Accepted Manuscript

The use of rivaroxaban in patients with antiphospholipid syndrome: A series of 12 cases

Maksim Son, Ewa Wypasek, Magdalena Celinska-Lowenhoff, Anetta Undas

PII: S0049-3848(15)00048-1
DOI: doi: 10.1016/j.thromres.2015.01.028
Reference: TR 5835

To appear in: *Thrombosis Research*

Received date: 22 December 2014
Revised date: 26 January 2015
Accepted date: 29 January 2015

The use of rivaroxaban in patients with antiphospholipid syndrome: A series of 12 cases

Maksim Son,[1] Ewa Wypasek, [1,2] Magdalena Celinska-Lowenhoff, [3] Anetta Undas[1,2]

[1]Institute of Cardiology, Jagiellonian University Medical College, Cracow, Poland; [2]John Paul II Hospital, Cracow, Poland; and [3]Department of Medicine, Jagiellonian University Medical College, Cracow, Poland

Running title: Antiphospholipid syndrome and rivaroxaban

Correspondence to:

Anetta Undas MD, PhD

Institute of Cardiology, Jagiellonian University Medical College

80 Prądnicka St., 31-202 Kraków, Poland

Tel.: +48126143004, Fax: +48124233900

E-mail: mmundas@cyf-kr.edu.pl

Word count: 779

Number of tables: 1

Dear Editors,

Vitamin K antagonists (VKAs) remain the mainstay treatment for antiphospholipid syndrome (APS), a common acquired thrombophilic disorder that presents as arterial or venous thromboembolism (VTE), or recurrent pregnancy loss. Non-vitamin K oral anticoagulants (NOACs) offer several advantages over VKAs such as a predictable dose response, fewer drug and food interactions, and no need for laboratory monitoring of the international normalized ratio (INR) – a frequent challenge in patients with APS (1). NOACs are already being used in patients with atrial fibrillation, which is the most common indication for a long-term anticoagulation therapy, as well as in those with VTE (1,2). Owing to the paucity of clinical data, the use of NOACs in managing APS remains controversial. There have been a few reports suggesting that NOACs compared with VKAs are less beneficial in VTE patients with APS (3,4). On the other hand, some experts have recommended NOACs as an alternative to VKAs in the prevention of VTE in APS (5).

We present 12 consecutive white patients with APS (two positive results obtained 3-5 months apart as recommended [6]) and previous single VTE episode and/or ischemic stroke (7 women and 5 men; mean age 42±10 years) who were switched from VKAs (warfarin or acenocoumarol) to rivaroxaban for at least 2 months at our institution. Prior to the switch, the target INR range was between 2.0 and 3.0, with the value on the day of the first dose of rivaroxaban between 1.9 to 2.5. Patients with a history of stroke and/or multiple risk factors for thrombotic events additionally received low-dose acetylsalicylic acid (ASA). The duration of treatment with rivaroxaban (20 mg daily) in secondary prevention of VTE ranged from 2 to 16 months (Table). In all cases the change of anticoagulation therapy was due to logistic problems with INR monitoring that interfered with the professional activities of the patients and/or unstable INR values resulting in time in the therapeutic range below 50%. Inherited thrombophilia screening was negative in this group. All patients had normal creatinine clearance, liver function and plasma D-dimer below 500 ng/ml on the first day of the use of rivaroxaban. The patients declared regular rivaroxaban intake during follow-up. Peak rivaroxaban concentration (2-4 hours since the drug intake) was measured by the anti-Xa chromogenic assay, Biophen DiXaI (Hyphen Biomed, Neuilly-sur-Oise, France) at the time of symptoms of VTE recurrence or after 1-3 months since the therapy onset in the remaining subjects to check adherence to the drug (7).

Two of the 12 patients developed a recurrent deep vein thrombosis (DVT) within the first few months of starting rivaroxaban (Table).

Case 1

A 36-year-old female with APS and coexisting systemic lupus erythematosus (SLE) was treated with warfarin for 19 months following idiopathic DVT. She was managed with rivaroxaban for 5 months before developing a second DVT during the exacerbation of SLE. Her antiphospholipid antibodies involved positivity for lupus anticoagulant (LA), elevated immunoglobulin G (IgG) anti-beta-2 glycoprotein I antibodies (aβ2GPI; 99.2 SGU) and IgG anti-cardiolipin antibodies (aCL; 36.7 GPL) above the 99th percentile.

Case 2

A 56-year old female with APS and coexisting SLE was initially treated with acenocoumarol and low-dose ASA for 44 months before switching to rivaroxaban. Her history was significant for ischemic stroke, idiopathic DVT and hypertension. While on remission of SLE, she developed a second DVT following a minor lower limb injury with a 7-day enoxaparin use instead of rivaroxaban. After 2 weeks while back on rivaroxaban the symptoms of DVT occurred. The patient was managed with rivaroxaban for 2 months prior the accident and DVT. The patient was positive for LA, high IgM aβ2GPI (203.1 SMU), as well as IgG aCL (72.3 GPL) and IgM aCL (190.1 MPL) above the 99^{th} percentile each.

Previous reports mainly focused on the treatment of patients with a history APS cases that were complicated by multiple episodes of VTE or arterial thrombosis. Schaefer et al. (3), as well as Win and Rogers (4) have presented 3 APS patients each with recurrent thrombotic events after starting NOACs. We included all consecutive APS patients who wanted not to use VKAs to assess the effectiveness and safety of NOACs. Therefore, our findings provide a real-life experience with rivaroxaban in the setting of APS. The two treatment failures occurred in patients with the highest risk profile, including triple positivity, combined with autoimmune disease. Unsatisfactory adherence to therapy cannot be excluded in these patients. Interestingly, we observed elevated factor VIII activity above 200% on the day of the switch to rivaroxaban in the two patients with VTE recurrence. The 10 patients who did not experience recurrent VTE are still managed with rivaroxaban in our center. Although the present findings do not substitute the outcomes of clinical trials on the effectiveness of NOACs in APS, notably Rivaroxaban in Antiphospholipid Syndrome (RAPS) study in North America (8) and Rivaroxaban in Antiphospholipid Syndrome (TRAPS) study in Europe (9), we suggest that the use of NOACs be considered on a case-by-case basis and confined mainly to patients with a poor INR control or those who refused VKA treatment until the results of ongoing studies will clarify this issue. However, it should be highlighted that a high recurrence rate is observed also on warfarin treatment in high risk APS patients (10), therefore one might suspect that rivaroxaban is non-inferior to warfarin in this clinical setting.

Acknowledgements

none

Sources of funding

This study has been supported by a grant of Jagiellonian University Medical College (K/ZDS/002936 to A.U.).

Disclosures

none

References

1. Chighizola CB, Moia M, Meroni PL. New oral anticoagulants in thrombotic antiphospholipid syndrome. Lupus 2014;12:1279-82.

2. Undas A, Pasierski T, Windyga J, Crowther M. Practical aspects of new oral anticoagulant use in atrial fibrillation. Pol Arch Med Wewn 2014;124:124-135.

3. Schaefer JK, McBane RD, Black DF, et al. Failure of dabigatran and rivaroxaban to prevent thromboembolism in antiphospholipid syndrome: a case series of three patients. Thromb Haemost 2014;112:947-950.

4. Win K, Rodgers GM. New oral anticoagulants may not be effective to prevent venous thromboembolism in patients with antiphospholipid syndrome. Am J Hematol 2014;89:1017.

5. Arachchillage DJ, Cohen H. Use of new oral anticoagulants in antiphospholipid syndrome. Curr Rheumatol Rep 2013;15:331.

6. Miyakis S, Lockshin MD, Astumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost 2006; 4:295-306.

7. Zalewski J, Rychlak R, Góralczyk T, Undas A. Rivaroxaban concentration in patients with deep vein thrombosis who reported thrombus progression or minor hemorrhagic complications: first Polish experience. Pol Arch Med Wewn. 2014;124:553-5.

8. Rivaroxaban in Antiphospholipid Syndrome (RAPS) Trial. Available at: http://isrctn.org/ISRCTN68222801. Accessed on November 29, 2014.

9. Rivaroxaban in Thrombotic Antiphospholipid Syndrome (TRAPS) Trial. Available at: http://clinicaltrials.gov/NCT02157272. Accessed on January 22, 2015.

10. Pengo V, Ruffatti A, Legnani C, et al. Clinical course of high-risk patients diagnosed with antiphospholipid syndrome. J Thromb Haemost. 2010;8:237-42.

11. Pengo V, Tripodi A, Reber G, et al. 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; 7:1737-40.

Table. Patients with antiphospholipid syndrome treated with rivaroxaban

Case	Age (years)	Sex	Clinical manifestations of APS			Presence of aPL	Months from last event	Factor VIII (%)*	Rivaroxaban treatment (months)	Drug concentration (ng/ml)**	Recurrent VTE
			VTE	Arterial thrombosis	Pregnancy morbidity						
1 (S)	36	F	DVT	-	Miscarriage	aβ2GPI, aCL, LA	24	254	5	68	DVT
2 (S)	56	F	DVT	Stroke	-	aβ2GPI, aCL, LA	46	232	2	219	DVT
3	46	F	DVT	-	-	aβ2GPI, aCL, LA	18	157	15	101	-
4	52	F	DVT	-	-	aβ2GPI	16	135	15	88	-
5 (S)	29	F	PE	-	Miscarriage	aβ2GPI, aCL, LA	13	127	10	176	-
6 (S)	44	F	DVT	-	-	aβ2GPI, aCL, LA	12	170	10	209	-

7	50	F	DVT	-	-	aβ2GPI, aCL	34	184	12	95	-
8	50	M	DVT, PE	-	-	aβ2GPI, aCL	38	121	10	248	-
9	33	M	PE	-	-	aCL	22	116	12	136	-
10	22	M	DVT	-	-	aCL	20	152	14	144	-
11	49	M	DVT	Stroke	-	aβ2GPI	24	169	16	103	-
12	44	M	DVT	-	-	aβ2GPI, aCL	19	193	16	116	-

(S) indicates antiphospholipid syndrome associated with systemic lupus erythematosus.

At least one of the clinical criteria and at least one of the laboratory criteria must be satisfied to diagnose antiphospholipid syndrome (6). Lupus anticoagulant (LA) activity detected according to the current guidelines (11).

F denotes female; M, male; DVT, deep venous thrombosis; PE, pulmonary embolism; aPL, antiphospholipid antibodies; aβ2GPI, beta-2 glycoprotein I antibodies; aCL, anticardiolipin antibodies; LA, lupus anticoagulant; VTE, venous thromboembolism.

*Factor VIII activity measured immediately prior to the start of rivaroxaban treatment

**Plasma concentrations of rivaroxaban determined using an assay based on anti-Xa activity as stated in the text.