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Real-life experience of edoxaban treatment for venous thromboembolism (VTE)/pulmonary embolism (PE) in patients with isolated positive Lupus Anticoagulant (LAC) during the COVID-19 pandemic lockdown in Italy

L. PUCCETTI[1], V. SAMMARTANO[2], P. CALZONI[3], F. BACCHIARRI[2], A. SANTONI[2], D. FINESCHI[3], M. BOCCHIA[2]

[1]Hemostasis and Thrombosis Unit, "Santa Maria alle Scotte" University Teaching Hospital of Siena, University of Siena, Siena, Italy
[2]Hemathology Unit, "Santa Maria alle Scotte" University Teaching Hospital of Siena, University of Siena, Siena, Italy
[3]Coagulative Disorders Laboratory Unit, "Santa Maria alle Scotte" University Teaching Hospital of Siena, Siena, Italy

Abstract. – OBJECTIVE: Direct-acting oral anticoagulants (DOACs) have established indications, according to recent guidelines for the treatment and prevention of venous thromboembolism (VTE), including pulmonary embolism (PE), with a safer profile compared to vitamin K antagonist (VKA) in terms of a lower risk for major bleeding and no need of blood coagulation tests. However, DOACs are not indicated in the treatment of patients with triple positive antiphospholipid syndrome (APS). This limitation is often extended in clinical practice to patients with isolated positivity. The COVID-19 pandemic has sometimes made it difficult to maintain a safe VKA treatment, due to the practical difficulties of performing INR.

PATIENTS AND METHODS: We evaluated 39 patients with a previous unprovoked VTE/PE, who were no longer eligible for VKA treatment due to the difficulty of performing INR during the COVID-19 pandemic lockdown, in Italy. All patients had a positive LAC and refused a long-term anticoagulation with low molecular weight heparin. They were shifted to edoxaban.

RESULTS: Any recurrence of VTE/PE occurred during the observation period (up to eight months of treatment), while only one minor bleeding event was recorded (Hazard ratio=0.06, 95% confidence interval 0.03-0.11, *p*=0.094). No arterial events occurred during the observation period. Hemoglobin, platelets, and creatinine were unchanged during the observation period.

CONCLUSIONS: Edoxaban treatment may be safe and effective in preventing the recurrence of VTE/PE in patients with isolated LAC positivity, without the occurrence of arterial events.

Key Words:
DOAC, VKA, antiphospholipid syndrome, Lupus anticoagulant, COVID-19.

Introduction

Direct-acting oral anticoagulants (DOACs) have established indications, according to recent international guidelines, for the treatment and prevention of venous thromboembolism (VTE), with a safer profile than vitamin-K antagonists (VKAs), especially due to a lower risk of major bleeding1.

Antiphospholipid syndrome (APS) is characterized by an increased risk of both arterial and venous thrombosis and by the presence of an autoimmune profile, including lupus anticoagulant (LAC), anti-cardiolipin (anti-CL) and anti-β2 glycoprotein I (anti-β2GPI) antibodies[2]. Accordingly, APS in both primary and secondary forms is considered a major thrombophilic condition[3].

The recommended treatment for thromboembolic complications in APS is a VKA, possibly associated with an antiplatelet drug[4]. VKAs need frequent laboratory monitoring and may interact with various drugs and types of food, and thus patient compliance may decrease.

In 2018 Pengo et al[5] performed the first randomized controlled trial directly comparing VKAs and DOACs in patients with APS. The trial was terminated early due to an excess of arterial events in the rivaroxaban arm. Therefore, the European Medicine

Corresponding Author: Luca Puccetti, MD, e-mail: luca.puccetti@unisi.it

Agency (EMA) concluded that all DOACs are not recommended in patients with APS and specific guidelines were issued by the International Society on Thrombosis and Haemostasis (ISTH)[6,7].

During the first phase of COVID-19 pandemic in Italy, many patients on VKAs had to face mainly logistic challenges in maintaining a correct treatment regimen due to difficulties with timely evaluation of the international normalized ratio (INR)[8].

In this setting, our Centre for coagulative disorders was involved by General Practitioners (GPs) for evaluating a possible switch from VKAs to DOACs in patients with indication for long-term anticoagulant treatment.

Patients and Methods

Study Population

Between March and June 2020, we assessed 39 patients (17 male, 22 female) treated with Warfarin after unprovoked VTE with pulmonary embolism (PE, all patients with a PE severity index [PESI] < 3) and with indication to be treated for 12 months[9,10], a period during which INR monitoring was no longer possible. All patients previously showed LAC positivity, which was mostly isolated, as part of a screening for thrombophilia performed by the various hospital specialists who had initially managed the patients (i.e., cardiologists [n=15], doctors of internal medicine [n= 13], pneumologists [n=5] and, after discharge, by the doctors of the surveillance centers for anticoagulant therapy [n=11][8] and by the GPs [n=28]). When contacted for a second opinion, the prescribing physician denied the switch to DOAC, in accordance with the indications of the Italian regulatory agency for definite APS[6]. All patients had negative swab for SARS-CoV-2 at the time of PE and our first evaluation. Patients' characteristics are reported in Table I.

Table I. Patients' characteristics.

Patients	Characteristics
Age	53.3±6.2
Male	55.7±5.5
Female	50.1±9.4
Sex	
Male	17
Female	22
Body mass index, kg/m²	
Male	26.5±1.8
Female	23.8±1.6
VTE	
Caused	0
Not caused	33
Risk factors for VTE	
yes	2
no	31
PESI	All < 2
SCORE	All < 5

Clinical Management

Once it was established that the correct duration of anticoagulant therapy was effectively 12 months[9,10], all patients on warfarin were switched to a therapeutic dose of low molecular weight heparin (LMWH). The estimated on-treatment duration ranged between 8 and 9 months. Indeed, based on the patients' characteristics, treatment with antiplatelets or anticoagulants for only three months was not indicated, in accordance with specific guidelines[10]. All patients refused injective treatment for such a long period of time. Therefore, DOACs remained the only option available.

All the 39 patients were treated with enoxaparin 100 U/kg body weight subcutaneously every 12 hours for 7 days. For baseline assessment and to rule out a complete APS, platelet count, levels of hemoglobin, creatinine, fibrinogen, D-dimer, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), LAC, anti-CL and anti-β2GPI IgG and IgM, anti-phosphatidylserine/prothrombin (anti-PS/PT) IgG and IgM were measured 36 hours after the last dose of enoxaparin, which was immediately resumed after blood collection. This procedure was considered safe because each patient was on continuous anticoagulant treatment for at least 3 months[10] and also appropriate in reducing potential methodological problems of LAC measurement[11]. Indeed, such patients were considered as LAC positive, although it was not straightforward to clearly established if the initial evaluation was performed according to specific methodological indications[12].

In 31 patients, an isolated LAC positivity was confirmed whereas 8 patients were excluded from the protocol because a female tested positive for LAC and anti-β2GPI IgG and a male for LAC and anti-CL IgG. The remaining 6 patients were excluded because they were negative for LAC and APS.

Thus, the 31 patients observed were proposed to receive therapy with a DOAC. Rivaroxaban was excluded due to previous specific observations[5,6] and edoxaban was the final choice because patients preferred once daily administration over twice daily of apixaban or dabigatran. A total of

28 patients were treated with edoxaban 60 mg per day whereas 3 patients received 30 mg per day (two of them due to a body weight less than 60 kg and one of them for a creatinine clearance of 30-50 ml/min/kg).

After treatment initiation bi-monthly telemedicine visits were carried out with the aim of evaluating any clinical updates. All patients were further evaluated for the above parameters at the end of the observation period. The cardiovascular risk, in agreement with the data of excess arterial events in the Trial on Rivaroxaban in AntiPhospholipid Syndrome (TRAPS)[5,13] was estimated using the SCORE[14]. We assessed any bleeding according to the ISTH criteria[15] and the bleeding risk using various scores[16].

Laboratory Methods

Hemoglobin level and platelet count were measured in a DXH 800 Beckman Coulter Counter (Brea, CA, USA); creatinine, ALT, AST and GGT levels were measured in a COBAS 8000 Roche-Hitachi analyzer (Mannheim, Germany); measurement of the levels of fibrinogen (Clauss; Werfen, Barcelona, Spain), D-dimer (EIA, Biomerieux, Marcy l'Etoile, France), LAC (Hemosil, Werfen, Barcelona, Spain), IgG and IgM of anti-CL, anti-β2GPI (QUANTA Flash, Werfen, Barcelona, Spain) and, anti-PS/PT (QUANTA Lite, INOVA Diagnostics, San Diego, CA, USA) were all made according to the ISTH guidelines[17].

Statistical Analysis

VTE/PE recurrence and bleeding incidence were assessed through the Cox-proportional Hazard Risk model, with differences presented using 95% confidence intervals. One-way analysis of variance (ANOVA) was used to assess putative differences in measurable variables within the study population at the end of the observation period. A p-value <0.05 was considered as statistically significant. All analyses were performed using the software SPSS v27 (IBM, Armonk, NY, USA).

Results

A male patient dropped out of the study due to the need to manage a large hematoma on the right leg that occurred after a major provoked trauma. Thus, the evaluation of the cumulative anticoagulant therapy at 12 months was performed in the remaining 30 patients.

No VTE/EP recurrence or arterial event occurred during the 8-9 months of treatment with edoxaban. A female patient treated with edoxaban 30 mg/day due to low body weight (53 kg) presented a minor bleeding event, according to ISTH criteria[16], after 5 months of therapy (HR=0.06, 95% CI 0.03-0.11, p=0.094). The other patients showed no signs of minor or major bleeding during the observation period.

No significant change in the levels of haemoglobin, platelets, creatinine, fibrinogen, D-dimer and other biochemical parameters were found during the observation period (Table II).

A male patient who presented progressive dyspnea was diagnosed with a lung cancer 20 days before the end of the observation period, showing no sign of previous PE or new VTE.

Table II. Biochemical parameters found during the observation period.

Parameters	Baseline	End of treatment	p
Hemoglobin (g/dL)			
Male	15.1±1.1	15.2±0.9	ns
Female	12.8±0.9	13.1±1.1	ns
Platelets (10^3/uL)			
Male	306±51	301±53	ns
Female	274±42	277±49	ns
Creatinine (mg/dL)	1.13±0.1	1.19±0.1	ns
Fibrinogen (mg/dL)	321.5±31.4	313.2±26.7	ns
D Dimer (ug/L)	326.4±31.9	311.8±28.3	ns
AST (IU/L)	21.3±1.9	21.1±1.8	ns
ALT (IU/L)	26.5±2.1	27.2±1.9	ns
GGT (IU/L)	53.2±7.8	50.8±7.1	ns

AST: aspartate aminotransferase, ALT: alanine aminotransferase, GGT: gamma glutamyl transferase. ANOVA, p>0.05 = not significant (ns).

Discussion

In our experience, although DOACs are a well-established treatment for VTE and its recurrence including PE[9,10], however, they are not indicated in definite APS due to specific concerns and for this reason warfarin is the preferred choice[13,18].

In this setting, an isolated LAC positivity represents a prothrombotic state although it probably expresses a thrombotic profile different from the definite APS[19].

During COVID-19 pandemic lockdown in Italy, many patients found practical difficulties for the management of warfarin, and thus alternative strategies were suggested[8]. In particular, it was proposed in stable patients to prolong the intervals between INR monitoring and mainly young patients were provided with self-checking and self-management household systems. However, in our real-life experience, these situations turn out to be impractical and potentially dangerous.

Such aspect represents a major challenge particularly for patients requiring several months of therapy in accordance with the treatment guidelines of PE[9,10]. Thus, in patients with an isolated LAC positivity we propose using DOACs when other therapeutic options are not feasible.

Furthermore, sometimes the diagnosis of LAC positivity is not made according to recommended criteria and both an over-diagnosis or an undefined diagnosis of APS may emerge[11].

Our data showed that treatment with edoxaban for 8 to 9 months and up to 12 months in warfarin-shifted patients with isolated LAC positivity is both safe and effective in preventing recurrence of VTE/PE. In this context, given the characteristics of the study population, the duration of warfarin treatment (3-4 months) cannot be the main mechanism for prolonged efficacy after its discontinuation[9,10].

In our experience, no arterial events were reported during edoxaban therapy although the temporal range of treatment was overlapping with the period of onset in the TRAPS[5]. We cannot exclude that the low SCORE index in our population (Table II), alongside a different pro-thrombotic status in patients between isolated LAC positivity and definite APS[19] is a relevant factor for the difference in arterial events.

Moreover, our data in patients with isolated LAC positivity add evidence to the recent findings in a large cohort on unselected subjects for thromboembolic risk factors, in which the replacement of AVK with DOACs showed to be safe and effective, for the prevention of recurring VTE and cardiac embolism[20].

Conclusions

Edoxaban may be considered a safe and effective drug for long-term anticoagulation in patients with previous unprovoked VTE/PE and isolated LAC positivity. Further studies with edoxaban or other DOACs are needed in larger cohorts of patients with confirmed exclusive LAC positivity and VTE/PE in order to substantially validate our findings.

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Conflict of Interests

The authors declare that they have no conflict of interest.

References

1) Kakkos SK, Gohel M, Baekgaard N, Bauersachs R, Bellmunt-Montoya S, Black SA, Ten Cate-Hoek AJ, Elalamy I, Enzmann FK, Geroulakos G, Gottsäter A, Hunt BJ, Mansilha A, Nicolaides AN, Sandset PM, Stansby G, Esvs Guidelines Committee, de Borst GJ, Bastos Gonçalves F, Chakfé N, Hinchliffe R, Kolh P, Koncar I, Lindholt JS, Tulamo R, Twine CP, Vermassen F, Wanhainen A, Document Reviewers, De Maeseneer MG, Comerota AJ, Gloviczki P, Kruip MJHA, Monreal M, Prandoni P, Vega de Ceniga M. Editor's Choice - European Society for Vascular Surgery (ESVS) 2021 Clinical Practice Guidelines on the Management of Venous Thrombosis. Eur J Vasc Endovasc Surg 2021; 61: 9-82.
2) El Hasbani G, Viola M, Sciascia S, Taher AT, Uthman I. Antiphospholipid Antibodies in Inflammatory and Autoimmune Rheumatic and Musculoskeletal Diseases Beyond Lupus: A Systematic Review of the Available Evidence. Rheumatol Ther 2021; 8: 81-94.
3) Sayar Z, Moll R, Isenberg D, Cohen H. Thrombotic antiphospholipid syndrome: A practical guide to diagnosis and management. Thromb Res 2021; 198: 213-221.
4) Arachchillage DRJ, Laffan M. What is the appropriate anticoagulation strategy for thrombotic antiphospholipid syndrome? Br J Haematol 2020; 189: 216-227.
5) Pengo V, Denas G, Zoppellaro G, Jose SP, Hoxha A, Ruffatti A, Andreoli L, Tincani A, Cenci C, Prisco D, Fierro T, Gresele P, Cafolla A, De Micheli V, Ghirarduzzi A, Tosetto A, Falanga A, Martinelli I, Testa S, Barcellona D, Gerosa M, Banzato A. Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome. Blood 2018; 132: 1365-1371.

6) Pharmacovigilance Risk Assessment Committee (PRAC). EMA/PRAC/219985/2019. https://www.ema.europa.eu/en/documents/prac-recommendation/prac-recommendations-signals-adopted-8-11-april-2019-prac-meeting_en.pdf. 2019.
7) Zuily S, Cohen H, Isenberg D, Woller SC, Crowther M, Dufrost V, Wahl D, Doré CJ, Cuker A, Carrier M, Pengo V, Devreese KMJ. Use of direct oral anticoagulants in patients with thrombotic antiphospholipid syndrome: Guidance from the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. J Thromb Haemost 2020; 18: 2126-2137.
8) Barcellona D, Marongiu F. Thrombosis centres and AVKs monitoring in COVID-19 pandemic. Intern Emerg Med 2020; 15: 1365-1368.
9) Konstantinides S, Meyer G. Management of acute pulmonary embolism 2019: what is new in the updated European guidelines? Intern Emerg Med 2020; 15: 957-966.
10) Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing GJ, Harjola VP, Huisman MV, Humbert M, Jennings CS, Jiménez D, Kucher N, Lang IM, Lankeit M, Lorusso R, Mazzolai L, Meneveau N, Ní Áinle F, Prandoni P, Pruszczyk P, Righini M, Torbicki A, Van Belle E, Zamorano JL, ESC Scientific Document Group. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J 2020; 41: 543-603.
11) Tripodi A, Cohen H, Devreese KMJ. Lupus anticoagulant detection in anticoagulated patients. Guidance from the Scientific and Standardization Committee for lupus anticoagulant/antiphospholipid antibodies of the International Society on Thrombosis and Haemostasis. J Thromb Haemost 2020; 18:1569-1575.
12) Devreese KMJ, de Groot PG, de Laat B, Erkan D, Favaloro EJ, Mackie I, Martinuzzo M, Ortel TL, Pengo V, Rand JH, Tripodi A, Wahl D, Cohen H. Guidance from the Scientific and Standardization Committee for lupus anticoagulant/antiphospholipid antibodies of the International Society on Thrombosis and Haemostasis: Update of the guidelines for lupus anticoagulant detection and interpretation. J Thromb Haemost 2020; 18: 2828-2839.
13) Pengo V, Hoxha A, Andreoli L, Tincani A, Silvestri E, Prisco D, Fierro T, Gresele P, Cafolla A, De Micheli V, Ghirarduzzi A, Tosetto A, Falanga A, Martinelli I, Testa S, Barcellona D, Gerosa M, Denas G. Trial of Rivaroxaban in AntiPhospholipid Syndrome (TRAPS): Two-year outcomes after the study closure. J Thromb Haemost 2021; 19: 531-535.
14) Conroy RM, Pyörälä K, Fitzgerald AP, Sans S, Menotti A, De Backer G, De Bacquer D, Ducimetière P, Jousilahti P, Keil U, Njølstad I, Oganov RG, Thomsen T, Tunstall-Pedoe H, Tverdal A, Wedel H, Whincup P, Wilhelmsen L, Graham IM, SCORE project group. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J 2003; 24: 987-1003.
15) Schulman S, Kearon C, Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005; 3: 692-694.
16) Vedovati MC, Mancuso A, Pierpaoli L, Paliani U, Conti S, Ascani A, Galeotti G, Di Filippo F, Caponi C, Agnelli G, Becattini C. Prediction of major bleeding in patients receiving DOACs for venous thromboembolism: A prospective cohort study. Int J Cardiol 2020; 301: 167-172.
17) Pengo V, Tripodi A, Reber G, Rand JH, Ortel TL, Galli M, De Groot PG, Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardisation Committee of the International Society on Thrombosis and Haemostasis. Update of the guidelines for lupus anticoagulant detection. Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardisation Committee of the International Society on Thrombosis and Haemostasis. J Thromb Haemost 2009; 7: 1737-1740.
18) Dufrost V, Wahl D, Zuily S. Direct oral anticoagulants in antiphospholipid syndrome: Meta-analysis of randomized controlled trials. Autoimmun Rev 2021; 20: 102711.
19) Yin D, de Groot PG, Ninivaggi M, Devreese KMJ, de Laat B. Clinical Relevance of Isolated Lupus Anticoagulant Positivity in Patients with Thrombotic Antiphospholipid Syndrome. Thromb Haemost 2021; 121: 1220-1227.
20) Patel R, Czuprynska J, Roberts LN, Vadher B, Rea C, Patel R, Gee E, Saul G, Coles E, Brown A, Byrne R, Speed V, Patel JP, Arya R. Switching warfarin patients to a direct oral anticoagulant during the Coronavirus Disease-19 pandemic. Thromb Res 2021; 197: 192-194.