Received: 31 October 2020 | Accepted: 11 November 2020

DOI: 10.1111/dth.14644

ORIGINAL ARTICLE

DERMATOLOGIC THERAPY WILEY

# Increased risk of late-onset, immune-mediated, adverse reactions related to dermal fillers in patients bearing HLA-B*08 and DRB1*03 haplotypes

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**Funding information**
SEMCC (Sociedad Española de Medicina y Cirugía Cosmética -Spanish Society of Cosmetic Medicine&Surgery; ZonMw

## Abstract

Even though manufacturers claim that the dermal fillers are nontoxic and non-immunogenic, adverse events may occur. Clinically and histologically, most of the late onset adverse events present as an inflammatory response. To assess whether HLA polymorphisms are associated with late-onset inflammatory adverse events related to dermal fillers. A total of 211 patients were included, of whom 129 experienced late-onset inflammatory adverse events to different fillers (Inflammation group) and 82 who did not (Reference group). Patients completed a standardized questionnaire and provided a blood sample or oral swap for HLA testing. The study population consisted of 188 (89%) women and 23 (11%) men. The two study groups were similar in the distributions of filler type, location of injecting, allergy, autoimmune disease, gender, age, ethnicity, and smoking status. Of the 211 patients in the sample, 25 had the combination of HLA subtype-B*08 and HLA subtype-DRB1*03. This was 16.3% of the inflammatory group and 4.9% of the reference group. This combination of HLA subtypes was associated with an almost 4-fold increase in the odds of developing immune mediated adverse events (odds ratio = 3.79, 95% CI 1.25-11.48). Genetic polymorphisms such as HLA combinations may identify patients at risk of developing late onset immune mediated adverse events to dermal fillers.

**KEYWORDS**
adverse reaction, cosmetic dermatology, dermal filler, haplotypes, HLA, immunogenetics, late-onset reaction

## 1 | INTRODUCTION

An ever-increasing number of people undergo dermal filler injections for aesthetic indications or to reduce the signs of skin aging. Improvements that were previously achieved only by surgery can now be mimicked by dermal fillers treatment at lower cost and with limited-to-none recovery time. For aesthetic reasons alone, almost 2.7 million dermal fillers have been injected in the United States in 2018, a 50%

  

increase since 2010.[1] A recent study in the Netherlands shows that each year, 1 out of 49 women receive at least one injection treatment.[2]

Physicians have different types of dermal fillers at their disposal, consisting either of resorbable or nonresorbable materials. Manufacturers claim that marketed fillers are nontoxic and nonimmunogenic, which are requirements for any biomaterial intended for aesthetic uses. However, unwanted adverse events of various clinical relevance may occur in a low percentage of patients implanted with dermal fillers, such as medical grade silicone, polyalkylimide, hyaluronic acid, poly-L-lactic acid, polyacrylamide, or methacrylate fillers.[3-6] Reports suggest incidences of 0.3%-0.4% for hyaluronic acid (HA)[7] and of 5% for acrylamides.[8-10] Early onset inflammatory adverse events start within 2-4 weeks after injection.[3] Late onset inflammatory adverse events to dermal fillers appear between 1 and 60 months postimplantation, with 14 months as mean period.[3] Clinically and histologically, most of the late onset adverse events present as an inflammatory response.[3] In fact, a variety of adverse events has been associated with fillers, including granulomas, inflammatory nodules, angioedema, skin induration, human adjuvant disease, sarcoidosis and sarcoid-like disease, panniculitis, Sjögren syndrome, autoimmune thyroiditis, localized and systemic sclerosis, inflammatory myositis, autoimmune inflammatory syndrome related to adjuvants (ASIA), and cutaneous vasculitis.[14,15] Most of these adverse events seem to have an immunological basis, where the fillers act as adjuvants more than as direct T-cell activators, on a possible background of genetic predisposition.[16] Even though the origin of these complications is not completely clear, they can be due to exacerbated immune responses of the body against foreign body material.[16] Problems with long term safety and reversibility of adverse events due to foreign body material also occur in plastic surgery (breast implants),[11] cardiology (pacemakers),[12] and orthopedics (hip implants).[13] When looking at the genetic predisposition leading to immune-mediated, adverse reactions, and genes within the major histocompatibility complex (MHC) have been shown to be associated with auto-immune diseases as M. Bechterew.[17] And there is also speculation about the HLA subtype-B*08 and HLA subtype-DRB1*03 in immune mediated disorders in women with silicone breast implants.[18-23] Because of the low-prevalence of late-onset immune-mediated complications, we hypothesize about the potential role of genetic polymorphism affecting immune-related gene functions, as a subjacent cause.

Genetic polymorphisms are defined as the occurrence of multiple alleles at a given locus, where at least two alleles occur with a frequency greater than 1%.[24] Accordingly, the human leukocyte antigen (HLA) system is the most polymorphic region within the human genome.[25] The HLA system is a super locus that contains a large number of genes clustered on a 4 Mb-segment of the short arm of chromosome 6 in humans, related to immune system function. Indeed, HLA region comprises six major classical HLA loci that encode structurally homologous proteins which are classified into HLA class I (HLA-A, B, Cw) and class II (HLA-DRB, DQ, DP).[26]

In this candidate gene study, we tested all HLA subtypes A, B, and DRB for their association with late-onset immune-mediated adverse reactions related to foreign biomaterials, used as implant fillers.

## 2 | MATERIAL AND METHODS

### 2.1 | Study population

We used a convenience sample of 211 patients, of which 92 were from of the Systemic Autoimmune Diseases Unit at Vall d'Hebron University Hospital in Barcelona and 119 of the Dermatology Department, Erasmus MC, the Netherlands in the period between 2016 and 2018.

Late onset immune mediated adverse event was defined as the appearance of two or more local clinical signs of inflammation (ie, edema, skin induration, swollen/tender nodules with or without fistulation, or discharge of pus or filler material) three or more months after initial filler injection. Patients with these inflammatory complaints formed the Inflammation group (N = 129). The Reference group (N = 82) was formed by people treated with dermal fillers at least 3 months earlier, without any inflammatory complaints. Patients with isolated soft lumps without inflammatory signs were also included in this Reference group.

Patients with and without late-onset inflammatory complaints were compared through HLA genotyping and a questionnaire regarding age, ethnicity, smoking status, autoimmune diseases, type I or IV allergies, and location of the injection of the dermal filler.

### 2.2 | HLA genotyping

DNA was obtained by means of oral swab or blood extraction. Briefly, DNA was isolated from the buccal swabs using QIA-AMP kit according to the manufacturer's instructions (Qiagen, Venlo, the Netherlands). Blood was collected from the antecubital vein of arms through Vacutainer method (Becton Dickinson, Franklin Lakes, New Jersey). Samples were stored at −80°C until further analyses. Low-intermediate resolution genotyping of HLA-A, HLA-B, and DRB alleles of all patients were performed by sequence-specific oligonucleotide probe (SSOP) methods using the Luminex microbead technology in Barcelona, Spain (Lifecodes HLA typing kits, Gen-Probe, San Diego, California) and in Amsterdam, Netherlands. (Sanquin Diagnostic Services, Amsterdam, the Netherlands). This method maps all alleles of the HLA-A, HLA-B, and HLA-DRB subtypes.

### 2.3 | Statistical analysis

Descriptive statistics were reported comparing the distribution of patient and filler characteristics possibly associated with adverse reactions to filler injections between the inflammatory group and the reference group. The degree of association between adverse reactions and having a possible specific HLA-A, HLA-B, and DRB alleles combination was estimated by the odds ratio (OR) with 95% confidence interval (CI) and Nagelkerke's $R^2$ along with a likelihood ratio (chi-square) test.

To assess the impact of potential confounders and effect modifiers on the estimated odds ratio, we first conducted contingency table analyses to see if there were any significant associations among the selected characteristics of the patients and both the presence of the HLA combination and the appearance of adverse reactions.

Variables considered as potential confounders or moderators were filler type, location of injecting, allergy, autoimmune disease, gender, ethnicity, and smoking status. A full assessment of possible confounding and effect modification was conducted. For all analyses, the significance level was set to 0.05. To evaluate the predictive properties of the logistic regression model we also calculated the sensitivity, specificity, and the area under the curve (AUC) parameters. Analyses were conducted with SPSS software (IBM Corp. Released 2017. IBM SPSS Statistics for Apple, Version 25.0. Armonk, NY: IBM Corp.).

The study was approved by the medical ethics committee of both University Hospitals.[27]

## 3 | RESULTS

A total of 211 patients were eligible for this study, of whom 129 experienced late-onset inflammatory adverse events to different fillers (Inflammation group) and 82 did not (Reference group). Table 1 displays selected characteristics of the two groups. No systemic complaints potentially related to the filler adverse event was seen in the inflammatory group. The distributions of filler type, location of injecting, allergy, history of autoimmune disease, gender, age, ethnicity, and smoking status were comparable between two groups. Both groups were also comparable in types of fillers received, being nonresorbable ones (polyalkylimide, liquid silicone) and resorbable hyaluronic acid fillers (of various brands).

Of the sample of 211, there were in total 25 patients with the HLA combination of HLA subtype-B*08 and HLA subtype-DRB1*03 (11.8%; 95% CI 8.2%-16.9%). The proportion of patients with this specific combination was significantly higher in the Inflammation

**TABLE 1** Descriptive statistics of patient characteristics for inflammation and reference group

| | Inflammation | Reference | $\chi^2$ | *P*-value |
|---|---|---|---|---|
| Gender | | | | |
| Female | 114 | 74 | 0.18 | .671 |
| Male | 15 | 8 | | |
| Age (in years) | | | | |
| Mean (SD) | 53.2 (10.6) | 54.3 (10.0) | $t = 0.69$ | .490 |
| Ethnicity | | | | |
| Caucasian | 120 | 77 | 0.06 | .803 |
| Non-Caucasian | 9 | 5 | | |
| Smoking | | | | |
| Yes | 28 | 26 | 2.63 | .105 |
| No | 101 | 56 | | |
| Autoimmune diseases | | | | |
| Yes | 16 | 6 | 1.39 | .239 |
| No | 113 | 76 | | |
| Allergy | | | | |
| Drugs | 10 | 5 | 1.41 | .494 |
| Atopy | 25 | 11 | | |
| No | 95 | 66 | | |
| Filler type | | | | |
| Nonresorbable | 99 | 62 | 0.04 | .580 |
| Resorbable | 30 | 20 | | |
| Injection location | | | | |
| Periorbital | 10 | 9 | 5.50 | .358 |
| Lips | 27 | 14 | | |
| Nasolabial folds | 35 | 29 | | |
| Cheeks | 26 | 12 | | |
| Zygoma | 27 | 18 | | |
| Buttocks/legs | 4 | 0 | | |

*Note:* $\chi^2$, Chi-square value for test for independence.

**TABLE 2** Risk of adverse events[a] after dermal implantation for Inflammation and Reference group in relation to presence of HLA haplotype (B*08, DR3, or B*08/DR3 combined)

| B*08/DR3 | Inflammation | Reference | Total | OR (95% CI) | *P*-value[b] |
|---|---|---|---|---|---|
| No | 108 | 78 | 186 | 3.79 (1.25, 11.48) | .008 |
| Yes | 21 | 4 | 25 | | |
| Total | 129 | 82 | 211 | | |
| B*08 | Inflammation | Reference | Total | OR (95% CI) | *P*-value |
| No | 103 | 71 | 174 | 1.63 (0.76, 3.51) | .203 |
| Yes | 26 | 11 | 37 | | |
| Total | 129 | 82 | 211 | | |
| DR3 | Inflammation | Reference | Total | OR (95% CI) | *P*-value |
| No | 98 | 68 | 166 | 1.54 (0.76, 3.10) | .224 |
| Yes | 31 | 14 | 45 | | |
| Total | 129 | 82 | 211 | | |

Abbreviations: 95% CI, 95% confidence interval; OR, odds ratio.
[a]Adverse events include granulomas, inflammatory nodules, angioedema, skin induration, human adjuvant disease, sarcoid-like disease, cutaneous vasculitis.
[b]Likelihood ratio test.

**TABLE 3** Predictive measures

| Specificity | Sensitivity | AUC |
|---|---|---|
| .951 | .163 | .557 |

*Note:* The cut-off value is set to .70.
Abbreviation: AUC, area under the curve.

group (n = 21, 16.3%) than in the Reference group (n = 4, 4.9%), giving $\chi^2 = 6.98$, $P = .008$.

Table 2 presents the cross tabulation of the presence of HLA subtype-B*08, the presence of HLA subtype-DRB1*03, and the simultaneous combination for both the Inflammatory group and the Reference group. The presence of either the antigen HLA subtype-B*08 or HLA subtype-DRB1*03 was not significantly associated with the risk of developing dermal filler induced adverse reactions (Table 2). However, the combination of HLA subtype-B*08 and HLA subtype -DRB1*03 was associated with an increased risk of late-onset adverse reactions (Nagelkerke's $R^2 = .04$). The odds ratio was 3.79 (95% CI 1.25-11.48), indicating that the likelihood of developing adverse reactions may increase by a factor 3.8 in people showing this HLA combination.

The analyses showed that there were no other statistically significant associations among the selected characteristics of the patients and both the presence of the HLA combination and the appearance of adverse reactions (all *P*-value's >.10). Accordingly, based on the present model, the probability of correctly classifying that a patient will experience adverse reactions is about 16.3% (Table 3). The AUC of 55.7% indicates that model-based classification is only marginally better (5.7%) than classification based on random guessing.

## 4 | DISCUSSION

In this study we found a significant correlation between the combined presence of HLA subtype-B*08 and HLA subtype-DRB1*03 and inflammation in a group of patients with dermal fillers. We used clinical signs to distinguish between inflammatory and noninflammatory reactions. Also, we had to rely on patient's clinical history regarding the absence of past adverse reactions. An inflammatory response to dermal fillers develops slowly and insidiously and may even spontaneously subside. In fact, it is conceivable that some of the subjects in the Reference group may develop an inflammatory response later in life or may have had subclinical symptoms. In this context, the HLA subtype-B*08 and HLA subtype-DRB1*03 combination was found in 5% of the Reference group. The expected percentage within the general population in Europe is 1.6%.[28] Also, in the inflammatory group some patients might have had a nonimmunological condition leading to inflammation, that is, bacterial infection of the implant. Therefore, it can be argued that both groups are not homogeneous. Accordingly, in this study positive HLA subtype-B*08 and HLA subtype-DRB1*03 combination has low sensitivity 16.26% and high specificity 95.12%. The HLA combination identifies only one out of six people at risk for an inflammatory adverse event after filler use. Further testing in prospective studies on larger groups and with tighter criteria may reveal higher sensitivity.

For this study HLA class I A, B, and HLA class II DR (and DR subtypes) were selected because of the relationship between HLA-B and HLA-DR and the predisposition to suffer autoimmune and/or granulomatous disorders.[17,19-22]

HLA-C was left out because of its very high polymorphic complexity and very complicated to relate with human pathology.[28] HLA-D or HLA-E appear to play a major role in the viral responses (NK cells and NK-KIR receptors) and in women, with the tolerance degree to embryo-paternal antigens by maternal NK cells and Tregs, but no relation to human diseases have been described as far as we know.[29]

This study suggests a link between specific HLA-subtypes and an immune mediated reaction to a foreign implant, meaning that some persons may be more prone to display a reaction than others based on their immunogenetic profile. We found that people with HLA

subtype-B*08 and HLA subtype-DRB1*03 combination have a 3.8-fold increase in risk of developing inflammatory adverse events due to fillers in clinical practice.

Interestingly, certain auto-immune diseases like inflammatory arthritis are also related to the presence of specific HLA subtypes, in particular HLA-B27 and HLA-DR1-11, DR3, and DR4.[31,32] In addition to this, there is increasing evidence that adverse reactions to implanted materials like scleroderma-like syndromes are also related to certain HLA combinations.[24] Bell et al. demonstrated in 1996 that an increased frequency of HLA-A1, HLA-B1, and HLA-B2 in patients with chronic graft-vs-host disease (cGVHD) who developed scleroderma-like complications.[32] This suggests that a genetic predisposition may be linked to the development of more severe scleroderma-like symptoms in cGVHD. Of note, when looking to our patient group, the presence of the combination of HLA subtype-B*08 and HLA subtype-DRB1*03 was also associated higher rates of fibrotic reactions of the skin. None of the patients from the Reference group did show any of those reactions.

This study on late-onset inflammatory adverse events after dermal fillers injections can be a starting point in genetic research for the prediction of adverse events of dermal filler treatments. This study provides for the first time an in vitro method for the analysis of the genetic predisposition of an individual to develop late onset immune mediated adverse events related to dermal fillers.

In conclusion, this is the first study to show that HLAs B*08 and DRB1*03 is associated with late-onset cutaneous inflammatory adverse events to dermal fillers injection, suggesting an immunological pathway for this problem in some patients. Although this HLA combination may be biomarker for these adverse events induced by biomaterials, larger studies including genetic polymorphisms such HLA subtypes are warranted before they can be used to identify people at risk of developing cutaneous inflammatory adverse events due to fillers in clinical practice.

## ACKNOWLEDGMENTS

This study has been supported in part, by a grant from the SEMCC (Sociedad Española de Medicina y Cirugía Cosmética –Spanish Society of Cosmetic Medicine&Surgery) and ZonMw (Dutch Ministry of Health).

## CONFLICTS OF INTEREST

JA-R and SS have an issued patent related to the use of HLA haplotypes as risk markers of adverse reactions in dermal filler implantations (P201030604).

## DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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**How to cite this article:** Decates TS, Velthuis PJ, Schelke LW, et al. Increased risk of late-onset, immune-mediated, adverse reactions related to dermal fillers in patients bearing HLA-B*08 and DRB1*03 haplotypes. *Dermatologic Therapy*. 2021;34:e14644. https://doi.org/10.1111/dth.14644