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ANTITHROMBOTIC EFFECTS OF SULODEXIDE: A REVIEW ARTICLE

Clinical Science

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ABSTRACT

Objectives: To review the current knowledge regarding the mechanisms of action and the clinical indications of Sulodexide, a glycosaminoglycan with established efficacy for the prevention of recurrent venous thromboembolism, with reduced bleeding risk. **Methods:** A critical review of the literature regarding Sulodexide in several data sources between 1975 and 2020. A total of 481 articles were found and analyzed but only 21 articles were considered for this review. **Results:** Antithrombotic effects of Sulodexide include vascular endothelial protection, diminished platelet aggregation in response to several stimuli, inhibition of plasma coagulation factors Xa and thrombin, enhancement of fibrinolysis secondary to reducing PAI-1 and increasing of tPA, and decreased blood viscosity. Compared with other extended treatments, Sulodexide decreases mortality and bleeding episodes. **Conclusions:** Due to its broad range of pleiotropic effects and mainly antithrombotic, Sulodexide has emerged as a therapeutic option for the prevention of recurrent venous thromboembolism in subjects with high risk of bleeding, including elderly patients.

KEYWORDS

Sulodexide, Thrombosis, Venous Thromboembolic Disease, Deep Vein Thrombosis, Pulmonary Embolism

INTRODUCTION

Thrombosis, either arterial or venous, is the leading cause of death world-wide. Deep vein thrombosis (DVT), and its most serious consequence, pulmonary embolism (PE), collectively called venous thromboembolic disease (VTD), remain a common clinical problem causing high rates of morbidity and mortality. The annual incidence of venous thromboembolism (VTE) has been calculated at 0.72 to 2.69/1,000 inhabitants and it is more frequent in those individuals over 70 years old (1-3). In addition to mortality, DVT is frequently followed by post-thrombotic syndrome (PTS), which has a significant impact on patients' quality of life (4).

Antithrombotic treatment includes the use of antiplatelet, anticoagulant and thrombolytic drugs. Antiplatelet and anticoagulants are used in the long-term prevention and treatment of thrombosis. To date, the cornerstone of the chronic prevention and treatment of VTE has been the vitamin K antagonists (VKAs), a group of drugs capable of inhibiting the production of the vitamin K-dependent hemostatic factors mainly factor VII (FVII), with the consequent prolongation of the prothrombin time test (PT) (5). A continuous monitoring of their effect is required based on the international normalized ratio INR (5). Main advantages of VKAs are their efficacy, apparent direct low cost, and the possibility to quickly reverse the anticoagulant effect. However, use of VKAs is complicated by several factors leading to a poor patient compliance and to a cumbersome control of their effect (6).

Analysis of the most frequent causes of hospitalization consistently found that VKAs and antiplatelet drugs are the medications most frequently associated with hemorrhage (7,8). Indeed, anticoagulants are associated with a high degree of bleeding and hospitalization as well as death, especially in the elderly (9,10). The frequency of hemorrhagic episodes related to VKAs ranges from 1.7-17% (11,12). AVKs overdose is nearly 70% non-intentional and account for 33% of all drug-related adverse effects in individuals >50 year-old (13). As a consequence, despite the well established utility of VKAs, hemorrhagic complications are the main reason to explain why they are underused drugs (14). The introduction of direct oral anticoagulants (DOACs), improved some of the concerns and clinical problems associated with VKAs however, lack of reliable tests to control their anticoagulant effect and bleeding are still matters of concern.

Sulodexide is a pharmacological agent composed of 80% fast moving heparin fraction and 20% dermatan sulphate with beneficial effects in vascular diseases, especially in chronic venous disease. Studies regarding the antithrombotic effects of Sulodexide have shown a high degree efficacy with a substantial security rate making this drug a suitable antithrombotic option especially in aged individuals and in other cases at high risk of bleeding. Therefore, our aim was to review some of the current basic knowledge and clinically important characteristics regarding Sulodexide.

MATERIAL AND METHODS

A critical review of the literature regarding Sulodexide in several data sources including PubMed, Scopus, SCIMAGO, EMBASE, Ovid, and the Cochrane Library between 1975 and 2020 was performed. This search was performed by crossing the terms VTE, DVT, PE, superficial vein thrombosis, chronic vein thrombosis, venous insufficiency, anticoagulants, antiplatelet drugs, fibrinolytics, and endothelial glycocalyx. A total of 481 articles were found and we analyzed and selected the evidence that was relevant for the purposes of this review regarding the mechanisms of action and clinical applications of Sulodexide (based mainly on randomized clinical trials). At the end, only 21 articles were considered for this review.

RESULTS

Antithrombotic Mechanisms Of Sulodexide

In the mid 1800´s, German pathologist Rudolf Virchow provided the basis for understanding VTE. In the 20th Century, the Virchow´s Triad concept was coined and represents the basis for the pathogenesis of thrombosis: endothelial injury, circulatory stasis, and hypercoagulability. These three factors are still in force today (15,16) and explain cases of VTE as well as arterial thrombosis although the precipitating factors are quite different (17). Arterial thrombosis is the most common cause of cerebral and myocardial infarction in which the precipitating factor is usually the loss of endothelium of an atherosclerotic plaque, subsequent recruitment and activation of platelets, and initiation of thrombus formation. In venous thrombus, the role of endothelium and platelets is less obvious, although it is essential (18,19). Sulodexide acts on at least two of the components of the Virchow´s Triad: endothelium and hemostasis.

Sulodexide protects the vascular endothelium.

Vascular endothelium has a thin layer of glycosaminoglycans and proteoglycans, called the glycocalyx. The endothelial glycocalyx has multiple functions and its deterioration may set off several pathological disorders (20,21). Glycocalyx thinning allows platelet adhesion (22), and activation of plasma hemostasis (23). There is evidence showing that Sulodexide restores endothelial glycocalyx (24). In endothelial cell cultures, cells subjected to damaging conditions such as high glucose concentrations, experimental aging, and exposure to serum of patients with advanced venous disease, Sulodexide prevents the release of proinflammatory cytokines and free radicals and accelerates the healing of mechanical wounds (25-28). In a sophisticated experiment, Sulodexide was shown to prevent

apoptosis of endothelial cells after deprivation of oxygen and glucose; this protective effect was dose-dependent and it was mediated by an antioxidant effect through increasing superoxide dismutase and glutathione peroxidase (29).

Sulodexide also increases the endothelial release of nitric oxide and inhibits vasoconstriction in segments of aortic and mesenteric arteries treated with phenylephrine (30). The relaxing action of Sulodexide in these arteries depends on the endothelial release of nitric oxide because this effect disappears by stripping them off the endothelium and when various nitric oxide blockers are applied. In these vascular segments, the production of nitric oxide is induced by acetylcholine and it increases in the presence of Sulodexide (30). On the other hand, improvement of endothelial dysfunction has also been demonstrated *in vivo*. In rats with streptozotocin-induced diabetes, Sulodexide has been shown to restore the arterial relaxation in response to acetylcholine, while reducing endothelial cell shedding as measured by the number of these circulating cells (31).

Sulodexide inhibits induced platelet aggregation.

In vitro studies have shown that Sulodexide and other glycosaminoglycans inhibit the release of enzymes by polymorphonuclear leukocytes stimulated with formyl-methionyl-leucyl-phenylalanine (fMLP). Cathepsin G, an enzyme found in the azurophil granules of polymorphonuclear cells, is released when these leukocytes are activated. This enzyme induces platelet aggregation. Sulodexide, heparin, and dermatan sulphate inhibit platelet aggregation by cathepsin G. The effect is likely due to electronegative sulphate groups, since desulphated heparin loses this property. Thrombin-induced platelet aggregation is also reduced with Sulodexide and heparin (32). Platelet aggregation caused by tissue factor is inhibited in vitro with Sulodexide and enoxaparin (33).

Sulodexide effects on plasma coagulation.

Three decades ago, it was demonstrated that Sulodexide prevents the formation of thrombi induced by venous stasis (vena cava ligation) in rats (34). Adiguzel et al (32), studied *in vitro* the effects on hemostasis in healthy individuals and compared enoxaparin vs. Sulodexide under equigravimetric conditions. They found that both substances prolonged the PT at high concentrations (25 µg/ml), however Sulodexide was more potent than enoxaparin because activated partial thromboplastin time (aPTT), and thrombin time (TT) tests were more prolonged with Sulodexide than with enoxaparin. Inhibition of thrombin and FXa was similar with both drugs but slightly higher with Sulodexide for thrombin and higher for FXa with enoxaparin. These authors found that the generation of tissue factor-induced microparticles showed a significant inhibition with Sulodexide as compared with enoxaparin at all concentrations tested ($p < 0.001$). The microparticles are released from activated cells (monocytes, platelets, endothelial cells, and others), subjected to chemical stimuli such as cytokines, thrombin, endotoxins, and physical stimuli, namely shear stress and hypoxia. These microparticles can activate both, the liquid phase of hemostasis and platelets. The expression of P-selectin in platelets, an activation marker, showed more inhibited with Sulodexide than with enoxaparin, while the inhibition of platelet aggregation was similar with both products (33).

The antithrombin action of Sulodexide is due to both, the fast-moving heparin fraction that acts in the catalysis of antithrombin (AT), and the dermatan sulphate fraction that acts in the catalysis of heparin cofactor II (HCoII), as it was demonstrated in AT- and HCII-depleted platelet poor plasma. The effect of Sulodexide is the consequence of both fractions (35) (Fig. 1). However, several studies have shown that orally administered Sulodexide has antithrombotic activity and does not considerably modify the coagulation parameters (PT, aPTT, TT), although it does enhance fibrinolysis (36,37).

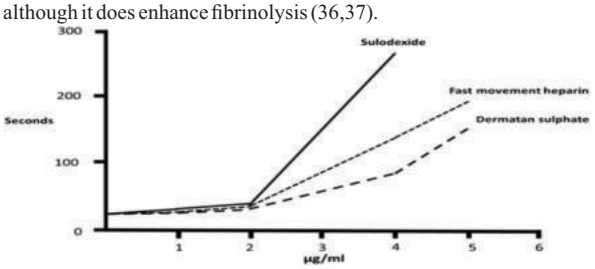

Figure 1. Thrombin time is prolonged by adding different concentrations of the components of Sulodexide, the dermatan sulphate, and the fast movement heparin fractions in vitro, the effect is higher with complete Sulodexide (35).

Sulodexide promotes fibrinolytic activation.

Sulodexide prevents thrombus formation in a murine model and also, it was observed that in thrombi formed six hours before, Sulodexide could decrease their weight and extension (34). Oral administration of single or repeated doses of Sulodexide as a medium-term treatment to healthy volunteers or patients with phlebopathies, induces a decrease of both, plasminogen activator inhibitor -1 (PAI-1), and circulating concentrations of fibrinogen while increasing fibrinolytic activity as measured in a fibrin plate (Fig. 2), without affecting the levels of plasminogen, PT, aPTT, TT and Xa inhibition (35). Tissue plasminogen activator has also been found to be elevated (38). When oral Sulodexide is administered it probably does not reach sufficient circulating levels to modify the blood coagulation tests but, since the drug is concentrated in the vascular endothelium, it appears to be sufficient to activate fibrinolysis. Other effects of Sulodexide at different points of the fibrinolysis and fibrinogen are shown in Fig. 3.

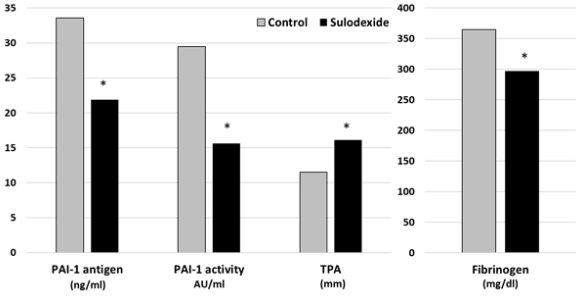

Figure 2. In a crossover study, patients received Sulodexide 500 LSU BID for 30 days vs. placebo. The results are illustrated by combining the data from both periods. PAI-1: plasminogen activator inhibitor-1; TPA = fibrinolytic activity. *: $p < 0.01$. With data from Mauro et al (36).

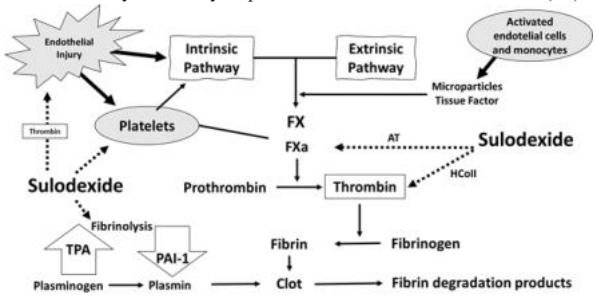

Figure 3. Summary of antithrombotic effects of Sulodexide (dotted lines). After interaction with factor Xa (FXa) through antithrombin (AT) and with thrombin through Heparin Cofactor II (HCoII), Sulodexide protects the endothelium, and under certain conditions inhibits platelet aggregation. In addition, it promotes fibrinolysis by increasing tissue plasminogen activator (TPA) and reducing its inhibitor (PAI-1), thus favoring the lysis of the clot.

Sulodexide effects of the blood flow.

Although Sulodexide does not have a direct action on blood circulation, cardiac ejection fraction, blood pressure, or peripheral resistance, in patients with chronic venous disease, Sulodexide improves various parameters of venous hemodynamics (39-41). Clinical improvement with the use of Sulodexide has been repeatedly demonstrated in occlusive atherosclerosis of the lower limbs in observational, prospective, double-blind, randomized, multicenter, placebo-controlled trials (42-48). Sulodexide-induced positive hemorrheological changes are likely due to improvement of venous and arterial circulation. Moreover, it has been shown to decrease blood viscosity along with decreased fibrinogen and serum triglycerides (41-43). Therefore, antithrombotic effects of Sulodexide depend on the protection of the endothelium, its positive effects on hemostasis and fibrinolysis, as well as on hemorrheological improvement.

Evidence For Sulodexide In The Treatment And Prevention Of VTE Recurrence

In the treatment of VTE, early anticoagulation is essential and it must be prolonged until the resolution of the thrombosis at least for three months since it usually recurs during this initial period if no treatment

is indicated. The suggested treatment includes anticoagulant drugs like VKAs or DOACs such as apixaban, dabigatran, rivaroxaban, edoxaban, or betrixaban. The duration of anticoagulant treatment depends on the cause of the VTE. When it was caused by an acute direct event such as a bone fracture or surgery, the recommended treatment may be shorter while in cases without a clear associated factor (unprovoked DVT), anticoagulant treatment will last at least 6 months although the current trend is extended or indefinite duration of treatment (Table 1) (49,50).

Table 1. Duration of anticoagulation according to the etiology of VTD (50)

Short anticoagulation after a first VTD episode:	Extended anticoagulation (indefinite):
• Bed rest >4 days • After major surgery (3 months) • Immobilization, cast, splint (3 months) • After major trauma (3 months) • High bleeding risk	• History of VTD • Severe PE • Pulmonary hypertension • Cardiopulmonary insufficiency (NYHA 3-4) • Cancer • Primary thrombophilia

VTD: venous thromboembolic disease; PE: pulmonary embolism; NYHA: New York Heart Association

Extended anticoagulation is based on the demonstration that, after unprovoked DVT, there is a trend towards the repetition of thrombotic events. In an 8-year follow-up period of patients who recovered from a first episode of VTE it was observed that, within two years, 17.5% of cases suffered a new episode while 30% of them had a recurrence in 8 years. These recurrences were more frequent in those patients with cancer or primary thrombophilia while those with an episode secondary to a bone fracture or surgery were less frequent. Furthermore, according to more recent statistics, recurrence of VTE episodes may be even higher (51). In patients with VTE, some factors that increase the possibility of recurrence have been identified: primary thrombophilia, male gender, PE, proximal DVT, residual venous obstruction, PTS, and increased D-dimer upon anticoagulation discontinuation (52). Moreover, PTS is a complication that occurs as high as 29% of cases (53). On the other hand, prolonged anticoagulant treatment has implicit the risk of hemorrhagic episodes, especially in individuals with risk factors for bleeding, even with DOACs. An alternative to these treatments may be Sulodexide.

Sulodexide effects include protection of the vascular endothelium, decreasing vascular inflammation, decreasing metalloproteinases 2 and 9 (MMP-2, MMP-9), inhibiting electronegative LDL uptake by monocytes (probably by binding of Sulodexide with LDL (-)), as well as antithrombotic effects (54-57). Three randomized controlled trials on the use of Sulodexide for the prevention of VTE recurrences have been published (58-60) (Fig. 4). Regarding these three multicentric, randomized trials, two of them compared Sulodexide with no treatment or placebo and the other vs. acenocoumarin. All patients enrolled in these trials received anticoagulation with low molecular weight heparin (LMWH) during the initial period of treatment. In two of these studies patients were treated for several months with VKAs prior to randomization and in the other one patients received placebo as a control group. In two studies Sulodexide dose was 1,000 LRU/day for two years; in the trial with acenocoumarin, Sulodexide dose was 600 LRU/day, the treatment period was 3 months and the evaluation period was 6 months. These studies showed a significant reduction in the frequency of VTE recurrence compared to the control group without an increase in bleeding frequency.

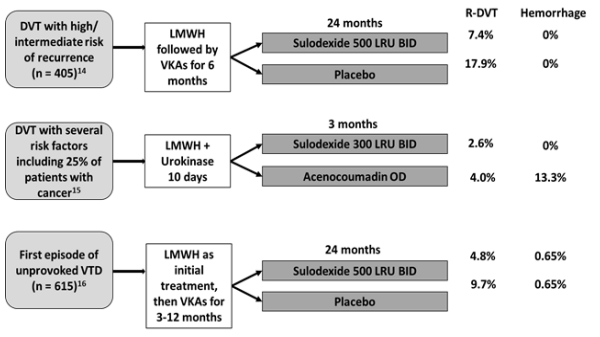

Figure 4. Summary of three prospective, controlled trials to evaluate the effect of Sulodexide to prevent recurrence of VTE (58-60). LMWH: low molecular weight heparin; VKAs: vitamin K antagonists; R-DVT = recurrence of deep vein thrombosis; LRU = lipasemic release units.

In addition, another observational study of non-parallel groups but with comparable initial characteristics, included 339 patients with DVT who were allocated to receive Sulodexide 250 LSU BID for 60 months (n= 124), compared with standard treatment without Sulodexide (n = 167), and a group with acetylsalicylic acid (n = 48). The study was designed to assess the frequency of PTS which occurred in 8.8% of cases with Sulodexide, 19.5% with standard treatment ($p<0.05$) and 23.5% with acetylsalicylic acid ($p<0.05$). Recurrence of DVT was observed in 4.08% of cases treated with Sulodexide, 6.09% with standard treatment, and 8.8% with acetylsalicylic acid ($p<0.05$) (61).

Recently, a systematic meta-analysis on Sulodexide for the secondary prevention of VTE recurrence was published. The four analyzed studies included 1,461 patients. It was concluded that Sulodexide reduces the risk of VTE recurrence by 50% (RR 0.51, 95%CI = 0.35-0.74, p = 0.0004), and the risk of superficial vein thrombosis (RR 0.41, 95% CI: 0.22-0.74, p = 0.005). This last finding seems quite important because it is well known that superficial vein thrombosis is today considered today as a strong risk factor for DVT. On the other hand, bleeding was observed in 0.28% of the cases treated with Sulodexide and in 1.60% in the control group; none of the bleeding episodes was severe (62).

When to use Sulodexide as antithrombotic?

For the treatment of an episode of VTE experts recommend using a LMWH or DOACs (49,50). Sulodexide does not has a place as an antithrombotic in the initial treatment of the event. Although some physicians may use it in association with anticoagulants in order to reduce venous inflammation, no research has been published in this regard.

On the other hand, in a multicenter, randomized, placebo-controlled trial of patients with unprovoked VTE, individuals who received anticoagulants for 24 months had significantly fewer recurrences than the group who received 6 months of anticoagulants and 18 months of placebo. However, 24 months after the end of treatment the beneficial effect was lost (63). Prolonged anticoagulation prevents VTE recurrences but discontinuation is associated with a loss of the protective effects. Although the duration of anticoagulant prophylaxis is still under discussion (10), it has been suggested that it should be maintained for an indefinite time period (6). Indeed, recent evidence shows a trend for extended anticoagulant therapy mainly in patients with high risk or recurrence and in those with unprovoked VTE (64-66)

Currently, for the prevention of recurrence of VTE, DOACs are preferred because they are at least as effective as VKAs, do not require periodic laboratory controls with dose adjustment, and have a lower risk of bleeding. The most concerning side effect of prolonged anticoagulation is bleeding, which in some cases can be severe or life-threating. Representative investigations of prolonged treatments to prevent VTE recurrences are depicted in Table 2 (67-71). DOACs are clearly very effective in decreasing the risk of new episodes of VTE. However, they also increase the risk of hemorrhage. The risk of bleeding is higher in individuals with liver or kidney disease, cancer, especially in the gastrointestinal tract or metastatic cancer, a history of bleeding, and in the elderly, even more so if they are over 75 years old (5). In patients with high hemorrhagic risk, a balance must be made between the potential of benefits and risks. Sulodexide may be indicated in these groups of patients since it reduces the recurrence of VTE, without increasing the risk of bleeding when compared with placebo.

Table 2. Placebo-controlled studies to evaluate the extended treatment for prevention of recurrences of VTD

Treatment	Relative risk vs. placebo	
	VTD recurrence	Hemorrhage*
Warfarin (INR 2-3) (67)	0.05	>3.8
Warfarin (INR 1.5-2) (67)	0.36	2.50
Rivaroxaban (68)	0.18	5.19
Dabigatran (69)	0.07	2.90
Apixaban 5 mg (70)	0.23	1.59
Apixaban 2.5 mg (70)	0.21	1.18
Acetylsalicylic acid (Aspire) (71)	0.78	1.83

VTD: venous thromboembolic disease; *: the relative risk of recurrence and the risk of clinically significant major or minor bleeding are noted

There are no studies that directly compare Sulodexide in the preventive treatment of recurrent VTE versus other extended treatments. Recently, a meta-analysis included 25 articles in which DOACs, VKAs, acetylsalicylic acid and Sulodexide were analyzed. DOACs were more effective in preventing VTE, but Sulodexide significantly reduced mortality from any cause (RR = 0.81) and from vascular causes (VTE, PE, myocardial infarction, cerebrovascular event) (RR = 0.65). Sulodexide is significantly associated with a lower frequency of major bleeding (RR 0.5) and clinically significant minor bleeding (RR = 0.47). It was more effective than acetyl salicylic acid in preventing VTE (72) (Table 3, Fig. 5).

Table 3. Hierarchical estimates of extended treatments to prevent recurrent venous thromboembolism compared with placebo. Results of a network meta-analysis (72)

	DOACs	VKA	Sulodexide	ASA
R-DTV	0.19	0.36	0.51	0.71
Pulmonary embolism	0.33	0.41	0.43	0.80
Major bleeding	1.51	2.82	0.20	1.03
Non-major bleeding	2.31	3.1	0.59	1.9
Cardiovascular death	0.55	0.73	0.27	1.47
Death of any cause	0.54	0.81	0.34	0.94

DOACs: direct oral anticoagulants; R-DTV = recurrent deep venous thrombosis. DOAC = direct oral anticoagulants. VKA = vitamin K antagonists. ASA= acetylsalicylic acid; Cardiovascular death = venous thromboembolism/pulmonary embolism/myocardial infarction/stroke

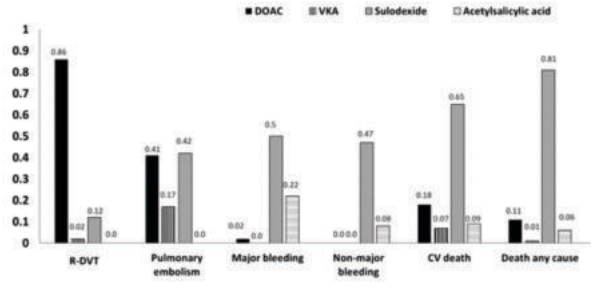

Figure 5. Probability to be the best treatment in a random model estimate. Results of a network analysis (data from Pompilio et. al.) (72). DOACS = direct oral anticoagulants; VKA = vitamin K antagonists; ASA = acetylsalicylic acid.

CONCLUSIONS

In summary, for the prevention of VTE recurrences in individuals with high hemorrhagic risk, Sulodexide seems a solid alternative treatment due to its antithrombotic effect and scarce safety concern.

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none declared.

Declaration Of Conflict Of Interest

Alberto C Frati-Munari and Nora Lecuona are currently employed by Alfasigma Laboratories Mexico (ALM). Abraham Majluf-Cruz has been speaker for ALM and Bayer.

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