Is Useful Rivaroxaban in all Clinical Presentation of Venous Thromboembolism? A Clinical Overview by Campania Section of Italian Society of Vascular Pathology (SIAPAV)

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Abstract

The treatment of a VTE is frequently performed with DOACs and rivaroxaban is one of the main used DOAC in the clinical practice. However, rivaroxaban according to the experience of phase III trials is commonly used in common clinical condition associated to VTE and mainly in case of DVT of lower limbs with or without PE.

Little is known about the usefulness of rivaroxaban in chronic inflammatory disease as vasculitis or in case of unusual sites of DVT as abdominal vein DVT.

Background

The usefulness of direct oral anticoagulants (DOACs) and in particular of rivaroxaban in the treatment of venous thromboembolism (VTE) has been well established by international guidelines [1]. However guidelines derive from results of clinical phase III trials of DOACs in VTE that are all focused on episodes of deep vein thrombosis (DVT) of lower limbs with or without pulmonary embolism (PE) [2-4]; this section of treatment of VTE is dedicated from guidelines to DVT and PE. Also in clinical practice most common clinical presentation of a VTE are DVT and PE and this clinical forms from an epidemiological point of view represent nearly the 70% of all VTE episodes; yet, other clinical presentation of VTE are superficial vein thrombosis of lower limbs, superficial vein thrombosis of upper limbs, cerebral vein thrombosis, abdominal deep vein thrombosis, retinal vein occlusion and so on. In these clinical conditions the usefulness of DOACs has not been clearly tested and all information available in the literature derive from personal clinical case reports or small clinical series.

Furthermore, according to the PADUA risk score [5], the most common conditions associated to VTE that were considered in phase III trials on DOACs were cancer, recent surgery, recent medical illness (as stroke, COPD, AMI), prolonged hormonal treatment, ageing and personal history of VTE with or without thrombophilia and only these conditions were considered as responsible of provoked VTE in these studies, while remaining forms were considered idiopathic VTE. However, as well known, there are also further clinical conditions and risk factors associated to VTE as chronic inflammatory disease (e.g. inflammatory bowel diseases or erythematous systemic lupus) or vasculitis that are frequently associated to VTE. Also in these clinical conditions the usefulness of DOACs has not been completely tested.

This short review is focused to the use of rivaroxaban to treat VTE occurring in unusual sites as deep abdominal veins or during an inflammatory disease as vasculitis.

Rivaroxaban for the treatment of VTE associated to Vasculitis

Thrombotic complications of vasculitis are frequent in clinical practice. Churg Strauss disease, Bechet disease and livedoid vasculopathy are more at risk according to epidemiological studies [6].

Eosinophilic granulomatosis with polyangiitis (EGPA; ie, Churg-Strauss Syndrome CSS) is a systemic small-sized vessel vasculitis, characterized by severe asthma, transient pulmonary infiltrates, and blood and tissue eosinophilia. Several studies have focused...
on venous thromboembolic events in CSS. Patients with CSS are at a greater risk of VTE, than those with systemic vasculitis [6-7]. Rivaroxaban has been successfully used in sporadic cases of CSS associated to VTE [8] and further data are needed on large based population to better understand the clinical impact in this setting.

Behçet syndrome frequently shows vascular complication as venous thrombosis or aneurysmosi, also with an increased rate of recurrent VTE episodes [9]. The incidence of relapse in fact is nearly 36% in 5 years and more than 55% in 20 years. One of the most common site of venous thrombosis is the femoral vein, so Behçet disease may induce typical proximal DVT. Little is known about the best anticoagulant treatment to take for VTE in Behçet disease [10]. Recently a long term follow up of nearly 36 months without VTE recurrences has been reported with rivaroxaban 20 mg daily in one case report. Rivaroxaban was chosen because its fixed daily dose, no need for laboratory monitoring and the limited drug-drug or food-drug interactions [9]. No data are available in literature about the usefulness of DOACs in prolonged therapy for improving disease’s outcomes.

Livedoid vasculopathy is a disorder which is a local vasculitis associated to dysregulation of coagulation, resulting in the formation of fibrin thrombi in the superficial dermal plexus [11]. Associated to this trend to develop superficial microthrombosis of dermal plexus, also an association with deep vein thrombosis has been described but its real incidence is not well established. Owing to the postulated pathophysiology systemic anticoagulation with low-molecular-weight heparin (LMWH) and warfarin have been reported as treatment but rivaroxaban recently was suggested as a treatment modality. Good outcomes with reduced local and systemic recurrence of thrombotic events were reported by patients treated with rivaroxaban at daily dose of 20 mg in several case reports.

Rivaroxaban in Abdominal Deep Vein Thrombosis

Thrombosis in the abdominal and portal venous system (i.e. mesenteric, splenic and portal veins), are collectively defined as abdominal or splanchic deep vein thrombosis and are classified as unusual sites of DVT. Acute abdominal DVT may be symptomatic, but many episodes are detected incidentally in imaging studies performed for other indications, such as staging or assessing response to therapy in patients with cancer or liver diseases and this is one of the reason that explain the increase of diagnosis of abdominal DVT. Current guidelines from the American College of Chest Physicians (ACCP) recommend anticoagulant therapy in patients with symptomatic splanchic vein thrombosis SVT (Grade 1B) and suggest no routine anticoagulation in those with incidentally found SVT (Grade 2C) [12,13] but the intensity and the duration of anticoagulation is still matter of discussion in daily clinical practice.

Also the type of anticoagulant drugs to be used in the long term therapy of abdominal DVT is an open issue: actually international guidelines suggest over 6 months of therapy with anti-vitamin K drugs but also low molecular weight heparins are largely used because a great percentage of oncological patients with incidental abdominal DVT. However both categories of drugs show such difficulties in the daily practice because the increased risk of bleeding complications and because the difficult laboratory monitoring of antivitamin K drugs in this clinical setting or the long term needed subcutaneous daily injections in the case of low molecular weight heparins.

The use of DOACs is not suggested by international guidelines because there are not randomized clinical trials dedicated to the treatment of this kind of DVT, but in the real world DOACs have rarely been used to treat abdominal DVT.

Such study report the use of DOACs in portal vein thrombosis but without univocal results in term of efficacy and safety of this kind of anticoagulation [14], while case reports or small case series report an acceptable long term outcome of this kind of patients treated with rivaroxaban at adapted doses [15-16] as reported in table 1.

So, because in small series of patients hitherto published, the DOACs showed good efficacy and safety, it could be reasonable to support the use of DOACs in prospective cohort studies and randomized controlled trials in order to validate their use in abdominal DVT.

Further Open Issues on Rivaroxaban and Conclusion

The growing knowledge of DOACs and the growing request to use an oral anticoagulant without required monitoring instead of anti-vitamin K drug or low molecular weight heparins induce each to the administration of DOACs also in off label conditions.

The occurrence of a VTE in conditions that are not described in clinical trials or reported in guidelines could be treated as a common VTE? The occurrence of a VTE event in an unusual site could be managed with DOACs as DVT of lower limbs or non-hemodynamic PE? These questions are really intriguing physicians around the world and because in such situation the number of patients to enrolled to perform a specific randomized trial to answer this question could require several years, real life studies and personal clinical experiences are supporting the literature to answer to this clinical question.

In this clinical aspect DOACs are an emerging support to treat VTE in every patients but more data are needed before to open this clinical scenario to these antithrombotic drugs. Interesting results of DOACs in the treatment of VTE associated to vasculitis have been reported in this review but not similar data are available for the use of rivaroxaban in portal vein thrombosis. These aspect has also been reported by the RIETE investigators when they analyzed patients treated for classic VTE (i.e. lower limb DVT with or without PE) with rivaroxaban but that showed exclusion criteria for DOACs’ treatment (i.e. ageing, renal impairment, metastatic advanced cancer and so on). These patients seemed to have a stronger trend to clinical complications

| Table 1: Studies in which DOACs are used to Treat Splanchnic Vein Thrombosis |
|---|---|---|---|
| Privanka et al | >100 | review | Mainly rivaroxaban 20 mg | Good |
| Lenz K et al | 1 | Case report | Rivaroxaban 10 mg | good |
| Pannach S et al | 1 | Case report | Rivaroxaban 15 mg | good |
if compared to those that show classic clinical characteristic to receive DOACs [16,17].

Yet, although this trend may be expected because the clinical complexity of these clinical situations it may help us to understand that the management of each clinical types of VTE may require a particular experience as we report in this review for abdominal DVT and for DVT associated to vasculitis. Further clinical data are so needed actually in each scientific presentations as clinical series, case reports, real world studies and when possible randomized clinical trials in order to better understand where we are going with VTE therapy.

References


