Treatment of Postherpetic Neuralgia

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ABSTRACT

Postherpetic neuralgia (PHN) is a serious complication of herpes zoster that has a predilection for older individuals. PHN is often associated with significant morbidity, and it can cause insomnia, fatigue, depression and interference with daily activities in affected individuals. Treatment for PHN is initiated with antivirals during the acute herpes zoster outbreak. Acyclovir, valacyclovir or famciclovir can be used to treat herpes zoster, and all three have been shown to reduce the duration of the herpetic rash and zoster-associated pain. These antivirals are most effective when used within the first 72 hours of the onset of the rash. Side-effects of these antivirals are low and include nausea, vomiting, abdominal pain and headache. Other treatment options for PHN include topical analgesics, opioid analgesics, tricyclic antidepressants and gabapentin. Because of the complexity of PHN, most patients require a combination of treatment modalities for adequate pain relief.

Key Words: postherpetic neuralgia, herpes zoster

Herpes zoster is initially characterized by a prodromal phase that is associated with pain and paresthesia in the affected dermatome. Hours to days later, a papular rash appears and progresses to vesicles, then pustules and finally crusts and heals 3-4 weeks later. In some patients, the pain persists weeks to months, or years after the rash has healed, hence the term postherpetic neuralgia (PHN). Studies have demonstrated that there are three phases of PHN: acute, subacute, and chronic.1 The acute phase occurs with the onset of the rash and lasts for approximately 30 days, the subacute phase lasts 1-3 months after the onset of the rash, and the chronic phase, or PHN, lasts 3 months or longer after the onset of the rash.2 Risk factors for PHN include prodromal symptoms and severity of pain at the onset of the rash.3 The most significant risk factor for the development of PHN is age, as the incidence of PHN increases with age. While studies have demonstrated the overall incidence ranges from 10% to 27%,6,7 the incidence for individuals over the age of 50 is 40%, and 75% for those over the age of 75.8,9 The persistent pain associated with herpes zoster is variable in nature, and can be characterized as any of the following: (1) burning background pain with fluctuating severity; (2) sudden, sharp shooting pain; (3) mechanical or thermal allodynia (pain produced by non-noxious stimulus).10 As a result of this severe, often debilitating pain, a patient’s quality of life is often adversely affected. In addition to interfering with activities of daily living, PHN may lead to fatigue, insomnia, anxiety, and depression.11 Because of the severity and complexity of the disease, treatment is initiated at the onset of the rash and may be necessary months to years later.
**Antivirals and PHN**

Acyclovir, valacyclovir, or famciclovir can be used to treat acute herpes zoster and to reduce the severity and duration of viral replication. Through this inhibition of viral replication, acyclovir decreases the appearance of new lesions and accelerates crusting of the lesions.12 Despite this highly therapeutic effect of acyclovir in acute herpes zoster, many previously published studies demonstrated that acyclovir had no benefit in reducing the duration or incidence of PHN. However, more recent meta-analysis studies of all placebo-controlled trials with acyclovir for herpes zoster established that there is a significant reduction in zoster-associated pain in patients who received acyclovir.13,14

Similar results have also been observed with valacyclovir, as it, like acyclovir, minimizes the severity and duration of the acute herpes zoster outbreak.15 In addition, valacyclovir is more effective than acyclovir at reducing the duration of PHN. Studies have shown an average reduction of the duration of pain from 60 days, as seen with acyclovir, to 40 days with valacyclovir. Similar reductions in pain were also noted at 6 months after healing of the rash, as only 19% of patients taking valacyclovir reported pain, compared to the 26% of patients taking acyclovir.15

Famciclovir also promotes cutaneous healing and reduces the duration of acute pain. Patients who receive famciclovir have PHN resolve two times faster than those who receive placebo, resulting in a 3.5 month reduction in the average duration of pain.16 When comparing famciclovir to valacyclovir, both drugs equally hasten the resolution of zoster-associated pain and PHN.17

All three antiviral agents are approved for the treatment of herpes zoster. The most beneficial effects of the drugs are seen if they are used within the first 72 hours of the onset of the rash. Therefore, early clinical diagnosis and treatment of the disease results in faster cutaneous healing and reduced duration of PHN.

**Antiviral Drug Profile**

Acyclovir, valacyclovir and famciclovir are highly selective for thymidine kinase (TK), an enzyme encoded by the herpes zoster virus. TK converts acyclovir into acyclovir monophosphate, a substrate that is ultimately modified into acyclovir triphosphate via cellular enzymes. In famciclovir, the active metabolite is penciclovir rather than acyclovir (as in valacyclovir), and it also undergoes phosphorylations via TK and other cellular enzymes to form penciclovir triphosphate. Penciclovir and acyclovir triphosphate inhibit DNA replication of the virus through (1) competitive inhibition and inactivation of viral DNA polymerase; and (2) via incorporation and termination of the growing viral DNA. By inhibiting viral replication, these antivirals reduce viral shedding, hasten cutaneous healing and reduce the severity and duration of pain.

Acyclovir, valacyclovir, and famciclovir share a similar safety profile. All three are considered very safe, with nausea, vomiting, diarrhea, abdominal pain, and headache being the most commonly reported side-effects. Although extremely rare, nephropathy, and neurotoxicity have been reported in acyclovir.

The difference in these antiviral agents lies in the bioavailability and cost. Unlike acyclovir, which has an oral bioavailability of 10%-20%, valacyclovir and famciclovir have an advantage of increased oral bioavailability of 65% and 77%, respectively, over acyclovir.19 As a result of this increased bioavailability, both famciclovir and valacyclovir have a more convenient dosing schedule and both are taken three times daily (see table 1). In addition, since all three antiviral agents reduce the duration of PHN, cost is often a factor when choosing among these drugs. Famciclovir is typically more expensive than valacyclovir, which is more expensive than generic acyclovir.

**Treatment Modalities for PHN**

Topical analgesics are commonly used for the short-term relief of PHN. Capsaicin cream, applied 3-4 times daily, is commonly prescribed and functions to reduce pain by depleting substance P via neurogenic vasodilatation. Side-effects include intolerable burning pain.20 A topical 5% lidocaine patch can also provide relief of PHN for approximately 12 hours after application.21 Side-effects are mild and include local skin reactions such as erythema.

Tricyclic antidepressants (TCAs) have been used extensively for the treatment of PHN, as they have been shown to provide moderate-to-excellent pain relief.20 Amitriptyline is the most widely prescribed TCA, but other TCAs such as nortriptyline

**Table 1: Antivirals Approved for Treatment of Herpes Zoster.**

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<thead>
<tr>
<th>Antiviral Agent</th>
<th>Dosage</th>
<th>Adverse Effects</th>
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<tr>
<td>Acyclovir</td>
<td>800mg, po, 5 times daily for 7-10 days</td>
<td>Nausea, vomiting, headache, diarrhea, dizziness, fatigue, anorexia, edema, and sore throat</td>
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<tr>
<td>Valacyclovir</td>
<td>1gm, po, t.i.d. for 7 days</td>
<td>Nausea, vomiting, headache, dizziness, and abdominal pain</td>
</tr>
<tr>
<td>Famciclovir</td>
<td>500mg, po, t.i.d. for 7 days</td>
<td>Nausea, vomiting, headache, diarrhea, abdominal pain, and fatigue</td>
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and desipramine can also be used effectively to treat PHN.22 Despite their widespread use, side-effects are common, and careful consideration is often required prior to prescribing TCAs to older patients. TCAs are associated with dry mouth, constipation, urinary retention, blurred vision, glaucoma, and weight gain. Cardiovascular side-effects have also been associated with TCAs and include orthostatic hypotension, arrhythmias, and EKG abnormalities.

Opioid analgesics are also commonly employed for the treatment of PHN. Short-acting analgesics provide acute relief of pain, but long-acting agents, such as controlled release morphine and oxycodone, can also be used for an extended duration of pain relief.23 Side-effects of these analgesics include drowsiness, nausea, constipation, and loss of appetite. Patients should also be evaluated for a history of substance abuse before they are prescribed these analgesics.

Gabapentin, a second-generation anticonvulsant, has been shown to significantly reduce the duration of PHN.23,24 Patients receiving gabapentin have lower daily pain scores and fewer disturbances in mood and sleep when compared to those receiving placebo. Although there is no standard dosing regimen, recent studies indicate that treatment can be initiated at 900mg/day, and additional titration to 1800mg/day is often necessary for additional efficacy.25 Dosages of up to 3600mg/day may be required in some patients, and it should be noted that doses should be prescribed based on the individual tolerance of the medication.25 Gabapentin has a good safety profile, especially among older patients. Side-effects that have been reported include somnolence, dizziness, and gait disturbances such as ataxia. Because both gabapentin and the lidocaine patch are approved by the US FDA for the treatment of PHN and are associated with minimal side-effects, some consider these two agents to be first-line treatments for PHN.4

Although corticosteroids (oral or parenteral) have been used for the prevention of PHN in the past, they are currently not recommended in patients with PHN.26 Recent studies show that while patients treated with corticosteroids, such as prednisone, have a shorter duration of acute pain and faster resolution of the herpes zoster rash, no long-term benefits of PHN have been documented.27 As such, short-term corticosteroid use (i.e., 40-60mg prednisone taper for 15-21 days) can be utilized to reduce the severity of pain and improve quality of life in the acute phase;27,28 however, long-term use of corticosteroids is not recommended as they can facilitate bone loss and impair the host immune system, factors particularly of concern in the elderly.

Conclusion

Postherpetic neuralgia is a debilitating disease, especially in older individuals. The early use of antivirals (i.e., within the first 72 hours of the onset of the rash) not only reduces the duration of rash, but also reduces the duration of PHN. Thus, treatment of PHN begins with early diagnosis and treatment of herpes zoster. Other treatment modalities such as topical analgesics, TCAs, gabapentin, and opioid analgesics are often necessary, as many patients continue to have pain despite the early use of antivirals. A combination of different treatment modalities is usually implemented, as no single therapy is completely effective. Although most of these therapeutic agents are used after the resolution of the rash, the use of one or more of these treatments (i.e., gabapentin, opioid analgesics, or TCAs) with antivirals during the acute herpes zoster infection may help not only to alleviate acute pain, but also to prevent and reduce the duration of PHN.

References

The cutaneous application of lasers and intense pulsed light sources for the treatment of pigmented lesions can be divided into the following categories:

a) Tattoos
b) Epidermal pigmentation such as lentigines and café au lait patches
c) Dermal pigmentation such as nevus of Ota, acquired bilateral nevus of Ota, and melanocytic nevi

Tattoos
The use of lasers has been effective in the removal of some, but not all, tattoos. Q-switched lasers have been found to be safe and effective in the treatment of tattoos. The response to laser treatment can vary greatly due to the wide range of tattoo ink. Previous in vitro quantitative chemical analysis of tattoo pigments found that the most common elements were aluminium, titanium, and carbon. Titanium overrepresentation was identified as the main reason for a poor response to laser treatment. Picosecond lasers were found to be more effective in achieving a greater degree of clearing. To improve the clinical outcome, more recent developments have included the external application of magnets to improve the removal of magnetite skin tattoos after Q-switched laser treatment, and the use of intradermal focusing of the Q-switched laser.1,2 In terms of complications, tattoos can darken after laser treatment due to the reduction of ferric oxide to ferrous oxide. This can be rectified with repeated Q-switched laser treatment and the use of a resurfacing laser. Less common complications include the development of allergic dermatitis or even anaphylactic shock after the laser surgery. Such reactions are thought to occur due to the release of allergic pigment into the extracellular space after laser exposure.

Epidermal Lesions
Lentigines
Lasers have been used for the treatment of lentigines, and although this is often effective for light-skinned patients with limited complications, for dark-skinned patients with a higher epidermal melanin content it can be associated with complications such as hyperpigmentation. Two years ago, our group performed an in vivo study of 34 patients and compared a Q-switched 532nm Nd:Yttrium-Aluminum-Garnet (QS 532nm Nd:YAG) laser to a long pulse 532nm Nd:YAG laser.3 We found that the long pulse 532nm Nd:YAG laser (2msec pulse duration, 6.5-8J/cm² fluence, 2mm spot size, with slate gray appearance as the clinical end-point) can result in a lower risk of PIH when used in the treatment of lentigines in Asians.3 We created controversy when we suggested that the photomechanical effect of QS lasers might not be desirable when used in such treatment. Intense pulsed light sources (IPL), which emit a broad band of visible light from a non-coherent filtered flashlamp, produce only photothermal effects. Recent studies that investigated the use of IPL to remove lentigines in Asians confirmed their effectiveness.4 Interestingly, no case of PIH was observed in two independent studies. These observations confirm our hypothesis that the photomechanical effect of Q-switched laser for the treatment of lentigines in Asians is not desirable. The main concern regarding the use of the long-pulse laser for the treatment of cutaneous pigmented lesions is the potential of thermal diffusion from the epidermis to the dermis, which increases the risk of scar formation. To prevent such an occurrence, the pulse duration should be shorter than the thermal relaxation time of the epidermis basal layer, which was estimated to be in the range of 1.6-2.8ms if the epidermal basal layer thickness was 20 µm.

Abstract
Lasers and intense pulsed light sources are frequently used for the treatment of pigmented lesions, and the appropriate selection of devices for different lesions is vital to achieving satisfactory clinical outcomes. In dark-skinned patients, the risk of post-inflammatory hyperpigmentation is of particular importance. In general, long-pulse laser and intense pulsed light sources can be effective with a low risk of post-inflammatory hyperpigmentation (PIH) when used for the treatment of lentigines. However, for dermal pigmentation and tattoo, Q-switched lasers are effective, with a lower risk of complications. In the removal of melanocytic nevi, a combined approach with a long-pulse pigmented laser and a Q-switched laser is particularly applicable.

Key Words: pigmented lesions, hyperpigmentation, lasers, intense pulsed light sources
It is now our routine approach to test patients with a long pulse 532nm Nd:YAG laser (2ms pulse duration, 6.5J/cm² fluence, 2mm spot size), and if they respond well, we offer them full treatment. Those who do not wish to have down time, or those who develop post-inflammatory hyperpigmentation after the test, are offered IPL treatment, which requires several more treatment sessions to achieve the desired clinical outcome.

Café au lait patch

The use of lasers in the treatment of the café au lait patch has yielded variable results, and although some early studies indicated complete removal without recurrence, such findings have not always been repeated. Previous studies showed that 510nm pulsed dye lasers and copper vapor lasers can be used successfully, with no recurrence, at least one year after treatment. These reports were confirmed by others. Grossman, et al. used a QS Ruby laser and a frequency double Q-switched Nd:YAG laser, and found that the degree of clearance varied across lesions. Moreover, the categorization of the patches into the two histological subtypes that they identified did not help to predict the extent of the clinical response. We looked at the use of normal-mode ruby laser (NMRL) and compared it to QS Ruby laser in the clearing of café au lait patches in 33 patients. Our preliminary data indicated that there was a lower risk of recurrence when the NMRL was used (42.4% of recurrence, as compared to 81.8% recurrence in those who were treated with QS Ruby laser) 3 months after a single treatment. By affecting the follicular melanocytes, the long-pulse laser may reduce the recurrence rate. Further histological study is necessary to confirm this hypothesis.

Dermal Lesions

Nevus of Ota

Q-switched Alexandrite (QS Alex), QS Ruby, and QS 1064nm Nd:YAG have been used for the treatment of nevus of Ota with excellent results and minimal risk of complications. The clinical efficacy of the QS Ruby was confirmed when Watanabe and Takahashi studied 114 nevus of Ota patients and found that a good-to-excellent degree of lightening was achieved after three or more treatment sessions. The side-effects were few, with transient hyperpigmentation after the first treatment being the most common. Studies comparing the use of QS Alex and QS Nd:YAG lasers found that most patients better tolerated the former. However, QS Nd:YAG laser appeared to be more effective than QS Alex in the lightening of nevus of Ota after three or more laser treatment sessions. In terms of complications, hypopigmentation was common, especially among those treated with QS Ruby. The original pigmentation could also recur in patients after complete laser-induced clearing, which is an important issue, especially for pediatric patients. The risk of such recurrence is estimated to be between 0.6% and 1.2%. However, the use of QS Ruby laser for the treatment of nevus of Ota in children can achieve an excellent result in fewer sessions and at a lower complication rate than later treatment. Hence, the advantages and disadvantages of treating nevus of Ota early in childhood should be thoroughly discussed with the patient’s relatives.

Acquired Bilateral Nevus of Ota-like Macules (ABNOM) or Hori’s Macules

Acquired bilateral nevus of Ota-like macules (ABNOM), or Hori’s macules, are a pigmentary disorder that is clinically characterized by speckled or confluent brownish-blue or slate gray pigmentation over the face, and histologically characterized by diffuse upper dermal melanocytosis. Unlike nevus of Ota, the pigmentation occurs in a symmetrical bilateral fashion, has a late onset in adulthood, and does not involve the mucosa.

One hundred forty patients with ABNOM were treated with a Q-switched Ruby laser (7-10J/cm² fluence at a repetition rate of 1Hz, 2-4mm spot size). Complete clearance was obtained in 131 patients, and hyperpigmentation was observed in 7%. Hypopigmentation persisted in 2.1% of the patients, and there was no recurrence after 6 months to 4.3 years of follow up (mean was 2.5 years). QS Nd:YAG laser was also used to treat ABNOM, and the rate of PIH was estimated to be between 50% and 73%. Our group showed that QS Alex laser is effective in the treatment of ABNOM. Post-operative pigmenitary changes were frequent, and the use of topical bleaching agents was necessary to achieve a satisfactory result. The risk of transient hypopigmentation was high, and it affected up to 50% of the patients. More recently, a combination approach with a scanned carbon dioxide laser followed by a Q-switched Ruby laser has been found to be effective.

Figure 1a: Before laser treatment
Melanocytic nevi are common, and often removed for cosmetic reasons. Various pigmented lasers have been used in their removal. A previous study using a QS Ruby laser found that an average clearance of 76% occurred after eight treatment sessions. However, recurrence can be a problem depending upon the depth of the nests of melanocytes. The use of a normal mode ruby laser (NMRL) for the treatment of melanocytic nevi is based upon the principle that with longer pulse durations, a greater degree of clearance is achieved when nests of cells are destroyed. A combined approach with a QS Ruby laser followed immediately, or 2 weeks later, with an NMRL has more recently been used with the intention of removing the superficial pigment first with the QS Ruby laser, thereby enhancing the penetration of the NMRL. A previous study found that although 52% of the nevi showed a visible reduction in pigment, no lesion had complete histological clearance. The short- and long-term histological findings of congenital nevi that have been treated with the NMRL indicated that subtle microscopic scars of up to 1mm in diameter are frequent. It has been proposed that such scars cover the underlying nevus cells, which leads to cosmetic improvement. Better cosmetic results were produced by first using an NMRL to remove the epidermis, immediately followed by multiple passes of a QS Ruby laser. This approach effectively removes the epidermis, and in doing so enables a greater degree of penetration by the QS Ruby, of which multiple passes further enhance the clinical efficacy. A similar approach using a long-pulse pigmented laser immediately followed by multiple passes of a Q-switched pigmented laser can obtain similar results (see Figure 1).

Conclusion

For epidermal pigmented lesions, long-pulse pigmented laser or IPL can be effective with a lower risk of post-inflammatory hyperpigmentation, especially when used on dark-skinned patients. Q-switched laser is necessary to remove dermal pigment and tattoo in order to avoid the risk of scarring. A combination approach can be used for the removal of melanocytic nevi.

References

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<tr>
<th>Class</th>
<th>Name/Company</th>
<th>Approval Dates and Comments</th>
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<tbody>
<tr>
<td>Immunomodulatory Agent</td>
<td>Iniquimod</td>
<td>The US FDA approved this immune response modifier in July 2004, for the treatment of biopsy-confirmed, primary superficial basal cell carcinoma in adults with normal immune systems. It is the first prescription therapy to be approved in nearly a decade for this condition.</td>
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<td></td>
<td>Aldara® Cream, 5%</td>
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<td>3M Pharmaceuticals</td>
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<td><strong>Leflunomide</strong></td>
<td>The European Committee for Human Medicinal Products approved a new indication in June 2004, for this product for the treatment of adult patients with active psoriatic arthritis. It is the first oral disease modifying anti-rheumatic drug therapy to be approved for this indication by the European Commission.</td>
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<td>Arava®</td>
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<td>Aventis</td>
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<td><strong>Efalizumab</strong></td>
<td>The European Committee for Human Medicinal Products recommended approval in June 2004, of this psoriasis product for the treatment of adult patients with moderate-to-severe chronic plaque psoriasis who have failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including cyclosporine, methotrexate, and PUVA. Marketing authorization is expected during the 3rd quarter of 2004.</td>
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<td>Oncologic Agent</td>
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<td></td>
<td><strong>MDX-010</strong></td>
<td>The US FDA granted orphan drug designation to this fully human anti-CTLA-4 antibody in June 2004, for the treatment of high risk Stage II, Stage III, and Stage IV melanoma.</td>
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<td>Medarex</td>
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<td><strong>Tazarotene, oral</strong></td>
<td>The US FDA’s Joint Dermatologic &amp; Ophthalmic Drugs and Drug Safety &amp; Risk Management Advisory Committee recommended against approval of oral tazarotene in July 2004, for the treatment moderate-to-very-severe psoriasis. It is currently approved to treat mild-to-moderate psoriasis and acne.</td>
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**Drug News**

**Drug recall**

Aventix Behring L.L.C. voluntarily decided to initiate a recall of Gammar®-P.I.V, lots A639110 and A639210 in April 2004, because they exhibit an increased frequency of non-serious, labeled adverse events of an allergic type, principally hives. Gammar®-P.I.V is indicated for the treatment of Primary Immune Deficiency in adolescents and children who are at an increased risk of infection.

**Antibacterial Agent**

Data from two pivotal Phase III clinical trials studying the safety and efficacy of the antibiotic CUBICIN (daptomycin for injection, Cubist Pharmaceuticals) were published in the *Journal of Clinical Infectious Disease*. CUBICIN demonstrated comparable efficacy to the comparator against methicillin-susceptible and methicillin-resistant *Staphylococcus aureus*, and was found to be safe and well tolerated.


**Antipsoriatic Agent**

Data released in June 2004, from a phase III clinical trial with REMICADE® (infliximab, Centocor) showed improvement in both arthritis and psoriasis associated with psoriatic arthritis. In this trial, this monoclonal antibody provided a 70% improvement (as measured by ACR 70) in symptoms of arthritis in nearly one-third of patients, compared to only 2% of patients in the placebo group at 24 weeks. These findings from the IMPACT 2 Psoriatic Arthritis Phase III trial were presented at the European League Against Rheumatism (EULAR) Annual European Congress of Rheumatology and the International Psoriasis Symposium (IPS).