Thrombosis Research 125 (2010) 137–141

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Regular Article

Parnaparin versus aspirin in the treatment of retinal vein occlusion. A randomized, double blind, controlled study☆

Walter Ageno [a,*], Roberto Cattaneo [b], Elisa Manfredi [c], Paolo Chelazzi [c], Luigi Venco [c], Angelo Ghirarduzzi [d], Luca Cimino [d], Esmeralda Filippucci [e], Angela Luisa Ricci [e], Donatella Romanelli [e], Carlo Incorvaia [f], Sergio D'Angelo [f], Fiamma Campana [g], Francesco Molfino [g], Gianluigi Scannapieco [h], Flavia Rubbi [i], Davide Imberti [j]

[a] University of Insubria, Varese, Italy
[b] S. Antonio Abate Hospital, Gallarate, Italy
[c] University of Insubria, Varese, Italy
[d] Lazzaro Spallanzani Hospital, Reggio Emilia, Italy
[e] University of Perugia, Perugia, Italy
[f] S. Anna Hospital, Ferrara, Italy
[g] Santa Croce e Carle Hospital, Cuneo, Italy
[h] Ca' Foncello Hospital, Treviso, Italy
[i] University of Bologna, Bologna, Italy
[j] G. da Saliceto Hospital, Piacenza Italy

ARTICLE INFO

Article history:
Received 24 March 2009
Received in revised form 5 May 2009
Accepted 6 May 2009
Available online 27 May 2009

Keywords:
Retinal vein occlusion
Low molecular weight heparin
Aspirin

ABSTRACT

Introduction: Retinal vein occlusion (RVO) is a common cause of unilateral visual loss. Evidence based treatment recommendations for patients with RVO cannot be made because of the lack of adequate clinical trials. To compare the efficacy and safety of aspirin and of a low molecular weight heparin, parnaparin, in the treatment of RVO.

Materials and Methods: In a multicenter, randomized, double blind, controlled trial eligible patients with a delay between symptoms onset and objective diagnosis of less than 15 days were randomized to aspirin 100 mg/day for 3 months or to a fixed daily dose of parnaparin, 12.800 IU for 7 days followed by 6.400 IU for a total of 3 months. Primary end-point of the study was the incidence of functional worsening of the eye with RVO at 6 months, as assessed by fluorescein angiography, visual acuity, and visual field. Study end-points were adjudicated by an independent committee.

Results: Sixty-seven patients were enrolled in the study and 58 of them (28 treated with parnaparin, 30 with aspirin) were evaluable for the analysis. Baseline characteristics were well balanced between groups. Functional worsening was adjudicated in 20.7% of patients treated with parnaparin and in 59.4% of patients treated with ASA ($p = 0.002$). Recurrent RVO was diagnosed in 3 patients, all treated with ASA (p = n.s.). Bleeding rates were similar between the two groups.

Conclusions: Parnaparin appears to be more effective than aspirin in preventing functional worsening in patients with RVO. The results of this study need to be confirmed in a larger clinical trial.

Trial registration number: Clinical trials.gov NCT00732927.

Introduction

Retinal vein occlusion (RVO) is the second commonest retinal disease after diabetic retinopathy, and is a common cause of unilateral visual loss. It occurs with an estimated incidence of 0.53 to 1.6/1000 persons/year [1–3]. The clinical severity of RVO is related to the site and size of the thrombus. It is estimated that approximately 70% of patients with central retinal vein occlusion have a residual visual acuity of equal to or less than 1/10 [4].

The most common identified risk factors for RVO include systemic cardiovascular risk factors, such as hypertension [5,6], hyperlipidaemia [7], and diabetes mellitus [8–10], and local risk factors, such as chronic open-angle glaucoma [11,12]. An association between RVO and thrombophilia has also been reported [13,14].

☆ Presented at the Italian Society on Thrombosis and Haemostasis Meeting, Florence, Italy, Sunday, September 28th, 2008.

* Corresponding author. Department of Clinical Medicine, University of Insubria, Viale Borri 57, 21100 Varese – Italy. Tel.: +39 0332 278594; fax: +39 0332 393640.
E-mail address: agewal@yahoo.com (W. Ageno).

0049-3848/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.thromres.2009.05.007

There are two aims in the management of RVO: the identification of modifiable risk factors and their medical management and the recognition and management of sight-threatening complications. The management of the disease includes laser therapy [15–19] and the control of systemic associated diseases [20,21]. Many other treatments have been proposed but there is no evidence on their efficacy in modulating the outcome of branch or central RVO. There are currently no adequate clinical trials that have evaluated the efficacy and safety of antithrombotic agents in this setting. Previous reports have described the use of either systemic or loco-regional thrombolytics [22,23], warfarin [24], and either unfractionated or low molecular weight heparin [25,26]. However, most of the published studies have several limitations: absence of control groups, small sample sizes, and a high variability in the timing between symptoms onset and starting of treatment. The few randomized clinical trials evaluating ticlodipine and streptokinase showed a limited or no benefit of these medications [27]. Antiplatelet agents are frequently used in clinical practice. The most plausible rationale for their use is the common association between RVO and cardiovascular disease [28,29]. Anticoagulant drugs, either heparins or coumarins, are also used in this setting as they represent the first line therapy for the treatment of venous thromboembolism.

To address the lack of clinical trials in this area, and to specifically address the lack of evidence for current anticoagulant strategies, we have carried out a multicenter, randomized, double blind, double dummy, controlled clinical trial to compare the efficacy and safety of aspirin and of a low molecular weight heparin, parnaparin, in the treatment of RVO.

Materials and methods

The study was carried out in 6 Italian centres (Varese, Reggio Emilia, Perugia, Ferrara, Cuneo and Treviso). Consecutive patients with an objectively confirmed diagnosis of RVO were eligible. All patients underwent the measurement of visual acuity and of visual fields within 24 hours of the diagnosis of RVO and fluorescein angiography within 72 hours of the diagnosis of RVO.

Study population

Inclusion criteria were age between 18 and 85 years, a body weight of greater than 50 Kg, and a requirement that no more than 15 days had passed between symptomatic presentation, confirmation of RVO and entry into the study. The study was approved by the local ethics committees and all patients provided written informed consent according to Helsinki protocol. Exclusion criteria included ophthalmologic and general criteria. Ophthalmologic criteria were the following: modification of the optic media transparency that could compromise the evaluation of fluorescein angiography, such as cataract or corneal degeneration; history of major ocular surgery (with the exclusion of cataract extraction); previous RVO; other ocular conditions that, in the opinion of the investigator, could have affected macular edema or altered visual acuity during the course of the study. General exclusion criteria were the following: contraindications to the study drugs (e.g. major bleeding or neurosurgical procedures in the previous 3 months, serum creatinine levels of greater than 2.0 mg/dL, severe liver insufficiency, platelet count $<100{,}000\ mm^3$, known active peptic gastric ulcer), active malignancy, pregnancy, inability to attend for follow up or anticipated non-compliance, and ongoing treatment with aspirin or anticoagulant drugs at the time of RVO diagnosis.

Study treatment

Patients were randomized to receive a low molecular weight heparin, parnaparin (Alfa Wassermann S.p.A, Bologna, Italy), administered subcutaneously at a fixed daily dose of 6.400 IU bid for the first 7 days of treatment followed by a fixed daily dose of 6.400 IU qd from day 8 to day 90 and one daily tablet of placebo for 90 days, or to receive aspirin 100 mg daily for a total of 90 days and 2 subcutaneous injections of placebo for the first 7 days followed by a daily placebo injection from day 8 to day 90. The choice of a single fixed dose of parnaparin was made to simplify the design and the management of the study. The choice of reducing the dose of parnaparin after one week of treatment was entirely arbitrary and was made to improve the safety of our approach. Study drugs and placebo were provided by Alfa Wassermann, Bologna, Italy. Randomization was performed centrally in balanced blocks and was stratified for each participating center. The random allocation sequence was computer generated and was implemented by the use of numbered containers and the sequence was concealed until interventions were assigned.

Data collection

After enrolment, all patients underwent ophthalmologic evaluation and blood testing (complete blood count, INR, aPTT, liver and kidney function) at baseline, blood testing on day 7 (complete blood count, INR, aPTT, liver and kidney function), ophthalmologic evaluation and blood testing (platelet count, INR, aPTT) on day 30, ophthalmologic evaluation, and blood testing on day 90 (complete blood count, liver and kidney function), and ophthalmologic evaluation on day 180 and 360.

Ophthalmologic evaluation included: 1) the examination of the best corrected visual acuity (BCVA) expressed on decimal scale; 2) intraocular pressure measurement; 3) relative afferent pupillary defect (RAPD); 4) slit-lamp undilated and dilated examination, including anterior segment evaluation, gonioscopy, and fundus examination; 5) fluorescein angiography and 6) visual field.

Fluorescein angiography was performed with digital equipments on the 7-standard field [30]. For each patient, the presence of the following parameters was documented: intraretinal, pre-retinal and vitreous haemorrhages, venous dilatation, retinal oedema, macular oedema, retinal ischemia, soft and hard exudates, optic disc oedema, and neovascularisation of the optic disc or elsewhere. Each parameter was evaluated and scored according to standard classification [31,32]. The images were sent to a centralized independent reading center in Bologna, Italy.

Automated visual perimetry was performed by Humphrey (Humphrey Systems, Dublin, California, USA) 24-2 full threshold strategy and mean deviation (MD) and pattern standard deviation (PSD) were analyzed for each examination.

Study end-points

Primary end-point of the study was the incidence of functional worsening of the eye with RVO at 6 months. Functional worsening was blindly adjudicated by an independent committee and was defined based on the evaluation of three tests: fluorescein angiography, visual acuity, and visual field. Evaluation of efficacy based on fluorescein angiography was defined by the comparison between angiograms performed at baseline and after 180 days. If this latter was not available, the fluorescein angiographies performed at 90 days were considered. In the absence of both tests, the fluorescein angiographies performed at 360 days were considered.

Fluorescein angiography results were defined as improved, unchanged or worsened according to the Branch Vein Occlusion Study and Central Vein Occlusion Study standards [16,17,31]. BCVA worsening was defined as the reduction of visual acuity of at least 1/10 and the worsening of visual field was based on the difference of values of MD and PSD. The primary end-point of functional worsening was adjudicated in the concomitant presence of a worsened fluorescein angiography (defined by the comparison between the first and second test), a worsened BCVA, and a worsened visual field. When the 3 parameters were discordant, or when BCVA and/or visual field were