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REVIEW ARTICLE

Hyaluronic acid-based fillers in patients with autoimmune inflammatory diseases

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Abstract

The use of hyaluronic acid (HA)-based aesthetic therapies is growing steadily, and according to the International Society of Aesthetic Plastic Surgery, more than 4.3 million aesthetic procedures using HA were performed in 2019, an increase of 15.7% than 2018. More people are offering these types of services, often without proper training or qualifications. Therefore, there is an increasing number of reports in the literature relating to possible adverse events, with subsequent therapeutic problems and more or less serious consequences for patients. The aim of this research is to carry out a review of the literature in order to evaluate the impact of hyaluronic acid-based fillers in patients with autoimmune inflammatory diseases, in particular scleroderma and Systemic Lupus Erythematosus (SLE). Although HA plays a central role in the inflammatory process, the use of HA-based fillers in patients with autoimmune inflammatory diseases is still controversial. HA, in fact, in inflamed tissues helps to propagate the inflammatory response and, injected in the form of a dermal filler, could potentially promote reactivation of the underlying disease. For this reason, many specialists do not perform HA-based aesthetic treatments in patients with scleroderma or SLE. However, recent scientific evidence suggests that the use of HA-based fillers in patients with scleroderma can lead to improvement of skin lesions, with satisfactory results. In the literature, there are no clinical studies that contraindicate the administration of HA-based dermal fillers in patients with inflammatory disease.

Hyaluronic acid (HA) is a glycosaminoglycan naturally released into the extracellular matrix by dermal fibroblasts, synoviocytes, endothelial cells, smooth muscle cells, adventitious cells, and oocytes. As a non-organ-specific molecule, it shows minimal risk of immunogenicity, so due to its stability at the implantation site, it represents a first-choice molecule for use as a dermal filler in aesthetic treatments. HA, in fact, due to its rheological and viscoelastic properties, influences the extracellular environment through complex molecular interactions with both cellular and matrix receptors. HA due to its hydrophilicity forms very extensive conformations with water molecules similar to a gel, resulting in tissue hydration and increased skin turgor. HA exists in three forms of different molecular weight, each showing a different effect. HA with highest molecular weight (1000 kDa) has an anti-angiogenic effect. Oligomers of intermediate

size (200 kDa) are involved in tissue repair through an inflammatory effect, while low molecular weight HA fragments (20 kDA) stimulate dendritic cells and up-regulate collagen I and III gene expression in fibroblast cells.[1]

The use of HA-based aesthetic therapies is growing steadily, and according to the International Society of Aesthetic Plastic Surgery, more than 4.3 million aesthetic procedures using HA were performed in 2019, an increase of 15.7% than 2018. More people are offering these types of services, often without proper training or qualifications. Therefore, there is an increasing number of reports in the literature relating to possible adverse events, with subsequent therapeutic problems and more or less serious consequences for patients.[2] To minimize the risk of complications it is important to manage and follow the patient proactively, but above all to select patients carefully, so that only the appropriate patients are treated. Soft-tissue augmentation is a medical procedure agreed upon between physician and patient, and not everyone who wants the treatment represents suitable candidates for medical reasons. Therefore, it is important to avoid treating those patients who have pre-existing medical conditions that clearly dictate against HA-based dermal fillers. Are not suitable candidates for superficial or medium depth placement of dermal fillers patients with skin atrophy, anethoderma, vermiculate atrophoderma or skin thinning as well as patients with active infections in the region to be treated, such as viral infections (herpes simplex and human perioral papilloma viruses, bacterial infections with streptococci or staphylococci, yeast infections, etc.). In fact, several studies have shown that HA injected into the superficial dermis may produce unwanted inflammatory skin reactions that, although mild, in subjects with pre-existing skin diseases could lead to a clinical worsening of the current pathology.[3,4] Similarly, physicians should carefully evaluate patients with active inflammatory dermatitis, including atopic dermatitis.

Relative to patients with generalized or systemic skin conditions and autoimmune-based connective tissue diseases (Systemic Lupus Erythematosus—SLE, active scleroderma, etc.), administration of HA fillers could promote a progressive increase in the inflammatory state, resulting in a worsening of the existing pathology.[5]

HA is produced and excreted by cells to form a pericellular or extracellular matrix and is present in all tissues of the body. Its size and shape is indicative of healthy or inflamed tissue, and HAs interactions with immune cells can influence their response. Specifically, HA of higher molecular weight predominates in healthy tissues, whereas in cases of tissue damage and/or infection, HA is broken down, resulting in an inflammatory response. When the inflammation is resolved, the extracellular matrix is restored and HA in the form of large glycosaminoglycan again predominates in tissues. Immune cells interact with HA in both tissues and lymphoid organs, and respond to it differently according to its molecular mass. In particular, HA fragments present in inflamed tissues are associated with the propagation of the inflammatory response. Activation of immune cells by pro-inflammatory cytokines, inflammatory stimuli, or antigen can cause them to bind HA through the CD44 receptor. CD44 expression increases when the immune cells are activated and proliferate, resulting in increased binding to HA. It is not completely understood why inflammation induces binding to HA; however, it is plausible that immune cells use HA to migrate to the site of infection and to retain them in inflamed tissues. Therefore, HA provides these cells with a cytokine-rich supportive environment, which aids their survival, proliferation, and function. In addition, HA fragments show to stimulate, in vitro, the expression of chemokines and pro-inflammatory cytokines in macrophage cell lines. This effect is mediated by *Toll-like receptor* (TLR) 4, TLR2, TLR2/TLR4, CD44/TLR4 or a combination of TLR4, CD44 and inflammasome. However, it remains uncertain whether HA fragments can directly activate TLRs. Therefore, further studies are needed to determine whether purified HA fragments and HA oligomers are pro-inflammatory and, if so, with which receptors they interact to mediate this effect.[6,7]

Although HA plays a central role in the inflammatory process, the use of HA-based fillers in patients with autoimmune inflammatory diseases, such as scleroderma and SLE, is still controversial. HA, in fact, in inflamed tissues helps to propagate the inflammatory response and, injected in the form of a dermal filler, could potentially promote reactivation of the underlying disease. For this reason, many specialists do not perform HA-based aesthetic treatments in patients with scleroderma or SLE. However, recent scientific evidence suggests that the use of HA-based fillers in patients with scleroderma can lead to improvement of skin lesions, with satisfactory results. In the first case, a 42-year-old woman with symptomatic systemic sclerosis and skin lesions on hands and mouth was treated with botulinum toxin and HA-based fillers. One month after treatment, the patient showed significant improvement in the skin lesions, with no occurrence of adverse events or worsening of the disease.[8] In another case report, a 35-year-old woman with asymptomatic localized sclerosis and an atrophic scar on chin was treated with HA 1 mL. No adverse events were reported, and the procedure was well tolerated. One-year follow-up after treatment showed that the patient maintained the filler, with no loss of its effect. In fact, the skin appeared smooth and the scar on the chin barely visible.[9] HA-based injectable treatment in patients with lupus, similarly to those with scleroderma or other autoimmune or connective tissue disorders, was avoided due to the theoretical risk of disease exacerbation or reactivation caused by tissue stimulation. Although more studies are needed to understand the pathogenesis of lupus and the tissue effects of HA-based fillers in this patient population, some studies have demonstrated the success of such treatment on atrophic lupus skin lesions. Clinical cases concerning the use of HA in the SLE population showed satisfactory results without aggravation of the disease. The most common adverse reaction, besides transient edema and erythema, tenderness, and ecchymosis, was the appearance of nodules immediately after injection, caused by the rather deep volumes to be filled. This disorder, however, may resolve with expansion of the underlying tissue by saline. More rarely, however, has been reported the appearance of late-onset immune-mediated nodules, particularly with fillers of the Vycross family,

based on the combination of high molecular weight HA molecules with medium-low molecular weight ones.[10] These nodules are resistant to treatment and requiring multiple sessions of hyaluronidase and triamcinolone injections to reduce their size. Therefore, until the pathogenesis of these post-filling nodules is more clear, it has been recommended to avoid the use of HA fillers of the Vycross family in patients with a history of autoimmune inflammatory disease.[11]

Confirming these findings, a recent prospective, single-center, open-label study shows that HA-based fillers, together with platelet-rich plasma, could be a viable therapeutic alternative for patients with systemic scleroderma. In the study were enrolled 10 female patients aged 18–70 years with systemic scleroderma cutaneous (SSc) and unresponsive to common treatments. In particular, 20% of patients (n = 2) had limited SSc, while the remaining 80% (n = 8) hah diffuse SSc. They were treated with three injections of HA filler and platelet-rich plasma at an interval of 15–20 days and followed up at 1, 3, and 24 months after the end of treatment. Patients had significant improvement in skin lesions already after the first injection, showing greater mouth opening and increased thickness of the upper lip. The treatment significantly improved the patients' quality of life, showing that HA fillers, together with platelet-enriched plasma, could be a viable therapeutic alternative. Due to its capacity to bind water molecules, hyaluronic acid fills wrinkles and softens, hydrates, and moisturizes the skin. Moreover, it stimulates the dermal creation of type I collagen, which could explain its protracted effects. Instead, platelet-rich plasma is a rich source of growth factors that are essential for promoting cell development, angiogenesis, and the control of inflammation. Thus, the combination of hyaluronic acid and platelet-rich plasma has demonstrated potential as a regenerative treatment for the facial fibrotic skin of patients with SSc, but these findings still need to be verified using a large cohort of patients.[12]

Although such evidence shows a positive effect of HA-based fillers on the healing of skin ulcers induced by autoimmune inflammatory diseases, a retrospective observational study, which examined the use of some HA-based creams, showed that the efficacy of the treatment depends on the etiology of the chronic ulcer (vascular, sclerodermal, or postoperative). A retrospective analysis was performed on 79 patients with multiple skin ulcers, who were divided into two groups according to ulcer etiology: patients with scleroderma ulcers and patients with non-scleroderma ulcers (vascular, postoperative). Patients with scleroderma ulcers developed a rapid inflammatory response resulting in a worsening clinical situation and skin wounds (92.7%). In contrast, only 1.5% of patients with non-sclerodermic skin ulcers had a severe inflammatory reaction. These results show that HA, in a cream formulation, has a pro-inflammatory effect in patients with scleroderma.[1]

Based on the clinical results in the literature, the use of HA products in patients with autoimmune inflammatory diseases is controversial. In fact, HA molecules are implicated in inflammatory processes, potentially going to exacerbate the patient's inflammatory disease, as shown by the previous retrospective analysis. However, no clinical studies contraindicates the administration of HA-based dermal fillers in patients with inflammatory disease. HA-based fillers in fact have not only shown important clinical and aesthetic benefits in treated patients with scleroderma or lupus, with a good safety profile, but also would represent, in combination with platelet-enriched plasma, a new therapeutic strategy for patients with systemic scleroderma, although these results need to be confirmed by a larger cohort of patients.

AUTHOR CONTRIBUTIONS

Conceptualization: C.R. and G.P., Writing: F.F. and M.D., Data curation: R.C., G.L., F.C., Supervision: A.C. and G.N; All authors have read and agreed to the published version of the manuscript.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

ETHICAL STATEMENT

None to declare.

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