Intravenous Immunoglobulin: Use in Dermatology

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ABSTRACT
A manufactured blood product derived from fractionated human plasma, intravenous immunoglobulin (IVIg) contains supra-physiologic levels of IgG. IVIg is currently used in the treatment of immunodeficiency syndromes, inflammatory disorders and infectious diseases. Uncontrolled clinical studies and anecdotal case reports recommend its use in dermatology, but randomized clinical trials are lacking. In selecting the most appropriate IVIg for the patient, convenience, efficacy, safety and tolerability of the different products should be considered. With several measures in place to ensure its safety, IVIg offers new hope for the treatment of many severe dermatologic conditions.

KEY WORDS: Intravenous immunoglobulin, IVIg, immunodeficiency syndromes, inflammatory disorders, autoimmune disease, infectious disease

Intravenous immunoglobulin (IVIg) is currently used in the treatment of primary and secondary immunodeficiency diseases, autoimmune disorders and certain infectious states. Off-label (non-approved) uses for high-dose IVIg are becoming increasingly common in dermatology. As a blood product derivative, IVIg is manufactured from the sterilized, purified human plasma of between 10,000 to 20,000 donors per batch. The final IVIg preparation is primarily composed of IgG, with trace amounts of IgA, IgM and albumin.

For the treatment of autoimmune diseases such as dermatomyositis and pemphigus, the precise mechanism of action is unknown. The immunomodulatory effects may be exerted through one or more of the following: 1) functional blockade of the Fc receptors; 2) inhibition of complement-mediated damage; 3) alteration of cytokine and cytokine antagonist profiles; 4) reduction of circulating antibodies via anti-idiotypic antibodies; and 5) neutralization of toxins which trigger autoantibody production. In toxic epidermal necrolysis, IVIg blocks Fas (CD95) mediated keratinocyte death by inhibiting Fas – Fas ligand interactions.

Use in Dermatology
The efficacy of IVIg is best documented in patients with graft-versus-host disease, Kawasaki’s disease and dermatomyositis; however, its utility in dermatology continues to grow. A number of case series have found IVIg effective in the treatment of patients with pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid, mucous membrane pemphigoid, herpes gestationis and epidermolysis bullosa acquisita (EBA). A consensus statement was recently published on the use of IVIg in patients with autoimmune mucocutaneous blistering diseases.

For autoimmune bullous disease the recommended guidelines for IVIg are as follows: 1) failure of conventional therapy; 2) significant adverse effects from conventional therapy; 3) contraindications, relative or absolute, to the use of high-dose long-term systemic therapy; 4) progressive disease despite conventional therapy; 5) uncontrolled, rapid debilitating disease; and 6) rapidly progressive EBA with generalized cutaneous involvement.
<table>
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<tr>
<th>Disease</th>
<th>Trial Design</th>
<th>Demographics</th>
<th>Treatment</th>
<th>Additional Therapy</th>
<th>Outcome</th>
<th>Response Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatomyositis</td>
<td>Double-blind, placebo-controlled crossover study (n=15)</td>
<td>10F, 5M Av. age 36 yrs</td>
<td>1g/kg/day x 2 days per month vs. placebo</td>
<td>Prednisolone (azathioprine, methotrexate, cyclophosphamide in some but not all)</td>
<td>IVIg: 11/12 improved; 1 unchanged Placebo: 3/11 minimal improvement; 3 no change, 5 worse</td>
<td>1-2 month to response; maximal response at 3 months</td>
</tr>
<tr>
<td>Pemphigus Vulgaris</td>
<td>Case series of patients with recall citrat PV (n=21)</td>
<td>11F, 10M Av. age 56 yrs</td>
<td>2g/kg over 3 days, monthly infusions until clear, followed by a maintenance schedule</td>
<td>Prednisone (azathioprine, cyclosporine, cyclophosphamide, tacrolimus, dapsone, gold, methotrexate in some but not all)</td>
<td>IVIg produced a sustained remission in all 21 patients, had a steroid-sparing effect and improved quality of life</td>
<td>Mean effective clinical response 4.5 months</td>
</tr>
<tr>
<td>Pemphigus Foliaceus</td>
<td>Case series of patients with recall citrat PF (n=11)</td>
<td>8F, 3M Av. age 55 yrs</td>
<td>2g/kg over 3 days, monthly infusions until clear, followed by a maintenance schedule</td>
<td>Prednisone (azathioprine, dapsone, gold cyclosporine, cyclophosphamide, tetracycline, nicotinamide, methotrexate in some but not all)</td>
<td>IVIg produced a sustained remission in all 11 patients, had a steroid-sparing effect and improved quality of life</td>
<td>Mean effective clinical response 5.3 months</td>
</tr>
<tr>
<td>Mucous Membrane Pemphigoid</td>
<td>Case series of patients with recall citrant, ocular MMP (n=10)</td>
<td>5F, 5M Av. age 74.6 yrs</td>
<td>2-3g/kg over 3 days, repeated every 2 to 6 weeks</td>
<td>Prednisone (dapsone, tacrolimus, cytosine arabinoside, azathioprine, methotrexate, cyclophosphamide in some but not all)</td>
<td>Visual acuity stabilized or improved, subjective complaints decreased in all 10 patients</td>
<td>Maximum response between 4 and 12 cycles</td>
</tr>
<tr>
<td>Bullous Pemphigoid</td>
<td>Case series of patients with recall citrant BP (n=15)</td>
<td>5F, 10M Av. age 76 yrs</td>
<td>2g/kg over 3 days, monthly infusions until clear, followed by a maintenance schedule</td>
<td>Prednisone (azathioprine, dapsone, gold cyclosporine, cyclophosphamide, tetracycline, nicotinamide, methotrexate in some but not all)</td>
<td>IVIg produced a sustained remission in all 15 patients, had a steroid-sparing effect and improved quality of life</td>
<td>Mean effective clinical response 2.9 months</td>
</tr>
<tr>
<td>Toxic Epidermal Necrolysis</td>
<td>Case series (n=10)</td>
<td>4F, 6M Av. age 39.4 yrs</td>
<td>0.2-0.75g/kg/day for 4 days</td>
<td>None</td>
<td>IVIg rapidly halted disease progression and produced a favorable outcome in all patients</td>
<td>Mean time to response: 1.5 days Mean time to skin healing: 6.9 days Survival rate: 100%</td>
</tr>
<tr>
<td>Toxic Epidermal Necrolysis</td>
<td>Retrospective analysis (n=16)</td>
<td>8F, 8M Av. age 42.8 yrs</td>
<td>1g/kg/d for 4 days (n=15); 0.4g/kg/day for 4 days (n=1)</td>
<td>None</td>
<td>IVIg significantly decreased mortality (observed vs. SCORTEN predicted mortality rate)</td>
<td>Mean time to response: 3.75 days Mean time to skin healing: 8.50 days Survival rate: 93.75%</td>
</tr>
<tr>
<td>Toxic Epidermal Necrolysis</td>
<td>Multicenter retrospective analysis (n=48)</td>
<td>24F, 24M Av. age 43 yrs</td>
<td>0.65-5.8g/kg (average 2.7g/kg) over 1-5 days</td>
<td>None</td>
<td>IVIg rapidly halted disease progression and produced a favorable outcome in the majority of patients</td>
<td>Mean time to response: 2.3 days Mean time to skin healing: 15 days Objective response rate: 90% Survival rate: 88%</td>
</tr>
<tr>
<td>Steven-Johnson Syndrome</td>
<td>Prospective, non-comparative study (SJS, n=9; SJS-TEN, n=5; TEN, n=20)</td>
<td>22F, 12M Av. age 47 yrs</td>
<td>1g/kg in 3 patients; 2g/kg in 31 patients; over 2 days in 27 cases and 3-5 days in 7 cases</td>
<td>None</td>
<td>No arrest in progression; no improvement in skin healing; no improvement in mortality rate</td>
<td>Mean time to skin healing: 18 days Survival rate: 68%</td>
</tr>
</tbody>
</table>

Table 1. A review of the major clinical trials and case series of IVIg in dermatology.
The evidence for the use of IVIg in toxic epidermal necrolysis has been recently the subject of debate. No consensus has been reached due to the lack of randomized clinical trials. The anecdotal results differ from one center to another. Yet, IVIg remains commonly used as initial therapy for toxic epidermal necrolysis. Current data are insufficient to recommend the routine administration of IVIg in patients with pyoderma gangrenosum, atopic dermatitis, chronic urticaria and Steven-Johnson syndrome. For a review of the major clinical trials and larger case series, refer to Tables 1 and 2.

Prior to starting IVIg therapy, complete blood cell counts, liver function and renal function studies are performed. Immunoglobulin levels are measured to exclude IgA deficiency. In the absence of IgA, or in the presence of low IgA, anti-IgA titers are ordered to minimize the risk of anaphylaxis. Screening for rheumatoid factor and cryoglobulins is recommended as these patients are at an increased risk of acute renal failure. In patients with compromised cardiac or renal function, IVIg must be carefully administered in order to prevent fluid overload. For medicolegal reasons, baseline testing for hepatitis B, C and the human immunodeficiency virus is advisable. Lastly, a small sample of serum should be stored for future analysis in the event of infectious disease transmission.

### Table 2. Guidelines for use of IVIg in dermatology.

upon the product recommendations (Table 3).

**Product Differences**

IVIg is distributed by the Canadian Blood Services with the exception of Québec, where Hema Québec is the main distributor. There are four licensed IVIg preparations available in Canada (Table 3). While there are no studies which compare the safety and efficacy of the four products, there are some differences that may be clinically important.

Variability of the manufacturing processes may lead to differences in the marketed IVIg products. The use of additional production steps (i.e., stabilization, purification and/or pathogen safety) has the potential to impact negatively the biological activity and integrity of the IgG molecule, tolerability and yield. As shown in Table 3, IVIg preparations are available in both liquid and lyophilized formulations. While the lyophilized formulations require reconstitution, the liquid formulations are ready-to-use. If the lyophilized form is reconstituted to a higher than recommended concentration, the final osmolarity will be significantly increased above physiologic levels. Moreover, the higher the concentration of the IVIg product, the less volume required for infusion. For example, a 70-kg individual receiving 1g/kg would require either 700ml of a 10% solution, or 1400ml of a 5% solution. In high-risk patients, such as those with cardiac or renal failure, these factors must be taken into consideration. In selecting the most appropriate IVIg for the patient, convenience, efficacy, safety and tolerability of the different products must be considered.

**Safety**

Adverse effects with IVIg are usually rare and self-limiting. Infusion-related side effects include: headache, flushing, chills, myalgias, low back pain, nausea, wheezing, chest pain, tachycardia and blood pressure changes. These symptoms are generally mild and begin within 30-60 minutes of the infusion. If encountered, the symptoms are easily managed by slowing or temporarily discontinuing the infusion. If symptoms are anticipated, the patient may be premedicated with antihistamines or intravenous steroids.

Anaphylaxis has been reported in IgA-deficient patients with anti-IgA antibodies. As most IVIg preparations contain trace amounts of IgA, administration of IVIg may result in antigen-antibody complex formation. Aseptic meningitis, often presenting with headache and photophobia, occurs in up to 11% of patients treated with IVIg. More common in patients with a history of migraines, aseptic meningitis may last several days. Both hematological and dermatological reactions (i.e., eczema, erythema multiforme, urticaria) have also been described.

Patients with cardiac or kidney disease must be closely followed to prevent fluid overload. Those receiving lyophilized formulations or sucrose containing products (US and Europe only) are at increased risk of renal failure as a result of osmotic injury to the proximal renal tubules. An association between IVIg and thromboembolic events has been reported in the literature. Sugar-stabilized and hyperosmolar products may increase serum viscosity. The risk appears to be greater in the patients receiving high doses or rapid infusion rates. By lowering the dose and slowing the rate of infusion, the risk of thrombotic events may be minimized.

While donors are carefully selected and screened to ensure pathogen safety, a number of viral inactivation methods are used as part of the IVIg manufacturing process. These include: physical inactivation steps (i.e., heat and pasteurization) and chemical inactivation steps (i.e., solvent/detergent, low pH, trypsin, pepsin and caprylate). Pathogens are removed by precipitation, chro-

<table>
<thead>
<tr>
<th>Product</th>
<th>Gammagard</th>
<th>Iveegam</th>
<th>Gamimune</th>
<th>Gamunex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer</td>
<td>Baxter</td>
<td>Baxter</td>
<td>Bayer</td>
<td>Bayer</td>
</tr>
<tr>
<td>Form</td>
<td>Lyophilized</td>
<td>Lyophilized</td>
<td>Liquid</td>
<td>Liquid</td>
</tr>
<tr>
<td>Concentration</td>
<td>5%</td>
<td>5%</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Infusion rate</td>
<td>4.0ml/kg/hr</td>
<td>2.0ml/kg/hr</td>
<td>3.6ml/kg/hr</td>
<td>8.4ml/kg/hr</td>
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<tr>
<td>Time to infuse 70g</td>
<td>5.3 hr</td>
<td>12 hr</td>
<td>2.3 hr</td>
<td>&lt;2 hr</td>
</tr>
<tr>
<td>Viral Inactivation</td>
<td>Solvent/Detergent</td>
<td>Solvent/Detergent</td>
<td>Solvent/Detergent</td>
<td>Caprylate</td>
</tr>
<tr>
<td></td>
<td>Polyethylene glycol</td>
<td>pH 4.25</td>
<td>pH 4.25</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trypsin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Storage</td>
<td>Room Temperature</td>
<td>2-8°C</td>
<td>2-8°C</td>
<td>2-8°C, Room Temp.</td>
</tr>
<tr>
<td>Shelf-Life</td>
<td>24 months</td>
<td>24 months</td>
<td>36 months</td>
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<tr>
<td>pH</td>
<td>6.8</td>
<td>6-7.2</td>
<td>4.25</td>
<td>4.25</td>
</tr>
<tr>
<td>Osmolarity (mOsm/L)</td>
<td>636 at 5%</td>
<td>&gt;240</td>
<td>278</td>
<td>260</td>
</tr>
<tr>
<td>Sugar Content</td>
<td>2% glucose</td>
<td>5% glucose</td>
<td>No sugar (Glycine)</td>
<td>No Sugar (Glycine)</td>
</tr>
<tr>
<td>Sodium Content</td>
<td>0.85%</td>
<td>0.3%</td>
<td>Traces</td>
<td>Traces</td>
</tr>
<tr>
<td>IgA (mg/mL)</td>
<td>&lt;3.7</td>
<td>&lt;10</td>
<td>210</td>
<td>46</td>
</tr>
</tbody>
</table>

**Table 3.** Comparison of the various IVIg preparations available in Canada.
matography and filtration techniques. In the Gamunex process, the combination of caprylate precipitation, cloth filtration and chromatography has further been shown to significantly reduce prion transmission.3,23

**Pharmacoeconomics**

Over the years, there has been an increase in both the cost and utilization of IVIg in Canada. At an average cost of $70 CDN per gram, the pharmacoeconomic impact of IVIg is significant.28 For a 70-kg pemphigus patient receiving IVIg at a dose of 2g/kg, the cost for one cycle amounts to $9,800 CDN. As the average number of cycles required is 18, the total drug bill approaches $176,400 CDN.15 With an incidence of 1 per 100,000 population, the overall cost for the Canadian health care system exceeds $52 million CDN.

In toxic epidermal necrolysis, a 70-kg patient would receive 1g/kg for three consecutive days, amounting to an overall drug cost of $14,700 CDN. At an estimated annual incidence of 1 per million population, an aggregate cost for Canada is projected at over $400,000 CDN. Laboratory expenses, nursing costs and hospital expenditures must also be considered when determining the economic impact of IVIg. These costs must be balanced against improvement of symptoms and quality of life, reduced costs of conventional therapy, decreased complications, fewer hospital admissions and time off work.

**Conclusion**

IVIg has become increasingly recognized as a safe, effective therapy for a number of dermatological conditions. The cost impact of this medication is potentially large if the list of indications continues to expand. Formal pharmacoeconomic burden of illness studies and collaborative clinical trials are required to further explore the role of IVIg in dermatology.

**References**

23. Hagman JH, Carrozzo AM, Campione E, et al. The
New Approaches to Surgery of Lentigo Maligna
C.C. Huang, MD
Department of Dermatology, University of Alabama at Birmingham, Birmingham, AL, USA

ABSTRACT
Lentigo maligna (LM) is a pigmented lesion that occurs most commonly on the sun-exposed skin of the head and neck of an older patient. LM can be difficult to completely remove due to its occasional extensive subclinical extension. Surgical treatments, including standard excision and margin-controlled excision (Mohs micrographic surgery or rush permanent sections), are reviewed. Immunostains that can increase sensitivity and specificity of margin-controlled excision are discussed, and other nonscalpel treatments including destruction, topical imiquimod, radiation therapy and cryotherapy are briefly discussed. The gold standard treatment for LM is margin-controlled excision.

KEY WORDS: lentigo maligna, lesion, margin-controlled excision

Clinical Features
Lentigo maligna (LM) is a pigmented lesion that occurs most commonly on the sun-exposed skin of the head and neck of an older, fair-skinned patient. LM can display heterogeneous pigmentation with areas of brown, black, pink, and white (signifying regression). LM frequently has ill-defined borders and microscopic extension that can make determination of the clinical borders and complete removal of the lesion difficult.1

Histology
Typically, atypical solitary or nested melanocytes can be seen along the basal layer or extending periadnexally. Multinucleated melanocytes can be seen.2 Consistent with LM appearing most commonly in the elderly, elastosis, epidermal atrophy, and effacement of rete ridges are common associated findings.1 Atypical melanocytes in LM can extend significantly beyond what appear, to the naked eye, to be the clinical margins of the lesion. This phenomenon has been well-documented in the literature where complete removal of a relatively small LM results in the creation of a surprisingly large wound.3-5 While the significance of these solitary and/or focal extensions of atypical melanocytes is unknown, the current standard of treatment is to excise them completely.

Risk of malignant transformation
It is believed that an LM will slowly increase in surface area until it invades the dermis and becomes lentigo maligna melanoma (LMM). There are numerous case reports that document this and argue against observation of LM and for its prompt surgical excision.6-9 To date, there are no longitudinal, prospective studies that measure the incidence of this malignant transformation. Therefore, we are left with expert opinion estimates which place this risk at 33%-50%.10-12 To date, one study has used epidemiologic analysis in an attempt to quantify the annual and lifetime risk of malignant transformation.13 This study used three comprehensive data sources that were representative of the Caucasian population of the United States. The authors deduced that for a 45-year-old Caucasian patient with LM, the corresponding risks were 1.2% and 2.2%. The authors acknowledged limitations to their study, including the fact that data was retrospective and not gathered expressly for the purpose of determining the incidence of malignant transformation of LM. Nevertheless, the incidence determined from this study is the closest thing to evidence-based data that currently exists.

Biopsy Technique
Whenever possible the entire suspected lesion, or as much of the suspected lesion as possible should be biopsied. Deep shave biopsy, excisional, or multiple incisional biopsies (e.g., multiple shaves or punch biopsies) are acceptable techniques. Submitting the suspected lesion as much of it as possible should be biopsied. Deep shave biopsies, multiple incisional biopsies (e.g., multiple shaves or punch biopsies) are acceptable techniques. Submitting the suspected lesion as much of it as possible should be biopsied. Deep shave biopsies, multiple incisional biopsies (e.g., multiple shaves or punch biopsies) are acceptable techniques. Submitting the suspected lesion as much of it as possible should be biopsied.

Treatment
Surgical
Surgical excision is the current most definitive treatment for LM. The most widely utilized excisional techniques are standard excision, “slow Mohs” (staged, margin-controlled excision with rush permanent sections), and Mohs micrographic surgery (staged, margin-controlled excision with frozen sections). Per the 1992 National Institutes of Health Consensus Conference, recommended margins for standard excision are 0.5 cm.19 This margin is often inadequate due to the subclinical extension that can occur with LM.5-9 Note in Tables 1 and 2 that the average margin required in clear LM in 90%-95% of cases is significantly greater than 0.5 cm. One should take care to avoid having to perform a reexcision due to positive margins since reexcision is wasteful of normal surrounding tissue, results in rewounding of the patient, exposes the patient to the risks of surgery a 2nd time, requires more physician and patient time, and increases medical costs. Thus, excisional techniques that yield the highest tumor costs. Thus, excisional techniques that yield the highest tumor.
removal rate while at the same time preserving maximal normal tissue are favored by those who deal with LM frequently. Two techniques in particular are “slow Mohs” and Mohs micrographic surgery (MMS).

“Slow Mohs” is the staged excision of peripheral and deep margins with rush permanent sections, followed by repair of the resulting wound. Several variants have been described such as the “square” procedure and the “polygonal method”.20-22 They all accomplish the common goal of verifying clear peripheral and deep margins before wound repair to minimize the risk of persistent or residual disease while simultaneously sparing normal tissue. Initially, circumferential, full-thickness skin strips 2mm in width are harvested 0.5cm from the LM. This 0.5cm margin is measured under both bright surgical lighting and Wood’s lighting. The outside circumferential margin of the strips is marked with permanent ink, and the pathology lab is instructed to section the strips tangentially along this inked margin. Strips are divided so that they are approximately 2.5cm long and will fit inside a standard paraffin embedding cassette. Various mapping methods to document the location of the harvested skin strips such as marking suture, permanent marking ink, or incisional nicks in the skin are used. The resulting trough-like wound is closed with a running or interrupted cutaneous suture until pathology results are available. The central tumor is left intact until all peripheral margins are cleared. Reexcision of additional skin strips is done with a 0.5cm margin ONLY from areas of positivity. This spares excision of normal tissue. Strips are harvested and the resulting trough-like wounds closed until all peripheral margins are clear. Then, all tissue within the incised skin strips is excised and submitted for deep margins. Since LM is an epidermal lesion, deep margins are generally clear. However, two studies to date have documented significant incidence of invasive tumor upon breadloafing of the central tumor (Table 1).21,22 For this reason, some advocate excising the central tumor with the initial harvesting of skin strips in order to better guide treatment.21,22 If there is an invasive component noted, further appropriate treatment should be done as indicated by the pathology report. The discussion of treatment of invasive melanoma is beyond the scope of this article, and the reader is directed to other comprehensive reviews.23 Using this method, 5-year cure rates approaching 100% have been reported.1,21,22 (See Table 1).

MMS theoretically accomplishes the same result in less time since frozen section results are available within the hour instead of the 24 hours that rush permanent sections require. With MMS, the initial tissue layer encompassing the entire tumor is taken with a 2-3mm margin. The deep and peripheral margins of the layer are examined and any residual tumor is precisely excised with the aid of a tissue map. This process is repeated until margins are clear. Some Mohs surgeons then send an additional tissue layer or melt and send the final clear layer from MMS for permanent sections and wait for those margins to be called clear before repairing the wound. Others close the wound immediately without sending additional tissue. Using this method, 5-year cure rates approaching 100% have also been reported.24-28 (See Table 2).

While “slow Mohs” has gained practically universal acceptance as an effective way to completely remove LM while sparing maximal normal tissue, MMS has not been as widely accepted due to several technical limitations that lie mainly in difficulties of processing and interpreting frozen sections of atypical melanocytes. Freeze artifact can cause normal keratinocytes to become vacuolated and to resemble melanocytes. Inflammatory cells, epidermal spongiosis, or coincident actinic keratoses may obscure melanocytes. Tissue may become folded or compressed at the epidermis during its transfer from the cold environment of the cryostat to a warm slide. Other confounding artifacts are tissue chatter, tangential sectioning of the epidermis, and bubbles. Ultimately, the Mohs surgeon may be faced with distinguishing between malignant scattered melanocytes and scattered atypical melanocytes seen in sun damaged skin. This is a challenging task even for a dermatopathologist.26-31

In a recent study specifically concerning this challenge, five pathologists graded 301 slides taken from 27 patients who had

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**Table 1:** Summary of studies of “Slow Mohs” for LM

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th># of lesions</th>
<th>Follow up</th>
<th>Recurrence</th>
<th>Margin required</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td>Agarwal-Antal et al10</td>
<td>92 LM</td>
<td>Up to 4 yrs</td>
<td>0</td>
<td>• 42% clear with 0.5cm&lt;br&gt;• 69% clear with 1.0cm&lt;br&gt;• 84% clear with 1.5cm&lt;br&gt;• 91% clear with 2.0cm&lt;br&gt;• 100% clear with 4.0cm</td>
<td>• Central tumor positive for invasive tumor 16%.</td>
</tr>
<tr>
<td>1998</td>
<td>Hill et al22</td>
<td>38 LM, 28 LMM</td>
<td>Average 25 mos (range 10-48 mos)</td>
<td>1</td>
<td>• 62% clear with 0.5cm&lt;br&gt;• 92% clear with 1.0cm&lt;br&gt;• 100% clear with 2.0cm</td>
<td>• 32% were invasive melanoma.&lt;br&gt;43% of these (14% of the 66 original cases) were diagnosed as invasive melanoma only after breadloafing of the central tumor.&lt;br&gt;LMs &gt;300mm² required more than 1 layer in 50%. LMs ≤300mm² required more than 1 layer in 26%.</td>
</tr>
</tbody>
</table>
Concordance between pathologists was measured by the K statistic where a negative value indicates less agreement than would occur by chance, a 0 value would indicate exactly the amount of agreement indicated by chance, and positive value would indicate more agreement than would occur by chance. A value of 1 indicates perfect agreement. The study was divided into three phases. In phase 1, all slides were randomized and diagnosed as positive or negative. Agreement was moderate with K=0.4-0.5. In phase 2, every 3rd slide was read as positive or negative. Agreement was good with K=0.6-0.9. In phase 3, slides were organized into cases allowing evaluation of the slides with the benefit of positive control (central tumor) and negative control (when available). Agreement was moderate with K=0.4-0.5.

Slides from this study were processed as rush permanent sections in the setting of “slow Mohs.” One would expect for interpretation, reproducibility, and agreement to be less in the setting of the frozen sections used with MMS.

To make this task easier, some Mohs surgeons use immunostains including HMB-45, Mel-5, MART-1, and S-100 (see Table 3).32-36 No stain can reliably differentiate between melanoma cells and benign melanocytes; however, one that reliably stains all melanocytes and the epidermal component of melanoma allows for diagnosis based on pattern recognition. While immunostains can improve the sensitivity and specificity of Mohs frozen sections, they do increase tissue processing time to 60-90 minutes per layer and are relatively costly, adding roughly $50 US to each layer of tissue processed. At the present time, the majority of cases of “slow Mohs” and MMS for LM do not use immunostains.

### Destructive

**Electrodessication and curettage and laser ablation**

Destructive methods of treatment such as electrodessication and curettage and laser are rarely used to treat LM due to several major disadvantages.37-38 These methods are usually relatively superficial and do not adequately treat deeper periadnexal melanocytes. At some point after treatment, these melanocytes can migrate back to the epidermal surface and result in recurrence. Lastly, there is no pathology generated from a destructive method, and, therefore, margins cannot be assessed.

### Cryotherapy

While there are reports documenting the efficacy of cryotherapy, this type of treatment is generally only considered if the patient does not wish to have or cannot have surgical excision.39-42

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**Table 2: Summary of studies of Mohs micrographic surgery for LM**

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th># of lesions</th>
<th>Follow up</th>
<th>Recurrence</th>
<th>Margin required</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995</td>
<td>Cohen19</td>
<td>26 LM, 19 LMM</td>
<td>Average 58 months</td>
<td>1</td>
<td>NA</td>
<td></td>
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<tr>
<td>1994</td>
<td>Robinson20</td>
<td>16 LM</td>
<td>5 yrs</td>
<td>1</td>
<td>• 19% clear with 0.3cm • 88% clear with 1.0cm • 100% clear with 1.3cm</td>
<td>• Central tumor positive for invasive tumor 0%. • 1.3cm margin was needed for 2 LMs &gt;3cm in diameter.</td>
</tr>
</tbody>
</table>

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**Table 3: Summary of studies of the use of immunostains with Mohs micrographic surgery for LM**

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th># of lesions</th>
<th>Immunostain</th>
<th>Antigen</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td>Kelley, et al33</td>
<td>7 LM</td>
<td>MART-1 (Melanoma Antigen Recognized by T-cells)</td>
<td>MART-1, transmembrane protein expressed on benign and malignant melanocytes</td>
<td>• 100% correlation between MART-1 frozen sections paraffin embedded sections. The same tissue was used for both.</td>
</tr>
<tr>
<td>2001</td>
<td>Menaker, et al34</td>
<td>18 MMis, 2 MM</td>
<td>HMB-45</td>
<td>HMB-45, cytoplasmic antigen partially composed of sialic acid and localized to immature melanosomes.</td>
<td>• 1/10 stained positive on the 1st layer of Mohs surgery. There was 100% correlation between HMB-45 frozen sections paraffin embedded sections. The same tissue was used for both. • 1 of the above 11 stained positive on layers 2 and 3 with HMB-45 but these layers were negative on paraffin embedded sections. • Therefore, there was 1 false positive layer (95% specificity) and 0 false negative (100% sensitivity) layers.</td>
</tr>
<tr>
<td>1999</td>
<td>Gross, et al35</td>
<td>2 LM</td>
<td>Mel-5, a murine IgG antibody</td>
<td>TRP-1, tyrosine-related protein.</td>
<td>• Both cases were clear with the 1st tissue layer, but there was 100% correlation between frozen section positive and negative controls and H&amp;E stains.</td>
</tr>
<tr>
<td>1993</td>
<td>Stonecipher, et al36</td>
<td>3 LM, 2MM</td>
<td>HMB-45</td>
<td>See above</td>
<td>• 5 case reports demonstrating the utility of HMB-45 (1 case) and supplemental vertical sections (3 cases).</td>
</tr>
</tbody>
</table>
Radiation therapy

Radiation therapy is not a first line therapy and probably has its best use as an adjuvant therapy in high-risk disease or for metastatic LMM.33-45

Medical

Imiquimod

There are case reports documenting the effectiveness of imiquimod cream in the treatment of LM. This is a developing treatment modality that may have utility in the future. At present, further adequately powered controlled trials with appropriate follow up are needed to establish efficacy.46-49

Conclusion

- Lentigo maligna (LM) is a pigmented lesion that occurs most commonly on the sun-exposed skin of the head and neck of an older, fair-skinned patient.
- LM is at risk to undergo malignant transformation. The best estimate of malignant transformation is that a 45-year-old Caucasian will have a 3.3% chance by age 75 and a lifetime risk of 4.7%. The corresponding percentages for a 65-year-old Caucasian are 1.2% and 2.2%.
- When biopsying a suspected LM, as much of the lesion as possible should be biopsied to give the most accurate histologic microstaging information. A significant number of suspected LM will also have an invasive component.
- Excision is most often the treatment of choice. Guidelines from the 1992 NIH Consensus Conference recommend an excisional margin of 0.5 cm. By using "slow Mohs" and Mohs micrographic surgery (MMS), one can potentially obtain more specific tumor removal while maximally sparing normal tissue. MMS is probably the less favored of the two techniques due to technical difficulties in the frozen section preparation. Various immunostains have been used to help increase the sensitivity and specificity of MMS frozen sections. Five-year cure rates can approach 100% with these two specialized techniques.
- Destructive techniques such as electrodessication and curettage and laser ablation are not favored, since they are superficial in effect and can result in incomplete tumor removal and recurrence. Cryotherapy and radiation therapy are generally considered for nonsurgical candidates.

References


### Class | Name/Company | Approval Dates and Comments
---|---|---
Skin Fillers | Hyaluronic acid based filler | The US FDA advisory panel, in December 2003, recommended approval for this filler on the condition that:

- this product must be studied on a post-approval basis for safety in the African-American population
- patients be assessed for avian protein allergies before injection
- the labeling must state that safety and effectiveness for lip augmentation has not been established.

Hylaform®

Inamed/Genzyme

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Antisense Therapy | Oblimersen sodium | The US FDA accepted a New Drug Application in January 2004, for this systemic antisense therapy. The NDA proposes the use of this product in combination with dacarbazine for the treatment of advanced melanoma in patients who have not previously received chemotherapy.

Genasense®

Aventis/Genta

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Fabry Disease | Agalsidase alfa | TPP Canada approved this enzyme replacement therapy in February 2004, for the treatment of Fabry disease under its Notice of Compliance with Conditions Policy. Under this policy, TKT may begin selling Replegal™ in Canada while the company conducts post-marketing studies.

Replegal™

Transkaryotic Therapies

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Immunomodulatory Agent | Imiquimod cream 5% | The US FDA granted marketing approval in March 2004, for this immune response modifier for clinically typical, nonhyperkeratotic, nonhypertrophic actinic keratoses on the face or scalp in immunocompetent adults.

Aldara®

3M Pharmaceuticals

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Antipsoratic Agent | Efalizumab | Swissmedic, the Swiss regulatory authority, approved this humanized therapeutic antibody in March 2004, for the treatment of adult patients with moderate-to-severe plaque psoriasis.

Raptiva®

Serono

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Scleroderma Agent | Abetimus sodium | The US FDA accepted a New Drug Application in February 2003, for this product which is designed to treat lupus patients with renal disease.

Riquent™

La Jolla Pharmaceuticals

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### Drug News

**Phase II Study Results**

Genmab A/S announced in December 2003, that their high affinity human antibody, HuMax-CD4 did not achieve statistically significant results in a 118 patient Phase Ib study to treat psoriasis. Genmab has no further plans to develop HuMax-CD4 for the treatment of psoriasis, but is continuing its two Phase II studies with HuMax-CD4 to treat cutaneous T-cell lymphoma.

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**Phase III Study Underway**

Genelabs Technologies announced in February 2003, that patient enrollment has been completed for a Phase III clinical trial for Prestara™ (prasterone), a proposed treatment to limit bone loss in women with SLE who are taking glucocorticoids. The study will take place in 26 study centers located in the US and Mexico. The primary endpoint is bone mineral density at the lumbar spine, and the treatment duration is 6 months with either 200mg/day of Prestara™ or placebo.

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**Phase III Study Results**

A positive outcome was reported in February 2003, of a Phase III double-blind, placebo-controlled study to evaluate the safety and efficacy of Periostat® (doxycycline hyclate tablets, 20mg, b.i.d., CollaGenex Pharmaceuticals) for the treatment of rosacea. Patients treated with this product showed a continuous improvement during the 16-week course when compared to placebo.