COVID-19 Pandemic Leading to the Accelerated Development of a Virtual Health Model for Isotretinoin

Sierra Kane and Shehla Admani

ABSTRACT: Isotretinoin is a highly efficacious medication for the treatment of acne vulgaris; however, its prescription is subject to the strict requirements of the iPLEDGE restricted distribution program. These requirements have placed significant financial, time, and logistical burdens on patients taking the medication. The stay-at-home ordinances enacted by many states during the 2019 novel coronavirus (COVID-19) global pandemic have accelerated previous trends toward utilization of telehealth and decreased laboratory monitoring in the care of patients on isotretinoin. Recent changes to the iPLEDGE program allowing use of at-home pregnancy tests to meet monthly pregnancy test requirements during the pandemic have increased availability of testing options for patients of childbearing potential on isotretinoin. The change to use of at-home pregnancy test monitoring as well as long-term trends toward increasing access to isotretinoin through the use of telehealth are discussed.

Key words: Isotretinoin, Acne, COVID-19 Pandemic, Stay-at-Home Ordinance, Telehealth

Oral isotretinoin is used for the treatment of acne vulgaris, most commonly for severe nodulocystic, scarring, or recalcitrant acne (Owen, 2019). Isotretinoin is effective in the treatment of acne, but concerns about its teratogenicity resulted in the formation of the iPLEDGE program in 2006 (Owen, 2019). The program, introduced by the U.S. Food and Drug Administration (FDA), is a restricted distribution program designed to prevent fetal exposure to isotretinoin (iPLEDGE, 2016). All prescribing physicians, dispensing pharmacies, drug manufacturers, and patients taking isotretinoin must comply with the requirements of the iPLEDGE program, which mandates the following:

- All patients of childbearing potential utilize two forms of birth control for at least 1 month before starting isotretinoin, during therapy, and for 1 month after therapy.
- All patients of childbearing potential have two negative urine or blood pregnancy tests before starting therapy.
- Each month of therapy and 1 month after completing therapy, patients of childbearing potential receive evaluation, counseling, education, and a pregnancy test conducted by a laboratory certified by Clinical Laboratory Improvement Amendments (CLIA).
- Prescribing physicians (or their office designees) complete and document patient counseling on the iPLEDGE website. This counseling must include knowledge of the birth defects that may result from the use of isotretinoin during pregnancy (iPLEDGE, 2016).

The iPLEDGE program requires that the prescriber ensure the patient receives monthly patient counseling on

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The authors declare no conflict of interest

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DOI: 10.1097/JDN.0000000000000595

medication side effects and pregnancy prevention but does not specify how or with whom this should be completed. The traditional interpretation has been that this should be completed in-clinic with the prescribing physician. However, offering this counseling via telehealth and/or with an advanced practice provider or registered nurse has the potential to make these counseling visits more convenient and accessible for patients. The key demographic age for isotretinoin patients is 15–25, although the number of patients > 30 years old receiving isotretinoin is increasing (Layton, 2009). The isotretinoin patient demographic is one that traditionally juggles work/school, childcare, and other responsibilities that may impede access to medical care—characteristics that result in a higher level of satisfaction with telehealth services (Polinski et al., 2015). These patients often find it easier to access medical visits remotely, meaning that increased access to telehealth options for isotretinoin patients has the potential to increase medication compliance and satisfaction with care.

PREPANDEMIC

Initial concerns about hyperlipidemia, liver abnormalities, and thrombocytopenia during isotretinoin therapy often led to regular laboratory monitoring of patient lipids, liver enzymes, and complete blood cell counts. However, reports over the last 20 years have questioned the utility of frequent laboratory monitoring, with the 2003 Global Alliance to Improve Outcomes in Acne even recommending that only baseline laboratory tests and a repeat set 1–2 months later be obtained for healthy patients without comorbidities (Barbieri et al., 2020). Abnormalities in lipids and liver enzymes, when seen during isotretinoin therapy, are often clinically insignificant and reversible once isotretinoin therapy is discontinued (Öktem et al., 2019). A retrospective review of electronic records for patients prescribed isotretinoin from 2008 to 2016 shows there has been a statistically significant decrease in the frequency of laboratory monitoring, with only 65.3% of patients receiving baseline triglyceride levels and 39% receiving follow-up triglyceride levels (Barbieri et al., 2020). Similar decreases have also been seen in liver enzyme monitoring without significant increases in reported adverse medication effects (Barbieri et al., 2020).

In addition to changes in laboratory monitoring, advances in telemedicine and increasing acceptance of telehealth as a safe and efficient means for providing care have resulted in an increased number of isotretinoin follow-up appointments being offered through virtual platforms (Frühauf et al., 2014). Development of virtual symptom surveys offers remote follow-up options for patients. Symptom surveys ask patients to report on common side effects of isotretinoin, including dryness of the skin and mucous membranes, vision changes, headaches, abdominal pain, muscle or joint pain, bowel changes, and mood changes, including

depression or thoughts of suicide (Owen, 2019). Surveys also ask about the patient's perceived acne improvement and request attestations confirming the patient is utilizing two methods of birth control (for patients of child-bearing potential), agrees not to share the medication, and agrees not to donate blood during and for 1 month after therapy. Utilizing a store-and-forward telehealth system, patients complete the surveys and attestations and submit photos of the treatment area to their prescribing provider for review. For male patients who do not require pregnancy tests, this serves as a reliable method for meeting the iPLEDGE requirements and significantly reduces the burden of follow-up visits caused by missed work/school and cost of transportation to and from visits. The follow-up burden has not been well quantified in the literature, but some estimates for pediatric patients indicate it is at least \$59 per visit for families with an annual income of less than \$50,000 (Mori et al., 2016). With a typical treatment length of 4–8 months and including pretherapy and posttherapy follow-ups, the financial burden of lost wages and transportation for the length of treatment can surpass \$590, and this does not include the cost of appointment and laboratory copays or the medication itself (Layton, 2009).

Despite trends toward decreased frequency of laboratory monitoring and increased availability of telehealth follow-ups, the burden of monthly pregnancy testing for isotretinoin patients of child-bearing potential has remained high. iPLEDGE requirements that patients of childbearing potential obtain a monthly pregnancy test through a CLIA-certified laboratory have meant these patients must continue to visit a clinician and/or laboratory monthly. For practices with a CLIA-certified laboratory, iPLEDGE-mandated pregnancy tests are often completed during the in-clinic follow-up visit. The same-day result reporting has allowed dermatology practices to confirm the patient immediately and maximize the 7-day window, which is activated by the completion of the pregnancy test and during which the patient can obtain their prescription from the pharmacy. For dermatology practices without a CLIA-certified laboratory, or for patients completing their follow-ups through a telehealth platform, patients must still travel to a CLIA-certified laboratory to complete the requisite pregnancy test. For this reason, the financial and logistical burden for this patient population has remained steady. In addition, the requirement of a CLIA-certified laboratory creates unique challenges for this patient population, because those obtaining the testing at an outside laboratory may experience delays in iPLEDGE confirmation due to the average turnaround time for laboratory reporting or clinic receipt of results. For example, a specimen collected on a Friday, which may take two business days to report out, would result in the patient not receiving iPLEDGE confirmation until they are already 4 days into their 7-day prescription window. Should a patient of childbearing potential then miss this shortened window, the pregnancy test must be redone.

CHANGES DURING THE PANDEMIC

The 2019 novel coronavirus (COVID-19) global pandemic and subsequent stay-at-home ordinances issued by 42 states resulted in a mass transition to telehealth and video visits for almost all dermatology diagnoses. On March 22, 2020, the FDA issued a statement that, for all drugs subject to Risk Evaluation and Mitigation Strategy programs with laboratory testing requirements, such as isotretinoin's iPLEDGE program, prescribing physicians "should consider whether there are compelling reasons not to complete these tests or studies during this public health emergency and use their best medical judgment in weighing the benefits and risks of continuing treatment in the absence of laboratory testing" (U.S. FDA, 2020, para. 3). Many providers who were previously slow to adopt decreased laboratory monitoring for isotretinoin rapidly converted to a minimal monitoring protocol (baseline laboratories followed by laboratories 2 months later) in alignment with the FDA's statement and to comply with local ordinances prohibiting all nonurgent healthcare visits. Shortly after, iPLEDGE announced in a program update that they would accept at-home pregnancy tests obtained at a drug store, a grocery

store, or an online retailer in place of the previously required CLIA-certified laboratory pregnancy test (iPLEDGE, 2016). For patients of childbearing potential, this represents a significant change in monthly monitoring requirements. At-home urine pregnancy tests (UPTs) can be completed quickly and effectively at home, decreasing the logistical and time burden for these patients. The transition to the use of an at-home UPT requires trust between the provider and the patient. The patient must verbally attest or submit photo documentation of the test, and the prescriber must accept the patient's word that the documentation has not been forged, such as submitting the same UPT photo each month (Figure 1). The cost of at-home UPT may also be a barrier for some patients. At-home UPT are not covered by standard health insurance plans. At an average cost of \$5 per test for the duration of a 4- to 8-month isotretinoin course, out-of-pocket costs for at-home UPT can exceed \$50. As a result, patients with insurance plans that covered laboratory pregnancy testing may be stuck with a higher out-of-pocket cost for testing with at-home UPT. However, at-home pregnancy tests are covered under health benefit programs like a health savings account or flexible spending

FIGURE 1. Patient submission of at-home urine pregnancy test indicating date and time of test completion. Photo courtesy of Meghan Dickman, MD, Stanford Health Care. Used with permission.

account, so it is important to discuss this with patients who may be eligible for such programs. These programs may require an accompanying note from a physician explaining the medical necessity, which can be emailed or mailed to the patient to submit with their reimbursement claim. Despite potential barriers of cost and reporting accuracy, anecdotal reports from patients and providers show they are satisfied with the at-home UPT alternative.

For prescribers wishing to initiate an isotretinoin course with a patient utilizing a virtual model, PDF versions of the iPLEDGE booklets and consent forms are available on the iPLEDGE website (iPLEDGE, 2016). Patients can print and sign the consent forms and then mail or attach images of the signed consent forms via a secure patient health portal. These documents, if sent in advance of the patient's virtual visit, can be reviewed with the provider during the virtual visit and then signed by the provider before registering the patient in iPLEDGE.

SPECIAL CONSIDERATIONS

The reduced laboratory monitoring and transition away from in-person visits seen during the COVID-19 pandemic may not be appropriate for all isotretinoin patients. Patients on multiple medications or with comorbidities, such as hyperlipidemia, fatty liver, or known risk factors for leukopenia, may continue to require monthly blood tests to monitor for abnormalities (Owen, 2019). For patients with acne fulminans or severe inflammatory acne who require a slower dose escalation and, subsequently, a longer time interval in achieving their goal dose may also require additional laboratory draws over the course of therapy. In addition, transgender female to male patients may prefer a blood draw for serum beta hCG testing over a UPT. As we pledge to provide inclusive care within the framework of the binary iPLEDGE program, serum beta hCG testing is a more inclusive and less stigmatizing option for meeting the iPLEDGE requirements for patients with reproductive capability (Boos et al., 2018).

Prescribers may also wish to continue in-clinic visits for isotretinoin patients early in their treatment course with multiple inflammatory lesions that require treatment with intralesional triamcinolone. Patients at the end of their treatment course with persistent comedones may also benefit from in-clinic visits where extraction can be provided.

When initiating therapy for patients who are under the age of consent (<18 years), the virtual platform may make having private and candid discussions about sexual activity challenging. Except under circumstances of emancipation or threat to the patient, a legal guardian must be present to provide consent when starting isotretinoin (McNary, 2014). However, in many states, minors may provide their own consent for birth control, and many prescribers will often ask parents or guardians to step out of the room during contraceptive counseling to allow for one-to-one discussion with the patient. In a virtual

environment, creating this one-on-one time may be difficult, in which case having these discussions in-clinic may be beneficial.

CONCLUSIONS

The trend toward decreased laboratory monitoring and increased use of telehealth modalities for isotretinoin patients, recently accelerated by the COVID-19 pandemic stay-at-home guidelines, have resulted in a reduction of in-person visits required for patients on isotretinoin. For the average patient on isotretinoin, one who is tech-savvy and prefers the virtual model as one that is more conducive to their busy academic and professional lives, these changes have resulted in improved access to this effective and life-changing medication. As stay-at-home restrictions lift, it remains to be seen whether iPLEDGE will continue to offer at-home UPTs as an alternative to CLIA-certified laboratory testing, but its use in the current telehealth framework has been shown to be an effective care model.

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