Intraarticular Hyaluronic Acid in the Treatment of Arthroses

R. Kausch¹, U. Lahne², R. Thomas³, C. Kipshoven⁴, M. Schuld⁴

Abstract

This observational study (OS) examined the efficacy, the treatment effect persisting beyond therapy, and the safety of injections of an intraarticular sodium hyaluronate solution (GO-ON®) under practical conditions in a non-selected patient population. 1743 patients (88 % with gonarthrosis (osteoarthritis of the knee), 4.4 % with coxarthroses (osteoarthritis of the hip), 2.9 % with omarthrosis (osteoarthritis of the shoulder) were treated. Efficacy was examined two weeks after the conclusion of the injection series and twelve weeks after the start of the injection series. Relative to the total number of joints treated the treatment resulted in statistically significant pain relief and functional improvement. Adverse effects that could be associated with the trial preparation were reported extremely rarely. The i.a. therapy with the trial preparation can, therefore, be considered effective beyond treatment and very safe in therapeutic routine.

Introduction

The arthroses are among the most frequent pathologies of advanced age but are not rare even in middle age. They impair routine activities of more than half of 70-year olds. The knee joint is by far the most frequently affected joint and patients with gonarthrosis represent the lion’s share of patients in this observational study (OS). Specialists recommend a stepped procedure with physiotherapy, analgesics/NSAIDs, if required, SYSA-DOA (Symptomatic Slow Acting Drugs in Osteoarthritis), such as glucosamine hemisulfate or intraarticular (i.a.) hyaluronic acid injections, intraarticular glucocorticoid injections, joint lavage, and endoprostheses for the therapy of osteoarthritis.

Intraarticular injection of exogenous hyaluronic acid comes under consideration when the initially planned therapeutic steps are insufficiently effective or are contraindicated. It can also be combined with other procedures. Hyaluronic acid, which is formed endogenously by synoviocytes in the joint lining and chondrocytes of the cartilage, is a principal component of synovial fluid. The endogenous hyaluronic acid is quantitatively and qualitatively reduced in an arthritic joint. This results in impairment of the lubricating and shock-absorbing function of the synovium and mechanical joint stressing increases. This favours loss of cartilage tissue whose elasticity and metabolism benefit likewise from a high hyaluronic acid component in the synovium. Improvement and supplementation of endogenous hyaluronic acid with exogenous hyaluronic acid (viscosity supplementation) can thus clearly improve the joint situation. Numerous clinical studies and meta-analyses have shown that this improvement is expressed in patients as pain relief and better joint function. The latest Cochrane-Reviews by Bellamy et al. (1, 2) found that i.a. hyaluronic acid is clinically more effective than placebo and in comparison to i.a. corticosteroids has a longer therapeutic carry-over effect. A meta-analysis on the safety of i.a. hyaluronic acid in gonarthrosis (3) demonstrated a positive safety profile, even in comparison with other standard therapies. In large observational studies with a total of more than 1,500 patients with gonarthrosis (4, 5), pain and mobility improved in the course of follow-up following treatment with i.a. hyaluronic acid and there was a regression in the analgesics requirement. I.a. therapy with hyaluronic acid figures as one of the standard therapies.

Keywords: Intraarticular – Hyaluronic acid – Functional improvement – Pain relief – Arthrosis – Practice conditions – Tolerability
in the recommendations of important specialist associations (e.g. German Orthopedics and Orthopedic Surgery Association, Professional Association of Orthopedic Specialists, European League Against Rheumatism, American College of Rheumatology). In the most recent recommendation of the Osteoarthritis Research Society International (OARSI) on the treatment of patients with gon- or coxarthroses (6) it is emphasized that i.a. hyaluronic acid injections are beneficial to patients and have a prolonged effect compared with i.a. corticosteroids.

Study Procedure and Method

This non-interventional study examined the efficacy, the treatment effect carrying over beyond the administration phase, and the safety of administration of the GO-ON® product under practice conditions in a large, non-selected patient population. One GO-ON® ready-to-use syringe contains 2.5 mL of a 1% sodium hyaluronate solution. According to the current instructions for use GO-ON® is injected up to five times into the joint space of the diseased joint, with a one week interval between injections. Efficacy after three or five injections is examined comparatively.

This non-interventional study was conducted at a number of centres between October 2005 and May 2006. Patients over 18 years of age, from the normal patients' pool, who are receiving by their treating physicians GO-ON® treatments independently of the study, were eligible to participate. The indication or administration of the treatment and any necessary procedures (diagnostics, supplemental therapies) were not affected by participation.

Procedure

Depending on individual requirements, patients received a three-week treatment with three injections or five-week treatment with five injections. For this non-interventional study this resulted in five visits (A to E) in the case of three injections and seven visits (A to G) in the case of five injections. The sequence is shown in Table 1 in which the examination parameters collected at the individual visits are given. Patient findings were recorded at three points in time: initial findings (baseline) at Visit A, one to two weeks after the last injection (corresponding to Visit D after three injections and Visit F after five injections) and twelve weeks after commencement of therapy (corresponding to Visit F or G). Pain, function, and impairment of movement in the treated joint were recorded at all three points in time. The overall assessment of treatment outcome by the patient and the physician as well as recording of changes in NSAR/analgesic use was done at the conclusion. Side effects were reported and documented at all visits.

Efficacy analysis parameters

In order to assess the efficacy of the trial preparation and to compare the treatment effects with three or five injections, the following parameters were recorded and statistically evaluated:

- Pain assessment by the patient
- Functional impairment assessment by the patient
- Impairment of movement using the neutral-zero-method
- Overall assessment by the patient and the physician
- Change in the dosage of the NSAR/analgesics
patient

• Overall assessment by the physician

For pain assessment by the patient, which was done at all three examination times mentioned, a score of 1 to 5 points was used. 1 = very intense, 2 = intense, 3 = moderate, 4 = slight and 5 = no pain. For evaluation of efficacy the mean at baseline (initial values) were compared with the means one to two weeks after the start of therapy. The statistical analysis was done using a T-test for paired random samples. In order to compare the effect of therapy with two or five injections the mean changes under the two variants were analyzed using a T-test for independent random samples.

For the assessment of functional impairment by the patients that was done coevally with the pain assessment, a similar score of 1 to 5 points was used: 1 = very severe, 2 = severe, 3 = moderate, 4 = mild, and 5 = no functional impairment. The results were evaluated as in the case of pain assessment.

Restriction of movement in the diseased joint was determined by the physician at all three examination times using the neutral-zero method. Extension and flexion was documented with respect to the knee joint and the other joints. Ab- and adduction and external and internal rotation was determined in the hip joint; only adduction and external rotation was determined in the case of the shoulder joint. The results were analyzed as in the case of pain assessment.

In the global evaluation by the patients 12 weeks after the start of therapy, the number of patients, who observed an improvement of their condition in comparison to the start of therapy, was determined. In the global evaluation by the physician, this group of patients increased from the perspective of the physician. The percentages attained with three or five injections were compared using the chi-square test.

When results for one of the efficacy parameters from the second or third examination point were lacking, they were replaced by the baselines for the statistical interpretation. The statistical interpretation (SPSS 11.5) was done by the Biostatistics Unit under the direction of Giampaolo Giacovelli (PhD, Director, Biostatistics, Data Management and Clinical System Department) at Rottapharm S.p.A. (Via Valosa di Sopra, 20052 Monza, Italy).

**Study Results**

**Patients and treated joints**

Of the 1745 patients recruited for the OS 1743 were treated with at least one injection of the trial preparation and were, therefore, included in the efficacy and safety analysis. All patients who received up to three injections were assigned to the 3-injection treatment group. Of these 268 patients (15 % of the total group) 255 received three injections. All 1475 patients with four or five injections (85 % of the total group) formed the 5-injection treatment group. Of these, 1408 patients received five injections. 56.2 % of patients were female.

<table>
<thead>
<tr>
<th>Joints</th>
<th>Total Group</th>
<th>With Three Injections</th>
<th>With Five Injections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knee joints</td>
<td>1533</td>
<td>216 (14%)</td>
<td>1317 (86%)</td>
</tr>
<tr>
<td>Hip joints</td>
<td>77</td>
<td>10 (13%)</td>
<td>67 (87%)</td>
</tr>
<tr>
<td>Shoulder joints</td>
<td>50</td>
<td>14 (28%)</td>
<td>36 (72%)</td>
</tr>
<tr>
<td>Other joints*</td>
<td>83</td>
<td>28 (34%)</td>
<td>55 (66%)</td>
</tr>
<tr>
<td>All joints</td>
<td>1743</td>
<td>268 (15%)</td>
<td>1475 (85%)</td>
</tr>
</tbody>
</table>

*Radiocarpal joint (n=31), ankle (n=24), metatarsophalangeal joint (n=14), metacarpalphalangeal joint (n=4), elbow joint (n=3), finger joint (n=3), small spinal joint (n=3), carpometacarpal joint (n=1)

In the global evaluation by the patients 12 weeks after the start of therapy, the number of patients, who observed an improvement of their condition in comparison to the start of therapy, was determined. In the global evaluation by the physician, this group of patients increased from the perspective of the physician. The percentages attained with three or five injections were compared using the chi-square test.

When results for one of the efficacy parameters from the second or third examination point were lacking, they were replaced by the baselines for the statistical interpretation. The statistical interpretation (SPSS 11.5) was done by the Biostatistics Unit under the direction of Giampaolo Giacovelli (PhD, Director, Biostatistics, Data Management and Clinical System Department) at Rottapharm S.p.A. (Via Valosa di Sopra, 20052 Monza, Italy).

**Safety analysis**

All treated patients were included in the safety analysis. Adverse effects were reported at every visit and were then documented. Changes in general condition, disease symptoms that occurred after the start of treatment, and relevant changes in laboratory values that were possibly associated with the treatment were considered adverse effects.

**Table II: Treated joints.**

<table>
<thead>
<tr>
<th>Time</th>
<th>Total Group</th>
<th>With Three Injections</th>
<th>With Five Injections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>2.14</td>
<td>2.07</td>
<td>2.15</td>
</tr>
<tr>
<td>1-2 weeks after the end of therapy</td>
<td>3.54 (p &lt; 0.000)</td>
<td>3.22 (p &lt; 0.000)</td>
<td>3.60 (p &lt; 0.000)</td>
</tr>
<tr>
<td>12 weeks after start of treatment</td>
<td>3.84 (p &lt; 0.000)</td>
<td>3.60 (p &lt; 0.000)</td>
<td>3.88 (p &lt; 0.000)</td>
</tr>
</tbody>
</table>

**Table III: Pain assessment by the patients (pain score).**
5 injections the results were statistically significant compared with the baseline. Pain relief continued to increase up to the last examination; at the end pain was equated with mild symptoms (Fig. 1). In the comparison between the two treatment groups there was a significant advantage for five injections (p < 0.000 one to two weeks after the end of therapy. p=0.002 twelve weeks after the start of therapy).

The mean functional impairment at the start for the patients was 2.94 ± 1.06 which equated with moderate impairment. Table IV shows changes under therapy. The same applies to the course of the total and the individual treatment groups as for the pain parameters. In the comparison between the two treatment groups there was a significant advantage for five injections one to two weeks after the last injection (p < 0.015).

In all joints – with the exception of the hip and shoulder joints – extension, normal position, and flexion were measured for assessing the therapeutic effect. Here, at the start, a mean extension of 3.32 degrees ± 16.95 degrees and a mean flexion of 108.68 ± 28.94 degrees was documented. Table V shows changes under therapy. All changes were significant (except in the case of extension in the treatment group receiving three injections after twelve weeks) and particularly clear in the case of flexion (Fig. 2). There was no significant difference in the comparison between the two treatment groups.

Twelve weeks after the start of therapy 92.5 % of patients reported an improvement. The physicians noted improvement in 93.6 % of their patients. In both overall assessments the comparison between the two treatment groups showed a significant advantage for five injections (p = 0.010 for patient, p = 0.039 for physician). In the treatment of all diseased joints i.e. sodium hyaluronate had a statistically significant and clinically relevant effect on the parameters examined. Severe pain became mild pain at 12 weeks after the start of therapy; moderate functional impairment became mild impairment. Joint mobility benefited, particularly manifestly in terms of flexion. More than 90% of patients perceived an improvement which was also confirmed by the physician. In the majority of efficacy parameters, there was a significant advantage for five versus three injections.

Results of the total group

Of the 1743 treated patients 85% received therapy with five and 15% with three injections. The mean pain score at the start for the patients was 2.14 ± 0.79 which equated with severe pain. Table III shows changes under therapy: Both in the group receiving 3 injections and in the group receiving
ding pain relief under therapy with i.a. sodium hyaluronate is exactly the same as for the total group. This concerns also the significant advantage with five injections (p < 0.000 at the first, p = 0.003 at the time of the second examination). Twelve weeks after the start of therapy severe pain due to osteoarthritis of the knee became mild pain, with "pain score" 3.85 in the total group, 3.89 after five, and 3.60 after three injections (all p < 0.000).

The mean functional impairment in patients with osteoarthritis of the knee at the start was 3.01 ± 1.05 which equated with moderate impairment. Here, too, therapy resulted in a significant improvement at both examination points (all p < 0.000). Twelve weeks after the start of therapy there was only mild impairment, with "function score" 3.97 in the total group, 3.81 after five, and 4.00 after three injections (Fig. 3). There was no significant difference between the two treatment groups.

In the knee joints, at the start, a mean extension of 2.96 degrees ± 17.20 degrees, a mean deviation from the normal position by 2.50 degrees ± 5.52 degrees and a mean flexion of 113.08 ± 22.82 degrees were documented. A significant improvement was observed for extension after five injections and twelve weeks (p = 0.034) and for the normal position, and flexion at both points in time (p = 0.017 at the first, p = 0.005 at the second examination point for the normal position, p < 0.000 for flexion). After twelve weeks, there was a significant advantage for five injections (p = 0.042) in the case of the normal position.

Twelve weeks after the start of therapy 93.0 % of patients reported an improvement. The physicians noted improvement in 93.7 % of their patients. In both overall assessments the comparison between the two treatment groups showed a significant advantage for five injections (p = 0.013 for patient, p = 0.046 for physician). In the treatment of all osteoarthritis of the knee, i.a. sodium hyaluronate had a statistically significant and clinically relevant effect on the parameters examined. Severe pain became mild pain at 12 weeks after the start of therapy; moderate functional impairment became mild impairment. Joint mobility benefited, particularly in terms of flexion. More than 90 % of patients perceived an improvement which was also confirmed by the physician. In the majority of efficacy parameters, there was a significant advantage for five versus three injections.

Results in hip joints
In the context of the OS, 77 patients with osteoarthritis of the hip were treated; 87 % received five and 13 % received three injections. At the start of treat-
In the treatment group comparison, a significant advantage was observed for five injections at the first examination point (p = 0.015).

In the hip joints, at the start, a mean abduction of 22.29 degrees ± 13.61 degrees, a mean adduction of 22.07 degrees ± 27.05 degrees, a mean external rotation of 20.80 degrees ± 11.00 degrees, and an average internal rotation of 10.51 ± 10.33 degrees were measured.

Table VI shows changes under therapy: significant improvements in mobility were observed for abduction in the total group and in the group with five injections after twelve weeks, and for adduction, external and internal rotation in the total group, and in the group with five injections at both examination points. The treatment group comparison showed no significant difference.

In the overall assessment at twelve weeks after the start of treatment, 90.8 % of the patients reported an improvement, which was observed also by the physicians in 94.7 % of the patients. The treatment group comparison showed no significant difference. In the treatment of all osteoarthritis of the hip, i.a. sodium hyaluronate had a statistically significant and clinically relevant effect on the parameters examined. Severe pain became mild pain at 121 weeks after the start of therapy. Severe to moderate impairment of function became moderate to mild impairment. Joint mobility benefited, particularly in terms of adduction and rotation. More than 90 % of patients perceived an improvement which was confirmed by the physicians. In the hip joint a pronounced efficacy advantage was noted for five versus three injections.

In the context of the post-marketing study, 50 patients with osteoarthritis of the shoulder were treated, 72 % received five and 28 % received three injections. At the start of treatment the patients had a mean pain score of 2.04 ± 0.86 which equates with severe pain. I.a. treatment with sodium hyaluronate produced at both examination points observable statistically significant pain relief in the total and in both treatment groups (all p < 0.000). There was no significant difference in the group comparison. The mean function impairment at the start was 2.47 ± 1.06 and thus between severe and moderate impairment. The therapy produced for all groups a significant improvement in function at the two examination points (all p < 0.000). In the treatment group comparison, a significant advantage was observed for five injections at the first examination point (p = 0.015). In the hip joints, at the start, a mean abduction of 22.29 degrees ± 13.61 degrees, a mean adduction of 22.07 degrees ± 27.05 degrees, a mean external rotation of 20.80 degrees ± 11.00 degrees, and an average internal rotation of 10.51 ± 10.33 degrees were measured. Table VI shows changes under therapy: significant improvements in mobility were observed for abduction in the total group and in the group with five injections after twelve weeks, and for adduction, external and internal rotation in the total group, and in the group with five injections at both examination points. The treatment group comparison showed no significant difference.

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Results in shoulder joints

In the context of the post-marketing study, 50 patients with osteoarthritis of the shoulder were treated, 72 % received five and 28 % received three injections. At the start of treatment the patients had a mean pain score of 2.04 ± 0.86 which equates with severe pain. I.a. treatment with sodium hyaluronate produced at both examination points observable statistically significant pain relief in the total and in both treatment groups (all p < 0.000). There was no significant difference in the group comparison. The mean functional impairment at the start was 2.33 ± 0.99. Here, too, there was a significant improvement at both times in all groups (each p < 0.000, only for three injections after twelve weeks p = 0.001), while the treatment group comparison
did not reach significance. At the start of therapy a mean abduction of 73.29 degrees ± 25.45 degrees and a mean external rotation of 40.53 degrees ± 28.16 degrees were measured in the shoulder joints. Table VII shows the treatment results: significant improvement at both examination points was found in abduction in all groups, in external rotation in the total group and in the group with five injections. The treatment group comparison was not significant.

In the overall assessment twelve weeks after the start of treatment, 96.0 % of the patients reported an improvement, which was observed also by the physicians in 98.0 % of the patients. The group comparison did not result in any significant difference, which is not surprising with the small group of treated patients in the shoulder osteoarthritis group. In all patients with osteoarthritis of the shoulder, i.a. sodium hyaluronate had a statistically significant and clinically relevant effect on all parameters examined. Severe pain became mild pain at 12 weeks after the start of therapy; severe to moderate functional impairment became moderate to mild impairment. Joint mobility benefited. More than 95 % of patients perceived an improvement which was also confirmed by the physician.

Results in other joints

In the radiocarpal joints (n=31) both three and five i.a. sodium hyaluronate injections provided significant pain relief (after three injections p = 0.010 at the first, p = 0.001 at the second, after five injections p < 0.000) at both examination points and significant functional improvement (after three injections p = 0.011 at the first, p = 0.004 at the second, after five injections p < 0.000). Joint mobility was not significantly affected. There was no significant difference between three and five injections. 90 % of the patients perceived an overall improvement.

In the ankle joints (n = 24), five

Table VI: Hip joints – impairment of movement using the neutral-zero method.

<table>
<thead>
<tr>
<th>Time</th>
<th>Treatment Groups</th>
<th>Abduction [°]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total Group</td>
<td>With Three Injections</td>
</tr>
<tr>
<td>Baseline</td>
<td>22.29</td>
<td>20.00</td>
</tr>
<tr>
<td>1-2 weeks after the end of therapy</td>
<td>23.14 (n. s.)</td>
<td>21.11 (n. s.)</td>
</tr>
<tr>
<td>12 weeks after start of treatment</td>
<td>25.21 (p = 0.009)</td>
<td>23.33 (n. s.)</td>
</tr>
</tbody>
</table>

Table VII: Shoulder joints – impairment of movement using the neutral-zero method.

<table>
<thead>
<tr>
<th>Time</th>
<th>Treatment Group</th>
<th>Abduction [°]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total Group</td>
<td>With Three Injections</td>
</tr>
<tr>
<td>Baseline</td>
<td>73.29</td>
<td>77.50</td>
</tr>
<tr>
<td>1-2 weeks after the end of therapy</td>
<td>92.00 (p &lt; 0.000)</td>
<td>106.25 (p &lt; 0.046)</td>
</tr>
<tr>
<td>12 weeks after start of treatment</td>
<td>103.03 (p &lt; 0.000)</td>
<td>115.00 (p &lt; 0.022)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time</th>
<th>Treatment Group</th>
<th>External Rotation [°]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total Group</td>
<td>With Three Injections</td>
</tr>
<tr>
<td>Baseline</td>
<td>20.80</td>
<td>24.44</td>
</tr>
<tr>
<td>1-2 weeks after the end of therapy</td>
<td>23.04 (p &lt; 0.000)</td>
<td>25.00 (n. s.)</td>
</tr>
<tr>
<td>12 weeks after start of treatment</td>
<td>24.93 (p &lt; 0.000)</td>
<td>27.22 (n. s.)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time</th>
<th>Treatment Group</th>
<th>Internal Rotation [°]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total Group</td>
<td>With Three Injections</td>
</tr>
<tr>
<td>Baseline (Visit A)</td>
<td>10.51</td>
<td>11.11</td>
</tr>
<tr>
<td>1-2 weeks after the end of therapy</td>
<td>13.91 (p &lt; 0.000)</td>
<td>12.22 (n. s.)</td>
</tr>
<tr>
<td>12 weeks after start of treatment</td>
<td>3.22 (p &lt; 0.000)</td>
<td>13.89 (n. s.)</td>
</tr>
</tbody>
</table>
i.a. sodium hyaluronate injections brought about significant pain relief at both points in time (p < 0.000), three injections only after twelve weeks (p = 0.020). Significant functional improvement also occurred with five injections at both points in time (p = 0.006 at the first, p = 0.008 at the second point) and with three injections only after twelve weeks (p = 0.043). Joint mobility was not significantly affected. There was a significant advantage for five injections in the case of function after twelve weeks (p = 0.049). 83.3 % of the patients perceived an overall improvement.

In the metatarsophalangeal joints (n = 14) three or five injections brought about significant pain relief at both points in time (after three injections p = 0.033 at the first, p = 0.009 at the second, after five injections p = 0.015 at the first, p = 0.002 at the second). Significant functional improvement occurred only after 12 weeks (after three injections p = 0.038, after five p = 0.008).

A maximum of four of all other joints were treated; accordingly, no joint-specific statement can be inferred from this.

**Analgesics dose reduction**

Of the 1743 treated patients, 465 (26.7 %) did not report on changes in their NSAR/analgesic dosing in the course of the i.a. sodium hyaluronate injection therapy. 131 patients (7.5 %) were not asked about this. Of the remaining 1147 patients (65.8 % of all) 907 (52.0 % of all) reported that they reduced the dose of their NSAR/analgesics in the course of the injection therapy (Fig. 4).

**Safety / adverse effects**

Of the 1743 treated patients, two from the treatment group with three injections reported undesirable effects. One female patient withdrew from the study after the second injection because of pain which occurred on the day of the injection. One other female patient experienced a pulmonary embolism which occurred more than one month after the third injection, however.

**Discussion**

This OS describes the efficacy and safety of i.a. injection of sodium hyaluronate (GO-ON®) under practice conditions in a non-selected patient population or in therapeutic routine. The objective findings made in this OS and the subjective assessments of the patients show that the overwhelming majority receive a benefit from this treatment method. The efficacy results obtained one to two weeks after the end of the treatment series of three or five injections document an overwhelming statistically significant and, for the patients, also clinically relevant improvement vis-à-vis the baseline findings. The average pain at the start became mild to moderate pain within four to six weeks. Of the average moderate functional impairment at the start, there remained only mild impairment. The joint mobility determined using the normal-zero method improved significantly under treatment; in the treatment group with five injections, this applies to all degrees of freedom measured in the knee, hip, and shoulder joint. This OS with GO-ON® thus confirms the results of earlier post-marketing studies with other hyaluronic acid products (4, 5, 7, 8).

The same efficacy parameters, determined 12 weeks after the start of therapy, demonstrate a carry-over effect of around 7 or 9 weeks of the i.a. sodium hyaluronate injections beyond the immediate therapeutic administration. The carry-over effect of i.a. hyaluronic acid therapy was also recognized in the most recent Cochrane Report (2), in the cited observational studies (4, 5, 8), and in the meta-analysis by Arrich et al (9) as a characteristic of this therapeutic form.

An essential point of this OS is the comparison of the treatment groups with five injections, which 85 % of participants received,
and three injections. Here it was found that the patients receiving five injections were at no disadvantage whatsoever, but in many cases there was additional benefit. Significant advantages were observed in different parameters such as in pain relief at both examination points on the knee and hip joints or in the global assessment by the patient and by the physician in the knee joints, for example. There were also significant advantages of five injections in individual joints and individual examination points observed in functional and mobility impairment. In osteoarthritis of the hip a pronounced efficacy advantage associated with five injections was noted. Lower analgesics/NSAR requirement, which was reported in the OS in 52% of the patients, was reported also in earlier observational studies (4, 5) and is considered, together with the therapeutic carry-over effect, to be an argument for the feasibility of i.a. hyaluronic acid therapy. The very good tolerability of i.a. hyaluronic acid injections that is reported in all available meta-analyses and post-marketing studies was impressively confirmed in this post-marketing study. One single pain reaction in more than 7000 injections in 1743 patients speaks in favour of a not only highly effective but also safely tolerated treatment option.

**Literature**


**Author’s address:**
Dr. med. T. Kausch
Orthopädische Fachklinik Kurköln
Landgrafenschamide 32-38
D-53474 Bad Neuenahr-Ahrweiler