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REVIEW ARTICLE

HERPES ZOSTER DURING IMMUNOSUPPRESSIVE THERAPY FOR AUTOIMMUNE DISEASES

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Background: Patients on immunosuppressive therapy are at a greater risk for herpes zoster reactivation and are more likely to have adverse outcomes. Prophylactic antivirals and vaccinations may potentially prevent these complications. **Methods:** Medical literature addressing the clinical course and therapy of herpes zoster in patients receiving immunosuppressive therapy for autoimmune disorders, and the roles of anti-viral prophylaxis and vaccination was reviewed. Research databases including PubMed, Ovid, Medline, Google Scholar and Cochrane were utilized. **Results:** Acyclovir and its derivatives are most commonly used in this setting for treatment and reduction of post-zoster complications. Foscarnet may be used for acyclovir-resistant strains. At both conventional and ultra-low doses, acyclovir has proven effective when used as prophylaxis, reducing the incidence of zoster and its complications in immunosuppressed patients. Additionally, ultra-low doses are associated with significantly reduced side effects. The zoster vaccine, Zostavax, a live-attenuated vaccine has shown promising results in several clinical trials. However, live-attenuated vaccines should be cautiously used in immunosuppressed patients. For patients who require immunosuppressive therapy, vaccination 2–3 months prior to therapy may be appropriate. **Conclusions:** Prophylactic antiviral therapy and vaccination help significantly reduce morbidity and mortality from zoster reactivation in patients receiving immunosuppressive therapy.

Keywords: Herpes zoster; Auto-immune diseases; Immunosuppressive therapy; Prophylaxis; Vaccination

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INTRODUCTION

Varicella-zoster virus (VZV) causes two distinct clinical entities in humans. Primary infection due to VZV manifests as varicella, commonly known as chickenpox. Reactivation of the latent VZV virus after primary exposure manifests as a localized, painful eruption of vesicles with a distinct dermatomal pattern, known as herpes zoster (HZ).^{1,2} Patients with autoimmune disorders treated with immunosuppressive drugs are at a higher risk for developing herpes zoster.^{3,4} In recent years, potent immunosuppressive agents are increasingly being used in patients with rheumatoid arthritis (RA), inflammatory bowel disease (IBD), systemic lupus erythematosus (SLE), Wegner's Granulomatosis and other autoimmune diseases.⁵⁻⁷

After primary infection, VZV lies dormant in the dorsal root ganglia and is kept in check by T-cell mediated immunity.⁸ The increase in the risk of VZV reactivation in these patients occurs primarily by impacting T-cell number and/or T-cell function, all of which culminates in the depression of cell-mediated immunity.^{1,9-14} The fall in T-cell mediated immunity allows the virus to reactivate and cause HZ.^{15,16} Patients on immunosuppressive therapy for autoimmune disorders have a several times greater risk of developing VZV reactivation and HZ.¹⁷ Immunocompromised patients are also at higher risk of developing

complications associated with VZV reactivation.^{18,19} Up to 40% of immunocompromised patients with HZ reactivation have been reported to suffer from severe infections with cutaneous and visceral dissemination.¹⁹ Despite aggressive anti-viral therapy, mortality remains high at up to 37% in immunocompromised patients.^{19,20}

This review aims to highlight the treatment of overt HZ in patients on immunosuppressive therapy and discuss the protective roles of prophylactic antiviral drugs and vaccinations to prevent this complication in patients receiving immunosuppressive therapy.

LITERATURE SEARCH

The PubMed database was searched for articles published in the English-language literature. Medical subject headings (MeSH) including 'zoster', 'herpes zoster', 'shingles', 'immunosuppression', 'immunosuppressed', 'immunocompromised' were cross-referenced in the search, which was supplemented with a secondary manual search of PubMed, Ovid Medline, Google Scholar and Cochrane databases. Further manual searching was carried out by reviewing the articles listed in the references of the articles obtained from the primary search.

Clinical presentation and management of herpes zoster in immunocompromised patients

Diminished immunity is a major risk factor for VZV reactivation, and several immunosuppressed patients

suffer from HZ. The presentation for HZ is considerably variable, with some patients presenting without dermatological manifestations or with atypical features, such as, ataxia and retinitis.²¹ Generally, HZ follows a localized and benign course in a majority of patients, and complications, including but not limited to disseminated disease, visceral involvement and post-herpetic neuralgia (PHN), tend to be uncommon. However, the incidence of disseminated disease is higher in immunocompromised patients, with the incidence being an estimated 10% for severely immunocompromised patients compared to 0.009% for all cases.²²⁻²⁴

The objective of initiating early anti-viral therapy is to decrease the risk of visceral and cutaneous dissemination as well as to reduce morbidity, mortality and complications associated with HZ.²⁵ Anti-viral agents, especially acyclovir, its derivatives like valacyclovir and famciclovir, and systemic vidarabine have been the mainstay of therapy for HZ in immunocompromised patients.²⁶ Early treatment with these agents has been shown to be associated with a favourable outcome in several studies.^{22, 25-27}

The optimal time to start anti-viral therapy is within 72 hours of onset of rash. Initiating anti-viral therapy early is associated with rapid clearance of the virus from herpetic lesions, resulting in reduced infectivity, accelerated healing of lesions, reduced formation of new lesions, reduced risk of PHN and decreased risk of cutaneous and visceral dissemination.^{25,28} A randomized trial run by the National Institute of Allergy and Infectious Diseases Collaborative Anti-viral Study²⁸ showed that patients who were subjected to anti-viral pharmacotherapy within the first 5 days of onset of HZ did better in terms of cessation of viral shedding, crusting and healing of old lesions and formation of new lesions, than those who received antivirals later than 5 days after onset. However, antiviral therapy for dermatomal HZ in a patient on immunosuppressant therapy should be given even for patients who present later, unless lesions are present for more than 7 days and have already crusted.

The majority of immunocompromised patients with cutaneous HZ do not develop extensive and disseminated disease, but it is exceedingly difficult to gauge which patients will eventually develop disseminated disease. Therefore, early anti-viral therapy is recommended for all immunosuppressed patients who have clinical manifestations of dermatomal zoster, as a delay in therapy can lead to extensive HZ, an entity with a devastating disease course and poor prognosis.^{19,20} Oral anti-viral therapy with close outpatient follow

up is a reasonable approach to mildly immunocompromised patients, such as those taking non-biologic disease modifying anti-rheumatic drugs (DMARDs) or those with localized dermatomal HZ.^{25,26,29} Intensive therapy with hospitalization and intravenous anti-viral medications is warranted for patients with extensive disease, including those with localized ophthalmic involvement or those receiving highly immunosuppressive agents such as tumour necrosis factor inhibitors.³

When comparing the outcome of patients treated with either acyclovir or vidarabine in randomized clinical trials, acyclovir and its derivatives have been shown to be superior for the treatment of HZ in immunocompromised patients than vidarabine.^{27,30} Patients treated with acyclovir showed a shorter duration of time during which viral cultures from the lesions were positive, thus correlating with a shorter duration of viral shedding and infectivity. Acyclovir also showed a remarkable decrease in the time needed for lesions to crust and eventually heal completely, as well as a shorter disease course to pain alleviation and symptomatic improvement. Follow-up of the patients participating in these trials also showed a significantly low incidence of PHN in patients treated with acyclovir than those receiving vidarabine.

In vitro sensitivity of VZV cultures isolated from subsequent episodes of HZ from patients who had previously suffered from HZ showed no remarkable change in isolates in terms of sensitivity to acyclovir.³¹ This indicates that while resistance is always a concern with the frequent use of anti-microbial therapy, resistance of the VZV to acyclovir remains rare. Nonetheless, cases of resistant strains of VZV, non-responsive to DNA polymerase inhibitors, such as acyclovir, have been reported in literature.^{1,25,32} For such cases, foscarnet is an effective alternative, but is associated with significantly higher renal toxicity.^{1,25,32,33}

Role of anti-viral prophylaxis

HZ and its neurological complications such as PHN, as well as superimposed bacterial infections have a significant impact on the clinical course and outcome of patients receiving immunosuppressive therapy. Prophylaxis with anti-viral drugs is an attractive approach to prevent HZ in patients who are expected to receive immunosuppressive medications.¹²

Acyclovir is very effective in the treatment of primary infections as well as prophylaxis of reactivation infections by herpes viruses. It has proven to be very efficacious with a limited side effect profile, making it a suitable choice for the prevention of HZ in immunosuppressed patients.^{12,29} Several studies have noted the efficacy of acyclovir or valacyclovir prophylactic administration in

significantly reducing incidence of HZ in comparison to those not receiving prophylaxis.^{8,34} In addition, anti-viral prophylaxis also reduces the duration and severity of disease in patients who suffer from HZ despite prophylaxis. Prophylaxis has also shown to reduce the need for hospitalization due to HZ, and the incidence and duration of PHN and other complications that may follow as a result of HZ.⁹

Another approach that may serve as a potentially useful alternative for patients on long-term immunosuppressive therapy is ultra-low dose therapy. Asano-Mori *et al.*³⁵ conducted a trial, demonstrating the effectiveness of acyclovir prophylaxis at doses far lower than the conventional dose in patients receiving hematopoietic stem cell transplantation (HSCT). At an ultra-low dose of 200 mg once daily, acyclovir showed remarkable capability of preventing HZ, with only 1 out of 137 patients developing HZ while on prophylaxis. This ultra-low dose prophylaxis was continued from after post-transplant hospital discharge till the end of immunosuppressive therapy and at least one year after HSCT. This approach is a potentially useful alternative for patients on long-term immunosuppressive therapy. The benefits of ultra-low, dose prophylaxis being its cost-effectiveness, ease and convenience of dose administration and compliance and far fewer adverse effects in comparison to therapeutic doses of acyclovir. The same strategy may be applied to patients receiving immunosuppressive therapy for autoimmune and rheumatologic diseases, though prospective clinical studies and trials are needed to objectively validate this proposal before its implementation into routine clinical practice.

Regimens intended for prevention of infection with other herpes viruses are also protective against the reactivation of HZ. For example, prophylaxis for genital herpes simplex virus (acyclovir; 800 mg twice daily or 400mg thrice daily or valacyclovir; 500mg once daily) and cytomegalovirus prophylaxis (ganciclovir; 1000mg twice daily or 5mg/kg intravenous dose twice daily).^{19,22,34,36}

Role of vaccination

Zostavax vaccine, developed by Merck & Co., was approved for HZ prevention in 2006.^{37,38} Like the varicella vaccine, Zostavax is a live, attenuated viral vaccine that contains the vOKA strain of the VZV.³⁹ The key difference between the varicella vaccine and Zostavax is the much higher dose of plaque-forming units (PFU) of infectious virions in Zostavax (19,400 PFU) in comparison to the varicella vaccine (1,350 PFU).^{10,37,39} Already approved by the Advisory Committee of Immunization Practices, Zostavax is licensed to be used in immunocompetent individuals

above the age of 60 years.^{40,41} The vaccine effectively reduces the incidence and severity of HZ by as much as 51%, and in patients who suffered from HZ despite immunization, the incidence of neurological complications, especially PHN, was also reduced by as much as 67%.^{9,37,42}

However, since it is a live viral vaccine, Zostavax has the potential to cause disease in patients with compromised immune systems and reduced cell mediated immunity, depending on the degree of immunosuppression.⁶ This is of concern in patients receiving chemotherapy for cancer, and patients with rheumatologic and autoimmune diseases receiving biologic agents and high dose non-biologic DMARDs, where vaccination with live viruses is usually contraindicated.^{6,41} The role of vaccination in moderate immunosuppression caused by low doses of non-biologic DMARDs, or even low dose biologics, is controversial. However, it should be noted that some studies have demonstrated benefit of vaccination in patients with moderate doses of immunosuppressants, hypothesizing that the fall in cell mediated immunity is not sufficient to allow the virions in the vaccine to cause disease.^{39,43} Cheetham *et al.*⁴⁴ recently conducted a large study involving 14,554 patients receiving immunosuppressive therapy. Majority of the patients in this study were receiving low dose oral corticosteroids. Out of these 14,554 patients, 25 (0.51%) out of 4826 patients with receiving current immunosuppressant drug therapy experienced HZ. None of the patients suffered from disseminated VZV infection.⁴⁴ These reports highlight a potential role of zoster vaccination in a subset of patients who receive less intensive immunosuppressive therapy, with enough residual immune system functionality to mount an adequate immune response to derive benefit from immunization.

The effectiveness and tolerance of the Zostavax vaccine in patients receiving immunosuppressants has been investigated in several studies.^{6,41,42} It has been well tolerated and has proven to be sufficiently immunogenic in adult patients with various autoimmune disorders including RA, psoriasis, psoriatic arthritis, ankylosing spondylitis and IBD.^{10,17,45} For example, in the study by Zhang *et al.*⁴⁵ immunization with the zoster vaccine was associated with a reduced risk of HZ (hazard ratio: 0.61; 95% CI, 0.52-0.71) at a median follow up of 2 years. It is notable that despite there being patients who were receiving biologic agents for immunosuppressive therapy, there was no short term increased risk of HZ after vaccination in this study. It may be reasonable to consider vaccinating patients for HZ who are anticipated to receive immunosuppressive therapy, though this approach

has not been adequately studied in research studies or clinical trials.⁴¹ Since the attenuated virions in the vaccine continue to replicate in vaccine recipients for an uncertain period of time, a reasonably safe time to initiate immunosuppressive therapy would be after approximately 3 months after vaccination.^{10,17,45} Vaccination may also be considered for patients receiving immunosuppressive therapy after discontinuing their medications, provided an appropriate period of time has passed following discontinuation.^{41,46}

CONCLUSION

In summary, HZ is a frequently observed infectious disease in patients receiving immunosuppressive therapy. Though it follows a relatively benign course, some patients may develop more complicated disease resulting in severe morbidity, complications and mortality. Therefore, early diagnosis and appropriate therapy are critical in this group of patients. Acyclovir and its derivatives (valacyclovir and famciclovir) show the most promise in terms of reducing infectivity, healing of lesions, and reducing the incidence and severity of complications associated with HZ. Foscarnet, owing to a worse side effect profile, is reserved for cases of acyclovir resistant disease.

Anti-viral agents, principally acyclovir, can also be used as prophylaxis in patients who are scheduled to receive immunosuppressive therapy. Several studies have demonstrated this to be an attractive choice for such patients. Studies investigating the use of ultra-low doses have also been used, showing encouraging results with significantly reduced side effects, easier dosage schedule and higher patient compliance as compared to conventional doses of anti-viral agents.

The zoster vaccine, Zostavax, has been used as another method of prophylaxis for such patients, showing promising results. While some recommend against the use of Zostavax and other live attenuated vaccines in immunocompromised patients, it may be prudent to vaccinate such patients approximately 3 months before the start of immunosuppressive therapy.

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