IM - COMMENTARY

Retinal vein occlusion: time for action has come

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Retinal vein occlusion (RVO) is considered as a rare site vein thrombosis. However, the estimated incidence of RVO ranges between 0.53 and 1.6/1000 persons/year, an incidence that is comparable to that of "more usual" venous thromboembolic events, such as deep vein thrombosis of the lower limbs and pulmonary embolism [1, 2]. Furthermore, RVO is one of the major causes of unilateral visual loss, and it seems to be associated with a significantly increased long-term risk of cardiovascular morbidity and mortality [3, 4]. Unfortunately, despite this clear epidemiological and clinical burden, there is a substantial lack of adequate clinical studies upon RVO patients, and the optimal management of this disease remains a major unmet clinical need.

In this issue of Internal and Emergency Medicine, Marcucci et al. [5] provide an exhaustive review on the pathogenesis and management of RVO, with a particular focus on the role of the internist. The interaction between ophthalmologists and internists or vascular specialists is indeed crucial in the light of the main therapeutic goals for these patients. After objective diagnosis of RVO, internists should assist ophthalmologists in the general assessment of the patients, with the aim of identifying non-ocular causes of RVO, to define the risk for subsequent cardiovascular events, and to evaluate the risk to benefit ratio of antithrombotic therapies aimed at improving visual acuity, preventing local complications, and preventing long-term events.

Based on the current evidence, Marcucci et al. [5] propose a long list of diagnostic tests for this general work up, and have suggested potential therapeutic strategies.

Although the role of some of the proposed tests is far from being proven in this setting (e.g. echocardiography, evaluation for autoimmunity, most thrombophilic tests, hemorheological studies), this call for action for the internist should not be underestimated because a well-structured diagnostic work up may indeed result in an improvement in the prognosis of these patients. Ideally, the proposed tests should be organized in a multi-step approach, with a first step that is common to all patients, including routine laboratory tests and blood pressure measurement, and subsequent steps that are differentiated according to the age of the patients and on the results of first level tests. Over the next few years, we should aim to validate similar approaches by means of adequately designed clinical studies. In these studies, the number of included patients with previously unknown cardiovascular risk factors (i.e. arterial hypertension, hyperglycemia, dyslipidemia), with known, but inadequately controlled cardiovascular risk factors, and with asymptomatic cardiovascular disease (e.g. atherosclerotic plaques in the carotid arteries) should be calculated. Available cardiovascular risk scores can then be used as surrogate end-points to calculate the number needed to screen to identify one high-risk patient among patients with RVO. Subsequently, prospective, controlled studies should determine whether the detection and management of these and other systemic risk factors for RVO effectively reduce the risk of recurrences. Unfortunately, the rates of recurrence of RVO are still poorly defined, and thus a good estimate of the sample size required for similar studies is currently not feasible.

The direct management of sight-threatening complications in patients with RVO primarily involves the ophthalmologist with the potential application of different strategies including surgical approaches, laser therapy, the administration of intravitreal steroids or hemodilution, and

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other promising treatments such as intravitreal anti-vascular endothelial growth factor drugs [3, 4, 6–9]. This management should also involve the internist when it comes to the choice of an antithrombotic drug, for both the short and the long-term treatment of RVO. To date, none of the several proposed therapeutic approaches is supported by good quality evidences. However, antiplatelet and anticoagulant drugs are commonly used in clinical practice based on some biological plausibility because: with antiplatelet agents RVO is commonly associated with cardiovascular risk factors; with anticoagulant drugs the thrombotic event occurs in the venous system; venous stasis is one of the major provoking factors for venous thrombosis; and venous stasis is likely also one of the main mechanisms for thrombi occurring in the retinal veins. Thus, at least theoretically, anticoagulant drugs may be effective for the acute phase treatment of RVO, and antiplatelet agents may be effective for the long-term secondary prevention of both recurrences and cardiovascular disease, at least in some patient groups.

In a recent systematic review of the literature, we find only one placebo controlled study with ticlopidine, two studies comparing intravenous fibrinolytic therapy followed by warfarin or aspirin with either hemodilution or no treatment, and three studies comparing therapeutic doses of low molecular weight heparin (LMWH) with low-dose aspirin in the acute phase treatment of RVO [10]. All studies report partial improvement of visual acuity, but studies comparing LMWH with aspirin suggest that anticoagulant treatment may be more effective than antiplatelet treatment in the first few weeks after RVO, in particular if the occlusion involves the central retinal vein [11–13]. The results of these three studies were subsequently meta-analyzed, and LMWH shows a visual acuity improvement at 6 months (-0.23 logMAR units or 2 lines), and a 78% risk reduction for developing adverse ocular outcomes with no increased risk of vitreous hemorrhage [14]. Studies are highly heterogeneous in terms of inclusion and exclusion criteria, timing between onset of symptoms and first treatment dose, and in the definition of study end-points. Moreover, all studies have some major limitations, including the small sample size and the imbalance in our study between patients with central and branch RVO. Finally, it must be acknowledged that no randomized controlled study has compared anticoagulant treatment with placebo. In our study, this was originally planned, but it turned out not to be possible because in many participating centers the administration of placebo was considered unethical, despite the lack of solid evidences to support the use of antithrombotic drugs.

However, these studies provided for the first time some important background information for the design of future studies, which are now warranted to confirm these preliminary observations. Several issues will need to be considered when designing future studies on the acute phase treatment of RVO. These include the maximum delay allowed between the onset of symptoms and the starting of treatment, since timely starting of the therapy may greatly impact its chances of success; the stratification of patients according to the site of RVO, or the inclusion of patients with central RVO only, since this may be the group that benefits the most from antithrombotic drugs; the stratification of patients according to the type of RVO (ischemic vs. non-ischemic), since an initial stratification can improve the assessment of the clinical outcomes; and a general agreement on a commonly accepted and easily reproducible definition of the primary efficacy outcome, since several parameters have been proposed for the evaluation of efficacy, including visual acuity, visual field, and the results of fluorescein angiography.

In addition to new studies on the acute phase treatment of RVO, clinical trials aimed at the assessment of long-term secondary prevention therapeutic strategies should also be planned. In addition to LMWH for the first few weeks of treatment, and antiplatelet agents for long-term secondary prevention, the role of new anticoagulant drugs including direct Factor Xa and direct thrombin inhibitors for both the acute and long-term treatment may be worthy of exploration.

Conflict of interest   None.

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