

technique and that centers and surgeons were selected because of their experience, details about antithrombotic management and flow measurement were indeed left to the discretion of each surgeon and center. When the group of patients assigned to off-pump CABG was divided according to the use or nonuse of aortic manipulation (255 patients underwent the procedure with the anaortic technique, 277 with an anastomotic device, and 655 with partial aortic occlusion (clamping), rates of stroke were similar in each group (2.4% with the anaortic technique, 1.8% with the anastomotic device, and 2.3% with clamping).

Bonchek asks whether it is justified to put patients at risk while gaining expertise in off-pump CABG without a proven benefit of the procedure. Avoidance of a “learning curve” is a challenge for clinical researchers, especially in the surgical arena. We now know that off-pump CABG has excellent results when performed by expert surgeons. If studies showed a benefit of off-pump CABG performed by expert surgeons, the consequence would be that all other surgeons would need to follow and adapt the off-pump technique with all necessary efforts for training under a strict quality control. The aim of randomized trials is to investigate whether or not there is a need for a paradigm change.

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Since publication of their article, the authors report no further potential conflict of interest.

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**Table 1. Frequency of the Composite Primary End Point, According to Quartile of German Coronary Score.\***

Variable	On-Pump CABG <i>no. of patients/total no. (%)</i>	Off-Pump CABG <i>no. of patients/total no. (%)</i>	Odds Ratio (95% CI)
Quartile 1	12/296 (4.1)	10/272 (3.7)	0.95 (0.46–1.99)
Quartile 2	24/314 (7.6)	21/322 (6.5)	0.84 (0.46–1.53)
Quartile 3	22/287 (7.7)	21/307 (6.8)	0.85 (0.47–1.55)
Quartile 4	41/310 (13.2)	41/286 (14.3)	1.12 (0.70–1.78)

\* German coronary scores range from 0 to 100, with higher scores indicating greater risk. CABG denotes coronary-artery bypass grafting, and CI confidence interval.

VA. Emergency conversion to cardiopulmonary bypass during attempted off-pump revascularization results in increased morbidity and mortality. *J Thorac Cardiovasc Surg* 2004;128:655-61.

DOI: 10.1056/NEJMc1306329

**THE EDITORIALIST REPLIES:** Bonchek raises an important point about how a person gains experience in either off-pump or on-pump CABG surgery. Training in new surgical techniques that do not provide a proven benefit, such as the off-pump CABG technique, should ideally be conducted in established training programs that provide appropriate oversight and supervision from experienced surgeons. This is probably true not only for off-pump CABG surgery but for other procedures as well.

Data from empirical research are currently lacking on the experience necessary to both develop and maintain expertise in cardiac and other surgical procedures.

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Since publication of his article, the author reports no further potential conflict of interest.

DOI: 10.1056/NEJMc1306329

## Progressive Multifocal Leukoencephalopathy Associated with Ruxolitinib

**TO THE EDITOR:** Ruxolitinib, an inhibitor of Janus kinases (JAKs) 1 and 2, has been approved in the United States and Europe for the treatment of myelofibrosis.<sup>1</sup> We report a case of progressive

multifocal leukoencephalopathy (PML) in a patient with myelofibrosis after initiation of ruxolitinib therapy.

A 75-year-old man with intermediate-2-risk

myelofibrosis that was refractory to hydroxyurea therapy received ruxolitinib at a dose of 20 mg twice daily. While he was receiving ruxolitinib, his constitutional symptoms resolved and his blood count normalized. Ten weeks after ruxolitinib therapy was initiated, he reported minor symptoms consistent with cognitive impairment and expressive dysphasia. Over the following few weeks, the symptoms progressed, and worsening confusion, receptive and expressive dysphasia, ataxia, and gait instability developed.

Magnetic resonance imaging (MRI) showed an extensive T<sub>2</sub>-dependent signal change within the right temporoparietal and posterior frontal white matter, with further smaller lesions within the left middle frontal lobe and the left posterior temporal lobe that were highly suggestive of PML. Since it was not known whether these lesions were associated with ruxolitinib, it was gradually withdrawn. An initial lumbar puncture did not detect JC virus, and all other tests of the cerebrospinal fluid were unremarkable. Testing for the human immunodeficiency virus was negative, and although the absolute lymphocyte count was low at 885 cells per cubic millimeter, the absolute CD4 and CD8 T-lymphocyte counts were normal.

The patient continued to have disease progression, with severe left upper-motor-neuron facial droop, bilateral pyramidal signs, and severe dysphasia, dysarthria, and ataxia. A repeat MRI showed evolution of the diffuse signal abnormality in the right posterior frontal and parietal lobes, with further patchy signal abnormality contralaterally.

The patient eventually underwent a brain biopsy. The histologic findings showed florid reactive gliosis that was consistent with PML. The diagnosis was confirmed on immunochemical analysis of the biopsy specimens, which showed simian virus 40 (SV40) in some nuclei. Despite discontinuation of ruxolitinib, neurologic deterioration rapidly continued. After the patient was discharged home from hospice care, the deficit continued but his motor skills improved.

The JAK–signal transducer and activator of transcription (STAT) pathway has an important role in host defense and autoimmunity. JAK mu-

tations are associated with primary immunodeficiency, and complete STAT-1 deficiency, which blocks interferon signaling, can lead to lethal viral and bacterial infection.<sup>2</sup> PML recently has been described in association with a number of therapies.<sup>3</sup> This case suggests that PML may be associated with ruxolitinib treatment. After discontinuation of this medication, the worsening of the neurologic signs may have been consistent with the immune reconstitution inflammatory syndrome.<sup>4</sup> Although the neurologic signs developed a few weeks after the initiation of ruxolitinib therapy, it is not yet clear whether the PML was directly related to this agent.

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Supported by the National Institute of Health Research Biomedical Research Centre funding scheme of the United Kingdom.

Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

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DOI: 10.1056/NEJMc1302135

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