Obesity and severity of joint space narrowing are associated with a higher risk of viscosupplementation failure in patients with knee osteoarthritis. Post-hoc analysis of a double-blind, controlled, multicentre, randomized trial

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BACKGROUND

- Viscosupplementation (VS) is widely used for symptomatic knee osteoarthritis (OA).
- The recommendations from international societies (ACR[1], EULAR[2], OARSI[3] and AAOS[4]) are somewhat conflicting.
- Some international experts have expressed reservations or disagreements about these recommendations[5].
- Uncertainties remain about the use of VS in knee OA given:
  - the variability of hyaluronic acid (HA) intrinsic properties:
    - ➢ animal origin or not
    - ➢ molecular weight
    - ➢ concentration
    - ➢ crosslinking
  - the intra-articular (IA) injection protocol:
    - ➢ fluoroscopy, ultrasound or visual guidance
    - ➢ 1-5 weekly injections
  - the variability of OA phenotype and of clinical or radiological severity.
- Identifying predictive factors of VS outcome could help clinicians to define the patients who would best benefit from VS.
- The HAV-2012 study was a prospective, multicentre, randomized, non-inferiority trial comparing 3 weekly injections of HANOX-M (HAppyVisc®, LABRHA SAS, Lyon, France), combining sodium hyaluronate (1–1.5 MDa, 31 mg/2 ml) with mannitol 3.5% to BioHA (Euflexxa®, Ferring Pharmaceuticals, Parsippany, USA, 2.4-3.6 MDa, 20 mg/2 ml), in patients with symptomatic knee OA with a 6 months follow-up.

OBJECTIVES

To identify clinical and radiologic factors associated with lack of a relevant response according to OMERACT-OARSI criteria after IA HA injections in symptomatic knee OA patients.

METHODS

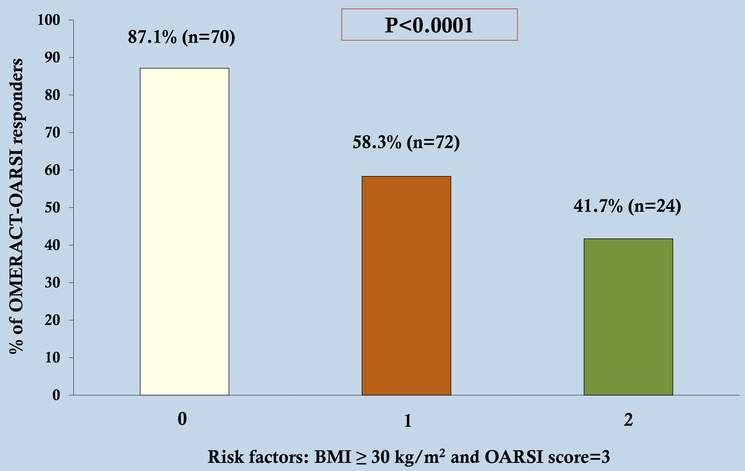
•We included 166 patients with available data from the intent-to-treat population (n=205) of HAV-2012 study.
• At inclusion, investigators recorded:
  - demographic, anthropometric, clinical data (patient global assessment, WOMAC, knee effusion)
  - radiologic data (tibiofemoral joint space narrowing according to OARSI grade, patellofemoral OA).
•Patients received 3 weekly IA injections of HA.
•At 6-month of follow-up, VS response was defined according to OMERACT-OARSI criteria: ≥ 1of 3 following criteria
  - Decrease ≥ 50% and ≥ 20 points of WOMAC pain
  - Decrease ≥ 50% and ≥ 20 points of WOMAC function
  - Decrease ≥ 20% and ≥ 10 for at least 2 of the 3 following criteria:
    - ➢ WOMAC pain
    - ➢ WOMAC function
    - ➢ Patient global assessment

Characteristics of patients at baseline and after 6 months of follow-up

	ITT population (n=166)
Age (years)	65.2 [63.6–66.8]
Age > 65 years	80 (48.2)
Sex (female)	101 (60.8)
BMI (kg/m²)	27.7 [26.9–28.5]
Obesity (BMI ≥30 kg/m²)	47 (28.3)
Disease duration (months)	48.7 [38.4–59.0]
Kellgren-Lawrence score	
Grade 3	116 (69.9)
Grade 4	50 (30.1)
OARSI score	
Grade 1	32 (19.3)
Grade 2	61 (36.7)
Grade 3	73 (44.0)
Patellofemoral OA	31 (18.7)
IA effusion	78 (47.0)
Patient global assessment at baseline (0-10)	6.2 [5.9–6.4]
WOMAC pain at baseline (0-20) †	9.8 [9.3–10.3]
WOMAC function at baseline (0-68) †	27.5 [25.7–29.4]
Painkiller intake (NSAID/other analgesics)	99 (59.6)
Patient global assessment at 6 months (0-10)	3.9 [3.6–4.3]
WOMAC pain at 6 months (0-20) †	5.5 [4.8–6.2]
WOMAC function at 6 months (0-68) †	15.6 [13.4–17.7]
Decrease in patient global assessment	34.6% [28.4-40.7]
Decrease in WOMAC pain †	43.4% [36.4-50.4]

Data are no. of patients (%) or mean [95% CI]. † Each WOMAC item was measured on a 5-point Likert scale. ITT, intent-to-treat. BMI, body mass index. WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index. IA, intra-articular. NSAID, non-steroidal anti-inflammatory drug

Cumulative impact of predictors of OMERACT-OARSI response after VS



CONCLUSIONS

- Radiological severity and obesity may be predictors of lack of a relevant response after VS.
- Disease duration and symptom severity did not alter the response to VS.
- A more stringent selection of patients eligible for HA injection could optimize the effectiveness of treatment and limit the number of VS injections in those with risk factors for poor outcome.
- This finding may impact our daily practice and help in considering VS in future international recommendations.

RESULTS

- At the 6-month visit, 113 patients (68.1%) were considered as VS responders according to OMERACT-OARSI criteria.
- On univariate analysis, increased BMI and greater OARSI or Kellgren and Lawrence scores were associated with VS failure (p=0.002, p=0.005 and p=0.001, respectively).
- On multivariate analysis, increased BMI and tibiofemoral joint space narrowing severity (OARSI grade 3 vs 1-2) were associated with VS failure [OR=0.88 (95% CI 0.81-0.95), p=0.001 and OR=0.39 (0.19-0.81), p=0.011].
- We noted a significant cumulative impact of obesity and radiological severity on VS response.

Predictive factors of OMERACT-OARSI response after VS

Univariate analysis

	OMERACT-OARSI response (n=113)	OMERACT-OARSI non-response (n=53)	P-value
Age (years)	64.5 [62.5–66.4]	66.8 [64.3–69.4]	0.158
Age > 65 years	50 (44.2)	30 (56.6)	0.137
Sex (female)	67 (59.3)	34 (64.2)	0.550
BMI (kg/m²)	26.8 [25.9–27.6]	29.8 [28.2–31.4]	0.002
Obesity (BMI ≥30 kg/m²)	22 (19.5)	25 (47.2)	0.0002
Disease duration (months)	50.3 [37.0– 63.6]	45.2 [30.0– 60.3]	0.684
OARSI grade			0.005
Grade 1	25 (22.1)	7 (13.2)	
Grade 2	48 (42.5)	13 (24.5)	
Grade 3	40 (35.4)	33 (62.3)	
OARSI grade 3 vs 1-2	40 (35.4)	33 (62.3)	0.001
Kellgren-Lawrence grade 4 vs 3	25 (22.1)	25 (47.2)	0.001
Patellofemoral OA	22 (19.5)	9 (17.0)	0.701
IA effusion	50 (44.2)	28 (52.8)	0.302
Patient global assessment at baseline (0-10)	6.2 [5.9–6.5]	6.1 [5.7–6.5]	0.621
WOMAC pain at baseline (0-20) †	9.9 [9.3–10.5]	9.7 [8.8–10.6]	0.753
WOMAC function at baseline (0-68) †	27.3 [25.2–29.4]	28.0 [24.3–31.7]	0.662
Painkiller intake (NSAID/other analgesics)	68 (57.6)	31 (64.6)	0.408

Data are no. of patients (%) or mean [95% CI]. †Each WOMAC item was measured on a 5-point Likert scale.

Multivariate analysis

	Odds ratio	95% CI	P-value
Sex (female)	0.67	0.31-1.44	0.300
Age	0.98	0.94-1.02	0.237
BMI (kg/m²)	0.89	0.82-0.95	0.001
OARSI grade 3 vs 1-2	0.38	0.18-0.77	0.008
WOMAC pain at baseline	0.98	0.83-1.16	0.834
WOMAC function at baseline	1.01	0.97-1.06	0.662
Patient global assessment at baseline	1.09	0.84-1.42	0.504

1. Hochberg MC, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res. 2012;64:465–74.
2. Jordan KM, et al. EULAR Recommendations 2003: an evidence based approach to the management of knee osteoarthritis: Report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). Ann Rheum Dis. 2003;62:1145–55.
3. McAlindon TE, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthritis Cartilage 2014;22:363–88.
4. Brown GA. AAOS clinical practice guideline: treatment of osteoarthritis of the knee: evidence-based guideline, 2nd edition. J Am Acad Orthop Surg. 2013;21:577–9.
5. Migliore A, et al. The discrepancy between recommendations and clinical practice for viscosupplementation in osteoarthritis: mind the gap! Eur Rev Med Pharmacol Sci. 2015;19:1124–9.