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Response of 21 Hyaluronic Acid Fillers to Recombinant Human Hyaluronidase

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Background: One benefit of hyaluronic acid fillers is the ability to dissolve them using hyaluronidase. With the increasing number of fillers entering the market, it is crucial to understand each of these fillers' responsiveness to hyaluronidase.

Methods: Twenty-one hyaluronic acid fillers of 0.2 mL aliquots each were placed on slides. Twenty units of recombinant human hyaluronidase were injected into the aliquots every 30 minutes for a total of 120 units recombinant human hyaluronidase injected over 3 hours. With each injection, videos and photographs were taken from bird's eye and lateral views to measure aliquot height. Stirring videos were graded by three oculoplastic surgeons, and these grades were used to categorize each filler's responsiveness.

Results: Restylane Lyft, Restylane-L/Eyelight, and Resilient Hyaluronic Acid (RHA) 1/Redensity were the least resistant. The moderately resistant group comprised of Restylane Silk, Juvéderm Volbella, Revanesse Versa/Lips, and Belotero Balance on the less resistant side to Juvéderm Vollure, RHA 2, Restylane Contour, Juvéderm Ultra, Restylane Refyne, Belotero Intense, Restylane Kysse, RHA 3, Juvéderm Ultra Plus, and Restylane Defyne on the more resistant side. The most resistant were RHA 4, Juvéderm Voluma, Belotero Volume, and Juvéderm Volux. The most resistant fillers required 120 units of hyaluronidase per 0.2 mL filler to dissolve.

Conclusions: With the increasing popularity of fillers comes the increasing need to dissolve them for both ischemic and nonischemic complications. The majority of hyaluronic acid fillers available on the market are very resistant to hyaluronidase, which must be considered when determining the amount of hyaluronidase to dissolve a particular filler. *(Plast Reconstr Surg Glob Open 2023; 11:e5457; doi: 10.1097/GOX.0000000000005457; Published online 22 December 2023.)*

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INTRODUCTION

Hyaluronic acid (HA) fillers are the most commonly used soft tissue fillers and are used for both aesthetic and clinical purposes.[1] When compared with other fillers such as calcium hydroxylapatite, polymethylmethacrylate, and poly-L-lactic acid fillers, the reversibility of HA fillers through hyaluronidase, which breaks down HA, a glycosaminoglycan, into monosaccharides, is a distinct advantage.[2,3] Hyaluronidase is used for both dangerous complications of HA filler (such as ischemia and acute infection) as well as less-acute complications like discoloration, hypersensitivity reactions, nodules, biofilms, granulomas, and overfilling.[4]

There are many HA fillers to choose from, all with differing parameters, including the elastic modulus (G'), viscous modulus (G"), cohesivity, particle size, HA concentration, and degree of crosslinking. These properties

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contribute to how a certain filler may be better suited for certain procedures or skin types, how it reacts to mechanical stress once in the body, and how it dissolves in response to hyaluronidase.

To help clinicians make informed decisions on when and how to use the various fillers available on the market, much research on the rheology of these fillers has been conducted. The most commonly used metric for characterizing HA fillers is with G', or the elastic modulus.[5] This is because G' accounts for multiple important factors, including HA concentration and degree of crosslinking, with increasing crosslinking and HA concentration in turn elevating G'.[5,6] Fillers with lower G' tend to be "softer," and vice versa.[6,7] However, G' is not a perfect metric. One study found that for a single filler, differences in measured G' could range from 1.6 to 7.4 times in value due to differing experimental settings across studies.[8]

Because of the inherent discrepancies in rheological measurements, in vitro and in vivo observations are helpful for visualizing the differences between various fillers, particularly with their responsiveness to hyaluronidase. We began this process with an in vivo study comparing Restylane-L, Juvéderm Ultra XC, and Juvéderm Voluma, and then conducted further in vitro studies to extrapolate the in vivo results to more fillers.[9,10] We found that the amount of hyaluronidase necessary to dissolve the HA gels corresponded in the in vivo and in vitro studies. For example, Restylane-L started dissolving with very low amounts of hyaluronidase (2.5 units/0.2 mL of filler), whereas Juvéderm Voluma required at least 20 units per 0.2 mL in both studies.[9,10]

Because most of the fillers were not dissolved with 20 units per 0.2 mL of filler, this study sought to titrate up to see how much hyaluronidase may be ultimately needed for the vast majority of fillers which are more resistant. We directly compare hyaluronidase responsivity of 21 HA fillers, including all United States Food and Drug Administration (FDA)–approved fillers as well as several of which are not yet available on the United States market, in an in vitro setting. To our knowledge, there are no other studies that have included this many fillers for comparison.

Takeaways

Question: How resistant to dissolution are the hyaluronic acid fillers currently on the market when necessary to treat ischemic and non-ischemic complications?

Findings: Twenty-one hyaluronic acid fillers of 0.2 mL aliquots each were placed on slides. Twenty units of recombinant human hyaluronidase was injected every 30 minutes for a total of 120 units. Videos taken while stirring the fillers were graded and used to categorize each filler's responsiveness. Restylane Lyft, Restylane-L/Eyelight, and RHA 1/Redensity were the least resistant fillers. The most resistant were RHA 4, Juvéderm Voluma, Belotero Volume, and Juvéderm Volux, requiring 120 units of recombinant human hyaluronidase to dissolve.

Meaning: There is a wide range of susceptibility to dissolution by hyaluronidase, with the majority of hyaluronic acid fillers being highly resistant.

MATERIALS AND METHODS

We examined the response of 21 HA fillers to recombinant human hyaluronidase (RHH). The HA gels used were Belotero Balance (CPMBB; Merz Aesthetics, Frankfurt, Germany), Belotero Intense (CPMBI; Merz Aesthetics, Frankfurt, Germany), Belotero Volume (CPMBV; Merz Aesthetics, Frankfurt, Germany), Juvéderm Ultra XC (Hylacross XC; Allergan, Dublin, Ireland), Juvéderm Ultra Plus XC (Hylacross XC plus; Allergan, Dublin, Ireland), Juvéderm Volbella (VYC-15L; Allergan, Dublin, Ireland), Juvéderm Vollure (also known as Volift) (VYC-17.5L; Allergan, Dublin, Ireland), Juvéderm Voluma (VYC-20L; Allergan, Dublin, Ireland), Juvéderm Volux (VYC-25L; Allergan, Dublin, Ireland), Restylane Lyft (NASHLyf; Galderma, Lausanne, Switzerland), Restylane-L/Eyelight (NASHR; Galderma, Lausanne, Switzerland), Restylane Silk (NASHSyl; Galderma, Lausanne, Switzerland), Restylane Refyne (XpresRR; Galderma, Lausanne, Switzerland), Restylane Defyne (XpresRD; Galderma, Lausanne, Switzerland), Restylane Contour (XpresRC; Galderma, Lausanne, Switzerland), Restylane Kysse (XpresRK; Galderma, Lausanne, Switzerland), Revanesse Versa/Lips (TMB; Prollenium Medical Technologies, Toronto, Canada), Resilient Hyaluronic Acid (RHA) 1/Redensity (RHAT1; Teoxane, Geneva, Switzerland), RHA2 (Teoxane, Geneva, Switzerland), RHA3 (Teoxane, Geneva, Switzerland), and RHA4 (Teoxane, Geneva, Switzerland). The hyaluronidase used was the recombinant human hyaluronidase Hylenex (Halozyme Therapeutics, San Diego, Calif.). Although there are four commercially available hyaluronidase products in the United States, we chose to use Hylenex as it is preferred clinically due to its lower immunogenicity risk profile.

An estimated 0.2 mL aliquots of each filler were placed on microscope slides with standardized barriers (2.0 cm × 2.5 cm) created using hardened liquid plastic (Bondic, Aurora, Canada). Twenty units of RHH standardized to 0.15 mL of volume using saline were injected into the center of the filler aliquot every 30 minutes for a total of six injections, or 120 total units of RHH. Standardized photographs were taken before any injections to obtain starting height. With each subsequent injection, photographs were taken immediately postinjection, 5 minutes postinjection, 15 minutes postinjection, and 30 minutes postinjection. Photographs were taken with standardized lighting against a black background from bird's eye and lateral views with a ruler to measure height of the filler aliquots. Additionally, the filler aliquots were stirred and videographed for 10 seconds with injections 5 and 6 at the immediate postinjection and 30 minute time points. The gel aliquots were left for an additional 6 hours for a total of 9 hours from the first injection, at which point they were stirred, videographed, and photographed for the final time. We repeated the experiment using saline instead of RHH to serve as the control group. Both the RHH and saline experiments were repeated in triplicate.

Stirring videos were anonymized and graded by three expert oculoplastic surgeons using a standardized four-point reference scale with video examples that we

developed: 3, gel aliquot mostly intact while stirring; 2, gel aliquot diminished or breaking up while stirring; 1, gel aliquot mostly dissolved when stirring; 0, no gel aliquot visible when stirring. [**See Video 1 (online),** which displays the grading scale used to grade filler dissolution (3, gel aliquot mostly intact while stirring; 2, gel aliquot diminished or breaking up while stirring; 1, gel aliquot mostly dissolved when stirring; 0, no gel aliquot visible when stirring)]. Each filler was graded at two timepoints: at 2.5 hours with a total of 100 units RHH (immediately after injection 5) and at 3 hours with a total of 120 units RHH (30 minutes after injection 6) for all three runs.

The height measurements of the fillers were graphed as percentages of their starting preinjection heights. Video dissolution grades were averaged and graphed with standard error. All data analyses and graphs included were executed using Stata version 16.1 (StataCorp LLC, Lake Station, Tex.) or Microsoft Excel 2022 (Microsoft Corporation, Wa.).

This retrospective study adhered to the tenets of the Declaration of Helsinki and was approved by the institutional review board of the University of Southern California.

RESULTS

Figure 1 displays dissolution grades for all fillers. The intraclass correlation coefficient for the grades was 0.921. Restylane Lyft, Restylane-L/Eyelight, and RHA 1/Redensity received dissolution grades of 0.11 or lower and thus were classified as the least resistant. Restylane Silk, Juvéderm Volbella, Revanesse Versa/Lips, Restylane Silk, and Belotero Balance received dissolution grades between 0.44 and 1.1. Belotero Intense, Belotero Volume, Juvéderm Ultra XC, Juvéderm Ultra Plus XC, Juvéderm Vollure, Restylane Contour, Restylane Defyne, Restylane Kysse, Restylane Refyne, RHA 2, and RHA 3 received dissolution grades from 1.3 to 2.0. RHA 4, Juvéderm Voluma, Belotero Volume, and Juvéderm Volux were close to 2.0 and above and were clearly the most resistant. These last two groups of fillers were still not completely dissolved at the 3-hour time point, at which a total of 120 units RHH had been injected. All fillers were dissolved by the nine hour time point. [**See Video 2 (online),** which displays the fillers being stirred immediately after injection 5 (after 2 hours with a total of 100 units RHH) and at 30 minutes after injection 6 (after 3 hours with a total of 120 units RHH)]. Saline controls were performed for all fillers in triplicate as well. None were dissolved even at the final time point of nine hours in contrast to the hyaluronidase trials.

Figure 2 shows trends in height of selection of fillers over the course of 9 hours. The fillers that lost less than 25% of height at the one hour time point included Juvéderm Vollure, Juvéderm Voluma, Juvéderm Volux, Juvéderm Ultra XC, Juvéderm Ultra Plus XC, and RHA 3 (Fig. 2). The fillers that lost more than 50% of their original height were Belotero Balance, RHA 1/Redensity, Restylane Silk, Restylane Lyft, and Restylane-L/Eyelight.

Controls using saline in the place of RHH demonstrated loss of height in similar patterns to that of their RHH counterparts, though to a lesser extent. Although height did sometimes increase after multiple injections of RHH in the experimental group due to the increase in overall volume, the overall trend in height was typically downward. However, with the saline controls, height

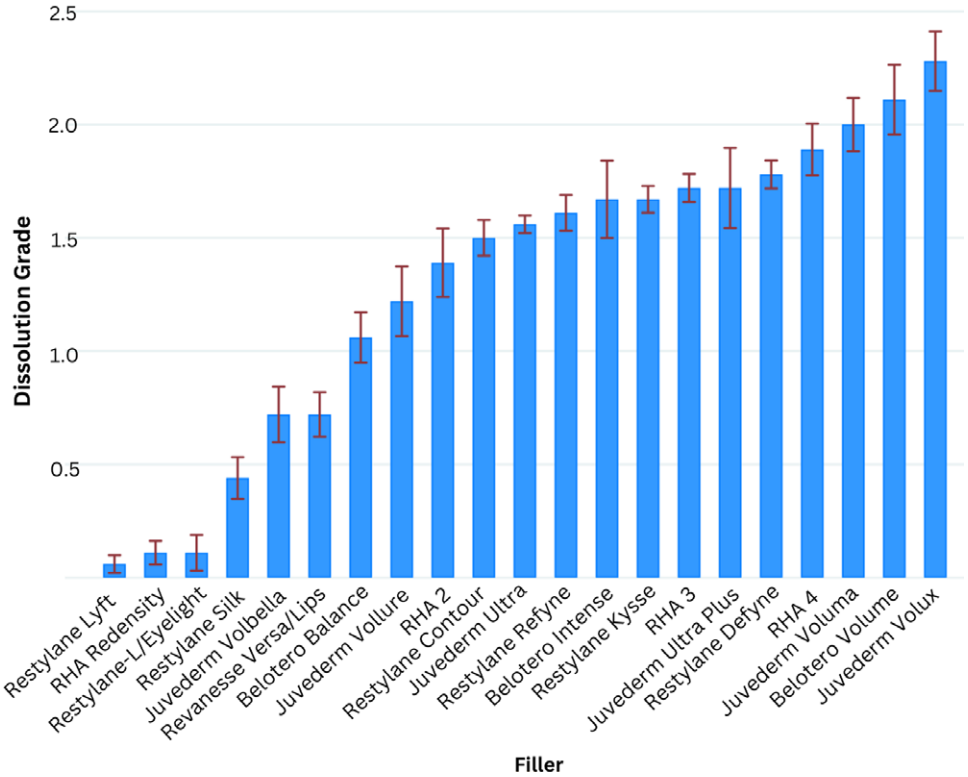

Fig. 1. A chart that displays average dissolution grades with standard error.

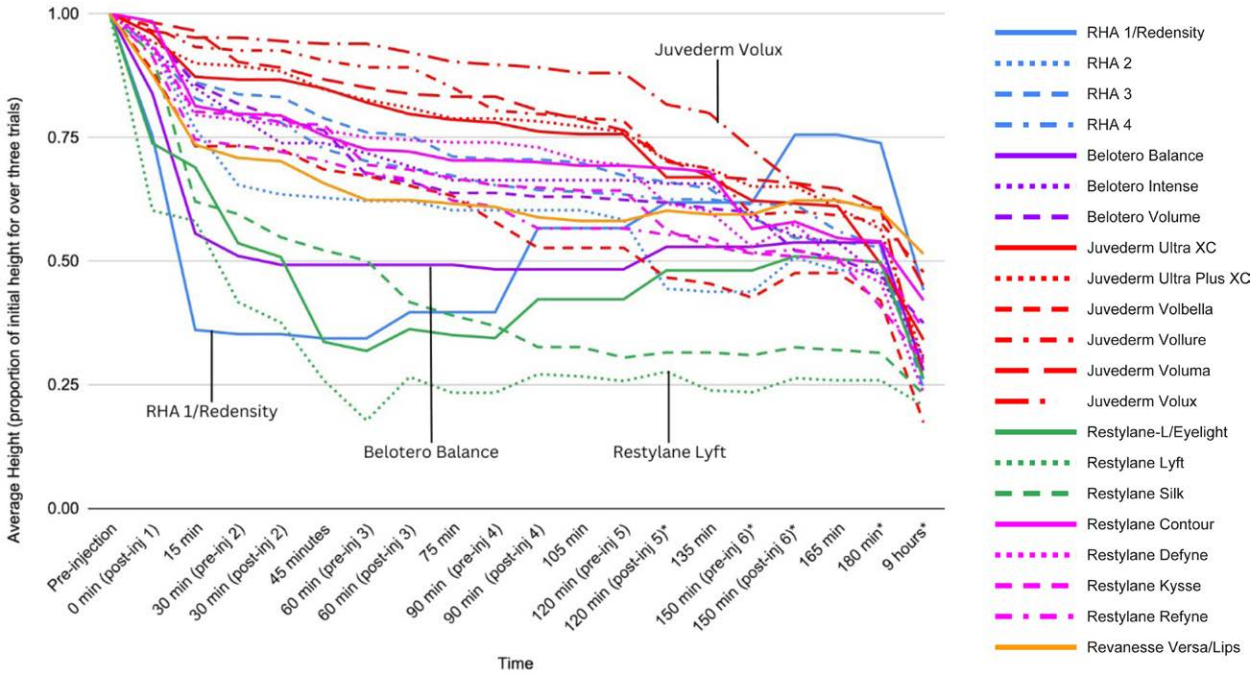

Fig. 2. A graph that shows height of all fillers over 9 hours in response to six progressive 20-unit injections of RHH displayed as proportion of preinjection height. *Indicates that the aliquot was stirred at this timepoint.

increased over time in more than half of the fillers. All saline control fillers were undissolved nine hours after starting the experiment.

Finally, photographs of the fillers from both the bird's eye and lateral views were compiled to help show variations in rates of dissolution over time. A selection of widely used fillers can be seen in Figure 3, and all fillers can be seen in the Supplemental Digital Content. (**See figure, Supplemental Digital Content 1**. Photographs of fillers from bird's eye and lateral views showing appearance and height of filler aliquots at various time points. Each row represents one filler aliquot over time with subsequent additions of recombinant human hyaluronidase. **http://links.lww.com/PRSGO/C921**.)

DISCUSSION

Although knowing the rheology of fillers is helpful for theoretically predicting how they may behave in the clinical setting when exposed to hyaluronidase, it is nevertheless important to also study them in practice. This is further made necessary, as filler manufacturing companies do not provide clinical guidance on the methods or amounts of hyaluronidase necessary to reverse effects, likely because filler dissolution is not an FDA-approved indication for hyaluronidase.

For our study, it was helpful to examine the various fillers' dissolvability in conjunction with their crosslinking technology. As crosslinking is the basis for the mechanical strength of a gel, it is not surprising that fillers of the same crosslinking technology would have similar dissolvability.[5] For example, RHA 2, RHA 3, and RHA 4, which are formulated with RHA crosslinking technology, all exhibited low dissolvability. At the other end of the spectrum, Restylane Lyft and Restylane-L/Eyelight (nonanimal stabilized HA, or NASHA, crosslinking technology) were the most dissolvable fillers by a large margin. There are certainly still differences in the dissolvability of fillers of the same crosslinking technology, as each has other unique rheological properties. XpresHAn fillers (Restylane Kysse, Defyne, Refyne, Contour) have varying degrees of crosslinking and gel extrusion screen size; Hylacross fillers (Juvéderm Ultra XC and Ultra Plus XC) have differing crosslinking percentages; and Vycross fillers (Juvéderm Voluma, Vollure, Volbella, and Volux) have differing hyaluronic acid concentration.[11]

Varied degrees of modification and/or crosslinking, particle size, and HA concentration within the same technology will affect aspects of the microscale interactions of hyaluronidase molecules with the hydrogel framework, which further contributes to dissolvability differences. For example, Restylane Silk (50–220 μm), Restylane-L/Eyelight (330–430 μm), and Restylane Lyft (750–1000 μm) dissolved slightly differently despite their same crosslinking (~1%) due to their differing particle sizes, with Restylane Silk being surprisingly less dissolvable and Restylane Lyft being most dissolvable. Additionally, while Restylane Kysse and Restylane Contour have the same degree of crosslinking (7%), the large size structures of Restylane Contour dissolved more easily than the smaller size structures of Restylane Kysse. This may be due to larger particle sizes exposing a larger total surface area to hyaluronidase and allowing for easier dissolution.

Higher HA concentration, higher degree of crosslinking, and less free hyaluronic acid are all associated with

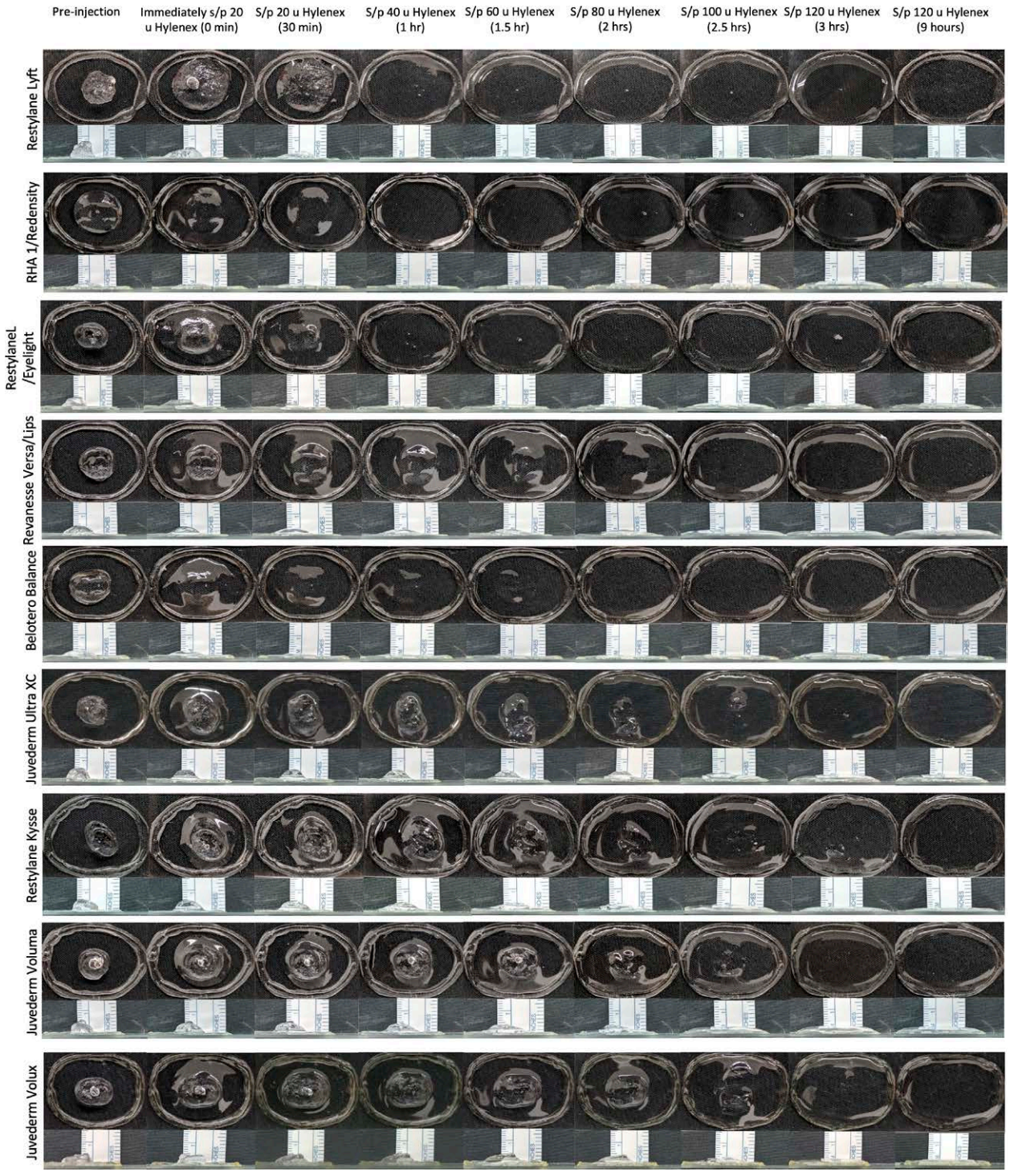

Fig. 3. Bird's-eye and lateral views of selected filler photographs showing appearance and height of filler aliquots at various time points. Each row represents one filler aliquot over time with subsequent additions of RHH. The full photograph compilation can be found in the supplemental digital content (**see figure, Supplemental Digital Content 1**, **http://links.lww.com/PRSGO/C921**).

greater resistance to dissolution by RHH.[11] For example, Restylane products, with their higher amounts of free hyaluronic acid, tend to be less resistant to hyaluronidase than fillers with less free hyaluronic acid such as the Juvéderm products—something our findings supported (Fig. 1).

Generally, the results of our study correspond with both our own and others' in vitro and in vivo studies.[9,10,12,13] Our previous in vivo study found Restylane-L/Eyelight to be most dissolvable, Juvéderm Ultra to be moderately resistant, and Juvéderm Voluma to be the most resistant.[9]

The ensuing in vitro studies, including this study, are consistent with the original in vivo findings.[9,10,14] Therefore, these in vitro results may be considered a reliable extrapolation of our previous studies. Some differences from our prior study may be noted due to differences in methodology; our earlier studies examined the effect of a single injection of smaller amounts of RHH (up to 40 units total) over time, with none of the resistant fillers fully dissolving by the end of the experiment.[10,14] Even with the increase in the amount of RHH used to 120 units in this study in light of our prior one, we found that with the exception of Restylane-L/Eyelight, Restylane Lyft, Restylane Silk, and RHA 1/Redensity, all the fillers required a minimum of 120 units RHH to dissolve. Of note, Belotero Intense and Belotero Volume, both of which are not yet FDA-approved in the United States, were also found to be very resistant to hyaluronidase. Of the recently approved fillers, RHA 1/Redensity was found to be very responsive, whereas Juvéderm Volux was found to be extremely resistant.

All fillers were dissolved by the 9-hour time point, suggesting that in addition to the amount of hyaluronidase itself, allowing adequate time for it to take effect is crucial. Our in vivo study showed that the most dramatic degradation occurred between 30 minutes and 3 hours, with gradual degradation through day 1, slight degradation through weeks 1 and 2, followed by continual degradation.[9] In contrast, one mouse-model study evaluating the optimal time to reinject HA filler after dissolution found that hyaluronidase had an effect for approximately 3–6 hours after subcutaneous injection. However, the study used 600 units of hyaluronidase as well as a filler and hyaluronidase not commercially available in the United States.[15]

We were also interested in seeing whether filler height loss over time would be correlated with dissolvability, which it generally was. For example, Restylane Lyft and Restylane-L/Eyelight, which were the most quickly dissolved, also lost the most height by a large margin (Fig. 2). However, height decrease was not an adequate proxy for dissolvability. For example, although Belotero Balance displayed rapid height loss, it was moderately resistant to RHH. Some fillers eventually began to gain height as more volume was added with each injection; most notably affected was RHA 1/Redensity, which dissolved so quickly that its height was determined by the volume of liquid rather than the filler aliquot.

The discrepancies seen between dissolution and filler height loss may be attributed to the different rheological principles that determine these properties—namely, cohesivity, which is determined by the weak interactions between cross-links in the filler and ultimately creates adhesion.[16] Cohesivity allows fillers to maintain vertical projection and their initial shape while under stress and compression.[16] However, cohesivity is still not well understood. Although Pierre et al and de la Guardia et al hypothesize that low cohesivity fillers are the most spreadable and moldable, Fagien et al suggest that it is in fact high cohesivity gels that hold these same properties.[5,6,16] Even in our own study, it is clear that cohesivity alone cannot explain why some fillers were more resistant to height decrease than others. We found Restylane Lyft, Restylane-L/Eyelight, and Belotero Balance to have the greatest initial height decrease. However, these fillers have very different cohesive properties. Studies have found Belotero Balance to be the most cohesive filler both under light microscopy and when placed into saline, where it was the only filler to remain in a single, continuous strand.[17,18] The same studies found that Restylane, which is the same formulation as Restylane-L/Eyelight without lidocaine, disintegrated most readily into discrete particles when placed in saline, indicating it to be a particularly noncohesive filler.

It is important to keep in mind that each filler will require different amounts of hyaluronidase for partial or complete dissolution. In nonischemic complications, when partial dissolution may be desired, one can start with a smaller amount of hyaluronidase.[19] Our past in vivo study found that Restylane-L/Eyelight started to dissolve with just 2.5 units RHH per 0.2 mL, Juvéderm Ultra XC with 5–10 units RHH per 0.2 mL, and Juvéderm Voluma with greater than 20 units RHH per 0.2 mL.[9]

For ischemic complications, large amounts of hyaluronidase will be necessary. Our findings show that the majority of fillers available on the market today are very resistant to hyaluronidase, with more than half of the fillers requiring at least 120 units of RHH to completely dissolve. Regardless of how low crosslinking percentages or HA concentrations may be, modern formulations and technology have made these fillers very durable (Table 1). To obtain faster results (or even in the case of emergencies like vision loss), it may be wise to use larger concentrations of RHH with highly resistant fillers versus with highly dissolvable fillers like Restylane-L/Eyelight, Restylane Lyft, and RHA 1/Redensity. Additionally, it may be prudent to consider use of more dissolvable fillers in vascularized areas that are prone to vascular complications, such as the glabellar or nasal regions, as well as in less forgiving areas such as the under-eye region. One must also keep in mind that if an injection becomes intravascular, the embolus would be a mix between the HA gel and an additional thrombus that would form due to obstruction by the HA gel. Thus, reversing ischemia is not as straightforward as one would hope. It would likely be prudent to emergently send a patient with blindness to a stroke hospital for emergent ophthalmology evaluation and central retinal artery obstruction treatment. It should also be noted that fillers such as Belotero Balance may flatten easily and thus seem to be dissolving with small amounts of hyaluronidase, but in reality require larger amounts of hyaluronidase or repeated injections to fully dissolve.[10]

For nonischemic complications, one should also consider the risks associated with excessive use of hyaluronidase in these reversals. One theoretical risk is that the naturally-present HA in the skin may be depleted with larger amounts of hyaluronidase, a phenomenon that although not reported in the literature yet, has been described clinically by multiple injectors. In terms of allergic reaction, experiments using up to 300 units of hyaluronidase have reported only mild allergic reactions such as swelling, pain, and itching with an incidence rate of less than 0.69%.[3] However, one study using systemic injections of 200,000 units as a part of cancer treatment did cause

Table 1. Filler Properties

Filler	Crosslinking Technology*	Concentration HA (mg/mL)*	Percentage Crosslinking (%)[20]†	G'[5]‡
RHA 1/Redensity	Preserved network technology	15	1.9[7]	48
RHA 2	Preserved network technology	23	3	144
RHA 3	Preserved network technology	23	3.5	184
RHA 4	Preserved network technology	23	4	296
Belotero Balance	Cohesive polydensified matrix	22.5	3.57[21]	49.9[21]
Belotero Intense	Cohesive polydensified matrix	25	1.06[21]	136.41[21]
Belotero Volume	Cohesive polydensified matrix	26	0.41[21]	233.5[21]
Juvéderm Ultra XC	HYLACROSS	24	6	76
Juvéderm Ultra Plus XC	HYLACROSS	24	8	148
Juvéderm Volbella	VYCROSS	15	Proprietary	159
Juvéderm Vollure/Volift	VYCROSS	17.5	Proprietary	273
Juvéderm Voluma	VYCROSS	20	Proprietary	307
Juvéderm Volux	VYCROSS	25	Proprietary	650
Restylane-L/Eyelight	Nonanimal stabilized hyaluronic acid	20	1.2	544
Restylane Lyft	Nonanimal stabilized hyaluronic acid	20	1.2	545
Restylane Silk	Nonanimal stabilized hyaluronic acid	20	1.2	344
Restylane Contour	XpressHAn	20	7	171[22]
Restylane Defyne	XpressHAn	20	8	260
Restylane Kysse	XpressHAn	20	7	156
Restylane Refyne	XpressHAn	20	6	47
Revanesse Versa/Lips	Thixofix technology	22-28	7	112[23]

*All information other than G' and crosslinking percentages were gathered from informational materials produced by the manufacturer or the United States FDA.
†All crosslinking percentages were obtained from Wu et al[24] unless indicated otherwise.
‡All G' values were obtained from Fagien et al[5] unless indicated otherwise.

anaphylaxis.[20] Although the amounts used in HA filler dissolution should be well under this threshold, allergic reactions should still be considered.

In conclusion, Restylane-L/Eyelight, Restylane Lyft, and RHA 1/Redensity were the least resistant to RHH. Fifteen of 24 fillers (Belotero Balance, Belotero Intense, Belotero Volume, Juvéderm Ultra XC, Juvéderm Ultra Plus XC, Juvéderm Vollure, Juvéderm Voluma, Juvéderm Volux, Restylane Contour, Restylane Defyne, Restylane Kysse, Restylane Refyne, RHA 2, RHA 3, and RHA 4) required more than 3 hours, with a total of 120 units of RHH to fully dissolve. Clinicians should be aware of these differences when reversing HA fillers, as well as of the generally resistant nature of many of the fillers on the market. In the future, we would like to explore other clinical applications such as whether multiple smaller doses of hyaluronidase or one larger dose is more effective for HA filler reversal and further discern more specific titrations of RHH needed for dissolution of each filler. We would also like to test more highly concentrated hyaluronidase, which is not currently available in the US market.

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DISCLOSURES

Dr. Woodward: Allergan (speaker and consultant), Galderma (speaker and consultant), Prollenium (speaker and consultant), Merz (speaker and consultant), SkinCenticals (consultant). Dr. Lee: Allergan, Galderma, Revance, Evolus, RoC, Tarsus, RVL, Horizon, NovaBay. Dr. Kherani: Abbvie, Horizon, Santen, SunPharma, Tarsus. Dr. Foster: Horizon, Tarsus. Dr. Zhang-Nunes: Horizon Therapeutics, Tarsus Pharmaceuticals, Bruder, Sciton. Drs. Park and Mehta have nothing to disclose.

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