to prescribe DRSP-containing combined OC as a first choice for women starting OC.

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Conflict of interests

Jan Rosing: the laboratory of Jan Rosing acts as a reference laboratory for the ETP-based APC-resistance test in a study conducted by Schering AG.

References

1 Vandenbroucke JP, Rosing J, Bloemenkamp KW, Middeldorp S, Helmerhorst FM, Bouma BN, Rosendaal FR. Oral contraceptives and the risk of venous thrombosis. *N Engl J Med* 2001; **344**: 1527–35.
2 Rosing J, Middeldorp S, Curvers J, Thomassen MCLG, Nicolaes GA, Meijers JC, Bouma BN, Buller HR, Prins MH, Tans G. Low-dose oral contraceptives and acquired resistance to activated protein C: a randomised cross-over study. *Lancet* 1999; **354**: 2036–40.
3 Tans G, van Hylckama Vlieg A, Thomassen MC, Curvers J, Bertina RM, Rosing J, Rosendaal FR. Activated protein C: resistance determined with a thrombin generation-based test predicts for venous thrombosis in men and women. *Br J Haematol* 2003; **122**: 465–70.
4 van Grootheest K, Vrieling T. Thromboembolism associated with the new contraceptive Yasmin. *BMJ* 2003; **326**: 257.
5 Vasilakis-Scaramozza C, Jick H. Risk of venous thromboembolism with cyproterone or levonorgestrel contraceptives. *Lancet* 2001; **358**: 1427–9.
6 van Hylckama Vlieg A. Causes of Venous Thrombosis: Procoagulant Factors and Oral Contraceptives, Dissertation. Leiden: Leiden University, 2003.

Thalidomide, deep venous thrombosis and vasculitis

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Thalidomide has been employed in recent years for its anti-inflammatory and antiangiogenic properties in the treatment of several conditions including leprosy, systemic lupus erythematosus (SLE), Behcet's disease (BD) and solid and hematological malignancies [1,2].

An increased incidence of deep venous thrombosis (DVT) has been observed in malignancies, especially in multiple myeloma, during treatment with thalidomide combined with chemotherapy. Pathogenetic mechanisms of thalidomide associated DVT have not been clearly assessed. A possible role for acquired APC-R, increased levels of factor VIII coagulant activity, von Willebrand factor antigen and vascular endothelial growth factor has been suggested. The role of thrombophilia is unclear [3,4].

We describe a case of proximal DVT in a patient with SLE treated with thalidomide for cutaneous vasculitis.

A 65-year-old female satisfied the American College of Rheumatology criteria for SLE. Recurrent cutaneous vasculitis had been observed during a period of 5 years. Her medical history was remarkable for obesity, varicose veins and venous thromboembolism, having suffered of recurrent idiopathic superficial thrombophlebitis of lower limbs in the last 2 years. She had been treated with corticosteroids for 3 years.

In an attempt to spare corticosteroids, thalidomide (100 mg) was added. Fifteen days later the patient presented right lower limb swelling, pain and discomfort. No chest pain, dyspnea or hemoptysis was reported. Venous ultrasonography of the lower limbs was diagnostic for proximal DVT (right superficial femoral/popliteal vein) associated with recurrence of superficial thrombophlebitis (great saphenous vein). A perfusional lung scintigraphy was negative for signs of pulmonary embolism. The search for antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibodies, antibeta2-GPI antibodies), FV

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Leiden and G20210A prothrombin gene mutation was negative. Thalidomide was stopped and the patient was treated with dalteparin 100 U kg^{-1} bid and warfarin (target INR 2–3).

Venous thromboembolism is a multifactorial disease. Our patient had multiple risk factors for DVT (varicose veins, obesity, previous superficial thrombophlebitis). However the occurrence of the thrombotic event a few days after the onset of thalidomide indicates a possible role of this drug as a precipitating factor. The highest risk of thrombosis occurs early after initiation of thalidomide treatment in patients with multiple myeloma, indicating a possible cause–effect relationship.

BD is a multisystemic inflammatory disease of unknown cause characterized by recurrent oral aphtous ulcers, genital ulcers, uveitis, and skin lesions. Vasculitis is the pathological lesion common to most of its clinical manifestations [5]. BD is a prothrombotic condition and thrombotic events, which may be catastrophic, have been described in 20–30% of the cases [6].

We are treating six patients with BD with thalidomide (M/F = 4/2, mean age 34 years), with a daily dose of 100 mg for recurrent orogenital lesions resistant to corticosteroids [7]. Two of these patients had two episodes of DVT prior the starting of thalidomide therapy. However, after a median follow-up of 2 years (range 1–3 years), no thrombotic events have been reported.

Thalidomide may have been the precipitating factor of DVT in our patient with SLE who had predisposing factors for DVT. However in a prothrombotic condition as BD the treatment with thalidomide has not been associated with thrombotic events. A clear relationship between increased incidence of thrombotic events and thalidomide therapy in non-malignant conditions has not yet clearly been demonstrated.

References

1 Rodeghiero F, Elice F. Thalidomide and thrombosis. *Pathophysiol Haemost Thromb* 2003; **33** (Suppl. 1): 15–8.

2 Ossandon A, Cassar EAM, Priori R, Valesini G. Thalidomide: focus on its employment in rheumatologic diseases. *Clin Exp Rheumatol* 2002; **20**: 709–18.

3 Minnema MC, Fijnheer R, De Groot PG, Lokhorst HM. Extremely high levels of von Willebrand factor antigen and of procoagulant factor VIII found in multiple myeloma patients are associated with activity status but not with thalidomide treatment. *J Thromb Haemost* 2003; **1**: 445–9.

4 Barbui T, Falanga A. Thalidomide and thrombosis in multiple myeloma. *J Thromb Haemost* 2003; **1**: 421–2.

5 Sakane T, Takeno M, Suzuki N, Inaba G. Behcet's disease. *N Engl J Medical* 1999; **341**: 1284–91.

6 Salvarani C, Calamia K, Silingardi M, Ghirarduzzi A, Olivieri I. Thrombosis associated with the prothrombin G-A20210 mutation in Behcet's disease. *J Rheumatol* 2000; **27**: 515–6.

7 Hamuryudan V, Mat C, Saip S, Ozyazgan Y, Siva A, Yurdakul S, Zwingenberger K, Yazici H. Thalidomide in the treatment of the mucocutaneous lesions of the Behcet's syndrome: a randomised double-blind, placebo-controlled trial. *Ann Intern Med* 1998; **128**: 443–50.

Thalidomide in front line treatment in multiple myeloma: serious risk of venous thromboembolism and evidence for thromboprophylaxis

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Recently Thalidomide (Thal) was shown to be effective in relapsed or refractory multiple myeloma, but the role of this novel agent as 'front line treatement' is still under investigation [1–4].

To address this issue, a multicentric, open, randomized trial was started in January 2002 in 30 departments of hematology in Italy. Myeloma patients at diagnosis were included, if aged more than 65 or less if they refused transplantation for personal