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Acne Scars, Stretch Marks, and Similar Skin Defects Qualify as Medical Problems. A Real-World Survey on a Hyaluronic Acid Medical Device

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ABSTRACT

Introduction: *Beyond impacting the quality of life, unpleasant stretch marks, skin aging, the dermal scars secondary to acne and chickenpox, and wrinkles expose those harboring these skin defects to psychiatric problems like anxiety, depression, ADHD, and insomnia more often than one might suspect. Remodeling skin scarring and supporting the deteriorated networks of dermal elastic fibers also have medical value. The moisturizing properties and skin-protective scavenger action against free radicals rapidly developed by non-cross-linked hyaluronic acid offer a powerful rationale to help with those problems.*

Methods: *The study focused on a survey questionnaire administered by the investigators to a prospective cohort of 45 subjects of both genders with stretch marks, dermal scars, and skin aging. Before the survey, all individuals had undergone a three-session treatment cycle with a Class-III CE-marked medical device containing 40 mg of non-cross-linked HA in 2-mL prefilled disposable syringes with 30G½ needles (IALEST®, Mastelli Srl, Sanremo, Italy). The primary observational efficacy assessment tool was the six-score Wrinkle Severity Rating Scale (WSRS); the secondary efficacy assessment tool was the five-score Global Aesthetic Improvement Scale (GAIS). Timing of WSRS and GAIS assessments: at baseline (T0), before the first intradermal treatment session, and three to four weeks after T2 (end of the treatment cycle).*

Results: *The mean WSRS scores for skin quality significantly improved between the T0 baseline visit (2.8 ± 1.17) and the T2 final follow-up visit (1.6 ± 1.09; –42.9%, p <0.001). The cohort distribution of the GAIS skin quality descriptors assessed by the investigators improved by one severity level in 66.7% of surveyed subjects, two severity levels in 20.0%, and four levels in 2.2%. Only a tiny cohort minority (2 individuals out of 45, 4.4%) reported no subjective improvement in skin quality. Among surveyed participants, 95.6% reported a clinically meaningful skin quality improvement. The device safety was high.*

Conclusions: *The real-world survey, performed within the framework of a long-term program to monitor the device's clinical performance and safety over time, demonstrated that the HA-based medical device retains its long-standing record of efficient performance and excellent safety with no variations over time.*

Keywords

Acne scars, Chickenpox scars, Dermal scarring, Hyaluronic acid, Skin quality, Stretch marks.

Introduction

"The global hyaluronic acid (HA)-based dermal fillers market size was valued at USD 2,680.9 million in 2018 and is projected to reach USD 4,884.6 million by 2026, exhibiting a compound annual

growth rate of 7.8%", according to Fortune Business Insights, a leading business magazine [1]. The low HA immunogenicity and tissue stability explain the success of HA-based gel fillers. Moreover, the quick reversion of effects with hyaluronidase enzymes has also contributed to the HA worldwide success [2,3].

The hydrophilic HA matrix draws water leading to tissue turgor; the ensuing swelling pressure allows the hydrated HA complex to withstand local compressive forces. Moreover, extracellular HA interacts with specific binding proteins and cell surface receptors named hyaladherins that regulate cellular behavior [2]. CD44, the HA-binding hyaladherin receptor most widely distributed on cell surfaces, regulates keratinocyte proliferation and motility and preserves native HA. Moreover, the interaction of HA with membrane RHAMM (receptor for hyaluronate-mediated motility) participates in the control of skin cell growth and migration. Skin elasticity and the loss and deprivation of elastic fibers also improve in an HA-rich dermal environment [2,3].

Through the described properties and the scavenger action against free radicals, HA-based gel fillers restore volumes and contours and counteract the skin concavities and shadows caused by changes in soft tissue distribution—in the skin, fat pads, bones, and muscles [3,4]. The remodeling of stretch marks and skin scars secondary to acne and chickenpox is a no less critical goal of HA intradermal injections, possibly combined with other anti-aging techniques, as demonstrated by clinical studies [4-6].

Counteracting the age-related derangements in tissue distribution leading to skin shadows and loss of skin harmony also has a medical value. Feeling stressed is a burden for 70% of individuals with forehead and upper facial lines [7]. Even more dramatically, an April 2023 retrospective study from the Massachusetts General Hospital, Harvard Medical School, individuated psychiatric problems — most commonly anxiety, depression, ADHD, and insomnia — in 49% of a thousand subjects undergoing dermatologic procedures for wrinkles, skin aging or scarring. By comparison, the retrospective control cohort of patients with internal medical conditions showed a prevalence of 33% of psychiatric problems—a highly significant difference [8]. Moreover, 44% of patients in the first group were on psychiatric medication (1.67 psychiatric drugs per subject, on average), compared with 28% of medical controls (1.48 psychiatric medication per patient, on average). Again, such a highly significant difference highlights how skin scarring and other conditions of loss of skin harmony often are a severe medical burden far beyond the mere appearance impact [8]. The decreased skin quality leading to poor self-image is also associated with chronic illness and fewer healthy behaviors like physical exercise [9]. To say nothing of the skin wrinkling above the nose and between the eyebrows similar to the Greek letter omega—the "omega sign" diagnostic of melancholia, the little-known Charles Darwin's contribution in 1872 to dermatology intertwined with psychiatry [10].

The favorable properties of non-cross-linked HA formulated as fluid gels include ease and precision of injection, even of minute gel quantities — translating into easy sculptural correction even of slight skin defects [11]. The paper reports the outcomes of a real-world survey that followed an HA-based treatment cycle in subjects with deteriorated skin quality, stretch marks, and skin scarring.

The survey tool was a paper questionnaire that the participating investigator-surveyors, plastic surgeons, and dermatologists answered. The office-treated patients with compromised skin quality and scarring lesions also answered the survey. To simulate a real-world situation as far as possible, the clue that supports the study value, the investigator-surveyors acted with minimal inclusion and exclusion criteria.

The survey study is the first step of a long-term program to monitor the clinical performance and safety of a proprietary Class III CE-marked, non-cross-linked HA-based medical device for intradermal injections. Confirming the profile of known side effects and contraindications and identifying any unknown side effects or emergent risks was another purpose of the study as of the long-term monitoring program.

Materials and Methods

Design

Single-arm prospective cohort of 45 individuals of both genders and over 18 years old with stretch marks, dermal scars, and skin aging. All participating subjects sought specialist help to improve their deteriorated skin quality and were interviewed by the investigators in a real-world setting. Before the survey, all individuals had undergone a three-session treatment cycle with a Class-III CE-marked medical device containing 40 mg of non-cross-linked HA in 2-mL prefilled disposable syringes with 30G½ needles (IALEST®, Mastelli Srl, Sanremo, Italy). All investigators already used the surveyed device in their practice. Only a few conditions prevented participation in the survey study—known hypersensitivities or previous allergic reactions to ingredients of the medical device, pregnancy, diabetes mellitus, susceptibility to keloids, hypertrophic scarring or clinically significant skin pigmentation disorders, and history of connective tissue disease.

All subjects underwent three intradermal injection sessions, in agreement with regulatorily accepted procedures in the private-practice offices of investigators—at baseline (T0), two to three weeks after baseline (T1), and after two to three further weeks.

The survey interview session, carried out 2-4 weeks after the last treatment session, was purely observational with no further active intervention. After being informed about its purposes, all subjects agreed to answer the survey. Beyond monitoring the persisting safety and efficacy of the HA formulation on skin quality and skin scarring lesions, the investigators also registered the reasons for seeking ambulatory anti-aging procedures. Questionnaires allow information collection more quickly than face-to-face interviews and without time constraints for the investigator.

Observational Efficacy Assessments

Primary Efficacy Endpoint

Objective skin-quality improvement based on the validated and reproducible six-score Wrinkle Severity Rating Scale (WSRS), assessed at baseline (T0), before the first intradermal treatment session, and three to four weeks after T2 (end of the treatment cycle) (Table 1). Within the inevitable limits of a semi-quantitative scoring scale, the WSRS objectively evaluates the skin-quality benefit after therapeutic procedures with fillers. Validation means that each unit change in WSRS scores proportionally mirrors the corresponding variation in skin quality deterioration [12].

Table 1: Descriptors of the WSRS assessment instrument [12].

Wrinkle Severity Rating Scale (WSRS)	
Score	Descriptor
0	No wrinkles/scars
1	Just perceptible wrinkles/scars
2	Superficial wrinkles/scars
3	Moderately deep wrinkles/scars
4	Deep wrinkles/scars, well-defined edges
5	Very deep wrinkles/scars, redundant folds

Secondary Efficacy Endpoint

Improvement, assessed objectively and subjectively, of overall skin appearance based on the validated, five-score Global Aesthetic Improvement Scale (GAIS, Table 2), with scores attributed by the investigators and treated subjects and outpatients three to four weeks after T2 in comparison with the skin-quality situation assessed (investigators) or self-perceived (treated individuals) before the first treatment session.

Table 2: Rating categories and descriptors of the GAIS skin-quality assessment instrument [12].

Global Aesthetic Improvement Scale (GAIS)	
Score	Descriptor
1 (worse)	Appearance worse than the original condition.
2 (no change)	Appearance is essentially the same as the original condition, but not completely optimal for this patient.
3 (improved)	Obvious improvement in appearance from the initialcondition, but a touch-up or retreatment is indicated.
4 (much improved)	Marked improvement in appearance from the initialcondition, but not completely optimal for this patient. A touch-up would slightly improve the result.
5 (very much improved)	Optimal result for this patient.

Beyond being validated, the five-score and six-score WSRS and GAIS assessment tools have a statistical advantage. Outcomes assessed on scales with a few score levels have unimodal and symmetric distributions; conversely, scales with a higher number of score levels have highly skewed J-shaped and U-shaped distributions. Outcomes assessed on scales with a few score levels also have lower means and less appreciable floor and ceiling effects. At the same time, regression analysis shows that assessment scales with a few score levels account for a significant fraction of total variance and minimize the contribution of unknown and uncontrolled factors [13].

Observational Safety Assessments

Based on spontaneous reporting by cohort individuals, supported by open questionnaire questions, to identify known side effects, describe their presentation and severity with the help of an impromptu three-level scale (descriptors: “mild”, “moderate”, and “severe”), and identify any previously unknown adverse event or emergent risk. Investigators complemented the individual spontaneous reports by actively questioning subjects for adverse events at the final assessment visits.

Statistics

The sample size was estimated with the G*Power statistical program version 3.14. Based on the published literature with the surveyed device, the sample size calculation assumed a 70% improvement in the mean WSRS score (effect size) after the HA treatment cycle. Under this assumption, the statistical power (1-ß-error probability) to detect a significant divergence, under the no-effect null hypothesis, in the evolution of the WSRS score curve would have been equal to 0.95 in a 29-subject cohort [14].

Primary Efficacy Endpoint

Comparison of mean WSRS scores at T0 and T2 using the Wilcoxon test, the non-parametric equivalent of the paired two-sample Student’s t-test for within-subject variations (null hypothesis: no mean difference between the baseline and end-of-treatment sets of observations). More analytically, comparison of the percent of treated individuals and outpatients with WSRS improvements vs. baseline (at least one descriptor level) both objectively (investigators) and subjectively (surveyed cohort subjects). Changes in the overall distribution of skin quality severity descriptors were assessed with the chi-square test for proportions [15].

Secondary Efficacy Endpoint

Comparison of mean GAIS scores at T0 and T2 (Wilcoxon test) [15]. All statistical tests were two-sided with a 5% significance level (two-tailed alpha-error probability = 0.05); statistical program: StatPlus release v7 [15,16].

Results

Table 3 illustrates the cohort demographics and the individual characteristics of the 45 cohort subjects.

Table 3: Cohort demographics and individual characteristics of cohort individuals (SEM = standard error of the mean).

Cohort demographics	
Mean age ± SEM (years old)	47.5 ± 13.27
Median age (years old)	44
Age range (years old)	25 to 80
Women in the study cohort	41 (91.1%)
Men in the study cohort	4 (8.9%)
Smokers	18 (40%)
Fitzpatrick skin classes	
Phototype 1	None
Phototype 2	10 (26.3%)
Phototype 3	19 (50.0%)
Phototype 4	6 (15.8%)
Phototype 5	3 (7.9%)

Efficacy outcomes

The mean WSRS scores for skin quality, the primary efficacy endpoint, significantly improved between the T0 baseline visit and the T2 final follow-up visit by 42.9% (p <0.001) (Figure 1). Median WSRS scores improved from 3.0 to 1.0, meaning the distribution of skin quality scores appeared skewed towards more clinical severity at baseline and less severity at the final follow-up visit.

Table 4 illustrates the changes in the overall distribution of skin quality descriptors.

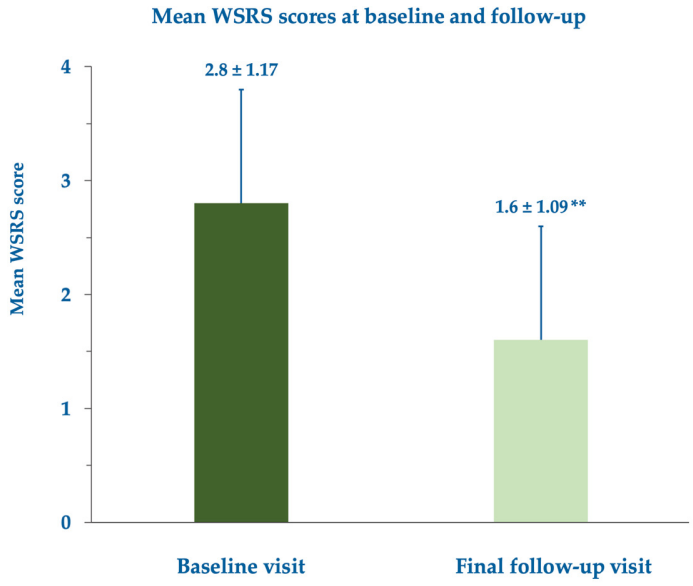

Figure 1: Comparison of mean WSRS scores at the baseline and the final follow-up visits; 45 surveyed cohort subjects. ** p <0.01 vs. baseline.

Table 4: Changes in the cohort distribution of skin quality descriptors between T0 (baseline) and T2 (end of treatment), according to investigators.

Skin quality descriptors, changes in distribution (T0 vs. T2)		
No change in descriptors	5	11.1%
Descriptor improvement: one level	30	66.7%
Descriptor improvement: two levels	9	20.0%
Descriptor improvement: three levels	0	//
Descriptor improvement: four levels	9	2.2%

The GAIS scores, objectively and subjectively assessed by investigators and scored subjects, confirmed the WSRS outcomes. At T2, the mean GAIS scores, the secondary efficacy endpoint, were 2.6 ± 0.61 for investigators and 2.7 ± 0.60 for surveyed subjects, with medians equal to 3.0 for the investigators and the surveyed individuals. At the end of the follow-up period, investigators labeled 95.6% of cohort subjects as GAIS responders with impressive efficacy outcomes ("Much improved" or "Very much improved" skin quality) for 29 of the surveyed individuals (64,4%). The investigators considered the residual 14 GAIS responders (31.1%) as "Improved" with "No change" for only a tiny minority (2 subjects, 4.4%).

The GAIS score changes self-assessed by surveyed subjects were similar—self-perceived "Much improved" or "Very much improved" skin quality in 32 of surveyed individuals (71.1%) and "Improved" in 11 (24.4%), with a clinically meaningful skin quality improvement for 95.6% of the cohort.

Figure 2 illustrates two representative examples of the skin quality evolution following treatment with the HA-based device between T0 and T2.

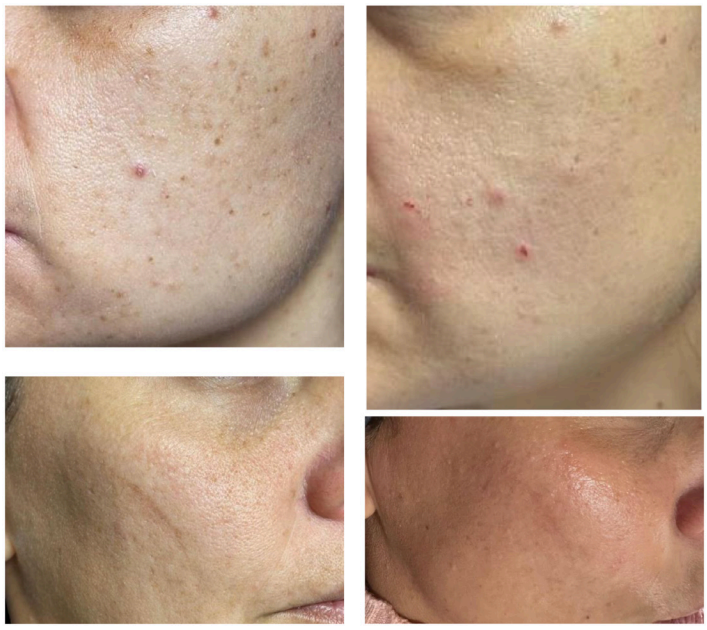

Figure 2: Skin quality evolution between baseline before treatment (T0, photographs on the left) and the final assessment visit (T2, photographs on the right). Anonymized photographs taken by a consultant and author of the Skin Quality Study Group and published with her permission.

Safety Outcomes

The treatment cycle was well tolerated, with a few mild and known adverse effects at the injection sites that disappeared rapidly and spontaneously with no sequelae. Seventeen surveyed individuals (37.8%) reported some erythema, the only local side effect that needed more than some hours or one day to wane. Thirteen subjects lamented bruising (28.9%), eleven participants had edema (24.4%), while occasional surveyed individuals reported local tumefaction or painful swelling and dyschromia. No cohort individual required treatment for those mild and expected side effects, and there were no unexpected untoward events.

Discussion

Dissatisfaction with skin appearance in people with no defined skin disease, but only with sequelae of everyday life events like acne or chickenpox scars or stretch marks, is widespread and well acknowledged. More than twenty years ago, a survey study covering several psychosocial and body image parameters showed that 81% of women with anorexia nervosa and bulimia nervosa vs. 56% of the controls were not satisfied with their skin appearance, primarily because of skin dryness and roughness, but also skin

laxity and shadows described as "bags" and "darkness" [17]. More than twenty years ago, such a significant percent difference already soundly justified supporting the medical value of all skin procedures, like intradermal hyaluronic acid injections that aim to improve skin hydration and smoothness [17]. The connection appears so strong that a recent review even advocated looking at striae distensae as diagnostic indicators of eating disorders pathologies [18]. The opposite is also true, with stress as an under acknowledged actor in extrinsic skin aging through dysfunctional molecular mechanisms of epigenetic regulation of gene expression leading to aberrant adaptative responses to stressful events [19].

IALEST® enjoys the same properties previously described for non-cross-linked HA. Besides the moisturizing action and general improvement of skin appearance, it is effective in remodeling dermal scars like stretch marks and lesions secondary to acne and chickenpox. It also acts on depleted skin elasticity and protectively as a free radical scavenger. A real-world study that does not diverge remarkably from everyday clinical practice is most helpful in monitoring whether the device's efficacy and safety persist over time [20].

The primary endpoint of persisting efficacy (mean WSRS score) improved independently of the Fitzpatrick phenotype. Interestingly, the median WSRS score changes were compatible with a progressive shift of the skin quality scores towards a less severely skewed distribution between the baseline and the final follow-up visits. The investigators reported a change of one or two WSRS severity levels in an impressive 86.7% of surveyed individuals. The subjective impressions of a self-perceived "Much improved" or "Very much improved" skin quality in more than 70% of surveyed subjects with excellent safety — no clinically significant event beyond a few mild and rapidly transitory episodes of local edema or bruising —confirmed the objective judgments by investigators.

Even if only conceived as a monitoring study to be replicated over time, the unsatisfied need for a control group is a methodological weak point of the study. However, relying on two validated and reliable WSRS and GAIS assessment instruments compensated for the bias, at least partially. The risk of failing to detect a significant skin quality difference between baseline and end of study (ß-risk of a falsely negative efficacy outcome) can never be dismissed and could be another sensitive issue. However, the surveyed cohort was over-dimensioned compared with the estimated size needed to reduce to almost zero the ß-risk of a falsely negative efficacy outcome. The lack of a more extended follow-up period might be a further bias. Only replicating the study in the not-so-remote future within the medical device's monitoring program will overcome this possible limit.

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