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REVIEW

Prevention and Management of Complications With a Hyaluronic Acid–Calcium Hydroxyapatite Hybrid Injectable

Wolfgang G Philipp-Dormston[1,2], Koenraad De Boulle[3,4], David B Eccleston[5], Rachna Murthy[6], Karim Sayed[7–9], Philippe Snozzi[10,11], Fernando Urdiales-Galvez[12]

[1]Hautzentrum Köln, Cologne, Germany; [2]Faculty of Health, University Witten/Herdecke, Witten, Germany; [3]Aalst Dermatology Clinic, Aalst, Belgium; [4]University College London, London, UK; [5]MediZen, Birmingham, UK; [6]FaceRestoration, Ltd, London, UK; [7]Nomi Oslo Clinic, Oslo, Norway; [8]Ouronyx Clinic, London, UK; [9]University of South-Eastern Norway, Drammen, Norway; [10]Smoothline, Zurich, Switzerland; [11]University of Amsterdam, Amsterdam, Netherlands; [12]Instituto Médico Miramar, Málaga, Spain

Correspondence: Wolfgang G Philipp-Dormston, Hautzentrum Köln, Schillingsrotter Str. 39-41, Köln, 50996, Germany, Tel +49 221 390 00 200, Fax +49 221 390 00 201, Email wdormston@outlook.com

Background: A ready-to-use hyaluronic acid–calcium hydroxyapatite (HA-CaHA) hybrid injectable has a dual mode of action for soft-tissue augmentation. Although previous studies have reported a favorable safety profile for HA-CaHA, there is a need for guidelines and recommendations based on real-world clinical experience for the management of complications associated with HA-CaHA.

Purpose: This publication provides guidelines and recommendations for the prevention and management of HA-CaHA–related complications. A case study example, treatment algorithms, and injection techniques are included to illustrate the management of complications.

Materials and Methods: On January 25, 2023, 13 European physicians were invited to an advisory board meeting to discuss strategies for optimizing patient care, minimizing adverse events (AEs), and identifying data gaps for the prevention and management of complications with HA-CaHA.

Results: The management of a subset of AEs, including skin discoloration and edema, was discussed. Small group workshops also shared management algorithms for late noninflammatory adverse reactions, late inflammatory adverse reactions, localized vascular complications, and retinal vascular complications. Best practices for optimal injection techniques were discussed, and injection-technique protocols were developed for treatment sites. Treatment strategies for HA-CaHA–related complications are considered similar to treatment of those resulting from single-agent fillers, and knowledge of anatomy, aseptic technique, correct injection techniques, and appropriate posttreatment care is emphasized.

Conclusion: These recommendations on the management of HA-CaHA–related complications may serve as a reference for the broad range of clinicians using HA-CaHA hybrid injectable for different indications and can help optimize patient outcomes and safety.

Keywords: hyaluronic acid, calcium hydroxyapatite, prevention, complications

Introduction

A growing trend in panfacial rejuvenation is combination treatment using different products to address multidimensional aesthetic needs.[1] Injectable fillers, including hyaluronic acid (HA) and calcium hydroxyapatite (CaHA) fillers, are commonly used to restore soft-tissue volume and provide structural support.[1] Because most fillers are composed of a single agent, they are unable to provide the combined benefits of volume restoration and lift together with improved skin quality and lasting collagen stimulation.[1]

HA-CaHA (HArmonyCa; Allergan Aesthetics, an AbbVie Company, Irvine, CA) is a hybrid injectable consisting of approximately 70% (v/v) crosslinked HA gel (20 mg/mL) with approximately 30% embedded CaHA microspheres (55.7% [w/w], 25–45 µm in diameter).[2] In terms of rheology, HA-CaHA has an elastic modulus (G') of 644 (Pa at 5 Hz),

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cohesiveness of 58 cohesivity/Fn (gmf), and maximum water retention of 501%.[2] Unlike single-agent CaHA fillers, in which the microspheres are suspended in carboxymethyl cellulose (CMC),[3] HA-CaHA does not contain a carrier vehicle, although it does contain lidocaine hydrochloride (0.3% [w/v]) to reduce pain during injection.[2] HA-CaHA has a synergistic dual mode of action for facial soft-tissue augmentation. The HA component provides volume for an immediate filling and lifting effect in the injected area,[3] and CaHA is a biostimulator that induces production of endogenous collagen, resulting in a sustained lifting effect over time in the injected area.[4]

It is very important to distinguish between combining different products on site (product blending) and the use of a manufactured, ready-to-use hybrid product such as HA-CaHA. Product blending may alter the original properties of each individual filler product, including cohesivity and rheology, thus affecting lift capacity and the ability to restore volume and stimulate neocollagenesis.[1] Physicians should also consider the potential breach of sterility and risk of contamination when multiple syringes are used for product blending. Previous studies have investigated the safety and effectiveness of combining HA and CaHA filler products for aesthetic treatment in different facial areas.[5–8] Although these studies have established a favorable safety profile of blended products,[5–8] these published studies lacked a standardized methodology. To date, several studies have reported on the safety and effectiveness of the ready-to-use HA-CaHA hybrid injectable,[2,9–11] but guidelines and recommendations based on real-world clinical experience are needed to advise physicians on the management of complications associated with HA-CaHA.

The objective of this article is to provide guidelines and recommendations for the prevention and management of complications associated with the ready-to-use HA-CaHA hybrid injectable. Treatment algorithms, as well as injection techniques and protocols, are discussed; case study examples are provided to illustrate the management of complications for optimizing patient care.

Materials and Methods

Thirteen European physician advisors (dermatologists, plastic surgeons, aesthetic medicine physicians), including 1 faculty advisor, were invited by a sponsor to discuss guidelines and recommendations during an advisory board meeting held on January 25, 2023. The 13 European physician advisors who attended the advisory board meeting were individuals with the most experience with the product in question and also complication advisors for their individual country. The goals of this meeting were to discuss strategies for optimizing patient care and minimizing adverse events (AEs) and complications with the use of HA-CaHA hybrid injectable, gain insight into treatment protocols and recommendations for managing complications, and share recommendations on identified data gaps for the prevention and management of complications associated with HA-CaHA.

Results and Discussion

HA-CaHA Safety Data Overview

Previous studies reported safety data for HA-CaHA.[2,9–11] A single-center prospective study (N=15) with a 4-month follow-up period reported only 1 AE (papule), along with only a few reports of localized side effects such as mild edema, pain, and ecchymosis and no reports of vascular complications or infections.[11] In a prospective, nonrandomized interventional study (N=15) with a 6-month follow-up, the most commonly reported AEs included redness and inflammation, which resolved within 2 days; all the reported AEs were mild in severity.[2] Also, long-term studies have confirmed the favorable safety profile of HA-CaHA. A multicenter retrospective study conducted in Brazil (N=403), which included patients with long-term safety data (≥12 months posttreatment with HA-CaHA), reported AEs such as edema, implant site nodules (product accumulation), inflammation, hypersensitivity, and skin induration; the majority of treatment-related AEs were also mild in severity.[9] A retrospective study (N=104) evaluating late-onset AEs (≥18 months posttreatment with HA-CaHA) did not observe long-term AEs; furthermore, no treatment-related skin abnormalities, AEs, allergic reactions, or infections were detected by dermatoscopy or ultrasonography.[10] Representative patient photographs and ultrasonography images of AEs related to HA-CaHA hybrid injectable are shown in Figures 1 and 2.

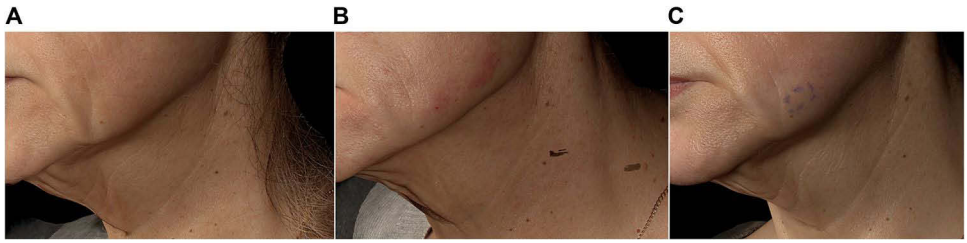

Figure 1 Case photographs of a 58-year-old female patient before (**A**) and immediately after (**B**) treatment with hyaluronic acid–calcium hydroxyapatite (HA-CaHA) hybrid injectable in the pre-jowl sulcus using a 22-G cannula injected into the subdermal plane. A small area of redness was observed at the entry point of the needle. (**C**) Five months after HA-CaHA treatment and following bariatric surgery, a late noninflammatory adverse reaction, presenting as a nodule, was observed. The nodule was palpable but did not cause pain and was observed at the site of needle entry (marked here with a blue surgical marker). The nodule was treated with a localized 75-U injection of hyaluronidase and completely resolved. Photographs courtesy of R. Murthy.

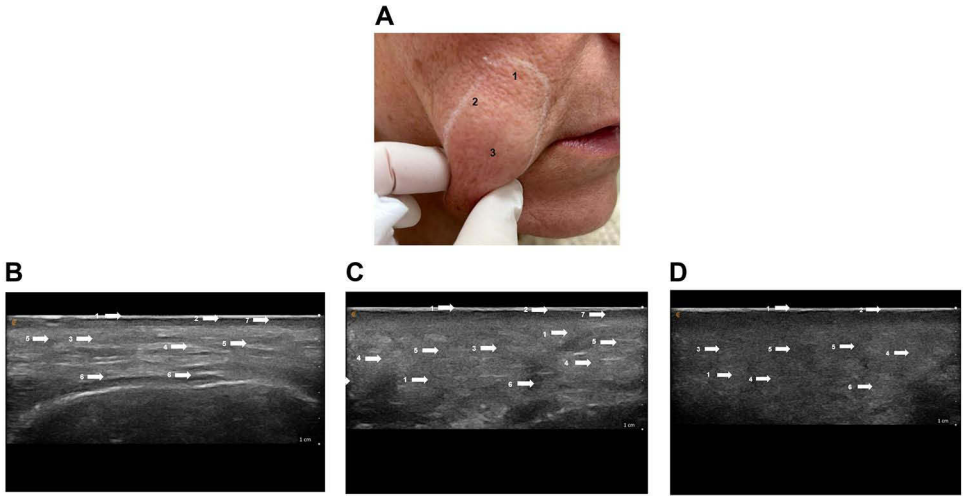

Figure 2 Images of a 53-year-old female patient 2 months after treatment with hyaluronic acid–calcium hydroxyapatite (HA-CaHA) hybrid injectable at ck 5 (submalar/buccal area) and jw 4 (lower prejowl) using a 22-G cannula injected into the subcutaneous plane. The patient presented with inflammation at ck 5 resulting from HA-CaHA overcorrection. There was no pain, redness, or liquid collection. (**A**) Photograph of patient showing inflammation at ck5 and jw4. Areas 1, 2, and 3 correspond to the ultrasound images in B to D. (**B**–**D**) Ultrasound images corresponding to areas 1, 2, and 3 in A show a heterogenous pattern with anechoic/hypoechoic areas and inflammation. A heterogenous pattern with anechoic/hypoechoic areas is characteristic of normal healthy skin and demonstrates integration of HA, whereas a "coarse snow grain" pattern is due to the presence of CaHA.[10] (**B**) Ultrasound image corresponding to area 1. 1. Epidermis, 2. Dermis, 3. Subcutaneous cellular tissue, 4. Fibrillar collagen area, 5. "Coarse snow grain" pattern, 6. Anechoic/Hypoechoic areas, 7. SLEB. (**C**) Ultrasound image corresponding to area 2. 1. Epidermis, 2. Dermis, 3. Subcutaneous cellular tissue, 4. Inflammation area, 5. "Coarse snow grain" pattern, 6. Anechoic/Hypoechoic areas, 7. SLEB. (**D**) Ultrasound image corresponding to area 3. 1. Epidermis, 2. Dermis, 3. Subcutaneous cellular tissue, 4. Inflammation area, 5. "Coarse snow grain" pattern, 6. High-density echogenic areas. Photographs courtesy of F. Urdiales-Galvez. **Abbreviations:** CaHA, calcium hydroxyapatite; ck, cheek; HA, hyaluronic acid; jw, jawline; SLEB, subepidermal low-echogenic band.

Clinical Opinions and Best Practices for Management of HA-CaHA–Related AEs and Complications

As a result of the advisory board meeting, recommendations on the management of a subset of AEs, including skin discoloration and edema, were provided. Small group workshops also discussed and shared management algorithms for the following 4 HA-CaHA–related complications: late noninflammatory adverse reactions, late inflammatory adverse reactions, localized vascular complications, and retinal vascular complications. Careful patient selection, knowledge of patient history and facial anatomy, use of aseptic and correct injection techniques, and appropriate posttreatment care contribute to the prevention of AEs and complications.[12–14]

Skin Discoloration

Skin discoloration includes hematoma, neovascularization, hyperpigmentation, optical chamber effects, and skin whitening.[15] Optical chamber effects result from HA and are therefore normally treated using hyaluronidase, whereas skin whitening results from excess superficial CaHA particles and therefore requires treatment to dilute the excess particles with saline. Some physicians have observed hyperpigmentation in certain skin types, especially when there is delayed inflammation. Algorithms similar to those used for HA fillers can be used to manage skin discoloration resulting from HA-CaHA (Figure 3).[15]

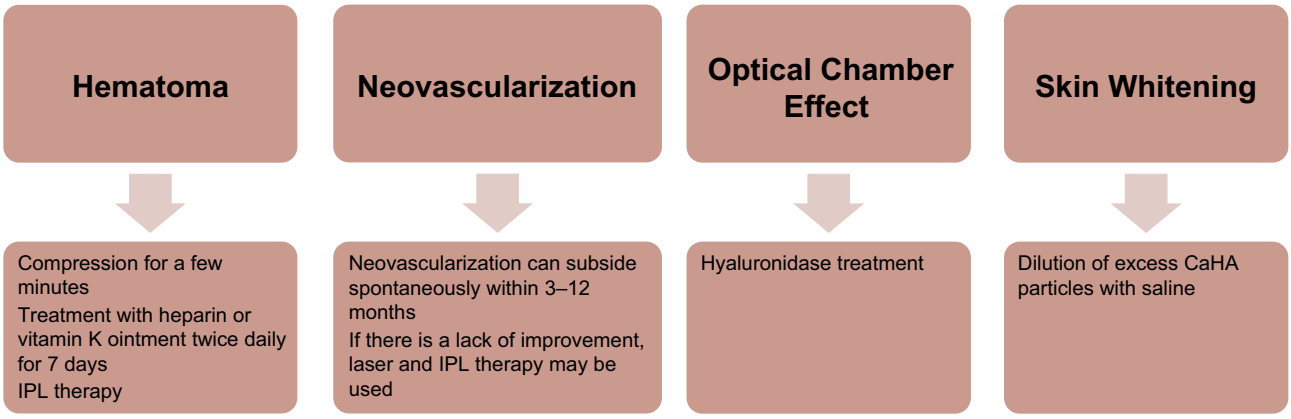

Figure 3 Management of skin discoloration.[15]
Abbreviations: CaHA, calcium hydroxyapatite; IPL, intense pulsed light.

Edema

Edema can be characterized as immediate postinterventional edema, malar edema, immediate-type allergy (type I), or delayed-type allergy (type IV).[12,15] Based on the clinical experience of the authors, higher incidences of edema with HA-CaHA during the first 3 to 10 days posttreatment versus HA or CaHA fillers alone have been observed. Although this may be a result of the CaHA component of HA-CaHA, which is less physiologic than HA, future studies will be needed to more firmly delineate this point. Because edema is common to facial fillers and is usually not severe, it often does not require intervention. Previous algorithms for identifying and addressing different types of edema have been published.[12,15] Edema should be considered a product-related side effect rather than an AE.

Late Noninflammatory Adverse Reactions

Noninflammatory adverse reactions, commonly presenting as nodules, are likely due to product accumulation, and they can be identified by ultrasonography to detect collagen formation.[15,16] An event that occurs ≤2 weeks after injection is considered "early"; any event ≥2 weeks postinjection is considered "late." Physicians should maintain communication with their patients. Recommended algorithms for managing noninflammatory adverse reactions are shown in Figure 4A.[16,17] As a first-line treatment, hyaluronidase is recommended because HA-CaHA contains approximately 70% HA. Various mechanical approaches also have been reported for reducing CaHA accumulation.[17–19] A case study suggested focused mechanical vibration as a possible aid in reducing accumulation of CaHA,[18] while another study reported the use of syringe suction to mechanically remove excess CaHA.[19]

Late Inflammatory Adverse Reactions

Early inflammatory adverse reactions can occur as a result of acute infection, and the degree and type of inflammation affect the heterogeneity of the reaction.[15] Late inflammatory adverse reactions, often presenting as nodules, edema, or induration, can be complex and involve different factors (eg, genetic, product, and immunological).[15] For example, during the COVID-19 pandemic, inflammatory responses associated with infections and vaccinations were observed,[12] and most patients improved on their own. Autoimmune/Inflammatory syndrome induced by adjuvants should also be treated as an inflammatory reaction. There is limited literature on the interaction between HA and CaHA and the development of late inflammatory adverse reactions.

Anti-inflammatory antibiotics have historically been recommended as treatment for inflammatory reactions in HA-only and CaHA-only fillers (Figure 4B).[15–17] However, physicians should prescribe them responsibly to prevent antibiotic resistance; furthermore, physicians should be cognizant of how antibiotic treatment could affect a patient's microbiome. Some protocols also recommend the use of macrolides (eg, azithromycin, clarithromycin), which have anti-inflammatory potential, and antibiotics as first-line treatment.[20] If there is little improvement after 2 to 3 weeks, the use of

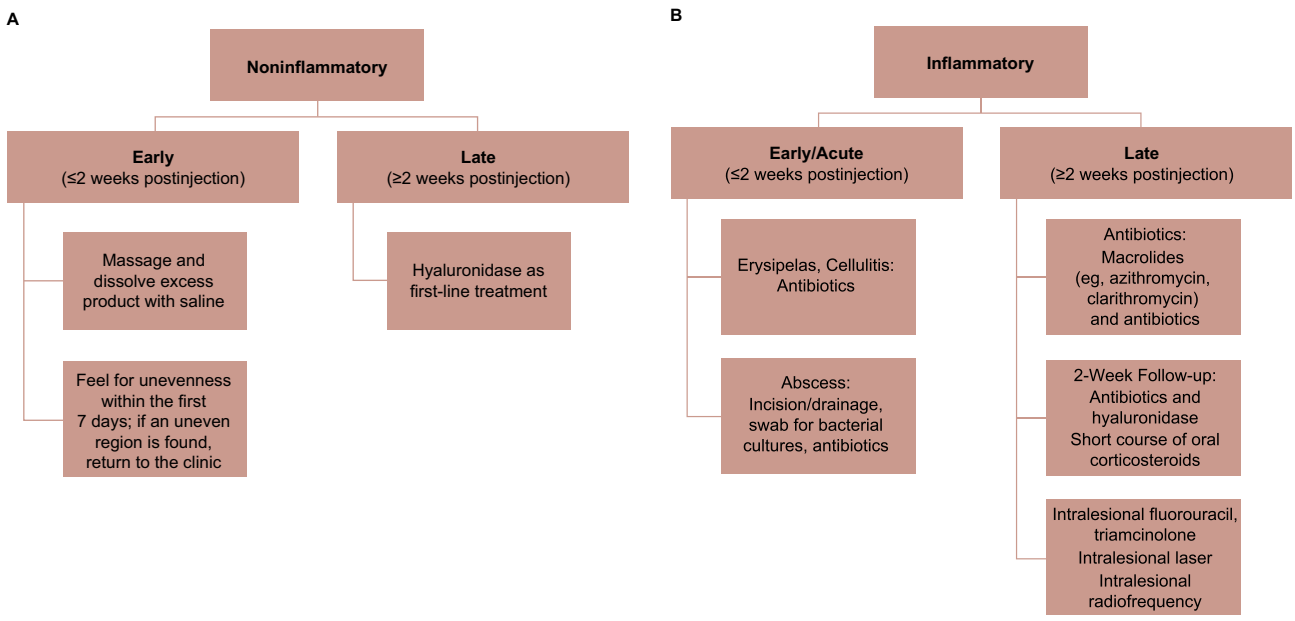

Figure 4 Management of noninflammatory (**A**) and inflammatory (**B**) adverse reactions.[16,17]

hyaluronidase is recommended based on need.[20] A short oral course of corticosteroids may also be provided as supportive, adjuvant treatment to address inflammation. In rare cases, fluctuant abscesses may present as a late adverse reaction and may need incision or drainage; however, physicians should be cautious because noncritical surgical procedures may worsen the situation in primarily immunologic cases.

Localized Vascular Complications

Vascular complications normally result from vessel occlusion due to an embolism containing HA or HA-induced choke vessel contraction.[15,21,22] A good understanding of vascular anatomy is important, especially because a patient's vascular architecture may be altered by previous surgery. Injecting HA-CaHA in the superficial layer may minimize local vascular complications. On-label regions for HA-CaHA (eg, posterior zygoma, preauricular area, mandibular angle, jaw ramus) are generally safer with regard to vascular structures, whereas the superficial layers in the midface (eg, submalar and nasolabial fold areas), temporal regions, and marionette lines are riskier. Injectors should be cautious when treating marionette lines, although it is an on-label indication. The facial artery, which generally runs lateral to the marionette fold and is often not superficial, may have anatomic variations.

Treatment strategies include using warm compresses and immediate hyaluronidase treatment (Figure 5).[15,23] In certain cases, a gentle massage may also be considered, while being cautious to avoid further distribution of the material. Because HA-CaHA is mostly composed of HA, the use of hyaluronidase to manage complications is emphasized and historically based on previous recommendations involving HA-only fillers.[15,22] However, published literature on CaHA-only fillers also recommend the use of hyaluronidase due to its overall anti-inflammatory properties.[23,24] Previously published consensus panel recommendations suggest the use of hyaluronidase for the management of vascular compromise after CaHA injections.[23] Therefore, hyaluronidase may impact both the HA and CaHA components of the hybrid injectable. More recently, a now widely used procedure, termed the high-dose pulsed hyaluronidase (HDPH) protocol, involves hourly administration of hyaluronidase to maintain sufficiently high concentrations of hyaluronidase throughout the ischemic zone, with the goal of completely hydrolyzing the HA within the vessels.[25] This dosing strategy is based on the volume of the affected tissues, unlike traditional methods in which fixed doses of hyaluronidase are administered but may lead to partial breakdown and potential obstruction further downstream of the ischemic zone.[25] Other options for treating vascular complications include using low-molecular-weight heparin, pentoxifylline, or hyperbaric oxygen therapy; however, the level of evidence for each of these therapies is low.[15] More recently, nitrous oxide was reported

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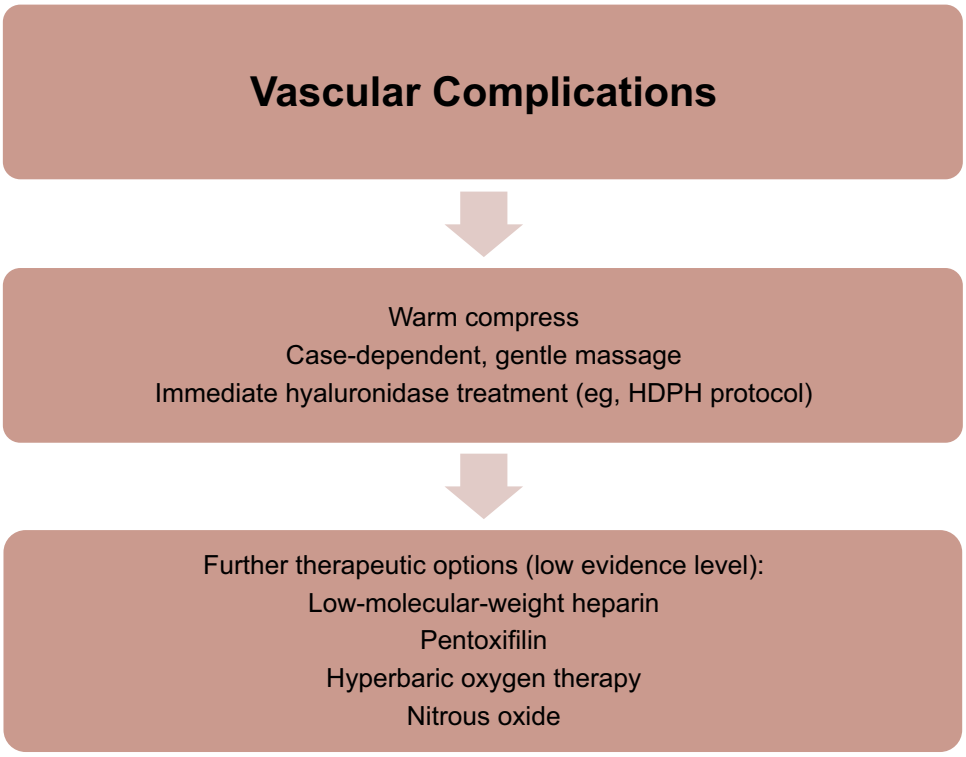

Figure 5 Management of localized vascular complications.[15,23,26]
Abbreviation: HDPH, high-dose pulsed hyaluronidase.

as an adjunctive treatment option with hyaluronidase for vascular occlusion[26]; however, nitrous oxide is contraindicated with the use of medications such as tadalafil and may cause AEs, including headaches. Sodium thiosulfate may also be used to dissolve CaHA; however, there is limited evidence to support this practice.[17]

New imaging modalities for treating vascular occlusions include high-frequency Doppler ultrasonography.[27] This modality can be used for mapping ischemic zones caused by HA, determining the quantity of HA to guide HDPH treatment protocols, and providing image-based guidance for injections of hyaluronidase to treat obstructed vessels. However, this method should be performed by experienced practitioners who are trained to use and interpret ultrasonography.[27]

Retinal Vascular Complications

Retinal vascular complications may result from vessel occlusion or vessel spasms due to increased inflammation induced by HA.[15,21,22] Retinal vascular complications are a relatively rare complication.[28] The risk of blindness and visual complications is higher when injecting fillers into specific regions of the face, including the temples, nasolabial folds, periorbital area, glabella, nose, and forehead.[29] Injecting HA-CaHA into the periocular and glabellar areas is contra-indicated, as documented in its instructions for use.

Although there are documented risks of visual impairment after injections with HA and CaHA products,[28] at the time of this writing, no such complications related to vision loss have been reported for HA-CaHA. The risk of vascular complications with HA-CaHA is low because most physicians do not use the product (on-label) in high-risk areas except for the temples. Acute treatment algorithms for retinal vascular complications, including retrobulbar hyaluronidase treatment, have been published previously[15,21,22]; however, this treatment is not generally recommended because the level of evidence is low and may further harm the patient's eyes. A comprehensive and individualized risk-benefit assessment is paramount, and the procedure should only be reserved for selected cases and performed by an experienced ophthalmologist or oculoplastic surgeon.

Clinical Opinions and Best Practices for Injection Techniques

Best practices for optimal facial filler injection techniques have been published previously,[13,14] and specific recommendations are highlighted in Table 1. Injection-site protocols have been developed for clinicians (Figure 6).[30] These protocols are based on the published MD Codes™ methodology, a system developed to provide specific anatomic sites and procedures for the injection of HA fillers (Figure 6A).[31] Entry points located in the jowl, jaw angle, jaw ramus, and cheek (ck) can be utilized to achieve full coverage of different treatment areas. HA-CaHA treatment sites using the C approach include the zygomatic arch, jaw ramus, and jawline (jw) (Figure 6B). For patients who may benefit from additional treatment in the prejowl sulcus and submalar area (C-plus approach), the jowl entry point can be utilized to reach these new treatment areas (Figure 6C). An additional jw entry point that covers jw1, jw3, and jw4 may also create an upward pulling effect based on integrity of the superficial fat compartments and not the mandibular ligament or heavy tissue. Additional injections in the ck, specifically upward toward ck1, ck2, ck3, and ck4 and injections toward ck2 and ck5, may allow for crossing of the mandibular ligaments in a superficial plane, thus achieving lift (Figure 6D). The jawline angle injection point may be challenging for anyone using a 50-mm cannula and syringe because the patient's thorax may obstruct the way. HA-CaHA is injected in the subcutaneous plane using a retrograde fanning technique with a 22-G cannula that is 50 or 70 mm long.

An anterograde technique may also be used to account for the effect of lidocaine; however, this technique can be challenging because of the risk of unintentionally pushing the product to accumulate at the end of the cannula and creating an undesired bolus. The tip of the cannula could penetrate a vessel and provoke an occlusion. Although existing protocols vary in terms of indications, injection points, and techniques, there is more than 1 approach to injecting HA-CaHA to generate the same desired aesthetic effects.

Table 1 Best Practices for Optimal HA-CaHA Injection techniques[13,14]

Preinjection
Keep the needle/cannula sterile
Thoroughly clean the skin on the injection site (even a second time just before injecting) using a disinfection agent. Some experts prefer an alcohol with a quaternary ammonium agent (eg, propanol plus benzalkonium chloride)
Clearly mark the facial areas to be treated
During Injection
Inject slowly using low pressure
Avoid injecting large volumes/boluses
Inject in the superficial plane, avoiding the zygomatic bone and deeper structures such as blood vessels and the parotid gland
Inject HA-CaHA preferably in the subcutaneous plane within the limit of the reticular dermis and subcutaneous cellular fat tissue
Use a retrograde fanning technique with a 22-G cannula 50 or 70 mm long; an anterograde technique may also be used, but there is a risk of unintentionally pushing the product to accumulate at the end of the cannula
Avoid folding the skin to introduce the cannula; instead, locate the appropriate layer, and stretch the skin in the same direction of the cannula
For the jawline angle injection point, clinicians may have to bend the cannula to avoid the patient's thorax, which may be obstructing the injection site.
Injecting forward while standing beside or behind a patient and upward while standing in front of the patient
After injection, gently massage the treated area to ensure even distribution of the gel
Consider the injection area and the 9 muscles in the submalar area that may displace the injected product; overcorrections with HA-CaHA have been frequently observed in this region

Abbreviation: HA-CaHA, hyaluronic acid-calcium hydroxyapatite.

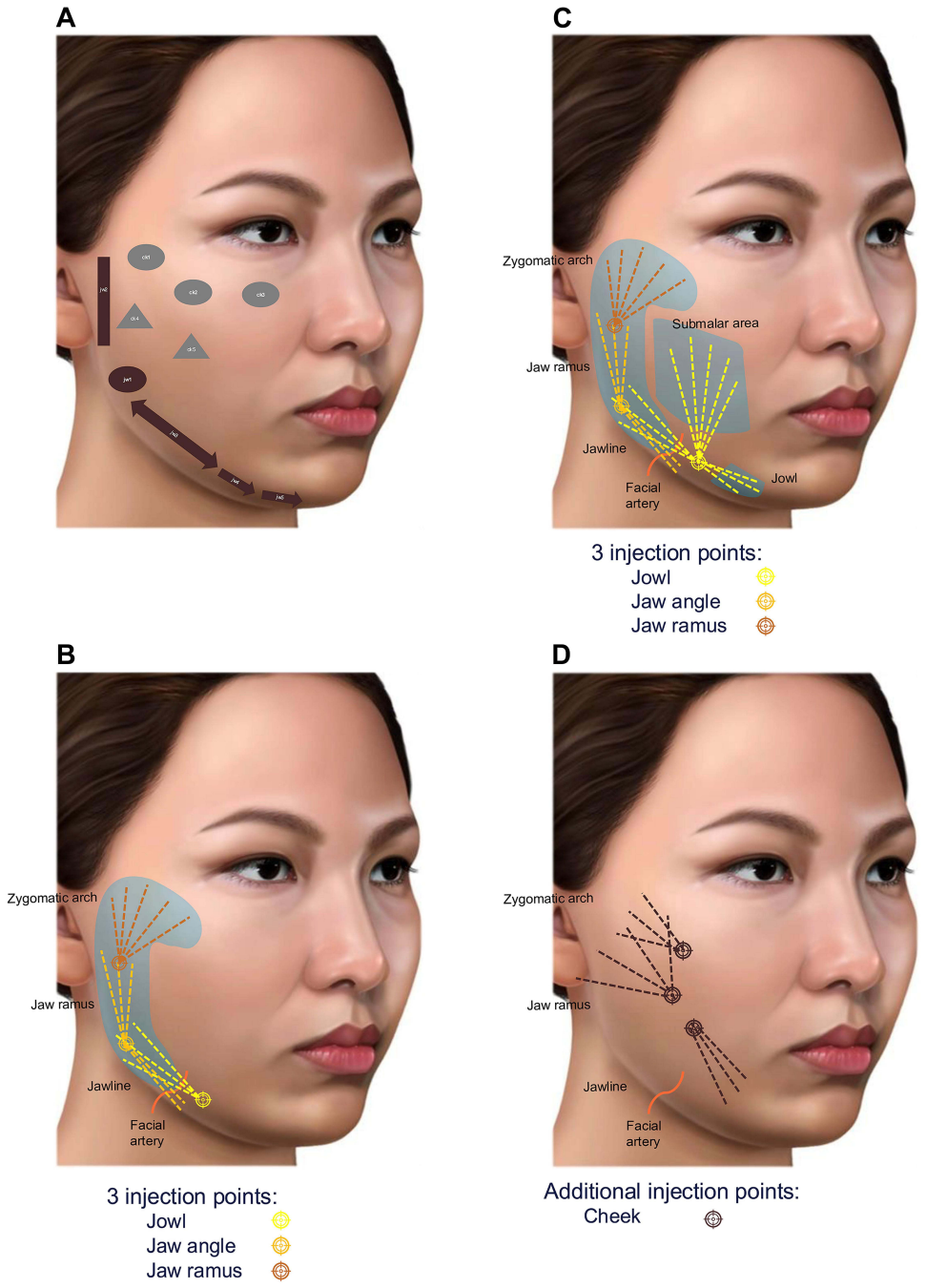

Figure 6 (**A**) MD Codes anatomical associations, which are relevant to hyaluronic acid–calcium hydroxyapatite (HA-CaHA) treatment sites: ck, cheek; ck1, zygomatic arch; ck2, zygomatic eminence; ck3, anteromedial cheek; ck4, lateral lower cheek/parotid area; ck5, submalar/buccal area. jw, jowl; jw1, mandible angle; jw2, pre-auricular area; jw3, mandible body; jw4, lower prejowl; jw5, lower anterior chin. Adapted from De Maio 2021.[31] Recommended HA-CaHA injection-site protocols: (**B**) the C approach, which includes the zygomatic arch, jaw ramus, and jawline; (**C**) the C-plus approach, which includes the aforementioned areas plus the submalar area and jowl; and (**D**) additional sites in the ck can be injected with HA-CaHA to achieve more lift.

Conclusion

Properly managing skin discoloration, edema, late noninflammatory adverse reactions, and late inflammatory adverse reactions, as well as localized and retinal vascular complications, resulting from HA-CaHA can help optimize patient outcomes and safety. Injection-technique protocols and product indications should be continuously developed and optimized. It is essential to consider clinical outcomes from all aspects of the patient–doctor–product triangle. The considerations

presented here are based on best practices, and although data were from a small sample size, these recommendations may serve as a reference for the broad range of clinicians using HA-CaHA for different on-label indications.

Author Roles

All authors have made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; have been involved in drafting the manuscript or revising it critically for important intellectual content; and have given final approval of the version to be published. Each author has participated sufficiently in the work to take public responsibility for appropriate portions of the content and have agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data Sharing Statement

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual, and trial-level data (analysis data sets), as well as other information (eg, protocols, clinical study reports, or analysis plans), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent, scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP), and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time after approval in the US and Europe and after acceptance of this manuscript for publication. The data will be accessible for 12 months, with possible extensions considered. For more information on the process or to submit a request, visit the following link: https://vivli.org/ourmember/abbvie/ then select "Home."

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Ethics Statement

All patients shown in photographs in this article provided informed consent for their photographs to be used in medical publications. Ethical approval was not required as this was a noninterventional study.

Disclosure

Wolfgang G. Philipp-Dormston is a consultant, key opinion leader, and ad board speaker for AbbVie and a recipient of honoraria and grants for speaking and clinical trial commitments. Koenraad De Boulle is a consultant, key opinion leader, and ad board speaker for AbbVie and a recipient of honoraria and grants. David B. Eccleston is a consultant, key opinion leader, and ad board speaker for AbbVie and a recipient of honoraria and grants for speaking and clinical trial commitments. Rachna Murthy is a consultant, key opinion leader, and ad board speaker for AbbVie and a recipient of honoraria and grants. Karim Sayed is a consultant, key opinion leader, and ad board speaker for AbbVie and a recipient of honoraria. Philippe Snozzi is a consultant and ad board speaker for AbbVie and a recipient of honoraria. Fernando Urdiales-Galvez is a consultant, key opinion leader, and ad board speaker for AbbVie. The authors report no other conflict of interest in this work.

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