

Effectiveness of a Hybrid Hyaluronic Acid Gel for the Face and Neck in Men: Pilot Observation on Male Subjects

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Abstract

Introduction: While upper-class men had been taking care of themselves for centuries, this changed somewhat in the first half of the 20th century. And by the 1980s the cult of the body and the metrosexual man had emerged, with a marked upsurge in male cosmetic treatments. There was also an increased demand for treatment of wrinkles such as glabellar lines or nasolabial folds.

Intradermal mesotherapy was the first branch of general medicine to meet a growing demand- mainly among women- for moisturizing the skin and filling in wrinkles.

The Swiss company IBSA Derma-Suisse presented us with a hybrid hyaluronic acid gel based on two Hyaluronic Acids (HA) of different molecular weight, principally intended for correcting the skin aging process and repairing the dermal tissue.

This article examines the results obtainable in some male members of PM's personal aesthetic patients.

Four patients agreed to test this hybrid HA gel. Two of them were treated on the face and neck, one exclusively on the neck and one exclusively on the face.

Material: The injected gel contains highly concentrated HA due to the combination of two HA with different molecular weights. This gel is manufactured by IBSA Farmaceutici Italia, marketed by IBSA in Switzerland.

Method: The test volunteers were injected according to the protocols established by IBSA, on the face and/or neck, at J0, J30.

The results were evaluated on photographs of the face and three-quarter left and right, by the test individuals, 2 experts and the injector at J0, J30 and three months after the second treatment.

Results: The photographic assessment indicates a discrete improvement in the clinical condition of the test volunteers. However, due to the few test patients enrolled in this observation, it cannot be drawn a definitive conclusion on the efficacy in man skin. Larger studies with a multi-ethnic approach are needed.

Conclusion: There is an undeniable improvement after two treatments with hybrid hyaluronic acid gel in the subject tested. Two things have however to be considered. The first one is that there is no visual analogue scale for aging in males, thus complicating the skin judgement. The second one, based on this observation, is that in some subjects, the two sessions, and probably also the volume injected may be not always sufficient, to obtain a fully satisfying result on the skin.

Keywords: Hydration; Hybrid hyaluronic acid; BAP technique

Introduction

While upper-class men have taken more or less care of themselves for centuries, in the first half of the 20th century it was somewhat different. And in the 1980s, the cult of the body and the metrosexual man appeared, with a clear upsurge in male cosmetic care. There was

also an increased demand for treatments of wrinkles such as glabellar lines or nasolabial folds. A metrosexual is a city dweller of all genders and sexual orientations who is very concerned about his appearance.

It is a neologism coined in 1994 by Mark Simpson, a British journalist at "The Independent" [1,2].

Intradermal-mesotherapy was the first branch of general medicine to respond to patients' demand for moisturizing the skin and filling in wrinkles, mainly concerning women [3-7].

In the 1980s, cosmetic companies finally started to focus on men's cosmetics, not just shaving foams and aftershaves.

We have seen a plethora of brands flourish, sometimes only for men, such as, not to mention: Nickel', a brand of cosmetics and skincare products for men, created in 1996, belonging to the L'Oréal group since 2013. The brand disappeared the following year [8].

IBSA Farmaceutici Italia has formulated a hybrid hyaluronic acid gel based on two Hyaluronic Acids (HA) of different molecular weights, whose main indication is: "correction of the skin aging process and repair of the dermal tissue".

The main purpose of this article is to present the results obtained in a few male subjects from the main author's personal aesthetic patients.

The secondary goal is to see how well male subjects tolerate the injection of medical substances that do not contain lidocaine. The effectiveness of adding lidocaine to HA gel can no longer be denied [9].

Young men prefer botulinum toxin injections, whatever the indication, as long as they do not feminize them. The mature man will opt for a face lift rather than repeated injections, the only exception being botulinum toxin [2].

Materials

Profilo

Hybrid Hyaluronic Acid (HA) gel is manufactured by IBSA Farmaceutici Italia, whose parent company, IBSA-Pharma, is located in Collina d'Oro, Ticino, Switzerland, and marketed in Italy since 2015 [10].

Composition: The HA used in the manufacture of the tested gel is of non-animal origin (*Streptococcus equi ssp.*), of pharmaceutical grade, produced by the IBSA company itself. The gel consists of two solutions containing an HA of low molecular weight (L-HA) (80-100 kDa) and a high molecular weight HA (H-HA) (1100-1400 kDa) [11]. The production of hybrid complexes is obtained by thermization of the two mixed solutions (L-HA+H-HA). Once the product is finished, the viscosity of the solution containing the hybrid complexes is lower than that of the initial solution.

The hybrid HA gel comes in a 2 ml syringe, each ml containing 16 mg of the 2 HAs of different molecular weights. This gives a concentrated HA gel at 32 mg/ml, in a physiological sodium chloride buffer solution. [12].

Hybrid HA gel does not contain any chemical cross-linking agents; it is the result of a thermal process, using NAHYCO® Hybrid Technology, patented by IBSA.

Thermization changes the contacts between the hydrogen atoms of the two HA solutions and increases their cohesion. With the finished product, we observe:

- On the one hand a low viscosity
- On the other hand, a strong cohesion of the molecules

Which allows a good distension but not diffusion in the tissue. In the face of hyaluronidases, Profhilo' hybrid complexes are more resistant than their non-hybridized alter-egos of the same molecular weight. As a result, they should last longer *in vivo* [11,12].

Indications: Hybrid HA gel can be used on the face, specifically the zygomatico-malar and sub-malar region, as well as on the whole body [10-14] for:

- Correcting the skin's aging process by rehydrating the tissues and preventing or combating the skin's aging process.
- The 2nd indication for this gel: the repair of dermal tissue in the case of superficial post-traumatic skin scars.

We have already presented our results with some female subjects: improvement of the neckline and of aging arms [15].

In this article, we look at the results of face and neck treatment in male subjects from our private aesthetic practice.

Injection mode: The hybrid HA gel is injected through a 29G needle (0.33 × 12 mm), intradermally, according to the instructions for use [14].

There is a 5 bolus per side injection scheme "BAP technique" ("BioAesthetic Points technique") for treatment of the face and neck, recommended by IBSA Farmaceutici Italia [15,16].

The hybrid gel does not contain lidocaine. The so-called "Tenting technique" is suggested for injecting it.

For this injection technique, the area to be injected is pinched and the needle is implanted either perpendicular to the skin plane, or perpendicular in line with the fold created [15] (Figure 1).

Regardless of the needle implantation axis chosen, with the so-called "tenting" injection technique one almost always injects into the subcutaneous fat plane. We will not argue about the depth of injection achieved [17-19].

Digital camera

The camera used is a Nikon® DX digital camera, AF-S DX Nikkor, ED 18-55 mm 1: 3.5-5.6 GII lens.

Pain assessment scale

The pain experienced with the injection is measured on a Visual Analogue Scale (VAS), graduated from 0 to 100 (0 =no pain, 100=unbearable pain) (Figure 2 top).

Clinical Assessment Scales

Face: To our knowledge, there is still no approved whole-face aging scale for men. We have therefore estimated the degree of ageing of the whole face based on the various existing visual scales of Merz Pharma, made with only female subjects and which we have in our possession.

Neck: There does not seem to be a visual analogue scale for the neck in men either. All the scales we have seen are scales with women.

For this area, which is new to medical aesthetics in humans, we use the visual analogue scale for Ultherapy® from Merz Pharma [20] (Figure 3).

GAIS scale: The improvement brought by the injections was evaluated by the subjects, the experts and the injector thanks to the GAIS (Global Aesthetic Improvement Scale), comprising 5 grades (Figure 2, bottom) [21-23].

Patients: Three men among our private aesthetic medicine patients have, after verbal and written explanations in compliance with the Helsinki declaration, and a 15-day reflection period, agreed to participate in this follow-up. An informed consent as well as a document for the right to the image was signed. The fourth subject is none other than the principal author of this observation.

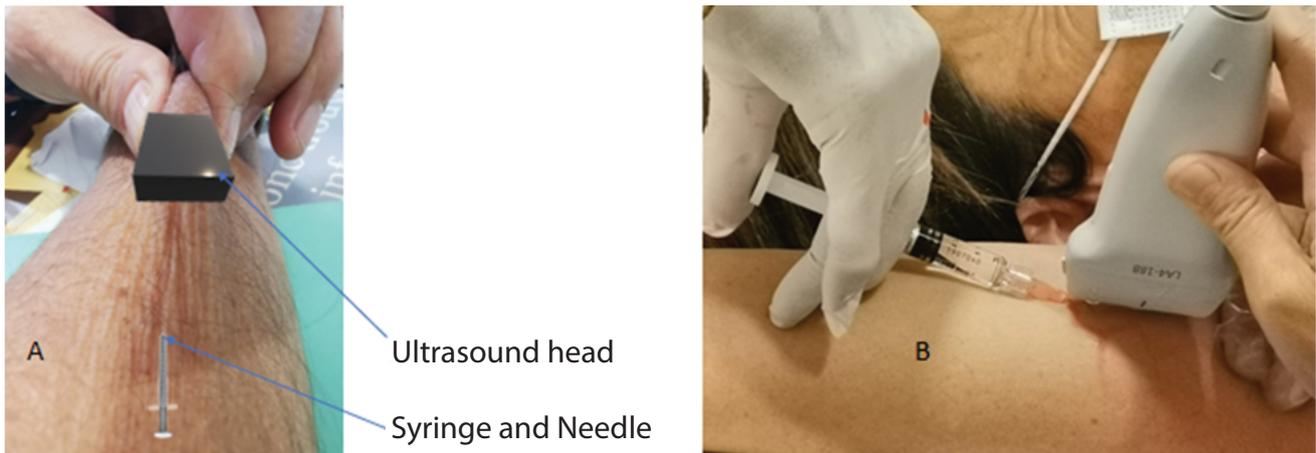


Figure 1: A: Left: simulation of needle implantation tangential to the skinfold with the «tenting technique», under ultrasounds. B : *In vivo*.



Classification	Degré d'amélioration
4	Très nette amélioration-traitement optimal
3	Nette amélioration. Mais pas optimale pour le sujet, peut-être une « retouche » à 3 mois
2	Amélioration visible, mais demandant un 2 ^{ème} traitement
1	Pas de changement par rapport à J0
0	aggravation

Figure 2: Above: Left: the «blind» face of the scale, presented to the subjects. Right: the graduations, visible by the experts (here 10= 1; 100=10). Below: Left: GAIS scale (Global Aesthetic Improvement Scale).

The three subjects, one 53 years old, one 54 years old and one 63 years old, were injected in the face.

- The first subject with lot No. 1911020- Exp: 2022-11.
- The other two with lot No.1907040- Exp: 2022-07.

Three subjects, those aged 53 and 63 years and one subject aged 72 years, were injected in their neck.

- The first subject with lot No.1911020- Exp: 2022-11.

- The two others with lot No.1907040- Exp: 2022-07.

Supplementary table 1 and supplementary figure 1 shows the demographic data, skin type according to Fitzpatrick and photo-aging according to Glogau for the subjects.

Method

Photographs

At J0, in the injector's office, photographs of the subjects from the

Supplementary Table 1: Classification of skin aging according to Glogau [22].

Group Classification	Typical age	Description	Skin Characteristics
I Mild	28-35	No wrinkles	Early Photoaging: mild pigment changes, no keratosis, minimal wrinkles, minimal or no make up
II Moderate	35-50	Wrinkles in motion	Early to Moderate Photoaging: Early brown spots visible, keratosis palpable but not visible, parallel smile lines begin to appear, wears some foundation
III Advanced	50-65	Wrinkles at rest	Advanced Photoaging: Obvious discolorations, visible capillaries (telangiectasias), visible keratosis, wears heavier foundation always
IV Severe	60-75	Only wrinkles	Severe Photoaging: Yellow-gray skin color, prior skin malignancies, wrinkles throughout- no normal skin, cannot wear makeup because it cakes and cracks

Examples of calculating the area of a sphere and multiple small spheres ($4 \times \pi \times r^2$)

Volume of a sphere: $V = 4/3 \times \pi \times r^3$.

- On a sphere of 1mm radius, we have a surface of 12.56mm².

- The volume of this sphere: 4.19mm³.

if I divide it into 10 equal spheres, then I get 10 spheres with a radius of 0.46 mm or an area for the 10 spheres of 26.6mm².

THE FITZPATRICK SCALE

HOW YOUR SKIN TYPE AFFECTS SCARRING



TYPE 1: VERY FAIR
Always burns, never tans, may scar if slow to heal



TYPE 2: FAIR
Usually burns, tans with difficulty, may scar if slow to heal



TYPE 3: MEDIUM
Sometimes burns, gradually tans, higher potential for scarring



TYPE 4: OLIVE
Rarely burns, tans with ease, scars easily



TYPE 5: BROWN
Very rarely burns, tans very easily, high risk of scarring



TYPE 6: BLACK
Black, never burns, tans very easily, very high risk of scarring



Supplementary figure 1: Classification of phototypes according to Fitzpatrick [23].

front and $\frac{3}{4}$ in a seated position are taken with their heads resting against a wall; at J30, just before the 2nd treatment and 3 months after the second treatment.

Injections

At J0 and J30, the injection of the BAP technique, approved by IBSA Farmaceutici Italia, was done using the “Tenting technique”; [16] in order to reduce as much as possible the pain experienced.

Evaluations

After classification at J0, before the first treatment, a preliminary evaluation was performed by the subjects, the experts and the injector at J30, just before the second treatment. The last evaluation was done three months after the latter, according to the above-mentioned scales.

In this article, for the sake of clarity, we will only present our evaluation results at J0 before injection and 3 months after the second treatment.

Side effects

Subjects see only a continuous green line and must place the cursor of the VAS scale at the estimated degree of pain experienced (Figure 2, top left).

The pain felt is of very short duration (<1 minute) at the time of the injection. On the VAS scale graduated from 0 to 100, the greatest pain mentioned by one of the three subjects was evaluated at 50/100 during the 1st treatment. In the second treatment, the pain was evaluated at 35/100.

Subject 3 experienced a warm sensation for 30 minutes at the injection sites. (Lot No. 1911020 - Exp: 2022-11).

We observed in subject 3, and only on the 2 cheekbones, the persistence during 48 hours of a zone elevation to the level of the bolus carried out (lot No. 1911020 - Exp: 2022-11- see above) (Figure 4).

Supplementary table 2 shows the pain sensations felt by the subjects, using the VAS scale from 0 to 10.

Results

Between J0 and 3 months after the 2nd treatment, which is J120, we estimate between the subjects and the experts the following:

Face

MAS and GAIS scale

a. Subject 1: From the front, there is a clear improvement in the facial volume without the subject having gained weight. His jugal hollows and tear trough are clearly improved.

- The three-quarter view also shows an improvement, even if the lighting is not strictly identical. The position is superimposable between J0 and J120.

Supplementary Table 2: Demographic data of the 4 subjects in this observation.

Subject	Face			Neck		
	1	2	3	1	2	3
Age	53	54	63	53	72	63
Fitzpatrick [22]	IV	IV	II	III	III	II
Glogua [23]	III	III	III	III	III	III

b. Subject 2: From the front, there is a distinct improvement in the skin quality (Figure 5).

- In the three-quarter view from the right, there is an improvement of the nasolabial fold and the periocular rim in terms of wrinkle depth. We do not observe any improvement of the left three-quarter view.

c. Subject 3: From the front, there is an improvement in the right jugal cavity, more marked than in the left jugal cavity.

- In the three-quarter view the marionet folds are improved, the jugal hollows too, probably more on the right than on the left, the pictures not being 100% superimposable due to the position of the subject and the lighting.

Supplementary table 3 shows the evaluations by the subjects, the two experts and the injector.

Neck

MAS and GAIS scale

a. Subject 1: From the front, there is an improvement of the skin aspect on the central part of the neck.

- In the three-quarter view, while there is a possible improvement on the right $\frac{3}{4}$, it is difficult to make a statement on the left $\frac{3}{4}$.

b. Subject 2: despite his advanced age: From the front, there is a reduction in the depth of wrinkles, and an improvement in the quality of the skin.

- In the three-quarter view, the improvement is better highlighted on the right $\frac{3}{4}$ than on the left.

c. Subject 3: From the front, we can observe an improvement in the depth of wrinkles and in the luminosity and radiance of the skin.

- In the three-quarter view, although the subject is not strictly in the same position, especially the left $\frac{3}{4}$, there is however an improvement in the wrinkles, which was noticed by all around him (Figure 6).

Supplementary table 3 shows the evaluations by the subjects, the two experts and the injector.

Discussion

Pain

Among the 4 subjects whom we had the opportunity to follow up and question, there does not seem to be any real difference between women and men in the pain experienced with regard to the product injected with the “Tenting technique” [15]. However, it should be noted that the sample of subjects is very small and precludes any hasty or derogatory conclusion.

Effectiveness

The two treatments with the hybrid hyaluronic acid in Profillon visibly improve the appearance of the skin in the treated area.

We further believe, considering the results of our trials with hybrid complexes of hyaluronic acids that this new form of gel can be useful not only for rejuvenation of face, but also other parts of the body exposed to skin laxity. After injection, the boluses should not be massaged. The hybrid gel naturally expands within the extracellular matrix. Massage, by “breaking” the bolus, prevents the gel from fully exploiting its hydrophilicity and from attaining its volume. In fact, the attack surface offered to the hyaluronidases will be much greater when faced with multiple small particles than when faced with a large cohesive bolus. Remember the mathematical formula for calculating surface areas: $4 \pi \times R^2$.

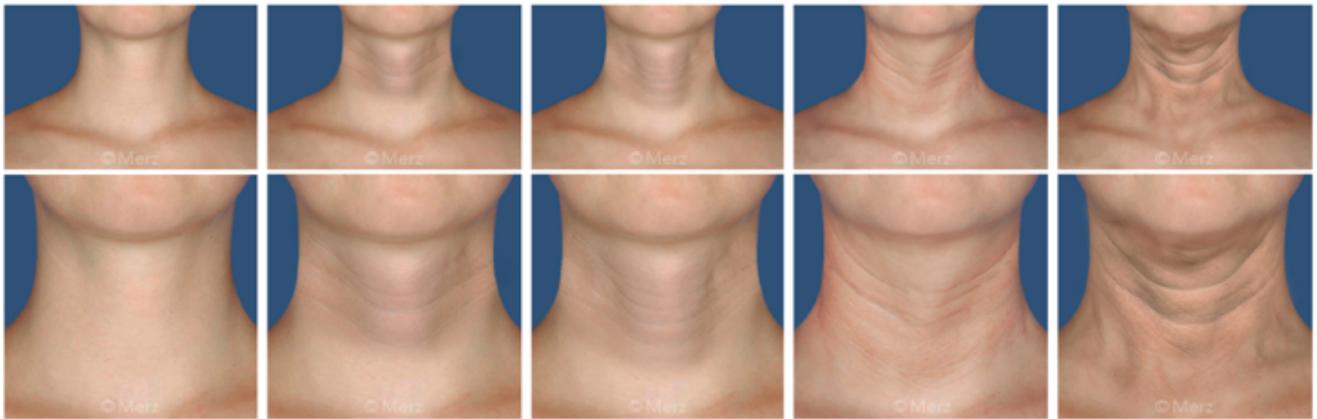


Figure 3: MAS Scale for evaluation of ageing neck - Ultherapy® Scale from Merz.



Figure 4: Subject 3

On 05.11.2020 A = before injection, B = just after injection, C = 06.11.2020: 24h after *PROFHILO*®. Blue arrow: naevus. White spots: points of injection on the face and the neck («BAP technique»)..



Figure 5: Subject face and neck: Grey T-Shirt 19.10.2020 before *PROFHILO*®
Green and blue shirts: 3 months after the 2 sessions of injections.



Figure 6: Above: Left pictures: before Profhilo® and 3 months after the 2 sessions of injection. Right: Above: aspect of the neck before Profhilo® and Below: 3 months after the 2 sessions of injection.



Figure 7: Oldest subject before PROFHILO® 20.10.2020 and 3 months after 2 sessions of injection.

Supplementary Table 3: Assessment of pain according to a VAS scale graduated from 0 to 10 (0 = no pain; pain- 10 = unbearable pain).

Face 1 st treatment	Topic 1	Topic 2	Topic 3	Neck 1 st treatment	Topic 1	Topic 2	Topic 3
T0	5	5	2	T0**	2	2	4**
T5'	0	0	2 (heat)	T5'	0	0	2 (heat)
T10'	0	0	2 (heat)	T10'	0	0	2
T30'	0	0	2	T30'	0	0	0
2 nd treatment				2 nd treatment			
T0	5	5	2	T0'	5-3	2	4
T5'	0	0	2	T5'	0	0	0
T10'	0	0	0	T10'	0	0	0
T30'	0	0	0	T30'	0	0	0

*5/10 for 3 points on the median line. The other points: 3/10

**4/10 for 3 points on the median line. The other points: 2/1

Supplementary Table 4: Evaluation before and 3 months after the second injection of the appearance of the face, according to the VAS and GAIS scales, in men.

Men		Before				M3 after 2 nd			
FACE		MAS			GAIS			MAS	
	Face		¼ D/G	Face		¼ D/G	Face		¼ D/G
Topic 1	3		3/3	2		2/2	2		2/2
Exp 1	3.5		3/4	2		2/2	2		3/3
Exp 2	2		2/2	1		1/1	2		2/2
Exp 3	3		3/3	3		3/3	2.5		2.5/2.5
Evaluation Average	2.88		2.75/3.00	2.00		2.00/2.00	2.13		2.38/2.38
Gain							0.75		0.37/0.62
Topic 2	3.5		3/3	1		1/1	3		3/3
Exp 1	3		3/3	1		1/1	3		3/3
Exp 2	2		2/2	2		2/2	1		1/1
Exp 3	2		2/2	1		1/1	2		1/1
Evaluation Average	2.88		2.00/2.00	1.25		1.25/1.25	2.25		2.00/2.00
Gain							0.63		0.00/0.00
Topic 3	3		3/3	2		2/2	2		2/2
Exp 1	2.5		2/3	2		2/2	2		2/2
Exp 2	2		2/2	2		2/2	1		1/1
Exp 3	2.5		2/3	2		2/2	3		3/3
Evaluation Average	2.50		1.50/2.75	2.00		2.00/2.00	2.00		2.00/2.00
Gain							0.50		-0.50/0.75

We observe, on average among this small number of subjects, deterioration in the ¼ right views. This may be the consequence of the Jacquet massage suggested to the subjects at this stage.

Supplementary Table 5: Evaluation of the appearance of the neck before and 3 months after the 2nd injection according to the VAS® and GAIS scales, in men.

Men		Before				M3 after 2 nd			
COU		MAS			GAIS			MAS	
	Face		¼ D/G	Face		¼ D/G	Face		¼ D/G
Topic 1	2.5		2/2	3		3/3	2		2/2
Exp 1	3		3/3	3		3/3	2		2/3
Exp 2	3		3/3	2		2/2	2		2/2
Exp 3	3		3/3	3		3/3	2		2/2
Evaluation Average	2.87		2.75/2.75	2.75		2.75/2.75	2.00		2.00/2.25
Gain							0.86		0.75/0.50
Topic 2	3		3/3	3		3/3	2		2/2
Exp 1	4		3/3	2		2/2	3		3/3
Exp 2	3		3/3	1		1/1	3		3/3
Exp 3	3		3/3	1		1/1	3		3/3
Evaluation Average	3.25		3.00/3.00	1.75		1.75/1.75	2.75		2.75/2.75
Gain							0.50		0.25/0.25
Topic 3	2.5		2.5/2.5	3		3/3	2.5		2.5/2.5
Exp 1	1.5		1/2	1		1/1	1		1/2
Exp 2	2		2/2	1		1/1	2		2/2
Exp 3	1		1/1	3		3/3	1		1/1
Evaluation Average	1.75		1.63/1.88	2.00		2.00/2.00	1.63		1.63/1.88
Gain							0.12		0.00/0.00

It may be necessary, depending on the patients, to inject more hybrid gel into the areas to be treated.

1. Depending on the type of skin aging the patient has, it may be necessary to consider a third or even a fourth treatment.

2. The pace and timing of the maintenance sessions need to be codified in a longer-term study with a larger number of subjects and a multi-centre, ethnically diverse study.

3. There is an urgent need to create Visual Analogue Scales (VAS) for males of various ethnicities. Indeed, the male market is growing rapidly. So we must adapt to it (Figure 7).

Conclusion

We present our first treatment results with the hybrid HA gel on the face and neck of male subjects. There is a visible improvement in the areas treated with this new gel on the market, whose indication is not wrinkle filling or volumetric correction of the face and body.

Based on the encouraging results obtained in these four candidates we speculate, that the injected volume should be even augmented for the treatment of other areas as the face, meanwhile leaving the number of session at 2 to 30 days apart.

Larger-scale, multi-centre, multi-ethnic studies are needed, given the growing mix of populations in our countries.

It's important to instruct the subjects not to massage the treated area, in order to allow the hybrid gel to develop all its qualities (Supplementary tables 2-5).

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References

- Larousse dictionary: Metrosexual (2017): 731.
- ICI Radio Canada: Tout le Monde en Parle - Saison 7 [archive].
- Ravilly G (1998) Atlas clinique de mésothérapie. Edition. PMI, 28: 108-111.
- Tordjman M (2003) Cutaneous rejuvenation of the décolletage by mesotherapy. *J Med Esth et Chir Derm* 118: 111-118.
- Grand-Vincent A, Boisnic S, Salomon C, Prinderre P, Peccerelle P, et al. (2017) Clinical assessment of a Mesotherapy formulation for skin rejuvenation in healthy volunteers. *J Cosmet Dermatol sci appl* 7: 291-305.
- Boisnic S, Branchet MC (2006) Evaluation of the anti-ageing effect on human skin maintained in survival and after injection of a mixture of hyaluronic acid and multivitamins with the help of the U225 Biophymed® meso-injector. *J Med Esth et Chir Derm* 132: 253-258.
- Smit R (2019) Bio-skin-gineering: a novel method to focus cutaneous aging treatment on each individual layer of the skin specifically and precisely. *Aestht Med* 5: 14-21.
- Wikipedia: Nickel® Cosmetics.
- Wahl G (2008) European evaluation of a new hyaluronic acid filler incorporating lidocaine. *J Cosmet Dermatol* 7: 298-303.
- Agolli E, Diffidenti B, Di Zitti N, Massidda E, Patella F, et al. (2018) Hybrid cooperative complexes of high and low molecular weight hyaluronans (Profilo®): review of the literature and presentation of the Vision HA project. *Edizioni Minerva medica* 20: 5-14.
- D'Agostino A, Stellavat A, Busico T, Papa A, Tirino V, et al. (2015) *In vitro* analysis of the effects on wounds Healing of high-and low-molecular weight chains of hyaluronan and their hybrid H-HA /L-HA complexes. *BMC Mol Cell Biol* 16: 1-19.
- Stellavat A, Corsuto L, D'agostino A, La Gatta A, Diana P, et al. (2016) Hyaluronan hybrid cooperative complexes as a novel frontier for cellular bioprocess re-activation. *PLoS One* 11: e0163510.
- Dictionary "Le Petit Robert" online.
- Profilo®: Instructions for use. (2019) IBSA Farmaceutici Italia srl, Italy.
- Micheels P, Mosafer-Salomon M, Besse St, Bezzola Th. Hydration of the skin of cleavage and arms with hybrid HA gel: Pilot observation of patients.
- Laurino C, Palmieri B, Coacci A (2015) Efficacy, safety and tolerance of a new injection technique for high-and low- molecular-weight hyaluronic acid hybrid complexes. *Eplasty* E46: 427-437.
- Micheels P, Goodman L (2018) Injection Depth in Intradermal Therapy: Update and Correction of Published Data. *J Drugs Dermatol* 17: 611-618.
- Micheels P, Besse S, Flynn TC, Sarazin D, Elbaz Y (2012) Superficial dermal injection of hyaluronic acid soft tissue fillers: Comparative ultrasound study. *Dermatol Surg* 38: 1162-1169.
- Micheels P, Besse S, Quinodoz P, Vandeputte J, Viski S (2020) Behaviour of Hyaluronic Acid gels injected under ultrasound guidance in the mid and deep reticular dermis, the hypodermis, and in the muscle, near the bone: Comparative observation on Day 0. *Ann Plast Aesthet Surg*.
- Fabi S, Bolton J, Goldman MP, Guiha I (2012) The Fabi-Bolton chest wrinkle scale: a pilot validation study. *J Cosmet Dermatol* 11: 229-234.
- Landau M, Geister TL, Leibou L, Gurk BB, Görtelmeyer R, et al. (2016) Validated assessment scales for décolleté wrinkling and Pigmentation. *Dermatol Surg* 42: 842-852.
- H L Brannon (2019) How the Glogau Classification System Measures Photoaging.
- Gupta V, Sharma VK (2019) Skin typing: Fitzpatrick grading and others. *Clin Dermatol* 37: 430-436.