(11.1%) always did. The main factors influencing caution in using the loading dose were gastrointestinal side-effects and other toxicity. Some consultants had adopted a starting dose of 10 mg/day increasing to 20 mg/day if tolerated. Thirty-two (59.3%) advised patients that occasional alcohol consumption was acceptable, 12 (22.2%) advised no alcohol restriction, and only 10 (18.5%) followed the recommendation of the SPC of avoiding alcohol. Some consultants commented that patients may refuse leflunomide if there was an alcohol ban.

Against SPC recommendations, 26 (48.1%) never used a cholestyramine or activated charcoal washout for swapping leflunomide to another DMARD and 16 (29.6%) used one occasionally. Not all consultants indicated whether the full 11 days washout was used but some commented that they used shorter washout periods as few patients tolerated the 11 days. Although the SPC warns against combination therapy, 31 (57.4%) and 8 (14.8%) combined leflunomide with methotrexate occasionally and usually, respectively. Combination therapy was never used by 14 (25.9%) consultants. The main concern raised with combination therapy was the potential for liver toxicity.

Thirty-five (64.8%) monitored bloods fortnightly in the first 6 months, in keeping with SPC recommendations. The remainder had variable monitoring regimes, ranging from fortnightly for 2 months then monthly, to fortnightly for 2 months, monthly for 4 months, then 3-monthly. Blood pressure monitoring was conducted fortnightly and monthly in 23 (42.6%) and 22 (40.7%), respectively. One responder never checked the blood pressure.

In summary, this survey has demonstrated that for most rheumatologists in the Midlands leflunomide has established a firm footing in their clinical practice, and usually follows the failure of sulphasalazine and methotrexate. This survey confirmed the marked variation in the prescribing and monitoring of leflunomide. In some regards, the majority of consultants are disregarding the SPC and national guidelines [3]. This applies to the infrequent use of the loading dose, failure to ban alcohol, not using a washout to transfer patients from leflunomide to another DMARD, and combining the drug with methotrexate. The percentage of rheumatologists who were monitoring full blood counts less frequently than the SPC recommends was 35.2%, and one person was not checking blood pressure at all.

These discrepancies between clinical practice and the recommendations of the SPC can be interpreted in two ways. The first interpretation is that the SPC is too restrictive, and increasing experience with the drug is influencing confidence in deviating from recommendations. If this is the case, then information needs to be collected to be able to modify the SPC. The second interpretation is that consultants have become too relaxed in their approach to the prescribing and monitoring of leflunomide, and this may lead to medicolegal consequences. We would like to suggest that the former is closer to the truth than the latter, and that urgent attention needs to be given to modifying the SPC.

There are already data on the safe and efficacious use of combinations of leflunomide and methotrexate [4, 5], despite warnings about possible adverse liver reactions [6]. Full blood count abnormalities are infrequent [7–12], suggesting that fortnightly blood tests for 6 months is excessive. More information is required on the efficacy and toxicity of using or avoiding the loading dose [13]. More data are needed on the safety of alcohol with leflunomide, and the need for washing patients out prior to switching from leflunomide to another DMARD.

The difficulty with SPCs is that, once a recommendation has been made, evidence is needed before it can be modified with confidence. We believe that for leflunomide there is already enough data and a sufficient groundswell of clinical practice and experience to modify the SPC.

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1. Arava Summary of Product Characteristics. Aventis Pharmaceuticals, July 2002.
2. Jobanputra P, Wilson J, Douglas K, Burls A. A survey of British rheumatologists' DMARD preferences for rheumatoid arthritis. Rheumatology 2004;43:206–10.
3. British Society for Rheumatology. National guidelines for the monitoring of second line drugs (online), July 2000. http://www.msecportal.org/portal/editorial/PublicPages/bsr/536883013/3.doc
4. Weinblatt ME, Kremer JM, Coblyn JS *et al*. Pharmacokinetics, safety, and efficacy of combination treatment with methotrexate and leflunomide in patients with active rheumatoid arthritis. Arthritis Rheum 1999;42:1322–8.
5. Kremer JM, Genovese MC, Cannon GW *et al*. Concomitant leflunomide in patients with active rheumatoid arthritis despite stable doses of methotrexate. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 2002;137:726–36.
6. The European Agency for the Evaluation of Medicinal Products. Post-authorisation evaluation of medicines for human use. EMEA public statement on leflunomide (Arava)—severe and serious hepatic reactions. Document reference EMEA/H/5611/01/en. London, 12 March 2001.
7. Strand V, Cohen S, Schiff M *et al*. Treatment of active rheumatoid arthritis with leflunomide compared with placebo and methotrexate. Leflunomide Rheumatoid Arthritis Investigators Group. Arch Int Med 1999;159:2542–50.
8. Smolen JS, Kalden JR, Scott DL *et al*. and the European Leflunomide Study Group. Efficacy and safety of leflunomide compared with placebo and sulphasalazine in active rheumatoid arthritis: a double-blind randomised multicentre trial. Lancet 1999;353:259–66.
9. Emery P, Breedfeld C, Lemmel EM *et al*. and the multinational leflunomide study group. A comparison of the efficacy and safety of leflunomide and methotrexate for the treatment of rheumatoid arthritis. Rheumatology 2000;39:655–65.
10. Cohen S, Cannon GW, Schiff M *et al*. Two-year blinded randomized controlled treatment of active rheumatoid arthritis with leflunomide compared with methotrexate. Utilization of Leflunomide in the Treatment of Rheumatoid Arthritis Trial Investigator Group. Arthritis Rheum 2001;44:1984–92.
11. Scott DL, Smolen JS, Kalden JR *et al*. Treatment of active rheumatoid arthritis with leflunomide: two year follow up of a double blind, placebo controlled trial versus sulfasalazine. Ann Rheum Dis 2001;60:913–23.
12. Kalden JR, Schattenkirchner M, Sorensen H *et al*. The efficacy and safety of leflunomide in patients with active rheumatoid arthritis: a five-year follow up study. Arthritis Rheum 2003;48: 1513–20.
13. Sinha A, Amos N, Lawson TM. Leflunomide—the Welsh experience. Rheumatology 2003;42(Suppl. 1):97–8.

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Coronary atherosclerosis in Behçet's syndrome: a pilot study using electron-beam computed tomography

Sir, Behçet's syndrome (BS) may involve vessels of virtually all types and sizes but coronary artery disease has been reported sporadically. Coronary atherosclerosis in BS has not formally been studied thus far.

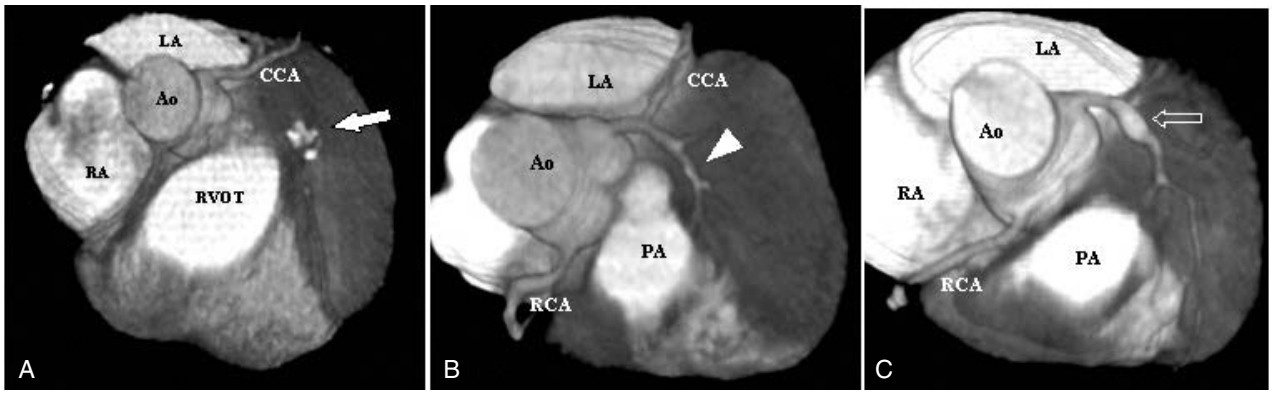


FIG. 1. Cranial right anterior oblique (RAO) views: volume-rendered three-dimensional EBCT angiography of the heart after segmentation of the ascending aorta and pulmonary artery. (**A**) 39-yr-old male patient with vena cava thrombosis and chest pain. CAC score 600. There is proximal occlusion of the LAD with a calcified, thrombosed mid-LAD aneurysm (arrow). Flow in distal LAD is retrograde via collaterals. Thallium scintigraphy was consistent with anterobasal ischaemia. Conventional coronary angiography was also in accord with the finding of EBCT. Although severe, the occlusion in the proximal part of the LAD was too short and narrow for a surgical intervention so medical treatment was carried out. (**B**) 40-yr-old male patient with pulmonary artery aneurysm and inferior vena cava occlusion. CAC score 58. There is intermediate stenosis of the mid-LAD (arrowhead). Calcified plaques are also noted in the proximal LAD and 2nd diagonal branch. (**C**) 36-yr-old male patient with pulmonary artery aneurysm and inferior vena cava occlusion. CAC score 7. Non-calcified proximal LAD aneurysm (open arrow). No further investigation was done in the last two patients as their scintigraphy was normal. RVOT, right ventricular outflow tract; LA, left atrium; RA, right atrium; Ao, aorta; PA, pulmonary artery; RCA, right coronary artery; CCA, circumflex coronary artery.

Electron beam computed tomography (EBCT) has emerged as a simple and non-invasive technique for the diagnosis of coronary atherosclerosis [1, 2]. It detects coronary artery calcification, which is a potential indicator of significant future coronary risk and also shows the wall morphology and patency of coronary arteries with contrast enhancement [1–3].

We investigated the frequency of coronary atherosclerosis, by using EBCT, in a group of male BS patients selected specifically for having major vessel disease and long disease duration. Our hypothesis was that coronary atherosclerosis would be frequent in this group of BS patients. We defined major vascular involvement as the presence of an aneurysm and/or arterial occlusion and/or thrombosis of the venae cavae. All patients were initially screened for cardiovascular risk factors. Total and individual coronary calcium scores were calculated according to the method described by Agatston *et al.* [3]. Coronary artery calcium scores were stratified as follows: (i) no calcification; (ii) 1–100, minimal to slight calcification; (iii) 101–400, intermediate calcification; (iv) score greater than 400, extensive calcification. The study was approved by the local ethics committee of Cerrahpaşa Medical Faculty and informed consent was obtained from all patients.

We studied 24 patients [mean age 37.8 ± 4.5 (S.D.) yr; duration of vascular involvement 10.1 ± 3.7 yr]. The main vessels involved were the pulmonary arteries (nine patients), abdominal aorta (four patients) and vena cava (nine patients). Seven patients had more than one diseased vessel. Fifteen patients (63%) had used corticosteroids previously, with a mean duration of 3.9 ± 3 yr. All patients were previous or current users of cyclophosphamide or azathioprine. The mean duration of treatment with these drugs was 4.3 ± 3 yr. The majority (88%) smoked and 42% had at least mild lipid abnormalities. One patient had diabetes mellitus. No patient had arterial hypertension or myocardial infarction. Coronary artery calcium scores were zero in 21 (88%) patients. Two patients had scores suggesting minimal or slight calcification (58 and 7) and one patient had a calcium score of 600, indicating extensive calcification. These three patients (12%) were also the only ones with abnormal imaging on EBCT coronary angiography, as shown in Fig. 1. One patient had total occlusion and calcified aneurysm in the proximal part of the left anterior descending artery (LAD) (Fig. 1, left panel). The second had mild stenosis with calcified plaque formations in the LAD (Fig. 1, middle panel), and the third had non-calcified aneurysm in the LAD (Fig. 1, right panel). Our results suggest that coronary artery abnormalities are not common in BS even in a selected group of male patients.

In a recent study using EBCT, coronary artery calcification (CAC) was described among 31% of 65 SLE patients with no history of coronary artery disease, compared with 9% of 69 controls. The patients and controls in this study were predominantly women and had an average age of approximately 40 yr [4]. The prevalence of CAC among women is estimated to be half that in men until the age of 60 yr [1]. Extrapolating from this, and not forgetting the limitations of indirect comparisons, especially among different ethnical groups, the frequency of CAC among our selected male patient population seems to be at least not increased when compared with what is found in the general population. Unfortunately, data on coronary calcification in the general population of Turkey are not available and our study did not include a formal control group.

Among 350 patients with BS who were followed up between 1974 and 1993 in France, three (0.09%) had coronary arterial involvement [5]. Furthermore, in a 20-yr outcome survey on 387 patients from our centre, only three of the 42 deaths (0.7%) were due to coronary artery disease [6]. In that study the mortality in BS was mainly due to extracardiac vascular or neurological disease, and these complications showed a tendency to decrease in frequency with the passage of time during the disease course. This mortality pattern is different from what is found in RA and SLE [7, 8], in which there is an increased or bimodal mortality pattern with increased atherosclerotic coronary artery disease with the prolonged disease course.

It is believed that the classical risk factors, such as smoking and high lipid levels, are important in the coronary atherosclerosis of inflammatory diseases. Disease duration, corticosteroid use and inflammatory activity are implicated as additional risk factors [9]. In our study, coronary atherosclerosis was lower than what we expected, although our patients carried most of these risk factors. The relatively young age of our patients or the immunosuppressive treatment employed might have played a role in

this outcome. Another explanation could be that the disease activity in BS is more short-lasting compared with other diseases characterized by chronic and long-lasting inflammation, such as SLE and RA [6].

In summary, our preliminary findings indicate a relatively low frequency of coronary atherosclerosis in BS even when studied under worst-case conditions. Further studies are needed, first to verify these preliminary observations in a controlled setting and secondly to elucidate their biological importance, if verified.

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Rheumatology	Key messages
	• EBCT is a suitable non-invasive method to detect coronary artery pathology in BS. • Patients with BS seem to have a relatively low frequency of coronary atherosclerosis.

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1. Wexler L, Brundage B, Crouse J *et al.* Coronary artery calcification: pathophysiology, epidemiology, imaging methods, and clinical implications. A statement for health professionals from the American Heart Association. Writing Group. Circulation 1996;94:1175–92.
2. Budoff MJ, Oudiz RJ, Zalace CP *et al.* Intravenous three-dimensional coronary angiography using contrast enhanced electron beam computed tomography. Am J Cardiol 1999;83:840–5.
3. Agatston AS, Janowitz WR, Hildner FJ *et al.* Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol 1990;15:827–32.
4. Asanuma Y, Oeser A, Shintani AK *et al.* Premature coronary artery atherosclerosis in systemic lupus erythematosus. N Engl J Med 2003; 349:2407–15.
5. Le Thi Huong D, Wechsler B, Papo T *et al.* Arterial lesions in Behcet's disease. A study in 25 patients. J Rheumatol 1995;22: 2103–13.
6. Kural-Seyahi E, Fresko I, Seyahi N *et al.* The long-term mortality and morbidity of Behcet syndrome: a 2-decade outcome survey of 387 patients followed at a dedicated center. Medicine (Baltimore) 2003;82:60–76.
7. Urowitz MB, Bookman AA, Koehler BE, Gordon DA, Smythe HA, Ogryzlo MA. The bimodal mortality pattern of systemic lupus erythematosus. Am J Med 1976;60:221–5.
8. Gabriel SE, Crowson CS, O'Fallon WM. Mortality in rheumatoid arthritis: have we made an impact in 4 decades? J Rheumatol 1999; 26:2529–33.
9. Manzi S. Systemic lupus erythematosus: a model for atherogenesis? Rheumatology 2000;39:353–9.

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A case of reversible posterior leucoencephalopathy syndrome after rituximab infusion

Sir, PV, a 38-yr-old patient with a 13-yr history of SLE, was admitted to our hospital because of occipital headache, blurring of vision and seizures after treatment with the second weekly course of intravenous infusion with rituximab (monoclonal antibody against CD20) for recurrence of renal disease. A similar episode had occurred after the first infusion, which was uneventfully resolved 24 h later.

The patient was diagnosed with SLE in 1995. For 6 yr she had had a mild disease, expressed mainly as skin rashes and arthralgias. In February 2001 she presented with nephrotic syndrome, active urinary sediment and pancytopenia. Immunology testing revealed high anti-DNA and low complement levels, while a bone marrow biopsy was consistent with peripheral destruction. Renal biopsy revealed the presence of diffuse proliferative glomerulonephritis (WHO IV). The patient was placed on intravenous pulses of cyclophosphamide, and responded efficiently with resolution of proteinuria and haematuria and complete haematological recovery.

In December 2001 a small brain infarct was detected on MRI scan after an episode of diplopia and blurring of vision. Anticardiolipin antibodies of the immunoglobulin G type were increased and oral anticoagulation therapy with a therapeutic international normalized rescue (INR) ranging from 2.5 to 3.0 was instituted.

In June 2003, while on quarterly intravenous infusions with cyclophosphamide, a recurrence of renal disease had occurred and weekly infusions with rituximab were started (375 mg/m^2), without prior steroid prophylaxis.

On her current admission, one day after the second rituximab infusion, blood pressure was 210–120 mmHg. An S3 gallop was present. Funduscopic examination revealed chronic hypertensive changes without evidence of papilloedema. No focal neurological signs were present. Laboratory evaluation revealed the presence of thrombotic microangiopathy. Renal function was deteriorating and soon anuria developed, requiring haemodialysis. Increased levels of anti-DNA antibodies and low levels of complement were present, consistent with increased lupus activity.

Six days later, a third scheduled infusion with rituximab was given. Six hours after the medication was administered, headache, severe hypertension, blurring of vision and seizures developed. An MRI scan revealed the presence of high-intensity signal in the cortical and subcortical white matter of the parietal lobes and the lateral posterior and lateral portions of the temporal lobes, consistent with the radiological findings of reversible posterior leucoencephalopathy syndrome (RPLS) (Fig. 1) [1].

The patient was placed on hypertensive and anticonvulsant therapy. Twenty-four hours later the neurological symptoms had abated. Plasmapheresis was started and intravenous cyclophosphamide and methylprednisolone were administered. One and a half months later, MRI findings had completely disappeared. Haematological and renal function parameters had returned to the normal range.

Therefore, we present a case of RPLS in a patient with SLE and secondary antiphospholipid syndrome, after rituximab therapy.

RPLS, first recognized in 1996, is characterized by the presence of reversible white matter oedema involving predominantly the