Safety and efficacy of a single intra-articular injection of mannitol-modified cross-linked hyaluronic acid (HappyMini®) in patients with hallux rigidus. A prospective open-label multicentre pilot study (REPAR trial).


*Rheumatology
*Orthopaedic surgery

Belfort, Auch, Cornebarrieu, Lyon, La Crau, Montélimar, Nevers, Viry-Chatillon, Nancy, FRANCE
Osteoarthritis of the first metatarso-phalangeal (FMP) joint – Hallux Rigidus- is a frequent and painful condition that has a significant impact on quality of life.

The conservative treatment usually consists in analgesics, NSAIDs intraarticular injections of corticosteroids or hyaluronic acid (HA) preparations, and the use of semi-rigid insolses.

In case of non-response to medical therapy, surgical procedure should be contemplated.
HAnox-M-XL in Hallux Rigidus

✓ To assess the safety and the efficacy on pain relief of a single intra-articular injection of a new mannitol-modified cross-linked hyaluronic acid (HANOX-M-XL) viscosupplement, in patients suffering from hallux rigidus.

✓ To study the predictive factors of response to viscosupplementation, with a particular focus on the radiological stage.
HAnox-M-XL in Hallux Rigidus

✓ Patients with **symptomatic FMP OA** were included in a 3-month prospective multicentre open-label trial.

✓ Investigators were **rheumatologists or orthopedic surgeons**, specialized in foot OA

✓ The study received the French health authorities approval and was conducted in accordance with the Ethical standards of the Declaration of Helsinki.
To be included in the study patients must have **symptomatic Hallux Rigidus, not adequately relieved** by analgesics/ NSAIDs therapy and/or by the use of a plantar orthotic.

Patients with history of inflammatory (i.e. psoriasis arthritis) or crystal deposition disease (i.e. gout), hallux valgus and those who previously received intra-articular injections with corticosteroids into the target toe were excluded.
All patients must have standard radiographs, for the assessment of the radiological grade (0-3).

Menz et al. Osteoarthritis Cartilage 2007 15, 1333-38

<table>
<thead>
<tr>
<th>X-Ray grade</th>
<th>Joint space narrowing</th>
<th>Ostéophyte</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0</td>
<td>Absence</td>
<td>Absence</td>
</tr>
<tr>
<td>Grade 1</td>
<td>Mild</td>
<td>Mild</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Severe</td>
<td>Large</td>
</tr>
</tbody>
</table>
HAnox-M-XL in Hallux Rigidus

Treatment consisted in a single injection of 1 ml of HANOX-M-XL in the TMC joint under fluoroscopic or ultra-sound guidance.

HANOX-M-XL (Happymini®, LABRHA SAS, Lyon, France) is a viscosupplement, that combines:

- **IPN technology cross-linked HA** of non-animal origin (16 mg/ml)
- **High concentration** (35 mg/ml) of **MANNITOL**, a polyol known for its **antioxidant** properties by scavenging radical oxygen species (ROS)
- **Very long IA residence time** > 30 days
HAnox-M-XL in Hallux Rigidus

✓ **Primary endpoints** were the variation between injection (D0) and D90 of the toe pain on 11 point-Likert scale (0-10) and the patient's self-assessment of efficacy (0-3).

✓ **Predictive factors of response** including clinical, demographic and radiographic data were also studied.

✓ **Statistical tests were carried out on the ITT population**. The statistical analysis was performed using Statview© software version 5.0 (SAS institute Inc).
HAnox-M-XL in Hallux Rigidus

✓ 65 patients (72.3% women, mean age: 60, mean symptom duration: 24.9 months, BMI 25) were included in the trial. 9 patients (13.5%) were lost to follow-up.

✓ Treatments at inclusion:
  ✓ Analgesics 63%,
  ✓ NSAIDS 41%,
  ✓ SYSADOA 13%,
  ✓ Insoles 17%,

✓ Guidance:
  ✓ Radio 59%,
  ✓ US 41%

✓ There was no statistically significant correlation between the radiological stage and the pain score at baseline (p = 0.69).

Mean Pain (SD) at D0
6.5/10 (1.6)
No significant difference according to the radiological grade

Results: population

Mean Pain (SD) at D0

<table>
<thead>
<tr>
<th>JSN grade</th>
<th>1 (N=30)</th>
<th>2 (N=29)</th>
<th>3 (N=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS score at Day 0</td>
<td>8</td>
<td>7</td>
<td>7</td>
</tr>
</tbody>
</table>

R=0.25; p=0.69
At baseline and end-point, the median pain score was respectively 7 (range 3-10) and 2 (range 0-9).

The difference in the pain score between baseline and endpoint was highly significant (p < 0.0001).

At D90, 59% of patients reduced their analgesic or NSAID consumption.
Results: Pain

HAnox-M-XL in Hallux Rigidus

Pain score: Individual data at D0 and D90

Number of patients according to pain score categories (numerical rating scale 0-10) at baseline (N=65) and 3 months after viscosupplementation (N=59).

Patients with pain score ≤4 fulfilled the Patient Acceptable Symptom State (PASS) criterion.

Number of patients

Pain score 0-10

PASS +

0 1 2 3 4 5 6 7 8 9 10

D0 D90
HAnox-M-XL in Hallux Rigidus

In univariate analysis response to viscosupplementation was:

✓ Unrelated to:
✓ Age
✓ Gender
✓ BMI
✓ Disease duration
✓ Level of pain on VAS at baseline
✓ Type of guidance (US versus X-rays)

✓ Related with:
✓ Joint space narrowing grade (p=0.001)

In multivariate analysis Joint space narrowing grade remained the only predictive factor of response to viscosupplementation (p=0.02).
HAnox-M-XL in Hallux Rigidus

Walking pain score (0-10) at time of injection and month 3, in 65 patients with hallux rigidus treated with 1 intra-articular injection of HANOX-M-XL (N=65), according to the radiological joint space narrowing (JSN) score

Between-group difference: Grade 1 versus Grade 2-3; p=0.001, Intra-group differences all p<0.0001.
HAnox-M-XL in Hallux Rigidus

There was no safety issue.

- 15 treatment/injection procedure-related adverse events (22.7%) occurred.
- All AEs were local pain during or following HA administration and resolved without sequel within 1 to 7 days.
- No severe or systemic AEs
Thanks to its powerful anti-oxidant properties, Mannitol decreases reactive oxygen species (ROS) related-degradation of hyaluronic acid, compared to cross-linked viscosupplements not containing mannitol.
Topical Mannitol exhibits anti-inflammatory and anti-oedematous effects similar to that of diclofenac and ketoprofen.

These two properties of mannitol may explain the present results that contrast with those of Munteanu et al (ARD 2011) showing no statistical difference between hylan GF-20 and saline.
HAnox-M-XL in Hallux Rigidus

✓ A single injection of 1 ml of HANOX-M-XL, performed under imaging guidance in FMP joint, reduces significantly pain at walking, for at least 3 months, especially in patients with mild to moderate joint space narrowing.

✓ However the majority of patients with more advanced OA were also significantly improved.

✓ Although the overall tolerability was good, a careful information of the patient is necessary, regarding the risk of pain increase the few days following injection.

✓ Further controlled studies, with longer follow-ups, are needed to confirm these promising results.
Thanks