Behçet’s syndrome (BS) is a rare, heterogeneous multi-system inflammatory condition, characterized by recurrent orogenital ulcers and uveitis. Vascular involvement affects 10–30% of patients, is most frequently observed in young males and usually presents as superficial or deep venous thrombosis (DVT) [1]. The spectrum of thrombosis also includes vena cava occlusion (inferior or superior), Budd–Chiari syndrome and dural sinus thrombi. Arterial aneurysms may occur and confer a serious bleeding risk, particularly when occurring in pulmonary arteries. Pulmonary artery aneurysms may also occur with DVT in isolation (Hughes–Stovin syndrome), although this is probably a forme fruste of BS [2]. In any event, the perceived increased risk of bleeding from aneurysms in association with venous thrombosis leads to a significant management conundrum.

A number of studies have looked systematically for an intrinsic disorder of coagulation in BS, but no clinically useful correlates with thrombosis have been identified [3]. As the likely cause of thrombosis is venous inflammation, an immunosuppressive approach to management is therefore reasonable, although the evidence indicating specific treatments is very limited. Perhaps the best support comes from the well-cited 2-year randomized placebo-controlled double-blind trial of AZA in BS, in which analysis of the extra-ocular outcomes showed that the number of patients who developed DVT was fewer in the AZA arm [4].

What then of anticoagulation? The European League Against Rheumatism (EULAR) has recently published recommendations for the management of thrombosis in BS in which the use of corticosteroids and immunosuppressants (such as AZA, CSA or cyclophosphamide) is fully endorsed [5]. These guidelines discourage the use of anticoagulants and anti-platelet agents, both on account of the increased risk of bleeding and because protection from pulmonary embolism is seen as a low priority. Thus, pulmonary embolism in BS is thought by many to be unusual, perhaps because clots become tethered to the inflamed vessel wall.

Some support for the EULAR guidelines on thrombosis in BS comes from a recent small study which compared the use of immune suppression and anticoagulation [6]. Thirty-seven patients with BS and venous thrombosis were retrospectively divided into three groups: immunosuppression alone (16 patients), combination immunosuppression and anticoagulation (17 patients) and anticoagulation alone (4 patients). Re-thrombosis was the study efficacy end-point. Three of four patients who were treated using warfarin without immunosuppression showed recurrence or progression of venous thrombosis, suggesting that anticoagulation therapy alone is not effective in treating DVT. As there were no significant differences in coagulation profile or the thrombosis recurrence rate in the immunosuppressant group and the combination therapy group, the authors suggested that anticoagulation in addition to immunosuppression may be unnecessary.

We have recently reviewed vascular complications in patients with BS attending our tertiary referral centre practice between 1994 and 2009, and the results highlight the difficulties presented by this group of patients and call for a tempered view on the contraindication to anticoagulation in regions such as the UK where BS is not endemic. Of 657 patients reviewed, 62 (9%) had a history of thrombosis, consistent with other series. Among these 62 patients, thrombosis was the event that eventually led to the diagnosis of BS in 39, and 17 were considered to have had a pulmonary embolus. Importantly, the large majority [55 (89%) patients] were treated with warfarin without immunosuppression and the other due to an upper gastrointestinal bleed. Given (i) the rarity of BS in the UK; (ii) the lack of familiarity of most acute physicians with the condition; (iii) the frequent ambiguity of the diagnosis of BS in the UK; (iv) the chances of thrombosis in an undiagnosed patient being due to more common causes; and (v) the risk of pulmonary embolism in BS patients being as great, or greater, than that of bleeding, these patients were often, if not usually, appropriately managed. While accepting that the mainstay of treating thrombosis in BS is immunosuppression, the practical problems are often how best to limit the risk of anticoagulation and for how long to anticoagulate.

Unquestionably, anticoagulation should be conducted in BS with extreme caution. Modern imaging provides an increasing armamentarium for screening the vasculature for aneurysms, and both CT and magnetic resonance angiography (MRA) are suitable. However, MRA is preferable if available, given the possible need for serial imaging and the need for minimizing radiation exposure. We
recommend systematic arterial imaging at the time of thrombosis, with due consideration of follow-up scanning.

Assuming a negative screen for aneurysms, there are no data to indicate when to discontinue anticoagulation in those already on treatment. One approach is to wait for clinical evidence of response to immunosuppression, and, in the absence of methodology to evaluate the inflammatory state of the vasculature, this needs to be guided by improvement in other manifestations such as orogenital ulceration, skin lesions (particularly subcutaneous nodular lesions and superficial thrombophlebitis) and ocular disease, as well as a fall in acute-phase reactants.

A further unanswered question is whether the presence of a coincidental genetic thrombophilic risk factor makes a difference to initiation or duration of anticoagulation [7]. Indeed, the association of a genetic risk factor (factor V Leiden) with retinal venocclusive disease in some patients may even argue that anticoagulation could positively influence the underlying disease [8]. However, tests for heritable thrombophilia may not accurately identify those at high risk of recurrence among patients with idiopathic thrombosis [9]. With our current state of knowledge, it is therefore not clear how the results of heritable thrombophilia testing should guide management in patients with BS.

In summary, there is a poor evidence base for optimal treatment of thrombosis in BS in non-endemic regions. There is a consensus that immunosuppression is indicated to settle underlying vessel wall inflammation. Anticoagulation may not be required in the long term and carries significant extra risk of bleeding if there are rare coexistent aneurysms. In practice, however, patients in the UK tend to be anticoagulated at the time of thrombosis before referral to specialist centres, and we would argue that this is often appropriate, at least until the diagnosis is confirmed and inflammation controlled. The development of better imaging techniques for the evaluation of functional and structural vascular abnormalities will provide the clinician with better tools for evaluating and treating this difficult group of patients.

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