Varicella-Zoster Virus Infections in Patients Treated With Fingolimod
Risk Assessment and Consensus Recommendations for Management

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IMPORTANCE Varicella-zoster virus (VZV) infections increasingly are reported in patients with multiple sclerosis (MS) and constitute an area of significant concern, especially with the advent of more disease-modifying treatments in MS that affect T-cell–mediated immunity.

OBJECTIVE To assess the incidence, risk factors, and clinical characteristics of VZV infections in fingolimod-treated patients and provide recommendations for prevention and management.

DESIGN, SETTING, AND PARTICIPANTS Rates of VZV infections in fingolimod clinical trials are based on pooled data from the completed controlled phases 2 and 3 studies (3916 participants) and ongoing uncontrolled extension phases (3553 participants). Male and female patients aged 18 through 55 years (18-60 years for the phase 2 studies) and diagnosed as having relapsing-remitting MS were eligible to participate in these studies. In the postmarketing setting, reporting rates since 2010 were evaluated.

INTERVENTIONS In clinical trials, patients received fingolimod at a dosage of 0.5 or 1.25 mg/d, interferon beta-1a, or placebo. In the postmarketing setting, all patients received fingolimod, 0.5 mg/d (total exposure of 54,000 patient-years at the time of analysis).

MAIN OUTCOMES AND MEASURES Calculation of the incidence rate of VZV infection per 1000 patient-years was based on the reporting of adverse events in the trials and the postmarketing setting.

RESULTS Overall, in clinical trials, VZV rates of infection were low but higher with fingolimod compared with placebo (11 vs 6 per 1000 patient-years). A similar rate was confirmed in the ongoing extension studies. Rates reported in the postmarketing settings were comparable (7 per 1000 patient-years) and remained stable over time. Disproportionality in reporting herpes zoster infection was higher for patients receiving fingolimod compared with those receiving other disease-modifying treatments (empirical Bayes geometric mean, 2.57 [90% CI, 2.26-2.91]); the proportion of serious herpes zoster infections was not higher than the proportion for other treatments (empirical Bayes geometric mean, 1.88 [90% CI, 0.87-3.70]). Corticosteroid treatment for relapses might be a risk factor for VZV reactivation.

CONCLUSIONS AND RELEVANCE Rates of VZV infections in clinical trials were low with fingolimod, 0.5 mg/d, but higher than in placebo recipients. Rates reported in the postmarketing setting are comparable. We found no sign of risk accumulation with longer exposure. Serious or complicated cases of herpes zoster were uncommon. We recommend establishing the patient's VZV immune status before initiating fingolimod therapy and immunization for patients susceptible to primary VZV infection. Routine antiviral prophylaxis is not needed, but using concomitant pulsed corticosteroid therapy beyond 3 to 5 days requires an individual risk-benefit assessment. Vigilance to identify early VZV symptoms is important to allow timely antiviral treatment.
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aricella-zoster virus (VZV) is a neurotropic, epidermotoxic, and lymphotropic α-herpesvirus that infects more than 90% of people worldwide.1 Primary infection with VZV (varicella) is usually acquired in childhood or early adolescence, and infection in adults is rare and often more severe than in children. Fatal cases with multiple-organ diseases, such as pneumonia, hepatitis, and coagulopathy, are significantly more common in healthy adults than in children. Respiratory mucosal epithelial cells are presumed to be the first site of infection. The T cells become infected with VZV in the tonsils and regional lymph nodes and then transport virions to the skin, where VZV replication results in the typical vesicular lesions of varicella-zoster virus (VZV) infection, predominantly herpes zoster (HZ), commonly termed shingles.2 In individuals unable to produce VZV IgG antibodies, T-cell immunity is sufficient to protect against a second episode.3 Varicella-zoster virus antibodies do not protect against HZ, regardless of the levels detected in the serum.4 After mid-adulthood, T-cell-mediated immunity declines with increasing age, and a significant decrease in VZV-specific early effectors and cytokine-producing CD4+ and CD8+ T cells increases the risk for reactivation of latent virus and the incidence of HZ.4

The available literature on the incidence of clinically symptomatic VZV infections or HZ in patients with multiple sclerosis (MS) is limited. Herpes zoster has been reported in patients who receive disease-modifying treatments (DMTs) for MS, such as natalizumab, alemtuzumab, and fingolimod.5-10

Fingolimod, 0.5 mg/d (Gilenya; Novartis Pharma AG), has shown superior efficacy to the approved first-line treatment, interferon beta-1a, and placebo in three phase 3 studies6-10 and is currently approved as a once-daily oral therapy for relapsing forms of MS. The therapeutic effects of fingolimod are mediated via the modulation of sphingosine 1-phosphate (S1P) receptors by fingolimod phosphate, a phosphorylated active moiety of fingolimod. In vivo, fingolimod-phosphate binds as an analogue of S1P to S1P receptor 1 (S1P1) receptors on lymphocytes to trigger receptor internalization and degradation. This process leads to the inhibition of S1P signaling and the selective retention of CCR7+ lymphocytes in the lymphoid organs. As a consequence, predominant levels of CD4-naive T cells and central memory T cells (TCM), but not effector memory T cells (TEM), are reduced in the circulation.11,12

The recently approved MS DMTs all lead to distinct alterations of immune surveillance.13-15 Infections with VZV may be seen more frequently with the more efficacious DMTs in clinical practice, and increased vigilance is warranted. Preven-


tion and management of VZV infections, predominantly HZ in adults with MS receiving DMTs, is a topic of clinical relevance.

Methods

Patient Population

We based our analyses on the pooled data from the double-blind phases of 6 completed phase 2 and 3 studies (3916 participants) of fingolimod in MS and from any ongoing extension phases of these studies as of August 31, 2012 (3553 participants) (clinicaltrials.gov identifiers: NCT00333138, NCT00235430, NCT00289978, NCT00340834, and NCT00355134).8-10,16 Institutional review board approval was obtained at all sites, and participants provided written informed consent, as detailed previously.8-10,16 Male and female patients aged 18 through 55 years (18-60 years for the phase 2 studies) and diagnosed with relapsing-remitting MS were eligible to participate in these studies. Details of the study population have been presented elsewhere.8,10,16 Serologic testing using an enzyme-linked immunosorbent assay for VZV IgG antibodies was introduced as a protocol amendment during the pivotal phase 3 studies. All patients with positive test results after randomization continued the study. For patients with negative test results after randomization, increased vigilance for infections was implemented. Patients who were found to be seronegative for antibodies before randomization were not included in these studies.

Assessments and Analysis

Calculation of the incidence rate of VZV infections was based on the reporting of adverse events in the respective trials. The incidence is reported per 1000 patient-years, which was defined as the sum of days all patients in each treatment group received the study drug divided by 365.25 days. The number and percentage of patients with VZV infection were summarized for patients who received concomitant systemic corticosteroid dosages of no more than 1000 mg/d for the treatment of relapses. For the postmarketing incidence of VZV infection, we conducted a search of the US Food and Drug Administration Adverse Event Reporting System database to identify spontaneously reported adverse events consisting of HZ.17-20 The search included reported frequency and proportion of HZ infection for all drugs, including fingolimod and other DMTs for MS, from January 1, 1994, through June 30, 2012. Point estimates of the disproportionality in reporting fingolimod vs other DMTs for MS were assessed using the adjusted value of a ratio of observed to expected reports (empirical Bayes geometric mean [EBGM]). The lower limit of a 90% CI of the EBGM above the threshold of 2.0 is considered to indicate a potential signal that deserves further investigation. All these analyses were undertaken using the following preferred terms from the Medical Dictionary for Regulatory Activities, version 15.117: herpes zoster, herpes zoster disseminated, herpes zoster infection neurological, herpes zoster dermatomal, herpes zoster ophthalmic, herpes zoster oticus, and postherpetic neuralgia.
Table 1. Incidence Rate of HZ Events per 1000 Patient-years by Severity in Clinical Trials and Extensions

<table>
<thead>
<tr>
<th>HZ Event</th>
<th>Double-blind Controlled Studies</th>
<th>Double-blind Controlled Studies and Long-term Extensions</th>
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<tbody>
<tr>
<td></td>
<td>Fingolimod, 1.25 mg/d</td>
<td>Fingolimod, 0.5 mg/d</td>
</tr>
<tr>
<td></td>
<td>(1661 Patient-years)</td>
<td>(1716 Patient-years)</td>
</tr>
<tr>
<td></td>
<td>Placebo (1305 Patient-years)</td>
<td>Fingolimod, 1.25 mg/d switched to 0.5 mg/d</td>
</tr>
<tr>
<td></td>
<td>(4402 Patient-years)</td>
<td>Fingolimod, 0.5 mg/d</td>
</tr>
<tr>
<td></td>
<td>(4136 Patient-years)</td>
<td>(4113 Patient-years)</td>
</tr>
<tr>
<td>Skin involvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2 contiguous dermatomes</td>
<td>17 (10.2)</td>
<td>18 (10.4)</td>
</tr>
<tr>
<td></td>
<td>7 (5.3)</td>
<td>41 (9.3)</td>
</tr>
<tr>
<td></td>
<td>6 (1.3)</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Bilateral or &gt;2 contiguous dermatomes</td>
<td>3 (1.8)</td>
<td>0</td>
</tr>
<tr>
<td>Disseminated*</td>
<td>1 (0.6)</td>
<td>0</td>
</tr>
<tr>
<td>Ophthalmic</td>
<td>0</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Oticus</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviation: HZ, herpes zoster.

* Diagnosis of HZ is based on clinical symptoms and investigating physicians’ judgment. Data cutoff was August 31, 2012.

Calculating the following formula: No. of cases/(patient-year × 1000).

* Treatment time in the double-blind and extension phases of the clinical trials was as long as 4 years for fingolimod, 0.5 mg/d (FREEDOMS, TRANSFORMS, extension studies), and as long as 7 years for fingolimod, 1.25 mg/d, switched to 0.5 mg/d (phase 2 extension study).

* Indicates presence of bilateral lesions or lesions affecting more than 2 contiguous dermatomes (cutaneous dissemination) or in other organs than the skin.

Results

Fingolimod Clinical Studies Data

Although the overall incidence of VZV infection was low, the incidence was higher in fingolimod recipients (11 per 1000 patient-years) compared with placebo recipients (6 per 1000 patient-years) in the MS randomized clinical trials. More cases occurred during the first 6 months of fingolimod treatment. Uncomplicated cutaneous HZ involving a single dermatome or 2 adjacent dermatomes was the most common presentation of HZ across all treatment groups (Table 1). No increase in incidence was observed for up to 7 years in the extension studies, and the profile of patients who developed HZ did not differ from that of patients without HZ with respect to age, duration of fingolimod treatment, other treatments, or previous DMT use.

Two fatal cases of VZV infection were reported in patients treated with fingolimod. In a clinical trial, a patient who had received fingolimod, 1.25 mg/d, for 10 months died of disseminated VZV primary infection (reported in May 2008). The second fatal case was VZV reactivation (reported in April 2013) that occurred in a patient who was seropositive for VZV antibodies before initiating fingolimod therapy, 0.5 mg/d, for 6 months in a postmarketing observational study (the prior DMT was natalizumab, and the washout period was approximately 3 months) (Novartis Pharma AG; annual Periodic Safety Update Report to US Food and Drug Administration; submitted on October 18, 2013 [data not available in the public domain]). Both cases received approximately 10 days of concomitant corticosteroid therapy. Details of the cases are given in the eAppendix in the Supplement.

After this second case was reported, integrated analysis of the data was conducted to assess the potential impact of concomitant administration of corticosteroids as a risk factor for VZV infection or severity in patients receiving fingolimod. No apparent relationship between HZ and systemic corticosteroid use for fingolimod (all dosages) or placebo was noted. Of 41 cases in the fingolimod arm, only 5 occurred during or within 30 days of concomitant corticosteroid use (Table 2). However, corticosteroid use was limited to a maximum of 5 days per the protocol.

Postmarketing Data

Reporting Rate of VZV Infections

As of February 28, 2013, a total of 60,873 patients had received fingolimod therapy in the postmarketing setting, which constituted approximately 54,000 patient-years of drug exposure. The reporting rate of HZ infection is 7 per 1000 patient-years and has remained stable since the launch of fingolimod in 2010 (Figure 1). These incidence rates are slightly lower than those observed in the clinical trials. In a separate analysis performed using databases that report spontaneous adverse events to identify any disproportionate reporting of an adverse event, higher rates of HZ were observed for fingolimod (all dosages) and placebo compared with other DMTs for MS (Novartis Pharma AG; annual Periodic Safety Update Report to US Food and Drug Administration; submitted on October 18, 2013 [data not available in the public domain]).

Severity

Serious or complicated cases of HZ were uncommon. The involvement of more than 2 dermatomes was reported in 27 of 339 HZ cases (8.0%). The overall incidence rate of complicated HZ is estimated at 1 per 1000 patient-years. The disproportionate reporting assessment showed that the proportion of serious HZ infections during fingolimod treatment is not higher (lower confidence limit, <2) compared with those...
**Table 2. Incidence Rate of HZ Events per 1000 Patient-years by Corticosteroid Use in Controlled Clinical Trials**

<table>
<thead>
<tr>
<th>VZV-Related Adverse Event</th>
<th>No. of Patients With Event/No. of Patients Treated With Corticosteroids (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fingolimod, 1.25 mg/d (n = 1313)</td>
</tr>
<tr>
<td>Yes</td>
<td>3/445 (0.7)</td>
</tr>
<tr>
<td>Outside 30-d corticosteroid window</td>
<td>10/445 (2.2)</td>
</tr>
<tr>
<td>No</td>
<td>432/445 (97.1)</td>
</tr>
</tbody>
</table>

Abbreviations: HZ, herpes zoster; VZV, varicella-zoster virus.

* Treatment time in the double-blind phase of clinical trials was 6 months (phase 2 study) and 24 months (FREEDOMS and FREEDOMS II) for placebo and 12 months (TRANSFORMS, only fingolimod arms included) and 24 months (FREEDOMS and FREEDOMS II) for fingolimod.

**Discussion**

Although it is unclear whether patients with MS have increased susceptibility to HZ, several population-based epidemiological and case-control studies suggest that they might be at greater risk for HZ compared with healthy control subjects.\(^{20-23}\) In an age-adjusted retrospective analysis of claims databases, HZ incidence was approximately twice as high in patients with MS as in the general population (6 per 1000 patient-years) (Novartis Pharma AG; annual Periodic Safety Update Report to US Food and Drug Administration; submitted on October 18, 2013 [data not available in the public domain]). The observed rate of HZ was higher in patients receiving fingolimod compared with those receiving placebo in the clinical trials. The rates were similar and remained stable for patients continuing to receive fingolimod during the long-term extensions for up to 7 years. In the postmarketing setting, reporting rates were lower than those of clinical trials, and no increase in the cumulative reporting rate since 2010 was observed (exposure, 54,000 patient-years as of February 28, 2013). However, the postmarketing reporting of spontaneous adverse events has limitations, such as underreporting, lack of exposure data, validation of clinical details, and potential biases (eg, stimulated reporting).\(^{24}\) Effective risk mitigation, such as VZV immunization recommended by the fingolimod label, may affect the actual risk. Comparison of the fingolimod experience with that of other DMTs is difficult owing to study differences in patient characteristics, reporting of HZ occurrence, and concomitant medications (Figure 2).\(^{6,7,25-29}\) Based on reports of adverse events, HZ was documented more often with fingolimod than with other DMTs, such as interferon beta, but the proportion of complicated HZ cases was not higher (reporting rate, 1 per 1000 patient-years in the postmarketing setting). We acknowledge that the analysis of HZ severity is based on limited case numbers and the reported 90% CI is wide (0.80-3.70). Disproportionality analysis methods other than EBGM are available but were not applied for this analysis.\(^{30}\) These reporting rates may be influenced by increasing awareness about VZV infections over time and by recommendations in the product information and educational materials (for Gilenya) and may be confounded by differences in MS disease characteristics and previous DMT exposure.

To control VZV reactivation, T-cell immunity is critical. Central memory T cells are intermediate memory T cells that do not yet display effector function. However, TCMs are the basis for long-term immunity and form the reactive memory, rapidly proliferating and giving rise to TEMs on strong antigen challenge. In the case of VZV infections, fingolimod may reduce the recirculation of specific CD4+ TCMs by retaining...
them in the lymph nodes, thereby preventing their wider distribution to the sites of VZV replication, such as the skin (and possibly the ganglia). As a consequence, the generation of TEMs from TCMs would be restricted to tissues that harbor sufficient numbers of TCMs, which may reduce VZV-specific immune control and may be especially problematic as a result of confounding factors, such as immune suppression by corticosteroid use. In contrast, antiviral CD8 T-cell immunity would be largely preserved during treatment with fingolimod because CD8 T-cell immunity predominantly results from CCR7-linked TEMs that are not retained in the lymph nodes by the drug.11,12

Studies showing intact T-cell immune responses to non-specific and specific stimuli during fingolimod treatment suggest that the pharmacodynamic effect of fingolimod leading to the ubiquitous reduction of circulating TCMs may not be responsible for increased HZ incidence.12 However, information about the effects on VZV-specific T-cell responses is limited at present.11 Varicella-zoster virus-specific T cells are normally present at low frequencies, and the occurrence of HZ infection in individuals without underlying disease is associated with a rapid and substantial increase in these cells.12 Varicella-zoster virus-specific T cells have multiple functions, including production of key cytokines that orchestrate local

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**Figure 2. Incidence of Varicella-Zoster Virus (VZV) Infections in Fingolimod Trials and Comparison With Other Treatments and Conditions**

- **Interferon-beta**
- **Placebo**
- **Fingolimod, 0.5 mg/d**
- **Fingolimod, 1.25 mg/d**

- **Natalizumab**
- **Placebo**

- **Dimethyl Fumarate, 240 mg BID**
- **Dimethyl Fumarate, 240 mg TID**
- **Placebo**

- **Rituximab**
- **Alemtuzumab, 24 mg/d**
- **Alemtuzumab, 12 mg/d**

Vertical dashed lines at 3.7 and 5.6 per 1000 patient-years are background rates in the general population and patients with multiple sclerosis (MS) that one would expect in a population of the same age distribution as the patients treated in fingolimod clinical trials. Because the incidence of VZV varies with age, the background rates were adjusted to the age of the patient population enrolled in fingolimod clinical trials. The shaded area throughout the graph represents the incidence rate in controlled clinical trials for fingolimod, 0.5 mg/d.6-8,10,16,25-29 Error bars indicate 90% CIs.

BID indicates twice daily; CARE, Comparison of Alemtuzumab and Rebif Efficacy in Multiple Sclerosis; CONFIRM, Comparator and an Oral Fumarate in RRMS; DEFINE, Determination of the Efficacy and Safety of Oral Fumarate in Relapsing-Remitting Multiple Sclerosis (RRMS); RA, rheumatic arthritis; REFLEX, Randomized Evaluation of Long-term Efficacy of Rituximab in RA; TID, thrice daily.
Box 1. Recommendations to Mitigate Risk for VZV Infection During Fingolimod Treatment

**Varicella (Chickenpox) Vaccination: Prevention of Primary Varicella**
Evidence of immunity to varicella should be sought before initiating MS therapy.

Patients with no varicella immunity should be vaccinated (if they have no contraindication) with 2 doses of Varivax/Varilrix separated by 4 weeks.

In case of treatment with high-dose corticosteroids, vaccination should be administered at least 30 days after the last corticosteroid dose.

Live-attenuated vaccines are contraindicated during fingolimod therapy. Varicella vaccination should not be given during fingolimod treatment; initiation of treatment with fingolimod should be postponed for 1 month after the second dose of vaccine.

**Corticosteroid Treatment**
Use of corticosteroids may increase the risk for VZV reactivation.

When possible, corticosteroid treatment for relapses should be limited (3-5 days of intravenous methylprednisolone without tapering) in patients receiving fingolimod.

Corticosteroid treatment with a higher dosage or for a longer duration should be evaluated on an individual basis.

Antiviral prophylaxis is not recommended routinely but can be considered in patients requiring prolonged or repeated high-dose corticosteroid treatment.

**Vigilance Toward Early Recognition and Treatment of VZV Infections**
In patients who have evidence of dissemination, including symptoms of severe abdominal pain, MS therapy should be discontinued and intravenous antiviral therapy as per the current CDC-ACIP guidelines should be initiated.

Antiviral treatment in case of suspected VZV infection should be implemented as per CDC-ACIP guidelines.

Patients receiving immunomodulatory therapies should be educated to identify signs and symptoms of primary varicella and recurrent HZ infections with VZV and report them promptly.

Prolonged antiviral treatment may be required for immunocompromised patients.

**Recommendations for Management and Risk Mitigation**
Three areas of risk minimization for VZV infections in patients with MS have been identified. These may also apply to patients treated with DMTs other than fingolimod (Box 1).

**Prevention of Primary VZV Infection**
Any adult who has not had varicella should be vaccinated (in the absence of contraindications) with one of the licensed live attenuated varicella vaccines because primary VZV infection is significantly more severe and occasionally fatal in adults. The VZV immune status of adults should be determined at the time of MS diagnosis (Box 2). However, commercially available assays have limited sensitivity; 10% to 15% false-negative and 8% to 11% false-positive results often occur. Previous VZV infection can also be confirmed by the assessment of the patient’s history of varicella diagnosis by a health care professional (Box 2). If a patient with a history of household exposure did not develop varicella, preexisting immunity may be the reason. Few individuals with MS will have been given varicella vaccine because it was only licensed in 1995 or later. However, if the patient’s medical record shows that he or she received 2 doses of varicella vaccine, serologic testing is not indicated and additional doses of vaccine are not needed.

If the clinical history and serologic testing suggest that the patient is susceptible to primary VZV infection, varicella vaccination should be given as listed in Box 1. Vaccination of individuals who may be in the false-negative serologic group is not detrimental. The vaccine should not be given while the patient is receiving antiviral drugs active against VZV to avoid cell-mediated control of infection and cytotoxic effects against infected cells. In a 4-week study in healthy volunteers, fingolimod at the 0.5 mg/d dosage had a mild to moderate inhibitory effect on T-cell-dependent and T-cell-independent immune responses. However, the immunogenicity of the neoantigen keyhole limpet hemocyanin was similar to the effect observed with placebo. Recall antigen responses, as assessed by anti–tetanus toxoid immunogenicity and delayed-type hypersensitivity, were not affected. In a smaller study that included fingolimod-treated patients with MS and untreated healthy controls, humoral immune responses to influenza vaccine and the induction of circulating influenza-specific T cells were comparable. Despite CD4+ and CD8+ T-cell lymphopenia, the recently activated T cells may override the dependency on Sip, signaling for egress from the lymph nodes by down-modulation of CCR7. Thus, the functionality of T cells appears to be intact during fingolimod therapy. A recent study assessed the immune responses to VZV in patients treated with fingolimod compared with healthy controls, untreated patients with MS, and patients treated with other DMTs (glatiramer acetate or interferons). The study reported that fingolimod treatment of patients with MS lowered VZV-specific immunity and suggested that subclinical VZV reactivation, demonstrated by polymerase chain reaction detection of VZV DNA in the saliva, was higher among patients treated with fingolimod compared with untreated patients with MS and healthy controls. However, patient groups were combined in the statistical analysis, and the numbers were small. Varicella-zoster virus DNA was not detected in blood, and none of the fingolimod-treated patients developed clinically apparent HZ. Compared with CD4+ TEMs, CD8+ TEM cells are less affected by fingolimod treatment and might help to control VZV reactivation despite a drop in CD4 cell levels. Other immune responses, such as production of interferon-γ by CD3+ T cells and by tissue-resident T cells, may provide antiviral control that is unaffected by fingolimod. In some cases, a subclinical reactivation may trigger the recruitment of lymphocytes from naive and TCM pools in lymph nodes to support the TEM response and prevent clinically apparent VZV infection.
blocking efficacy. If a vaccine recipient develops a rash presumed to be caused by the vaccine virus, appropriate antiviral therapy with acyclovir or related drugs should be initiated promptly.38

Assessing the level of VZV T-cell–mediated immunity in patients with MS is not possible in the clinical setting. Repeative attempts to quantitate circulating VZV IgG antibodies have no predictive value for assessing the risk for HZ. Consistent with the epidemiological data from the general population, more than 95% of the adult MS population undergoing testing in the fingolimod clinical trials was found to be seropositive for VZV antibodies. Based on limited testing results, fingolimod had no apparent effect on the VZV antibody status of participants in the clinical trials.

Prevention of HZ
The risk for HZ infection is reduced in individuals without underlying diseases when they are given a single-dose HZ vaccine (Zostavax; Merck & Co, Inc).39 However, the efficacy and safety of this live-attenuated vaccine have not been established in patients with MS.

Concomitant treatment with corticosteroids may increase the risk for VZV reactivation. Duration of corticosteroid treatment for relapses in fingolimod clinical trials was limited (3-5 days of treatment with intravenous methylprednisolone without tapering). Decisions regarding dosage and duration of corticosteroid treatment in individual patients require the physician's judgment. Current data do not support the general use of antiviral prophylaxis in patients receiving fingolimod given the low incidence of HZ infection. However, antiviral prophylaxis may be considered when prolonged or repeated high-dose corticosteroid use is deemed necessary.

Vigilance Toward Early Symptom Recognition and Treatment of HZ
Patients receiving fingolimod should be educated about early symptoms and signs of varicella or HZ and the need to report them promptly, as well as the possible increased risk when concomitant corticosteroids are prescribed. Antiviral treatment for suspected VZV infection should be implemented as per the guidelines for such treatment in immunocompromised patients.38 The route of administration and the dose of acyclovir are determined by the extent of the immunosuppression and severity of infection. Because fingolimod has a half-life of 9 days,40 continuing its use in patients presenting with uncomplicated HZ is reasonable because treatment interruption is unlikely to affect the recovery from HZ in response to antiviral therapy.

Conclusions
Analysis of all available data has not identified obvious risk factors for VZV infections, such as duration of treatment, age, previous treatment, or concomitant corticosteroid use, in patients treated with fingolimod. That corticosteroids suppress the immune system and extended corticosteroid treatment is expected to be associated with additional risks are well established. Therefore, the longer-term use of concomitant corticosteroids (beyond 3-5 days of high-dose intravenous methylprednisolone for MS relapses) requires a careful risk-benefit assessment. Proper patient education along with implementation of the recommendations and risk mitigation strategies (Boxes 1 and 2) provide a systematic approach for management of VZV infections in patients receiving fingolimod.
REFERENCES


