Letters to the Editor

The New Face of Fillers: Why Evidence and Experience Both Count

To the Editor:

When the first hyaluronic acid (HA) soft tissue filler (Restylane, Medicis) was approved by the U.S. Food and Drug Administration almost eight years ago, our focus was on its greater longevity compared to the collagen fillers we had worked with previously. While filler longevity remains a priority for patients and clinicians alike, we could not have predicted then that Restylane and subsequently approved HA products including Juvéderm Ultra and Ultra Plus (Allergan) and Perlane (Medicis) would bring far more than this isolated clinical benefit and ultimately catalyze a paradigm shift in philosophy. We have evolved from wrinkle-chasing to pan-facial volumization as our palette of fillers has expanded to encompass not only a variety of HA products but also calcium hydroxylapatite, poly-L lactic acid and polymethyl methacrylate.

Our early concepts of how to achieve the best results with each filler product stemmed from a process of clinical observation and deduction that brings to mind Albert Einstein's aphorism that the only source of knowledge is experience. It was clinical experience, and the intellectual curiosity this engendered, that led us into the laboratory to explore the physicochemical characteristics of fillers—most notably, the rheologic (flow-related) properties of elasticity and viscosity. HA filler products have much in common, but it became apparent to those using them that they also manifest significant differences in behavior—for example, in their degree of firmness and how much they spread after implantation. The seminal paper that provided a rationale for these differences, by Kablik and Monheit,[1] included an engaging analysis of each product's insoluble and soluble HA concentrations, elastic modulus (G prime) and capacity to absorb water after implantation. Dr. Gary Monheit has subsequently championed the study of rheology and other physicochemical characteristics as the key to furthering our clinical understanding of HA fillers.

The paper that appears in this issue of the *Journal of Drugs in Dermatology*[2] confirms that the Restylane/Perlane and Juvéderm families of HA products differ in their rheologic properties of gel elasticity and viscosity. It also demonstrates that all these products have a particulate component and that there is variation in the range and distribution of particle sizes. An understanding of these differences (which are based upon manufacturing methods) and how they can predict the clinical behavior of HA fillers is the foundation of rheologic tailoring—the process by which specific products can be selected to most efficiently achieve specific clinical objectives during facial rejuvenation.

While the level of evidence of in vitro studies is currently classified as lower than that of controlled clinical trials, it is nonetheless essential to appreciate that in vitro data, with the appropriate clinical correlation, are the foundation of an evidence-based approach towards current filler products and can markedly shorten the learning curve with new products. I feel that it is equally important for us to acknowledge, as Einstein did, the value of experience. As we continue to refine our strategies for soft tissue augmentation, science will guide us clinically, but the knowledge derived from our clinical experiences can be of equal utility in guiding our further scientific investigations.

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Commentary: Rheological Evaluation of the Physical Properties of Hyaluronic Acid Dermal Fillers

To the Editor:

I would like to congratulate Mr. David Stocks, Dr. Sundaram, et al. for the excellent evaluation of rheology as a determinant of the physical properties of hyaluronic acid fillers. Though cross-linking is a major determinant in the physical characteristics of fillers, other factors include calibration—or, particle size—and concentration. These factors determine G' but also the unique characteristics found in the different manufactured hyaluronic acid fillers. An understanding of these properties allows us to choose the best particular filler for the clinical treatment site. Cross-linking and concentration can give us the stability and firmness of robust fillers for the tear trough or the softness and malleability best for the lips. The calibration or particle size can fulfill our need for deep lifting or volumizing. Understanding the physical parameters of each filler will help us use their differences for our clinical advantage in customizing our injection procedures.

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Doxycycline vs. Minocycline for the Management of Acne

To the Editor:

Approximately 40 years ago, immediate release (IR) tablet and capsulated delivery forms of minocycline and doxycycline were made available for prescription. These dosage forms resulted in a rapid release of drugs in the digestive tract and subsequently into the systemic circulation, with peak serum concentrations being reached several hours after administration. While the IR dosage forms are associated with certain adverse events (AEs), there are well-known methodological challenges in determining comparative rates, and even types, of AEs for drugs. Voluntary case reporting is non-systematic and is therefore limited in obvious ways, and AE reports from clinical trials suffer from variability of treatment protocols among agents studied, small numbers of participants, short duration of follow up and selective eligibility criteria for study populations. Nevertheless, clinical trial AEs are more systematically reported and are thought to be most useful in profiling the most common AEs. With respect to the IR formulations of doxycycline and minocycline, clinical trial estimates indicate the most common AEs are esophagitis and photosensitivity (doxycycline), gastrointestinal upsets (both drugs) and acute vestibular events (minocycline).[1]

The AE rates for both IR antibiotics are relatively low and each is well-tolerated.[1] Nevertheless, in the interests of improving safety and patient compliance, new extended release formulations of minocycline and doxycycline have been made available in recent years that moderate and better control the rate of dissolution and bioavailability, resulting in less gastrointestinal and vestibular disorders.[2-7]

In the recent publication by Kircik,[8] AEs observed for enteric-coated doxycycline are reviewed in conjunction with those observed for traditional IR dosage forms of minocycline and doxycycline. Additionally, comparisons of effectiveness are made for IR minocycline and doxycycline suggesting that there is no difference between the two drugs. With regard to published studies evaluating the effectiveness of these older formulations, the author addresses studies published between 1976 and 2005, which precedes the approval of extended release (ER) minocycline. Although the author briefly mentions ER minocycline (SOLODYN® (minocycline HCl, USP) Extended Release Tablets, Medicis, Scottsdale, AZ), which was introduced in 2006, his review neglected to include six important studies that were conducted for this FDA-approved dosage form.[3-5]

In the author's review, a number of non-comparative studies are referenced which consisted of variable patient counts and employed IR minocycline utilizing a variety of dosage strengths.[8,9] The author then highlights three studies conducted with head-to-head comparisons of doxycycline and IR minocycline. One comparison study occurred in a small number of patients (n=64) with a dosage regimen of 50 mg IR minocycline twice per day for four weeks and then once per day for the next eight weeks. Two additional studies involved a smaller number of patients (n=18 and 34, respectively), and in one of these studies patients used salicylic acid 5% and resorcinol 5% in addition to IR minocycline or doxycycline. Kircik concluded that IR formulations of doxycycline and minocycline do not differ in effectiveness on the basis of small studies that were severely underpowered for the purpose of showing equivalence with IR antibiotics. The author's conclusions are not supported by reliable statistical analysis. These comparisons did not contemplate ER formulations.

Extended release minocycline was the first systemic antibiotic approved by the U.S. Food and Drug Administration (FDA) for the treatment of only inflammatory lesions of non-nodular moderate-to-severe acne vulgaris in patients 12 years of age and older. Overlooked in this review were three prospective (one phase II and two phase III), multicenter, randomized, double-blinded, placebo-controlled clinical trials investigating the safety and effectiveness of ER minocycline in more than 1000 patients >12 years old with moderate-to-severe facial acne, as well as three bioavailability studies, all published in 2006.[3-5] In summary, these studies demonstrated that ER minocycline (a) moderates the rate of minocycline release and peak serum concentration compared to non-modified release minocycline,[3] (b) is not bioequivalent to non-modified release minocycline products,[3] (c) has an FDA approved dosage regimen of ~1 mg/kg once per day (which is lower than traditionally dosed IR minocycline at 100 mg twice daily),[4] (d) demonstrates a similar incidence of AEs when compared to placebo (ER minocycline 56.2%, placebo 54.1%), including those of a transient vestibular nature,[5] (e) is unaffected by foods or dairy intake[3] and (f) significantly reduced the percentage of inflammatory lesion counts in patients when compared to placebo treatment.[5]

When comparing products, it may be useful to the practicing clinician to include studies that lend themselves to rigorous meta-analysis standards, wherein results are combined from similar studies that meet accepted criteria such as comparable formulations, randomization, double-blindness and placebo-controlled trials with adequate numbers of patients, or in head-to-head clinical studies meeting these same guidelines. The studies cited in this review did not meet these criteria, and as of the day of this letter's composition no head-to-head study comparing minocycline (for either the IR and ER formulations) vs. doxycycline exists which meet these standards.

When prescribing an anti-acne medication, the clinician is likely confronted with two important questions: (1) the likelihood of his patient experiencing AEs and (2) the medication's known effectiveness for the condition being treated. A review that compares two different drugs for the same use would potentially be valuable to the clinician, provided a thorough and comprehensive review of the literature is conducted for both medications and differences with regard to formulations (e.g., immediate release vs. extended release) are identified in a consistent manner throughout.

Disclosures

Mitchell S. Wortzman, PhD, is Chief Scientific Officer of Medicis Pharmaceutical Company, Scottsdale, AZ and has stock options.

Alan R. Shalita, MD, is a consultant for Medicis, Allergan, DUSA, Johnson & Johnson, Galderma, Graceway, Quinova and Steifel (a GSK company). Guy F. Webster, MD, is a consultant for Medicis, Allergan, Galderma, Cutanea, GSK, Valocor, Tolmar, Vicept and Anterios. Diane B. Nelson, BSN, MPH, is an employee of Medicis Pharmaceutical Company, Scottsdale, AZ.

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Commentary: Doxycycline vs. Minocycline for the Management of Acne

I believe that the letter by Dr. Wortzman and his colleagues at Medicis was written in the spirit of constructive criticism and scientific debate.

The intent of my review article was not to advertise the "six important studies" of extended-release (ER) minocycline (SOLODYN® Medicis, Scottsdale, AZ), which is approved by the U.S. Food and Drug Administration (FDA)[2] solely for treatment of inflammatory lesions of non-nodular, moderate-to-severe acne vulgaris.

In those studies referenced by Wortzman et al., 17.3 percent and 15.9 percent of subjects in the SOLODYN group were "clear" or "almost clear" according to the Evaluators Global Severity Assessment versus 7.9 percent and 9.5 percent of subjects who were clear or almost clear in the placebo group.

Surprisingly, the authors of the letter made no mention of these results.

However, I do not disagree with Dr. Wortzman and colleagues as to the need for a head-to-head study comparing ER minocycline versus ER doxyclycline for the treatment of acne vulgaris.

Further, I wholeheartedly invite Medicis to initiate such a study, one that will meet the high standards and statistical power required by the letter's authors.

Disclosures

Dr. Leon H. Kircik has served as an investigator, speaker, consultant or advisory board member for Allergan, Amgen, Astellas Pharma US, Colbar, CollaGenex, Connetics Corporation, Ferndale Laboratories, Galderma, Genentech, Intendis, Johnson & Johnson, Leo Pharma, 3M, Nano Bio, Novartis AG, Onset Therapeutics, OrthoNeutrogene, Promius, PharmaDerm, SkinMedica, Stiefel, Valeant, Warner-Chilcott; a speaker for Abbott Laboratories, Dermik, Embil, Innovail, Merck Serono and Triax; an investigator for Acambis, Asubio, Bayer HealthCare, Biolife, Biopelle, Brekenridge Pharma, Centocor, Combinatrix, Coria, Dow Pharmaceutical Sciences, Dusa, GSK, Health Point, Medicis, Nucryst, Obagi, QLT, Quatrix, TolerRx and UCB; and as a consultant for Laboratory Skin Care, Medical International Technologies and ZAGE.

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