Efficacy and durability of two hyaluronic acid based fillers in the correction of nasolabial folds: results of a prospective, randomized, double-blind, actively-controlled clinical trial.

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ABSTRACT

• BACKGROUND

This study compared a monophasic hyaluronic acid dermal filler with a biphasic filler for the correction of nasolabial folds.

• METHODS

Patient and assessor blinded, randomised clinical trial, involving patients with moderate to severe nasolabial folds. Split-face design with TEOSYAL® Deep Lines (mono-HA/TEOSYAL®) and RESTYLANE® Perlane (bi-HA/RESTYLANE®) used as study products. Injection with touch up after one month. Wrinkle improvement was measured before and after injection as well as after 1, 2, 4, 7 months, using WSRS and GAIS as outcome criteria. An optional treatment was offered at the end of the study, when patients could choose one of the products.

• OBJECTIVE

Evaluation of efficacy and safety was done through rating of photographs by blinded experts, assessment by a blinded investigator and patient self-assessment.

• RESULTS

Both products showed immediate, good results after injection and touch up, and demonstrated good durability over time. Some assessment criteria showed statistically significant better results for mono-HA/TEOSYAL®. Patient preference for optional treatment at the end of the study favoured mono-HA/TEOSYAL®. Both products were very well tolerated without serious adverse events.

• CONCLUSION

The effect after injection of mono-HA/TEOSYAL® and bi-HA/RESTYLANE® is generally comparable, although there were statistically significant findings in favour of mono-HA/TEOSYAL® in terms of durability. Patients preferred mono-HA/TEOSYAL®.

INTRODUCTION

Injectable fillers are one of the corner stones of aesthetic medicine[1].

Over the last decade, the use of injectable fillers has increased continuously, with hyaluronic acid (HA) preparations being used most frequently. HA is strongly hydrophilic; due to its natural hydrating function within the dermis, it promotes skin suppleness. HA has a very rapid turnover; the chemical cross-linking of HA results in the formation of a viscoelastic polymer and ensures persistence.

Several types of HA fillers exist.
In this study, two types of fillers were investigated:

- the bi-phasic injectable filler **RESTYLANE® Perlane**, which is based on individual particles with a HA content of 20 mg/g
- the mono-phasic injectable filler **TEOSYAL® Deep Lines**, which is based on a homogenous HA preparation with a HA content of 25mg/g.

Both are based on HA produced by bacterial fermentation and therefore are free from products of animal origin. In both products, the HA is cross-linked with butanediol diglycidyl ether (BDDE). The crosslinking strategy yields to two different viscoelastic polymer gels. The mono HA is less elastic (lower G') and more cohesive than bi-HA. Differences in the structural and mechanical properties of the two implants led us to expect differences in filling properties and implant durability in vivo.

TEOSYAL® products were introduced in Europe in 2004 and more than 2 million injections have been performed at the end of 2010. **TEOSYAL® Deep Lines** is recommended for filling deep facial wrinkles, such as nasolabial folds and marionette lines, and is intended for injection into the deep dermis.

METHODS

1. PATIENT POPULATION

Main inclusion criteria

- Females and males (n = 60)
- Age ≥ 30 years
- Clinical evidence of moderate or severe bilateral aging defects in the nasolabial area of both sides, grade 3 or higher[1] using the validated Wrinkle Severity Rating Scale (WSRS)

Main exclusion criteria

- Contraindication for HA as defined in the instructions for use
- Treatment with a biodegradable filler in the last 2 years or with non-biodegradable filler at any time, or facial injections of botulinum toxin A for wrinkle reduction in the last 6 months.

2. STUDY DESIGN

Randomisation was done electronically using standard statistical software. Each patient received mono-HA/TEOSYAL® in one nasolabial fold and bi-HA/RESTYLANE® on the contralateral side of the face.
Patients were blinded during injection. Efficacy and safety assessments were performed by blinded physicians and a blinded independent panel of 3 experts.
The response to the initial injection of TEOSYAL® Deep Lines or RESTYLANE® Perlane was evaluated after 4 weeks. If the blinded assessor determined the result to be unsatisfactory and if the patients agreed, a "touch up" re-injection was done using the same product on the same side by the investigator.
The investigators who did the injections had comparable experience with both products.
A mixture of lidocaine 2.5% and prilocaine 2.5% (Emla®, AstraZeneca, Germany) was applied at least 45 minutes prior to the injection using an occlusive dressing (Tegaderm®, 3M, Austria). HA was injected into the deep dermis using the tunnel technique in combination with the serial puncture technique. The injection volume was selected at the discretion of the investigator doing the injection until a full correction was achieved. The exact injection volume was documented.

3. DATA COLLECTION

Efficacy and safety assessment

6 outcome parameters were used to evaluate efficacy:

1. comparison of the change in the Wrinkle Severity Rating Scale (WSRS) score by the independent expert panel using standardized photographs
2. comparison of the change in the Wrinkle Severity Rating Scale (WSRS) by the blinded investigator
3. comparison of the change in the Global Aesthetic Improvement Scale (GAIS) by the blinded investigator
4. comparison of the change in Global Aesthetic Improvement Scale (GAIS) by the patients themselves
5. the Patients' Self Satisfaction Scale (PSSS) assessment and assessment of implant texture
6. the amount of HA re-injected at month 6 if correction was needed

The assessment of wrinkles was performed using the 5-point WSRS which ranges from 'none' (1), to 'extreme' (5). The GAIS has a value range from 'very much improved' (1), to 'worse' (5). In addition, patients performed the Patients' Self Satisfaction Scale (PSSS) which has values from 'very satisfied' (1), to 'very dissatisfied' (5). Patients were followed for 7 months after the first injection. Efficacy evaluations using the WSRS were done at visit 1 (before and after the first injection), visit 3 (after one month - if touch up treatment was done again before and after injection), visit 5 (2 months after Visit 1), visit 6 (4 months after Visit 1), visit 7 (7 months after visit 1). Assessment of GAIS was done at visit 3, 5, 6 and 7. Additional safety assessments were performed during a telephone interview 3-5 days after the injections (visit 2 and visit 4).

RESULTS

A total of 60 patients were randomized:

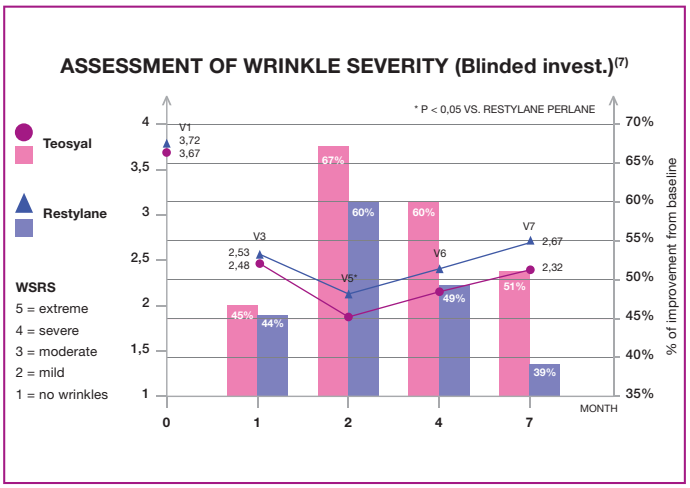
- 86.7% female
- 13.3% male
- Mean age 54.8 ± 8.8 years
- Wrinkle severity prior to the injection as measured (independent expert panel assessment, photographs) by the WSRS was similar between both groups (mono-HA/TEOSYAL® 3.17 ± 0.83; bi-HA/RESTYLANE® 3.16 ± 0.79 (p =0, 94))
- A touch up treatment performed for 53 patients (88%) at V3 (31 ± 4.45 days)

EFFICACY

I. BLINDED INVESTIGATOR ASSESSMENT

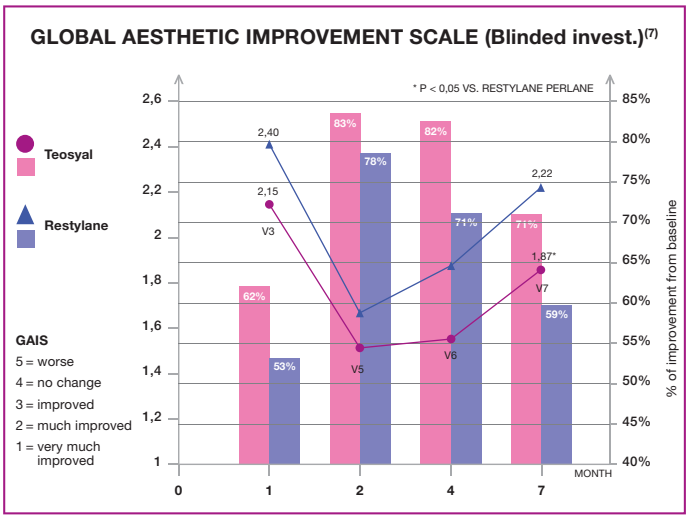
• Wrinkle Severity Rating Scale (WSRS)

The initial average wrinkle severity (V1) as judged by the blinded investigator was 3.67 for the side randomised to be treated with mono-HA/TEOSYAL® and 3.72 for the side to be treated with bi-HA/RESTYLANE® (p=0.71). One month after the injection, the average wrinkle severity was reduced to 2.48 in the mono-HA/TEOSYAL® treated side and to 2.53 for the bi-HA/RESTYLANE® treated side. After 7 months the average wrinkle severity was 2.32 for the mono-HA/TEOSYAL® treated side and 2.67 for the side treated with bi-HA/RESTYLANE®. **Statistically significant (V5) superiority of mono-HA/TEOSYAL® compared to bi-HA/RESTYLANE® was observed over time, which indicates better durability of mono-HA/TEOSYAL®.**



• Global Aesthetic Improvement Scale (GAIS)

One month after the first injection (V3), the mean GAIS was 2.15 for the mono-HA/TEOSYAL® treated side and 2.40 for the bi-HA/RESTYLANE® treated side. After seven months (V7), the mean GAIS was 1.87 for mono-HA/TEOSYAL® and 2.22 for the bi-HA/RESTYLANE® treated side (p= 0.008). **Statistically significant (V7) superiority of mono-HA/TEOSYAL® compared to bi-HA/RESTYLANE® was observed over time, which indicates better persistence of mono-HA/TEOSYAL®.**



II. PATIENT SELF-ASSESSMENT

• Patients' preference for optional treatment after clinical study

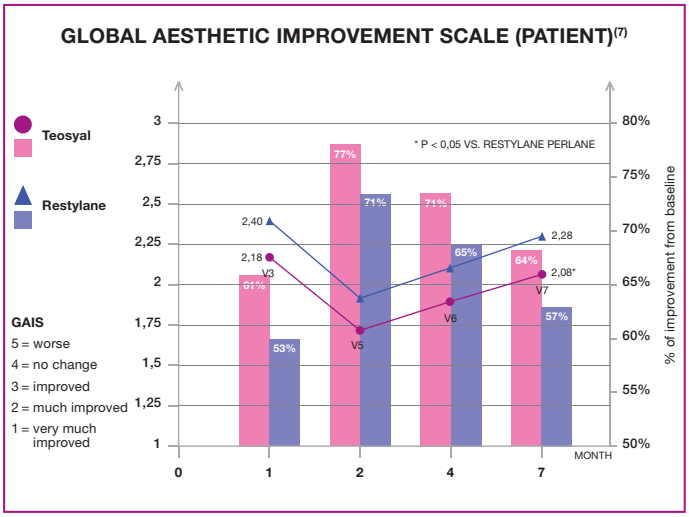
At the end of the study, patients could choose one of the two study products for an optional treatment. There were 49 recorrections 28 patients preferred mono-HA/TEOSYAL®, 3 patients preferred bi-HA/RESTYLANE®. 15 patients did not have a preference. Of those, 14 were treated with mono-HA/TEOSYAL® and one was treated with bi-HA/RESTYLANE®. **In summary there was a preference for mono-HA/TEOSYAL® treatment at the end of the study.**

• Patients' Self Satisfaction Assessment (PSSS)

Seven months after the injection (V7), 81.7 % of the patients were very satisfied or satisfied with the treatment result on the mono-HA/TEOSYAL® treated side and 70 % of the patients were very satisfied or satisfied with the result on the bi-HA/RESTYLANE® treated side, which indicates **greater patient satisfaction with mono-HA/TEOSYAL®.**

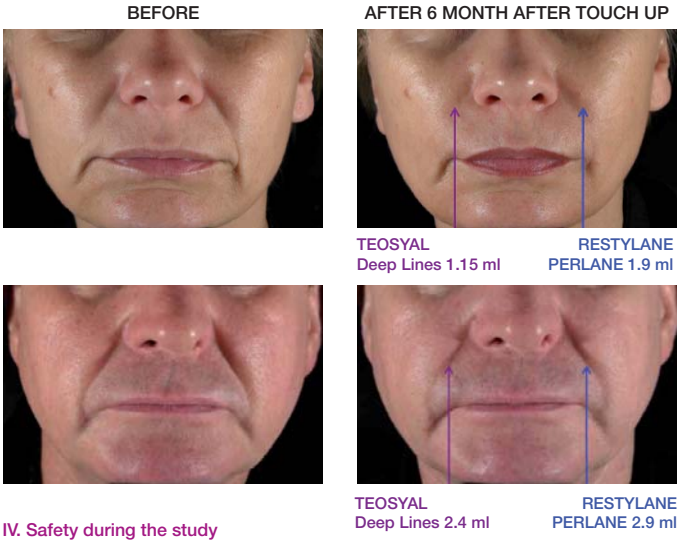
• Global Aesthetic Improvement Scale (GAIS)

One month after the first injection (V3), the GAIS showed a mean result of 2.18 for the mono-HA/TEOSYAL® treated side and 2.40 for the bi-HA/RESTYLANE® treated side. After 7 months (V7), the mean GAIS was 2.08 for the mono-HA/TEOSYAL® treated side and 2.28 for the bi-HA/RESTYLANE® treated side. **Statistically significant (V7) of superiority of mono-HA/TEOSYAL® compared to bi-HA/RESTYLANE® was observed over the whole study period for the patient self-assessment.**



III. Necessary volume for correction

The overall injection volume necessary to achieve optimal correction after V1 (first injection) and V3 (reinjection) **was lower with mono-HA/TEOSYAL® (1.36 ± 0.41 ml) than with bi-HA/RESTYLANE® (1.64 ± 0.64 ml). The non-parametric Mann Whitney test showed a significant difference (p<0.05) in favour of mono-HA/TEOSYAL®.**



IV. Safety during the study

- No severe adverse event occurred following the use of either product
- Minor adverse events included erythema and oedema:
  - no oedema at all for 56.7 % of the patients
  - 26.7 % did not show erythema on either side after the first injection

DISCUSSION

This is the first study were a HA preparation of bacterial origin had been compared to another bacterial HA product for efficacy, durability and safety. Nearly all previous studies used Zyplast®, a bovine collagen, as a comparator[2, 3]. It was appropriate to use Zyplast® [4, 5] or Hylaform®, an avian-derived HA [5, 6] as a comparator for the previous RESTYLANE® studies as they were the gold standards at that time. As both comparators were less durable than the new products being evaluated, it was not difficult to show superiority of the new product. In the present study there are only differences in structural and mechanical properties between the 2 products studied that could affect the filling and durability properties.

This pilot study showed good efficacy for both products immediately after the first injection in terms of wrinkle severity improvement. Both products showed good and comparable efficacy after 6 months. For some of the efficacy criteria, TEOSYAL® Deep Lines showed a trend towards better results compared to RESTYLANE® Perlane. This needs to be confirmed in future studies. Signs of a clinically relevant superiority may be drawn from patient preference. **The majority of the patients preferred TEOSYAL® Deep Lines as their product of choice at the end of the study for the reinjection.**

SWISS INNOVATION APPLIED TO BEAUTY

HYALURONIC ACID

TEOSYAL Deep Lines

- HA **25 mg/g**
- Volume-creating capability: ●●●●○○
- Indications: **Filling deep wrinkles**
- Injection aera: **Deep dermis**
- Blister pack: **2 x 1 ml**
- Estimated duration*: **9 months on average**

*average duration depends on several factors : patient's skin type, severity of the wrinkle to be corrected, type of injection (superficial, medium or deep dermis) and the volume injected.

CONCLUSION

- Best durability for Teosyal® (blinded investigations assessment)
- Best patient's satisfaction for Teosyal®
- Total injected volume of Teosyal® lower than Restylane® for the same aesthetic result

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LABORATORIES
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