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Original article

Safety and efficacy of filler injections in patients with immune-mediated inflammatory diseases

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Abstract. *Background:* Dermal fillers, particularly hyaluronic acid (HA) fillers, are commonly used in aesthetic medicine. However, their safety and efficacy in patients with immune-mediated inflammatory diseases (IMIDs) require further study. *Aim:* This study aims to evaluate the safety and efficacy of HA fillers in IMID patients over a five-year follow-up period. *Methods:* A prospective observational study was conducted in Milan, enrolling 170 patients with IMIDs who received HA fillers at least twice per year. Clinical assessments focused on adverse reactions, flare-ups, and the durability of HA fillers in an inflammatory environment. *Results:* No significant adverse reactions or IMID flare-ups were observed at six months, with significant improvements in quality of life (Delta DLQI, $p < 0.001$). However, flare-ups were observed in a small number of patients over time, with an increased frequency of filler applications due to the accelerated degradation of HA. *Conclusions:* HA fillers are safe to use in IMID patients in remission, offering aesthetic and functional benefits. However, the accelerated degradation of HA in this population warrants more frequent treatments. Further large-scale studies are needed to refine clinical guidelines.

Key words: Hyaluronic Acid Fillers, Immune-Mediated Inflammatory Diseases, Prospective Observational Study, Safety and Efficacy, Accelerated Filler Degradation

Introduction

Dermal fillers have become increasingly popular in aesthetic medicine over the past decades, with millions of procedures performed annually[1]. While these treatments are generally considered safe and effective for addressing facial volume loss and wrinkles in healthy individuals, their safety in patients with immune-mediated diseases (IMDs) raises concerns[2,3]. IMIDs include a range of conditions where the immune system targets the body's own tissues through mechanisms such as cell-mediated reactions and the production of autoantibodies[4]. Despite the growing use of fillers in aesthetic procedures, there is no clear consensus in the literature regarding their safety and efficacy in patients with these diseases. This uncertainty presents potential medical-legal challenges for clinicians[5].

The aim of this study is to provide new insights into the use of hyaluronic acid (HA) fillers in patients with IMIDs. This study provides data to support evidence-based decision-making, moving beyond reliance on case reports to better inform clinical practice and improve patient outcomes.

While some studies caution against the use of dermal fillers in patients with autoimmune conditions, recent research suggests positive outcomes, particularly in patients with scleroderma. In these cases, HA-based fillers have been shown to improve skin lesions and provide satisfactory aesthetic results despite the induced tissue inflammation[6-8]. This study seeks to evaluate the safety and efficacy of HA fillers in patients with IMIDs, focusing on long-term clinical outcomes and the potential impact on disease management.

Materials and Methods

Study design

This study was conducted over five years in Milan and involved 170 patients with IMIDs who received HA filler treatments at least twice per year. Physicians specialized in Aesthetic Medicine performed the procedures in both hospital and private practice settings. Patients received various commercially available hyaluronic acid fillers with differing physical properties, including different degrees of cohesivity, elastic modulus (G'), concentration, and cross-linking. The fillers used were the result of cross-linked formulations.

Ethical approval

The study was approved by the Institutional Review Board of San Raphael Hospital (protocol code 178/INT/2021, approved on November 10, 2021). All patients provided an informed consent before participating.

Enrollment criteria

Eligible participants met the following criteria:

- Age ≥18 years
- Diagnosis of an IMID
- Disease in remission (stability defined as <10% variation in severity score between consecutive visits)
- Stable medication regimen (unchanged dosage for at least six months)
- No prior botulinum toxin injections

Assessment protocol

Patients were assessed at baseline, six months, one year, three years, and five years. Adverse reactions were evaluated using Naranjo criteria, while the impact on quality of life was measured with the Dermatology Life Quality Index (DLQI).

Statistical analysis

Continuous variables were analyzed using the t-test, while categorical data was compared using the chi-square test. Statistical significance was set at $p < 0.05$.

Results

The cohort comprised 170 patients (87 females, 83 males; mean age 47.3 ± 8.4 years) diagnosed with:

- Morphea (n=27)
- Systemic lupus erythematosus (n=45)
- Moderate-to-severe psoriasis (n=67)
- Rheumatoid arthritis (n=21)
- Psoriatic spondyloarthritis (n=10)

At six months, no adverse reactions or IMID exacerbations were reported. Quality of life showed significant improvement (Delta DLQI, $p < 0.001$). However, flare-ups were observed in 12 patients after one year, 89 after three years, and 93 after five years, although these episodes were inconsistently associated with filler procedures according to the Naranjo criteria. The distribution of adverse events across the different IMIDs did not suggest a clear correlation with the use of fillers.

A notable finding was the increased frequency of filler applications required by IMID patients, likely attributable to accelerated HA degradation driven by chronic subclinical inflammation and endogenous hyaluronidase activity.

Discussion and Conclusions

The findings align with existing literature indicating that HA fillers do not significantly contribute to IMID reactivation[6]. However, the underlying pro-inflammatory status in these patients appears to reduce the longevity of HA fillers, necessitating more frequent treatments.

The study also underscores the importance of HA filler composition. Modern fillers, derived from bacterial fermentation, exhibit reduced immunogenicity compared to earlier animal-based formulations[9]. However, residual contaminants, including bacterial DNA and stabilizers, can elicit hypersensitivity responses[9]. Cross-linking methods further modulate immune

reactivity[10]. PEGylated fillers demonstrate heightened resistance to degradation, consequently leading to reduced activation of the inflammatory cascade in comparison to fillers crosslinked with BDDE[9,11].

Another critical consideration is the potential risk of Autoimmune/Autoinflammatory Syndrome Induced by Adjuvants (ASIA), a phenomenon associated with genetic predisposition (HLA-DRB1 polymorphism). While ASIA is an idiosyncratic reaction rather than a dose-dependent effect, its occurrence underscores the necessity of individualized patient screening and long-term follow-up sessions[9,12].

From a clinical standpoint, the findings highlight the need for rigorous patient selection and an awareness of the accelerated degradation of HA fillers in IMID patients. Practitioners must ensure disease remission at the time of treatment and select high-purity, well-regulated filler products to minimize adverse effects.

In conclusion, HA dermal fillers are a viable option for patients with IMIDs in remission, offering aesthetic and functional benefits without significant risk of disease reactivation. However, the increased degradation rate observed in IMID patients should be acknowledged, with appropriate patient counseling regarding treatment expectations. A structured clinical approach, encompassing disease activity assessment, medication interactions, and filler selection, remains essential for optimizing outcomes in this patient population. Further large-scale, long-term studies are warranted to refine clinical guidelines for aesthetic procedures in IMID patients.

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Conflict of Interest: The authors declare no conflict of interest.

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