

Antithrombotic therapy in subjects with hereditary hemorrhagic telangiectasia: update of prospective data from a Multidisciplinary group

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Abstract

Subjects with **Hereditary Hemorrhagic Telangiectasia (HHT)** may develop medical conditions that require antithrombotic therapy (AT). However, safety of AT is uncertain in these patients.

A **prospective study** is currently ongoing at the HHT center of the 'Fondazione Policlinico Universitario A. Gemelli IRCCS' to evaluate safety of AT in HHT patients. The **primary outcome** is the **number of bleeding events** occurred during AT classified according to the criteria of the International Society on Thrombosis and Hemostasis (ISTH). **Another primary outcome is worsening of epistaxis**, assessed using the Epistaxis Severity Score (ESS). An additional outcome is change in hemoglobin levels after initiation of AT.

Here, we present an update of an interim analysis conducted on 15 HHT patients who have been enrolled so far. After a mean follow-up of 8.9±2.4 months, we reported **one clinically-relevant non major bleeding** (hematuria), but **no major bleedings and no minor bleedings except for epistaxis** were recorded. Worsening of epistaxis was documented in only one patient, but did not require discontinuation of AT. There were **no significant changes in the mean ESS** measured during and before the initiation of AT. Also, there were **no significant changes in mean hemoglobin levels** measured during AT and before the initiation of AT. These are the first prospective data on safety of AT in HHT patients. Our interim analysis suggests that, when prescribed by experienced physicians in a multidisciplinary setting, **AT is well tolerated** by HHT patients.

Introduction

Hereditary Hemorrhagic Telangiectasia (HHT), also known as Osler-Weber-Rendu syndrome, is a rare autosomal dominant disorder associated with **abnormal blood vessel formation** [1]. Despite the presence of an overwhelming bleeding propensity, **thrombotic conditions are relatively common** in patients with HHT. When HHT patients develop one of these medical conditions, clinicians are often reluctant to prescribe antithrombotic therapy (AT), as HHT is generally considered a contraindication to AT. Whatever decision is made, it can only be based on anecdotal evidence, since no prospective studies have been performed to evaluate efficacy and safety of AT in HHT patients and the few data available in the literature only consist of case reports and retrospective analyses [2-5]. **The purpose of our study was to determine in an objective manner number and severity of hemorrhagic complications in HHT patients treated with AT.**

Methods and materials

We performed a prospective study by enrolling subjects with a definite diagnosis of HHT who receive AT prescription by one of the physicians of our HHT Centre.

The **primary outcome** is the number of hemorrhagic events occurring during AT. Events are classified in major bleedings, clinically relevant non-major (CRNM) bleedings and minor bleedings with the exception of epistaxis, according to the criteria of the ISTH [6-7].

Another **primary outcome** is the worsening of epistaxis upon initiation of AT, using the internationally accepted ESS [8].

An **additional outcome** is change in hemoglobin levels, measured after at least 3 months of AT, compared to hemoglobin levels measured at enrolment.

Follow-up visits are scheduled 14 days, 1 month and 3 months after enrolment, and every 3 months thereafter.

Table 1. Baseline characteristics of patients

Mean age (years ± SD)	63.9 ± 13.4
Gender (male/female ratio)	8/4
Presence of epistaxis (N)	12/12
Presence of mucocutaneous telangiectases (N)	11/12
Family history of HHT (N)	11/12
Presence of pulmonary AVM (N)	5/12
Presence of hepatic AVM (N)	1/12
Presence of cerebral AVM (N)	0/12
Previous history of gastrointestinal bleeding (N)	5/12

Table 2. Characteristics of the AT courses

Number of AT courses / number of patients	15/15
Antiplatelet therapy (N)	7/15
Anticoagulant therapy (N)	8/15
Atrial Fibrillation (N)	5/15
Venous thromboembolism (N)	2/15
Stroke/transient ischemic attack (N)	5/15
Primary cardiovascular prevention (N)	1/15
Coronary artery disease (N)	2/15
Mean duration of follow-up (months)	8.9 ± 2.4

Results

Here, we present an update of an interim analysis conducted on **15 HHT patients** (Tab. 1) who have been enrolled so far: **7 in antiplatelet therapy and 8 in anticoagulant therapy** (Tab. 2). After a mean follow-up of **8.9±2.4 months**, we reported **one CRNM bleeding** (hematuria), but **no major bleedings and no minor bleedings** except for epistaxis were recorded. **Worsening of epistaxis was documented in only one patient**, but did not require discontinuation of AT. There were **no significant changes in the mean ESS** (3.2±2.6 vs 3.9±2.8 respectively, 95% CI -3.2-1.5, p=0.2988), as well as **in mean hemoglobin levels** measured during AT and before the initiation of AT (11.5±2.5 vs 11.4±2.9 g/dL, 95% CI -1.5-1.5, p=0.9609) (Tab.3; Fig. 1).

Table 3. Safety outcomes

Major bleedings (n/total)	1/15
CRNM bleedings (n/total)	1/15
Minor bleedings different from epistaxis (n/total)	0/15
Worsening of epistaxis (n/total)	1/15
ESS at enrolment vs during AT (mean ± SD)	3.2±2.6 vs 3.9±2.8, 95% CI -3.2-1.5, p=0.2988
Mean Hb at enrolment vs during AT (g/dl ± SD)	11.5±2.5 vs 11.4±2.9 g/dL, 95% CI -1.5-1.5, p=0.9609
Discontinuation of AT (n/total)	0/15

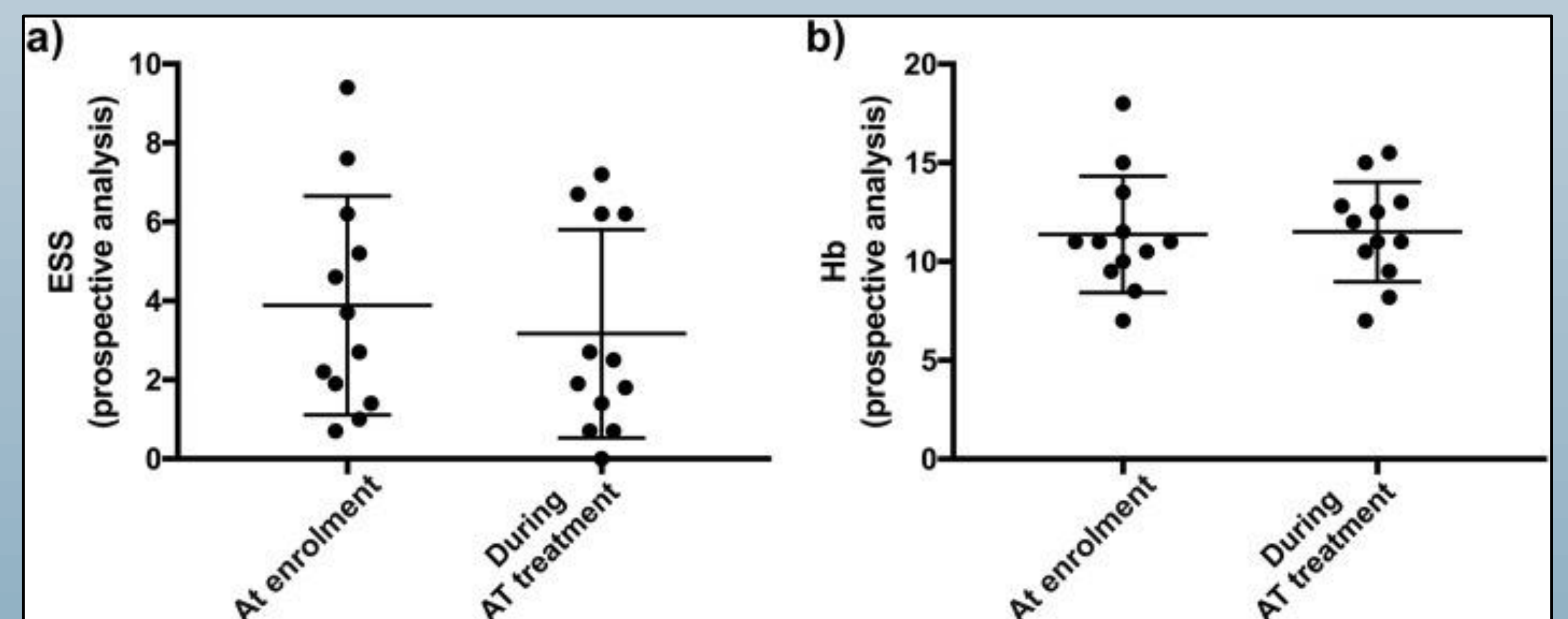


Figure 1. Impact of antithrombotic therapy (AT) on the severity of epistaxis and hemoglobin (Hb) levels. The severity of epistaxis, assessed using the Epistaxis Severity Score (ESS), was similar at enrolment (before starting AT) and after at least 3 months of AT (a). Hb levels were similar at enrolment and after at least 3 months of AT (b).

Discussion

This is the **first prospective study** evaluating the safety of AT in subjects with HHT. Our interim results indicate that, when prescribed by experienced physicians in the context of a multidisciplinary working group, AT is well tolerated by HHT patients [9]. A strength of our study is that all AT prescriptions were personally made by physicians with experience in the field of thrombosis, cardiovascular diseases and AT, thus warranting proper prescriptions for proper indications. Finally, the prospective nature of our study allowed us to assess in an objective manner not only the number, but also the severity of bleeding, with the possibility to distinguish between major, CRNM and minor bleedings, as established by the ISTH. Also changes in the severity of epistaxis, hemoglobin levels and need of blood transfusion were objectively evaluated.

Conclusion

In conclusion, the interim results of our prospective study provide preliminary evidence that HHT patients tolerate AT, when it is prescribed by experienced physicians in the context of a multidisciplinary setting. We call for a sustained multicenter research effort to further investigate this issue and reduce the burden of AT and its consequences in patients with HHT.

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