Highlights of the American Academy of Dermatology 61st Annual Meeting

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Melanoma Update 2003: Clinical Types, Genetic Testing

Barbara A. Burrall, MD

Introduction

Skin cancers make up about 40% of all cancers diagnosed in the United States. Although most skin cancers are basal and squamous cell carcinomas, the incidence of melanoma has been increasing rapidly -- by a factor of about 15 in the past 60 years.\[1\] At a symposium on cutaneous tumors held at the 61st Annual Meeting of the American Academy of Dermatology (AAD), Darrell S. Rigel, MD,\[2\] Clinical Professor of Dermatology, New York University Medical Center, New York, NY, reported that the expected incidence of new skin cancer cases in the United States will reach 1,350,000 in 2003, and that 54,200 of these will be invasive melanomas, thus raising the lifetime risk of invasive melanoma to 1 in 67. If the current rate of melanoma increase continues, this would extrapolate to a lifetime risk of invasive melanoma of 1 in 50 by the year 2010.

In men, melanoma makes up 4% of all cancers; in women it makes up 3%. Currently in the United States, there is 1 death per hour due to skin cancer, mostly melanoma. Furthermore, deaths from melanoma, the fifth most common cancer, generally occur...
at an earlier age than deaths due to most other cancers.\textsuperscript{[3-5]} Prevention, early diagnosis, and appropriate management are crucial to limiting this death toll.

**Clinical Types**

The 4 main clinical types of melanoma, the malignancy of melanocytes (pigment-producing cells), are superficial spreading, lentigo maligna, acrolentiginous/mucosal, and nodular. The general clinical characteristics have been described as the ABCDs of melanoma (Figures 1-4)\textsuperscript{[6]}:

A -- Asymmetry  
B -- Border irregularities  
C -- Color asymmetry or irregularity/different colors  
D -- Diameter > 6 mm

**Figure 1.** Melanoma: Asymmetry (courtesy NCI).

**Figure 2.** Melanoma: Border (courtesy NCI).
Melanomas may have only 1 of these features but usually have more. Amelanotic melanomas have little to no pigment and are very difficult to diagnose clinically.

Classically, melanomas have been thought to spend a variable amount of time in a "radial growth phase" in which radial spread is observed intraepidermally and in the upper papillary dermis. These lesions are considered to be in a nontumorigenic phase.[7] About 90% of melanomas have a nontumorigenic portion. The tumorigenic phase, or "vertical growth phase," exhibits a mass of melanoma cells within the dermis. Mitoses are frequently seen, indicating the tumor's potential for significant expansion or invasion.[7] Vertical growth also heralds the tumor's potential for metastasis.

Robert J. Friedman, MD,[2] Clinical Assistant Professor of Dermatology, New York University Medical Center, noted that neoangiogenesis is required for this switch to a potential for invasion and metastasis. These neoangiogenic blood vessels appear as large dilated vascular structures just below the neoplasm. Changes in the p53 gene may also play a role at the time of the angiogenesis switch. With the exception of the nodular melanoma, which does not show any significant radial growth pattern, all types of melanoma appear to progress through some degree of radial growth before the expansion/invasion of vertical growth begins.

Besides the clinical types of melanoma described below, Donald Lawrence, MD,[8] Division of Hematology-Oncology, Tufts-New England Medical Center, Boston, Massachusetts, reported during the melanoma symposium at the 61st Annual Meeting of the AAD that attempts at molecular classification have been made. Gene expression profiling has been used to identify subsets of melanoma by analysis of gene expression patterns.[9] It is hoped that characteristics such as biological aggressiveness will be predicted reliably by a tumor's gene expression pattern.
Superficial Spreading Melanoma

Superficial spreading melanoma is the most common type (70%). These melanomas are most often found on areas of the skin that are intermittently exposed to the sun. The upper back of men and the lower legs of women are the most frequent sites.[7] Early superficial spreading melanomas generally show the changes described by the ABCD rule but may be difficult to distinguish from atypical nevi (see below), which also may display these features. Early in their development, these melanomas are often flat or nearly flat, but they become more papular or nodular as they become more invasive.

Lentigo Maligna Melanoma

Lentigo maligna melanoma was described by Hutchinson more than 100 years ago. This type of melanoma represents about 10% of all melanomas. The term "lentigo maligna" is generally used to mean lentigo maligna melanoma in situ (confined within the epidermis). This form of melanoma usually occurs on the most chronically sun-damaged skin, most often the face, of older patients (mean age, 65 years). Extrafacial lentigo maligna melanoma accounts for only 17.5% of cases.[10] The lesion begins as an unevenly pigmented macule that grows peripherally, often reaching several centimeters in size. These lesions tend to remain noninvasive for a prolonged time, often many years. A papule may become apparent when the lesion becomes invasive.

Acral lentiginous/Mucosal Melanoma

Melanoma may arise on the hairless skin of the palms and soles, in and around the nails, and on mucosal surfaces (oral, nasal, vaginal, and anorectal). Of these, melanoma on the soles is the most common.[7] This form of melanoma is uncommon and of similar incidence in all racial and ethnic groups, but is the predominant form in persons of color. When located in the nail matrix, the development of a longitudinal pigmented band in the nail plate may herald its presence. The survival of patients has traditionally been poor, but this is likely due to late diagnosis.

Nodular Melanoma

Nodular melanoma comprises 10% to 15% of all melanomas and is solely made up of cells showing a tumorigenic, vertical growth pattern. It generally begins as a variably pigmented papule that grows rapidly to form a nodule. Because of the rapid growth, these lesions are often quite thick at the time of removal and hence have a poor prognosis. However, when controlled for thickness, survival is no worse than for other melanomas.[7]

Dysplastic/Clark's/Atypical Nevi

There is no general agreement on the terminology to use for nevi with characteristic, atypical features that may clinically be confused with melanoma; dysplastic, Clark's, or atypical nevi are all terms commonly used. Dr. Friedman[2] clinically distinguishes these large atypical (dysplastic) nevi (LAN) from common acquired nevi (CAN), in that CAN are symmetric, uniform in color, smooth-bordered, and small (< 6 mm), whereas LAN generally are asymmetric, variegated in color, blurred-bordered, and large (≥ 6 mm). Early in their growth, some small nevi (1-3 mm) may have features of both types of nevi, and it is difficult if not impossible to predict into which type they will evolve.

Dr. Rigel,[2] who prefers the term "dysplastic nevi (DN)," notes that DN have a low prevalence. In the United States and internationally, DN have been found in 2% to 8% of the populations observed in 19 studies. However, a strong relationship between DN and melanoma has been recorded. DN may play a role as markers for an increased risk of melanoma, or, alternatively, they may actually be precursor lesions of melanoma.

In patients with multiple DN, melanomas may arise both de novo as well as in association with a DN. Therefore, it appears likely that both relationships are operative, and the most important fact to remember is that patients with DN are at increased risk for the development of melanoma. Some of the evidence for this assertion includes the fact that both melanoma and the presence of dysplastic nevi are associated with sunburn before the age of 20. In addition, similar chromosomal abnormalities have been found in some DN and melanomas.[11]

The relative risks for the development of melanoma have been calculated in various groups of patients with DN. Dr. Rigel[2] studied 452 patients for an average of 27 months. Eighteen new melanomas developed in 16 patients, for a risk of 3.5% for 27 months. This risk was much greater than the 1% lifetime risk (900 months) expected for this group of patients. He further rated possible degrees of risk for new melanoma development in patients with DN, assigning 0 points for the presence of DN, 1 point for a prior history of melanoma, and 2 points for each family member with a history of melanoma. He found a risk gradient where DN alone (0 points) was associated with a 7% risk, which was higher than expected; a 1-point score was associated with a 12% risk; a 2-point score was associated with an 18% risk; and a score of 3 or more points was associated with a 50% risk.

Stam-Posthuma and colleagues[12] studied patients who developed 2 or more melanomas and found that 82% of these patients had clinically dysplastic nevi. Though increased numbers of small and large banal nevi are associated with a 4-fold increased risk for melanoma, the presence of 10 or more DN confers a 12-fold risk that remains very significant even if one adjusts for
total nevi. Even 1 DN produced a 2-fold risk. Therefore, melanoma is primarily related to the presence of DN, not banal nevi.

There is ample evidence that some melanomas arise from DN. Histologic changes of DN are found at the margin in 20% to 30% of melanomas. Dr. Friedman reported at last year's annual AAD meeting that melanoma arises in LAN (DN) 6 times more frequently than in banal nevi. However, when 200 patients with a history of melanoma were followed for 10 years, survival was much longer in patients whose melanomas arose in LAN than in patients whose melanomas arose de novo. Though patients with the familial, autosomal dominant syndrome of LAN and familial melanoma seem to have an earlier age of onset of melanoma and a tendency to have multiple melanomas, this syndrome may be associated with less biologically aggressive melanoma.

However, Jason K. Rivers, MD,[2] Department of Medicine, University of British Columbia, Vancouver, Canada, pointed out that the correlation between clinical atypia and histologic atypia may be poor. In addition, there is significant variation in the way dysplastic or Clark's nevi are described histologically, particularly with respect to whether degrees of atypia are noted. Though most dermatologists recognize that patients with dysplastic nevi are at increased risk for melanoma, and promote strategies to enhance prevention and early detection in these patients, no specific, widely practiced strategy exists. Dr. Rivers follows his patients from their late teens at 6- to 12-month intervals, lifelong, and recommends periodic ophthalmologic examinations.

**Congenital Melanocytic Nevi**

The strict definition of a congenital nevus is one that is observed at birth. However, Ashfaq Marghoob, MD,[14] has asserted that "tardive" congenital nevi likely exist. First, nevi that appear clinically and histologically identical to congenital nevi have been documented when there is photographic proof that they were not present at birth. Further, the satellite nevi that are common in patients with giant congenital nevi can develop years after birth. Dr. Marghoob has suggested that perhaps the definition should be changed to "clinically and histologically congenital nevi that become apparent within the first 2 years of life." Histology alone cannot be relied on because there is some overlap with common acquired nevi. Congenital nevi may be macular, speckled, hairy, rugous, or mammillated. Studies have not been done to correlate clinical type with risk of melanoma.

Congenital nevi are divided into small (< 1.5 cm), medium (up to 20 cm), and large (>= 20 cm). Although melanoma can develop in congenital nevi as it can in acquired nevi, Pearon G. Lang, Jr, MD,[17] asserted at last year's AAD meeting that there is no increased risk for the development of melanoma in small- and medium-sized congenital nevi. During the question and answer session following this year's melanoma symposium, Alfred Kopf, MD, Oncology Section, Skin and Cancer Unit, New York University Medical Center, stated that he does not routinely remove small or medium congenital nevi. Dr. Marghoob has reported a 4.6% to 6.3% lifetime risk of the development of melanoma in medium-sized congenital nevi. Controversy about prognosis has always clouded management decisions for small- and medium-sized congenital nevi, but large and giant congenital nevi are certainly associated with increased risk.

Dr. Rivers[2] noted that lifetime risks of 6% to 10% are reported for the development of melanoma in large congenital nevi. Small congenital nevi are generally histologically more superficial, and melanomas develop at the dermo-epidermal junction. In contrast, large congenital nevi tend to extend much deeper; two thirds of melanomas have deeper origins, making clinical observation less useful in detecting them. Therefore, palpation is an important part of follow-up examinations. Furthermore, 60% of melanomas that develop in large congenital nevi do so within the first 10 years of life, especially during the first 5 years. This contrasts with melanomas that may arise in acquired nevi or medium congenital nevi, which are rarely seen before 18 years of age. Therefore, surgical removal of large congenital nevi, when possible, is recommended early.

Dr. Rivers[2] noted that the management of large congenital nevi involves several modalities. Staged excision is recommended when possible. This may be combined with grafting and tissue-expanding techniques. Curettage of large congenital nevi, done before 7 weeks of age (some before 2 weeks), has been advocated as producing superior cosmetic and functional results. The results, however, are variable. Close follow-up is required because this procedure does not remove deep foci of the nevus, which can eventuate in melanoma.

Dermabrasion has also been used to remove superficial nevi. Again, caution is advised because a case of multicentric melanoma has been reported in a 46-year-old patient 20 years after extensive dermabrasion. A variety of laser techniques are being evaluated to lighten and partially remove congenital nevi. However, experience is limited and there are no long-term follow-up data.

Large congenital melanocytic nevi are also associated with neurocutaneous melanosis where melanocytic rests are present within the brain or leptomeninges, and may be associated with severe neurologic symptoms. Dr. Marghoob has reported the presence of neurocutaneous melanosis in 2.3% of patients with large congenital nevi. However, the percentage is much higher in patients whose nevi involve the dorsal spine or scalp.

Foster and colleagues used brain magnetic resonance imaging (MRI) to study 46 high-risk patients who did not have neurologic symptoms and found that 23% exhibited T1 shortening indicative of neurocutaneous melanosis. One of 11 patients studied with spinal MRI showed a tethered cord. At 5-year follow-up, 1 of the 46 patients developed neurologic symptoms. Structural cerebral abnormalities, particularly of the posterior fossa, have been reported in these patients.
Another marker for the risk of neurocutaneous melanosis is the presence of numerous satellite nevi in patients with large congenital nevi. Dr. Marghoob has noted that neurocutaneous melanosis was present in 60% of patients with more than 50 satellite lesions. A review of large congenital nevi and their relationship with neurocutaneous abnormalities was published recently.\textsuperscript{23} MRI is indicated in large congenital nevi, especially if the lesions are axial.

From these data, one can see that both severe physical and psychosocial problems can result from the presence of large congenital nevi. \textit{Nevus Outreach} is a nonprofit health organization that supports patients, parents, and research endeavors.

**Familial Melanoma/Genetic Testing**

In addition to skin type and sun exposure, a very important risk factor for the development of melanoma is the history of a family member with melanoma. Melanoma kindreds have been identified that show germline defects in several genes that relate to cell-cycle regulation.\textsuperscript{24} Genetic testing would be a means of identifying individuals who would be at high risk for the development of melanoma to allow rigorous promotion of prevention tactics and close surveillance.

Sancy A. Leachman, MD, PhD,\textsuperscript{2} University of Utah School of Medicine, Salt Lake City, Utah, discussed the currently available gene tests and how to use them appropriately. She believes that the only currently available test of clinical value is \textit{p16} (\textit{CDKN2A}) analysis. This gene is a tumor suppressor gene and its gene product inhibits the CDK4 cell-cycle protein kinase, an important enzyme in the regulation of cell growth.\textsuperscript{25} Between 20\% and 40\% of melanoma families carry abnormalities in this gene, which is also associated with familial pancreatic cancer.

The \textit{p16} gene analysis test (\textit{Melaris}; Myriad Genetic Laboratories, Inc; Salt Lake City, Utah) is available clinically. However, Dr. Leachman noted that 95\% of patients with a melanoma will not have the \textit{p16} mutation, and she believes that if testing is desired it should be done only in patients who have already had a melanoma and who fulfill the following criteria:

- The melanoma patient has 3 or more melanomas in other family members;
- The melanoma patient has only 1 family member with melanoma, but either the patient or the family member has had multiple melanomas;
- The melanoma patient has a family member with melanoma and another with pancreatic carcinoma; and
- The melanoma patient has multiple primary melanomas (3 or more).

Dr. Leachman is adamant that pre- and posttest counseling as well as referral to a facility with a research protocol is mandatory. A good resource for identifying genetic counselors is the National Society of Genetic Counselors.

When a decision is to be made concerning genetic testing, it must be remembered that there is a high incidence of melanoma in patients without identifiable mutations in melanoma-prone families, there is a large variation of penetrance, and that all patients with risk factors should practice preventative measures (sun protection) and be closely monitored. For these and other reasons, Kefford\textsuperscript{26} recently wrote, "It is currently premature to offer predictive DNA testing for melanoma outside of defined research protocols."

**References**

Melanoma Update 2003: Diagnosis and Prognosis

Barbara A. Burrall, MD

Introduction

The definitive diagnosis of melanoma is made histologically, sometimes with the help of special immunofluorescent stains that stain melanocytes. Tumor thickness in millimeters (Breslow thickness) is measured from the granular layer of the epidermis to the deepest tumor cells. In thin tumors (< 1 mm), the Clark's level of invasion (I-V) is also determined. However, diagnosis and correct thickness measurement may be difficult if the entire lesion is not included in the biopsy specimen. Therefore, whenever possible, suspicious lesions should be entirely removed for examination. Generally, this is done by excision, but Darrell S. Rigel, MD, 

Clinical Professor of Dermatology, New York University Medical Center, New York, NY, believes that a correctly performed saucerization shave will also yield an appropriate specimen, because in 88% of cases the entire lesion will have been removed. Generally, with a 2-mm margin around the visible lesion, 99% of lesions are completely removed. In large, suspicious lesions for which complete removal would produce a severe cosmetic deficit, such as with large lesions on the face, punch or incisional biopsies of suspicious areas are acceptable and do not increase the risk of spread.

The use of a Wood's light may help delineate the true margin. In the melanoma symposium held at the 61st Annual Meeting of the American Academy of Dermatology, Lisa Cohen, MD, 

Cohen Dermatopathology, Newton, Massachusetts, emphasized that it is imperative to give the dermatopathologist clinical information about the lesion and its location to aid in correct diagnosis. If a small biopsy is being taken from a large lesion, make sure that the pathologist knows this.

Identification of the appropriate pigmented lesions to remove requires considerable clinical expertise. The patient's history of a new, growing, or changing lesion is often helpful. However, both the patient's and doctor's memory may not be able to note subtle changes or recognize new lesions. Some patients with familial atypical nevi have hundreds of atypical nevi and, in these patients, changes are nearly impossible to detect unaided. Total-body photographic surveillance has been increasingly used to document baseline nevi for comparison at follow-up sessions. Kelly and colleagues reported that 11 of the 20 new melanomas detected in a population of 278 adults were found because of changes apparent in comparison with baseline photographs. Efficient digital systems are now also in operation at many medical centers.

Dermoscopy
Many atypical or dysplastic nevi and even some seborrheic keratoses and basal cell carcinomas are difficult to distinguish from melanoma. The technique of dermoscopy (epiluminescence microscopy) is now helping many dermatologists distinguish lesions that really need removal. Dermoscopy does not replace standard clinical inspection, but may be used as a second-level form of examination. A hand-held dermoscope, using an oil immersion or alcohol technique, allows macroscopic examination to the dermoepidermal junction.

Bafounta and colleagues[5] reviewed the available original studies on dermoscope use and concluded that for experienced users, dermoscopy is more accurate than clinical examination alone for the diagnosis of melanoma. Sensitivities of 90% to 95% in very experienced users can be attained, compared with 70% to 80% for clinical inspection.[6] Several systems of pattern analysis have been suggested, some of which partially use the ABCD principles. Most systems give attention to features such as asymmetry, irregular pigmentation network, blue-white veil, irregular streaks, dots or globules, and multiple colors to make the diagnosis. Slightly different criteria are used to evaluate lesions on the palms, soles, and face. Specific criteria to classify dysplastic nevi have also been described.[7] Web sites that provide dermoscopy tutorials are found at http://www.dermoscopy.org and http://www.dermoncology.com.

Prognostic Factors

Balch and colleagues[8] analyzed data from numerous single-institution studies that included data from 17,600 patients. In patients without evidence of nodal metastases, tumor thickness (mm) and the presence or absence of ulceration were the most important prognostic factors. Only for thin tumors (< 1 mm) did the Clark's level of invasion have significance. Tumor thickness was the single most powerful prognostic factor when melanoma was localized. However, in 4750 patients without clinical evidence for nodal metastasis who had their regional nodes examined pathologically after elective or sentinel lymphadenectomy, nodal status was the most important prognostic factor, followed by tumor thickness and ulceration.

In patients with metastatic melanoma in lymph nodes, the number of positive nodes was the most significant predictor of survival. Tumor burden (microscopic or macroscopic involvement) was the next most significant factor. In the lymph-node-positive patients, ulceration was the only characteristic of the primary tumor that had further adverse predictive value. According to Balch's group,[9] "The biologic events associated with invasion of a primary melanoma through the overlying epidermis rather than simply displacing it upward is clearly associated with a greater capacity to metastasize." Of course, distant metastases confer the worst prognoses.

Staging

Evaluation of the prognostic data from the 17,600 patients discussed above allowed the American Joint Committee on Cancer (AJCC) staging committee to assign staging designations, which have been finalized. The following Table summarizes the new system. It can be seen that tumor ulceration seems to decrease survival in every stage except IV.

<table>
<thead>
<tr>
<th>Pathologic Stage</th>
<th>5-Year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA thickness 1 mm or less</td>
<td>95.3%</td>
</tr>
<tr>
<td>IB thickness 1 mm or less, ulceration or level IV, V thickness 1.01-2.0 mm</td>
<td>90.9%</td>
</tr>
<tr>
<td>IIA thickness 1.01-2.0 mm, ulceration thickness 2.01-4.0 mm</td>
<td>77.4%</td>
</tr>
<tr>
<td>IIB thickness 2.01-4.0 mm, ulceration thickness &gt; 4.0 mm</td>
<td>63.0%</td>
</tr>
<tr>
<td>IIC thickness &gt; 4.0 mm, ulceration</td>
<td>45.1%</td>
</tr>
<tr>
<td>IIIA any thickness, 1 node pos, microscopic</td>
<td>69.5%</td>
</tr>
<tr>
<td>IIIA any thickness, 2-3 node pos, microscopic</td>
<td>63.3%</td>
</tr>
<tr>
<td>IIIB any thickness, ulceration, 1 node pos, microscopic</td>
<td>52.8%</td>
</tr>
<tr>
<td>IIIB any thickness, ulceration, 2-3 node pos, microscopic</td>
<td>49.6%</td>
</tr>
<tr>
<td>IIIB any thickness, no ulceration, 1 node pos, macroscopic</td>
<td>59.0%</td>
</tr>
<tr>
<td>IIIB any thickness, no ulceration, 2-3 node pos, macroscopic</td>
<td>46.3%</td>
</tr>
</tbody>
</table>
Melanoma Update 2003: Management

Barbara A. Burrall, MD

Guidelines

The American Academy of Dermatology (AAD) Guidelines/Outcomes Committee published their guidelines for the care of primary cutaneous melanoma in 2001.[1] After the histologic diagnosis is made on the conservatively excised melanoma, resection is required, and the recommended resection margin is determined by the thickness of the primary tumor. A number of studies have shown that thinner margins provide local tumor control similar to that of the old, traditional 4- to 5-cm margins.

The World Health Organization Melanoma Group showed that a 1-cm margin was as effective as a 3-cm margin for tumors < 2 mm thick.[2] Furthermore, Balch and colleagues[3] determined that for primary tumors with a thickness of 1-4 mm, a 2-cm margin of resection was as beneficial as a 4-cm resection margin. In response to these studies, the current guidelines practiced in most centers are:

<table>
<thead>
<tr>
<th>Tumor Thickness</th>
<th>Clinical Excision Margin</th>
</tr>
</thead>
<tbody>
<tr>
<td>In situ</td>
<td>0.5 cm</td>
</tr>
<tr>
<td>&lt; 1 mm</td>
<td>1 cm</td>
</tr>
<tr>
<td>1-2 mm</td>
<td>2 cm</td>
</tr>
<tr>
<td>&gt;/= 2 mm</td>
<td>2 cm</td>
</tr>
</tbody>
</table>

As Allan C. Halpern, MD,[4] Memorial Sloan-Kettering Cancer Center, New York, NY, noted at the 61st Annual Meeting of the AAD, for 1- to 2-mm tumors, a 2-cm margin generally is preferred, if possible. Currently, the appropriateness of a 1-cm margin in these patients is being studied.

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References

The AAD task force members believed that the evidence was strong that routine studies such as chest x-ray and blood work (lactic dehydrogenase) have limited value in the initial work-up of asymptomatic patients with primary tumors of 4 mm or less in thickness.[1] Dermatologists vary widely in their practices about ordering chest x-ray and laboratory tests. The task force recommends that studies such as these be obtained if evidence gathered during a thorough medical history and physical examination suggests suspicious findings. Recognizing that doing these tests may alleviate physician and patient anxiety, they recommend that obtaining these studies be optional if there is no evidence from the history and physical exam to indicate systemic involvement.

Role of Mohs Micrographic Surgery

Mohs micrographic surgery is a very controversial modality for melanoma treatment and is usually advocated for melanoma in situ (lentigo maligna) of the face or other cosmetically sensitive areas. This technique involves conservative tissue removal with preparation of frozen sections so that the entire circumferential border and deep margins are visualized. As with micrographic surgical treatment of nonmelanoma skin cancer, if a margin is positive, additional tissue is taken until clearing is achieved. Some Mohs surgeons then take an additional margin to be sent for permanent sections.

Ronald L. Moy, MD,[5] University of California at Los Angeles, pointed out at the AAD meeting that one of the main areas of controversy surrounding this procedure for melanoma is the concern about accuracy of diagnosis of melanoma in the frozen section slides. He believes that an experienced Mohs surgeon can achieve a sensitivity of 100% but a specificity of 90% due to the confusing appearance of single, atypical cells which may be seen in photodamaged skin that is not involved with tumor. Special stains such as S-100, Melan-A, HMB-45, and Mart-1 may aid in the diagnosis histologically. Dr. Moy also asserted that there is a steep learning curve for the procedure and that specificity and sensitivity vary widely among surgeons.

Another variation, "slow Mohs," employs Mohs surgery and tissue orientation technique, but permanent, traditionally processed slides are made. The patient's wound is not closed, and after viewing the permanent sections the next day, a decision is made whether to remove more tissue.

Besides possible tissue conservation in sensitive areas, another reason for promoting this procedure is that tumor extension beyond visible, clinical change is highly irregular and variable, so prescribing a set surgical margin can lead to recurrences. Zitelli[6] treated 553 patients, the majority of whom had melanoma in situ or melanoma with thickness < 0.76 mm; the most common location treated was the head and neck. Margins of 6 mm, 9 mm, and 1.2 cm were required to clear 83%, 95%, and 97% of the tumors, respectively.

Immune Response Modifiers

Immune response modifiers are nonendogenous substances that are used to modify immune responses. Mark Naylor, MD,[5] University of Oklahoma Health Sciences Center, Oklahoma City, reported using imiquimod in the treatment of selected melanoma in situ tumors. This treatment was first reported in an elderly patient who refused surgery.[7]

Imiquimod binds to a member of a class of receptors, called toll-like receptors (TLR), on antigen presenting cells. In particular, imiquimod binds TLR-7, and, as a result, genes are upregulated that lead to activation, cytokine release, and recruitment of additional antigen presenting cells. The drug seems to be active in inciting an immune response in all of the types of skin cancer in which it has been tried. Dr. Naylor treated 28 patients with lentigo maligna in whom imiquimod (5%) was applied daily for 3 months. Inflammation appeared within 1 week and was severe, leading to ulceration in some patients. Four quadrants and any remaining areas of pigment were biopsied. Twenty-six of the 28 patients had clearing histologically and have remained clear over 1 year of follow-up. At least 5 years of follow-up will be required to more fully evaluate for recurrences. Although Dr. Naylor was optimistic about this new treatment, he urged practitioners not to use this modality except under a closely monitored research protocol.

Sentinel Lymph Node Biopsy

Timothy M. Johnson, MD,[5] University of Michigan, Ann Arbor, recommended the use of sentinel lymph node biopsy (SLNB) in patients with melanomas of 1 mm or greater. With melanomas < 1 mm the chances of a positive SLNB are low -- approximately 5%.

Evidence has accumulated for the great utility of this examination. Prior to the re-excision of the primary melanoma, a radiographic tracer is injected at the tumor site (lymphoscintigraphy). A gamma probe may be used intraoperatively for best results. A visible dye is also often used. Later, the regional nodal basins are examined for localization of radioactivity. The "sentinel" node or nodes that receive initial, direct drainage from the tumor site can be accurately identified more than 98% of the time when both radiocolloid and visible dye are employed.[8,9] Morton and colleagues[9] found in a multicenter study of 1135 patients that after completing 30 SLNB procedures, surgeons could perform the procedure as accurately as surgeons who were much more experienced.

The procedure has few side effects. Mild-to-moderate lymphedema developed in only 1.7% of patients evaluated at Massachusetts General Hospital, and some of these patients had potential contributing causes.[10] The value of the procedure
in staging cannot be equaled by any other procedure. In a large multicenter study, Gershenwald and colleagues[^8] showed SLNB-determined nodal status to be the most important predictor of survival in melanoma stage I and II patients. Because it is such a strong prognostic factor, SLNB is required to define homogeneous patient populations for current clinical trials.

Though prior studies are frequently cited to show that elective lymph node dissection does not improve survival, it would have been difficult to show benefit, because only about 20% of patients with intermediate-thickness melanoma have subclinical nodal metastases. Therefore 80% could not possibly benefit.[^11] Furthermore, in lymph node dissections that are undirected by lymphoscintigraphy, the incorrect nodal basin could be chosen for surgery in up to 32% of cases, making a benefit of node removal even harder to demonstrate.[^12] A recent large study of 1117 patients evaluated by SLNB demonstrated very unusual sites for lymph node metastasis in 5%.[^13] These unusual sites included popliteal (13%), epitrochlear (14%), and ectopic/interval (73%). Another study showed that in 84% of the patients with a positive interval node, that node was the only positive node.[^14]

When only patients who actually had nodal metastases were considered, the 5-year survival rate was 48.2% in patients who had immediate lymph node removal that showed occult metastases vs 26.6% of patients who had node dissection delayed until the appearance of overt regional metastases.[^15] Therefore, the use of SLNB may identify patients who could benefit from lymph node dissection. The final proof of a survival benefit or lack thereof awaits the completion of the Multicenter Selective Lymphadenectomy Trial.

A recent multidisciplinary consensus panel, using the RAND/UCLA Appropriateness Method, judged SLNB to be appropriate when melanoma primaries are 1 mm or greater in thickness.[^16] Further commentary detailing the use and benefit of SLNB is also available.[^14,17]

SLNB is also important in identifying patients with occult nodal metastases who would therefore qualify for high-dose interferon alfa-2b treatment. Interferon alfa-2b was approved by the US Food and Drug Administration for adjuvant therapy in melanoma patients with thick tumors (> 4 mm) and patients with stage III (nodal) disease. This approval was based on the results of the Eastern Oncology Group (ECOG) trial E 1684.[^18] Though equivocal results were found in a second study, possibly due to the use of interferon in patients after relapse in the observation arm of the trial, a third trial (ECOG 1694) seemed to reaffirm survival benefit and was terminated early.[^19]

The study has been criticized because interferon was not compared with observation but with a vaccine therapy. One must remember that morbidity is significant in this year-long treatment. Nevertheless, the same multidisciplinary consensus panel using the RAND/UCLA Appropriateness Method judged it appropriate for patients with regional nodal and/or in-transit metastasis and for node-negative patients with thick primary melanomas.[^16]

**Follow-up**

There are no real data to suggest specific follow-up intervals for melanoma patients. Different institutions recommend slightly different intervals for skin examination, but all agree with "at least annually for life." The AAD Guidelines Committee recommends follow-up 1-4 times per year for 2 years; the interval is to be guided by the thickness of the primary tumor. After 2 years, evaluation 1-2 times per year is suggested.

At these appointments, physician skin and lymph node exams are performed and laboratory/x-ray data are evaluated (optional). Total-body skin exams as well as lymph node palpations are mandatory. Dr. Johnson reported that in melanoma patients, the incidence of a second primary melanoma is about 5%. Forty-two percent of subsequent melanomas were found within 3 years of the initial diagnosis.[^20] Dr. Johnson[^5] examines his low-risk patients (melanoma < 1 mm or > 1 mm with negative SLNB) every 6 months for at least 1 year and then annually. His higher-risk patients (> 1 mm without SLNB) are examined every 3 months. Dr. Halpern[^4] examines his patients every 3-4 months for several years, depending roughly on the patients' number of nevi and their ability to examine themselves. Dr. Johnson places importance on a patient's perception of change in a lesion, which he believes is the earliest sign of melanoma. He notes that "itch" is the earliest symptom that a patient might notice. A low threshold of suspicion is advised for removal of nevi in these patients. Patient education, particularly instruction about self-examination, is essential, because there is evidence that, most frequently, metastases and recurrences are discovered by the patient or a family member.[^1]

Besides teaching patients about surveillance, sun protection strategies are an essential part of patient education. Sun avoidance behavior, use of protective clothing, such as a 4-inch broad-brim hat, and adequate use of a broad-spectrum sunscreen should be stressed. June K. Robinson, MD,[^4] Loyola University, Chicago, Illinois, noted that most patients apply too little sunscreen, achieving only 27% of the sun protection factor stated on the label. In addition, sunscreen is typically applied unevenly and areas are often missed entirely. Linking sunscreen application to part of the daily routine such as brushing teeth or shaving also helps compliance.

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Psoriasis and Quality of Life

Psoriasis is a common skin disorder and was the subject of many discussions and posters at the 61st Annual Meeting of the American Academy of Dermatology (AAD).

Because psoriasis and psoriatic arthritis are chronic diseases that are not curable, and physicians have no adequate treatment, the quality of life (QOL) of psoriasis patients may suffer greatly. Psoriasis is widely agreed to have an impact on health-related QOL, meaning that the disease affects patients' functional health, their sense of well-being, and their participation in activities. Psoriasis, especially psoriatic arthritis, is associated with physical and mental disabilities, and may also increase the incidence of alcohol and obesity. The disease has a greater effect on patients who are having an active episode than it does on patients in remission, and patients with depressive symptomatology report a higher impact of psoriasis on their QOL than those without depressive symptomology.

This relationship between psoriasis and depressive symptomatology was elucidated in a poster presented at the AAD meeting.[1] Fifteen hundred psoriasis patients were queried by mail. Six hundred thirty seven (42.5%) returned the report, and of these approximately half were in remission and half had active disease. Fifty four percent of patients experiencing an active episode of...
Psoriasis and 42% of patients in remission had identifiable depression.

In another poster presentation, there was a striking correlation between improved QOL as measured by the Dermatology Life Quality Index and medication adherence as measured by psoriasis pill counts. It appears that compliance is a major factor related to the QOL of patients with psoriasis, although it is not clear which comes first: Does better QOL yield better compliance or does better compliance give better QOL?

When determining the QOL of psoriasis patients, Alexandra B. Kimball, MD, MPH,[3] Stanford University Medical School, Palo Alto, California, recommended using a combination of skin-specific and general questionnaires, such as the Skindex-29 and Short Form-36, respectively. The Psoriasis Quality of Life (PQOL) questionnaire is also useful, but uses 42 items, which can make the process more time-consuming.

The PQOL has been abbreviated into a 12-item questionnaire called the PQOL-12. This questionnaire covers self-consciousness, helplessness, embarrassment, anger/frustration, emotional well-being, capacity to enjoy life, itching, physical irritation, pain/soreness, and influence on choice of clothing. Findings have shown adequate construct validity and reliability for the abbreviated questionnaire, although psychometric validation still needs to be completed.

The Psoriasis Area and Severity Index (PASI) and other instrument scores do not correlate well with the PQOL, although the PASI is an important measure to evaluate psoriasis and psoriasis improvement with treatment.

Psoriasis in Children

Some precipitating factors of childhood psoriasis include streptococcal infection, Kawasaki disease, HIV, Turner/Down syndrome, drugs, trauma, and stress. Of these factors, streptococcal infection is the most common. This brings up the question of whether antibiotic treatment and/or tonsillectomies are useful treatments for childhood psoriasis. The answer is still unclear because there are few randomized, controlled trials enrolling children under the age of 16.

Most children with psoriasis are managed with topical treatments, and calcipotriol is a good choice. Trials on the use of tacrolimus for inverse psoriasis are ongoing. The 0.03% ointment formulation of the drug has US Food and Drug Administration (FDA) approval for the treatment of atopic dermatitis in children 2 years of age and older, and it causes no skin atrophy.

If a child has severe psoriasis, systemic treatment may be used. Phototherapy and retinoids are first-line systemic treatments for psoriasis in children. However, side effects of retinoids include osteoporosis, skeletal hyperostosis, growth retardation, and teratogenicity.

Of the new biologic medications, only etanercept is FDA-approved for children (for the treatment of juvenile rheumatoid arthritis), but its use in childhood psoriasis is not well characterized. Trials are ongoing with biologics, but, as Amy J. Theos, MD,[3] pointed out during the Psoriasis Symposium, their effect on children is as yet unknown.

Phototherapy

Phototherapy is a good treatment for psoriasis; however, poor reimbursement and other disincentives are preventing many physicians from prescribing it. At present, broad-band UVB, narrow-band UVB, and psoralen + UVA (PUVA) are the most commonly used phototherapies for psoriasis. Herbert Honigsmann, MD,[3] University of Vienna, Austria, presented studies demonstrating that PUVA has superior efficacy compared with narrowband UVB and provides longer remission. Bath PUVA has advantages over oral PUVA because it can be localized and fewer treatments are needed, so the cumulative dose of UVA is decreased. This may lead to fewer skin cancers developing.

In the future, we may see the increased use of excimer lasers. Excimer lasers are more expensive than other phototherapies; however, advantages of excimer laser treatment include cumulative doses of UVB 6.5 times less than narrowband UVB, fewer treatments, and no exposure to healthy skin. Other forms of localized UVB may offer similar advantages without the costs that are associated with laser treatment.

Combination therapy with alefacept and narrowband UVB is a treatment on the horizon which may offer more rapid psoriasis clearance. In a study of combination therapy with alefacept and UBV light, 30 patients were randomized to either alefacept alone, alefacept plus 6 weeks of narrowband UVB, or alefacept plus 12 weeks of narrowband UBV.[5] One hundred percent of the patients receiving alefacept plus either course of UBV achieved PASI 75 (75% or greater PASI improvement). It is interesting to note that 80% of subjects receiving alefacept alone achieved PASI 75. It appears from this small study that the combination of alefacept and ultraviolet light is well tolerated. While the combination appears quite effective, alefacept alone in this study appeared more effective than it has in previously reported trials.

New Vehicles, New Formulations

New formulations of clobetasol propionate 0.05% were introduced. A poster introduced a clobetasol propionate 0.05% spray, which seems effective in reducing the severity of plaque psoriasis with few side effects.[6] Another poster demonstrated that a clobetasol propionate shampoo was efficacious in treating moderate-to-severe scalp psoriasis.[7] In an efficacy study, topical
cyclosporine was shown to produce a modest improvement in psoriasis, but higher skin concentrations of cyclosporine were needed when used topically vs orally.\[8\]

**Oral Pimecrolimus**

Topical pimecrolimus 1% cream is an approved treatment for atopic dermatitis, and an oral form of the drug is currently being investigated as a treatment for psoriasis.

A randomized, double-blind, placebo-controlled, multiple rising-dose study of the safety, tolerability, and efficacy of oral pimecrolimus was performed in patients with moderate-to-severe chronic plaque psoriasis.\[9\] Forty-seven patients completed the study. Drugs were given for 4 weeks in doses ranging from 5 mg once daily up to 30 mg twice daily. The 20-mg and 30-mg twice-daily groups had PASI improvements of 60% and 75%, compared with -4% for placebo-treated patients. Glomerular filtration rate and renal plasma flow were unaffected by the medication. The development of an oral immunosuppressive agent without the renal toxicity associated with cyclosporine is a potential major advance.

Alice Gottlieb, MD,\[3,10\] The University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, New Brunswick, New Jersey, presented a larger oral pimecrolimus study of longer duration. Ten, 20, and 30 mg of oral pimecrolimus twice daily were tested for 12 weeks in a randomized, double-blind placebo trial. A total of 143 patients were randomized at 19 international centers. There was clear evidence of a dose response, as the 30-mg dose was the most effective, with slightly more than half of the 30-mg group achieving PASI 75. There were no differences among groups with respect to overall rates of adverse events. Feeling hot and headache were the most common adverse events. If confirmed in larger, longer trials, the efficacy and safety profile of oral pimecrolimus may prove to be a major advance for patients with cutaneous inflammatory diseases.

**Combination Therapies**

The combination of calcipotriol and tazarotene is comparable in efficacy to clobetasol. Therefore, by using this combination, the dermatologist can avoid topical corticosteroids. However, prudent use is advised, because both calcipotriol and tazarotene are irritating.

Acitretin can be safely used with methotrexate, although liver enzymes should be monitored. The combination of cyclosporine and methotrexate at low doses has been shown to improve psoriasis and is safer than using either drug alone because the combination requires less of each drug. Biologics in combination with methotrexate are now being tested in clinical trials. Mark Lebwohl, MD,\[3\] Mount Sinai School of Medicine, New York, NY, suggested avoiding this combination unless the dermatologist is weaning the patient off one drug to add the other. In rheumatoid arthritis patients, however, TNF alpha inhibitors (etanercept, infliximab) are often used in combination with methotrexate, and in some cases (particularly with infliximab) the combination may be advantageous.

A poster presentation compared the rates of adverse events in patients enrolled in 2 phase 3 alefacept trials who were on concomitant immunosuppressant therapy (methotrexate, cyclosporine, prednisone, etanercept, leflunomide, infliximab, mycophenolate mofetil). There were 21 patients in the alefacept IV study and 4 patients in the IM study, compared with 22 patients in the placebo group. No serious infections were reported in any of the patients who used concomitant immunosuppressive therapies. Moreover, there were no patterns in T-cell counts to suggest any greater increased risk of T-cell-count reduction in patients on combined therapies.

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**Immunobiologics for Psoriasis**

Steven R. Feldman, MD, PhD  Judy Hu, MD

**Psoriasis as a Chronic Immune Disease**

Although psoriasis primarily affects the skin, it is caused by the actions of the immune system. The immune system pathways involved in psoriasis are quite complex, and our understanding of these systems is rapidly evolving. While a complete summary of the immune function is beyond the scope of this article, we can consider those elements that are relevant to new and evolving treatment options.

An essential element of immune activity is the T cell, which plays a key role in orchestrating the activity of the immune system. T cells are activated by interactions with antigen-presenting cells. These cells present antigen to the T-cell receptor on the T cell. In addition, several other protein-protein interactions between the antigen-presenting cell and the T cell are essential to binding these 2 cells together and to effective signaling and activation of the T cell. Activated T cells travel to lymph nodes, where there is further activation and proliferation. Cytokines also participate in the signaling and proliferation processes. T cells then traffic back to the skin, where they effect development of the psoriasis phenotype. The migration to the skin is effected by expression of adhesion molecules on the vascular epithelium and by cytokines that serve to attract and direct T cells and other inflammatory cells. This multistep process provides multiple targets for intervention in psoriasis (as well as other immune-mediated diseases). These include blockade of T-cell activation, T-cell trafficking, T-cell proliferation, and cytokine messengers.

**Biologics for Psoriasis**

**Infliximab**

Infliximab (*Remicade*) is a hybrid human-mouse antibody that has US Food and Drug Administration (FDA) approval for treatment of Crohn's disease and rheumatoid arthritis. Clinical trials have shown rapid clearance of psoriasis and remissions that last for months after 3 injections.

In one of the more exciting reports presented at the 61st Annual Meeting of the American Academy of Dermatology, results from a 10-week, multicenter, randomized, double-blind, vehicle-controlled, phase 2 trial of infliximab in psoriasis were reported in a poster presentation.[1] Patients were 18 years of age or older and had moderate-to-severe plaque-type psoriasis (10% or more body surface area involvement and a Psoriasis Area and Severity Index [PASI] > 12) for more than 6 months. Patients were treated with placebo or 3 mg/kg or 5 mg/kg of infliximab at weeks 0, 2, and 6. The primary end point of PASI 75 (75% or greater PASI improvement) was assessed at week 10. Nearly 90% of patients in the 5-mg/kg infliximab group achieved PASI 75, while 72% of the patients in the 3-mg/kg group achieved PASI 75. These striking results not only confirm previous reports of infliximab in the treatment of psoriasis, but they also appear even more impressive, with a very high response rate and a low 6% PASI 75 in the placebo group.

**Alefacept**

Alefacept (*Amevive*) is a fusion of LFA-3 to the Fc portion of IgG1 and was approved on January 31, 2003 for the treatment of moderate-to-severe chronic plaque psoriasis. In phase 3 trials presented by Gerald Kreuger, MD,[2] University of Utah, Salt Lake, during the psoriasis symposium, alefacept achieved good response rates that continued to improve weeks after dosing. Forty percent of subjects achieved PASI 75.

One of the concerns about the use of alefacept has been that the drug reduces circulating T-cell counts. A poster presentation addressed this issue by looking at circulating T-cell subsets among placebo-treated patients with psoriasis in alefacept studies.[3] Significant reductions in T-cell counts were seen in some patients on placebo: 1% to 2% of placebo-treated patients developed T-cell counts less than 300, and 6% to 9% had T-cell counts below 400. The study authors concluded that psoriasis patients who were given placebo can experience a considerable degree of variability in their circulating T-cell counts, including
reductions below the lower limit of normal, and that these findings suggest that variability in T-cell counts may occur with psoriasis, regardless of therapy.

Another important poster on alefacept looked at clinical improvements in both skin lesions and arthritis correlated with the reduction in T cells in skin and synovial tissues. This small study enrolled 11 patients. Patients received alefacept 7.5 mg IV for 12 weeks, followed by a 4-week observation phase. End points included assessments of joint swelling and tenderness, PASI, and synovial biopsies. Arthritis improved, as evidenced by reductions in the tender and swollen joint counts. PASI scores improved by approximately 30%, and synovial biopsies showed improvement, with decreased inflammation in the synovium. This very small study suggests that alefacept will be effective for psoriatic arthritis in patients who are treated for psoriasis.

Efalizumab

Efalizumab (Raptiva) is a humanized monoclonal antibody of CD11a that works by blocking T-cell binding and trafficking into the dermis and epidermis. Efalizumab is undergoing phase 3 trials and, so far, has been shown to be effective, safe, well tolerated, and to have a rapid response.

The safety and efficacy of long-term treatment with efalizumab in patients with psoriasis was described in a poster presentation. During the initial 12-week treatment period, 339 patients received 2 mg/kg of subcutaneous efalizumab weekly. At the end of this treatment phase, 41% of patients had achieved PASI 75 and 80% had achieved PASI 50. Patients who achieved at least PASI 50 or an overall lesion severity of mild, minimum, or clear were then eligible to enter the open-label maintenance phase, in which subjects were maintained on 1 mg/kg of subcutaneous efalizumab weekly. In the event of relapse (defined as a loss of greater than 50% improvement of the PASI achieved during the first 12 weeks of treatment), patients had their efalizumab dose increased to 2 mg/kg weekly. Patients maintained their response through 60 weeks (12 weeks of treatment and 48 weeks of maintenance). Of the 228 patients who continued to receive efalizumab, 80% maintained PASI 50 and 65% maintained PASI 75. The major limitation of this study is that an intent-to-treat analysis was not performed and only 228 of the original 339 patients remained in the study through week 60. No new adverse events emerged during continuous, long-term efalizumab therapy. The most frequently reported adverse events included nonspecific infections such as cold and upper respiratory tract infections.

Etanercept

Etanercept (Enbrel) also shows significant improvement over placebo and is the only TNF-alpha inhibitor currently approved by the FDA for the treatment of psoriatic arthritis.

In phase 2 psoriasis trials at a dose of 25 mg twice a week, approximately 30% of subjects achieved PASI 75 at week 12 and over 50% at week 24. Phase 3 study data in psoriasis have been presented. Similar findings were observed; however, at a higher dose of 50 mg twice a week, nearly 50% of subjects achieved PASI 75 at week 12 and over 60% at week 24. Etanercept treatment appears to be a very good option for patients with psoriasis, particularly those with psoriatic arthritis.

Biologics vs Standard Treatment

How do biologics compare with standard psoriasis treatments? A comparison of methotrexate and alefacept yielded similar responses. The only side effect that presented more frequently with alefacept than with methotrexate was chills, which were associated with IV infusion. The reduction of pathogenic T cells may explain the duration of remission with alefacept. T-cell counts recover to normal limits in 100 days and no cumulative effect on T cells with increased doses of drug was found.

Office Aspects of Biologics

All biologics are parenteral and given as either an intravenous infusion, intravenous bolus, or intramuscular injection. To administer biologics in the office, a standard of practice is needed for the office staff. Precise and complete medical records must be kept for documentation, and a letter of medical necessity is usually required for insurance companies, although Medicare will not cover patient-administered drug. Patient education must take place as well, so that the patient understands the disease and can be part of medical decision making. Patients also need adequate training to administer the drug to themselves.

The contact lines for the biologic medications are:

Alefacept: 1-866-AMEVIVE
Etanercept: 1-888-4ENBREL
Infliximab: 1-800-REMICARE

Alefacept may be obtained through the Amevive Start Assistance Program (ASAP), a Biogen-supported program that helps initiate the order of alefacept to an office.

References
Notes on the Treatment of Acne

Arthur C. Huntley, MD

Treatment of acne continues to be important to the dermatologist. Over the last year, several refinements in the treatment of acne have emerged. These notes are drawn from recent journal articles, presentations at the recent American Academy of Dermatology meeting, and ongoing discussions of the RxDerm-L dermatology discussion group.

Antibiotics

Low-Dose Doxycycline for Acne

There has been recent discussion about using sub-MIC (minimal inhibitory concentration) doses of doxycycline in the treatment of acne.[1] Sub MIC doses are said to decrease levels of interleukin-1 and interleukin-6 and metalloproteinase enzyme activity, which are inflammatory mediators. The sub-MIC dose of doxycycline is 20 mg twice daily, which is not equivalent to 50 mg once a day because the latter dose is above the MIC. Sub-MIC doses are purported to decrease inflammation without drug resistance, photosensitivity, and yeast infections. In phase 2 trials for acne, after 6 months of treatment with doxycycline 20 mg twice daily, there was a greater than 50% reduction in both comedones and inflammatory lesions.[2] Visible results were achieved at 2 months. Because of this relatively slow onset of action, low-dose doxycycline may be more helpful for maintenance than for induction.

Trimethoprim-Sulfamethoxazole for Severe Acne

Sulfa drugs are less often used for acne today, probably due to the higher frequency of adverse reactions. Nevertheless, they may have a role when other antibiotics have failed, especially when isotretinoin is not an option.[3] Some dermatologists claim that the response to trimethoprim-sulfamethoxazole is as impressive as the response to isotretinoin. However, unlike isotretinoin, the effect of trimethoprim-sulfamethoxazole is not sustained after it is stopped. If one is concerned about possible side effects, then for how long is it safe to use this combination? It appears that the adverse effects almost always occur in the first 4-6 weeks of treatment. Long-term (more than 1 year) treatment is common in pediatric patients undergoing prophylaxis for chronic ear and bladder infections. Nevertheless, it is still advisable to check laboratory parameters periodically. One suggestion for reducing the dose is to administer it as 1 tablet at bedtime. The kidneys decrease in activity during the night, and substantial drug excretion doesn't occur until the morning.

Isotretinoin Failures That Are Not

Many patients termed "isotretinoin failures" may, in fact, have nonacne lesions or have complicating factors. These patients are best treated by identifying the problem and modifying treatment accordingly.

Follicular Forehead Papules in the Acne Patient

Some acne patients present with profuse follicular papules on the forehead and sometimes on the shoulders. This follicular involvement is separate from the acne, and may be a response to an overgrowth of Pityrosporum.[4] The condition seems to respond to antifungal treatment. While selenium sulfide applications may be adequate for achieving resolution, topical delivery may not provide sufficient penetration for full effect. Furthermore, some patients do not tolerate selenium sulfide on the skin for
long time periods.

Another choice of therapy for *Pityrosporum*-induced follicular papules is oral ketoconazole. Unlike other imidazoles, ketoconazole is lipophilic. A typical dosage regimen is ketoconazole 200 mg/day for 5 days followed by 400 mg once a week for 5 weeks (15 capsules total dose). Administering ketoconazole with grapefruit juice may enhance its effect. Although ketoconazole has antiandrogenic properties, the rapid response to a relatively low dose is more consistent with its antifungal properties.

**Sinus Tracts**

What may appear to be a failure of cystic acne treatment with isotretinoin is the presence of sinus tracts.[5] Often linear in presentation, sinus tracts are tongues of undermining epithelium dissecting into the surrounding skin. These are similar to the sinus tracts that develop in hidradenitis suppurativa or in pilonidal cysts. The development of sinus tracts appears to be a genetically determined response of the follicular epithelium. Patients often describe these as expanding cysts. The clinician may observe that the injection of 1 lesion will result in the expansion of an adjacent cyst. Although sinus tracts usually manifest in teenage patients, they may also present in young children or even infants.

First-line treatment of sinus tracts is intralesional corticosteroids. Lesions should be cultured frequently and antibiotics administered when indicated. Persistent lesions may require excision to achieve resolution.

**Excess Granulation Tissue**

At times the clinician may be confronted with the development of hemorrhagic, crusted lesions in patients receiving isotretinoin.[5] These lesions do not represent a flare of the acne but rather the development of pyogenic granulomas. This phenomenon is most often observed with the usual 1 mg/kg oral isotretinoin, but may even occur with topical tretinoin.

When encountering these hemorrhagic lesions, the instinctual response may be to increase the dose of isotretinoin. However, pushing the dose may result in fever, arthralgias, and time away from work or school. Proper treatment is actually to reduce the dose. When a patient is being evaluated as a candidate for isotretinoin, look for evidence of existing granulation tissue, such as the presence of crusted lesions or blood on a T-shirt. Patients who present with hemorrhagic lesions should be started on low-dose isotretinoin, 0.1 mg/kg/day, and that dosage should be slowly increased to be absolutely sure that the higher amount is tolerated.

**Eruptive Keratinous Cysts**

At times, patients being treated with isotretinoin at 1 mg/kg may have the explosive development of 1- to 2-cm firm palpable lesions in the treatment area.[5] A family history of sporadic "cysts" is common. Clinically, the lesions may appear similar to acne cysts, or they may look like large comedones. These lesions differ in that they are keratinous by histology. If the cyst wall breaks, the keratinous material may be extruded into the surrounding dermis, resulting in inflammation.

Treatment of keratinous cysts is by intralesional injection of triamcinolone, or by surgical removal of the lesions. Another choice appears to be low-dose isotretinoin, 0.1 mg/kg/day (or less) for about 1 year.

**Hormones and Acne**

**Hormones and Isotretinoin Relapses**

Children in their early preteens and young teenagers may require several courses of isotretinoin to achieve lasting remission. In some instances, these are patients who have androgen excess. Paradoxically, young women with androgen excess may have a rapid response (within 1 month) to isotretinoin. However, discontinuation of the drug may result in a relapse within a few months.[6] It may be helpful to identify women with excess androgens. They may give a history of decreased menstrual periods per year.

It may be helpful to treat these patients with measures to lower their androgen levels. Cyproytosterone acetate is reportedly very helpful, but it is not yet available in the United States. Current standard therapy in the US is spironolactone 100-200 mg/day, either alone or in conjunction with oral contraceptives. Many dermatologists are reluctant to use spironolactone because of concern over possible development of breast cancer in response to unopposed estrogen. This problem may be more theoretical than actual.

On the horizon is another promising agent, Yasmin (Berlex Laboratories; Wayne, New Jersey), currently being investigated in treatment of acne. Yasmin is the combination of ethinyl estradiol, the form of synthetic estrogen used in most oral contraceptives, with drospirenone, a synthetic progestin derived from 17 alpha-spirolactone, an analogue of spironolactone. European trials of this agent appear to show promise.

When prescribing Yasmin, or other oral contraceptive agents to treat acne, it is important to remember the occasional patient with coagulopathy.[6] There is said to be a 5% incidence of factor V Leiden mutation in the female population. A personal or
family history of clotting or of spontaneous abortion may indicate the need to obtain anticardiolipin antibody and the factor V Leiden mutation test before prescribing an oral contraceptive.

**Diet and Acne**

There is an astonishing difference in the prevalence of acne between non-westernized and fully modernized societies. This difference cannot be solely attributed to genetic differences among populations but likely results from differing environmental factors.[7] Although diet is an obvious major difference, its role in acne is still controversial.

There are situations in which diet may play a role in the pathogenesis of acne. Diet appears to affect the level of endogenous androgen production. Weight loss and the use of metformin are both associated with lower plasma insulin levels and decreased androgen levels. Insulin-like growth factor (IGF) levels are reported to be elevated in acne, and tolbutamide is reported to improve acne. With hyperinsulinemia, there may be an increase in androgen production, resulting in a stimulation of sebocytes. This sebocyte stimulation and comedone production may be demonstrated in vitro. Perhaps this effect is related to androgen levels.

In any case, for a small subset of acne patients, hyperinsulinemia may stimulate endogenous androgen production, resulting in development or worsening of acne. For this select subset of acne patients, a weight-loss diet may be helpful.

**New Approaches**

Recent investigations into treatment of acne have moved into physical methods of destroying either the Propionibacterium acnes or the sebaceous gland. Both of these approaches are currently accomplished through light therapy.

**Phototherapy**

Porphyrazins are natural products of P acnes, and they apparently render P acnes sensitive as targets of phototherapy. Exposure of the bacteria to blue light (405-420 nm) results in a bacteriocidal generation of peroxides. Open trials of blue light as monotherapy indicate that a majority of patients have a good response to this treatment.[8] In some cases, the response appears dramatic. A minority of patients do not improve or appear to worsen. Although this new form of treatment appears promising, there are some unanswered questions.[9] Will phototherapy eventually select out nonporphyrin-producing strains of P acnes? And how long after treatment is discontinued will the acne return?

**Lasers**

Lasers may be used as a light source for treating acne. Low-fluence pulsed-dye laser (585 nm) appears to be an effective treatment for inflammatory lesions in acne vulgaris. A single treatment appears to result in moderate reduction of inflammatory lesions for up to 12 weeks following treatment.[9]

Candela Corporation has obtained FDA approval for the treatment of back acne (not facial acne) with their 1450-nm Smoothbeam (diode) laser. The concept is selective photothermolysis of sebaceous glands.[10] With as few as four 20-minute laser sessions, there is a reported reduction in acne lesions exceeding 98%, with greater than 6 months' remission of the lesions.[10] Acne lesion count is significantly reduced after the first treatment. It has not yet been demonstrated that this treatment is tolerated or effective for facial acne. Another potential obstacle to adoption of this new therapy is the problem of third-party reimbursement.

**Summary**

Revisiting some of the recent issues in treatment of acne may be of value for the clinician. Low-dose doxycycline or long-term trimetoprim-sulfamethoxazole may be effective an therapeutic option. Not all papules, nodules, and cysts in the acne patient are acneiform lesions, and they may not respond to conventional therapy. The patient needs to be evaluated for sinus tracts, keratinous cysts, pyogenic granulomas, and follicular Pityrosporum. After years of being discounted as a factor in the development of acne, diet-related stimulation of insulin production may result in increased androgen production and stimulation of sebocytes. This is a new rationale to support diet being an important environmental factor associated with the development of acne. And new approaches to treatment using lasers or blue light may eventually replace the current pharmacologic approach. With a promise of new therapeutic options soon to come, acne remains a fascinating challenge for the clinician.

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Authors and Disclosures

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Disclosure: Dr. Feldman has disclosed that he has served as an advisor or consultant for Biogen, Amgen, Centocor, Genentech, and Roche. He has received grants for clinical research from Biogen, Amgen, Centocor, and Genentech. He has received grants for educational activities from Biogen, Amgen, Genentech, and Roche. Dr. Feldman reported that he discussed the investigational product efalizumab. He also discussed the unlabeled uses of infliximab and etanercept.

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Disclosure: Dr. Hu has no significant financial interests to disclose.

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