PROGNOSIS AND TREATMENT OF ACTINIC KERATOSES

An interview with Perry Robins, MD, and Victor A. Neel, MD, PhD
Conducted by Nanette J. Liégeois, MD, PhD

Dr Robins is Editor-in-Chief of the Journal of Drugs in Dermatology and is Chief of the Mohs’ Micrographic Surgery Unit and a Professor of Dermatology at the New York University Medical Center in New York, NY. Dr Robins has practiced medicine for over 40 years and has treated more than 40,000 patients with skin cancer. He does more than 1,000 procedures annually and conducts training workshops for his peers in advanced techniques of dermatologic surgery. Dr Robins also is the Founder and President of The Skin Cancer Foundation, a national organization dedicated to the research skin cancer and the education of the private and public sectors. In addition, Dr Robins is the Founder and President of the International Society of Dermatologic Surgeons, Founder and Former President of the Mohs’ Society, and Former President of the American Society of Dermatologic Surgery.

Dr Neel is Director of Dermatologic Surgery at Massachusetts General Hospital and is a dermatology specialist at Dermatology Associates in Boston, Mass. Dr Neel received his medical degree from Cornell University’s Weill Medical College in New York, NY, and completed his doctoral training at Rockefeller University, also in New York, NY. His clinical interests include Mohs’ surgery, cutaneous malignancies, and cosmetic dermatology.

Dr Liégeois is Assistant Professor at Johns Hopkins University School of Medicine where she is the Director of Dermatological Surgery in the Department of Dermatology. Dr Liégeois has researched basic molecular mutations in skin cancers and has recently been awarded the Career Development Award in Dermatologic Surgery from the Dermatology Foundation. Dr Liégeois received her medical degree and doctorate in immunology from the Albert Einstein College of Medicine in the Bronx, NY. She completed her internship at Beth Israel Deaconess Medical Center in Boston, Mass, and fulfilled her residency at Harvard University, where she was Chief Resident. In 2003, Dr Liégeois completed a fellowship in dermatologic surgery at the Lahey Clinic in Burlington, Mass.

Dr Liégeois interviewed Dr Robins and Dr Neel for Johns Hopkins Advanced Studies in Medicine to discuss their experience and recommendations regarding treatment options for actinic keratoses.

Dr Liégeois: Should all actinic keratoses (AK) be treated?

Dr Robins: Anyone who has seen a lot of skin cancers knows that many of these AKs will, over a period of time, develop into squamous cell carcinoma (SCC), which can be life-threatening. Therefore absolutely, unequivocally, it is important that they be removed.

Dr Neel: We know that a lot of AKs spontaneously resolve, and only perhaps 8% to 10% actually progress to SCC. Thus, it’s not medically necessary to treat every lesion. You can watch them, and if you see patients regularly, you can get a good sense of whether a lesion is progressing. However, because we sometimes lose track of patients and because some have underlying conditions that can affect outcome, most dermatologists will aggressively treat every AK.

Dr Liégeois: What factors do you consider when choosing a specific treatment plan for an individual patient?

Dr Robins: How many lesions a patient has, how long the patient has had them, the age of the patient, his or her occupation, where the patient lives, and how much time he or she spends in the sun.

Dr Neel: The most important factor is the number of lesions. Secondary factors include the patient’s history—for example, if the patient has had previous SCC—
and the patient’s immune status. Immunocompromised patients have a higher risk of developing SCC, thus I’d treat those patients much more aggressively.

Dr Liégeois: What treatments would you consider for an average man in his 50s who has a solitary AK?

Dr Neel: The majority of physicians would treat it with liquid nitrogen. Some dermatologists would use a light curette. Either way, it’s going to be a destructive process like cryotherapy, surgical removal, or curetting.

Dr Liégeois: How is cryotherapy done?

Dr Neel: We use liquid nitrogen, a gas under pressure at -196°C, in a spray gun. I apply 1 or several short bursts directly to the AK, which produces a frozen ball of tissue. The freezing time varies per lesion but generally lasts approximately 10 seconds; larger and thicker lesions require more cryotherapy. I usually use 2 cycles with a 10-second freeze/thaw time. Some of my colleagues use 1 cycle, but I’ve found a much higher recurrence rate if you don’t use 2 cycles with a short freeze time.

Dr Liégeois: What are the side effects of cryotherapy, and how long does it take to recover from it?

Dr Robins: Sometimes you see white spots, hypopigmentation, which is something to be concerned about, especially on the mid-face. Some patients have a higher propensity for this to occur. Rarely have I seen liquid nitrogen cause infection or sloughing off of large areas. Patients typically recover within 3 or 4 days.

Dr Neel: Unless you get the skin to a really low temperature and cause blistering and crusting, you’re probably not going to get a complete result. Because of this blistering and the subsequent immune reaction, hypopigmentation or hyperpigmentation of the skin—depending on the skin type—can occur. Scarring, which implies dermal damage, also can occur if the physician is too aggressive.

Dr Liégeois: Should other therapies be considered for a patient with only a few lesions? For example, laser therapy or photodynamic therapy (PDT)?

Dr Robins: I would not use laser therapy, chemical peels, or PDT for a few lesions. If the patient doesn’t want liquid nitrogen, I think it behooves us to use some 5-fluorouracil (5-FU). I like 0.5% 5-FU because it’s used once a day. I instruct my patients to put it on at night, and I would often recommend intermittent therapy.

Dr Neel: Laser therapy is a nonspecific destructive method. There’s no reason why an AK or an early SCC would respond preferentially to that treatment versus cryotherapy or any other surgical procedure, thus I’m not in favor of nonspecific destructive procedures, such as lasers. The interesting development in the last few years is PDT, which has a scientific basis for why it works on AKs and malignancies; it’s a much more targeted approach to treating damaged skin, and that puts it in a separate category from lasers.

Dr Liégeois: Please explain how PDT works to treat AKs.

Dr Neel: Basically, you apply aminolevulinic acid (ALA) or a related molecule to the affected area, and it is absorbed by cells and converted to a light-sensitive molecule, protoporphyrin IX. Shining light of a particular wavelength on the treated region causes lethal oxidative damage to cells. What makes PDT useful for AKs and malignancies is that precancerous or cancerous lesions absorb and process the ALA more effectively. Hence, PDT selectively targets cells that are rapidly dividing or are damaged; it affects damaged keratinocytes more than normal keratinocytes.

Dr Liégeois: Some healthcare practitioners claim that the light treatment causes a lot of pain. How do your patients tolerate it?

Dr Robins: I see the complete spectrum; some patients say it was not painful, one patient said it was really painful. A lot has to do with nationality, with the thinness or thickness of the skin, and how much sun damage the patient has. Only once in approximately 50 or 60 cases do I find a patient who can’t tolerate it.

Dr Neel: It is helpful to keep an assistant with the patient. I’m lucky that I have a dedicated nurse who can sit and chat with the patients while they undergo irradiation. I also let patients have a cold drink with them if they want to drink, and there’s a fan that’s constantly going. Also, the ALA incubation time can
make a big difference in the level of pain. Patients who have moderate disease can do very well with just 1 hour. Some dermatologists apply ALA overnight, but that can cause a severe reaction in some patients; therefore, I recommend limited contact with the photosensitizing agent at least in the first trial. If the first treatment doesn’t produce much of a clinical effect, then have the patient sit a little longer with the ALA.

**Dr Liégeois:** What specific treatments would you use to treat diffuse AKs?

**Dr Robins:** I like 0.5% 5-FU. There’s no limitation on how small or how extensive a lesion must be to benefit from treatment. I treat patients with diffuse lesions in partitions. For example, I’ll treat the forehead and the scalp first and then have the patient return 1 month later for treatment of the cheeks and nose. There is some discomfort when you do a large area, and this avoids some of the irritation. You can do the left side of the face one time and then do the right side, but I’ve found that people feel funny when one side looks so clean and the other still has multiple keratoses; therefore, I’d rather do the whole forehead, then the nose and the cheeks.

**Dr Neel:** I don’t use cryotherapy on more than 10 lesions at once. If someone has 20 lesions, I consider using a topical agent. I also factor in the patient’s risk of getting more lesions. If the patient has rough skin in exposed areas, he or she is going to develop a whole field of AKs there, thus I’ll discuss using a topical agent. Once-daily 0.5% 5-FU cream is usually my standard treatment because it’s easy to use and it’s fairly inexpensive. The track record with 5-FU is superior to any other topical agent’s. However, many patients prefer PDT because the treatment is complete in 1 short session; I haven’t had any patients treated with PDT who would rather go back to using topical treatments.

**Dr Liégeois:** 5-FU is available in several strengths. Do you have a preferred strength that you use?

**Dr Robins:** I think there’s no difference between the different concentrations of 5-FU in terms of effectiveness.

**Dr Neel:** Most patients tolerate the new preparation of 0.5% 5-FU in a once-daily formulation quite well. The side-effect profile is superior to that of other 5-FU formulations in my opinion. From my patients’ perspectives, the new preparation seems less irritating. They probably get the same amount of total irritation cumulatively, but because they only use it once a day versus twice a day, it seems like less irritation.

**Dr Liégeois:** Are you familiar with the clinical efficacy of diclofenac gel compared with that of 5-FU?

**Dr Robins:** I really don’t use it, thus I am not that familiar with it.

**Dr Neel:** Diclofenac is a topical cyclooxygenase inhibitor. I’ve never used it, mostly because of the long duration of treatment that’s required. The recommended treatment is twice-daily for 90 days.

**Dr Liégeois:** What about the new topical agent for treating AKs, imiquimod?

**Dr Robins:** I recommend it only on special occasions. It is expensive and takes a long time to work—approximately 4 to 6 months. My patients do not want to wait that long for dramatic results.

**Dr Neel:** Some patients respond really well to imiquimod; other patients don’t respond at all. Why it works for some people and not for others is unknown; clearly something other than the AK is determining whether patients have a good or a bad response. Theoretically, imiquimod works by stimulating the immune system. Generally it’s given once a day for 3 to 5 days a week for 6 to 12 weeks. Some people get a dramatic response quickly, and they stop using it because it’s so irritating. Others need that extra 6 or 10 weeks because they’re not getting a fulminant reaction. From my experience, the rate of cutaneous infection is much higher with imiquimod than with topical 5-FU. Many dermatologists give their patients a prescription for a topical antibiotic with their imiquimod prescription because they anticipate the development of a cutaneous infection. There are very few head-to-head studies comparing imiquimod with 5-FU, and those are needed.

**Dr Liégeois:** Do you have trouble with compliance when using topical modalities?

**Dr Robins:** We use a “double check,” which means first, I explain to the patient what he or she should expect from the treatment, how to apply the agent, and the importance of continuation and compliance. Then my nurse comes in with a checklist, literature, booklets, and pictures, and she goes over it again. As a result, the only time we have difficulty with compliance is when a patient realizes all of a sudden that he or she has an important meeting to go to and stops
treatment. That’s something I like about once-daily 0.5% 5-FU; it can be used intermittently, which can mean every other day for 2 weeks or 3 days on followed by 3 days off. I don’t think you need a brisk response to have efficacy.

**Dr Liégeois:** When lesions are refractory to treatment or they recur, at what point do you retreat versus do a biopsy?

**Dr Robins:** When you treat a patient with liquid nitrogen, you’re going to see the patient again after 1 month or sooner. If it has not healed by then, I would do a biopsy.

**Dr Neel:** I generally have a 2-strike rule: if the lesion comes back after 2 cryotherapy treatments, I do a biopsy. With immunocompromised patients, I perform a biopsy if the lesion recurs after 1 treatment.

**Dr Liégeois:** Do you recommend chemopreventive modalities, such as retinoids, for your high-risk patients who have had a great deal of sun exposure or who are immunosuppressed?

**Dr Robins:** We’ve used retinoids with only marginal success. My Mohs’ micrographic surgery patients come back for a follow-up visit in 1 year; therefore, I usually give them a prescription for 0.5% 5-FU to use prophylactically. When patients return for another prescription, their body gets checked. And patients who come in for a body check get a prescription so that works out well.

**Dr Neel:** I treat my transplant patients with PDT every other month, or topical 0.5% 5-FU if they prefer. Sometimes I use tretinoin, which has been shown to be effective against AKs and is not as irritating as 5-FU. If they’re taking topical tretinoin, they also get periodic treatment with 5-FU or PDT. Systemic retinoids are useful when many invasive lesions are developing, but the systemic side effects are often limiting.

**Dr Liégeois:** What alternative or emerging therapies hold promise for the treatment or prevention of AKs?

**Dr Robins:** An Australian company is researching a melanocyte-stimulating hormone that can be injected into the skin to stimulate the production of more melanin and give more protection against the rays of the sun. They also are working on administering it through the mucosal lining of the mouth instead of by injection. Others are trying to produce a sun pill that would allow people to go into the sun without burning for a longer period than they normally could, but I think that reality is a few years away.

**Dr Neel:** I’ve seen some anecdotal reports of patients being treated for internal cancers with systemic epidermal growth factor inhibitors that have had some effects on AKs. Ultimately, I think treatments with combined modalities will be most useful.