Jet Injection Of Hyaluronic Acid: A Regenerative Approach For Post-Acne Scarring

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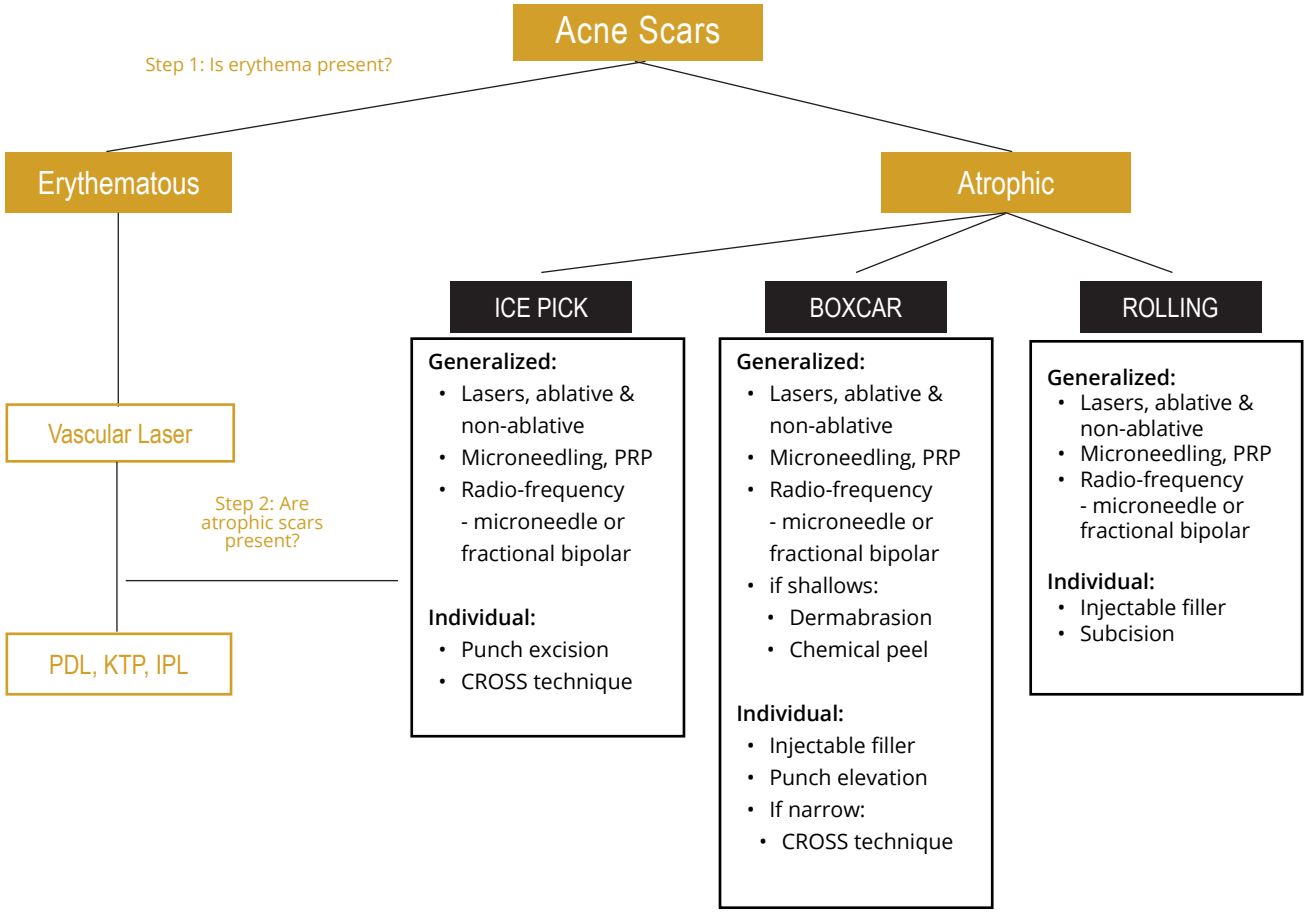
Introduction

Acne scars represent the end result of the "altered wound healing response to cutaneous inflammation" of acne vulgaris.[1] Inflammatory immune response causes atrophy of soft tissue and dermis and may result in its partial or even total replacement by fibrotic tissue.

Many treatment modalities are currently available for acne scars: filler injection, skin resurfacing, tissue augmentation, etc. (Figure 1). Most of them rely on a single mechanism that induces regeneration through an inflammatory process. Nevertheless, the complex pathogeneses and variability in the outcomes of the healing process cannot be addressed single-handed by a single treatment mechanism. The treatment process is usually highly unpredictable in its results and is accompanied by downtime. That is why tailored combination treatments need to be used in almost all patients.[1]

Figure 1. Acne scarring treatment algorithm (reproduced from Connolly et al. 2017)



EnerJet2.0 utilizes a liquid jet technology for needleless delivery of various therapeutic materials into soft tissues. Jet injection of hyaluronic acid (HA), synergistically volumizes the depressed scar while disconnecting fibrotic adhesions. New collagen and elastin can be formed thanks to the thorough distribution of HA in the treated area.[2]

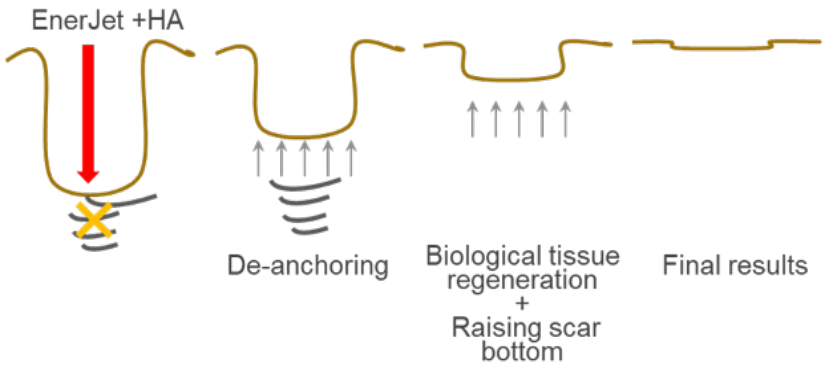
As a result, EnerJet treatment restores the original structure damaged during the inflammatory process and replaces fibrotic tissue with truly remodeled eutrophic dermis. The purpose of this paper is to present the clinical approach of EnerJet for the treatment of atrophic acne scars while explaining the mechanisms involved in this process.

Liquid jet: mechanism of action

The EnerJet2.0 device (PerfAction) can be effective on all types of acne scars – erythematous and atrophic. In both cases, HA may stimulate the needed regeneration. Furthermore, the anti-inflammatory effect of high molecular weight hyaluronic acid (HMW-HA) will hasten the resolution of the erythema allowing for further regeneration.[3]

Previously published data[4,5] demonstrated excellent results achieved by EnerJet in the correction of various types of acne scars. The needleless injection utilizes high-pressure in order to generate a high velocity liquid jet of hyaluronic acid resulting in a spherical spread of the material into the scar. Dispersed HA particles generate nanoscopic traumatic channels through the tissue fibers, which loosen the fibrotic scar structure. The result is comparable to manual subcision but the degree of the precision and thoroughness is much more predictable and reproducible. When the scar is deep and adheres to the deeper fascia (e.g. SMAS), it is immediately released and allowed to be leveled with the normal skin. The presence of the HA particles within the tissue allows for a temporary filling effect. The jet allows precise and controlled ability to deliver HA not only to the surface, but also to deeper layers of the scar – which are more difficult to reach with other energy-based treatments. The jet-administered HA easily reaches the bottom of the scar even in case of narrow, deep and steep-sided icepick scars.

Figure 2. EnerJet2.0 mechanism of action illustration



Biological effect of HA related to molecular weight

The biomolecular effect of the intralesional injection of HA contributes to reverse the formation of fibrotic scar tissue. This effect is very beneficial for acne scars: increase in the hyaluronan tissue level acts against fibroblast differentiation into scar-forming myofibroblast.[6] The bio-modulatory mechanism of hyaluronic acid normalizes fibroblasts activity and changes cell behavior to regenerative by regulating cellular response to growth factors and fibroblast migration. Furthermore, HA can either promote or resolve inflammatory response in tissues through phenotypic changes in macrophages activity.[7]

The pathways of biological response and the resulting tissue regeneration has been shown to depend on HA's molecular weight[8] (Table 1). HMW-HA contributes to diminish the inflammatory effect by inhibiting the production of pro-inflammatory mediators, whilst LMW-HA contributes to the specific stimulation of the inflammatory pathways.

An interaction between external HA and HA-specific cell receptors is an important factor in wound healing.[9] The binding between HMW-HA and CD44 receptors can induce cellular signaling and cell migration. Activation of the receptors for hyaluronan-mediated motility (RHAMM) has been proven to stimulate fibroblast proliferation. Additional interaction between low molecular weight HA (LMW-HA) and Toll-like receptors (TLRs) leads to a pro-inflammatory cascade at the injection site and initiation of appropriate wound healing. The increased fibroblasts' migration capacity from surrounding tissues into the wounded area results in tissue repair.[3]

Injected HMW-HA is enzymatically degraded by intrinsic hyaluronidase releasing low molecular-weight particles that may induce inflammation.[10] Inflammation itself is not totally undesirable in treatment of atrophic acne scars: a low level of inflammation can contribute to soft tissue regeneration without aggravating downtime. In severely atrophic areas, some degree of inflammation may be helpful in achieving more significant remodeling and improvement.

Table 1. Biological response of HA molecular weight through various cell surface receptors

Molecular size	Immune response	Inflammation	Angiogenesis	Anti-oxidative properties	Effect on CD44	Effect on RHAMM*	Effect on TLR**
High molecular weight HA	Immuno-suppression	Anti-inflammatory effect	Anti-angiogenic effect: inhibition of endothelial cell proliferation, motility, and sprout formation	Reduces oxidative stress, diminishes cell apoptosis	Prevention of cell apoptosis, stimulation of CD44 clustering and signaling	Induces an inflammatory response: stimulates fibroblast proliferation and migration	Suppression: inhibition of inflammatory cascade in acute injury
Low molecular weight HA	Activation of immune response in acute wounds	Pro-inflammatory effect	Pro-angiogenic effect: stimulation and proliferation of vascular endothelial cells	Antioxidant and protective effect, inhibits free radicals	Disruption of CD44 clustering		Activation: production of pro-inflammatory cytokines and stimulation of lymphocytes

*RHAMM - Receptors for Hyaluronan-Mediated Motility receptors; **TLR - Toll-Like Receptors. High molecular weight HA (HMW-HA) is a long linear polymer chain, with molecular weight reaching 5x106 kDa. Low molecular weight HA (LMW-HA) represents small fragments (up to 20 kDa) of the decomposed long HA polymer chain.

This correlates with the persistency of the dermal papules observed in some cases after treatment with EnerJet. Although they are perceived by patients and operators as a complication, the final results in the case of such persistence are usually better than in cases when the papules disappear within 24 hours.

Rheological properties of HA products

Acne scars vary in size, shape and depth. The surrounding skin differs from patient to patient in terms of thickness and quality due to the different age and degree of environmental damage (solar elastosis, smoking, etc.). It is important to customize the treatment for each single case. This can be done by taking advantage of the different behavior of the available HAs.

In some cases, (e.g. young skin of good quality with shallow scars), only a regenerative drive is needed. An excessive long-term filling effect shall result in ill-tolerated papules. The deeper scars will benefit from the temporary enhanced filling effect provided by less cohesive and more cross-linked HAs which typically have a relatively high elastic modulus G-prime (G'). However, when the deeper scars are surrounded by elastotic skin, a more thorough dermal regeneration is indicated: a combined high/low molecular weight cross-linked HA could be preferable. The adjacent retinaculum cutis and superficial fat could also possibly benefit from this action.

Scars' age and maturity should also be noted. In case of evolving scars (i.e. the erythematous macules left after the inflammatory papules have resolved), the pneumatic injection of HA can reverse the inflammatory process and promote a regeneration that will prevent the formation of the atrophic scars.

In some exceptional cases, the outcome of the post-inflammatory phase of acne scars is hypertrophy or keloid. Both can be reversed and normalized by the same treatment approach of EnerJet. The indication-specific recommendations for injectable HA are presented in Table 2.

Figure 3. Post-acne scarring treatment results.
Before and 1 month after 2 treatments. A - Before treatment; B - 1 month after 2 treatments.

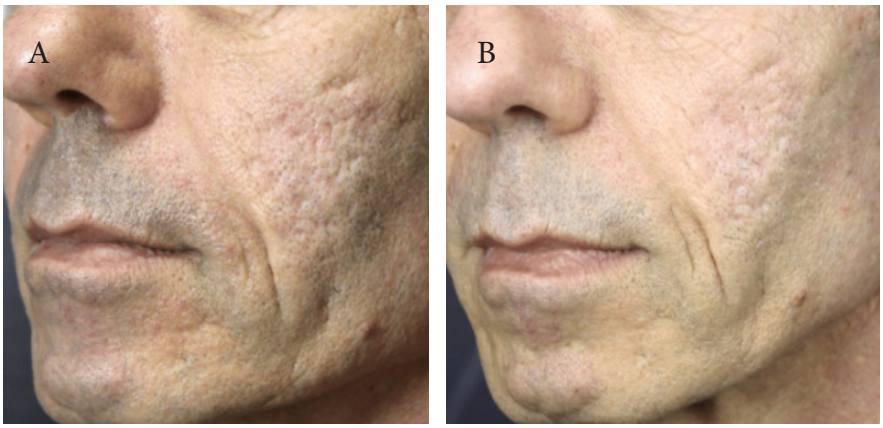


Table 2. Physicochemical and rheological properties of the indication-tailored HA fillers

Indications	Patient tolerates papules	Patient does not tolerate papules	Cross-linking	Cohesivity	G'
Skin atrophy	LMW+HMW	LMW+HMW	XL or NXL	High	Low
Elastosis	HMW	HMW	XL	High	Low
Stretch marks	LMW	LMW	XL or NXL	High	Low
Acne scars	N/A	N/A	XL+NXL (biphasic)	Low	High
Post-traumatic depressed scars	N/A	N/A	XL+NXL (biphasic)	Low	High
Hypertrophic scars	HMW	HMW	XL	High	Low
Keloid scars	HMW	HMW	XL	High	Low
Skin laxity, severe	LMW+HMW	LMW	XL+NXL (biphasic)	High	Low
Skin laxity, mild	HMW	HMW	XL	High	Low
Kinetic Lift, face	HMW+LMW	HMW	XL+NXL (biphasic)	High	Low
Kinetic Lift, neck	HMW+LMW	HMW	NXL	Highest possible	Lowest possible
Décolleté rejuvenation	HMW+LMW	HMW	NXL	Highest possible	Lowest possible

HMW-HA - long linear polymer chain, with molecular weight 5x106 kDa, LMW-HA – small fragments (up to 20 kDa), XL – cross-linked HA, NXL – non cross-linked HA

Conclusion

Administration of external HA through the pressure jet injection represents a beneficial therapy for improving of post-acne scarring. The therapy raises the skin depression through subcision of the scar and provides additional volume by due to the hydrating, filling and lifting effect on the depressed scar tissue.

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