anticoagulants may prevent warfarin-induced skin necrosis but cannot be recommended yet.

Finally, in reply to Grzybowski and Ascaso: the use of antithrombotic agents in ocular surgery remains highly controversial. The stated bleeding rate of 3% is excessive in modern cataract surgery. This avascular procedure, which is frequently performed with topical anesthesia, avoids potential retrobulbar hemorrhage due to retrobulbar anesthesia. However, retrobulbar anesthesia is frequently used in vitreoretinal surgery. Catastrophic bleeding during vitreoretinal surgery can be due to choroidal hemorrhage and neovascularization in proliferative retinal diseases. Bleeding after sutureless vitreoretinal surgery may be uncontrolled, since hypotonia in an open eye prevents tamponade.

**Case Reports of PML in Patients Treated for Psoriasis**

TO THE EDITOR: In their letters about patients who were receiving oral dimethyl fumarate for the treatment of psoriasis, Ernis et al.1 and van Oosten et al.2 (April 25 issue) state that progressive multifocal leukoencephalopathy (PML) had been diagnosed in two patients. Dimethyl fumarate is the active ingredient in Fumaderm, which since 1994 has been registered for the treatment of psoriasis in Germany. Leukopenia and lymphopenia are known adverse effects of such therapy.

The summary of product characteristics for Fumaderm and current guidelines recommend that in all patients receiving the drug, a differential blood count should be obtained every 2 to 3 months and the drug should be terminated if the leukocyte count is below 3000 per cubic millimeter or the lymphocyte count is below 500 per cubic millimeter.3,4 In the safety database of the German drug agency (BfArM), which covers more than 180,000 patient-years of Fumaderm exposure, no cases of PML have been documented in patients in whom these rules were applied. In contrast, in all cases of PML observed in association with therapy with dimethyl fumarate, physicians have not adequately treated lymphopenia. The two patients who are described in the Journal both had lymphocyte counts below the threshold of 500 per cubic millimeter for more than 2 years. It appears, therefore, that these cases of PML occurred after long-standing, severe lymphopenia, which has been identified as a primary risk factor for PML.5

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4. Nast A, Boehncke WH, Mrowietz U, et al. S3 — guidelines...
TO THE EDITOR: In their response to the case reports of PML, Sweetser et al. (April 25 issue) describe a patient with a history of sarcoidosis in whom PML was diagnosed after 1 month of exposure to Fumaderm for the treatment of psoriasis. This description was probably based on an adverse-event report form that was partially ambiguous, as noted now. However, the female patient they describe, who is now 61 years old, received continuous treatment with Fumaderm from August 2005 through October 2009, before PML was confirmed and treated at our department in November 2009. She had noted the onset of PML symptoms in September 2009. The patient recovered with mild-to-moderate residual symptoms. Early during Fumaderm treatment, grade 2 lymphocytopenia developed and persisted throughout therapy (minimal lymphocyte count, 445 per cubic millimeter). During this time, the dose of Fumaderm was tapered from 480 mg of dimethyl fumarate and 380 mg of monoethyl fumarate to 60/47.5 mg per day. After a diagnosis of pulmonary sarcoidosis on biopsy in July 2005, the patient was treated with oral prednisolone from August 2005 through June 2006 and oral methotrexate from February through May 2006 without the development of lymphocytopenia. Although established risk factors for PML were present in this patient, Fumaderm may have had an additional causal role, in our view.

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Dr. Buttmann reports receiving a travel grant from Biogen Idec, receiving travel grants, lecture and consulting fees, and a research grant from Merck Serono, serving on an advisory board and receiving a travel grant from Almirall Hermal, and receiving a travel grant and research grants from Teva and Novartis. Dr. Stoll reports receiving lecture fees from Boehringer Ingelheim, Bayer Vital, and Fresenius Medical Care, research grant support from Teva Pharma, consulting fees from Bayer HealthCare and CSL Behring, and travel expenses from the European Neurological Society and the European Federation of Neurological Societies. No other potential conflict of interest relevant to this letter was reported.


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DR. ERMS AND COLLEAGUES REPLY: The risk of PML is elevated among patients receiving immunosuppressive drugs and appears highest among those receiving monoclonal antibodies.1 Mrowietz and Reich agree with our statement that the dermatologist should have modified or stopped treatment with Fumaderm when lymphocyte counts below 500 per cubic millimeter occurred. The manufacturer’s prescribing information recommends obtaining complete white-cell counts annually in patients with multiple sclerosis who are treated with dimethyl fumarate (BG-12, Tecfidera). Because lymphopenia develops in 4 to 5%2,3 of such patients, we believe that assessments of white-cell counts, including absolute lymphocyte counts, should be performed more frequently than annually in patients treated with dimethyl fumarate and fumarate esters.

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DR. VAN OOSTEN AND COLLEAGUES REPLY: We agree with Mrowietz and Reich that dimethyl fumarate has a rather low risk profile on the basis of the long-standing experience and safety data in patients treated with Fumaderm for psoriasis. However, the true incidence of PML in patients treated with dimethyl fumarate might still be underestimated. Although we recognize the value of registries such as BfArM,4 such databases tend to be incomplete. For instance, in a search of the online BfArM database, we did not find the patient reported by Erms et al. who received a diagnosis of PML in 2010. We agree that the risk of PML in patients receiving dimethyl fumarate is probably the result of inadequate management of lymphopenia. We hope that the publication of

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these two cases will increase awareness of this side effect and lead to adequate monitoring of patients treated with dimethyl fumarate and other fumarates.

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DR. SWEETSER AND COLLEAGUES REPLY: Buttmann and Stoll provide additional information on the patient with a history of sarcoidosis in whom PML developed while she was receiving Fumaderm for psoriasis. This updated information on the previously reported case does not change the assessment cited in our letter that the occurrence of PML in this patient was highly confounded by sarcoidosis, which is a known risk factor for both lymphopenia and PML. Furthermore, it is important to clarify that according to published German S3 guidelines on the systemic treatment of psoriasis,1 and product labeling for Fumaderm, periodic monitoring of lymphocytes should be performed during treatment with Fumaderm, and guidance on dose modification should be followed. According to these guidelines, Fumaderm should have been discontinued in this patient with severe and prolonged lymphopenia, since this condition may increase the risk of opportunistic infections.

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38TH ANNUAL JOSEPH GARLAND LECTURE

The lecture, entitled “Adventures at the Intersection of Medical Journalism & Public Health,” will be held in Boston on Oct. 23.

Contact Roz Vogel, Countway Library of Medicine, 10 Shattuck St., Boston, MA 02115; or call (617) 432-4807; or e-mail rvogel@hms.harvard.edu.

WORLD FEDERATION OF HEMOPHILIA (WFH) 2014 WORLD CONGRESS

The congress will be held in Melbourne, Australia, May 11–15. It is jointly presented by the World Federation of Hemophilia and the Haemophilia Foundation Australia.

Contact WFH 2014 World Congress Secretariat and Housing Bureau, World Federation of Hemophilia, 1425 René-Lévesque Blvd. W., Suite 1010, Montreal, QC H3G 1T7, Canada; or call (514) 394-2834; or fax (514) 875-8916; or see http://www.wfh.org.

MAYO CLINIC

The following meetings will be held in Rochester, MN, unless otherwise indicated: “Mayo Clinic Internal Medicine Review for Nurse Practitioners, Physician Assistants & Primary Care Physicians” (Sept. 18–20); “29th Mayo Clinic Dermatology Symposium: The O’Leary Meeting” (Sept. 20 and 21); “Mayo Clinic Pediatric Days” (Sept. 23 and 24); “Mendelson Symposium on Advanced Facial Anatomy” (Sept. 27 and 28); “An Overview of Perioperative Medicine 2013” (Seattle, Oct. 9–12); “Hematologic Malignancies: New Therapies and the Evolving Role of Transplant” (Chicago, Oct. 11 and 12); “9th National Changing Patterns of Cancer in Native Communities: Strength Through Tradition and Science” (Albuquerque, NM, Oct. 26–28); “Mayo Clinic Nutrition and Wellness in Health and Disease” (Chicago, Nov. 4 and 5); and “23rd Annual Mayo Clinic Symposium on Sports Medicine” (Nov. 8 and 9).

Contact the Mayo School of Continuous Professional Development, 200 First St. SW, Rochester, MN 55905; or call (800) 323-2688 or (507) 284-0532; or see http://www.mayo.edu/cme; or e-mail cme@mayo.edu.

STEM CELL FORUM

A forum entitled “Stem Cells in Science and Medicine” will be held in Suzhou, China, Oct. 14–17.

Contact the International Society for Stem Cell Research, 5215 Old Orchard Rd., Suite 270, Skokie, IL 60077; or call (224) 592-5700; or fax (224) 365-0004; or e-mail iisscr@iisscr.org; or see http://www.iisscr.org/home/conferences.

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