TABLE. Frequency of RNFL Thinning According to Visual Field Classification

RNFL	Visual Field Classification			
	Normal	Mild	Moderate	Severe
Normal RNFL	38 (63.3%)	5 (16.7%)	0	0
RNFL thinning	22 (36.6%)	25 (83.3%)	28 (100%)	7 (100%)

Normal retinal nerve fiber layer (RNFL) = all 90° quadrants fell within ≤95th–> 5th percentile; RNFL thinning = at least one 90° quadrant fell into either ≤1st or ≤5th–>1st percentile.

identifying individuals with VAVFL, OCT RNFL imaging has a sensitivity and specificity of 92.3% and 63.3%, respectively (when using the classification criteria described).

RNFL thinning in at least 1 of the 90° quadrants was seen in 36.6% of individuals with normal visual fields, suggesting that RNFL thinning may be detected before VAVFL becomes clinically apparent. Because the interpretation of perimetric results is largely subjective, detection of early/mild visual field loss may be difficult compared to detecting small changes in RNFL thickness.[3]

In 5 individuals with mild VAVFL, RNFL thickness was normal in all 90° quadrants. It is possible that these individuals could have normal visual fields that were underestimated because of psychomotor slowing or impaired reaction time.

Longitudinal studies are needed to determine the utility of RNFL imaging in the assessment of VGB-exposed individuals, particularly in the early stages of VGB retinotoxicity, when visual fields may be normal.

Potential Conflicts of Interest

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Fingolimod Treatment for Multiple Sclerosis Patients What Do We Do with Varicella?

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Recently Cohen and Chun thoroughly reviewed mechanisms of action, clinical efficacy, and side effects of fingolimod (FTY 720), the newly available treatment for relapsing-remitting multiple sclerosis (MS).[1] Prompted by 2 fatal cases of herpes virus infections in the phase 3 trials, fingolimod[2] is the first MS therapy where varicella-zoster virus (VZV) antibody status has to be determined prior to initiation of treatment.[3,4] Fingolimod is contraindicated in patients not protected against VZV. This may lead to a dilemma in some patients without VZV antibodies. Antibodies specific to VZV are present in 95% of younger adults,[5] which means up to 5% of MS patients may be VZV antibody-negative and may need varicella vaccination. However, available VZV vaccines are live vaccines contraindicated during treatment with disease-modifying drugs or during MS progression.[6] In contrast to US Food and Drug Administration licensure,[4] in Europe fingolimod is approved as a second-line treatment, when other disease-modifying-drugs (DMDs) fail or in very active disease de novo.[3] Clearly, in the first setting a live VZV vaccine cannot be administered.

With respect to possible DMD treatment, we propose checking for VZV immunoglobulin G antibodies in MS patients without a clear history of chickenpox or a documented completion of the VZV immunization schedule at an early stage, before any MS-specific treatment is necessary, rather than waiting until fingolimod therapy is needed. The attenuated varicella vaccine is safe and does not seem to accelerate MS disease progression.[7]

The success of any vaccination during immunomodulating or immunosuppressive treatment should be determined by sufficient antibody titer increase following vaccination as a matter of principle.

Potential Conflicts of Interest

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Reply

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We thank Dr Winkelmann and colleagues for their interest in our article.[1] We would like to take the opportunity to reinforce some of the important issues they raised and clarify several points. There were 2 deaths related to herpes virus infection among participants in the TRANSFORMS phase 3 trial in the higher-dose (1.25mg) fingolimod group, 1 of which was due to disseminated varicella-zoster virus (VZV) infection.[2] This patient had a negative history of chicken pox and negative VZV serology and was exposed to a child with chicken pox while receiving high-dose corticosteroids. The other death was due to herpes simplex encephalitis, which was treated for 1 week with high-dose corticosteroids until the correct diagnosis was made. Although a role of fingolimod cannot be excluded in either case, it is important to note that fulminant infections can occur in the setting of high-dose steroids alone. In addition, >15,000 patients have been treated to date with fingolimod, and these remain the only cases of fatal herpes virus infection (Novartis, data on file).

Although fingolimod is the first multiple sclerosis (MS) therapy for which assessment of VZV status, including serologic testing of patients without a clear-cut history of chicken pox, is advised prior to initiating therapy, we agree with the authors that this recommendation should be considered prior to starting any potent immunotherapy. We also agree that it may be prudent to test VZV serology early in the course of MS and immunize seronegative patients, rather than waiting until a potent immunotherapy is being considered. Finally, negative VZV antibody status is not a contraindication to therapy with fingolimod. Fingolimod use in such situations is a decision by the patient and his/her physician based on the specifics of the MS disease course, predicted risk of neurologic disability, available treatment options, and immunological status including immune-compromising disease or prior exposure to immunosuppressive agents, as well as the risk of VZV infection (low, but with potentially serious sequelae).

Potential Conflicts of Interest

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