Seminars in Arthritis and Rheumatism ▮ (2013) ▮▮▮–▮▮▮

Contents lists available at SciVerse ScienceDirect

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit

Inflammatory, immune-mediated adverse reactions related to soft tissue dermal fillers ☆, ☆☆, ★, ★★

Jaume Alijotas-Reig, MD, PhD[a,b,c,*], Maria Teresa Fernández-Figueras, MD, PhD[d,e], Lluís Puig, MD, PhD[f,g]

[a] Ageing and Systemic Autoimmune Diseases Research Unit. Service of Internal Medicine-I. Aging Basic Research Unit, Molecular Biology and Biochemistry Research Centre for Nanomedicine (CIBBIM-Nanomedicine), Vall d'Hebron University Research Institute (VHIR), Barcelona, Spain
[b] Centro de Investigación Biomédica en Red Bioingeniería, Biomateriales y Nanomedicina (CIBER-BBN), Instituto de Salud Carlos III, Madrid, Spain
[c] Department of Medicine, Universitat Autonoma, Barcelona, Spain
[d] Pathology Department, Trias I Pujol University Hospital, Barcelona, Spain
[e] Universitat Autonoma, Barcelona, Spain
[f] Dermatology Department, Sant Pau University Hospital, Barcelona, Spain
[g] Department of Medicine, Universitat Autonoma, Barcelona, Spain

ARTICLE INFO

Keywords:
Dermal fillers
Hyaluronic acid
Ethylmethacrylate
Methylmethacrylate
Silicone medical grade
Poly-L-lactic acid
Collagen
Hydroxylapatite
Acrylamides
Alginate
Granulomas
Adverse reactions
Treatment

ABSTRACT

Background: An increasing number of persons seek medical solutions for esthetic indications and for diverse pathological conditions, such as malformations, trauma, or cancer. Despite manufacturers' and different authors' claims that fillers are non-immunogenic or that complications are uncommon, unwanted adverse reactions do occur.
Objectives: To review the literature regarding the multiple types of immune-mediated adverse reactions related to medical dermal filler injections/prosthesis.
Methods: A comprehensive MEDLINE, PubMed, and Google Scholar electronic database search was performed (2000–January 2012). Selected articles published before 2000 referring to general concerns regarding the studied topic were also included. The search provided almost 300 articles. Finally, 235 studies were selected and included.
Results: All known fillers present in the market have been shown to be able to provoke early- and late-onset inflammatory adverse reactions. Their true prevalence is unknown but appears to be significant. The majority of the late-onset adverse effects are inflammatory and immune-mediated in nature. Edema, granulomas, sarcoid-like disorders, and panniculitis are the findings most commonly seen. Rarely, systemic granulomatous and autoimmune diseases, and to lesser extent acute hypersensitivity reactions can be seen.
Conclusions: All implanted, injected, and blood-contact biomaterials trigger a wide variety of adverse reactions that may appear early or late and range from local to systemic. Most fillers act more as adjuvants than as direct T-cell activators, on a background of genetic predisposition. Their treatment has not been the subject of well-designed studies. Management of both acute and systemic reactions is often difficult and requires anti-inflammatory and occasionally immunosuppressive therapy.
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1. Introduction

An ever-increasing number of persons seek medical solutions for their aging skin, for purely esthetic and cosmetic indications or for diverse medical conditions, e.g. malformations such as Poland's syndrome, trauma, cancer, orthopedic, urological, or ophthalmological conditions. Only for esthetic reasons, more than 10 million of fillers have been injected in the United States in 2009, according to the American Society of Aesthetic and Plastic Surgery [1]. Currently, physicians have many different types of dermal and subdermal fillers, which may be classified according to their origin and average persistence in tissue [2,3]. Besides, an increasing number of new dermal fillers is currently available (Table 1). The properties of an ideal filler—namely to be safe, neither allergenic nor immunogenic, effective, injectable with reproducible technique and results, with high potential for use and low for abuse, noncarcinogenic, nonteratogenic, nonmigratory, cost effective, physiologic, and permanent—are not entirely accomplished by any of the available materials. Even though

☆The contents of the manuscript have not been previously published and are not being considered by any other journal at this time.
☆☆All authors agree with the contents of the article and also to having their names included in the list of authors.
★The authors also state that they do not have any commercial or any other type of interest that may have influenced the drawing up and the results of this paper.
★★We had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
*Correspondence to: Josep M[a] de Segarra, 2-F, 08190-Sant Cugat del Vallés, Barcelona, Spain. Tel.: +34 93 489 4194.
E-mail addresses: 16297jar@comb.es, jalijotas@vhebron.net (J. Alijotas-Reig).

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http://dx.doi.org/10.1016/j.semarthrit.2013.02.001

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Table 1
A non-comprehensive list of dermal fillers used at present and in the past

Composition	Commercial name	Permanence: Short (< 3 months) Medium (3–12 months) Long (12–24 months) Very long (> 24 months)	Source	Type of reaction*	Microscopical clue for identification	Reference*
Adipose-derived mesenchymal stem cells	No name	Very long duration	Autologous	ND	ND	ND
Agarose gel	Easy agarose	Medium	Synthetic	ND	ND	ND
Alginate	Novabel	Medium	Biological (sea algae)	GR*	Surrounding bluish deposits of variable size and shape with a blurred or spiky perimeter	[170]
Calcium hydroxylapatite (CaHA)	Beautyfill/Radiesse/Radiance	Considered of medium duration but it can last very long	Synthetic	Granulomas, clumping, migration	Bluish round structures	[78,79]
Collagen	Zyderml®/Zyderm II® Zyplast®/Evolence® Fibroquel® Permacol®/Cosmoderm® Cosmoplast®/Fascian®/ Cymetra® Resoplast/Sunmax i-plus/ Endoplast/Dermatogen	Short to medium duration	Biological (Human, Bobine,Porcine)	Non-specific inflammation. FB or granuloma annulare-like GR. Necrosis	Non-human collagen polarizes different than human	[78]
Dextranomeres + HA	Matridex/Redexis/Reviderm	Medium–Long	Biological HA is from bacteria) + Synthetic	Granulomas or non-specific chronic inflammation (delayed inflammatory reaction)	Spherical particles of dextrans	[171,172]
Fat		Very long duration	Autologous	Fat necrosis, Fibrosis Hypertrophy	Fat necrosis and granulomatous inflammation	[158]
Gelatin powdered and aminocaproic acid	Fibrel	Long	Synthetic	ND	ND	ND
Hyaluronic acid in different forms*	See table	Short to medium duration	Biological (animal or bacterial)	Granulomas, rare infections, occasional delayed inflammatory reactions	Bluish material (Alcian blue positive with better definite borders in "bioengineered molecules"	[7,24]
Hydroxyethylmethacrylate/ ethylmethacrylate	DermaLive/DermaDeep	Very long	Synthetic	GR	Polygonal translucent structures	[7,79]
Paraffin		Very long duration (Non-biodegradable)	Synthetic	FB-GR	Large cystic vacuoles of different size (Swiss cheese appearance	[159,160]
Polyacrylamide hydrogel (PAAG)	Beautical (Outline)/Bio-Alcamid/ Aquamid/Bio-formacril	Very long	Synthetic	FB-GR	FB-GR, collections surrounded by palisades of macrophages	[79]
Polyalkylimide	Bio-alcamid	Very long	Synthetic	Irregular encapsulation, dystrophic calcification, acute inflammation	Bluish material (Alcian blue positive) similar to HA	[8]
Polycaprolactone (PCL)	Ellanse	Very long	Synthetic	ND	ND	ND
Polydimethylsiloxane (Silicone oil)	Silikon 1000/Surgisil PermaLip/ Fluid silicone 350cs/Silskin 1000cs	Very long duration	Synthetic	Non-specific inflammation. FB-GR	Pseudoxanthomatous cells and pseudolipoblasts. Slighlty birefringent translucent material inside microvacuoles	[79]
Polyethylene glycol (PEG) di-acrylate	Remake®	Long (16 m)	Synthetic	Commented on websites	ND	〈www.simplycosmeticsurgery.com/fillers〉 (accessed 07.03.12)

Polyethylene oxide + cellulose carboximetil	Laresse Dermal Filler	Medium	Synthetic	ND	ND	〈http://messageboards.makemeheal.com〉 (accessed 07.03.12)
Poly-L-Lactic acid	Sculptra/New-Fill	Very long duration	Synthetic	GR	Translucent spicular structures	[10,79]
Polymethylmethacrylate (PMMA) microspheres/ Polyethyl methacrylate (pHEMA-EMA) with hyaluronic	ArteFill/ArteSense (Artecoll)	Very long duration	Synthetic	GR	Translucent round structures	[25]
Poly-tetrafluoroethylene (PTFE)/Expanded PTFE	Sortform (Gore-Tex)	Very long	Synthetic	Displacement, infections	Migration, May trigger herpes infections	[7,8]
Polyvinyl alcohol (PVA)	Bioinblue	Long (12–18 m)	Synthetic	ND	ND	ND
Polyvinylhydroxide microspheres in polyacrylamide gel	Evolution	Very long	Synthetic	GR	Translucent microspheres	[101]
Polyvinyl-pyrrolidone + Dimethylsiloxane	Bioplastique	Very long	Synthetic	GR	Translucent or "pop-corn" shaped particles	[6]

A non-comprehensive list of dermal fillers used at present and in the past is included in Table 1, encompassing the most frequent commercial denominations, permanence [Short (< 3 m) Medium (3–12 months) Long (12–24 months) Very long (> 24 months)], source, type of reaction and microscopic clues for identification when available. GR: granulomatous reaction; FB: foreign body.

* Brand names of HA compounds: Achyal, Amalian, Atlean, Balance, Belotero, CaptiqueTM, CRM (several forms), Cytocare, Dermyal (several forms), Elevess, Endotine Ribbon, Esthelis (several forms), Fortelis extra, Glytone Professional (several forms), HYAcorp H, Hyaluderm(several forms), Hydra Fill(several forms), Hylan(several forms), Ial-System, Isogel class (several forms), Jalupro, Jolesse (several forms), Jolidermis, Juvederm (several forms), Juvelift Corneal, Macdermol (several forms), Macrolane(several forms), Matrigel/matridur/Matrisoft, Mesolis(several forms), NCTF 135 and NCTF 135 HA, Perfectha (several forms), Phormae, Phormae plus, Prevelle silk and Prevelle volume), Princess volume, Puragen (Hyalite), Redexis (several forms), Renofill (several forms), Reparestim H.A., Restylane (several forms), Revanesse, Revitacare, Rofilan forte, Skin (several forms), Stylage (several forms), Succeev (several forms), Surgiderm (several forms) Surgilips and Surgilift plus, Teosyal (several forms), Varioderm (several forms), Viscontour (several forms), Visagel, X-HA3, Zetavisc, Hylaform (hylan B gel).

manufacturers and different authors claim that fillers are non-toxic and non-immunogenic or that complications are very uncommon [4,5], unwanted side effects do occur with all the compounds used [6–14]. Thus, two notions are lacking in the commonly used classifications of fillers: long-term safety and reversibility of their adverse effects. Over the last 10 years, different clinical profiles [7,8] as well as suggestive histopathological patterns have been described [13,14], and some authors have proposed a grading system classification of foreign body reactions induced by injected fillers into four categories [15].

Implanted and injected biomaterials trigger a wide variety of adverse reactions, including inflammation [16,17], thrombosis, [18] and fibrosis [19]. Usually, these adverse reactions are associated with the rapid accumulation of large numbers of mononuclear cells [20]. No well-designed studies have addressed the treatment of acute and late-onset inflammatory complications related to dermal fillers used for augmentation purposes.

In this review we will discuss the main clinical and pathological features of local, regional, and systemic adverse reactions, the histopathological findings related to soft tissue dermal filler injections and their immunopathogenic basis. Special attention will also be given to the diverse therapeutic schedules according to their different mechanisms of action.

2. Search strategy and selection criteria

A comprehensive MEDLINE, PubMed, and Google Scholar electronic database search was performed (2000–January 2012), which was restricted to papers published in English, using the relevant keywords: dermal fillers, soft tissue filler, injectable filler, tissue augmentation, hyaluronic acid, collagen, poly-L-lactic acid, hydroxylapatite, methacrylate, silicone, polyalkylimide, polyacrylamide, biofilm, granuloma, ASIA, autoimmune diseases, adverse reactions, and treatment.

Selected articles published before 2000 referring to general concerns regarding the studied topic were also included. Bibliographies of the retrieved articles were also scanned and searched manually for relevant papers. The initial search provided almost 300 articles. Finally, 235 studies were selected and included. Eight of the 65 were excluded because they were not written in English; 10/65 because we had access only to the abstract; 25/65 for not including significant information on adverse reactions; 12/65 for covering biomaterials outside our topic, i.e. gold threads, combination of topical antioxidants, and botulinum toxin; and 10/65 were considered non-adequate for inclusion in this review for diverse reasons in the opinion of the authors.

2.1. Types, classification, and characteristics of the most common injectable dermal fillers

Fillers are usually classified according to their source and average persistence in tissue. Currently, many different types of dermal and subdermal fillers have been launched in the market, which may be classified according to their origin and average persistence in tissue—resorbable, non-resorbable, or temporary, semi-permanent, and permanent [2,3].

A non-comprehensive list of fillers ever used in soft tissue augmentation is provided in Table 1, with detailed reference of their composition, brand names, permanence, source, types of adverse reactions reported, and histopathological clues to their identification.

3. Local early- and late-onset adverse reactions

The most common adverse events associated with fillers are local injection site reactions. In a randomized, double-blind, multicenter comparison of hyaluronic acid versus collagen for the treatment of nasolabial folds in contralateral sides in each patient ($n = 138$), injection site reactions occurred in more than 90% of treated sites regardless of the agent used [21]. Most fillers often result in some degree of injection site-related redness, swelling, or bruising for 4–7 days. Both erythema and edema are due to the inflammation associated with trauma caused by the injections, but may also be related to the hygroscopic properties of the injected material. Edema usually appears 24–72 h after the injection and tends to be more frequent when persistent materials are used; it has been reported to occur in up to 10% of patients following injection of poly-L-lactic acid [22]. Erythema usually resolves within a few hours, whereas edema may persist for several days; both can be minimized by applying cold packs after the procedure. Bruising is caused by accidental puncture of a vessel by the needle or when pressure is exerted on the vessel by the filler. Some products incorporate lidocaine as anesthetic; due to the vasodilator effect of this ingredient, such products tend to be more frequently associated with bleeding and hematomas.

3.1. Inadequate placement

Inappropriate placement of fillers, including injecting too superficially, can lead to whitish papules, visible or palpable nodules, or bluish bumps under the skin (Tyndall effect) with hyaluronic acid fillers. Nodules appear rather frequently after treatment with calcium hydroxylapatite, particularly in the lips, and they can migrate superficially due to the pumping effect of the orbicularis oris muscle, thus, the use of this dermal filler in the lips is no longer recommended [23]. All types of nodules due to superficial injection can be treated by firmly massaging the tissue. If the problem does not resolve, nodules can be pricked with a needle and drained; if nodules appear following a treatment with a hyaluronic acid filler, hyaluronidase can be injected in an attempt to eliminate them [24].

Collagen plus polymethylmethacrylate can also be associated with complications if placed too superficially, with some reports of long-lasting itching and redness, which can sometimes be treated with topical corticosteroid cream or intradermal corticosteroid injections [25]. In addition, excessively superficial placement of the product can rarely lead to hypertrophic scarring of the treated fold(s) [26].

3.2. Local alterations in blood flow

Injection site necrosis is a rare occurrence, secondary to external compression of the blood supply or to vessel occlusion secondary to direct intravascular injection of the product into the angular artery of the nasolabial fold or the supratrochlear artery in the glabellar region [27]. The glabellar region is considered a high-risk area because the blood vessels are of small caliber and collateral circulation is scarce; necrosis in this area has been reported after the implantation of bovine collagen [28], calcium hydroxylapatite [29], and hyaluronic acid [30,31]. Direct arterial embolization usually produces immediate blanching of the skin, followed by retiform or geographic violaceous discoloration and eventual erosion and ulceration [27]. Ophthalmologic complications, such as ocular ischemia and ischemic oculomotor nerve palsy secondary to vascular embolization, have also been reported [32,33]. Topical nitroglycerin, because of its vasodilatory properties, has been used in an attempt to reduce necrotic spread [34,35], and subcutaneous injection of hyaluronidase or low-molecular-weight heparin has been used in cases when arterial embolization arose following injection of hyaluronic acid [30,36].

3.3. Local infections

Infections caused by herpes símplex, with bacterial superinfection, changes in pigmentation, and small scars may occur at injection sites, but antiherpetic prophylaxis is recommended only in patients undergoing lip treatment who have a history of recurrent herpes símplex [37]. Infection or contamination can occur despite clean preparation of the skin using alcohol or chlorhexidine. Common skin pathogens, such as *Staphylococcus aureus*, are the usual culprits, and symptoms include fluctuating painful nodules, with or without fever, or erysipelas. If an infection is suspected, it is best to culture the exudate or pus aspirate, if available, and start empiric antibiotic treatment (e.g., clarithromycin, and ciprofloxacin) [38]. Severe facial abscesses have been reported to appear secondary to *Enterococcus faecalis* infection [39]. Late-appearing symptoms (usually after 2 weeks) should crop up a suspicion of atypical mycobacterial infection, which has been reported to occur in outbreaks [40].

Fillers, with the exception of autologous fat and collagen, are generally composed of foreign material and thus can trigger varying degrees of immune-based reactions, ranging from mild irritation and redness to anaphylaxis.

3.4. Acute and subacute hypersensitivity reactions

The occurrence of acute hypersensitivity to fillers is very rare, but cases of anaphylactic shock have been reported [41]. Angioedema has an estimated incidence of less than 1–5 cases per 10,000, and may be related to the antigenic protein content of the material [42]. A rare case of angioedema-type hypersensitivity has been reported by Leonhardt et al. [43] after non-animal-stabilized hyaluronic acid (NASHA) gel (Restylane^{R}) injection in the lips, 1 h post-procedure, without airway compromise. Lidocaine for nerve block and botulinum neurotoxin type A had been administered on the same day. The patient was treated with intramuscular dexamethasone and a 6-day prednisone taper, and edema resolved after 5 days. One mechanism proposed for hypersensitivity associated with hyaluronic acid would be its interaction with tissue resident mast cells through the CD44 receptor [43]. Delayed-type hypersensitivity reactions typically develop 48–72 h after injection and are mediated by macrophage or T-cell interaction, leading in many cases to the development of granulomatous inflammation. They have been reported to occur in the first days to weeks after injection of fillers, and appear to be more common in non-human-derived fillers with antigenic properties. Prior to bovine collagen injection, two skin tests are recommended to test for sensitivity: the first is usually placed in the left antecubital area, and the second is often placed in non-central facial skin. Approximately 3.5% of patients will have a positive first reaction; 70% of these reactions will manifest in 48–72 h, and a negative second test lowers the risk for reaction to less than 0.5% [44]. Recent biotechnological advances in protein purification have greatly reduced the need for skin testing prior to porcine collagen injection [45].

A possible reaction with human collagen has been documented in a report on two patients, one of whom had previously tested negative to a bovine collagen skin test at both 72 h and 30 days. Human collagen (1 mL) was subsequently administered into the nasolabial folds of that patient. Seventy-two hours later, the patient complained of an erythematous, indurated, and burning reaction in the face. In the second patient, bovine collagen had previously been injected with no reports of any apparent sensitivity. Human collagen (1 mL) was injected periorally, and 5 days

later a second 1-mL syringe was administered. The patient reported red lumps at the injection site 10 days after the first injection, with examination revealing palpable, perioral erythematous and non-erythematous subcutaneous lumps. Both patients were treated with 0.1% tacrolimus ointment, and lesions resolved within 3 and 6 weeks [46].

Both immediate and delayed-type hypersensitivity reactions have been described with non-animal-stabilized hyaluronic acid; the global incidence rate found was 0.8%, which decreased following a reduction in the amount of protein in the raw product [47,48]. Half of the reactions were immediate and resolved within 3 weeks, and the risk of delayed reactions was estimated to be 0.3%. In some cases the reaction starts within days after the procedure with swelling and pain at the injection sites, followed by erythema, which improves partially with low doses of systemic steroids and may become persistent, without significant lymphadenopathy [49]. Localized cutaneous reactions have been reported following a skin test with hyaluronic acid [50], and serum antibodies against certain types of hyaluronic acid have been found, even in the absence of clinical manifestations [51]. In other cases, the start of the reaction, which eventually becomes papulonodular, has been reported to occur 2 weeks following the injection of hyaluronic acid [52,53]. A 48-year-old female who received a hyaluronic acid agent in the lips for the purpose of augmentation developed discrete nodules initially associated with eczematous changes in the overlying skin in her upper lip 6 weeks post-injection [54].

In some patients, fluctuating nodules and sterile abscesses have been reported to start developing 2–4 weeks following injection of hyaluronic acid filler (Elevess^{R}) despite prior exposure to other hyaluronic acid fillers without incident [55].

3.5. Delayed, immune-mediated local reactions

Alijotas-Reig and Garcia-Gimenez [7] reported a series of 25 patients who developed delayed-type hypersensitivity reactions characterized by inflammatory nodules, induration, and facial edema following injections of fillers containing hyaluronic acid, either alone or combined with acryl hydrogel. The average latency period up to the beginning of symptoms was 14 months; six patients had recurrent bouts after an average of 16 months of follow-up. Interestingly enough, abnormalities in acute phase reactants, C-reactive protein and/or fibrinogen, increased angiotensin convertase levels, and low complement levels were detected in 55%, 36%, and 36% of 11 patients tested, respectively. Even though some fillers are able to perpetuate chronic granulomatous inflammation around the implant, bacterial colonization of these materials may also cause a chronic inflammatory reaction, and late appearance of inflammatory nodules and abscesses should be treated initially as a foreign body infection with empiric antibiotic treatment [42]. If there is fluctuation, the material obtained following incision and drainage should be subject to bacteriological, mycological, and mycobacteriological cultures. If there is no clinical improvement after 1 week, biopsy specimens should be obtained for histopathological exam and microbiological cultures, and antibiotic treatment with multiple drugs should be maintained for 3–4 additional weeks.

Product-related injection site nodules have been commonly seen with poly-L-lactic acid, particularly in the human immunodeficiency virus (HIV)-infected population. In clinical studies, such subcutaneous nodules were typically 5 mm or less in diameter, asymptomatic, and non-visible, but their incidence rate ranged from 6% to 52%, [35,56] and appears to be lowered by increasing the volume and time of reconstitution [57].

Poly-L-lactic acid induced nodules and foreign body granulomas are not uncommon and may be difficult to treat [58–63]. Curiously, a case of parotitis related to poly-L-lactic acid injection for malar augmentation has been described [64]. A prospective, case series study of 10 HIV-negative patients with delayed adverse effects related to poly-L-lactic acid injections showed that tender, inflammatory nodules and facial edema were commonly seen [10]. The average latency period at the onset of symptoms was 19 months (range: 6–60). After an average of 50 months of follow-up, 5 patients were in remission, 4 had recurrent bouts, and the last case had been lost to follow-up, but one case presented a systemic granulomatous disorder as a complication.

Late-onset granulomatous reactions and nodules are much more frequent after treatment with permanent filler materials than following the use of temporal fillers. The development of granuloma can be delayed, coming as late as 1–2 years after treatment with polymethylmethacrylate microspheres or methacrylate fillers [25,65–67]. Granulomas following injection of bovine collagen plus polymethylmethacrylate (Artecoll^{R}) are rare (0.01% of patients) and often appear after the second or third implantation of product; half of the patients experiencing them report an associated severe infection (influenza) or some type of facial injury [25]. This might be explained by increased serum levels of interferon, which can lead to an exacerbation of a preexisting low-grade chronic inflammation that is quite similar to interferon-triggered sarcoidosis, as illustrated by the case report of a 48-year-old woman who presented with disfiguring facial edema 10 weeks after she began antiviral therapy with peginterferon alfa-2a and ribavirin for chronic hepatitis C infection. The major affected sites had been treated 10 years before with Artecoll^{R} [68].

Polyacrylamide gels are usually employed to correct deep defects and have different molecular weights, water content, and viscosity, which may affect their complication rate. Aquamid^{R}, composed of 2.5% polyacrylamide and 97.5% water, has a high complication rate and is often associated with the formation of granulomas, has not been approved by the Food and Drug Administration, and its use is now increasingly rare [69]. Injections of polyalkylimide filler have also been associated with delayed complications of infection including abscess formation, migration of filler, recurrent swelling, and inflammatory nodules in up to 5% of treated patients [70–75]. The same applies to other polyacrylamide compounds.

A prospective case series of 25 patients injected with polyalkylimide implants who developed delayed adverse effects (inflammatory nodules in 24 cases, and systemic or distant manifestations in 5) showed that the average latency period was 13 months, and after an average of 21 months of follow-up, 10 patients still had recurrent bouts of inflammation [8].

Interestingly, puncture of old polyacrylamide gel implants placed 6 months to 4 years earlier has been reported to be associated with the development of acute pain, swelling, redness, and significant induration of the corresponding areas in a series of 12 patients. Cultures of removed gel were negative [76]. Further research is needed to assess the inflammation observed with repeated puncture of old implants and its implications.

Liquid silicone was widely used in Europe and Japan in the 1940s for body contouring, and became popular in the United States in the 1950s and 1960s when large volumes of material were injected, commonly admixed with olive oil, resulting in permanent deformities and often disastrous, even fatal, complications.[77].

Increasing demand of permanent fillers and the introduction of the microdroplet technique has led to a revival of medical-grade silicone gels and their off-label use in cosmetic surgery; its use in small quantities for lip augmentation seems to yield a low rate of foreign body granulomas. [78]. Silicone fluid stimulates a very

thin-walled fibrous capsule so that displacement by gravity along fascia and muscle planes can occur [79]. Late sclerotic reactions can develop around free silicone oil, and the typical features of soft silicone foreign body granuloma are well characterized [80,81]. Clinically, they develop suddenly many years after the injection, with redness and swelling of multiple areas of firm, fixed but rather soft nodules, and are not very painful but associated with local lymphadenopathy [82].

Five cases of women with a history of filler injections who developed hard and persistent facial edema followed by local subcutaneous nodules, 1–48 months post-procedure, have been recently reported [83]. They underwent exacerbations and remissions of angioedema, partially relieved with systemic steroids and might be related to granulomatous impairment of lymphatic drainage, as has been reported in Morbihan disease [84].

4. Systemic adverse reactions

4.1. Acute and/or immediate

Diverse systemic or disseminated complications have been reported with different filler materials, especially with silicone fluid injections of silicone medical grade (SMG) and other silicone gels, with certain acrylamide gels, bovine collagen, and with hyaluronic acid compounds (Table 2). Illicit subcutaneous injections of massive amounts of silicone fluid in male-to-female transsexuals have had devastating outcomes including embolism and multisystemic complications up to severe infections, after diverse periods of time [85,86]. Acute and latent pneumonitis after subcutaneous injections of silicone have also been reported in this population of patients [86–91].

Two forms of pneumopathy induced by silicone have been described [91–93]: an acute form, occurring within days of the silicone injection, and a latent or late form occurring up to 6 months after the last few injections. The acute form is clinically characterized by acute onset dyspnea on exertion, chest pain, and fever with hypoxemia. Chest X-ray films show bilateral patchy infiltrates. Transbronchial biopsies are very suggestive of silicone-induced alveolar injury. The clinical course of this acute form is usually self-limited, although several deaths have been reported [94]. Patients with latent pneumopathy may show progressive dyspnea with normal chest X-ray, but pulmonary function studies show either a restrictive pattern or a decreased carbon monoxide diffusing capacity [95].

Toxic shock syndrome (TSS), fulfilling the Center for Disease Control (CDC) 1981 modified criteria [96], has been reported in patients submitted to esthetic plastic surgical procedures such rhinoplasty, augmentation mammoplasty, or silicone fluid injections [97]. TSS resulting from infection with *S. aureus* typically manifests in otherwise healthy individuals with high fever accompanied by low arterial blood pressure, malaise, and confusion, which can rapidly progress to coma and multiple organ failure. The characteristic rash, often seen early in the course of illness, resembles sunburn and can involve any region of the body, including the lips, mouth, eyes, palms, and soles. In contrast, TSS caused by *Streptococcus pyogenes*, which is the most frequent etiologic agent in patients subject to filler injections [97], typically presents in people with preexisting skin infections with the bacteria. These individuals often experience severe pain at the site of the skin infection, followed by rapid progression of symptoms as described above.

Fulminant acute disseminated, multiorgan failure has also been reported in massively injected silicone fluid when this biomaterial is placed into the blood or lymphatic vessels [98,99].

The combination of methacrylate and bovine collagen usually provokes local inflammatory reactions, but some cases of allergic reactions and at least one case of anaphylactic shock have been reported after recurrent injections [100,101].

Acute hypersensitivity type I reactions have been related to both bioengineered hyaluronic acid compounds [41,43,102] and non-human collagen [103].

Table 2
Systemic reported complaints and/or diseases related to most common injectable fillers

Complication	Silicone	PAI*	PA†	MTC‡	HA□	PLA¶	Collagen	HAP□□
Flu-like symptoms	+	−	−	−	−	−	+	−
Lymphadenitis◇	+	−	+	−	−	−	+	−
Pneumonitis	+	−	−	−	−	−	−	−
NTPEϕ	+	−	−	−	+	−	−	−
Serositis	+	−	+	−	+	−	−	−
Hepatitis	+	−	−	−	−	−	−	−
Panniculitis	+	+	−	+	−	−	+	−
Angioedema	+	+	+	+	+	+	+	−
Bone erosion	+	−	−	−	−	−	−	−
Amyloidosis	+	−	−	−	−	−	−	−
Siliconosis	+	−	−	−	−	−	−	−
AHS▼	−	−	−	+	+	−	+	−
Distant nodules	+	+	−	+	−	−	+	+
Renal failure	+	−	−	−	−	−	−	−
HAD■	+	+	−	+	−	+	−	−
UCTD▲	+	−	−	−	−	−	−	−
Sarcoidosis□	+	+	−	+	−	−	+	−
Scleroderma	+	−	−	−	−	−	−	−
Inflammatory myopathy	+	−	−	−	−	−	+	−
Sjögren syndrome	+	+	−	+	+	−	−	−
Vasculitis	−	−	−	−	+	−	−	−
Bouts of UC■	−	−	+	−	−	−	−	−
Fibromyalgia	+	−	−	−	−	−	−	−
Hand's erythema⁺	+	+	+	+	+	+	−	−
ASIA	+	+	+	+	+	−	−	−

AHS: acute hypersensitivity syndrometype I; Collagen: refers to non-human-based collagen; ASIA: refers to Autoimmune/autoinflammatory syndrome induced by adjuvants; HA: animal and non-animal-derived hyaluronic acid compounds; HAD denotes human adjuvant disease; HAP: hydroxylapatite; MTC: methacrylate compounds—polymethylmethacrylate and ethylmethacrylate; ◇ non-infectious origin; NTPE: non-thrombotic pulmonary embolism; PA:

Several cases of non-thrombotic pulmonary embolism related to hyaluronic compounds have been communicated [43,104,105]. Interestingly, one of these cases was related to non-esthetic procedure.

4.2. Late-onset distant and/or systemic inflammatory reactions

Silicone injections, mainly silicone breast augmentation prosthesis, have been related to diverse autoimmune systemic diseases (ASD), mainly systemic sclerosis (SS), inflammatory myopathy, rheumatoid arthritis, adult Still disease, mixed connective tissue disease—Sharp disease, eosinophilic fasciitis, overlap SS/SLE, and fibromyalgia, [106–111], or with unspecific or undifferentiated connective tissue diseases [112,113]. Even though case reports are continuing to be reported, well-designed epidemiological studies have failed to demonstrate a true relationship between silicone injections and ASD [114–118]. To avoid the local and possible systemic side effects related to silicone liquid or fluid, "bag-gel" bioimplants were introduced, mostly for breast or buttock augmentation. However, leakage of silicone may also occur through these bags, either by diffusion or after trauma. Thus, silicone gel is capable of migrating to distant sites, where it may provoke inflammatory reactions [119–123]. Multiple distant inflammatory nodules and panniculitis have also been described with silicone filler injections [124], especially in dependent areas when silicone had been injected in the buttocks, thighs, or calf.

Late-onset inflammatory nodules have been reported following calcium hydroxylapatite injections both "in situ" and at a distance from the site of injection [125]. Axillary lymphadenitis related to polyacrylamide gel breast augmentation has also been related [126]. Distant panniculitis of thighs and buttocks, biopsy-proven, extensive livedo reticularis, sicca syndrome, and human adjuvant disease have been described in patients subject to polyalkylimide gel injections [8].

Generalized skin rash, sicca syndrome, sarcoid-like reactions, and cutaneous vasculitis [7,102,127] have been related to several implant fillers other than silicone injections, such polyalkylimide, methacrylate, and hyaluronic acid (Table 2). Interestingly, to the best of our knowledge, only polyacrylamide implants have been related to exacerbations or bouts of inflammatory bowel diseases in patients already diagnosed as having either ulcerative colitis or mainly, Crohn disease [128,129]. A relationship between bovine collagen and inflammatory myositis has also been reported [130]. Fig. 1 depicts several examples of this type of adverse reactions.

5. Pathogenesis

Inflammation around an implant particle is normal (Table 3) and always occurs, and eventually leads to its reabsorption in the case of biodegradable volumizers, which are expected to be immunologically inert and stimulate collagen neogenesis. The ideal permanent filler should cause as little immediate or late adverse tissue reaction as possible in order to prolong the persistence of the product and to avoid chronic or recurrent granulomatous reactions that can become troublesome to the patient [131]. Phagocytosis is a normal tissue reaction to any foreign body and appears to be the single most important factor in determining the longevity of the fillers [132]. Circulating granulocytes move into the soft tissue and are the first line of defense. Monocytes differentiate into macrophages that become dominant if polymorphonuclear cells are unable to phagocytose the particle. Particle size is an important determinant of the efficacy of phagocytosis: particles larger than 5 μm generally require aggregated macrophages (foreign body giant cells) to be phagocytosed, and particles larger than 15–20 μm are generally

Fig. 1. Clinical pictures of adverse reactions related to diverse fillers in different patients Panels A: recurrent pseudoabscess in the tail of the eyebrow after polyacrylamide injection; B: Multiple inflammatory nodules as a reaction to polyalkylimide involving the nasolabial folds and lips; C: Cutaneous sarcoidosis in a patient carrying several facial filler augmentation with polyalkylimide and polymethylmethacrylate; D: Large indurate areas, nodules, and edema after hyaluronic acid/polymethylmethacrylate injection; E: Large panniculitis in the buttocks and thigh after silicon-oil dermal augmentation; F: Cutaneous small vessel vasculitis secondary to facial non-animal hyaluronic acid injection.

Table 3
Suggested criteria for the diagnosis of "ASIA*"

Major criteria
- Exposure to an external stimuli (infection, vaccine, silicone, and adjuvant) prior to clinical manifestations
- The appearance of "typical" clinical manifestations:
  - Myalgia, myositis, or muscle weakness
  - Arthralgia and/or arthritis
  - Chronic fatigue, un-refreshing sleep, or sleep disturbances
  - Neurological manifestations
  - Cognitive impairment, and memory loss
  - Pyrexia, and dry mouth
- Removal of inciting agent induces improvement
- Typical biopsy of involved organs

Minor criteria
- The appearance of autoantibodies or antibodies directed at the suspected adjuvant
- Other clinical manifestations (i.e. irritable bowel syndrome)
- Specific HLA
- Evolvement of an autoimmune disease

* ASIA denotes Autoimmune/autoinflammatory syndrome induced by adjuvant (Shoenfeld's syndrome).

not subject to ingestion by macrophages and transportation to the local lymph nodes [133]. Particle shape may play a larger role in phagocytosis than mere size, since macrophages seem to have become evolutively specialized in recognition of bacterial pathogens [134]. Physical properties of the particles, such as surface charge or water affinity, may also influence phagocytosis: hydrophilic materials, such as hyaluronic acid, are less readily phagocytosed [132]. Cross-linking and increasing concentration has an inhibitory effect on phagocytosis in collagen implants and in hyaluronic acid. The failure of effective phagocytosis leads to granuloma formation, with aggregates of activated macrophages assuming an epithelioid morphology, giant cells of different types, and a surrounding infiltrate of T lymphocytes that secrete cytokines such as tumor necrosis factor (TNF) alpha, interferon gamma, and IL-12, responsible for ongoing macrophage activation (Fig. 2). Eventually, the granuloma becomes surrounded by a fibrotic rim and, in the case of infections, the center becomes necrotic. Particles with irregular surfaces are more likely to lead to active granulomas because they are less likely to become encapsulated [132]. Immunogenicity is an issue primarily with collagen implants, especially those of bovine origin, with late local and systemic reactions and elevations of immunoglobulins having been reported [133].

An acute inflammatory process involving a quiescent granuloma years after the injection might be related to the development of bacterial biofilms, or structured colonies of microorganisms encapsulated in an extracellular matrix that can surround a foreign body and can lead to a low-grade chronic infection with eventual spontaneous or injury-mediated reactivation [14,134], but they have not been found by electron microscopy studies in 10 patients with inflammatory nodules developing after injection of Dermalive [135]. The role of biofilm infections is indisputable on inert surfaces such as teeth, catheters, breast implants, and artificial hip and knee joint prostheses when certain bacteria in exudates settle to a smooth artificial surface and develop a polysaccharide biofilm that protects them from disinfectants and antibiotics, but evidence for their role in late reactions to fillers other than shelled silicone implants is far from settled [136–138].

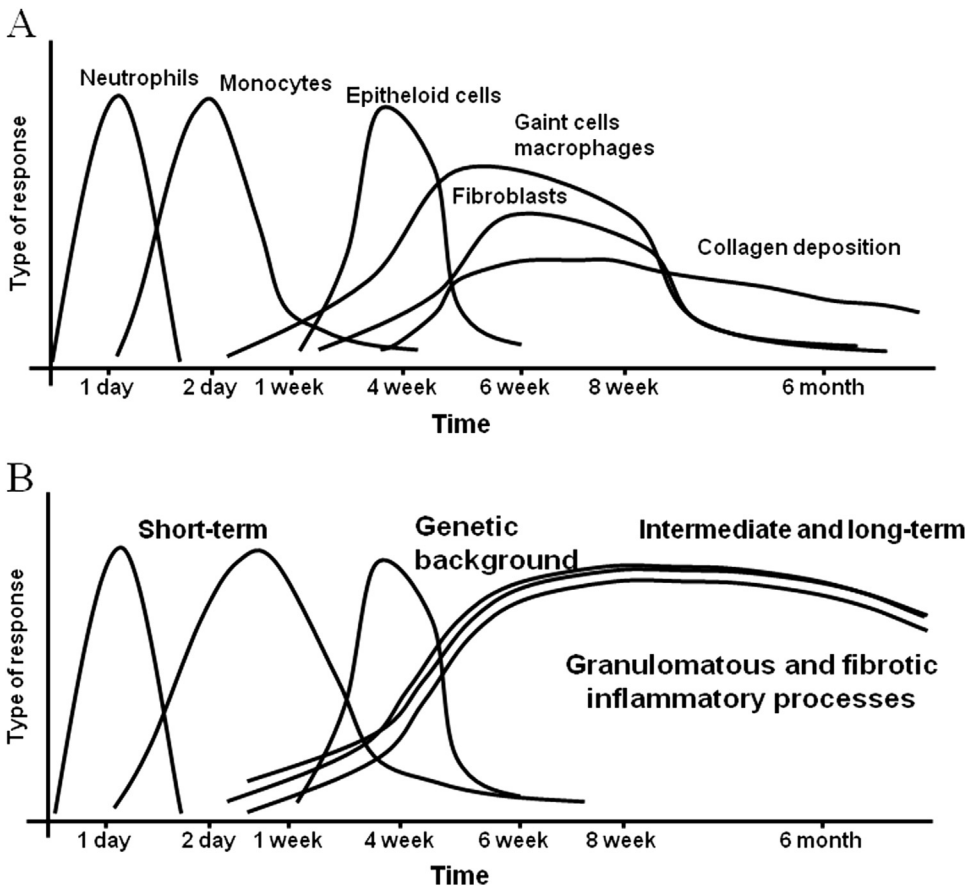

Fig. 2. Normal and pathological cell responses after foreign material injections in humans A: Normal events after filler injection B: Pathological events in late-onset inflammatory adverse reactions after filler injection.

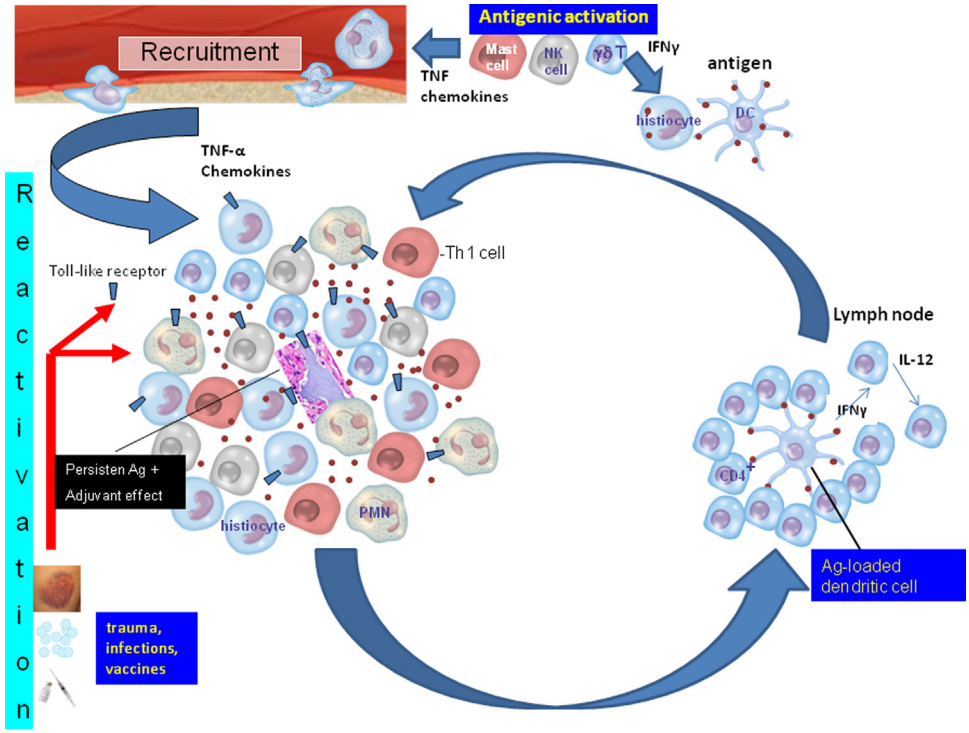

Fig. 3. Sequence of pathogenetic events leading to granuloma formation and reactivation of inflammatory response. Circulating granulocytes move into the soft tissue and are the first line of defense. Monocytes differentiate into macrophages, which eventually become the dominant cell type. Fillers may act as adjuvants and increase innate immune responses by mimicking evolutionarily conserved molecules, for instance bacterial wall components or unmethylated CpG-DNA residues, and binding to Toll-like receptors (TLRs); they also enhance the activities of antigen-presenting cells (APCs).The adjuvant effect of fillers and microbial molecules [in the case of superinfection], namely the non-antigenic activation of the innate and regulatory immunity, as well as the expression of various regulatory cytokines, may determine if an inflammatory/autoimmune response remains limited or evolves into a full-blown disease. Fillers may also elicit an APC-mediated adaptive immune response. The failure of effective phagocytosis leads to granuloma formation, with aggregates of activated macrophages assuming an epithelioid morphology, giant cells of different types, and a surrounding infiltrate of T lymphocytes that secrete cytokines such as tumor necrosis factor [TNF]-alpha, interferon gamma, and IL-12, responsible for ongoing macrophage activation and inflammatory cell recruiting. Eventually, the granuloma becomes surrounded by a fibrotic rim and, in the case of infections, the center becomes necrotic. Some biomaterials would affect the immune response acting as adjuvants rather than as antigens by themselves. In several cases of filler-related adverse effects triggering factors may be found, mainly local trauma, infections, or vaccines.

5.1. *Adjuvants, TLRs, immune response, and granuloma*

Bioimplants have been postulated to act as T-cell-specific activators, either directly or through the Toll-like receptors; they might act as adjuvants in individuals with predisposing genetic background (Fig. 2). Recently, we have demonstrated the adjuvant role played by silicone [139], hyaluronic acid compounds [140], and acrylamides (Alijotas-Reig J; unpublished results). Some biomaterials would affect the immune response acting as adjuvants rather than as antigens by themselves [139,140].

In several cases of filler-related adverse effects, triggering factors may be found, mainly local trauma, infections, or vaccines [8,12,14]. This clinical correlation highlights the possible role of infectious agents as a triggering factor for the development of these pathologic immune-mediated reactions [141]. The adjuvant effect of microbial molecules, namely the non-antigenic activation of the innate and regulatory immunity as well as the expression of various regulatory cytokines, may determine if an inflammatory/autoimmune response remains limited or evolves into a full-blown disease. Adjuvants enhance the immune responses in a non-specific manner. The adjuvant effect is accomplished by means of several mechanisms involving both the innate and adaptive immune pathways. Adjuvants increase innate immune responses by mimicking evolutionarily conserved molecules, for instance bacterial wall components or unmethylated CpG-DNA residues, and binding to Toll-like receptors (TLRs); they also enhance the activities of antigen-presenting cells (APCs). Thus, adjuvants increase local reactions to antigens with further release of inflammatory cytokines from T helper and mast cells [142,143]. Different bacterial molecules may activate several TLRs, mainly 1,4,5,7, and 9 [144,145]. Bacteria also produce high amounts of DNA molecules with unmethylated CpG residues that activate inflammation through TLR7 and TLR9. Besides, acylated microbial proteins may activate innate immunity through TLR1 and TLR6 recognition. TLR expression, in several different cell types, and the active cross-talk that antigen-presenting cells and B cells display with T cells may explain why these receptors are now accepted as a link between adaptive and innate immunity [143,145,146].

6. *Adverse reactions caused by subsequent injections of different fillers*

The possible increased risk of adverse reactions related to consecutive injections of different fillers in the same region has been suspected on clinical grounds [7,147]. Bachmann et al. [148] did not find evidence that consecutive injections increased the risk of adverse reactions, especially in the cases of biodegradable fillers. When we analyzed our own early series of 100 patients suffering from late-onset adverse reactions related to dermal fillers, we had the feeling that consecutive injections of different fillers increased the risk of these adverse reactions (Alijotas-Reig et al: unpublished results). In our subsequent review of 260 cases suffering from filler-related reactions, we found that repeated injections of different fillers in the same region or in different sites do not increase the risk of adverse reactions; nevertheless, when they appeared they were more likely to become chronic and more severe [7,149].

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7. Histopathological evaluation of filler implant reactions

As the number of filling treatments has increased and the local adverse reactions have become more frequent, dermatopathologists have been acquiring expertise on detecting the common features that betray their presence [81]. Even so, due to the constant increase in available fillers, identifying the specific causative material among the wide range present in the market has become tougher. The microscopic characteristics of some materials overlap, and often it is only possible to narrow down the differential diagnosis to a group of them (Fig. 3).

Frequently, the inflammatory process involves a large area of dermis and subcutaneous tissue in filler implant reactions. The infiltrate is predominantly made up of T lymphocytes, most of them CD4+ and to a lesser extent CD8+, with a small population of B lymphocytes and many macrophages, which engulf or surround particles of the injected material [150]. In some patients, these macrophages show mainly epithelioid—mononucleated cell features and may form palisades. In other cases, foreign body-type multinucleated giant cells are predominant. Foamy histiocytes can also be abundant, forming part of a lipogranulomatous reaction. Finally, eosinophils may be numerous, but a widespread eosinophilic infiltrate is rather uncommon. Soon after the beginning of the inflammatory reaction, the connective tissue becomes collagenized, usually encompassing a scant number of fibroblasts. This sclerosis not only involves dermis and subcutaneous fat but also can extend to the underlying striated muscle, surrounding isolated fibers and causing their atrophy. This phenomenon is particularly frequent around lips and eyes, where the striated muscle is more superficial. Foci of dystrophic calcification can also be present. Finally, the most severe cases contain large areas of tissue necrosis with ulceration and sinus tract formation. Additionally, there are some microscopic features that depend on the type of implanted material and can be highly distinctive (Table 1).

The initial attempts to obtain volume restoration with a filling material were made using autologous fat [151]. In these very first patients, untreated fat cells had a low chance of survival. Later on, the introduction of technical modifications improved the viability of this filler material that is still in use [152] and a new generation of adipose-derived mesenchymal stem cells is on the verge of clinical application [153]. Platelet-rich plasma contains a high concentration of platelets with neovascularization properties and it has been suggested to have the potential to promote fat graft survival and enhance the proliferation of human adipose-derived stem cells [154–156].

Few histological analysis of inflammatory reactions to autologous fat or of adipose-derived mesenchymal stem cells has been published [80,157].

Paraffin has been out of use for a long time, but some cases of late reactions can still be found. This non-resorbable implant is totally invisible in routinely processed histopathological sections, since the biopsy specimens are embedded in warm paraffin that melts with the paraffin filler. In spite of this, the presence of round wide spaces of different sizes that were originally occupied by the paraffin droplets impart a typical "Swiss cheese" appearance to the tissue that is characteristic enough to allow recognition of paraffin implants. Multinucleated giant cells are usually present and the connective tissue shows dense fibrosis and dystrophic calcifications [158]. The symmetrical location of this process in cheeks, breasts, or male genitalia is an additional feature that helps in making this diagnosis. Furthermore, the appearance of paraffin implants in computed tomography imaging is characterized by speckled-mass formation with fat-density and high-density nodules as well as nodular and rim calcifications contribute to its distinction from other tissue masses [159]. Used for more than 40 years, bovine collagen causes early hypersensitivity responses and to a lesser amount late inflammatory reactions that histopathologically correspond almost always to granulomas. These can be foreign body type [160], necrobiotic granuloma type [161], or sarcoid like [106]. The implanted collagen is ready visible in the center of these reactions and differs from native collagen by its texture and polarized light properties [162]. In one reported case, necrosis and abscessification was present in the area of collagen injection [163].

Microdroplet injections of medical-grade silicone are said to induce a gradual fibroplasia surrounding tiny droplets of this nonresorbable material. This process is considered to be valuable in consolidating its cosmetic action [164]. However, small amounts of silicone can be encapsulated by collagen causing a complication that is clinically known as "beading" and attributed to the injection of an excessive volume in the superficial dermis [164]. The inflammatory process directed against silicone can start early or after the implant has remained inert for a long period. In all cases, the hallmark of this reaction is the presence of macrophages containing vacuoles of irregular size looking like lipoblasts [165]. Many of these vacuoles are empty but in some of them tiny droplets of translucent silicone can be identified. In some occasions, the trigger that starts the inflammatory reaction to a silicone implant that had remained inert for a long time is the injection of a second filler of different nature. When this happens in the same area, both filling materials appear intermixed. Necrosis, ulceration, panniculitis, and lipogranulomatous inflammation are common in the most aggressive reactions.

Improper injections of large volumes of industrial silicone always result in an exaggerated version of this reaction, and the propensity of this material to become displaced may explain the spread of this reaction to other body areas, at a distance from the original sites of injection [165].

At present, HA-derived dermal fillers are probably the most popular with a large number of options and commercial names. It is considered among professionals that they carry a reduced risk of complications. Moreover, since hyaluronic acid is a resorbable compound, it is assumed that these complications will disappear spontaneously at the end of the filler lifespan. Nevertheless, increasing experience has demonstrated that, infrequent as they may be, not only severe acute local reactions [52] but also long-term complications [80,157,166] can be caused by hyaluronic acid-containing fillers. The marked differences among the wide variety of hyaluronic acid fillers may account for these diverse behaviors. Whereas the natural molecule obtained from cockscomb has a very short lifetime, new compounds containing insoluble cross-linked high-viscosity gels, varying in molecule and concentration, offer a more durable implantation.

Microscopically, the areas of hyaluronic acid injection show homogeneous light blue aggregates spreading through dermal and subcutaneous tissues. Using stainings for acid mucins (alcian blue or colloidal iron), hyaluronic acid acquires a deep blue color in tissue slides. When delayed reactions occur, collections of hyaluronic acid are surrounded by palisades of foreign body-type multinucleated giant cells (Fig. 3). The infiltrate may contain numerous eosinophils both at the periphery and in the center of the granulomas. Two cases of systemic complications related to hyaluronic acid have been reported. A granulomatous reaction that occurred after the first intradermal injection of Restylane gel, followed by scleromyxoedematous lesions on the patient's trunk and extremities was observed by Rongioletti et al. [167]. Another patient with chronic hepatitis C virus under pegylated interferon and rivabirin treatment initially developed a local foreign body granulomatous reaction and then sarcoidal granulomas that eventuated in a systemic sarcoidosis [168].

Permanent, long- and medium-lasting fillers are more prone to cause foreign body granulomatous reactions than short-term reabsorbable compounds. They usually consist of a foreign body reaction against particles of the injected material that can be recognized amongst the inflammatory process. The microscopic peculiarities of these materials may allow their specific identification (Table 1, Fig. 4). In some cases, these products have been withdrawn from the market shortly after being launched because of the high risk of adverse reactions [169], but the possibility of long-term complications cannot be ruled out, and a meticulous search of their presence is mandatory when an inflammatory process appears in the same location of the filler injection and even at a distance [135,170,171].

Finally, in some patients carrying permanent filler that has remained asymptomatic for many years, the local injection of a second material triggers an inflammatory reaction against both of them that can be identified in the same microscopic field.

8. Treatment

8.1. Acute systemic reactions

Acute urticaria, anaphylaxis—type I—hypersensitivity reactions should be managed with antihistamines, steroids, epinephrine, beta-mimetic drugs, and hemodynamic support when necessary [172].

8.2. Late-onset complications

The location of the inflammatory reactions induced by filler injections, usually subcutaneous, makes them rather unsuitable for a topical therapeutic approach. Despite that fact, diverse drugs have been used with variable success (Table 4).

8.3. Local corticosteroid injection

The usual first step in the treatment of local late-onset inflammatory adverse reactions related to fillers, that is, granulomas or inflammatory nodules or indurations, includes local injection of fluorinated corticosteroids, mainly triamcinolone acetonide (10–40 mg/mL) and betamethasone (5–6 mg/mL) [2,7–9,173]. This treatment appears to be especially useful in cases with few and small inflammatory nodules. Some authors use a 1:1 mixture of fluorinated corticosteroids with 5-fluorouracil (50 mg/ml) or bleomycin (1.5 IU/ml), [2,7–10,173]. Since repeated injections are usually required, they should not be done too superficially in order to avoid skin atrophy. Other potential complications related to repeated local injections of corticosteroids are skin discoloration and infection. Systemic adverse effects related to corticosteroid absorption, including Cushingoid changes, hypertension, and muscle atrophy, are possible but infrequent. Caution should be taken in cases with inflammatory reactions secondary to polyalkylimide, since according to the manufacturer data, a thin microcapsule appears after filler injection [174]. Thus, a second local injection (as a therapeutic attempt) can disrupt this microcapsule with extrusion of further material and expansion of the inflammatory reaction.

8.4. Hyaluronidase

Hyaluronidase, an enzyme that degrades hyaluronic acid of all known sources, has been proposed to treat hyaluronic acid overcorrections and hyaluronic acid-related granulomas. Its efficacy has been reported in some cases [24,175–177]. Other authors, including ourselves, advocate for a reconsideration of hyaluronidase use, because of the potential induction of hypersensitivity-mediated local or generalized reactions [178,179] or even the

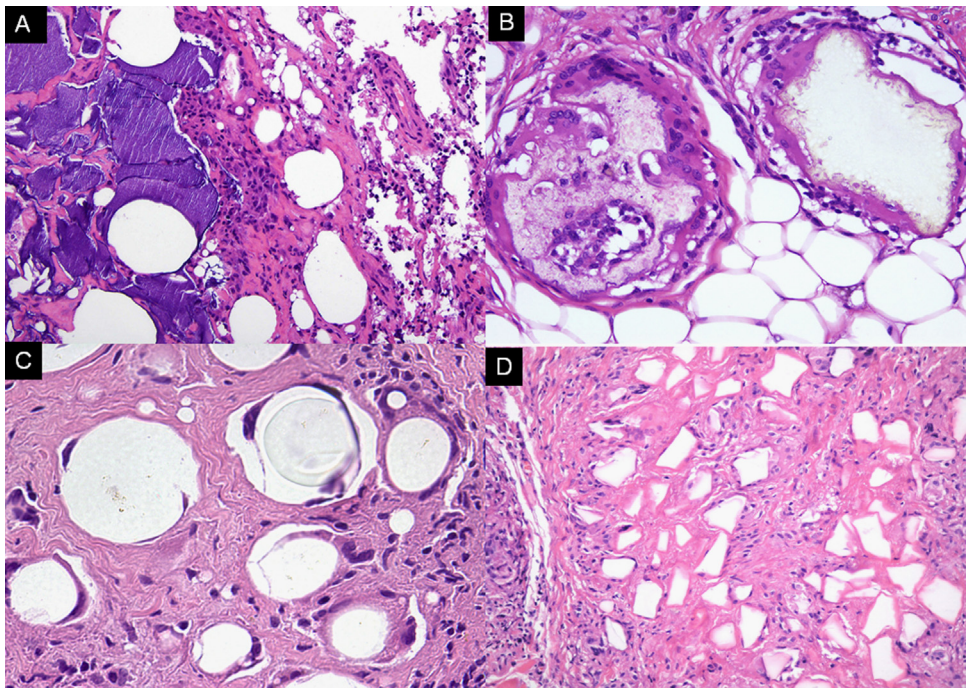

Fig. 4. Histopathogical patterns of different dermal fillers used in humans A/Upper left: Bio-Alcamid® (polyalkylimide) and silicon-combined foreign body reaction. Polyalkylimide hydrogel that appears as a basophilic material surrounded by multinucleated giant cells on the left side was injected many years after silicon injection that appears inside the microvacuolated histiocytes present on the right side. B/Upper right: Bioplastique® (polyvinyl-pyrrolidone + dimethylsiloxane). Multinucleated giant cells surrounding translucent particles with a crenulated border that retain a yellowish hue. C/Lower left: Artecoll® (bovine collagen plus methacrylate). Translucent spheres engulfed by giant cells. D/Lower right: Dermalive® (hyaluronic acid plus methacrylate). Polygonal structures immersed in a granulomatous reaction.

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Table 4
Normal host response to foreign material

24 h: neutrophils and small round cells predominate
48 h: monocytes predominate
7 days: early formation of foreign body giant cells occur
2 weeks: the cellular inflammatory response remains mild
4 weeks: monocytes differentiate into epithelioid cells; fibroblasts appear
6 weeks: foreign body giant cells common; increase of collagen deposition
8 weeks: chronic inflammatory cells and heavy collagen deposition
6 months: stable giant cells and low-grade cellular response; reduced amount of more dense collagen and conversion of fibroblasts into fibrocytes

possibility to provoke a delayed induction of prion-derived diseases [180].

8.5. Imiquimod

Imiquimod activates immune cells through the toll-like receptor 7 (TLR7) [181], and induces secretion of cytokines primarily interferon-α, interleukin-6 (IL-6), and TNF-α [182]. It has been used as an immunomodulatory treatment modality for superficial papillomavirus infections and non-melanoma skin cancers. Anecdotal reports of granulomas related to filler injections treated with imiquimod 5% ointment have been published [183,184]. Treatment-related reactions may include redness, swelling, itching, burning, pain/tenderness, thickening/hardening of the skin, peeling/flaking/scabbing/crusting, oozing, and permanent skin discoloration. Rarely, formation of sores/blisters/ulcers can occur. Flu-like symptoms, such as fever, tiredness, muscle aches, runny/stuffy nose, cough, diarrhea, nausea, and back pain may also occur [185]. Infrequent but serious side effects such as swollen lymph nodes and chest pain [186] as well as acute renal failure have been reported [187]. Imiquimod should be avoided in patients with history of photosensitivity or in those suffering from disorders with increased risk of skin sensitivity, such as scleroderma or lupus erythematosus [188]. Thus, considering the potential side effects related to imiquimod and the few data available regarding its effectiveness, we believe there is not enough experience that exists to recommend imiquimod use in this field.

8.6. Topical calcineurin inhibitors

Calcineurin inhibitors inhibit both T-lymphocyte signal transduction and IL-2 transcription and production. Their mechanism of action, indications, and side effects are summarized below. Some authors have used topical preparations of calcineurin inhibitors, mainly tacrolimus 0.1% twice a day and pimecrolimus 1% twice a day for the treatment of intralesional corticosteroid-"resistant" small granulomas, usually reporting good responses [2,35,189]. However, as occurs in the case of imiquimod, the number of reported cases is scarce.

9. Systemic treatments

Systemic corticosteroids, usually administered by mouth, are the most commonly used systemic treatment for filler-induced adverse reactions [2,7–10,13,35,37,42,56,81,173,184]. To the best of our knowledge, no refractory cases have been reported when using medium-high doses of prednisone (0.5–1 mg/kg/day) [2,7–10,173]. Lemperle et al. [173] only uses systemic prednisone in those cases they classify as exudative granulomas. Given the chronic nature of these pathological reactions, physicians are often forced to maintain corticosteroid therapy over time. Thus, the potential for systemic adverse effects related to corticosteroid treatment should not be underestimated. In these cases, combination treatment with a second or even a third drug is recommended in order to be able to taper down or minimize the dose of corticosteroids. Different drugs have been tried with this purpose (Table 4), including antimalarials, antibiotics, allopurinol, antihistamines, retinoic acid, cyclosporin, tacrolimus, and anecdotically, azathioprine, methotrexate, and mycophenolate mofetil [2,7,14,81,125,173,190]. Several of them have been used on the basis of their effect in other granulomatous diseases, either primarily inflammatory, autoimmune, or infectious. Unfortunately, no well-designed studies on the effectiveness of these therapeutic schedules have been reported. Usually, only isolated case reports or small case series have addressed this issue.

9.1. Antimalarials

Antimalarials, mainly chloroquine and hydroxychloroquine, are used based on the same rationale as in other granulomatous or autoimmune diseases [191]. Antimalarials have many anti-inflammatory, anti-aggregant, and immune-regulatory properties, mainly inhibiting phospholipase activity, stabilizing lysosomal membranes, and blocking production of several proinflammatory cytokines [192,193]. Cases of granulomatous reactions secondary to implant fillers have been treated with hydroxychloroquine, at doses ranging from 4–6.6 mg/kg/day, usually with acceptable results and a corticosteroid-sparing effect [7–10,194,195]. Its therapeutic effect often takes 4–6 weeks to appear.

9.2. Antihistamines

Antihistamines, blocking H1 and H4 histamine receptors, may exert anti-inflammatory and immunoregulatory actions [196]. Some antihistamines—mainly cetirizine, loratadine, or fexofenadine, are also capable of inhibiting the expression and production of intercellular adhesion molecule-1 (ICAM-1), IL-4, IL-6, and IL-12 [197,198]. These drugs also inhibit Toll-like receptor 3 (TLR3) expression [199]. Cetirizine, a second-generation antihistamine, has been shown to inhibit eosinophil chemotaxis and leukotriene B4 release [197], as well as endothelial vascular cell adhesion molecule-1 (VCAM-1) expression when used at high doses (20 mg/day). Thus, there seems to be some rationale behind the use of antihistamines for the treatment of adverse reactions associated with filler injections, but scientific evidence is lacking regarding which drug and dose should be preferable. At any rate, they might deserve therapeutic trial in association with other drugs.

9.3. Allopurinol

In addition to its well-known actions on xanthin metabolism and subsequent use as hypouricemic drug, allopurinol may exert anti-inflammatory properties [200]. Allopurinol has been used for the treatment of cutaneous sarcoidosis and in granulomas related to implant fillers, usually at a high dose (450–600 mg/d) with occasional success [2,42,201–203]. In other cases, it was ineffective even when used at a high dose [121]. Generally these few reports refer to patients having undergone prior injections of silicone fluid. Allopurinol is probably used not uncommonly for the treatment of adverse granulomatous reactions related to silicone injections, but not enough data are currently available to support a recommendation for the use of allopurinol at this time, taking into account the multiple and occasionally severe potential side effects of this drug. Paradoxically, several of the most severe side effects related to allopurinol are granulomatous in nature.

9.4. Antibiotics

Many doctors use antibiotics for treatment of late-onset adverse reactions related to fillers, even though the evidence for

a causal role of bacterial infection injections in granulomatous responses is inconclusive and still subject to debate. Christensen et al. [14] looked for evidence of bacteria in 28 biopsies from inflammatory nodules appearing with an intermediate or long delay after injection of different permanent fillers. They detected bacteria in some cases, although some of them were negative when using polymerase chain reaction techniques. Interestingly, many of the bacteria they isolated are not considered to be human pathogens. In another report, Beer [125] discussed the pathogenic role of microorganisms in late-appearing granulomas related to fillers, and they strongly advised antibiotic treatment, even though only 10 out of 55 cases from their series were cured with antibiotics alone or in combination with other drugs. Treatment of similar clinical conditions associated with other implant fillers, including polyacrylamide, has given conflicting results with regard to antibiotic treatment. As we have already mentioned, some adverse effects related to fillers have been related to infections, such as bronchitis, pharyngitis, flu, or pneumonia, suggesting that bacteria or viruses may play some pathogenic role. Thus, the exact value of the bacterial presence as a primary cause of idiopathic, immune-mediated or bioimplant-related granulomatous disorders is not truly known. Antibiotic treatment has not been effective in our own experience [7–10,64]. In cases where antibiotics seem to be useful, it is unclear whether the improvement might be related to their bactericidal properties or to their anti-inflammatory and/or immunomodulating effects [7,14,42,135,204,205].

9.5. Colchicine

Colchicine, an anti-inflammatory drug used in the treatment of gout, pseudogout, Sweet's syndrome, and a few autoinflammatory syndromes [206] has been claimed to be effective in the management of filler-induced granulomas [207]. Colchicine appears to interfere with several of the inflammatory response in which neutrophils play a central role, decreasing their motility, chemotaxis, and lysosomal degranulation [206,208]. As is the case of allopurinol, reports on its possible therapeutic effect in filler-induced granulomas are scarce [207]. Thus, definitive evidence regarding colchicine effectiveness is lacking, and a formal recommendation for its use cannot be done.

9.6. Retinoic acid

Retinoic acid and its derivatives are currently being used in different areas of medicine, mainly dermatology and hematology. Retinoic acid has anti-inflammatory and immunoregulatory properties, essentially downregulating the overproduction of proinflammatory cytokines [209,210]. Retinoic acid has been shown to be effective in the treatment of diverse immune-mediated disorders, such as cutaneous sarcoidosis, granuloma annulare, pemphigus, or scleroderma [211]. Evidence of its effectiveness in adverse reactions to fillers is scarce. Lloret et al. [212] reported good results in two cases of skin granulomatosis related to silicone implant, but both cases were also treated temporarily with oral corticosteroids. Similar results were communicated by Jansen et al. [213]. We have tried this drug in a few patients suffering from severe facial granulomas after silicone injection, and have achieved good responses using low doses of retinoic acid, since tolerance to doses higher than 0.5 mg/kg/day is usually poor.

9.7. Calcineurin inhibitors

Calcineurin inhibitors, mainly cyclosporin A and tacrolimus, inhibit both T-lymphocyte signal transduction and IL-2 transcription and production [214]. Calcineurin dephosphorylates the transcription factor NF-AT (nuclear factor of activated T cells), which moves to the nucleus of the T cell and increases the activity of genes coding for IL-2 and related cytokines [215].

Currently, the most used drug belonging to this family is tacrolimus. Tacrolimus was first approved by the Food and Drug Administration in 1994 for use in organ transplantation; this has been extended to diverse inflammatory and autoimmune diseases, including systemic lupus erythematosus, rheumatoid arthritis, ulcerative colitis, and sarcoidosis. Even though short-term immunosuppression is found to be similar between the two drugs, the safety profile of tacrolimus appears to be more favorable and this may have important implications for long-term treatment. Cyclosporin A has been used in a few cases of granulomas related to filler injections [2,216]. Alijotas-Reig et al. (unpublished results) tested the capability of different drugs to inhibit diverse proinflammatory cytokines in an "in vitro" model, and found that tacrolimus shows the strongest inhibition of IL-2 production, in addition to other proinflammatory cytokines, following stimulation of peripheral blood mononuclear cells with mitogens, silicone, hyaluronic acid, and acrylamides. The same group obtained good responses in a series of patients with delayed adverse reactions to fillers that were refractory to other commonly used drugs [124]. The use of tacrolimus at low doses (0.08–0.1 mg/kg/day) usually achieves full control of the clinical manifestations. In our own clinical practice, higher doses of tacrolimus have been required only in a small number of cases. Even though a wide range of side effects related to calcineurin inhibitors can be expected to appear, they have not been reported when calcineurin inhibitors have been used in this setting [124,216,217]. In daily clinical practice, tacrolimus has a significant advantage when compared with other drugs potentially useful in the treatment of this kind of adverse reactions: the therapeutic effects usually appear within the first week of treatment.

9.8. Biological therapies: TNF inhibitors

Tumor necrosis factor inhibitors (anti-TNF) are a new family of drugs that block circulating and/or cell-bound TNF. The three most commonly used TNF blocking agents are etanercept, infliximab, and adalimumab [218]. Interestingly, anti-TNF drugs may cause a wide range of immunologically mediated reactions, sarcoidosis included, which can be considered as paradoxic taking into account the therapeutic profile of these drugs [219,220]. TNF-alpha blockade has an inhibitory action on macrophages, which may lead to granuloma disruption and increase the risk of disseminated infections due to intracellular granuloma-forming microorganisms, as is specially the case with anti-TNF monoclonal antibodies [221,222].

Some cases of granulomatous reactions to dermal fillers, especially those caused by silicone, methacrylate compounds, or combinations of different fillers can be notoriously difficult to treat, and anti-TNF drugs were initially tried as a last resort. Pasternak and coworkers [223], Gutmann [224], and Desai et al. [225] reported good responses following their use. Furthermore, at least one author [226] has found the opposite effect with etanercept—the formation of new silicone granulomas in a patient after starting the drug. Obviously, and according to the possible severe side effects, further research is needed to determine the true benefit risk ratio of this family of immune-modulating drugs.

9.9. Combination of drugs

Even though no well-designed clinical trials that may support this practice have been published to date, several combinations of systemic drugs other than corticosteroids have been proposed for the treatment of the most severe, recurrent, extensive, or

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systemic cases. These combinations included the following: allopurinol plus hydroxychloroquine, hydroxychloroquine plus antihistamines, allopurinol or hydroxychloroquine plus antibiotics, or retinoic acid and antibiotics, mainly macrolides or doxycycline [2,7–10,54,64,100,190,212,217]. In certain cases, combination of all these drugs has been used, because of the severity of the patients' lesions and the needed to spare corticosteroids. In these cases, usually good results have been reported. Prescribers must be aware of the risk of developing benign intracranial hypertension that contraindicates the use of tetracycline and retinoic acid derivatives in combination.

9.10. Surgical options

In selected cases, surgical procedures are necessary to eliminate granulomatous reactions [2,6,12,42,100,204,217,227]. In our opinion, it is crucial to choose the adequate patients as well as the right time to perform surgical excision of granulomas or any inflammatory lesion related to filler injection. We agree with Sperling et al. [228] and Lemperle et al. [173] that only a few patients suffering from inflammatory adverse effects related to fillers should undergo surgical procedures. Likewise, only 10% of cases belonging to The Therapy of Adverse Reactions of Injectable Fillers (TARIF) Study [228] were subject to a surgical intervention. During active inflammatory processes or when patients have large and/or multiple lesions, surgical procedures should be avoided because of the risk of filler migration, infection, formation of fistulae, persistent granulation tissue, marked deformities, scars, and appearance of new inflammatory bouts related to injury [7,8,173]. Furthermore, the risk of provoking important and disfiguring sequelae, mainly in the facial area, following removal of excessive dermal and subcutaneous tissue, should also be considered and avoided when possible. Thus, only a few cases should undergo surgical procedures. Although based only on our clinical experience, and not on evidence-based medicine, we only recommend surgical procedures in cases that have remained for at least 6 months without clinical activity but with significant sequels or scars, or in those cases refractory to all known medical treatments, immunosuppressive therapy included.

9.11. Laser therapy

Based on the experience of treating facial granulomas with laser therapy [229,230], some authors have used this therapeutic modality in clinical practice on patients suffering from granulomas related to filler injections. Nevertheless, we are only aware of one publication on this subject, by Cassuto et al. [231], who reported on a series of 20 patients with granulomas related to synthetic gel fillers that were treated using a lithium triborate at 532-nm diode laser using intralesional technique. A possible role of bacteria as triggers of filler-related granulomas was assumed by these authors, who reported having obtained good responses after repeated treatments. However, the available evidence is still insufficient to recommend this kind of therapy, since adverse effects mainly cutaneous and subcutaneous necrosis related to laser therapy have also been seen (Alijotas-Reig J: unpublished data).

9.12. Proposal of a diagnostic and therapeutic schedule

A state-of-the-art review on facial soft tissue fillers has been recently sponsored and published by the American Academy of Dermatology [232] and the American Society of Plastic Surgeons [233]. However, neither all the currently existing fillers nor all the published articles have been collected systematically, and the information provided in these conference proceedings is focused on the available evidence on the effectiveness of facial fillers, and to a lesser extent, the early or short-term complications, rather than the inflammatory and more severe late-onset adverse effects. No information about long-term follow-up and treatments has been included, either. Thus, and unfortunately, according to the current available data, evidences and recommendations on the diagnostic procedures and subsequent therapeutic schedules regarding adverse reactions induced by fillers do not exist. Only information based in case series and in a few expert opinions can be drawn from the existing literature [6–10,12,100,173,212]. Nevertheless, several proposals can be made in the setting of these adverse reactions, especially when locally severe, disseminated, or associated with systemic manifestations. We [7–10] and others [212] agree on the following protocol: complete medical history and physical examination, blood tests with determinations of acute phase reactants, autoantibody panel, angiotensin-converting enzyme, lactic dehydrogenase and complement factors, imaging studies, mainly computerized tomography scans or magnetic resonance imaging, and cultures of skin or extruded/aspirated material when necessary. Either, cutaneous lesions or nodule biopsy are advised but not mandatory. Furthermore, many patients denied this diagnostic procedure. From a therapeutic perspective (Table 5), intralesional corticosteroids must be the first line of therapy. As second-line treatments, allopurinol, antimalarials, antibiotics with immunomodulatory effect, retinoic acid, or high doses of antihistamines can be used. The next step could be a combination of two or more of these drugs. Tacrolimus or biological therapy can be used as a last resort. These statements underscore our belief that well-designed studies regarding therapeutic schedules are required. Until this information becomes available, the above-mentioned therapeutic suggestions might prove to be helpful in the management of this kind of complications of filler injections. Nevertheless, we would like to warn our colleagues to be cautious in the use of these therapeutic options, since they are amenable to induce sometimes severe adverse effects.

Table 5
Drugs used in the management of inflammatory late-onset adverse effects related to implant fillers

- Intralesional corticosteroids* (triamcinolone/betamethasone)
- Intralesional 5-Fluorouracil* or bleomycin*
- Hyaluronidase*
- Topical tacrolimus cream 0.5%
- Imiquimod cream 5%
- Systemic steroids: 30–60 mg/day
- Non-steroidal anti-inflammatory drugs (i.e. ibuprofen 1800–2400 mg/day)
- Antihistamines (high dose)
- Antimalarials (chloroquine: 250 mg/day or hydroxychloroquine: 200–400 mg/day)
- Antibiotics (mainly macrolides or quinolones)
- Retinoic acid: isotretinoin 0.5 mg/kg/day
- Colchicine: 1–1.5 mg/day
- Allopurinol: 300–600 mg/day
- Azatioprine: 50–100 mg/day
- Calcineurin inhibitors: cyclosporin A: 5–6 mg/kg/day or tacrolimus: 0.08–0.12 mg/kg/day
- Biological agents, such anti-TNFα blockers: etanercept, adalimumab

* Diverse dilutions (see text).

10. Conclusions

An ever-increasing number of people are seeking medical solutions for their aging skin, for esthetic and cosmetic indications or for diverse medical conditions. Currently, physicians have access to many different types of dermal and subdermal fillers, which may be classified according to their origin and average

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persistence in tissue. So far, all known fillers present in the market have been shown to be able to provoke early- and late-onset adverse effects. Their true prevalence is unknown but appears to be significant, according to the huge amounts of original papers, case series, case reports, and consensus conferences, as well as basic research that has been published in the last few years. Several of the early complications can be related to technical procedures. Some others and the majority of the late-onset adverse effects are inflammatory and immune-mediated in nature. Edema, granulomas, sarcoid-like disorders, and panniculitis are the findings most commonly seen. Rarely, systemic granulomatous and autoimmune diseases, and to lesser extent acute hypersensitivity reactions and thrombosis can be seen. Clinicians should be aware of them, since the patient often denies the antecedent of injection or is unaware of the material employed. From an immunologic perspective, fillers apparently act as adjuvants rather than as direct T-cell activators, on a background of genetic predisposition. The role played by the infectious agents is still a matter of discussion. The treatment of these adverse events has not been the subject of well-designed studies. Management of both acute and systemic reactions is often difficult, and requires anti-inflammatory and occasionally immunosuppressive therapy.

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