Viscosupplementation using intra-articular (i.a.) hyaluronic acid (HA) is a recommended treatment option in the management of osteoarthritis (OA) of the knee.1-4

The symptomatic benefits of i.a. treatment with HA have been demonstrated in several studies in patients with knee OA, with beneficial effects lasting between 6 months10 and 1 year after the administration of one i.a. injection of HA per week for five consecutive injections.2

The long-term benefits of HA have been attributed to an improvement in the viscoelastic properties of the synovial fluid.1-4

We therefore carried out a study in patients with painful advanced knee OA, who were candidates for total knee replacement (TKR) within the next 3 months, with the aim of evaluating the dynamic viscosity and elasticity of the synovial fluid in patients treated with five i.a. injections of Ostenil® (Hyaluronan S, Sandoz Ltd, Basel, Switzerland) using a steriley supplied as a sterile, ready-to-use, pre-filled 5 mL syringe containing 45 mg of hyaluronic acid, obtained by bacterial fermentation.

Evaluation parameters: The primary efficacy criteria were pain on walking 20 m without support, assessed using the VAS, and pain using the WOMAC Index section A. The secondary efficacy criteria included joint stiffness and function (WOMAC Index sections B and C, respectively), physical examination of the knee, escape medication consumption, quality of life (SF-36 health survey), viscous/elastic moduli of the synovial fluid and efficacy judgements by the patients and the investigator.

Methods: As continuous analgesic or anti-inflammatory medication was an inclusion criterion, no washout period was necessary prior to study start. Efficacy parameters were assessed and synovial fluid collected prior to i.a. injection of Ostenil® on Days 0, 7, 14, 21 and 28 (i.e. Visit 1 to Visit 5). Intrusions were performed in the target knee under standardized conditions using the superolateral approach. When the anesthetizing process was required, the amount of synovial fluid obtained was recorded. The treated knee was mobilised immediately after each injection and patients were advised to refrain from strenuous physical activities involving the knee. The synovial fluid samples collected during the study were frozen within 4 hours at -20°C until analysis. Viscosity measurements were made using a RheoStress 1 rheometer (Haake, Karlsruhe, Germany) at a frequency of 1 Hz. Follow-up visits were scheduled for Days 56 and 84 (Visits 6 and 7). An open visit (Visit 8), which took place during the period from Day 84 up to Month 12, was foreseen to determine the time at which the patient returned for re-treatment because of worsening symptoms (time to re-treatment) or when the patient had TKR (time to TKR). Patients had access to analgesics or NSAIDs as rescue medication and intake was recorded. The treated knee was mobilised immediately after each injection and patients were advised to refrain from strenuous physical activities involving the knee.

Results: A total of 24 patients (average age 62.5 ± 10.6 years, average weight 78.9 ± 12.1 kg, 50% female) with painful advanced knee OA (Kellgren–Lawrence grade II [33.3%], III [58.3%] and IV [8.3%]) received continuous NSAID treatment and who were candidates for TKR within 3 months were included in the study.

Three patients dropped out of the study for personal reasons and 21 patients completed the treatment cycle with Ostenil®.

The primary efficacy parameter of pain in the affected joint on walking 20 m without support decreased significantly (p = 0.002) from 8.86 ± 3.02 (median: 7.0) at baseline to 2.43 ± 2.44 (median: 3.0) at Visit 8 (Figure 2).

The same trend was observed for the other primary efficacy criterion, WOMAC A, which showed a significant (p = 0.002) decrease from 43.67 ± 14.65 mm (median: 44.0 mm) at baseline to 16.67 ± 5.70 mm (median: 17.0 mm) at Visit 8 (Figure 2).

Joint stiffness (WOMAC B) (Figure 3) and impairment (WOMAC C) (Figure 4) improved significantly (p < 0.005) from Visit 3 onwards compared with baseline values. WOMAC B showed a significant decrease from 3.24 ± 2.02 (median: 3.0) at baseline to 1.76 ± 1.64 (median: 2.5) at Visit 3. The same trend was observed for WOMAC C, which decreased from 21.95 ± 9.55 (median: 21.0) at baseline to 14.29 ± 9.31 (median: 12.0) at Visit 3.

The relationship between the improvement in clinical signs and the improvement in symptoms.

Two adverse events (impaired joint function, of moderate intensity, due to effusion occurring one day after the second injection and lasting more than 1 day but resolving spontaneously without sequelae and without the need for other interventions) was reported in one patient.

Conclusions

This open, pilot, phase II study demonstrated that a treatment cycle with Ostenil® delayed TKR by 4.5 to 6 months in 3 patients and up to 12 months in the other 18 patients.

We therefore carried out a study in patients with painful advanced knee OA who were awaiting TKR.

was safe and significantly improved symptoms in patients with painful advanced knee OA who were awaiting TKR.

improved the quality of life of these patients.

improved the viscoelastic moduli of the synovial fluid, compared with baseline values, which seemed to correspond to the improvement in symptoms.

The relationship between the improvement in clinical signs and the change in viscosotropic properties of the synovial fluid should be further investigated in a larger study.

References


