

Manifesto for research on intradermal vaccines proposed by the Italian Society of Mesotherapy

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Abstract

The SARS covid 2 pandemic has seriously affected all countries. Some dermatological adverse reactions have recently been reported and some mechanisms responsible for dermatological events have been hypothesized. Identifying the trigger phenomena of these reactions is useful for selecting patients with risk of reactions to prevent them. However, these rare events must not prevent the vaccination campaign and for this reason we propose a manifesto in favor of vaccine research.

Introduction

Covid 19 is carrying out a triple threat, health, economic and social. It is urgent to vaccinate the entire population to ensure health on a global level. The Italian Society of Mesotherapy (SIM) has suggested a call to action to verify the non-inferiority of the intradermal route compared to the intramuscular route for immunization against Covid 19 [1]. Many intradermal vaccines are already available with the advantage that the dose required to induce an antibody response is lower than that required for the intramuscular route [2]. The intradermal route is the priority route of administration of mesotherapy. This technique consists in the creation of a series of micro deposits in a small area of the skin surface (site of the lesion or symptom to be treated) from which the small quantity of inoculated drug slowly diffuses into the underlying tissues [3].

The possible mechanisms of action of a drug injected into the superficial thickness of the skin have been described [4]. In fact, the products injected into the skin trigger a series of interactions with a multiplicity of dermal and subcutaneous cells that are also able to amplify the pharmacological response. These interactions, described with the term "mesodermal modulation", could explain many of the clinical benefits registered with this procedure in the analgesic [5-12], phlebological [13] and dermatological [14] fields. The mesotherapy technique is also used in the aesthetic field, although less evidence of efficacy and long-term tolerability is available. For this reason, the application of this technique was recommended according to precise methods and only by trained medical personnel [15]. In fact, several adverse reactions have been reported over the years with the use of incorrect substances injected through the skin [16]. These reactions were induced by an incorrect application of the mesotherapy technique, by products unsuitable for intradermal administration or sometimes by allergic reactions.

Discussion

In recent years, vascular infarction, soft-tissue necrosis and inflammatory reactions have been described following the administration of hyaluronic acid dermal filler (HAF) [17]. Even more

recently, dermatological adverse reactions have been reported after the administration of fillers in conjunction with coronavirus infection or covid 19 vaccines. These reports raise an important question: can the infiltration of products into the thickness of the skin constitute a trigger that favors dermatological reactions in conjunction with the administration of vaccines?

To answer this question, we analyzed some data available in the literature that report dermatological adverse reactions potentially related to covid 19 vaccination. We report the cases examined in Table 1 [18-21].

The causes of the dermatological reactions listed in Table 1 are not known. However, it can be hypothesized that a substance injected into the thickness of the skin may primarily involve the immune system [4]. In fact, it has been suggested that some allergic reactions could be caused by excipients contained in vaccines (also present in biomaterials, such as fillers or in some pharmaceutical products) [22,23]. Therefore, it cannot be excluded that some dermatological reactions, found following the administration of vaccines, were induced by immune-mediated reactions generated by T cells [24-27]. In particular, the risk of HAF-induced autoimmune reactions would be greater in genetically predisposed subjects [28]. However, it should be noted that there have been reports of dermatological reactions after hyaluronic acid dermal filler in conjunction with some triggering factors, such as dental procedures, viral diseases, or sinus infections [29-32] and that adverse skin reactions have been described with covid 19 vaccines but also with other vaccines [19,26,33].

Further suggestive hypotheses have been proposed to explain the occurrence of dermatological adverse reactions following the

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Received: June 27, 2021; Accepted: July 12, 2021; Published: July 16, 2021

Table 1. The table summarizes the clinical data relating to six cases of dermatological reactions (some following the administration of products for aesthetic purposes) [18-21].

Reported Case	Age	Gender	History	Reaction	Type of vaccine	Therapies administered against the dermatological reaction
1	50	F	The pts received two HA fillers injected into cheeks, lips, and tear troughs over the course of 12 months by nurse injector	Fifteen days after the last HA filler injections, the patient tested positive for COVID-19 by PCR nasal swab on August 7, 2020 after having symptoms of sore throat and mild cough for 3 days, no fever.	no covid 19 vaccine	Hyaluronidase; 40 mg prednisone for 14 days; 100 mg doxycycline daily for 14 days. Radiofrequency; Clarithromycin 500 mg bid × 2 weeks; 40 mg Prednisone taper over 1 week; intralesional triamcinolone acetamide (10 mg/cc)
2	51	F	The pts received HA fillers by nurse injector over the course of 18 months	5 weeks after the last filler injection to cheeks and lips, she enrolled into the Moderna Phase III pivotal clinical trial of investigational vaccine (mRNA-1273) for COVID-19	The pts received placebo	Medrol and Doxycycline. At each cheek was injected with 1 cc of recombinant hyaluronidase 150 U/cc. A total of 0.8 cc of intralesional 5-Fluorouracil was injected into the upper lip. Prednisone taper over 12 days and 10 mg hydroxyzine as an antihistamine. sulfamethoxazole and trimethoprim (cho- sen due to a prior medical history of antibiotic sensitiv- ity and pseudomembranous colitis) was prescribed total of 4 cc compounded bovine hyaluronidase at 150 U/ cc (O'Brien Pharmacy, Mission, KS) was injected to tear troughs, lips, and cheeks.
3	36	F	The pt received Filler in November 2019 (she had received fillers also in past without any reaction following injections or reactions following vaccinations for Influenza and Hepatitis B); no history of angioedema or positive COVID testing.	She reported myalgias and fever 12 h after first dose of vaccine	First dose of Moderna vaccine	acetaminophen; 10 mg of certirizine; 5 mg of lisinopril orally
4	43	F	Filler injection over the previous 2.5 years. No history of angioedema or allergies.	Twenty-four hours after second dose of vaccin a mild tenderness underneath the right eye, followed hours later by swelling under the left eye	First Pfizer vaccine dose with only mild arm injection site pain lasting 2 days; second vaccination with mild arm injection site pain.	Medrol dose pack with decrease in tear trough swelling bilaterally
5	46	F	received filler injections in her cheeks in March 2020.	The pt developed significant bilateral cheek swelling with no rash, pain, tenderness, oral or res- piratory symptoms. Symptoms were considered moderate and the reaction designated as serious.	first and second dose Moderna Vaccine	diphenhydramine and methylprednisolone and recovered
6	51	F	Pt received Filler and botulinum toxin injections in her cheeks 2 weeks previous vaccine	The pt developed bilateral facial swelling with the left side being more pronounced.	first and second dose of Moderna vaccine	The study participant received Prednisolone and recovered
7	29	F	History of prior dermal filler placement to the lips, of unknown duration prior to the trial	lip swelling occurred 2 days after vaccine injection, the reaction was termed angioedema and was classified as medical significant.	Moderna Vaccine	
8	41	F	dental procedure 2 weeks prior	Facial swelling, paresthesia, anxiety	No vaccine	

Table 2. Covid 19 vaccines in clinical development. Source WHO, data available at <https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines>

Protein subunit	32	31%
Viral Vector (non-replicating)	16	16%
DNA	10	10%
Inactivated Virus	16	16%
RNA	16	16%
Viral Vector (replicating)	2	2%
Virus Like Particle	5	5%
VVr + Antigen Presenting Cell	2	2%
Live Attenuated Virus	2	2%
VVnr + Antigen Presenting Cell	1	1%
	102	

administration of vaccines, in addition to immune-mediated reactions by antibodies or T cells, further suggestive hypotheses have been proposed. The skin, and in particular the fibroblasts and keratinocytes, have a high expression of ACE2 [34]. Indeed, it has been reported that the renin angiotensin system may play a role in hypertrophic scars and keloids [35]. In this regard, the correlation between ACE2 and viral infection has been reported [36,37]. This justified the treatment with ace inhibitor in case n. 3 shown in Table 1. Currently, due to the SARS COV-2 pandemic, it is desirable that the entire planetary population will soon be immunized. In fact, over one hundred covid 19 vaccines are in a clinical trial phase [Table 2].

Considering, the large number of vaccines that we will have available and the number of people who will have to be vaccinated, it

is crucial to identify the predisposing factors for adverse reactions. It is therefore desirable that manufacturers involved in the development of vaccines (or in the development of injectable products in the thickness of the skin) systematically collect the clinical history of the subjects enrolled in the experimental phases to identify the triggers of adverse reactions to identify patients at risk. Knowing patients potentially at risk allows you to prevent adverse reactions and reduce distrust of vaccines. Today it is not possible to identify which triggering events can induce an adverse reaction, nor do we know what interactions could occur following a covid 19 vaccine administered intradermally [38]. However, it is not possible to predict which subjects will develop adverse reactions, so we strongly recommend that a thorough clinical and drug history be taken to investigate at least the following 10 aspects:

1. previous treatments taken by subjects with allergic reactions.
2. allergy histories (and necessary drug treatments)
3. histories of surgery, viral diseases, or other infections
4. the time from a previous trigger event (even hypothetical)
5. if there have been previous symptoms such as swelling of the face following vaccines or infiltrations for aesthetic purposes, analgesics, etc.
6. if any drugs (or any other product, including cosmetics) have been taken.
7. previous vaccines administered/received.
8. previous intra-cutaneous treatments for preventive or curative purposes.
9. inform the patient precisely about the type of inoculated product, dose and trade name (so that he can report them in the future in case of any adverse reactions)
10. record each type of treatment administered in the medical record of the individual patient.

Theoretically, through an audit it could be possible to identify in which patient's adverse events have appeared and identify any triggering events. The systematic anamnestic collection will allow to correlate each precedent with any future adverse events and will allow to hypothesize which triggers are most significant. It is necessary to dedicate the right time to the anamnestic collection as the patient may not remember (or consider superfluous) a previous treatment received in past years. In fact, it has been reported that hyaluronic acid residues can be found several months later in the previously treated area [39]. As reported in table 1, some adverse reactions were recorded even after a few years from the administration of HAF. Although the relationship between such administrations and adverse events is uncertain, it is useful to record any previous past events. Obviously, the systematic collection of the clinical history of the subjects enrolled in the experimental phases of the Covid-19 vaccination is also important. As the reasons for adverse dermatological reactions are not known, even if very rare, the doctor is required to investigate what are the triggering factors [40]. Therefore, if healthcare professionals report all the adverse reactions and every possible (even hypothetical) triggering factor, in conjunction with the covid 19 vaccination, we will be able to identify and prevent the adverse reactions (even very rare) reported with the covid 19 vaccines. The small number of adverse events does not interfere with the good tolerability of the vaccines in use today. The collection of clinical history constitutes an important call for action for large-scale health prevention. In some countries the injector nurses can practice

the infiltration of products for aesthetic purposes (see case 1 and 2 in Table 1). We believe that some activities should be considered a medical act and we recommend that qualified and experienced personnel collect any anamnestic information before the therapeutic session and share the risk (albeit rare) of allergic reactions with the patient before obtaining informed consent [41]. Each stakeholder must be involved in the collection of useful information to identify triggering factors for the management of the patient to be vaccinated.

Final comments

The SARS Covid 2 pandemic has attacked humanity with very serious clinical and social consequences. The pandemic has involved many countries, even those that are less organized and unable to limit the spread of the infection. Therapies and vaccines are the most effective pharmacological weapon, but not all countries have access and availability to manage their own populations [42]. It is possible to predict that even from a single outbreak a variant of covid 19 can spread. Therefore, no country will be safe until all citizens are immunized. Many countries have achieved good covid 19 vaccination rates, while others still have low vaccination rates.

The scientific community is active, and many researchers are engaged in testing covid 19 vaccines (Table 2). Mesotherapy (intradermal therapy) has long been applied in various clinical areas [15]. In fact, several studies support the drug sparing effect and a relatively

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**Manifesto
for research
on covid
vaccines**

- COVID-19 has attacked the health of mankind with very serious economic and social implications.
- COVID-19 is a global pandemic: rich and poor countries are equally affected, but economic and technical-scientific resources are unequally distributed.
- The pandemic will not be defeated without universal access to treatment and immunization; no country will be safe until all countries are safe.
- Current vaccines, and those that will become available, must be made equally accessible to all countries.
- The intradermal administration of vaccines, as already demonstrated in the prevention of diseases, could allow a lower consumption of the dose necessary to have the immune response even against COVID-19.
- It is desirable that the health authorities and the scientific community verify this hypothesis which, if confirmed, could lead to a significant increase in accessibility to vaccines and a more rapid achievement of mass vaccination.

Figure 1. Available from <https://www.societadimesoterapia.it/media/attachments/2021/06/10/manifesto-for-research-on-covid-vaccines-sim.pdf>

enhanced clinical effect when a drug [5] or vaccine [2] is injected into the dermis compared to the systemic route of administration. We hope that scientific research confirms the need for a lower dose of covid 19 vaccine administered intradermally in order to have more doses available to combat the sars covid 2 pandemic [1]. Currently more than two hundred vaccines are in the experimental phase and achieving the production necessary to vaccinate the entire population (even several times if necessary) requires time and economic investments. The commitment of research in the immunological field has become urgent for the management of the pandemic. The current challenge is not only to win the fight against the coronavirus, but also to plan useful strategies to prevent any upcoming pandemics.

Doctors and researchers must prepare the population with advice on preventing the spread of infectious diseases and identify the most efficient lines of research, respectively. We hope that all stakeholders interpreted the cost of research as an investment in health and not as an expense without gain. Every scientific society should sensitize its target with messages in favor of counseling and research relevance. We propose a manifesto to raise awareness among doctors who apply mesotherapy (Figure 1). The pandemic attacks every human being, of any religion and political thought [43]. This attack requires a global alliance to effectively combat covid 19. Doctors, nurses, researchers, should focus every effort to limit the progression of covid 19. Scientific Editors could help by giving greater visibility to research and medical knowledge to combat the pandemic.

The more companies will give their endorsement to our manifesto, the more companies will create their own manifesto, the easier it will be to invest in research and development in every country of the world.

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