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Association between BNT162b2 vaccination and the development of delayed inflammatory reactions to hyaluronic acid-based dermal fillers - A nationwide survey

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A.S performed the research. A.S, D.D, O.A designed the research study. A.S, E.S and O.A analysed the data. A.S, E.S, L.S and O.A. wrote the paper.

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Summary

Background: Delayed inflammatory reactions (DIRs) to hyaluronic acid (HA)-based dermal fillers following COVID-19 vaccination has been reported in a few anecdotal reports and small series of cases.

Aim: To evaluate the clinical characteristics, incidence and management options relevant to BNT162b2 vaccination-associated DIR – A nationwide survey was conducted.

Methods: An online self-administered survey was sent to physicians who actively practice tissue filler injections. The data acquired included demographic and clinical characteristics of relevant DIR cases.

Results: Out of 262 responders, 20 cases with DIR following the vaccination were reported. 35% and 65% occurred shortly after the first and second vaccination dose, respectively. Overall, 65% of the DIRs appeared ≤5 days after vaccine administration and most DIRs resolved within 21 days. The filler's volume (P = .016) was associated with higher DIR severity, and the same tendency was noted among some filler types and locations of injection. Medical intervention was provided in 12 (60%) cases.

Conclusion: DIR associated with BNT162b2 vaccination is rare and tends to resolve spontaneously or with short-term medical intervention.

Keywords: COVID-19 vaccination, BNT162b2 vaccination, hyaluronic acid, delayed inflammatory reaction, dermal fillers.

Abbreviations used: HA, hyaluronic acid; DIR, delayed inflammatory reaction**;** ACE**,** angiotensin converting enzyme; QOL, quality of life.

Introduction

At the end of 2020, the Food and Drug Administration authorized emergency use of the mRNA-based vaccines BNT162b2 (Pfizer-BioNTech) and 1273 (Moderna) [1,2] in an attempt to contain the COVID-19 pandemic. A registry-based study that collected cases of cutaneous manifestations following vaccination with the two vaccines reported 9 cases of skin reactions to dermal fillers out of 414 vaccinated patients [3]. Eight cases were associated with 1273 and one case with BNT162b2. Munavalli et al.[4] observed 4 cases of delayed inflammatory reaction (DIR) that appeared shortly after mRNA-based vaccination. Five additional case reports described possible DIRs to hyaluronic acid (HA)-based fillers following COVID-19 disease or vaccination [5–9]. The true incidence and clinical features of these reactions, however, remain unclear.

Israel was among the first countries to initiate a massive vaccination campaign, with most of the population having been vaccinated with the first and second doses of the COVID-19 vaccine as of April 2021 with remarkable effect on the size of the pandemic and manifestations of the disease in the both general and high-risk populations[10,11]. Since the use of HA dermal fillers is becoming increasingly popular and given the fact that side effects may deter at-risk individuals from vaccination, we aimed at delineating the estimated incidence of DIRs secondary to vaccination against COVID-19 as well as prognostic characteristics and treatment options relevant to this condition. To achieve this goal, we conducted a nationwide survey among physicians performing dermal filler injections.

Methods and materials

Data acquisition and definitions

A national cross-sectional online self-administered questionnaire (**Supplementary Fig.1**) was sent to all physicians in Israel who actively practice tissue filler injections during April 2021. This list comprised 1063 physicians who had purchased HA fillers from the main Israeli distributing companies between March 2019 and April 2021. To avoid missing the more severe cases involving patients who required hospitalization, the same email was also sent to the chairs of all dermatology and plastic surgery departments in Israel. Three email reminders with the survey link were sent to all non-respondents at 2-weeks intervals. To avoid duplicate entries, each physician was able to fill out the form only once using the same email address. Once filling out the query, each physician was able to fill the form repeatedly based on the number of patients he had encountered with this type of reaction. However, to avoid duplicate entries, each participant could fill out the query only once using the same email address.
The electronic questionnaire was built with the Google-forms platform and included 20 multiple choice questions and 3 open questions. No identifying details about the patients were either requested or acquired. The questionnaire was approved by institutional review board in accordance with the principles of the Declaration of Helsinki.

For analysis of the positive cases, we categorized severity as mild for cases with 1-2 symptoms unnoticeable by others, moderate for 1-2 symptoms noticeable by others but not affecting normal quality of life (QOL), and severe for more than 2 symptoms noticeable by others and affecting normal QOL. The duration of symptoms was categorized into 3 groups: cases that resolved ≤5 days, those that lasted between 6-21 days, and those that lasted >21 days. For further analysis, another subdivision was performed by defining "prolonged time until resolution" as a reaction that had lasted over ten days.

Statistical analysis

The statistical analysis was performed with SPSS Statistics 27 (SPSS Inc., Armonk, NY: IBM Corp) and with R (R Core Team, 2020). The $\chi 2$ test was applied for categorical variables. Clinical parameter distributions were tested for normality by the Shapiro-Wilk test. The independent T-test was conducted for continuous variables with a normal distribution, and the Mann-Whitney U-test for variables with a non-normal distribution. A P value of $\leq .05$ on a 2-sided test was considered significant.

Results

Questionnaire responder characteristics

The questionnaire was sent to 1076 physicians. Two hundred and sixty-two physicians (24.6%) responded, of whom 93 (35.4%) were internists or primary care physicians, 74 (28.2%) were dentists, 55 (22.9%) were dermatologists or plastic surgeons, and 40 (15%) practiced other specialties or did not mention their specialty. Most survey participants (72%) have practiced dermal filler injections for 1-5 years. The 262 responders reported 20 cases of a recent encounter with patients who sustained a DIR related to vaccination with BNT162b2. Among them, thirteen (65%) had over ten years of professional experience, and ten (50%) were dermatologists or plastic surgeons.

Exposure

All 20 reported cases of DIR occurred following BNT162b2 vaccinations, and none were positive to COVID-19 by PCR at any time prior to the reaction. Thirteen of the 20 DIR events (65%) occurred after the second vaccine dose. There was no difference in DIR severity following the first or the second vaccination ($P = .63$). Most of the reactions (13/20, 65%) appeared ≤5 days after the vaccination.

Patient demographics and clinical characteristics

Table 1 summarizes the main demographic and clinical characteristics of the reported DIR cases. Average age of patients with DIR was 42.6 ± 13.22 years (range 21-64 years). Most of them were females (18/20, 90%). There was no significant age difference between the severity groups. Past medical history was positive for a recent dental procedure in one case, and for a Plaquenil treated systemic lupus erythematosus autoimmune disease in another. No prior history of allergic reactions was reported.

All patients who developed a DIR presented with local swelling and edema, 9/20 (45%) presented with palpable nodules, 8/20 (40%) with erythema, 7/20 (35%) with stiffness and induration over the injected areas, 7/20 (35%) complained of local pain, and 3/20 (15%) complained of local pruritus. When classified according to DIR severity, 10/20 (50%) exhibited a mild reaction, 2/20 (10%) moderate and 8/20 (40%) as a severe reaction. We combined the mild and moderate groups for further statistical analysis.

Most reactions resolved within 21 days (60%). Eleven out of twenty cases (55%) were defined as "prolonged time until resolution" (i.e., a reaction lasting over 10 days). Such reactions were noted in patients with

palpable nodules (n = 6, 66%, P = .34), those with stiffness and induration (n = 6, 85%, P = .04), and those with pain (n = 6, 85%, P = .04). Those symptoms and complaints were also found to be more pronounced in the severe group. DIR resolution was observed after >21 days in 7 of the 11 (63%) patients who had a prolonged resolution time. The only 2 males in this cohort experienced rapid resolution (<5 days). The sample size was not sufficient for statistical analysis of this finding.

Six of the 20 (30%) patients underwent imaging studies including ultrasonography (US), computed tomography, or magnetic resonance imaging for better characterization of the DIR. Four of them (66%) were in the severe reaction group.

Only 1 of the 20 (5%) patients was hospitalized for DIR. Twelve others (60%) received medical intervention: 6/12 (50%) of the mild-moderate group and 6/8 (75%) of the severe group were treated with one or more of the followings: antihistamines (8/12, 66.6%), oral steroids (7/12, 58.3%), oral antibiotics (6/12, 50%), filler dissolution with hyaluronidase (5/12, 41.6%), and ACE inhibitors (1/12, 8.3%). Antibiotics (P = .0096) and hyaluronidase (P = .035) were used more often in cases with severe reactions (**Figure 1**).

Time to resolution was also associated with the timing of symptom onset after the vaccination. The 4/7 (57.1%) patients whose DIR resolved after >21 days had experienced the reaction >5 days after the vaccination, while symptom onset was 3-5 days after the vaccination in 4/5 (80%) patients whose symptoms resolved in ≤ 5 days.

Effect of filler material on DIR

The time interval between dermal filler injection and DIR was ≥2 months for 11 patients (55%), 1-2 months for 3 patients (15%), and ≤1 month from injection for 6 patients (30%). Six of the 8 severe reactions (75%) appeared >2 months after the filler injection.

Juvederm (n = 6, 30%), Restylane (n = 6, 30%) and Revanesse (n = 4, 20%) were the most used dermal fillers among patients who developed DIR. There is not accurate data on the filler type usage distribution in Israel. However, it is agreed that the Stylage, Restylane, Revanesse and Juvederm (Vycross) products are the main fillers used.

Six reactions (mild-moderate – 2, severe – 4) were associated with Juvederm (Vycross), Six reactions (mild-moderate – 5, severe – 1) were associated with Restylane products and four (mild-moderate) were associated

with Revaness fillers **(Table 2)**. The injected filler's volume was directly associated with DIR severity, with all the patients who had severe reactions having been injected with >1 ml of filler, compared with 8 of the 12 (66.7%) patients who had mild reactions having been injected with only 1 ml of filler ($P = .01$). Six of the 7 (85.7%) reactions that resolved after >21 days occurred after injections of >1 ml of the filler (**Table 3**).

Severity of DIR also differed according to the locations of the filler injection. Fillers injected to the perioral areas or the lips in 6 patients tended to cause a mild-moderate reaction in 5 of them (66%) which resolved within <21 days in 5 of them (83.3%). Conversely, 12 of the 20 patients (60%) injected to the midface or the nasolabial areas had severe reactions that resolved in more than 21 days in 6 (50%) of the cases.

Discussion

The use of HA dermal fillers as a noninvasive aesthetic treatment is increasingly more popular worldwide, leading to a steady growth in the number of procedures performed annually[12]. Anecdotal reports have suggested the occurrence of DIRs triggered by vaccination against COVID-19 [3–8]. Here, we conducted a questionnaire-based survey to delineate the magnitude of this association in Israel, where vaccination efforts have been particularly intense, and according to data from Israel's MOH [13], around 85% of the Israeli population between ages 20-70 had been vaccinated with two doses of the Pfizer-BioNTech BNT162b2 vaccine by the time this survey was conducted.

This nationwide survey suggests that the risk for BNT162b2 vaccination-associated DIR is low, however, the following factors might predispose to longer and more serious reaction: time interval from vaccination to symptom onset; specific signs and symptoms at presentation such as palpable nodules, stiffness, induration and pain; location of the filler injection, filler type and volume injected.

The clinical manifestations of filler-related post-vaccination DIRs were similar to previous descriptions[14,15]. Most DIRs appeared <5 days following vaccination, were mild and resolved quickly in <21 days, with 60% of them requiring medical intervention. Reactions that appeared later on were often associated with longer time until resolution. The most common treatments were antihistamines, systemic antibiotics, and systemic steroids. Hyaluronidase was used in a stepwise approach in 41.6% of the cases, and one patient was reported to have rapidly responded to treatment with ACE inhibitors after failure to achieve resolution with other treatments.

The amount of the injected material was significantly associated with DIR severity, with all the severe reactions having been noted when >1 ml of the substance was injected. Injection into the tear trough and midface was found to cause more serious and prolonged reactions, whereas milder and shorter reactions were noted when the injection was performed to the perioral area or the lips. Differences in the severity of reaction between filler types were also noted: 4/6 (66.6%) patients injected with Juvederm (Vycross) developed severe reactions, while 5/6 (83.3%) patients injected with Restylane had mild-moderate reactions (**Table 2**). Symptoms of palpable nodules, stiffness, induration, and pain were associated with a more severe reaction that also lasted longer.

Delayed hypersensitivity may manifest weeks to months after HA filler injection, and many possible mechanisms and triggers have been suggested including viral infection, active sinusitis, low-quality fillers, combinations of different products, improper injection technique, and past and current dental procedures **[15].**

Comparing our findings and characteristics of DIR secondary to treatment with HA fillers according to previous retrospective reviews[16–18] showed similarities in many aspects: demographic characteristics (such as mean age, gender) and clinical manifestations. In cases where treatment was required - contrary to the most used treatment in our series, which was antihistamines, prednisone was the preferred modality. Differences were also noted in a longer median time from the filler treatment to onset of symptoms which was around 4 months in the published reviews, while in our series, 45% of patients developed symptoms < 2 months after the last injection. In addition, prolonged duration of symptoms until resolution (without treatment) was an average of 11.5 weeks, whereas in our series, most of the patients demonstrated resolution of symptoms after 3 weeks.

Accordingly, it seems that DIRs associated with vaccination against COVID-19 tend to occur sooner and resolve faster, thus suggesting a different pathomechanism [3–7,12].

Munavalli et al.[4,5] have proposed that local downregulation of angiotensin-converting enzyme receptor may interfere with conversion of proinflammatory angiotensin II to protective metabolites (angiotensin 1-7). In addition, elevated levels of angiotensin II leads to upregulation of proinflammatory cytokines, and potent chemoattractants which all lead to intensified inflammatory reaction [19]. Of interest these authors also reported beneficial effect of ACE inhibitors in the treatment of mild reactions. Alternatively, it is possible that COVID-19 mRNA vaccination leads to a systemic inflammatory response[20] and accelerates the breakdown of HA gels [7,21]. HA breakdown produces different-sized molecules with varying biological and immunological effects. While high-molecular-size HA particles (over 1,000 kDA) favor the anti-inflammatory and immunosuppressive reactions, low molecular weight fragments are considered to augment the proinflammatory state and regulate macrophage migration [22]. Macrophages are activated through the CD44 cell surface receptors, which are also upregulated because of the angiotensin II elevated levels[5], and have high binding affinity to low molecular weight HA, which might be part of the cascade leading to the formation of HA granulomas.

COVID-19 vaccine related inflammatory reactions have raised concerns regarding the safety of subsequent vaccinations. To our best knowledge, patients who developed symptoms after the first vaccination and were treated until resolution of symptoms, went on to undergo the second vaccination without DIR recurrence.

This study has several limitations. First, our data pertain only to vaccination with the BNT162b2 product. Second, 24% of the physicians we had contacted filled out the electronic questionnaire, so that a number of DIR cases may have been missed. Third, the survey was conducted retrospectively which may entail a selection bias

where only the more severe and non-spontaneously resolving DIR cases are reported. Forth, no serological data before DIR and after treatment could have been retrieved to explore the effect of a short-term treatment with steroids or other anti-inflammatory medications on the immunity status post vaccination. Fifth, 22% of physicians who applied to the survey were dermatologists or plastic surgeons, and most of the responders had 5 or fewer years of experience in aesthetic treatments. These findings might pose a risk of misdiagnosis of a DIR correctly. However, Shalmon et al[23] assessed the knowledge and experience of practitioners in Israel in the management of late-onset reactions following tissue filler injections. They found that most practitioners (especially those who were not dermatologists or plastic surgeons), referred the patients to a hospital for further investigation and diagnosis. In order to overcome this limitation and locate those patients diagnosed in a hospital, we also sent the same electronic survey to the chairs of all dermatology and plastic surgery departments in Israel. Finally, as the present and previous data have been obtained in the context of open studies and case series, they are not indicative of causality but only of synchronicity. Larger prospective studies are needed to confirm the present data. Of note, a recent well-controlled and well-powered study demonstrated significant association of COVID-19 vaccination with some but not all inflammatory complications [24].

We also aimed to define the estimated incidence of DIRs secondary to vaccinations against COVID-19. As stated, the fact that only 24% of the physicians replied to the questionary, raises concern regarding the possibility of generalizing these results to the population. However, we used the number of cases found as a very conservative estimate of the incidencse among vaccinated women by the following calculation: we retrieved demographic data on age and sex from the Israeli Central Bureau of Statistics, and statistical data from Israel's Ministry of Health (MOH) to determine the number of 20- 70 years old women who received vaccination from December 2020 to April 2021 (which represent 1 year). based on data provided by the main Israeli distributing companies – around 2-3% of 20-70 years old women are being injected with those fillers annually. Hence, conservative estimate of the incidence among women was found to be 0.026-0.04%.

To conclude, the results of this nationwide survey suggest that DIRs following administration of the BNT162b2 vaccine are rare, occurring mostly among women who were injected with HA-based dermal fillers shortly before vaccination. Although most of the reactions were mild and resolved quickly, we recommend, as recently advised by the Italian Society of Aesthetic Medicine[25], to notify patients of the possibility of developing

post-COVID-19 vaccination DIR In concordance with previous findings [26], given the rarity of the phenomenon, our data suggest that patients should not forsake receiving COVID-19 vaccines, nor should vaccinated patients avoid the use of dermal HA-based filler injections.

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References:

1 Baden LR, El Sahly HM, Essink B, *et al.* Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *N Engl J Med* 2021; 384:403–416.
2 Polack FP, Thomas SJ, Kitchin N, *et al.* Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med* 2020; 383:2603–2615.
3 McMahon DE, Amerson E, Rosenbach M, *et al.* Cutaneous reactions reported after Moderna and Pfizer COVID-19 vaccination: A registry-based study of 414 cases. *J Am Acad Dermatol* 2021; 85:46–55.
4 Munavalli GG, Knutsen-Larson S, Lupo MP, Geronemus RG. Oral angiotensin-converting enzyme inhibitors for treatment of delayed inflammatory reaction to dermal hyaluronic acid fillers following COVID-19 vaccination-a model for inhibition of angiotensin II-induced cutaneous inflammation. *JAAD Case Reports* 2021; 10:63–68.
5 Munavalli GG, Guthridge R, Knutsen-Larson S, *et al.* COVID-19/SARS-CoV-2 virus spike protein-related delayed inflammatory reaction to hyaluronic acid dermal fillers: a challenging clinical conundrum in diagnosis and treatment". *Arch Dermatol Res* 2021. doi:10.1007/s00403-021-02190-6.
6 Shome D, Doshi K, Vadera S, Kapoor R. Delayed hypersensitivity reaction to hyaluronic acid dermal filler post-COVID-19 viral infection. *J Cosmet Dermatol* 2021; 20:1549–1550.
7 Rowland-Warmann MJ. Hypersensitivity reaction to Hyaluronic Acid Dermal filler following novel Coronavirus infection - a case report. *J Cosmet Dermatol* 2021; 20:1557–1562.
8 Michon A. Hyaluronic acid soft tissue filler delayed inflammatory reaction following COVID-19 vaccination - A case report. *J Cosmet Dermatol* 2021; 20:2684–2690.
9 Savva D, Battineni G, Amenta F, Nittari G. Hypersensitivity reaction to hyaluronic acid dermal filler after the Pfizer vaccination against SARS-CoV-2. *Int J Infect Dis* 2021; 113:233–235.
10 Dagan N, Barda N, Kepten E, *et al.* BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting. *N Engl J Med* 2021; 384:1412–1423.
11 Angel Y, Spitzer A, Henig O, *et al.* Association Between Vaccination With BNT162b2 and Incidence of Symptomatic and Asymptomatic SARS-CoV-2 Infections Among Health Care Workers. *JAMA* 2021; 325:2457–2465.
12 Owczarczyk-Saczonek A, Zdanowska N, Wygonowska E, Placek W. The immunogenicity of hyaluronic fillers and its consequences. *Clin Cosmet Investig Dermatol* 2021; 14:921–934.
13 Israel COVID-19 Data Tracker [WWW Document]. URL https://datadashboard.health.gov.il/COVID-19/general?utm_source=go.gov.il&utm_medium=referral [accessed on October 18, 2021].
14 Alijotas-Reig J, Garcia-Gimenez V. Delayed immune-mediated adverse effects related to hyaluronic acid and acrylic hydrogel dermal fillers: clinical findings, long-term follow-up and review of the literature. *J Eur Acad Dermatol Venereol* 2008; 22:150–161.
15 Artzi O, Cohen JL, Dover JS, *et al.* Delayed inflammatory reactions to hyaluronic acid fillers: A literature review and proposed treatment algorithm. *Clin Cosmet Investig Dermatol* 2020; 13:371–378.
16 Humphrey S, Jones DH, Carruthers JD, *et al.* Retrospective review of delayed adverse events secondary to treatment with a smooth, cohesive 20-mg/mL hyaluronic acid filler in 4500 patients. *J Am Acad Dermatol* 2020; 83:86–95.
17 Artzi O, Loizides C, Verner I, Landau M. Resistant and Recurrent Late Reaction to Hyaluronic Acid-Based Gel. *Dermatol Surg* 2016; 42:31–37.
18 Sadeghpour M, Quatrano NA, Bonati LM, *et al.* Delayed-Onset Nodules to Differentially Crosslinked Hyaluronic Acids: Comparative Incidence and Risk Assessment. *Dermatol Surg* 2019; 45:1085–1094.
19 Chang Y, Wei W. Angiotensin II in inflammation, immunity and rheumatoid arthritis. *Clin Exp Immunol* 2015; 179:137–145.
20 Lu J, Lu G, Tan S, *et al.* A COVID-19 mRNA vaccine encoding SARS-CoV-2 virus-like particles induces a strong antiviral-like immune response in mice. *Cell Res* 2020; 30:936–939.
21 Beleznay K, Carruthers JDA, Carruthers A, *et al.* Delayed-onset nodules secondary to a smooth cohesive 20 mg/mL hyaluronic acid filler: cause and management. *Dermatol Surg* 2015; 41:929–939.
22 Mikkilineni R, Wipf A, Farah R, Sadick N. New classification schemata of hypersensitivity adverse effects after hyaluronic acid injections: pathophysiology, treatment algorithm, and prevention. *Dermatol Surg* 2020; 46:1404–1409.
23 Shalmon D, Cohen JL, Landau M, *et al.* Management patterns of delayed inflammatory reactions to hyaluronic acid dermal fillers: an online survey in israel. *Clin Cosmet Investig Dermatol* 2020; 13:345–349.

24 Barda N, Dagan N, Ben-Shlomo Y, *et al*. Safety of the BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Setting. *N Engl J Med* 2021; 385:1078–1090.
25 MODERN COVID-19 VACCINES & DERMAL FILLERS [WWW Document]. URL https://www.societamedicinaestetica.it/post/vaccino-covid-19-moderna-filler-nessuna-controindicazione-se-si-adottano-pratiche-prudenziali [accessed on October 19, 2021].
26 Gotkin RH, Gout U, Sattler S, *et al*. Global Recommendations on COVID-19 Vaccines and Soft Tissue Filler Reactions: A Survey-Based Investigation in Cooperation With the International Society for Dermatologic and Aesthetic Surgery (ISDS). *J Drugs Dermatol* 2021; 20:374–378.

Figure legend

Figure. 1 Number of patients reported being treated with one of the given treatment options

Figure. 1A The blue, grey and orange bars denote patients in whom the reaction resolved in less than 5 days, 6-21 days and more than 21 days, respectively

Figure. 1B The green and yellow bars denote patients with mild-moderate vs. severe reactions, respectively. (*, P value< 0.050)

Table legends

	Mild – moderate reaction (N=12)	**Severe reaction (N=8)**	**Total (N=20)**	***P* value**
Age (mean ± SD)	44.67 ± 13.47	39.5 ±13.07	42.60 ±13.22	.35
Sex				
Female	10	8	18	.22
Male	2	0	2	
Autoimmune Hx	1	0	1	.40
Previous allergic reaction Hx	0	0	0	1.00

Table 1. Baseline characteristics of patients with mild and moderate-severe DIR

DIR-delayed inflammatory reaction; N- number; SD- Standard deviation; Hx- history.

Injected Filler (Subtypes used)	DIR Severity				DIR Duration (days)			
	Mild To Moderate N=12 (%)	**Severe** N=8 (%)	**Total** N=20 (%)	***P* value**	**≤5** N= 5 (%)	**5-21** N = 8 (%)	**>21** N = 7 (%)	***P* value**
Juvederm (Volbella, Voluma, Volift) ⊥	2 (16.7%)	4 (50%)	6 (30%)	Descriptive	0 (0%)	4 (50%)	2 (28.6%)	0.227
Restylane (Lyft, Vital light)	5 (41.7%)	1 (12.5%)	6 (30%)		2 (40%)	2 (25%)	2 (28.6%)	
Revanesse (Contour, Ultra, Kiss)	4 (33.3%)	0 (0%)	4 (20%)		3 (60%)	1 (12.5%)	0 (0%)	
All others*	1 (8.3%)	3 (27.5%)	4 (20%)		0 (0%)	1 (12.5%)	3 (42.9%)	

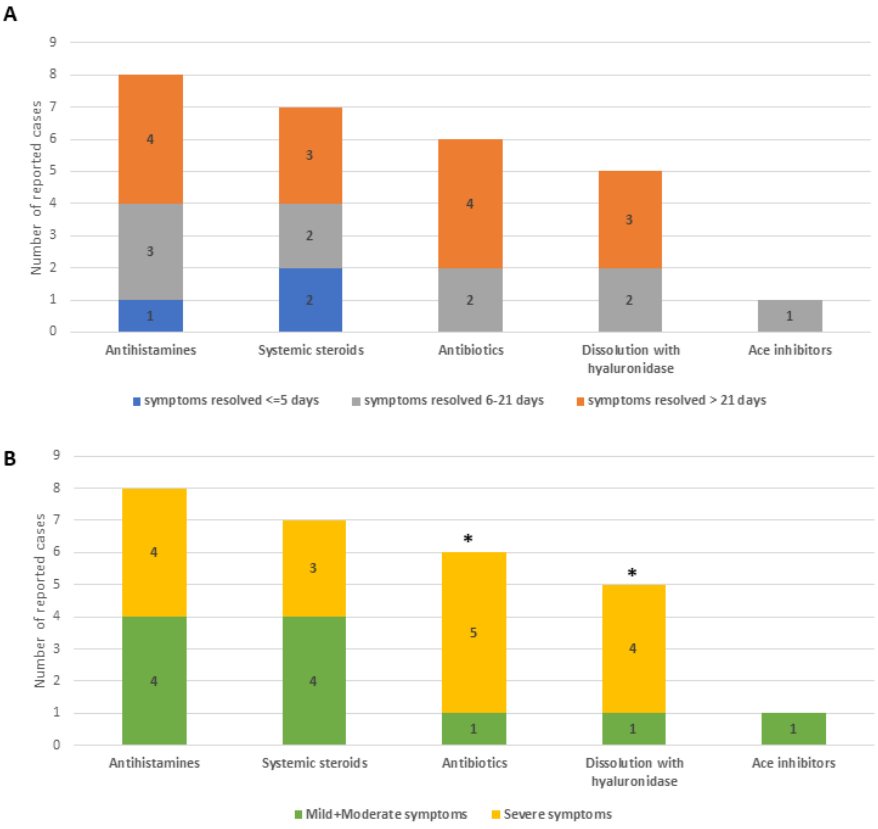
Table 2. Effect of type of filler on delayed inflammatory reaction (DIR) severity and duration.
DIR-delayed inflammatory reaction; N- number.

⊥, all part of Vycorss Juvederm fillers

*, Bellotero, Stylage and TEOSYAL dermal fillers.

Injected Filler Volume	DIR Severity				DIR Duration (days)			
	Mild To Moderate N=12 (%)	**Severe** N=8 (%)	**Total** N=20 (%)	***P* value**	**≤5** N= 5 (%)	**5-21** N = 8 (%)	**>21** N = 7 (%)	***P* value**
1 ml	8 (66.7%)	0 (0%)	8 (40%)	0.01	3 (60%)	4 (50%)	1 (14.3%)	0.1
2 ml	2 (16.7%)	5 (62.5%)	7 (35%)		0 (0%)	4 (50%)	3 (42.9%)	
3 ml	2 (16.7%)	3 (37.5%)	5 (25%)		2 (40%)	0 (0%)	3 (42.9%)	

Table 3. Effect of filler injection volume on delayed inflammatory reaction (DIR) severity and duration.
DIR-delayed inflammatory reaction; N- number; ml-milliliter.



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