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Original Article

Direct Oral Anticoagulants in Patients Affected by Major Congenital Thrombophilia

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Abstract. ***Background:*** **Thrombophilia is a condition that predisposes to a higher incidence of venous thromboembolisms (VTE), some also in atypical sites. Direct oral anticoagulants (DOACs) have proven to be effective in the treatment of deep vein thrombosis (DVT). However, their use can be sometimes challenging in particular settings of patients such as those with major thrombophilia - antithrombin, protein C and protein S deficiency, homozygous mutation of Factor V Leiden, homozygous mutation of Factor II G20210A, combined heterozygous mutation of factor V Leiden and Factor II G20210A – carrying a high thrombotic risk.**
Patients and Methods: **At our Center, 45 patients with major thrombophilia were treated with DOACs: 33 after an initial treatment with vitamin K antagonists (VKA) and 12 as first-line therapy for VTE. The median follow-up of DOACs treatment was 29 months.**
Conclusions: **No patient presented hemorrhagic or thrombotic complications during DOAC therapy. DOACs have proven to be effective and safe in this real-life series of patients with major thrombophilia.**

Keywords: Familial thrombophilia; Direct oral anticoagulant; Vitamin K antagonist; Protein C and S deficiency; Antithrombin-III.

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Introduction. Thrombophilia is defined as a predisposition condition towards thrombosis, in particular, venous thrombosis. This condition increases the risk and the recurrence of venous thromboembolism (VTE).[1] A thrombophilic phenotype occurs in approximately 4% of patients with idiopathic VTE.[2] Inherited thrombophilia includes physiologic coagulation inhibitors deficiency: antithrombin (AT), protein C (PC), protein S (PS), F V Leiden mutation, and prothrombin G20210A mutation. Major thrombophilia (physiologic inhibitors deficiency, homozygous F V Leiden, homozygous F II G20210A, combined defects) differs from minor thrombophilia (FV Leiden or F II G20210A heterozygous) because it exposes the affected patients to a higher risk of VTE complication.[3,4]

Treatment of VTE is represented by anti-vitamin K antagonists (VKA) or direct oral anticoagulants (DOACs). Clinical studies evaluating the use of DOACs in congenital thrombophilia include case reports[5-8] and post-hoc analysis of clinical trials;[9-11] these studies have analyzed minor and major thrombophilic patients. Few data are available to support the use of DOACs in the treatment of VTE in patients with major thrombophilia. We hereby report our experience on the use of DOACs for the treatment of VTE in patients affected by major thrombophilia. Aim of our study was to evaluate the efficacy - prevention of recurrent VTE - and safety - the absence of bleeding complications - in the above-mentioned

Table 1. Patients' characteristics.

Patients	45
AGE	40.3 (18-73)
SEX	M 24 (54.5%) F 21 (47.7%)
Diagnosis DVT DVT+PE	 32 (72.7%) 13 (27.3%)
VKA previously DOACs frontline	33 (73.3%) 12 (26.7%)
Major thrombophilia: AT deficiency PS deficiency PC deficiency Homozygous FV Leiden Homozygous FII G20210A Combined heterozygous FV Leiden and FII G20210A	 5 (11.2%) 18 (40%) 5 (11.2%) 12 (26.6%) 1 (2.2%) 4 (8.8%)

VKA = vitamin K antagonists; DOACs = direct oral anticoagulants; DVT = deep venous thrombosis; PE = pulmonary embolism; AT = antithrombine; PC = protein C; PS = protein S; F = Factor

population.

Methods.

Study population. We studied 45 patients affected by major thrombophilia: 5 patients with AT deficiency, 5 with PC deficiency, 18 with PS deficiency, 12 with homozygous mutation of Factor V Leiden, 1 with homozygous mutation of Factor II G20210A and 4 with a combined heterozygous mutation of Factor V Leiden and Factor II G20210A. Twenty-four were male and 21 female with an average age of 40.3 years (16-73) at the start of anticoagulant therapy. Patients were affected by VTE: 32 had a diagnosis of deep venous thrombosis (DVT), 13 presented a DVT and pulmonary embolism (PE) (**Table 1**). DOACs were administered front-line or after VKA. The patients were switched from VKA to DOACs because of a fluctuating international normalized ratio (INR), difficulty in carrying out a regular monitoring or patient request. The patients were treated with the following DOACs: rivaroxaban, dabigatran, apixaban, edoxaban (**Table 2**).

Results. Twelve patients were treated with DOACs front-line, 33 patients switched from VKA: 13 for a fluctuating INR with time in therapeutic range (TTR) lower than 50%, 12 patients for poor compliance and eight following their request. The median VKA treatment follow-up was 60 months (range 6-180); the median DOACs treatment follow-up was 29 months (6-66). Rivaroxaban was administered to 20 patients: front-line in 6 and after previous VKA treatment in 14. Dabigatran was administered to 6 patients (front-line 2, after VKA treatment 4). Apixaban was administered to 18 patients: 5 front-line and 13 after VKA. Edoxaban was administered to 1 patient front-line at the standard dose of 60 mg QD. During VKA treatment, we observed three hemorrhagic complications with an incidence rate of 1.82% patient-years and two thrombotic events with an incidence rate of 1.21% patient-years. The bleeding events were: an episode of mild gum bleeding; epistaxis in a patient with a PS deficiency who was also taking clopidogrel, hematuria. The two thrombotic events were: central retinal vein thrombosis and DVT recurrence in a patient with PS deficiency and TTR 26%. During treatment with DOACs, none of the 45 patients presented hemorrhagic or thromboembolic complications (**Table 3**).

Discussion. Patients affected by inherited thrombophilia present a high risk of DVT complicated by PE or thrombosis in atypical sites at a young age. These patients need to start anticoagulant therapy. The role of DOACs in the treatment of VTE complications in thrombophilic patients remains unclear. The prevalence of known thrombophilia in VTE trials with DOACs ranges from 2 to 18%.[12] RE-COVER, RE-COVER II and RE-MEDY studies compared dabigatran with warfarin,[9] Einstein studies compared rivaroxaban with warfarin,[13,14] Amplify and Hokusai studies compared warfarin with apixaban and edoxaban, respectively.[15,16] The post-hoc analysis of these studies shows no differences in the efficacy and safety of DOACs regardless of the presence or absence of thrombophilia. However, these clinical studies included patients affected by minor and major thrombophilia; in addition, the patients included were not routinely

Table 2. Major thrombophilia groups and DOACs administered.

Thrombophilia	Patients n	Rivaroxaban 20 mg QD	Rivaroxaban 15 mg QD	Apixaban 5 mg BID	Apixaban 2.5mg BID	Dabigatran 150 mg BID	Dabigatran 110 mg BID	Edoxaban 60 mg QD
AT deficiency	5	2		1	1		1	
PC deficiency	5	2	1		1			1
PS deficiency	18	4	3	2	7	1	1	
Homozygous F V Leiden	12	7		1	2	1	1	
Homozygous F II G20210A	1				1			
Herozygous F V+F II	4	1			2	1		

AT = antithrombine; PC = protein C; PS = protein S; F = Factor.

Table 3. Results.

Total patients	45
Previous VKA	33
DOACs front-line	12
Rivaroxaban (n patients) front line post VKA	20 6 14
Dabigatran (n patients) Front-line Post VKA	6 2 4
Apixaban (n patients) Front-line Post VKA	18 5 13
Edoxaban (n patients) Front-line Post VKA	1 1 0
Median FU during VKA (months)	60 (6-180)
Median FU during DOACs (months)	29 (6-66)
Bleedings during VKA Bleedings during DOACs	3 0
Thrombotic events during VKA Thrombotic events during DOACs	2 0

FU = follow up; VKA = vitamin K antagonists; DOACs = direct oral anticoagulants.

screened for congenital thrombophilia, and tests were not performed centrally. There are few data on the real-life use of DOACs in patients diagnosed with severe inherited thrombophilia.

The aim of our study was to evaluate the efficacy and safety of DOACs in the treatment and prevention of thromboembolic events in patients affected by major congenital thrombophilia. We studied the role of DOACS front-line and in patients who switched from VKA. The tests for the thrombophilic status were all performed in our dedicated laboratory.

The majority of our patients (73%) switched from VKA to DOACs. During VKA treatment, we observed three mild hemorrhagic complications and two thrombotic events. No adverse events have been reported in patients during DOACs therapy. Probably this result is influenced by the different length of the two treatments follow-up. We did not observe differences in the efficacy and tolerability in the 4 DOACs regardless of the type of thrombophilia. Conflicting reports have been published regarding the efficacy of DOACs in preventing recurrent VTE in patients with PC and PS deficiency.[6,8] Undas et al. reported VTE recurrence in 2 of 3 patients affected by PS deficiency during DOACs treatment.[10] We studied 18 patients with PS deficiency: 4 patients treated with DOACs front-line, 14 patients who switched from VKA. We did not observe any thrombotic complications. Regarding PC deficiency; a case report described treatment failure during DOACs treatment in a rare heterozygous mutation of the protein C gene.[17] In our cohort of PC deficiency patients (5 patients), DOACs have shown efficacy in treating VTE.

Another not negligible aspect is the quality of life of patients who switch from a treatment that requires periodic controls of INR to a less demanding regimen with fewer drug interactions.

Conclusions. Although the poor casuistry (partially due to the rarity of major thrombophilia) with a brief follow-up and the limitations of a retrospective study, our evidence suggests that DOACs are a promising therapeutic option for the treatment of acute VTE in the presence of major thrombophilia, in terms of efficacy, safety and quality of life.

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