Internal and Emergency Medicine (2019) 14:1171–1173
https://doi.org/10.1007/s11739-019-02118-z

CE - RESEARCH LETTER TO THE EDITOR

Direct oral anticoagulants in lipoprotein apheresis: handle with care

Francesco Sbrana[1] · Beatrice Dal Pino[1] · Angela Papa[2] · Federico Bigazzi[1] · Luca Panchetti[3] · Tiziana Sampietro[1]

Received: 5 April 2019 / Accepted: 27 May 2019 / Published online: 4 June 2019

Dear Editor,

Since 2009, direct oral anticoagulants (DOAC) are increasingly being used in clinical practice for stroke prevention in non-valvular atrial fibrillation and in treatment/prevention of thromboembolism. Their correct management is not only a concern for internal medicine [1] and surgical bleeding, but also for other therapeutic areas such as transfusion medicine [2]. In this setting, the extracorporeal anticoagulation circuit has to be added to the concomitant patient's antiplatelet and anticoagulant therapy to reduce the hemorrhagic risk.

In our Center for Lipoprotein-Apheresis (LA), where we have experience of more than 500 treatment/year, 21% (7/34) of subjects are on oral anticoagulant therapy, in addition to antiplatelet therapy. These patients undergo chronic LA for familial hypercholesterolemia and ischemic heart disease on maximally tolerated lipid-lowering therapy and/or hyperlipoproteinemia (a). Clinical characteristics, pre-LA lipid profile and lipid-lowering backbone therapy are summarized in Table 1. LA treatments were performed by the most common techniques: dextran sulfate absorption from plasma (Liposorber®-LA MA-03 systems; Kaneka, Osaka, Japan; 4/7 patients), heparin-induced LDL precipitation apheresis (HELP®, Plasmat Futura®; B. Braun, Melsungen, Germany; 2/7 patients), immunoadsorption (TheraSorb™—LDL pro Adsorber, Miltenyi biotec, Bergisch Gladbach, Germany; 1/7 patients). LA procedures were in agreement to guidelines and manufacturer's instructions with a median inter-apheresis interval of 14 [10–14] days, treating 4000 ml plasma/session for subjects in HELP system or 1.5 patient plasma volume/session with the other systems.

Among patients on oral anticoagulant therapy, six subjects (6/7) were treated for non-valvular atrial fibrillation and the other case (1/7) for pulmonary thromboembolism. One patient denied his consent to DOAC therapy and continued vitamin K antagonist. Another subject, after few months of therapy with dabigatran 110 mg BD, discontinued DOAC because of vasospastic angina, starting again vitamin K antagonist until the symptom's remission. She performed coronary angiography which excluded coronary stenoses and the symptoms were imputable to lower concentration of verapamil secondary to pharmacokinetic interaction between dabigatran and verapamil extended release formulation [3].

Table 1 Clinical characteristic, lipid-lowering backbone therapy and pre-LA lipid profile of patients on oral anticoagulant therapy

	Patients ($n=7$)
Mean age (years)	70 ± 7
Male gender	5/7 (71%)
BMI (kg/m^2)	27 ± 3
Concomitant hyperlipoproteinemia (a)	3/7 (43%)
Duration of apheresis treatment (years)	14 [9–23]
Lipid-lowering backbone therapy	
Statins	6/7 (86%)
PCSK9i	6/7 (86%)
Fibrates	3/7 (43%)
Ezetimibe	3/7 (43%)
Pre-LA lipid profile	
Total cholesterol (mg/dl)[a]	188 ± 45
Triglycerides (mg/dl)[a]	144 ± 51
HDL cholesterol (mg/dl)[a]	47 ± 13
LDL cholesterol (mg/dl)[a]	112 ± 37
Lp (a) (mg/dl)[b]	85 [80–100]

PCSK9i proprotein convertase subtilisin/kexin type 9 inhibitors

[a]Data are expressed as mean ± SD

[b]Data are expressed as median [interquartile range] calculated on subjects with concomitant hyperlipoproteinemia (a)

✉ Francesco Sbrana
francesco.sbrana@ftgm.it

1 Lipoapheresis Unit and Reference Center for Inherited Dyslipidemias, Fondazione Toscana "Gabriele Monasterio", Via Moruzzi 1, 56124 Pisa, Italy

2 Department of Laboratory Medicine, Fondazione Toscana "Gabriele Monasterio", Pisa, Italy

3 U.O. Elettrofisiologia interventistica, Fondazione Toscana "Gabriele Monasterio", Pisa, Italy

A third patient is currently being treated with rivaroxaban 15 mg OD, after pulmonary thromboembolism occurred during LA procedure, imputable to recent transcatheter mitral valve repair [4]. During the follow-up, the patient had a hospital admission for severe anemia (Hb 7.7 g/dl) caused by gastrointestinal bleeding, which required blood transfusions.

Thanks to the availability of a specific antidote (idarucizumab), the remaining four subjects are regularly being treated with dabigatran 110 mg BD, started more than 4 years ago. In this subgroup, during the follow-up, 3/4 subjects reported a significant decrease in hemoglobin levels (did not require blood transfusion but treated with iron i.v. therapy); one subject reported two acute coronary syndromes, but no ischemic stroke and/or transient ischemic attack was recorded. The clinical characteristics of the subjects are summarized in Table 2; Table 3 shows hemoglobin concentration and red blood cell indices.

Table 2 Clinical characteristics and outcomes of study subjects on dabigatran 110 mg BD therapy

Age (years)	68 ± 6
Male gender	4/4 (100%)
Weight (kg)	88 ± 5
eGFR (ml/min/1.73 m^2)	85 ± 22
Coronary heart disease	4/4 (100%)
Acetylsalicylic acid concomitant therapy	4/4 (100%)
Clopidogrel concomitant therapy	1/4 (25%)
Plasma peak concentration (µg/l)[a]	118 ± 15
Plasma trough concentration (µg/l)[a]	52 ± 11
Hb decrease ≥ 2 g/dl	3/4 (75%)
MACE	1/4 (25%)[b]
Ischemic stroke/transient ischemic attack	0/4 (0%)

Hb hemoglobin, *eGFR* estimated glomerular filtration rate, *MACE* major adverse cardiovascular events

[a]Diluted thrombin time assay

[b]Two episodes of acute coronary syndrome occurred in the same patient

The occurrence of four episodes of clinically relevant bleeding (Hb decrease ≥ 2 g/dl in three cases and a major bleeding) is a complication that invites caution (3/4 cases occurred in subjects treated with dextran sulfate absorption and the other case occurred in a patient treated with an immunoadsorption system). It is known that LA leads to chronic blood oozing and promotes iron deficiency anemia secondary to a decrease of ferritin, transferrin and vitamin B12 levels [5]. These conditions and the concomitant antiplatelet therapy are contributing factors to the high rate of bleeding episodes in subjects on DOAC therapy. To minimize the hemorrhagic risk, a low dose of DOAC was started (dabigatran 110 mg BD or rivaroxaban 15 mg OD). Compared to warfarin, this regimen is equivalent for stroke prevention and is associated with a significant lower risk of major bleeding. Furthermore, to better manage these subjects, given the lack of standardized cutoff values for dabigatran 110 mg BD, the diluted thrombin clotting time was performed and, even with the high inter-individual variability of DOAC plasma concentrations, we observed mean values slightly lower with respect to dabigatran 150 mg BD, showing a best benefit/risk ratio [1, 6, 7].

This monocentric experience, despite the small patient group, underlines the need to personalize medical treatment, especially in subjects with comorbidities and multiple drug therapy who had undergone extracorporeal procedure.

Table 3 Data of hemoglobin concentration and red blood cell indices in subjects treated with vitamin K antagonist or dabigatran 110 mg BD therapy

		Baseline value	Nadir value
Vitamin K antagonist therapy (*n* 2)	Hemoglobin (g/dl)	14.4 ± 1	14.1 ± 1.1
	Mean red cell volume—MCV (fl)	91.3 ± 3.7	89.9 ± 2.3
	Mean cell hemoglobin—MCH (pg)	30.9 ± 1.7	29.8 ± 1.1
Dabigatran 110 mg BD therapy (*n* 4)	Hemoglobin (g/dl)	14 ± 0.6	11.5 ± 0.6
	Mean red cell volume—MCV (fl)	88.0 ± 2.0	78.9 ± 2.4
	Mean cell hemoglobin—MCH (pg)	29.0 ± 1.2	25.6 ± 0.8

Acknowledgements The authors are grateful to Mascia Pianelli and Roberta Luciani for the excellent work in the apheresis unit.

Funding None.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statement of human rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent All participants provided informed consent prior to their participation.

References

1. Prisco D, Ageno W, Becattini C, D'Angelo A, Davì G, De Cristofaro R, Dentali F, Di Minno G, Falanga A, Gussoni G, Masotti L, Palareti G, Pignatelli P, Santi RM, Santilli F, Silingardi M, Tufano A, Violi F, SIMI (Italian Society of Internal Medicine), FADOI (Federation of Associations of Hospital Doctors on Internal Medicine), SISET (Italian Society for the Study of Haemostasis and Thrombosis) (2017) Italian intersociety consensus on DOAC use in internal medicine. Intern Emerg Med 12:387–406. https://doi.org/10.1007/s11739-017-1628-6
2. Shunkwiler SM, Pham HP, Wool G, Ipe TS, Fang DC, Biller E, Treml A, Weiss J, Baron BW, Berg M, Therapeutic Apheresis Subsection of the AABB (2018) The management of anticoagulation in patients undergoing therapeutic plasma exchange: a concise review. J Clin Apheresis 33:371–379. https://doi.org/10.1002/jca.21592
3. Härtter S, Sennewald R, Nehmiz G, Reilly P (2013) Oral bioavailability of dabigatran etexilate (Pradaxa(®)) after co-medication with verapamil in healthy subjects. Br J Clin Pharmacol 75:1053–1062. https://doi.org/10.1111/j.1365-2125.2012.04453.x
4. Sbrana F, Dal Pino B, Bigazzi F, Coceani M, Luciani R, Pianelli M, Panchetti L, Petersen C, Monti S, Sampietro T (2015) A case of pulseless electrical activity secondary to pulmonary embolism: a medical emergency occurring in an LDL apheresis center. Transfus Apheresis Sci 53:74–75. https://doi.org/10.1016/j.transci.2015.03.010
5. Bramlage CP, Armstrong VW, Zapf A, Bramlage P, Mueller GA, Koziolek MJ (2010) Low-density lipoprotein apheresis decreases ferritin, transferrin and vitamin B12, which may cause anemia in serially treated patients. Ther Apheresis Dial 14:136–142. https://doi.org/10.1111/j.1744-9987.2009.00715.x
6. Tripodi A (2013) The laboratory and the direct oral anticoagulants. Blood 121:4032–4035. https://doi.org/10.1182/blood-2012-12-453076
7. Tripodi A, Marongiu F, Moia M, Palareti G, Pengo V, Poli D, Prisco D, Testa S, Zanazzi M (2018) The vexed question of whether or not to measure levels of direct oral anticoagulants before surgery or invasive procedures. Intern Emerg Med 13:1029–1036. https://doi.org/10.1007/s11739-018-1854-6