EFFICACY OF ONE INTRA-ARTICULAR INJECTION OF 2% NATURAL SODIUM HYALURONATE IS NON-INFERIOR TO CHEMICALLY CROSSLINKED HYLAN G-F 20 IN THE TREATMENT OF PAINFUL TIBIOFEMORAL OSTEOARTHRITIS

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INTRODUCTION

As natural, non-crosslinked hyaluronic acid (HA) is perceived as having shorter efficacy compared with crosslinked HA in the treatment of osteoarthritis (OA),[1] this study compared the efficacy and safety of one intra-articular (i.a.) injection of a natural, medium-molecular weight HA with that of a crosslinked HA in patients with painful tibiofemoral OA.

METHODS

Design: Prospective, randomised, double-blind, controlled, parallel-group, multicentre, non-inferiority clinical trial.

Patients: Men and women aged 40 to 85 years, with Kellgren-Lawrence grade Ib to III uni- or bilateral tibiofemoral OA according to the ACR criteria, and WOMAC A pain on VAS of at least 40 mm.

Treatment: After an NSAID washout period, eligible patients received one i.a. injection in the most painful knee of either:

- 40 mg/2.0 ml sodium hyaluronate (SH) (Ostenil Plus, TRB Chemedica AG, Germany)
- 48 mg/6.0 ml hylan G-F 20 (hylan) (Synvisc-One, Genzyme Biosurgery, USA)

Statistics: The primary endpoint was the change from baseline in WOMAC A at Day 180. The lower margin of non-inferiority was pre-specified at -8 mm. The per protocol (PP) set was used for the main analysis.

RESULTS

Disposition of patients: This study was conducted from June 2011 through November 2012 at 50 sites in France. A total of 292 patients were randomised. Overall, 4 patients did not receive the injection and 22 patients dropped out of the study (Fig. 1).

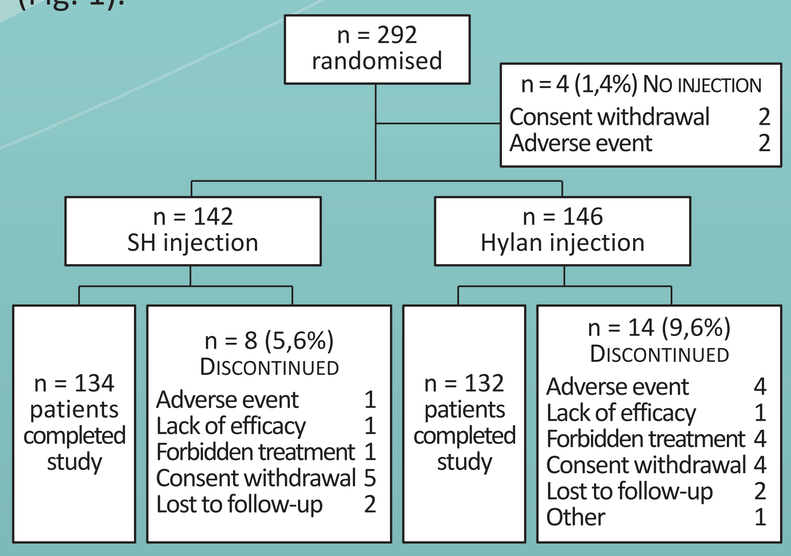

Figure 1: Disposition of patients by treatment group

Data sets: A total of 290 patients (SH: 143, hylan: 147) were included in the full analysis set (FAS) which was used for the descriptive analysis of baseline patient characteristics. Of these, 280 patients were evaluable for efficacy (SH: 139, hylan: 141). The PP data set included all patients who did not have a major protocol deviation and comprised 225 patients (SH: 113, hylan: 112).

Demographics and baseline disease characteristics: Both groups were homogeneous at baseline for demographic and OA characteristics, except for a lower male ratio in the SH group which had no significant effect on the results (Tab. 1).

Table 1: Baseline characteristics (FAS)

Characteristic		SH	Hylan	p
Gender	male – n (%)	39 (27.3)	58 (39.5)	0.0279[1]
	female – n (%)	104 (72.7)	89 (60.5)	
Age (years)	mean (SD)	67.1 (9.7)	66.6 (10.7)	0.6491[2]
BMI (kg/m²)	male – mean (SD)	26.9 (2.4)	26.7 (2.2)	0.7283[2]
	female – mean (SD)	26.2 (3.1)	26.0 (3.2)	0.6441[2]
Knee OA	unilateral – n (%)	73 (51.0)	71 (48.3)	0.6396[1]
	bilateral – n (%)	70 (49.0)	76 (51.7)	
	unicompart. – n (%)	101 (71.6)	96 (65.8)	0.2833[1]
	bicompart. – n (%)	40 (28.4)	50 (34.2)	
Duration (years)	mean (SD)	5.4 (5.4)	6.9 (6.7)	0.0608[3]
KL grade	grade Ib – n (%)	21 (14.7)	25 (17.0)	0.3408[1]
	grade II – n (%)	77 (53.8)	87 (59.2)	
	grade III – n (%)	45 (31.5)	35 (23.8)	

[1] Chi-square test ; [2] Two-tailed Student t test; [3] Wilcoxon test

Primary outcome:
In the PP data set, the mean WOMAC A improvement from baseline (μ) at Day 180 was 34.3 ± 19.0 mm and 36.2 ± 22.0 mm for SH and hylan, respectively. The mean observed difference between groups ($\mu_{SH} - \mu_{hylan}$) was -1.9 ± 20.5 mm, with a two-sided 95% confidence interval (CI) of [-7.3; 3.5] mm. Therefore, the lower bound of the CI was above the non-inferiority margin (-Δ). Results were similar for the FAS population (Fig. 2).

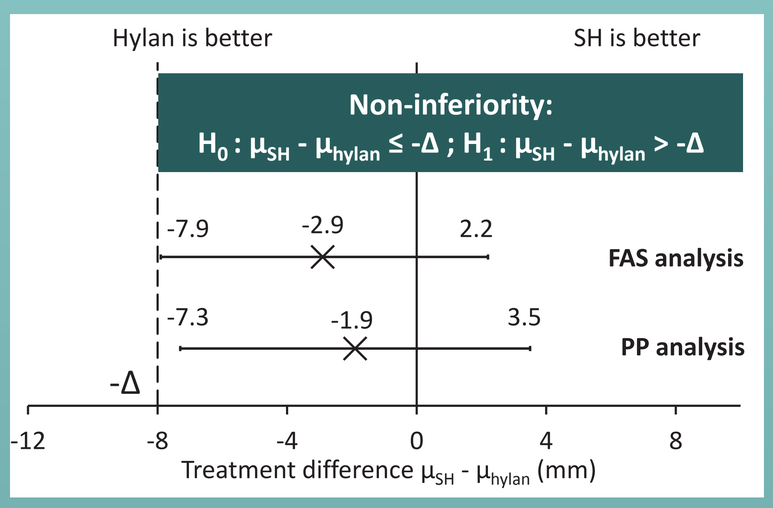

Figure 2: Point estimate and 95% CI of the difference in the primary outcome ($\mu_{SH} - \mu_{hylan}$)

Secondary efficacy outcomes: Other efficacy parameters improved from baseline in both treatment groups, as shown for the Lequesne and WOMAC scores (Fig. 3, Tab. 2).

At Day 180, improvement from baseline of the Lequesne index was 4.2 ± 3.7 points and 4.7 ± 4.0 points in the SH and hylan treatment groups, respectively.

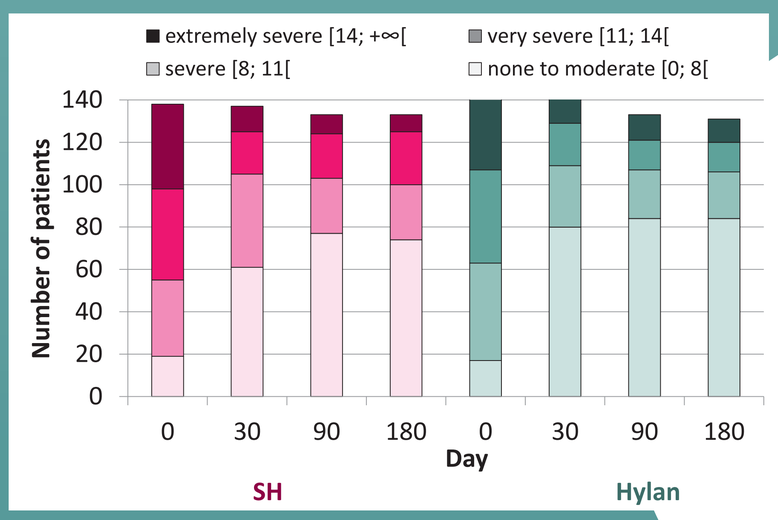

Figure 3: Disability measured using the Lequesne index (FAS)

Table 2: Mean (SD) pain, stiffness and functional impairment measured using the WOMAC score (FAS)

Day	Parameter	SH	Hylan	p [1]
0	WOMAC A pain	58.2 (11.4)	57.9 (11.6)	0.8556
	WOMAC B stiffness	48.2 (20.8)	48.3 (19.5)	0.9549
	WOMAC C function	46.8 (16.1)	47.5 (14.9)	0.7036
30	WOMAC A pain	28.5 (17.9)	27.8 (19.4)	0.7596
	WOMAC B stiffness	27.3 (21.4)	27.3 (19.4)	0.9765
	WOMAC C function	27.0 (17.0)	26.4 (17.9)	0.7835
90	WOMAC A pain	23.9 (18.4)	24.1 (21.5)	0.9340
	WOMAC B stiffness	22.2 (19.7)	24.0 (22.4)	0.4928
	WOMAC C function	23.7 (19.3)	23.3 (20.2)	0.8841
180	WOMAC A pain	24.8 (19.3)	22.0 (19.7)	0.2503
	WOMAC B stiffness	25.9 (23.3)	21.7 (20.5)	0.1251
	WOMAC C function	25.1 (19.3)	21.9 (19.5)	0.1897

[1] Two-tailed Student t test

The OMERACT-OARSI responder rate[2] at Day 180 was 81.1% in the SH group and 86.3% in the hylan group (p = 0.2543).

Safety outcome: Local reactions to the injection occurred only in 8.4% of patients in the SH group versus 13.0% in the hylan group. In the SH group, 4 patients had an OA flare or received a corticosteroid injection versus 7 patients in the hylan group. In this group, 1 patient had a knee prosthesis about 6 months post hylan injection and 1 had a meniscectomy. No serious reaction related to the injection was reported.

CONCLUSIONS

This multicentre clinical trial demonstrated the non-inferiority of one i.a. injection of 2 ml SH compared with 6 ml hylan for the primary efficacy outcome. Both preparations reduced pain and improved function in patients with painful tibiofemoral OA over 6 months.

REFERENCES

1. Raman R et al. Knee. 2008;15(4):318-24.
2. Pham T et al. Osteoarthritis Cartilage. 2004;12(5):389-99.