Cutaneous blood-filled vesicles on idraparinux

In the Amadeus study,1 patients in atrial fibrillation who had an increased risk of thromboembolic stroke were randomly assigned either a vitamin K antagonist or a weekly subcutaneous injection of idraparinux—a synthetic pentasaccharide that inhibits activated factor X. The study was stopped early because of excessive bleeding in patients assigned idraparinux. We report unusual skin lesions that occurred in 15 of 56 participants assigned open-label idraparinux compared with none of 59 patients assigned warfarin at our study site.

After noting skin lesions in two study patients, we did detailed skin examinations on all study participants at each follow-up visit. We saw raised, blood-filled vesicles 0·5–2·0 cm in diameter that were remote from the subcutaneous injection sites in 15 patients (figure). Most patients had two to eight lesions, usually on the arms and legs, which appeared on average 3 months (range 2–8) after starting idraparinux. From this time new lesions continued to appear, but the severity of the lesions did not increase despite ongoing medication.

On first appearance the lesions would be bright red, suggesting fresh blood. They would then darken before gradually resolving over 2 weeks. The lesions were not painful or itchy, and occurred spontaneously with no trauma. The skin lesions continued after onset during a median follow-up of 5 months (range 1–10). In two patients the lesions disappeared over the course of 2 weeks after temporarily stopping idraparinux, but returned within 1 month on restarting idraparinux. In all patients, new lesions stopped appearing and gradually resolved 1 week after the last injection of idraparinux at study end with no subsequent recurrence.2

These skin lesions did not meet the study definition of a clinically significant bleed, which included a subcutaneous haematoma of more than 25 cm² or more than 100 cm² after trauma. Patients with vesicular skin lesions were no more likely to have a clinically significant bleed than were idraparinux patients with no skin lesions (four of 15 vs 15 of 43), although both groups were more likely to bleed than were patients assigned warfarin (seven of 59). We found no evidence of other systemic abnormalities in patients with skin lesions, and the platelet count remained in the normal range for all patients.

These skin lesions are likely to be a specific adverse effect of idraparinux. Raised, blood-filled vesicles with no history of trauma are not typical of subcutaneous bleeding seen with vitamin K antagonists, antiplatelet drugs, and other antithrombotic treatments. Raised purpuric lesions can occur with hypersensitivity vasculitis to drugs,3 but the absence of local itching or burning, systemic symptoms, and lack of progressive severity make this diagnosis less likely. Skin biopsy was not done in our patients, and the pathophysiology and clinical significance of these lesions is currently uncertain. These skin lesions have not been reported in previous studies of idraparinux4,5 or fondaparinux (another pentasaccharide inhibitor of factor Xa).6 Future studies of idraparinux should include documentation of the occurrence of skin lesions, and additional investigations to determine their pathology.

JB and RAHS were investigators in the Amadeus study and have no conflicts of interest to declare.

Chronic kidney disease in Taiwan

Chi Peng Wen and colleagues (June 28, p 2173)7 are to be commended on their massive undertaking to characterise kidney disease and its potential effect on all-cause mortality in Taiwanese adults. However, we are concerned that the analysis is flawed and gives a misleading message.

The study participants were not representative of the general population but were fee-paying, with incentives given to members of large families. Chronic kidney disease (CKD) is known to prevail within families. Additionally, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative8 overestimates the prevalence of CKD owing to its use of an absolute threshold of estimated glomerular filtration rate (eGFR) for defining stage 3 CKD (30–59 mL/min/1·73 m²) without any adjustment for the effects of normal ageing on eGFR.3

We also question whether the excretion of small amounts of protein in the urine should be used to define CKD in the absence of other findings. If one assumes that the isolated finding of minimal proteinuria is not indicative of CKD and further that at least half stage...