique, https://www.ugent.be/fw/pharmaceutics/biochemphypharm/en/research/research-groups/fip/commission , accessed 30th June 2021.

Knee Osteoarthritis
(Meta-Analysis of Six Trials)

Aim of the Trial

Comparison of the effectiveness, tolerability and safety of an oral enzyme combination with the NSAID diclofenac in subjects with knee osteoarthritis based on the raw patient data of six clinical trials

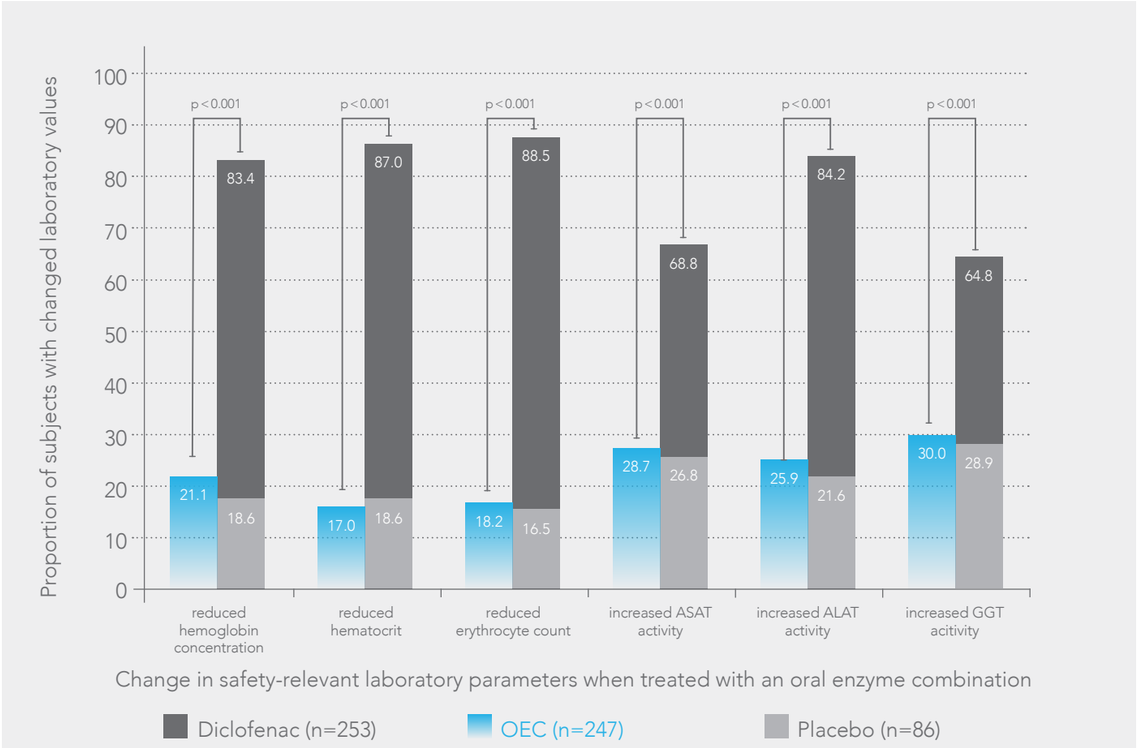
Methodology

- Meta-analysis based on individual raw patient data taken from six randomized, controlled trials in accordance with GCP guidelines against the reference substance diclofenac
- Data from a total of 774 patients with knee osteoarthritis
- Treatment either with an oral enzyme combination (OEC; with bromelain, trypsin, and the flavonoid rutoside) and diclofenac placebo or with diclofenac and OEC placebo (OEC 3 x 2 tablets/day, diclofenac 100–150 mg/day)
- Length of treatment: 3, 6, and 12 weeks
- Permitted emergency medication: 500 mg paracetamol up to 4x a day, not prior to the examination appointments
- Efficacy target parameters: change in the Lequesne index, leading to an assessment of pain, walking performance, and daily activity with knee osteoarthritis. Secondary endpoint: pain at rest and under stress
- Safety/tolerability target parameters: number of adverse side effects. Additional endpoints: changes in liver enzyme (AST, ALT, and GGT) activity and changes in red blood cell values (hemoglobin, hematocrit, and erythrocyte count)

Findings

- Significant, equivalent improvement of knee function and pain (Lequesne index) in subjects who either received diclofenac or OEC ($p<0.001$)
- Hence, comparable clinical effectiveness of OEC and diclofenac
- Significantly fewer adverse events occurred in the OEC group than in the diclofenac group (14.7% vs. diclofenac 21.1%); these were at 5.9% (enzyme group) and 10.2% (diclofenac group) at the conclusion of the trial
- Clear, significant increase in liver values in the diclofenac group (72.6% vs. 28.2%)
- Clear, significant change in red blood count in 86.3% of the diclofenac group (vs. 18.8% of the enzyme group)

Anti-Inflammatory Treatment of Osteoarthritis – Alternatives to NSAIDs?



Source: Arzt & Wirtschaft AUDIMAX 1, February 2017

CONCLUSION

The oral enzyme combination has comparable clinical efficacy as the NSAID Diclofenac with a more favourable safety profile and is hence especially qualified for long-term use.

Reference: Ueberall M.A. et al.: Efficacy, tolerability, and safety of an oral enzyme combination vs diclofenac in osteoarthritis of the knee: results of an individual patient-level pooled reanalysis of data from six randomized controlled trials. Journal of Pain Research 2016, Nov 4; 9: 941–961

Bolten et al. (2015)

Active Osteoarthritis of the Knee

Aim of the Trial

Comparison of the effectiveness and tolerability of an oral short-term enzyme therapy compared to the NSAID diclofenac in subjects with moderate to severe osteoarthritis of the knee.

Methodology

- Multi-center, randomized, placebo-controlled, double-blind trial against the reference substance diclofenac
- Treatment of 150 subjects with moderate to severe knee osteoarthritis over 12 weeks either with an oral enzyme combination (OEC; with bromelain, trypsin, and the flavonoid rutoside) + diclofenac placebo or with diclofenac + OEC placebo, or solely with a placebo (OEC: 3 x 2 tablets/day, diclofenac 3 x 50 mg/day)
- Permitted emergency medication: 500 mg paracetamol up to 4x a day, not prior to the examination appointments
- Target parameters: change in Lequesne index and WOMAC index after 12 weeks of treatment, assessing pain and function in the affected knee, joint stiffness, walking distances and daily activities.

Findings

- Significant, equivalent improvement of knee function and pain (Lequesne index) in subjects who either received diclofenac or OEC; both groups showed significant improvement compared to the placebo ($p<0.05$)
- Significant, equivalent improvement both in the WOMAC sub-scales and in overall scores
- Therefore, comparable clinical effectiveness of OEC and diclofenac
- Number of emergency tablets taken (paracetamol) significantly less in the OEC group than in the placebo group (median: 0.5 versus 10 tablets per subject over 12 weeks) – number of painful episodes reduced
- Adverse events were similarly rare in both the OEC group and the placebo group (7.2% vs. 9.1% of subjects), but significantly more frequent in the diclofenac group (15.6%)

CONCLUSION

An equivalent improvement in pain and knee function in subjects with knee osteoarthritis was observed with the oral enzyme combination and diclofenac. The enzyme combination proved to be an effective and safe alternative to standard NSAID treatment.

Reference: Bolten W. W. et al.: The Safety and Efficacy of an Enzyme Combination in Managing Knee Osteoarthritis Pain in Adults: A Randomized, Double-Blind, Placebo-Controlled Trial. Arthritis 2015, Article ID 251521, 7 pages, 2015. doi:10.1155/2015/251521

Klein et al. (2006)

Active Osteoarthritis of the Hip

Aim of the Trial

Investigate the effectiveness and tolerability of the oral enzyme combination bromelain,trypsin and the flavonoid rutoside (OEC) compared to a standard NSAID (diclofenac) in subjects with active coxarthrosis – evidence of non-inferiority.

Methodology

- Randomized, double-blind trial against a reference substance
- Treatment of 90 subjects with active osteoarthritis of the hip over 6 weeks either with OEC + diclofenac placebo or with diclofenac + OEC placebo (OEC: 3 x 2 tablets/day, diclofenac 2 x 50 mg/day)
- Target parameters: changes in Lequesne index and WOMAC index (parameters assessing pain, joint stiffness, function, and daily activities), subjective assessment of effectiveness and tolerability by physicians and subjects

Findings

- Significant, equivalent improvement in symptoms in both treatment groups based on Lequesne index and on all WOMAC sub-scales (pain, joint stiffness, and function)
- Subjective assessment of effectiveness as “very good” or “good” by the physicians: 72.1% OEC vs. 61.4% diclofenac; by subjects: 62.8% OEC vs. 50.0% diclofenac
- Statistically significant evidence of non-inferiority of the oral enzyme combination (OEC) in all target parameters
- Treatment variants subjectively evaluated as “very good” or “good” by the majority of patients, with a tendency for improved tolerance of OEC

CONCLUSION

The effectiveness of the oral enzyme combination and diclofenac was equivalent in subjects with painful, active osteoarthritis of the hip. Based on the generally improved benefit-risk ratio, oral enzymes can be recommended to treat patients with painful osteoarthritis.

Reference: Klein G, Kullich W, Schnitzker J, Schwann H: Efficacy and tolerance of an oral enzyme combination in painful osteoarthritis of the hip. A double-blind, randomized study comparing oral enzymes with non-steroidal anti-inflammatory drugs. Clin Exp Rheumatol 2006; 24 (1): 25–30.

Active Osteoarthritis of the Knee

Aim of the Trial

Investigate the effectiveness and safety of the oral enzyme combination bromelain, trypsin and the flavonoid rutoside (OEC) compared to diclofenac in patients with active gonarthritis – evidence of non-inferiority.

Methodology

- Randomized, double-blind trial against a reference substance
- Treatment of 103 subjects with painful osteoarthritis of the knee over 6 weeks either with OEC (3 x 2 tablets/day) + diclofenac placebo or with diclofenac (2 x 50 mg/day) + OEC placebo
- Target parameters: changes in the Lequesne index, changes in resting and movement pain as well as motion impairment, subjective assessment of effectiveness and tolerability by physicians and subjects

Findings

- Significant, equivalent improvement of symptoms in both treatment groups: The Lequesne index fell in the enzyme group from 13.0 to 9.4 vs. 12.5 to 9.4 in the diclofenac group, while the symptoms index fell in the enzyme group from 4.9 to 3.5 vs. 4.9 to 3.6 in the diclofenac group
- Statistically significant evidence of non-inferiority of the oral enzyme combination
- Subjective assessment of tolerability of OEC as “very good” or “good” by the majority of subjects (89.2%) and physicians (84.2%)

CONCLUSION

The effectiveness of the oral enzyme combination and diclofenac was equivalent in subjects with painful knee osteoarthritis. As such, OEC represents an effective and safe alternative to standard treatment with NSAIDs such as diclofenac.

Symptoms Index

(Resting and movement pain, motion impairment) over course of treatment

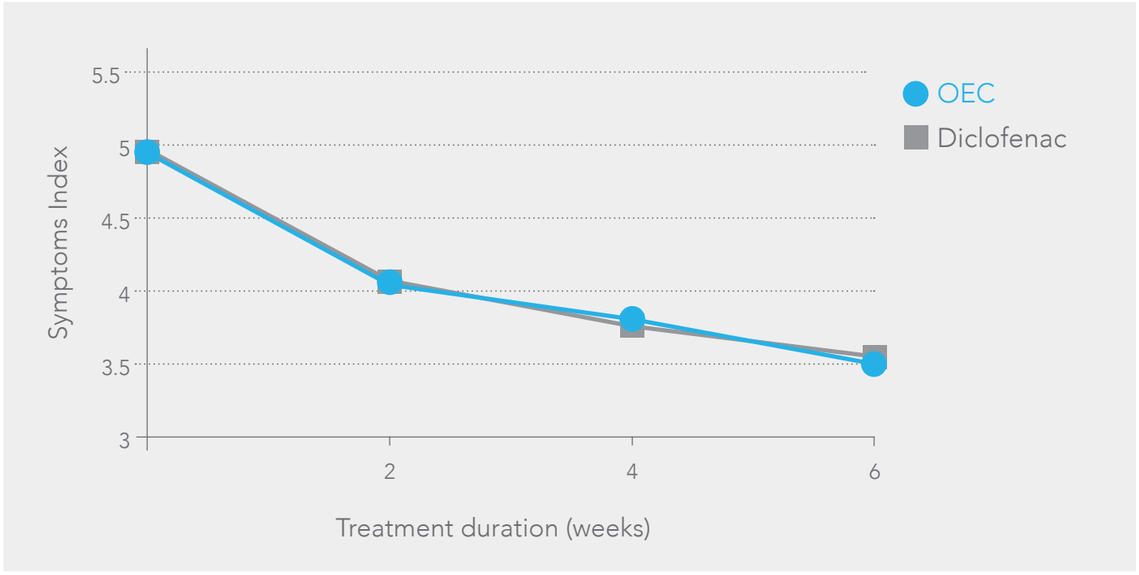


Diagram from Akhtar et al. (2004)

Reference: Akhtar NM, Naseer R, Farooqi AZ, Aziz W, Nazir M: Oral enzyme combination versus diclofenac in the treatment of osteoarthritis of the knee – a double-blind prospective randomized study. Clin Rheumatol 2004; 23: 410–415.

Active Osteoarthritis of the Knee

Aim of the Trial

Compare the effectiveness and tolerability of an oral short-term enzyme therapy (OEC; with bromelain, trypsin and the flavonoid rutoside) with the NSAID diclofenac in subjects with active knee osteoarthritis – evidence of non-inferiority.

Methodology

- Randomized, double-blind trial against a reference substance
- Treatment of 63 subjects with active knee osteoarthritis over 3 weeks either with OEC + diclofenac placebo or with diclofenac + OEC placebo (OEC: 3 x 2 tablets/day, diclofenac one week 3 x 50 mg/day, then 2 x 50 mg/day)
- Target parameters after 3 weeks of treatment followed by 4 weeks of observation: changes in the Lequesne index, assessment of resting and movement pain as well as mobility using visual analog scale (VAS), subjective assessment of effectiveness and tolerability by physicians and subjects

Findings

- Continuous decline on the Lequesne index and reduction of pain symptoms in both treatment groups during the 3-week treatment period
- Statistically significant differences at the end of the 4-week observation period: further reduction in the Lequesne index and in overall pain symptoms in the enzyme group vs. increase in values in the diclofenac group
- Evidence of non-inferiority of the oral enzyme combination
- No differences in the subjective assessment of effectiveness by physicians and subjects
- Subjective assessment of tolerability by physicians and subjects overwhelmingly "very good": OEC 92.3% vs. diclofenac 71.9%

CONCLUSION

The benefits of treatment with the oral enzyme combination can be observed in its long-lasting anti-inflammatory action and its very good tolerability. Long-term treatment with OEC can therefore be recommended in patients with osteoarthritis.

Total VAS score for pain

(Resting and movement pain, motion impairment) over course of treatment

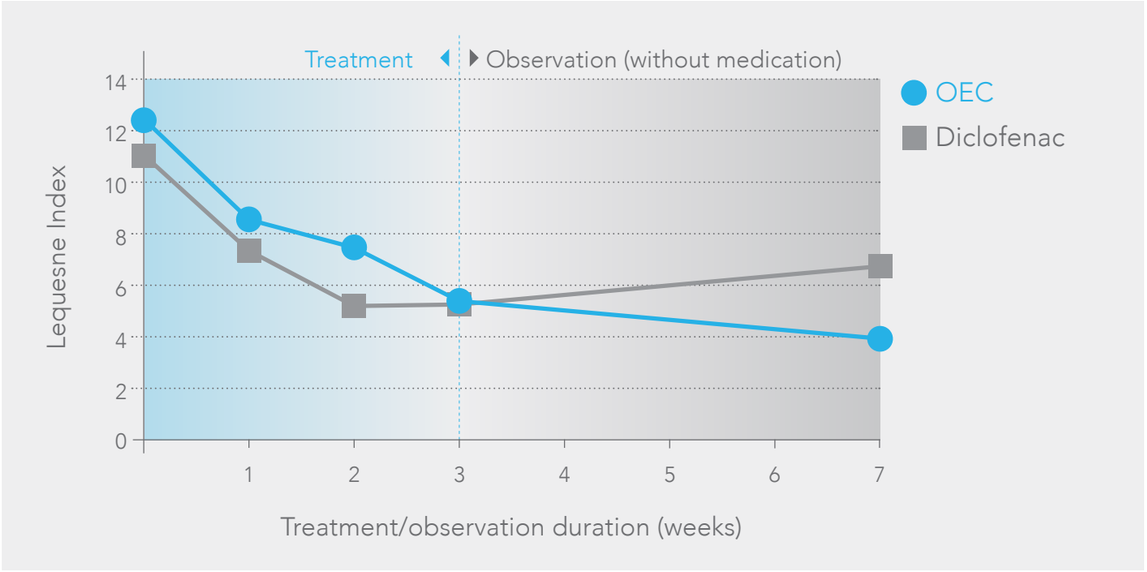


Diagram modified from Singer et al. (2001)

Reference: Singer F, Singer C, Oberleitner H: Phlogenzym versus diclofenac in the treatment of activated osteoarthritis of the knee. A double-blind prospective randomized study. Int J Immunotherapy 2001; 17(2/3/4): 135–141.

Wittenborg et al. (2000)

Rheumatic Illnesses

Aim of the Trial

Investigate the effectiveness of an oral enzyme combination (OEC; with bromelain, trypsin and the flavoured rutoside) in comparison in comparison to NSAIDs in the treatment of rheumatic illnesses.

Methodology

- Retrospective cohort study with parallel groups
- Comparison of treatment success for rheumatic illnesses (joint, spinal, and soft tissue rheumatic illnesses) based on the data of a total of 2,139 patients who either received OEC or NSAIDs
- Target parameter: symptom-free as an effectiveness factor at the end of the treatment

Findings

- Period of administration depending on diagnosis: OEC 23–35 days vs. NSAIDs 16–25 days
- Use of additional painkillers was necessary more often during treatment with NSAIDs than during treatment with OEC: 15.6% vs. 8.3%
- Subjective assessment of tolerability of OEC as “very good” by 87.2% of physicians vs. 30.1% with NSAIDs

CONCLUSION

In comparable initial and treatment scenarios, enzyme therapy was more likely to be successful (freedom from symptoms) than NSAID therapy. Oral enzyme therapy can be considered as generally unproblematic in terms of safety; compared to NSAIDs, the enzyme preparation had a significantly improved side effect profile.

Marzin et al. (2017)

Muscle Soreness

Aim of the Trial

Investigate the effectiveness of an enzyme combination (OEC; with bromelain, trypsin, and the flavonoid rutoside) to alleviate the symptoms of muscle trauma brought about by exhaustive, eccentric muscle activity

Methodology

- Randomized, double-blind, placebo-controlled study in accordance with GCP guidelines
- Inclusion of sports volunteers of intermediate strength
- Two stages:
  - Stage 1: 28 participants, crossover
  - Stage 2: 44 participants, parallel groups
- 72 hours before training to 72 hours after training: 3 x 4 OEC or placebo tablets a day
- Target parameters: strength in the quadriceps muscles after intensive, eccentric training eliciting muscle soreness, pain in the same muscles after 3, 6, 24, 48, and 72 hours
- Target parameter biomarkers: muscle metabolism, damage, inflammation, and immune system

Findings

Stage 1:

- Mainly runners/joggers (endurance training)
- Significant difference between the OEC group and the placebo group in terms of the maximum strength achieved and pressure pain after induced muscle soreness (p=0.0332)
- OEC group regained their initial strength after just 24 hours (placebo group only after 48 hours)

Stage 2:

- Primarily strength trained athletes
- No significant difference (mean=0.4379; p=0.8596)

Biomarkers:

- Statistically highly significant difference in the OEC group in both stages (combined p=0.0002)

CONCLUSION

The oral enzyme combination aids in the recovery of post-traumatic muscle damage (muscle soreness) to such an extent that recreational athletes had regained their initial strength with no pain after half the time. The objectively detectable biomarkers of muscle damage clearly demonstrated the effectiveness of the enzymes in both groups.

Reference: Marzin T, et al. (2017): Effects of a systemic enzyme therapy in healthy active adults after exhaustive eccentric exercise: a randomised, two-stage, double-blinded, placebo-controlled trial. BMJ Open Sport Exerc Med 2017;2: e000191. doi:10.1136/ bmjsem-2016-000191

Summary

Osteoarthritis is a long-term chronic disease creating stiffness, pain, and impaired movement in joints. The aim of the treatment is to slow down the progression of the disease, and especially target inflammation, which drives further deterioration. Non-steroidal anti-inflammatory drugs (NSAIDs) are regarded as the treatment of choice for osteoarthritis owing to their analgesic and anti-inflammatory action.

However, the principal drawback of NSAIDs is their unfavorable side-effect profile.

For this reason, alternatives to NSAIDs have often been sought. One option is oral enzyme combinations by means of the proteases bromelain, trypsin and the flavonoid rutoside. The oral enzyme combination restores the balance necessary for reducing inflammatory responses, acting therefore immunomodulatory by influencing cytokine composition. Furthermore, the enzymes, in particular bromelain, have an anti-edematous effect.[1]

The oral enzyme combination with bromelain, trypsin and the flavonoid rutoside has an immunomodulatory and, in particular, an anti-inflammatory action similar in strength to NSAIDs, with a more favourable safety profile.

This has been demonstrated in numerous clinical trials involving subjects with Osteoarthritis and rheumatic illnesses [2-6]. Clinical studies in patients with OA have demonstrated that the oral enzyme combination is effective in reducing joint pain, increasing joint function, and improving mobility.

In summary, the findings from all the studies indicate that, owing to its favorable benefit-risk profile, the oral enzyme combination with bromelain, trypsin and the flavonoid rutoside can be recommended as an effective and tolerable approach for patients with painful osteoarthritis.

Reference:
1: Maurer HR. Bromelain: biochemistry, pharmacology and medical use. Cell Mol Life Sci. 2001 Aug;58(9):1234-45. doi: 10.1007/PL00000936. PMID: 11577981.
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7: Bolten W.W. et al.: The Safety and Efficacy of an Enzyme Combination in Managing Knee Osteoarthritis Pain in Adults: A Randomized, Double-Blind, Placebo-Controlled Trial. Arthritis 2015, Article ID 251521, 7 pages, 2015. doi:10.1155/2015/251521