HA fillers have constantly been developed. Consequently, many with HA gels were dated around 1998 [3,4].

Animal Stabilized Hyaluronic Acid (NASHA™, Galderma Pharma employed in the year 1994 HA prefilled syringes based on Non-associated with specific rheological properties, the first author already

Given that natural Hyaluronic Acid (HA) undergoes extremely rapid
during clinical investigations in France, and then after its European Commission labeling in his clinical practice in Geneva, Switzerland. This hyaluronic acid gel benefits from the world’s first patented OxyFree™ technology. This article sought to present preliminary safety and efficacy data from the first

Material and methods: Like most of its competitors, MaiLi is available in various variants, including gel for filling fine wrinkles, for deeper wrinkles, folds, and for lip enhancement, in addition to gels for volumizing indications. This cohort study encompassed patients from the authors’ private esthetic clientele in Geneva, Switzerland. Depending on the indications, the injections were performed according to previously described techniques, ranging from the “blanching technique” to deeper injections.

Conclusion: The MaiLi hyaluronic acid fillers proved to be well tolerated and safe, with long-lasting effects. Remarkable properties revealed in this follow-up were their projection capacity and suppleness, as well as their ease of use and longevity, resulting in full patient satisfaction. No relevant undesirable effects were observed. There were no edematous reactions following the injections, nor were there any lymphatic circulation disorders.

Keywords: Hyaluronic acid; Volumizer gels; Skin rejuvenation; OxyFree technology

Introduction

The first injectable wrinkle fillers date back to 1980-1981, when bovine collagen was employed, following their approval by the American Food and Drug Administration as cosmetic drugs [1].

Given that natural Hyaluronic Acid (HA) undergoes extremely rapid turn-over within the skin, commercially available HAs needed to be cross-linked using different manufacturing techniques, resulting in products that still widely vary in formulation and cross-linking degree. Among the HAs manufactured with proprietary technologies associated with specific rheological properties, the first author already employed in the year 1994 HA prefilled syringes based on Non-Animal Stabilized Hyaluronic Acid (NASHA™, Galderma Pharma S.A., Lausanne, Switzerland) technology [2].

The first papers reporting the results obtained on subjects treated with HA gels were dated around 1998 [3,4]. Since then, numerous HA fillers have constantly been developed. Consequently, many more brands and formulations were manufactured, some of which presenting excellent results, whereas others were less effective [5,6]. In the author’s view, several HA fillers had to be only slightly modified to drastically improve their viscoelastic properties. Moreover, lidocaine was added to certain gels, which could markedly alter the gels’ viscoelastic properties compared to their formulation without any anesthetic, as previously observed [7-9].

Recently, a novel proprietary manufacturing technology for producing innovative HA fillers was elaborated, reference being here made to MaiLi’s OxyFree™ technology (Kylane Laboratoires S.A., Plan-les-Ouates, Switzerland). This new HA filler was launched by Sinclair Pharma under the name of MaiLi. Its basic principle consists in the cross-linking of the HA under inert atmosphere and the extraction of reactive oxygen upon the manufacturing process. This procedure was primarily designed to significantly preserve the intrinsic properties of the high-molecular-weight HA chains. Based on this new technology,
HA fillers with improved rheological properties are being produced that exhibit strong projection capacities and suppleness, along with their high ability to volumize facial tissues [10].

Owing to his "expertise", the publication’s principal author was integrated as injector expert in the clinical investigation of MaiLi variants, the HA gels benefiting from the world’s first Oxifree™ technology. This clinical investigation was conducted in France, prior to European Commission (CE) marking. Of note is that the trial’s data have been presented at several conferences, without being published yet. Once these products were registered in Europe, the author was given the opportunity to investigate the impact of these new MaiLi HA fillers on his patients, just after their official commercialization. This report has been primarily focused on the very first efficacy and safety observations made by the authors in their cosmetic practices, in Geneva, upon using these MaiLi HA gels manufactured according to the novel Oxifree™ technology.

**Material and Methods**

**Hyaluronic acid**

HA is a naturally occurring disaccharide biopolymer consisting of alternating units of D-glucuronic and N-acetyl-D-glucosamine [11]. Its structure is uniform across species, thus reducing the likelihood of immunogenic reactions. The agent is normally present in human tissues, including the skin and synovial fluid [12]. Using HA fillers has indeed revolutionized the management of age-related changes within various facial layers. Presently, numerous subtypes of HA fillers are available, presenting diverse characteristics that can be applied to each specific skin layer [13-15]. The HA gel used herein was the innovative MaiLi HA filler, launched by Sinclair Pharma.

**Oxifree™ technology**

The different manufacturing steps are illustrated in figure 1. Considering the Oxifree™ technology, long hyaluronan chains of non-animal origin and pharmaceutically manufactured were first hydrated (Step 1). The actual cross-linking procedure then followed, which was carried out under an inert atmosphere, with the extraction of reacting oxygen upon the manufacturing process. The intrinsic properties of high-molecular weight HA chains are thus further preserved, thus allowing for smaller amounts of cross-linking agent, Butanediol Diglycidyl Ether (BDDE), to be used while transforming the solution into a flexible gel (Step 2). MaiLi HA fillers, manufactured according to this technology, were demonstrated to be associated with rheological properties, meaning strong projection capacities [16]. The determinant outcome was a high ability to restore the volume of facial skin tissues, their ability being shown superior compared with that of other HA gels. Of note is that volumizer products manufactured using Oxifree™ technology should be injected into the subcutaneous tissues and supra-periosteal zone.

MaiLi HA fillers are available in the following variants:

- A gel for filling fine wrinkles, MaiLi® Precise, dosed at 15mg/mL, injected using a 30½G needle. This gel is also indicated to treat the periorbital area and tear trough. MaiLi Precise is reserved to specialists specifically trained in the injection technique, with sound knowledge of the anatomy and physiology of this periorbital area.

![Figure 1: Oxifree™ technology consisting of four steps.](image)

**Figure 1**: Oxifree™ technology consisting of four steps.

*Step 1: Hydration* of high molecular weight hyaluronic acid fibers; *Step 2: Cross linking* process under an inert atmosphere, using lower amounts of cross-linking agent butane dial diglycidyl ether (BDDE); *Step 3: Extraction* of reactive oxygen molecules; *Step 4: Sterilisation.*
A gel intended for deeper folds, and the lips: Maili® Define, dosed at 18mg/mL, which is injected using a 30½G needle.

A volumizing gel, Maili® Volume, dosed at 21mg/mL, intended for nasolabial folds and marionette lines, which is injected using a 27½G needle or cannula into subcutaneous or supra-periosteal fatty tissues. It can also create volume for the face that is becoming bony with age.

A more specific gel for facial contours, Maili® Extreme is concentrated at 24mg/mL, which is injected using a 27½G needle or cannula. It is intended for facial restoration, such as cheekbones, chin, and mandible.

Patients

Between January 7, 2021 and November 2, 2021, overall 45 patients from the principal author's practice, seeking nonsurgical improvement in the esthetic appearance, particularly but not exclusively in regard to their face, provided their written informed agreement to receive Maili HA injections, depending on the exact areas they wished to be treated. There were 33 women with a mean age of 68 (range: 18-88) years and 12 men with a mean age of 44 (range: 28-65) years.

We regularly examined the subjects during this post-CE observation following the Maili HA injections. The first 11 subjects, 1 male and 10 female patient, have a full 1 year follow-up. They were photographed after 12 months, and the others when they consulted Patrick Micheels' (PM) practice for diverse medical reasons. No subject of the current observation was re-injected upon satisfaction with the outcome obtained.

Method

Only the principal author (PM) had injected all the patients of this follow-up. The 2nd author had reviewed the French version of this paper.

The "blanching technique": As previously described, the "blanching technique", already used with the old bovine collagen injections in aesthetics in the 1980's, consists on injections in the superficial reticular dermis, implanting only the bevel of a 30½G needle-1mm, with an acute angle of penetration into the skin, comprised between 2 and maximum 10 degrees. The mean amount of gel deposit by injection point by point seems to be around 0.003-0.005mL [17-19].

Depending on either the indications or patients' sensitivity to pain, Maili HA gels were injected using a needle, point-by-point, or retrograde and at times prograde, or else, they were injected using a cannula, through a retro-trace process, or with fan-shaped or sandwich-shaped techniques. Generally, the use of needles was preferred for precise bolus injections at the supra-periosteal level or when precision was requested to treat fine lines in the subdermal plane. In contrast, the use of cannulas was preferred for subcutaneous injections or when the proximity of vessels was a matter of concern. Both the injection delivery and minimum volume of product to be injected were individually adapted to the targeted areas. Some patients were treated in several areas of their face. Besides, the so-called "blanching technique", which the authors had previously employed while using bovine collagen and certain HA gels, was similarly attempted [17-19].

As we became more skilled in using the various HA gels from the Maili range, we even expanded our indications to areas outside the scope of their intended use, under our own responsibility and at the request of the subjects consulting for esthetic treatment. This was made possible by our knowledge of the multiple HA gels available on the market. Based on our clinical judgment, we individually decided on the total Maili HA volume to be injected, depending on the patients' expressed needs.

The various HA gels pertaining to the Maili ranges were injected in different areas of the face, as listed in table 1. The injection characteristics, meaning delivery, tool and product volume injected, have been specified for a series of women and men in table 2. The volume utilizations, as listed in table 2, were established progressively by the principal author based on his past clinical experience involving hundreds of patients.

Ethical Considerations

All the subjects reported on in this paper were patients already familiar with injections in esthetic practice. All had been previously treated, between 6 months and a few years prior, yet not on the newly considered areas. They were provided with oral and written explanations, after which they were given a 15-day reflection period. All subjects signed an informed consent, including an authorization to employ their images, yet exclusively for scientific publications and conferences. The study was conducted in line with the ethical principles outlined in the Declaration of Helsinki and in accordance with the rules of good clinical practice, as well.

Results

Maili HA gels' efficacy was primarily assessed by patient satisfaction with treatment. Achievement of positive results was defined as a reduction in the patient's negative attributes and enhancement in their positive attributes concerning the anatomical zones they wished to be improved. Thus, efficacy was primarily based on the subjective assessments of patient satisfaction. Overall, most of the patients were very or totally satisfied with the results, and this was still the case for those who completed the full 1-year follow-up, except 1 female patient.

Table 1: Injection sites.

<table>
<thead>
<tr>
<th>Injected area</th>
<th>Number of men</th>
<th>Number of women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forehead</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Temples</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Glabella</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Nose</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Earlobe</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Crow's fee</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Valley of tears</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Hollow cheeks</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Cheek wrinkles</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Nasolabial folds</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>White lips (smoker's lines)</td>
<td></td>
<td>11</td>
</tr>
<tr>
<td>Red lips (helmine)</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Lip volume</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Cheekbones</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Marionette fold</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>Chin wrinkles</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hands</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glans (&quot;mushroom&quot; technique)</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Scars</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
For those latter, the treated areas were still improved, even if there was a light loss of gel, especially concerning the lips (Figure 2). As illustrated in figure 2, a young man had his lips injected with MaiLi, with his lower face seen prior to injection (A) and thereafter (B). At 1-year post-injection, we can observe that his red lip was smoother and less cracked, with a nice definition of the vermilion border (B).

MaiLi HA fillers are also adapted to colored people, as illustrated in figures 3 and 4. This female patient presented with nasolabial folds before treatment (A). Four months post-injection, we notice her improved facial signs, with a less sad look. This figure clearly illustrates the improvement in emotional facial attributes, which was achieved following one single treatment session.

The figures 5 and 6 illustrate for the reader two patients’ features prior to MaiLi HA injections and upon follow-up. It is worth mentioning that one woman who had been injected 1mL of MaiLi® Extreme per each side of her cheekbones did actually not fully...
Figure 2: Illustrative young male patient picture-lips: A. Before 1 session of 0.5mL MaiLi® Define injection; B. After 1 year; red lips are still nicely improved, with a perfect natural look.

Figure 3: Illustrative colored patient picture-nasolabial folds: A. Before; B. After 4 months MaiLi® Define (1 session, retrograde injection technique with a 27G canula).

Figure 4: Illustrative 64-year-old patient picture-lips and barre-code: A. Before; B. After 1 year (1 session needle and canula MaiLi® Define).

Figure 5: Illustrative 60-year-old patient picture-nasolabial folds and marionette lines: A. Before; B. After 1 year (1 session MaiLi® Define). This patient lost 20 kilos after breast and lung cancer (surgery, radiotherapy, and chemotherapy)
appreciate the original result, requesting a small correction in view of further improvement. PM corrected the too much projection by using a touch-up with MaiLi Volume to smooth her cheeks, so as to allow for a quite natural look. In the aftermath, the patient indicated to be very appreciative. Of note is that this patient was the first on whom PM employed MaiLi Extreme. Generally, it must be mentioned that most of PM’s patients actually wanted just a natural look, so avoiding excessive changes.

In the following table we present the satisfaction rate of our 11 first patients, treated with the OxiFree™ range (Table 3).

**Safety Issues**

No serious undesirable effects were observed. The very few treatment-related undesirable effects, noted in less than 5% of patients, were all very mild in intensity, and transient in nature. These were all expected post-injection reactions, such as mild pain or light swelling, bruising, and redness. Typically, these events occurred shortly after injection, were only mild, and resolved within 1 to 2 days on average. We have observed no relevant inflammatory reactions, whether immediate or delayed, even during the full COVID-19 pandemic. There were no edematous reactions following the injections, nor were there any lymphatic circulation dysfunction observed.

It must be mentioned that for a long time now, we no longer consider possible hematomas or bruises as undesirable product-related effects. If they occur, we rather consider them as being related to the act of penetrating the skin with a needle. Therefore, we at all times take special care when penetrating the skin with a needle, and based on our growing experience, we have been able to markedly improve our skills.

Besides, it must be mentioned that we initially attempted to apply the “Blanching Technique” on two or three subjects at the very beginning of this work. Nevertheless, we had to deplore a few visible lines of gel and also palpable gel, especially when injected superficially in the cheek wrinkles, even though the gel specifically indicated for fine lines was injected using the point-by-point procedure [17-19]. An illustration concerning these undesirable effects is provided in figure 7, showing the visible lines on the patient’s front. For this specific reason, OxiFree™ HA gels, including even the MaiLi Precise variant, were no longer injected into the superficial reticular dermis.

**Discussion**

For our discussion, it is essential to remember that one HA gel is not equal to another one, which may have the same indications, while being manufactured by another company. According to their compositions and cross linking technology, all HA-based soft tissue fillers exert unique properties that should as far as possible perfectly match their specific product designation. The HA products presented here were produced using the OxiFree™ cross-linking technology that significantly contributed to preserving the high-molecular weight HA chains' intrinsic properties. Because of its rheological properties, lower amounts of cross-linked HA gel were required to ensure MaiLi® HA filler treatment. We do not have injected more than 1mL of OxiFree™ gels per patient per side, except for the correction of the result of our first cheekbones improvement. In this case, the correction was realized with a lower cross linked OxiFree™ volumizing gel, with a maximum of 0.25mL each side. As already mentioned, respective data concerning the volumes injected can be made available by the principal author on request.

It has been published, comparing the Maili range (Volume and Extreme) with the Vycross™ technology volumizing gels (Juvederm® Voluma and Volux), that the MaiLi range has a higher projection capacity the Vycross™ one [20-24].

Our first patient treated for cheekbones improvement with MaiLi Extreme, 1ml each cheekbone, seems to confirm this previous scientific publication. This also seems to confirm the personal injector’s opinion and experiences with the Vycross™ volumizing gels.

Actually, because of this case, we do not inject more than 0.5mL per side, when patients ask for cheekbones improvement.

Another feature worth mentioning is that when using OxiFree™ technology, lower amounts of the cross linking HA agent was used or, in other words, 1mL of MaiLi HA gel allowed for treating more

face areas and also body areas, the latter being not official indications, without a marketing authorization (earlobes, glans, hands) (Tables 1 and 2). Of note, these lower amounts of MaiLi HA gel required were duly noted, and the specific amounts can be made available by the author on request.

For a long time, it was claimed that HA-based wrinkle-filling gels were reabsorbed within a few months. Contrasting with this observation, we presented results retrieved from 1-year follow-up biopsy studies at several conferences, and our data corroborated that HA gels lasted indeed longer than mostly advertised [20–22]. In regard to HA gels employed for volumetric purposes, we and other authors have clearly shown by means of Magnetic Resonance Imaging (MRI) and computer tomography that HA gels persisted well beyond the advertised 18 to 24 months [23]. Given this setting, the HA gels produced by OxiFree™ technology likely exert a duration of action at least as long as that of the other HA gels, most probably even longer (data on file for the EU registration) (see below). In this context, it must be noted that MRI follow-up on our case series is currently ongoing. This long-term follow-up will likely prove that MaiLi HA fillers display longer-term results, in comparison with other products. The long-lasting effects of the MaiLi HA fillers are most probably due to their rheological properties; these are indeed paramount, especially for those fillers dedicated to restoring facial volume loss, such as the MaiLi variants [24]. Likewise, this property probably also accounts for the ease with which these fillers are injected.

To this discussion must be added that the paper’s main author (PM) actively participated as investigator in the studies conducted for registration of MaiLi HA gels based on OxiFree™ technology in the European Union. Thanks to his knowledge of the laboratory that created the OxiFree™ range, along with his own expertise since 1994 in using HA gels, as reported in several publications [24–26], the principal author claims that the MaiLi HA gels are injectable products that have proven safe when used for esthetic purposes. This safety is insured in terms of their placement in the areas recommended in the instructions for use, if they are applied in accordance with the rules of the art. These MaiLi HA gels are quite easy to inject, and their injection is associated, following the principal author, with a short learning curve.

In an up-coming paper, in accordance with the Pharmacologic Department -Pr Y. Kalia, of the University of Geneva-Switzerland, we will publish the data-pressures applied on the plunger of the syringes (manometer FlexiForce®-Tekscan®, Norwood, Massachusetts-USA- and the extrusion force we observed, when injecting the MaiLi™ range in simili skin in silicone (Practi-Simskin™-Wallcur, San Diego, California-USA) and at the University of Geneva, with the Texture Analyzer TA.XT Plus (Stable Microsystems Ltd, Surry-UK). The mean pressure measured when injecting in the Simskin™, was 3N. This pressure exerted on the plunger is very low.

Their projection capacity, especially for volumizing products, is rather easy to get familiar with. This projection capacity is indeed an essential property for HA fillers, enabling them to efficiently restore facial volume. Using a new skin model assay, a comparative evaluation demonstrated that the HA fillers benefiting from the OxiFree™ technology, like the MaiLi variants, displayed a higher projection capacity than the Juvederm products based on Allergan’s patented Vycross technology™ [24].

Based on our experience, we confirm that the MaiLi HA fillers fully met the physicians’ and patients’ expectations over the entire observation period, up to 1-year follow-up for at least 11 patients. In our view, because of the principal author’s long experience, they are at least as safe as the other cross linked HA dermal fillers. A review paper published in 2013 including data stretching over more than 15 years clearly supported the favorable clinical safety profile of BDDE-cross linked HA fillers, and their degradation products, as well [27]. The authors concluded their review stating that, owing to the strength of the empirical evidence available, physicians could be confident when offering these products to their patients. This is entirely in line with our thinking, given that the OxiFree™ technology even requires smaller amounts of cross-linked gel to reach the esthetic goal of the treatment.

In conclusion, most of our subjects (>90%) expressed their satisfaction with the results obtained on this first post-marketing follow-up, and renewed their availability for new areas to be treated or for receiving a slight “touch-up” after one year. (Figures 5 and 6).

Conclusion

We can confirm as conclusion that the MaiLi HA fillers, based on OxiFree™ technology, proved to be well tolerated and safe, with long-lasting effects. In our opinion, remarkable properties revealed in this observational follow-up were their projection capacity and suppleness, with, when correctly injected a perfect bio-integration—even for the most volumizing declination of the OxiFree™ range (none palpable gel deposit), as well as their longevity, eventually resulting in full patient satisfaction. No relevant undesirable effects were observed, even upon the full COVID-19 pandemic. There were no edematous reactions following the injections, nor were there any lymphatic circulation disorders.

Declaration of Interest

Dr. Micheels received fees for consulting/training from Allergan, Antéis SA, Galderma-Q-Med-Suisse, IBSA pharma, KioMed, Kylane, Merz pharma, Sinclair, Téoxane, and Vivacy. Dr. Poiraud has no conflicts of interest to declare.

Table 3: Percentage of the 11 first subjects (with 1 year complete follow-up) and their degree of satisfaction at 1, 6 and 12 months.

<table>
<thead>
<tr>
<th>11 first patients</th>
<th>1 month</th>
<th>6 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Totally satisfied</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>9</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Moderately satisfied</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Somewhat satisfied</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not satisfied</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 female patients</td>
<td>1</td>
<td>1 female patient (gel still visible or palpable on the upper lip and on the cheeks)</td>
<td></td>
</tr>
<tr>
<td>1 male patient</td>
<td>3</td>
<td>1 female patient (gel still visible or palpable on the upper lip and on the cheeks)</td>
<td></td>
</tr>
</tbody>
</table>

Funding

This study received financial support from Sinclair.

References