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Editor's Letter

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Dear Colleague:

Gels are among the most commonly prescribed testosterone formulations for treating hypogonadism and are considered safe and convenient. The feature in this issue of *TU Times* surveys the range of testosterone formulations, focusing on the gels currently available and those in development.

We address the safety concerns prompted by reports of secondary exposure to testosterone from these once-daily topical formulations and explain how clinicians can optimize their efficacy and safety. In making treatment decisions, patients and physicians should routinely discuss the many factors that affect outcomes, including efficacy, treatment-related adverse effects, tolerability, cost, and patient preference.

The interview with my distinguished colleague Robert S. Tan, MD, MBA, presents the perspective of his clinical expertise and insight into optimizing safety and adherence to transdermal testosterone therapy.

We hope that you find the information in this newsletter informative and useful in your clinical practice. Please provide us with feedback by completing the **evaluation and posttest**.

Sincerely,

Feature Article

Glenn R. Cunningham, MD

The goal of testosterone therapy is to treat the signs and symptoms of hypogonadism to induce and maintain secondary sex characteristics and to improve sexual function, sense of well-being, muscle mass and strength, and bone mineral density by achieving eugonadal serum testosterone levels.[1] Symptomatic benefits of testosterone therapy include improvement in energy level and mood,[2-4] enhanced sexual function (libido and erectile function),[5-7] increased bone mineral density,[4,8-10] increased lean muscle mass and strength,[8,11] decreased fat mass,[6,11] and in some men, improved insulin sensitivity.[12-14]

Several testosterone therapy formulations are available, each with specific advantages and disadvantages, as delineated in the table.[1] Since the publication of the Endocrine Society clinical practice guideline, the US Food and Drug Administration (FDA) approved a topical testosterone solution (Axiron®) administered to the axilla (underarm) with an applicator.[15] Patient preference, the pharmacokinetic profiles of the various testosterone formulations, cost, and treatment burden should be considered when selecting a testosterone therapy.[1]

Testosterone gels are available in sachets, tubes, and pumps and are administered daily. When a testosterone gel is applied in the morning, its pharmacokinetic profile may mimic the diurnal variation of endogenous serum testosterone levels, because peak endogenous serum testosterone levels are highest at this time.[1] Serum testosterone and estradiol levels are restored to the physiologic range, however, serum dihydrotestosterone levels are higher and testosterone:dihydrotestosterone ratios are lower in hypogonadal men using testosterone gel than in healthy eugonadal men.

Two topical testosterone gels (Testim® and AndroGel® 1%) are available in the United States.[16,17] Many patients find these formulations to be convenient and prefer the dosing flexibility (based on achieved serum testosterone levels) and being able to immediately discontinue treatment if necessary (eg, in the case of an adverse event).[1] However, achieving eugonadal testosterone levels may be difficult for some patients.

To assess whether application site affects testosterone gel absorption, Guay et al studied the application of gel to 3 distinct anatomical sites (arms/shoulders [A], chest/abdomen [C], and calves/legs [L]) for 1 month in 21 hypogonadal men naive to testosterone therapy.[18] Pretreatment total testosterone (TT) and calculated free testosterone (FT) were compared with end-of-month measurements. Whereas overall TT and calculated FT increased significantly from pretreatment levels into the normal

Clinical Pharmacology of Some Testosterone Formulations

Formulation	Regimen	Pharmacokinetic Profile	DHT and E_2	Advantages	Disadvantages
Testosterone enanthate or testosterone cypionate	150-200 mg IM biweekly or 75-100 mg/wk	After a single IM injection, serum testosterone levels rise into supraphysiologic range, then decline gradually into hypogonadal range by end of dosing interval	DHT and E_2 levels rise in proportion to increase in testosterone levels; T:DHT and T:E_2 ratios do not change	Corrects symptoms of androgen deficiency; relatively inexpensive if self-administered; flexibility of dosing	Requires IM injection; peaks and valleys in serum testosterone levels
1% gel	Available in sachets, tubes, and pumps 5-10 g testosterone gel containing 50-100 mg testosterone daily	Restores serum testosterone and E_2 levels to physiologic male range	Serum DHT levels are higher and T:DHT ratios are lower in hypogonadal men treated with gel than in healthy eugonadal men	Corrects symptoms of androgen deficiency, provides flexibility of dosing, ease of application, good skin tolerability	Potential of transfer to female partner or to child by direct skin-to-skin contact; skin irritation in small proportion of treated men; moderately high DHT levels
Transdermal patch	1 or 2 patches, designed to nominally deliver 5-10 mg testosterone over 24 h applied daily on nonpressure areas	Restores serum testosterone, DHT, and E_2 levels to physiologic male range	T:DHT and T:E_2 levels are in physiologic male range	Ease of application, corrects symptoms of androgen deficiency	Serum testosterone levels in some androgen-deficient men may be in low-normal range; these men may need application of 2 patches daily; skin irritation at application site occurs frequently in many patients
Buccal, bioadhesive tablets	30 mg controlled release, bioadhesive tablets twice daily	Absorbed from buccal mucosa	Normalizes serum testosterone and DHT levels in hypogonadal men	Corrects symptoms of androgen deficiency in otherwise healthy, hypogonadal men	Gum-related adverse events in 16% of treated men
Pellets	3-6 pellets implanted subcutaneously; dose and regimen vary with formulation	Serum testosterone peaks at 1 mo and then is sustained in normal range for 3-6 mo, depending on formulation	T:DHT and T:E_2 ratios do not change	Corrects symptoms of androgen deficiency	Requires surgical incision for insertions; pellets may extrude spontaneously
17-α methyltestosterone	This 17-α alkylated compound should not be used because of potential for liver toxicity	Orally active			Clinical responses are variable; potential for liver toxicity; should not be used for treatment of androgen deficiency
Oral testosterone undecanoate	40-80 mg orally twice or 3 times daily with meals	When administered in oleic acid, testosterone undecanoate is absorbed through lymphatics, bypassing portal system; considerable variability in same individual on different days and among individuals	High DHT with testosterone ratio	Convenience of oral administration	Not approved in US; variable clinical responses, variable serum testosterone levels, high DHT:T ratio
Injectable long-acting testosterone undecanoate in oil[a]	European regimen 1000 mg IM, followed by 1000 mg at 6 wk and 1000 mg every 10-14 wk	When administered at dose of 750-1000 mg IM, serum testosterone levels are maintained in normal range in majority of treated men	DHT and E_2 levels rise in proportion to increase in testosterone levels; T:DHT and T:E_2 ratios do not change	Corrects symptoms of androgen deficiency; requires infrequent administration	Requires IM injection of large volume (4 mL); cough reported immediately after injection in very small number of men
Testosterone in adhesive matrix patch[a]	2 x 60 cm^2 patches delivering approximately 4.8 mg daily	Restores serum T, DHT, and E_2 to physiologic range	T:DHT and T:E_2 are in physiologic range	Lasts 2 d	Some skin irritation

[a]These formulations are not approved for clinical use in the United States but are available in many countries outside the United States. Physicians in countries where these formulations are available should follow the approved drug regimens.

DHT, dihydrotestosterone; E_2, estradiol; IM, intramuscular; T, testosterone.

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range ($P<.0001$), application sites differed with regard to TT levels achieved, with the greatest absorption occurring in the arms/shoulders group ($P=.011$). Further, the gel was applied sequentially in 3 patterns: ACL, CLA, and LAC. Though significant effects were not observed, the highest serum testosterone levels were achieved in patients receiving testosterone gel in the ACL pattern.

Novel testosterone formulations with a higher concentration of testosterone are in development and may improve efficacy in some patient populations for whom eugonadal levels are not attainable with available 1% testosterone formulations. The higher-concentration testosterone gel formulation may safely and effectively deliver testosterone transdermally using a lower volume of gel, thus covering a smaller skin surface area than available gels and possibly reducing the risk of transference.[19-23]

In a placebo-controlled phase 3 clinical trial (N=196: gel, 168; placebo, 28), 1.62% testosterone gel was applied to the upper arm/shoulder or abdomen.[19] After the titration period, 17 patients received 1.25 g/d, 66 received 3.75 g/d, and 91 received 5 g/d. Subsequent evaluation on day 14 showed that eugonadal testosterone levels were achieved in two-thirds of treated patients. On days 56, 112, and 182, eugonadal serum testosterone levels were achieved in 82% of treated patients versus 37% or fewer participants receiving placebo ($P<.0001$). Ten patients had "rare, brief, inconsistent, and unsustained" testosterone levels above 2500 ng/dL, believed to result either from contamination by venipuncture artifact (n=5) or from subject- or site-specific circumstances (n=5), giving the appearance of acute increases in systemic absorption. Luteinizing hormone, follicle-stimulating hormone, and interleukin-10 levels decreased significantly over the course of the study.

In a study by Miller et al, abdominal application of 1.62% testosterone gel provided approximately 30% to 40% lower bioavailability of testosterone compared to upper arm/shoulder application.[24] However, alternating upper arm/shoulder and abdominal application did not adversely affect the achievement of eugonadal testosterone levels. In a different study by Miller et al, application of moisturizer 1 hour after application of 1.62% testosterone gel was shown to increase AUC_{0-24} (area under the curve) by 14% and C_{max} (maximum concentration) by 17% compared to gel alone.[25] Application of sunscreen had no effect on AUC_{0-24} but increased C_{max} by 13% compared to gel alone. Individual and mean C_{max} and average concentrations remained within the eugonadal range, and increases were considered not clinically relevant.

Evidence suggests that serum testosterone levels are best maintained when the application site is not washed for 4 to 6 hours after application of testosterone gel.[1] However, another study by Miller et al demonstrated that showering or bathing at least 2 hours after application of 1.62% testosterone gel has minimal or no effect on systemic absorption while reducing the amount of testosterone on the skin by more than 80% and limiting the potential for transference of testosterone to others.[26]

Reports of adverse effects caused by transference of testosterone gel to children prompted the FDA to order a labeling change for testosterone gel formulations to advise about inadvertent transfer to female partners or to children[1,27,28] has the potential to cause, for instance, inappropriate virilization or advanced bone aging in children.[27,28] Physicians and patients should discuss the concerns about transference of testosterone gel and review how to minimize that risk by closely following the labeling protocol.[1]

The FDA also ordered a risk evaluation and mitigation strategy, including a medication guide to minimizing transference risk.[27] Men who have applied testosterone gel should wash their hands with soap and warm water after every application. Furthermore, after the gel has dried, the application site should be covered with clothing. Men should be cognizant of testosterone application sites to ensure that children and women are not inadvertently exposed to the testosterone gel residue that has not been fully absorbed into the skin.[1] Prior to skin-to-skin contact with another person, the application site should be washed thoroughly with soap and warm water. Patient education materials may reinforce the best techniques to improve efficacy and safe use of testosterone gel formulations.

An Interview With Dr Tan

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Q: How do you determine which testosterone formulation is best for a particular patient?

A: After diagnosing a patient, I usually go on to discuss the risks and benefits of testosterone therapy and the need for continuously monitoring for safety and, in turn, adherence. I explain the different routes of administration and involve the patient in an informed consent for the method of delivery. Generally, I would suggest a topical delivery system to start off with, and this includes gels and patches.

There are two commercially available gels, and I let the patient smell samples in the office to decide which he prefers. In terms of absorption differences, they vary based on the patient: Sometimes I start with one gel and end up with the other.

If topical therapy fails—for instance, there is no resolution of symptoms or a failure to achieve sufficient levels of testosterone—I might then move on to injectable therapy. Another reason I might change to injectable therapy is that the patient expresses a concern about issues with transference to a child or partner. Currently, we have short- to medium-acting ones, viz, propionate versus cypionate and enanthate. During the office visit, I teach the patient or partner to administer the injection themselves for reasons of adherence, cost, and convenience.

For a patient who tends to forget to apply the medication or finds it a hassle, I might suggest testosterone implants, which can last up to 3 months. There is a long-acting testosterone injection (testosterone undecanoate), but it is not available in the United States at this time.[29,30]

Recently, the FDA approved a topical testosterone solution applied to the armpit via an underarm applicator.[15]

A buccal delivery system is sometimes used for the patient who needs a faster rise in his testosterone levels to help resolve his symptoms, but it requires application every 12 hours, it may stick to the mouth or drop off, and the patient feels conscious of something in his mouth.

Q: What questions do you ask to determine whether a patient will adhere to a particular testosterone formulation?

A: I ask directly whether he has taken the medication as directed, and I track the refill rates. If the patient is nonadherent, I explore why he has not taken the medication. Is it because the drug is not working, or are there adverse effects, such as acne, rash, or leg swelling? If he says the drug is not working, I try to explain that perhaps the level is not adequate, which means we need to measure his blood levels of testosterone.

Q: Do you have clinical tips that help ensure adherence with a prescribed treatment regimen?

A: I spend quite a lot of time at onset to explain testosterone therapy to the patient. I tell him that therapy is for the long haul. I explain that, in the long term, if left alone, the hypogonadal state may lead to muscle loss and even osteoporosis. I also give him a handout explaining the effects of testosterone on different organ systems. The handout includes the time frames in which symptoms and physical effects occur.

In our practice, we store our medical records electronically. We plot the patient's testosterone, estradiol, and prostate-specific antigen (PSA) levels and complete blood counts and show him graphic representations of his androgenic state. We find that this helps with adherence, because when he sees a dip, he feels he has "failed" and looks forward to a "pass" on his blood levels.

We try to empower our patients to take charge, and when they do, adherence improves.

Q: What approaches do you use to improve adherence to treatment (eg, medication diary)?

A: Studies have shown the benefit of patient diary tools to improve adherence to a treatment regimen.[31,32] A recent study by Hou et al investigated whether daily text message reminders support adherence but did not demonstrate measurable improvement, perhaps because of the frequent use of alternative reminder systems in the control group.[33]

In our clinical practice, we have tried patient diaries and even e-mail and text messaging. Often, patients may be enthused initially but lose steam later on. I sometimes ask my patient to e-mail me about his progress, and this allows me to check on his adherence. Also, as my assistant makes phone calls to remind patients about follow-ups and blood work, she also checks on adherence and the need for medication refills.

Q: How do you ensure that a patient returns to the office for follow-up?

A: At the end of the visit, I tell the patient when to come back for follow-up, usually in 3- to 4-month intervals. The patient also needs an annual prostate examination. I ask the front desk to enter a "call follow-up" notation in the schedule, which triggers the staff to remind the patient regarding blood work and follow-up when the time comes. We also send reminder e-mails and text messages to the patient's cell phone.

I tend not to renew a medication until I have the blood work results as a safety measure, lest there is an unexpected rise in the PSA or hemoglobin level. If the patient cannot make it in in time, I might renew the medication for an extra month.

In Texas, testosterone is a controlled substance monitored by the Department of Public Safety. As such, it is prudent to conduct and document patient follow-up before renewing a prescription.

Q How do you assuage a patient's fears and concerns regarding media reports of person-to-person transference and possible virilization due to secondary exposure to testosterone gel?

A I remind the patient about the pharmacokinetics of topical testosterone gel formulations and that a window of 4 hours is needed to avoid transference issues. In addition, I suggest application in the morning instead of at night, because sexual activity is less common in the daytime. I also recommend that he apply the gel to the abdomen and wear clothing to cover it. The neck and arms may be exposed with T-shirts and can lead to transference issues. Finally, the patient should rub in the medication to ensure absorption and wash his hands thoroughly.

Lakshman et al. succinctly summarize the issues regarding transference and emphasize that patient education is crucial.[34]

Q What advantages, if any, do you anticipate with the higher-concentration testosterone gels in development?

A
1. Less volume may mean lower possibility of transfer
2. Higher testosterone levels may be achieved with smaller volumes
3. Smaller volumes are more aesthetic, less clumsy, and more streamlined
4. Volume restrictions in air travel will be less of a problem

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