COMMENTS AND RESPONSES

Obstructive Sleep Apnea and Stroke

TO THE EDITOR: The review on obstructive sleep apnea by Caples and colleagues (1) made for interesting reading, but the authors overlooked the association between obstructive sleep apnea and cerebrovascular disease. The most difficult challenge in understanding the link between hypertension and cardiovascular and cerebrovascular disease is the presence of significant obesity in most adult patients with obstructive sleep apnea. Obesity tends to be differentially distributed in the abdomen and upper body, probably producing much of its effect on sleep apnea through the deposition of fat in the neck, narrowing the pharyngeal airway. Whether this fat distribution pattern rather than obstructive sleep apnea itself actually explains the cardiovascular and cerebrovascular morbidity in affected patients is hotly debated. However, it has been shown beyond reasonable doubt that obstructive sleep apnea contributes to hypertension (1), also offering a potential causal link with stroke.

The strongest epidemiologic evidence indicating the association between obstructive sleep apnea and stroke comes from the Sleep Heart Health Study (2). In this study, in a large sample of 6424 persons who underwent unattended overnight polysomnography at home, even mild to moderate obstructive sleep apnea was significantly associated with development of coronary artery disease, congestive heart failure, and stroke, independent of known cardiovascular risk factors (2).

Another bone of contention regarding the association between obstructive sleep apnea and stroke has been the temporal relationship between the two. It has been argued that stroke may cause residual neuromuscular effects that may lead to obstructive sleep apnea. However, patients with transient ischemic attack (which by definition lacks the permanent sequelae of stroke) have also been shown to have higher prevalence of obstructive sleep apnea when compared with controls (3). These patients were also similar to patients with stroke when such variables as habitual snoring, apnea–hypopnea index, and maximal apnea duration were considered (3).

While the weight of evidence supporting obstructive sleep apnea as an independent risk factor for stroke is suggestive, cross-sectional studies can never give a definitive result about the cause-and-effect relationship. Confirmation awaits the results of large prospective studies evaluating the relationship between the polysomnographic indices of sleep-disordered breathing and stroke. Preliminary data from one such study, published so far only as an abstract (4), support the conclusion that obstructive sleep apnea is a risk factor for the development of stroke or transient ischemic attack, independent of sex, body mass index, diabetes, and hypertension.

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Potential Financial Conflicts of Interest: None disclosed.

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IN RESPONSE: We thank Dr. Madan for these comments about the association between obstructive sleep apnea and stroke. Because of the abundance of data published on obstructive sleep apnea, we limited our discussion of disease associations to those with the highest level of published evidence. The Sleep Heart Health Study has generated large amounts of data and has yielded a number of important publications. However, current evidence does not support a causal role of obstructive sleep apnea in stroke. Rather, studies like the Sleep Heart Health Study suggest that obstructive sleep apnea is prevalent in those who have a history of stroke (1).

As Madan suggests, confidently implicating obstructive sleep apnea in the etiology of cerebrovascular disease will require rigorous, long-term prospective data. Moreover, it has been shown that stroke may actually cause transient centrally mediated apnea. That said, the hemodynamic and hemostatic changes seen in obstructive sleep apnea, along with indirect effects related to the high prevalence of concomitant systemic hypertension, suggest a potentially important role of obstructive sleep apnea in cerebrovascular disease. Available evidence, however, has been conflicting. A prospective cohort study of patients admitted for stroke or transient ischemic attack demonstrated a higher prevalence of obstructive sleep apnea than in the general population (2). This was not the case in a small case–control study of patients with transient ischemic attack, which showed no significant difference in the severity or prevalence of obstructive sleep apnea between groups (3).

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Pegylated Interferon-α2b and Lamivudine in Hepatitis B e Antigen–Positive Chronic Hepatitis B

TO THE EDITOR: In Chan and colleagues' study of pegylated interferon in patients with hepatitis B e antigen (HBeAg)–positive chronic hepatitis B (1), the sustained virologic response (HBeAg seroconversion and hepatitis B virus DNA level less than 500 000 copies/mL) was 36% after 32 weeks of therapy with pegylated interferon-α2b plus 52 weeks of lamivudine. This percentage is comparable with the HBeAg seroconversion rates in 2 global studies investigating combination therapy with pegylated interferon and lamivudine for 1 year (2, 3). In one of these studies, coordinated by our group (2), patients were treated for 52 weeks with pegylated interferon-α2b and lamivudine, and HBeAg seroconversion was achieved in 25% at the end of treatment. In the study by Lau and colleagues (3), patients were treated with pegylated interferon-α2a and lamivudine for 48 weeks and 24% experienced HBeAg seroconversion at the end of treatment.

The 60% HBeAg seroconversion at the end of treatment in the study by Chan and colleagues is very high compared with previous studies, particularly considering the high prevalence of genotype C in their patients, which is probably associated with a less favorable outcome (2). Furthermore, for treatment-naive patients, the study by Chan and colleagues shows a very high percentage of lamivudine resistance (40%) in the lamivudine monotherapy group as determined by the INNO-LiPA assay (Innogenetics N.V., Ghent, Belgium). In the combination therapy group, the rate of lamivudine resistance was 21%. The lamivudine resistance rate in our study was only 11% in the combination therapy group as determined by the same assay. It is tempting to speculate that some of Chan and colleagues' patients were previously exposed to lamivudine therapy. We wonder whether the authors can explain the high end-of-treatment response and the high incidence of YMDD mutants.

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IN RESPONSE: We appreciate the interest and comments of Drs. ter Borg and Janssen. In our study, the proportion of patients who achieved HBeAg seroconversion at the end of combination treatment with pegylated interferon and lamivudine (60%) was indeed substantially higher than that reported in 2 other multicenter studies (25% to 27%) (1, 2). We agree that this result is surprising, since pegylated interferon was given for 32 weeks in our study compared with a longer treatment duration (48 to 52 weeks) in the other 2 studies. We started pegylated interferon-α2b 8 weeks before the commencement of lamivudine treatment, in contrast to the other studies, which administered the drugs simultaneously. We hypothesize that our staggered administration of an immunomodulator followed by lamivudine might have allowed maximal host immune stimulation by pegylated interferon because reduction of viral load by coadministration of an antiviral agent would have been avoided. This hypothesis, however, requires confirmation by future viral kinetics studies using different regimens of combination therapy. We suspect that the inclusion of a significant proportion of patients with previous interferon or lamivudine treatment failure in the 2 multicenter studies might have affected the overall treatment response (1, 2). Hepatitis B virus genotype may not be important in our study because it was not found to influence the sustained virologic response in our patients up to 3 years after treatment (3).

We concur with Drs. ter Borg and Janssen that the rate of lamivudine resistance was high in our report. We did extensive interviews and medical record searches to exclude previous use of lamivudine when we recruited patients. Because lamivudine was registered in Hong Kong in 1999, the year we started our study, a hidden but significant previous exposure to lamivudine seemed extremely unlikely. The rate of lamivudine resistance among patients treated with lamivudine monotherapy in our study (40%) was comparable to that reported by Lau and colleagues (34%) (2). The higher rate of lamivudine resistance as compared with previous early reports may be related to the higher sensitivity of the laboratory tool we use today. We are not certain why our patients receiving combination treatment have a higher incidence of lamivudine-resistant mutations (21%) than in the other 2 studies (11%). The relatively small number of patients in our study may have biased the results. Whether patient ethnicity or viral genotype plays a role will require further investigation.

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CLINICAL OBSERVATIONS

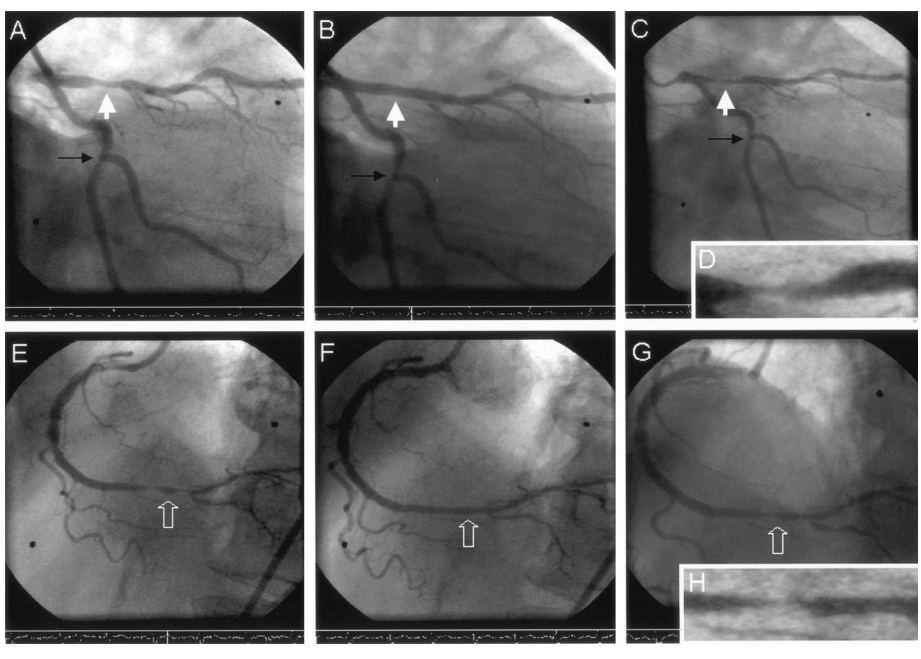
Late Restenosis in Patients Receiving a Polymer-Coated Sirolimus-Eluting Stent

TO THE EDITOR: *Background:* Drug-eluting stents have been broadly available for more than 2 years. Several studies have shown the efficacy of both sirolimus- and paclitaxel-eluting stents for prevention of coronary in-stent restenosis (1, 2). In-stent restenosis is usually detectable in bare-metal stents within the first 6 to 9 months after stent placement; therefore, this time frame is commonly used as follow-up in trials of drug-eluting stents (3). Angiographic results in bare-metal stents approximately 6 months after placement constitute the peak of neointimal obstruction in most patients (3), and angiographic follow-up at later time points often demonstrates decreased neointimal burden, most likely because of apoptotic or remodeling processes (4). Current commercially available drug-eluting stents use a nonbiodegradable polymeric surface, and there is ongoing discussion about increased late stent thrombosis in patients who receive them (5, 6). Besides late thrombotic events, especially after discontinuation of antiplatelet therapy with clopidogrel, the development of late in-stent restenosis is an important unresolved issue.

Objective: We describe 2 patients who presented with late in-stent restenosis and recurrent angina pectoris, but no evidence of acute coronary syndrome, 20.4 and 18.9 months, respectively, after placement of a sirolimus-eluting stent. Of importance, both of our patients had an excellent angiographic result immediately after stent placement and at the scheduled 7-month follow-up visit, with no or minimal in-stent restenosis (**Figures 1** and **2**).

Case Report: A 52-year-old man with arterial hypertension and hypercholesterolemia presented with stable angina pectoris that had lasted for more than 12 weeks. Three years earlier, he had received a bare-metal stent, 3.0 mm in diameter and 18 mm long, to treat a left circumflex lesion. Twenty months before the admission discussed here, he presented with stable angina. The left circumflex bare-metal stent showed no clinically significant in-stent restenosis; however, he received a sirolimus-eluting stent (Cypher, Cordis Corp., Miami Lakes, Florida) of the same dimensions to treat a proximal left anterior descending de novo lesion (**Figure 1**, *part A*). Scheduled follow-up coronary angioplasty 7 months later showed no restenosis in the sirolimus-eluting stent (**Figure 1**, *part B*). At that time, clopidogrel therapy was discontinued. Thirteen months later, the patient was admitted with stable recurrent angina. His medication consisted of a statin, an angiotensin-converting enzyme inhibitor, a β-blocker, and low-dose aspirin. His total cholesterol level was 4.24 mmol/L (164 mg/dL), and his low-density lipoprotein cholesterol level was 1.97 mmol/L (76.3 mg/dL). Results of electrocardiography performed at rest were normal, but exercise electrocardiography revealed significant ST-segment depression at 100 W. Levels of creatine kinase, creatine kinase–MB, troponin T, and C-reactive protein were

Figure 1. **Coronary angiograms of 2 patients who received sirolimus-eluting stents and presented with late in-stent restenosis.**



The first patient received a sirolimus-eluting stent to treat proximal left anterior descending stenosis (*part A, white arrow*) with an appropriate angiographic follow-up result at 7 months (*part B*). Later, after 20.4 months, the patient presented with late restenosis in the sirolimus-eluting stent (*parts C and D*). Of note, a bare-metal stent implanted around the same time did not reveal progressive restenosis (*parts A through C, black arrows*). The second patient received a sirolimus-eluting stent for treatment of de novo right coronary artery stenosis (*part E, arrow*) with adequate result at angiographic follow-up at 7 months (*part F*). Later, after 18.9 months, the patient presented with late restenosis in the sirolimus-eluting stent (*parts G and H*). Of note, a bare-metal stent implanted around the same time showed regression of in-stent neointima (see **Figure 2**).

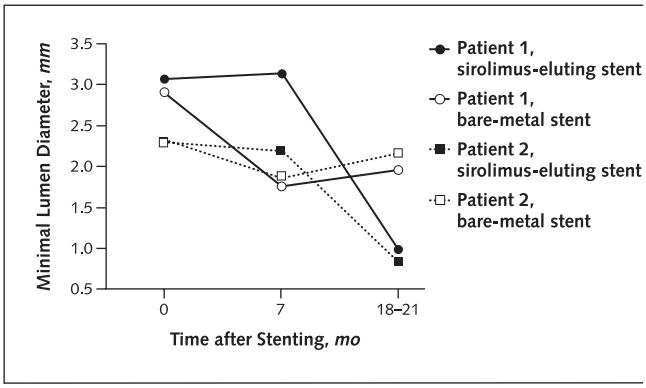
within normal ranges. Coronary angiography revealed marked late in-stent restenosis within the sirolimus-eluting stent (**Figure 1**, *parts C and D*) 20 months after implantation. In-stent restenosis was treated by percutaneous coronary intervention with no concomitant increase in myocardial markers. Of note, the bare-metal stent located in the left circumflex coronary artery showed no clinically significant restenosis, consistent with the preceding angiographic evaluation 13 months before. The patient's recovery was uneventful.

In March 2003, an 82-year-old man with 3-vessel coronary artery disease received a sirolimus-eluting stent (Cypher), 2.5 mm in diameter and 23 mm long, to treat severe stenosis of the distal right coronary artery (**Figure 1**, *part E*) with an adequate postinterventional result. His risk factors were arterial hypertension and hypercholesterolemia. Medical treatment included low-dose aspirin, a statin, an angiotensin-converting enzyme inhibitor, a β-blocker, and clopidogrel. His total cholesterol level was 4.53 mmol/L (175 mg/dL), and his low-density lipoprotein cholesterol level was 3.18 mmol/L (123 mg/dL). In September 2003, he presented for scheduled angiographic follow-up, which revealed an excellent angiographic result in the sirolimus-eluting stent (**Figure 1**, *part F*). However, because the patient's coronary artery disease had progressed, a bare-metal stent was placed into the left circumflex artery and clopidogrel therapy was continued. In January 2004, the patient presented with atypical angina and no signs of acute coronary syndrome. Coronary angiography showed adequate results within both the sirolimus-eluting stent and the bare-metal stent (images not shown). In September 2004, while still receiving combined antiplatelet therapy, including both aspirin and clopidogrel, the patient presented with recurrent angina at exertion, which lasted for approximately 6 weeks. Electrocardiography results and laboratory values ruled out acute cardiac syndrome, and the C-reactive protein level was normal. Coronary angiography revealed marked restenosis (**Figure 1**, *parts G and H*) within the sirolimus-eluting stent, whereas the bare-metal stent maintained its initial, adequate angiographic result. Percutaneous intervention and in-hospital stay were uncomplicated.

Discussion: To our knowledge, this is the first published report of recurrent angina and severe in-stent stenosis in patients presenting more than 18 months after receiving a sirolimus-eluting stent. Scheduled follow-up coronary angiography at 7 months revealed no evidence of sirolimus-eluting stent restenosis in either patient. Of note, bare-metal stents implanted at about the same time did not show clinically significant restenosis at any point in time or any significant decrease of minimal lumen diameter more than 7 months after stent placement (**Figure 2**).

Preclinical porcine studies have consistently demonstrated effective limitation of coronary neointima formation with several drug-eluting stents, in particular polymer-coated stents eluting paclitaxel (7) or sirolimus (8) 30 days after stenting. However, a recent study reports ongoing neointimal growth in sirolimus-eluting stents in this model and "catch-up" of neointimal formation after 90 days in pigs receiving sirolimus-eluting stents compared with bare-metal stents (9), thus indicating delayed neointimal growth. In a human trial, patients who received 7-hexanoyltaxol–eluting polymer stents (QuaDDS-QP2, Quanam, Santa Clara, California) to treat de novo coronary lesions had appropriate 6-month angiographic results but developed late, accelerated in-stent restenosis after 12 months (10). Examinations of tissue atherectomies from these patients suggested that ongoing inflammation might have caused the negative outcome (11).

Figure 2. **Development of in-stent minimal lumen diameter as a measure of neointimal growth in patients receiving a sirolimus-eluting stent and a bare-metal stent at approximately the same time.**



Minimal lumen diameter in bare-metal stents reached the minimum at 7-month follow-up in both patients and increased thereafter. In contrast, minimal lumen diameter steadily decreased in both polymer-coated sirolimus-eluting stents, demonstrating delayed neointimal growth.

In our patients, the exact mechanism for the development of late in-stent restenosis in sirolimus-eluting stents despite excellent immediate and 7-month angiographic results remains elusive. The regression of neointimal hyperplasia in the bare-metal stents of both patients (**Figure 2**) suggests that the delay of neointimal growth and consequently the development of late restenosis are due to the stent coating. Whether the polymeric coating, for which hypersensitivity reactions and delayed vascular healing are described (5), or the pharmacologic compound sirolimus or both are primarily responsible remains elusive.

Since long-term studies in "real-world" patients with drug-eluting stents are lacking, it is uncertain whether the phenomenon we observed is rare. Considering the clinical course and the angiographic appearance in our patients, late stent thrombosis is unlikely to have caused stent obstruction, although it cannot be ruled out entirely. Further studies should investigate the clinical relevance of this phenomenon and the appropriate length of follow-up in patients who receive drug-eluting stents.

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Table. **Clinical and Laboratory Findings in Patients with Active Takayasu Arteritis Enrolled in the Study***

Patient	Age, *y*	Prednisolone Dosage, *mg/d*	CRP Level, *mg/L*†		ESR, *mm/h*‡		MMP-2 Level, *ng/mL*§	
			Baseline	Post-Treatment	Baseline	Post-Treatment	Baseline	Post-Treatment
1	49	17.5	31	9	90	54	882	1140
2	63	5	8	1	38	28	1450	1370
3	47	15	19	2	43	28	807	926
4	25	10	13	3	54	37	968	943
5	26	20	10	1	38	25	840	762
6	63	12.5	4	1	58	34	712	837
7	29	10	5	4	24	21	1050	851
8	30	10	6	2	18	11	1060	728
9	29	10	21	2	54	21	935	899
10	24	20	34	10	38	32	866	922
11	20	20	45	62	98	90	805	881
Mean value (SD)	37 (16)	13.6 (5.2)	17.8 (13.7)	8.9 (17.9)	50 (25)	35 (21)	943 (199)	933 (180)
P value			0.026		0.003		0.93	

* All patients were women. Differences between the groups were analyzed by Wilcoxon signed-rank test using StatView software, version 5.0 (SAS Institute Inc., Cary, North Carolina). CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; MMP = matrix metalloproteinase.
† Normal value is <4 m/L.
‡ Normal value is <20 mm/h.
§ Normal ranges are 367–770 ng/mL for MMP-2, 17.3–59.7 ng/mL for MMP-3, and 12.0–71.0 ng/mL for MMP-9.
‖ A score of 1 indicates remission; a score of 2, 3, or 4 indicates active disease.

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Minocycline for the Treatment of Takayasu Arteritis

TO THE EDITOR: *Background:* Takayasu arteritis is a type of chronic vasculitis that primarily affects large elastic arteries. It tends to progress despite treatment with glucocorticoids or immunosuppressive agents (1, 2). Recently, we reported that matrix metalloproteinases (MMPs) might contribute to the pathogenesis and exacerbation of Takayasu arteritis and that circulating levels of MMPs could be diagnostic markers of the disease (3). While many MMP inhibitors are under development (4), minocycline has established MMP inhibitor activity that is independent of antimicrobial activity (5).

Objective: To assess the effect of combination treatment with minocycline and glucocorticoid for active Takayasu arteritis.

Methods and Findings: Of 35 consecutive patients with Takayasu arteritis who were referred to the Department of Internal Medicine and Molecular Science, Osaka University Hospital, from October 2001 to July 2004, 15 were receiving prednisolone therapy for active disease. Eleven of these 15 patients gave informed consent and enrolled in the study. Each fulfilled more than 3 of the American College of Rheumatology criteria for Takayasu arteritis (1) and were evaluated according to the National Institute of Health criteria for disease activity (disease activity score) (2). The Ethics Committee of Osaka University Graduate School of Medicine approved the study protocol.

The patients were treated with oral minocycline (100 mg twice daily) for 3 months without changes in prednisolone dosage. The **Table** shows changes from baseline to 3 months for disease activity score; C-reactive protein level; erythrocyte sedimentation rate; and levels of MMP-2, MMP-3, and MMP-9. The mean disease activity score improved from 2.8 (SD, 0.8) to 0.7 (SD, 1.0) ($P = 0.004$). Mean erythrocyte sedimentation rate and C-reactive protein values decreased in all patients from 50 mm/h (SD, 25) to 35 mm/h (SD, 21) ($P = 0.003$) and from 17.8 mg/L (SD, 13.7) to 8.9 mg/dL (SD, 17.9) ($P = 0.026$), respectively. Nine of 11 patients were considered to be in remission according to disease activity score. Furthermore, the mean serum MMP-3 and MMP-9 levels decreased from 141.9 (SD, 57.3) to 65.0 (SD, 41.1) ($P = 0.004$) and from 116.6 (SD, 52.3) to 47.1 (SD, 15.5) ($P = 0.004$), respectively. Mean serum MMP-2 levels did not change (943.2 [SD, 198.5] to 932.6 [SD, 180.3]).

Discussion: In recent years, minocycline has been used to treat a variety of diseases, including rheumatoid arthritis, osteoarthritis, osteoporosis, and cancer (5). Actions of minocycline in these diseases are thought to be independent of antimicrobial activity and are re-

Table— **Continued**

MMP-3 Level, *ng/mL*§		MMP-9 Level, *ng/mL*§		Disease Activity Score		Outcome‖
Baseline	**Post-Treatment**	**Baseline**	**Post-Treatment**	**Baseline**	**Post-Treatment**	
223.0	151.0	171.5	68.0	4	1	Remission
158.0	69.1	79.7	25.6	2	0	Remission
145.2	60.2	224.0	44.2	3	0	Remission
143.0	111.0	176.0	27.3	3	1	Remission
198.8	19.7	120.5	40.4	3	0	Remission
107.8	33.7	117.4	51.0	2	1	Remission
74.8	53.4	88.7	41.6	2	0	Remission
118.0	25.5	88.3	42.6	2	0	Remission
27.4	30.1	80.1	44.5	3	0	Remission
174.0	59.8	79.7	56.1	4	2	Treatment effective but no remission
191.0	101.5	56.3	77.3	3	3	Treatment not effective
141.9 (57.3)	65.0 (41.1)	116.6 (52.3)	47.1 (15.5)	2.8 (0.8)	0.7 (1.0)	
0.004		0.004		0.004		

lated to pleiotropic effects, including inhibition of MMP activities (5). We previously showed that MMPs might contribute to the pathogenesis and exacerbation of Takayasu arteritis (3), and those findings prompted us to test the pleiotropic effects of minocycline on patients with this disorder. In our case series, we observed a marked reduction of erythrocyte sedimentation rate and C-reactive protein values as well as disease activity score. In association with these improvements, circulating MMP-3 and MMP-9 levels also decreased. These results need confirmation in larger, controlled studies.

Conclusion: Minocycline may be a valuable additive to steroids or an alternative to immunosuppressive agents for patients with Takayasu arteritis and should be tested in randomized, controlled trials.

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CORRECTION

Correction: Patient-to-Patient Transmission of Hepatitis C Virus

Wenzel and Edmonds's editorial on patient-to-patient transmission of hepatitis C virus (1) contained an error. On page 941, in the fifth sentence of the first full paragraph, the upper end of the 95% CI around the point estimate of zero should have been reported as 4.2 per 1000, not 4.2%.

Reference

1. Wenzel RP, Edmond MB. Patient-to-patient transmission of hepatitis C virus [Editorial]. Ann Intern Med. 2005;142:940-1. [PMID: 15941703]