厚生労働科学研究費補助金（難治性疾患政策研究事業）
分担研究報告書

慢性血栓塞栓性肺高血圧症に関するレジストリ研究

研究分担者　阿部弘太郎
九州大学大学病院 循環器内科　助教

研究要旨

慢性血栓塞栓性肺高血圧症（CTEPH）は肺動脈内に器質化血栓が形成され肺血流が障害される疾患（国内患者 3000 人の希少疾患）である。保存的加療のみでは、肺動脈圧上昇による右心不全を発症し、5 年生存率 40%と極めて予後不良である。

主要な CTEPH の診療ガイドラインでは抗凝固療法、外科的血栓摘除術、経皮的バルーン肺動脈形成術、リオシグアトがクラス Ⅰ の治療として推奨されているが、いずれもエビデンスレベルが低く、ガイドラインであっても薄氷の EBM のもとに成り立っている。

CTEPH は希少疾患であるため、大規模な比較対照試験の実施は困難であり、リアルワールドデータを活用したエビデンス創出により、強固な根拠にもとづく治療法の確立が急務である。

A. 研究目的

病本研究の目的は CTEPH に関する全国規模のレジストリを構築して治療法に係るエビデンスを創出することである。

B. 研究方法

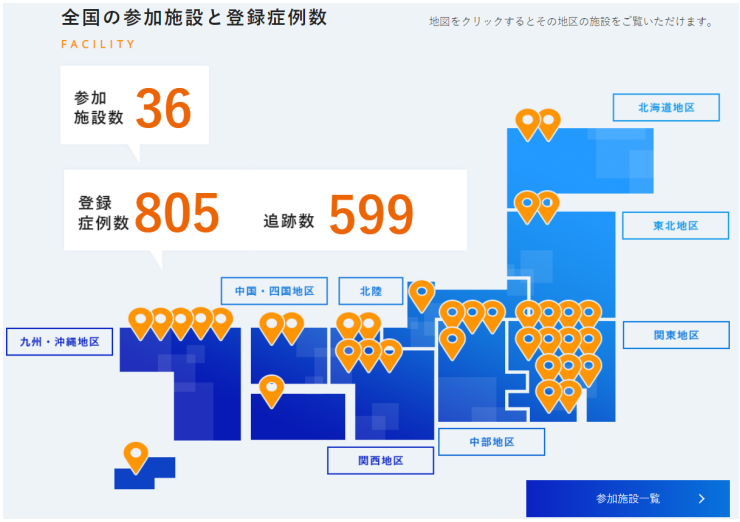
レジストリ構築は日本肺高血圧・肺循環学会公認の Electric date collection: EDC システム（日本肺高血圧レジストリ：JAPHR）上に追加する形で構築し、web 経由で多施設から収集する。

C. 研究結果

我々は 2018 年 AMED 難治性疾患実用化促進事業の支援を得て、約 800 名（2020 年 12 月時点）の CTEPH 患者の世界最大規模の CTEPH レジストリ（CTEPH AC レジストリ）を構築した。

D. 考察

今年度中に 1 年フォローアップを一斉に入力予定である。来年度以降も長期フォローアップ世界最大規模のプロスペクティブな CTEPH レジストリから長期経過を含めた臨床像および多様化した治療内容と治療反応性、予後が明らかにする。診断基準や診療ガイドライン作成・改定に資する高い質のエビデンスの創出が見込まれる。



CTEPH AC Registry ホームページより (URL: cteph-registry.jp) (2020 年 12 月 10 日)

E. 結論

全国規模の多施設登録により慢性血栓塞栓性肺高血圧症の長期の経過を前向きに解析したもので、抗凝固療法、外科的血栓摘除術、経皮的バルーン肺動脈形成術、肺血管拡張薬の治療すべてを集約したレジストリにより、それぞれの治療の有効性が明らかとなる。

F. 研究発表

1. 論文

Hosokawa K, Abe K, Tsutsui H. Use of direct oral anticoagulants prevents increase in pulmonary vascular resistance and incidence of clinical worsening in patients with chronic thromboembolic pulmonary hypertension. Thromb Res 2019;180:43–46.

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Letter to the Editors-in-Chief

Use of direct oral anticoagulants prevents increase in pulmonary vascular resistance and incidence of clinical worsening in patients with chronic thromboembolic pulmonary hypertension

1. Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) requires lifelong anticoagulation therapy to prevent thrombotic progression of the disease. Major guidelines have recommended the use of vitamin K antagonist (VKA) as an anticoagulant [1] [2]. On the other hand, there are few reports evaluating the safety or effectiveness of direct oral anticoagulants (DOACs) for the treatment of CTEPH. In contrast to venous thromboembolism (VTE), in situ thrombus formation in the pulmonary artery and/or abnormal coagulation and fibrinolytic conditions have also been suggested as possible pathogenetic mechanisms of CTEPH [3–5]. Therefore, it remains controversial whether DOACs would have a similar safety and efficacy as VKA in patients with CTEPH.

The purpose of this study was to clarify the safety and effectiveness of DOACs as anticoagulants in CTEPH patients. We evaluated the impact of DOACs on change in pulmonary vascular resistance (PVR), D-dimer level, and incidence of clinical worsening of CTEPH and clinically relevant bleeding.

2. Methods

2.1. Study design and patient selection

This retrospective observational study was conducted based on the medical records at Kyushu University Hospital. The protocol was approved by the Institutional Ethics Review Board (29-526). In our clinical practice, we continue DOACs if the patient had been administered with DOACs at the onset of VTE. In addition, if the patient had problems with VKA (e.g. bleeding concerns or labile INR), treatment was switched to DOACs depending on the physician's judgement. We extracted patient characteristics, type of anticoagulant, CTEPH/VTE risk and bleeding risk from the medical records. The change in PVR, D-dimer level, clinical worsening of CTEPH, and clinically relevant bleeding were collected as outcome measures.

2.2. Definition of outcome measures

Two PVR measurements satisfying the following criteria were extracted. PVR was measured by right heart catheterization:

1. Two PVR measurements at least 90 days apart without specific interventions (pulmonary endarterectomy, balloon pulmonary angioplasty, and/or changing/starting/discontinuing pulmonary vasodilators) between them. If there are three or more PVR measurements in a patient, two PVR measurements with the longest interval was adopted.

D-dimer level for spontaneous monitoring on regular outpatient visits was measured by latex agglutination immunoassay.

Clinical worsening in CTEPH was defined as a composite outcome of the following component endpoints using modified criteria described in a previous CHEST-1 trial [6]:

1. Death from any cause.
2. Lung transplantation.
3. Worsening pulmonary hypertension that resulted in hospitalization, start of new specific pulmonary hypertension treatment, rescue pulmonary endarterectomy or balloon pulmonary angioplasty (BPA).

Clinically relevant bleeding was defined as major bleeding under criteria described by the International Society on Thrombosis and Haemostasis or clinically relevant non-major bleeding, which was defined in Hokusai-VTE trial [7].

2.3. Statistical analysis

Descriptive statistics for categorical variables were reported as frequency and percentage. Continuous variables were reported as mean ± standard deviation. A p value < 0.05 indicated statistical significance. A chi-square test and a t-test were used for categorical and continuous variables, respectively. Statistical tests were conducted using Microsoft Office Excel 2016 (Microsoft Corp., WA, USA).

3. Results

3.1. Patient baseline characteristics

Eighty-four CTEPH patients were classified into two groups, those treated with VKA and those treated with DOACs. There were 38 patients in the VKA group and 46 in the DOACs group. Thirteen out of 46 patients in the DOACs group were subjects who were changed from VKA to DOACs due to labile INR and/or bleeding concern. Table 1 shows the patients' background. Longer medical records were available in the VKA group than in the DOACs group. The DOACs group underwent more BPAs reflecting recent therapeutic trends and resultantly had lower pulmonary arterial pressure than the VKA group. Common risk factors for CTEPH/VTE and bleeding were not significantly different between those groups.

3.2. Efficacy outcome measures

3.2.1. Change in PVR

The full analysis set for PVR evaluation included 21 patients in the VKA group and 21 in the DOACs group. Baseline PVR was higher in the

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