

SULODEXID FOR THE TREATMENT AND PREVENTION OF POST-THROMBOTIC SYNDROME

LAURA GHEUCĂ-SOLOVĂSTRU*, **, DAN VÂȚĂ*, **, LAURA STĂTESCU*, **, ELENA PORUMB-ANDRESE*, **, ALINA STÎNCANU**, ADRIANA-IONELA PĂTRAȘCU*, **, IOANA-ALINA GRĂJDEANU*

Summary

The post-thrombotic syndrome (PTS) is a frequent, potentially disabling complication of deep vein thrombosis (DVT). The more frequent are the episodes of DVT (recurrence) the higher is the risk of PTS. Clinical manifestations include symptoms and signs such as leg pain, heaviness, pitting edema, redness, varicose veins, hyperpigmentation (ochre and purple dermatitis) or leg ulcers in severe forms of the disease (stage C6/CEAP). Therefore, the best way to prevent PTS is DVT primary and secondary prophylaxis (prophylaxis of recurrences) using pharmacologic or mechanical solutions, especially in high risk patients. Sulodexide is a glycosaminoglycan with antithrombotic and profibrinolytic pharmacodynamics and vascular tropism which proved a low bleeding risk, especially in oral administration. SURVET study, published in *Circulation* in 2015, concluded that, for patients with idiopathic proximal DVT, the 2 years administration of 1000 ULS sulodexide (Vessel Due F)/day (4 caps of 250 ULS) after the previously 3-12 months administration of oral anticoagulants as recommended by the actual guidelines, succeeded to reduce by 50% the risk of DVT recurrences with a maximum safety profile regarding the bleeding risk which was insignificant. Due to its antithrombotic pharmacodynamics and vascular tropism, sulodexide, in chronic administration, could reduce the risk of DVT recurrences and, consequently, may decrease the risk of PTS in respective patients.

Key words: post-thrombotic syndrome (PTS), sulodexide, venous thromboembolism (VTE), prevention, glycosaminoglycan (GAG), deep vein thrombosis (DVT)

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Post-thrombotic syndrome (PTS; in prior terminology "postphlebitic syndrome) is defined as a complex spectrum of certain symptoms and signs of chronic venous insufficiency (CVI) after the occurrence of one or more episodes of deep vein thrombosis (DVT) that markedly reduces the quality of life and increases the medical costs.

Pathogenesis is related to chronic venous insufficiency based on important hemodynamic disturbances due to post-thrombotic recanalization defects, venous hypertension at the respective vascular level and its vicinity, followed by venous valve defects caused by prolonged tensile stress. In the end, the consequences are reaching the

microcirculation level, revealed by cutaneous trophic changes, ulcerations, arteriolar occlusions and obliterating lymphangiopathy[1,2,3].

Clinical features of PTS include pitting edema followed by induration which might be the most relevant PTS characteristics. Other signs of microcirculation damage are added, like perimalleolar telangiectasia, venous ectasia, varicose veins, hyperpigmentation (ochre and purple dermatitis) in mild cases and lipo-dermatosclerosis (acute or chronic skin fibrosis with blanch atrophy - Milium atrophy- and avascular white fibrotic plaques), swelling cyanotic dermatitis and chronic venous ulcers in the most

* University of Medicine and Pharmacy "Gr. T. Popa", Iasi.

** County Hospital for Emergency Medicine "St. Spiridon", Iasi, Dermatology Clinic.

severe cases. In case of mild dermatitis, symptoms may include also lower extremity pain, heaviness or tiredness, muscle cramps, paresthesia and itching. The intensity of symptoms and signs increases over the course of the day and with the progression of the disease[1,2,3].

Recent studies have improved understanding of the epidemiology, risk factors and PTS economic impact [3]. Epidemiological data show that PTS is frequent and occurs in 20% to 50% of patients with DVT and can be associated with arthritis, diabetes and chronic lung disease, leading to a markedly alteration of the quality of life and to an important decrease of productivity[1]. Epidemiological data in Romania show a 32% prevalence of chronic venous disease (CVD) which implies a high prevalence of PTS, too [4].

In USA, PTS diagnosis approach and its therapeutic and prevention measures are established by American Heart Association. Criteria used to diagnose PTS are represented by Villalta scale which includes 5 symptoms by patient self-report (pain, muscle cramps, heaviness, itching, paresthesia) and 6 signs assessed by clinical examination (edema, skin induration, hyperpigmentation, venous ectasia, redness, calf pain). Severity of each symptom and sign is rated as 0 (absent), 1 (mild), 2 (moderate) or 3 (severe). The points sum represents total Villalta score and its interpretation considers no PTS for values between 0–4, mild PTS for values from 5 to 9, moderate PTS for values from 10 to 14 and, finally, severe PTS for values higher than 15 or presence of leg ulcer [2,3,4]. The Villalta PTS scale is valid, reproducible and easy to be used by clinicians[5].

The PTS risk factors are the followings:

- older age;
- elevated body mass index (BMI);
- pre-existing primary venous insufficiency;
- characteristics of initial DVT (proximal DVT affecting especially iliac or common femoral vein indicates a higher PTS risk);
- quality of oral anticoagulation (PTS risk increases if level of anticoagulation is inadequate having under therapeutic INR

during the first 3 months of treatment with vitamin K antagonists);

- recurrent ipsilateral DVT;
- persistent venous symptoms/signs 1 month after acute DVT;
- residual thrombosis on Doppler ultrasound;
- persistent elevation of D-dimers[2, 6].

Recent data show that the best method to prevent PTS is to prevent the occurrence of DVT and its recurrences. Therefore, it is suggested the usage of pharmacologic or mechanical thromboprophylaxis in high risk DVT patients[7,8]. In order to prevent PTS development, three main methods have been applied to date and they are related with immediate, long-term and extended-term DVT correct treatment: endoluminal thrombolysis if this method is applied within the optimal therapeutic window in acute phase, anticoagulant/antithrombotic pharmacologic thromboprophylactic measures, continuous external elastic compression with adequate bandages or stockings (mechanical thromboprophylaxis) [9].

For a very good control of DVT recurrences and a maximum safety approach, present guidelines are recommending long-term anticoagulation for no less than 3 months (grade 1B) and for no more than 12 months (grade 1B). *N.B. The duration of long-term treatment less than 3 months increases the risk of DVT recurrences after the treatment stops, while the prolongation of long-term treatment more than 12 months increases significantly the risk of bleedings*[10].

However, the risk of DVT recurrences increases after withdrawal of oral anticoagulants and this risk depends on anticoagulant chemical structure. A randomized study, which included 897 DVT patients with or without pulmonary embolism (venous thromboembolism, VTE) followed for 10 years after the first episode, showed no additional benefit regarding the risk of recurrences after withdrawal of oral anticoagulants no matter if there was a 6 month or only a 6-week period of active vitamin K long-term treatment [11]. On the contrary, González-Fajardo et al. found that low-molecular-weight heparin (LWMH) was associated with a higher frequency of thrombus regression and a lower prevalence of DVT/VTE recurrences and PTS

[12]. Therefore, EXTENDED-term treatment, which could follow LONG-TERM anticoagulant treatment, might continue to reduce the risk of recurrences, but without neglecting the meanwhile associated bleeding risk which might increase.

Starting from these circumstances and keep the focus on extended-term treatment approach, researchers had tried to design a double-blind randomized placebo-controlled multicentric trial (SURVET) which explored how an antithrombotic drug (sulodexide), administered after anticoagulant withdrawal, could continue to control the risk of DVT/VTE recurrences, minimizing the bleeding risk. SURVET study included 615 patients with a first episode of unprovoked proximal DVT with or without pulmonary embolism and who completed anticoagulation for a period of 3 to 12 months. The patients included in this study were assigned randomly in two parallel groups, one receiving extended-term treatment with sulodexide (Vessel Due F manufactured by Alfa Wassermann) 1000 ULS (2 caps of 250 ULS twice a day) and the other placebo. The duration of extended-term treatment was 2 years. For all the patients included within this trial, elastic compression therapy was recommended during the whole extended-term treatment. The objective of the study was to evaluate whether the administration of extended-term treatment with Vessel Due F (4caps/day) for 2 years associated with elastic compression in patients with a first episode of DVT/VTE could effectively and safely reduce the risk of DVT/VTE recurrences. In other words, there were two major objectives, first one regarding the efficacy of extended-term treatment in decreasing the risk of DVT/VTE recurrences and the second one focusing on the safety of extended-term treatment in terms of minimizing the bleeding risk. In terms of efficacy, results showed that VTE returned to only 15 of the 307 Vessel Due F-treated patients in comparison to 30 out of the 308 placebo-treated patients. These results prove that a 2-year extended-term treatment with Vessel Due F may reduce by 50% the risk of DVT/VTE recurrences (hazard ratio - HR: 0.49; 95% confidence interval - IC: 0.27-0.92, $p=0.02$). In terms of safety, results showed the occurrence of a clinical relevant

bleeding episode in only 2 patients from each group which means similar bleeding risk for Vessel Due F and placebo (HR: 0.97, IC: 0.14-6.88, $p=0.98$). No major bleeding episode occurred within the two groups and there was no statistical significant difference between Vessel Due F and placebo in terms of clinical relevant bleedings. Adverse reactions from the Vessel Due F group were like those in the placebo group. The conclusion of SURVET study was that Vessel Due F 1000 ULS/day (2caps of 250 ULSx 2=4 caps/day) associated with elastic compression, administered for 2 years in patients with a history of VTE after the long-term (3 to 12 months) oral anticoagulant therapy, is a safe therapeutic approach which reduces effectively the risk of DVT/pulmonary embolism[13].

Sulodexide (Vessel Due F is the original brand manufactured by AlfaSigma, former Alfa Wassermann) is a biologic product with a unique and particular architecture which consists in a sulfate polysaccharide complex extracted from porcine intestinal mucosa and structured on 2 glycosaminoglycans (GAG): heparan sulfate (HS; 80%), a fast-moving heparin-like fraction and dermatan sulfate (DS; 20%) [14]. Sulodexide is a unique molecule among heparin-like substances and is biologically active both by parenteral and oral administration. Sulodexide has antithrombotic and profibrinolytic action with a low risk of bleeding, especially when is orally administered[13]. Many studies proved that sulodexide (especially when is administered parenterally) has an antithrombotic action comparable to that of heparin-like substances, but with less bleeding accidents. Moreover, the administration of sulodexide (especially the oral one) do not interfere with classical coagulation blood tests. Another major feature of sulodexide is its high concentration within vascular endothelium which implies important vasculotrope benefits on endothelial cells level and intercellular sub-endothelial matrix. Sulodexide is an active biological agent which restores, preserves and protects the integrity and permeability of endothelial cells, regulates the interactions between endothelial cells and blood cells and significantly reduces vascular parietal inflammatory and proliferative changes [17]. Being a heparinoid with antithrombotic and



Fig. 1. Clinical aspect of venous ulcerations on patient admission CVD stage C6/CEAP



Fig. 2. Clinical aspect of venous ulcerations after 60 days of treatment with sulodexide in a patient with CVD stage C6/CEAP



Fig. 3. Clinical aspect of venous ulcerations on patient admission CVD stage C6/CEAP



Fig. 4. Clinical aspect of venous ulcerations after 60 days of treatment with sulodexide in a patient with CVD stage C6/CEAP

vasculotrope actions, but having also hypolipidemic and angioprotective properties at both arterial and venous levels, sulodexide is recommended for the treatment of all vascular disorders at risk of thrombosis, like those frequent diagnosed within dermatological area: chronic venous disease insufficiency (CVD/CVI), PTS and calf/leg ulcers. In all these pathologies, sulodexide, associated with compressive therapy, is alleviating clinical signs and symptoms and is decelerating the evolution of the disease. In case of venous trophic ulcers sulodexide accelerates their healing through improving tisular perfusion and epithelization [13,14].

In addition to the basic therapy, there have been performed four randomized trials (three randomized trials [15,16,17] and a cross-over study [18]) to evaluate also the effectiveness of 'venoactive' drugs in PTS. The drugs involved were rutosides, defibrotide, hidrosmin, but the studies had a high degree of inconsistency and imprecision and a short treatment duration (8 weeks to few months), along with potential long-term side effects[19].

Moreover, within PTS treatment and prophylaxis solutions, there are also recommended physical training programs including exercises and sport activities for 6 months or more designed forleg strengthening[2].

Moving theory into practice, the CVD and PTS experience of the Dermatology Clinic from „Saint Spiridon“ Emergency Hospital in Iași shows that, for a period of five years (2012-2017), within the Clinic were hospitalized 3403 patients with CVD. 112 patients out of the total of 3403 had a history of DVT with or without pulmonary embolism and have been diagnosed with PTS complicated in time or not with chronic venous ulcers of the lower limbs (stage C6/CEAP). For these patients, treatment recommendations included Vessel Due F 600ULS (1 vial) iv initially for 15 days, then 1000 ULS/day (2x2 caps of 250 ULS/day) orally associated with venoactive drugs/phlebotonics (450 mg diosmină + 50 mg hesperidine, 2 tb/day), vasodilators (pentoxifiline, 2tb/day), topical treatment with cleansing agents, antibiotics in case of ulcer infection according to antibiogram results, reepithelization creams and compressive treatment with elastic bandages. This therapeutic scheme had favorable results, indicating acceleration of ulcer healing (decrease the ulcer diameter after 60 days of treatment) without any major bleeding episodes due to antithrombotic action of Vessel Due F. Moreover, Vessel Due F secured the risk of DVT recurrences, no new DVT episode being registered during the treatment period [4,20].

PTS is a complication in time of DVT and, in fact, represents a chronic venous insufficiency with high potential in reducing the quality of life and moving to important functional disabilities [2]. This pathologic condition requires a multidisciplinary approach consisting in a medical team which has to include the dermatologist, but also the cardiologist, vascular surgeon, internal medicine physician and family doctor. Multiple evaluations and a close controlled therapy are needed, particularly in case of potential complications, such as DVT recurrence or chronic venous trophic ulcers[4].

Prevention of PTS requires to follow DVT secondary prophylaxis recommendations which are meant to reduce venous hypertension, to alleviate blood flow within lower limb venous system, to restore the normal structure and function of vascular endothelium, to create better circumstances for a correct recanalization and to reduce the risk of DVT recurrences without major bleedings episodes. Therefore, the present studies and our medical experience are recommending sulodexide/Vessel Due F (1000 ULS/day) associated with compression therapy as the best solution for extended-term treatment in DVT secondary prophylaxis and PTS prevention [13,14].

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Conflict of interest

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Correspondance address:

Dan Vâță
Dermatology Department,
Faculty of Medicine,
University of Medicine and Pharmacy "Grigore T. Popa" Iași,
University Clinic Dermatology Emergency County Hospital "St. Spiridon" Iași
email: danvata@yahoo.com