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A new high-dose treatment with intra-articular hyaluronic acid facilitates the management of osteoarthritis

Summary
Intra-articular hyaluronic acid (HA) has an established place in the symptomatic treatment of osteoarthritis. We report, for the first time, data on a new "high-dose treatment" in 25 patients with radiologically ascertained symptomatic osteoarthritis of the hip or knee joint.
Within the scope of an open, prospective study patients received either one (in hip osteoarthritis) or three (in knee osteoarthritis) intra-articular injections of Ostenil® Plus, a new medical device that contains 40 mg fermentative hyaluronic acid and 10 mg mannitol in a terminally sterilised pre-filled syringe with a 2 ml fill volume. In this formulation mannitol functions as a free-radical scavenger which will protect the exogenous HA from rapid depolymerisation, especially in the activated stage of osteoarthritis. When the test product was administered repeatedly, an interval of two weeks between injections was respected.
In this study Ostenil® Plus proved to be safe and, in a high percentage of the patients, reliably effective. Of the 24 patients that were included in the analyses at the end of the study, 12 were free from pain on movement while 10 patients reported mild pain and 2 reported moderate pain. Regarding the global treatment satisfaction, both the Investigator and the patients assessed treatment as satisfactory in 87.5% of the cases. The tolerability of Ostenil® Plus was assessed as very good in 94.7% of the cases and good in 5.3%.
The reduced number of injections required facilitates the application of intra-articular HA in patients with a difficult access to the joint. Longer intervals between individual injections also allow a useful, temporal flexibility in planning and execution of the treatment.

Key words: osteoarthritis – intra-articular hyaluronic acid, high dose, efficacy, safety, medium term carry over effect.

Introduction
Osteoarthritis is the most frequent joint disease in the world. The prevalence of osteoarthritis increases with age and the incidence of elderly people in the population are constantly growing leading to an increased burden on the health system. Of the large weight bearing joints, the knee and the hip joint are most frequently affected by osteoarthritic changes (1). The patients do not only suffer from pain on load in the osteoarthritic joint but also from considerable restrictions in their physical range of movement and in their autonomous lifestyle.
Specialist medical societies recommend a gradual therapeutic approach in which intra-articular hyaluronic acid (HA) is recommended if physical measures and drug treatment are no longer adequate or possible, or when the use of NSAIDs and corticoids are restricted or contraindicated (2).
Endogenous hyaluronic acid has some very essential functions in the physiology of the joint. It contributes to the water binding capacity and elasticity of the joint cartilage and also protects the surface of the hyaline cartilage. It confers the required viscosity to the synovial fluid in the joint space. It acts as a shock absorber and a molecular sieve, which allows the diffusion of substances of cartilage metabolism from the joint space but stops the free passage of inflammatory mediators and cells into the joint space (3). Finally SH appears to shield the pain receptors of the synovial membrane from pain inducers (4, 5).
In osteoarthritis, the endogenous HA in the joint space is qualitatively and quantitatively reduced. This fact formed the rationale for an improvement of the endogenous hyaluronic acid through the use of exogenous hyaluronic acid (viscosupplementation), which can be obtained by its injection into the joint space of the concerned joint (3). This is, in general, obtained by administering extractive or fermentative hyaluronic acid, at a dose of 20 mg, three to five times at weekly intervals. In our study the effectiveness and safety of one to three intra-articular injections of a combination of a high dosed hyaluronic acid and mannitol were, for the first time, assessed in patients with symptomatic osteoarthritis of the knee or hip joint.

The test product Ostenil® Plus
The medical device Ostenil® Plus pre-filled syringe (manufacturer: TRB Chemedica AG, Haar, Munich) contains 40 mg fermentative hyaluronic acid per syringe. This is, in comparison with Ostenil®, twice the amount of the active substance in an identical syringe fill volume (2 ml). The free radical scavenging effect of 10 mg mannitol per syringe should prevent the rapid depolymerisation of the hyaluronic acid, mediated by ROS (reactive oxygen species), in the joint space. The net effect would be a more prolonged efficacy per application together with a more satisfactory therapeutic effect from fewer intra-articular injections.

Investigation and treatment scheme

We tested this hypothesis in a prospective, open, exploratory study in 25 patients with knee or hip osteoarthritis. The treatment was carried out under strict observation of the study plan. One to three injections of Ostenil plus were administered to the joint to be treated with, in cases where three syringes were used, intervals of two weeks between injections.

25 patients with x-ray ascertained osteoarthritis of the knee or hip joint, which caused them considerable pain for at least three months, were included into the study after verification of pre-defined inclusion and exclusion criteria, and were treated as out-patients.

Patients with osteoarthritis of the hip joint received one intra-articular injection of Ostenil® Plus, while patients with osteoarthritis of the knee joint received a total of three intra-articular injections of Ostenil® Plus at intervals of one injection every two weeks. The patients were treated with the medical device Ostenil® Plus pre-filled syringes containing 40 mg / 2.0 ml hyaluronic acid (TRB Chemedica AG, Haar, Munich). The fermentative hyaluronic acid in Ostenil® Plus has an average molecular weight of 1.6 million Daltons. The pre-filled syringes are individually sealed in a sterile pack and autoclaved so that both the contents and the surface of the pre-filled syringe are sterile.

The recommendations of the specialist societies for performing intra-articular injections and punctures were strictly adhered to. In patients with bilateral osteoarthritis, only the most symptomatic joint was treated.

The following visits were planned: Visit 1.1 on Day 0 for the assessment of the baseline values and then for the first injection, Visit 1.2 on Day 14 ± 1 after Visit 1.1. (2^{nd} injection) and visit 1.3 on Day 28 ± 1 (3^{rd} injection). Visits 1.2 and 1.3 were only carried out for patients with osteoarthritis of the knee joint. The final examination was planned at 3 months ± 1 week after the end of treatment at Visit 2.

The complaints and functional impairments typical of osteoarthritis were recorded using a patient questionnaire, the WOMAC Osteoarthritis Index (6, 7). This questionnaire contains five questions on subjective pain perception (WOMAC A - pain), two questions on the assessment of joint stiffness (WOMAC B - joint stiffness) and seventeen questions on the assessment of joint function (WOMAC C - joint function). In addition, signs or symptoms such as crepitation, morning stiffness, morning start-up pain, pain on load and pain at rest were assessed using a 4-point ordinal scale (absent, mild, moderate, severe), while tolerability was assessed as very good, good, moderate or bad using an ordinal scale.

The global treatment satisfaction (CGI) was also assessed by the doctor and the patients during the final visit V2 using a 4-point ordinal scale: very good / completely free of complaints, good / clear recovery, satisfactory / insignificant recovery, no improvement / constant deterioration.

Ethics Committee Approval

In accordance with the Helsinki Declaration, the German Medicine Products Law (MPG) and Good Clinical Practice (GCP) guidelines, the study protocol was submitted to the Freiburg International Ethics Committee for review: an approval was received.

Statistical evaluation

While the data of all 25 patients were used for the safety assessments, the data of 24 patients were taken into account for the efficacy evaluation. One patient was excluded from this analysis because he had received a treatment prohibited in the protocol (an intra-articular corticosteroid).

To demonstrate the statistical relevance of the results, the WOMAC total score, consisting of the 3 subsections WOMAC A, B and C, were subjected to a within-group analysis using the Wilcoxon-Pratt Test. For this purpose the five-point ordinal scale of the WOMAC total scores was normalised to a 0 - 100 scale. Thus on this normalised scale for the WOMAC total score, which consists of scales for pain, joint stiffness and activities of daily life, a score of 0 represents a recovered status while a score of 100 represents the worst conditions.

All other parameters (quantified using a 4-point ordinal scale / Likert scale) were represented in contingency tables and were analysed using a marginal homogeneity test for ordered categories.

The global effectiveness judgment (CGI), expressed by the Investigator and the patients, is presented in absolute numbers and as a percentage.

Due to the absence of a control group, the improvements in findings obtained in the study cannot be described as “statistically significant”: it is, however, correct to present the clear decrease in osteoarthritis symptoms documented by the Investigator and the patients as a “significant improvement”.

Results

Patient data

25 patients (9 male, 16 female), with an average age of 65.3 ± 9.1 years, were included into the study after prior explanation of the study procedure and after signature of an informed consent. They had an average height of 169.9 ± 9.21 cm, an average weight of 78.4 ± 13.75kg and a Body Mass Index (BMI) of 27.25 ± 4.91.

All patients suffered chronic pain due to their osteoarthritis condition, which existed for an average of 6.2 ± 3.23 months before the start of the study (5.5 ± 2.43 months in six patients with hip osteoarthritis; 6.4 ± 3.47 months in the 19 patients with knee osteoarthritis).

3 (50%) of the patients with hip osteoarthritis and 11 (57.9%) of the patients with knee osteoarthritis had bilateral osteoarthritis.

Treated joints and their x-ray findings

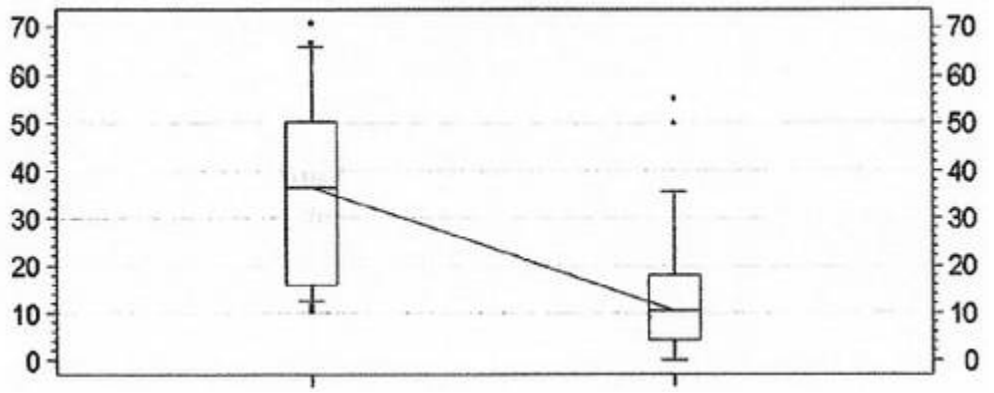
Of the 25 patients included, 6 were treated in the right hip joint and 19 in the knee joint (of which 12 patients were treated in the right knee and 7 in the left knee) with Ostenil® Plus. The X-ray classification of the osteoarthritis,

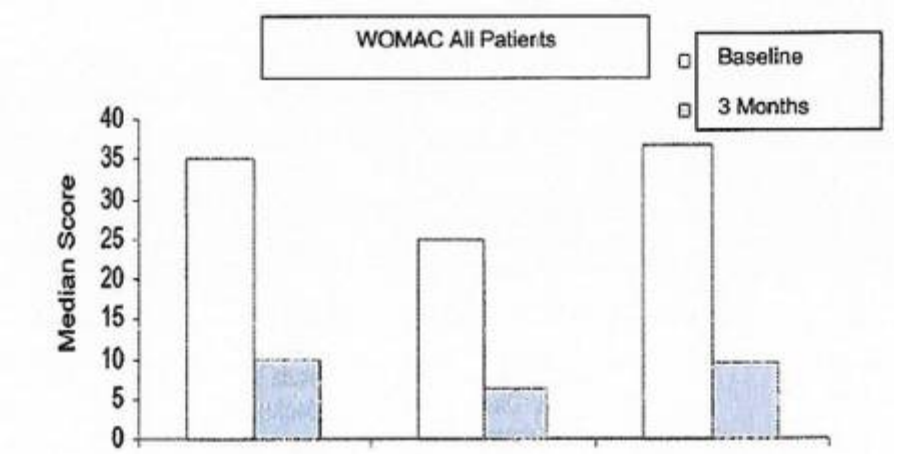
according to the Kellgren-Lawrence scale (8), showed that 3 patients with hip osteoarthritis and 5 patients with knee osteoarthritis had grade 3 severity, while the remaining 17 patients had grade 2 severity.

WOMAC Osteoarthritis Index

The WOMAC total score consists of the subscales for pain, joint stiffness and daily activities. A score of 0 indicates a complaint-free status while a score of 100 indicates maximum complaints. The WOMAC total score improved from a mean value of 36.81 (±19.59) points to 15.56 (±15.24) points following treatment with Ostenil® Plus and for the subscale pain from 36.60 (±21.73) points to 13.33 (±14.50) points, for joint stiffness from 38.50 (±25.50) points to 15.10 (±19.15) points and for activities of daily living from 36.67 (±19.91) points to 16.27 (±16.16) points. On statistical analysis, a proven improvement in osteoarthritis problems was observed ($p<0.0001$). Using weighted means (median), results showed that Ostenil® Plus achieved an even greater improvement in the total scores from 36.46 to 10.42 points (Figure 1). Figure 2 shows the improvement in findings for the subscales.

Figure 1: WOMAC total score (normalised)
Absolute values: available data
All data combined
Boxplot (P10, P90)



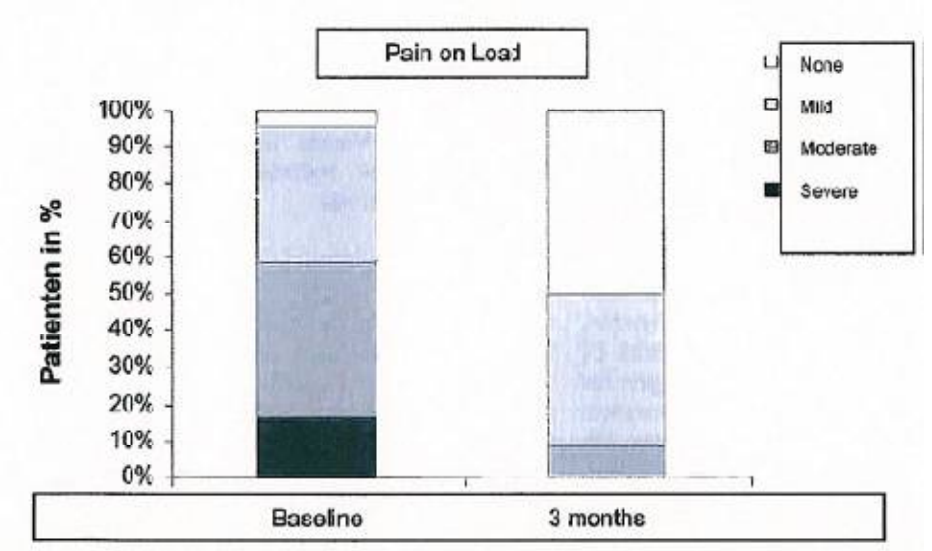


Crepitation

The sign crepitation was assessed using a four-point ordinal scale (none, mild, moderate, severe). It was present in 19 out of the 25 patients at baseline. At the end of the study, the sign was no longer present in 11 out of 24 (45.8%) evaluable patients, was mild in 9 patients (37.5%), moderate in 3 patients (12.5%) and severe in 1 (4.2%) patient. The statistical evaluation showed that there was no improvement at three months after the treatment.

Morning stiffness
This symptom was evaluated using a similar four-point ordinal-scale. At baseline it was absent in 6 patients. At the end of the study, the symptom was no longer present in 11 (45.8%) patients, while in 9 (37.5%) patients it lasted less than 30 minutes, in 3 (12.5%) it lasted up to 60 minutes and in 1 (4.2%) patient it lasted more than 60 minutes. On statistical evaluation an observed, but not proven, improvement was found for this symptom (Mann Whitney value = 0.6042).

Morning start-up pain
At baseline, 7 patients had no morning start-up pain. At the end of the study, this symptom was no longer present in 15 (62.5%) patients while it was mild in 8 (33.3%) patients and moderate in 1 (4.3%) patients. A proven improvement was observed at three months after treatment ($p<0.0006$).



Pain on load
At baseline, 1 patient had no pain on load. At the end of the study, the symptom was no longer present in 12 (50.0%) patients while it was mild in 10 (41.7%) and moderate in 2 (8.3%) patients. This corresponds to a proven improvement ($p=0.0001$). The results are presented as a bar graph in Figure 3.

Pain at rest
At baseline, 14 patients had no pain at rest. At the end of the study, the symptom was no longer present in 22 (91.7%) patients while it was mild in 2 (8.3%). Statistically, a proven improvement was observed ($p=0.0002$).

Global treatment satisfaction (doctor and patient)
At the end of the study, the assessment for 21 (87.5%) patients was very good, good and satisfactory while 3 (12.5%) patients did not benefit from the treatment. A deterioration was not observed in any patient.

Tolerability
Concerning the tolerability of the test product, patients with knee osteoarthritis were questioned at each follow-up visit after an administration of Ostenil® Plus, using a 4-point ordinal scale (very good/good/moderate/bad). Since the hip osteoarthritis patients only received a single injection, they were questioned on the tolerability only at three months after this treatment.

Identical results were recorded: 94.7% of the patients judged the tolerability of Ostenil® Plus as “very good” and 5.3% as “good”. The Investigator came to an identical judgment. Furthermore, no adverse events that could be attributed to the test product were observed.

Discussion
Intra-articular hyaluronic acid has established a solid place in the step-wise treatment for osteoarthritis. An “injection therapy” with five pre-filled syringes, each of which — like Ostenil® - contains 20 mg HA to be administered at weekly intervals can, in general, be regarded as standard therapy (9). This study now shows that one to three syringes of Ostenil® Plus can already develop a very reliable symptomatic effect in osteoarthritis of the large joints. With repeated application, the interval between injections can be two weeks. The “high dose therapy” with Ostenil® Plus, which contains 40 mg HA per pre-filled syringe, facilitates the treatment of patients who, for logistic reasons, cannot return five times at weekly intervals for treatment. The reduced number of injections facilitates the treatment of patients in whom the access to the joint is complicated e.g. in obese patients

with hip osteoarthritis. Finally, this would also further reduce the risk of joint infection, which is already, in principle, very low.
In German terminology, the concept “activated” osteoarthritis stands for an inflammatory phase of the, in principle, degenerative joint disease. In this phase, free radicals, mainly the so-called “reactive oxygen species” (ROS), cause a depolymerisation of the HA in the joint (10) resulting in a more rapid elimination of the HA from the joint space. In vitro studies show that different substances, such as mannitol — which, in high doses, is also used in osmotherapy - can reduce this effect (11). Besides containing a high dose of 40 mg hyaluronic acid, Ostenil® Plus therefore also contains 10 mg mannitol to protect the HA rapid depolymerisation. Medical device products with the same formulation have already been used in other fields (e.g. Visiol® as an intra-ocular viscoelastic or Viscontour® for intra-dermal application) and have proved to be effective and safe (12, 13).
The improvements in results, obtained using validated instruments, prove that a high percentage of the treated patients derived a clear benefit from the intra-articular administration of Ostenil® Plus. Furthermore, a favourable carry-over effect on the osteoarthritis symptoms after the immediate treatment phase can be observed at three months after the last injection. This carry-over effect of hyaluronic acid, observed in numerous controlled studies, was also shown for the test product Ostenil® Plus.
Since different hyaluronic acid products are available meanwhile, it must be pointed out that products containing fermentation origin hyaluronic add of medium molecular weight, which are heat sterilised in the final packaging (like Ostenil® Plus) should be used preferentially because of their efficacy and safety (14).
In conclusion it can be observed in this study that the new test product Ostenil® Plus has proved to be an effective and safe treatment option for patients with osteoarthritis complaints. Further studies with a larger patient population are recommended to confirm the results of this study.

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