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

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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 4000 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、肺血管拡張薬がクラス 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

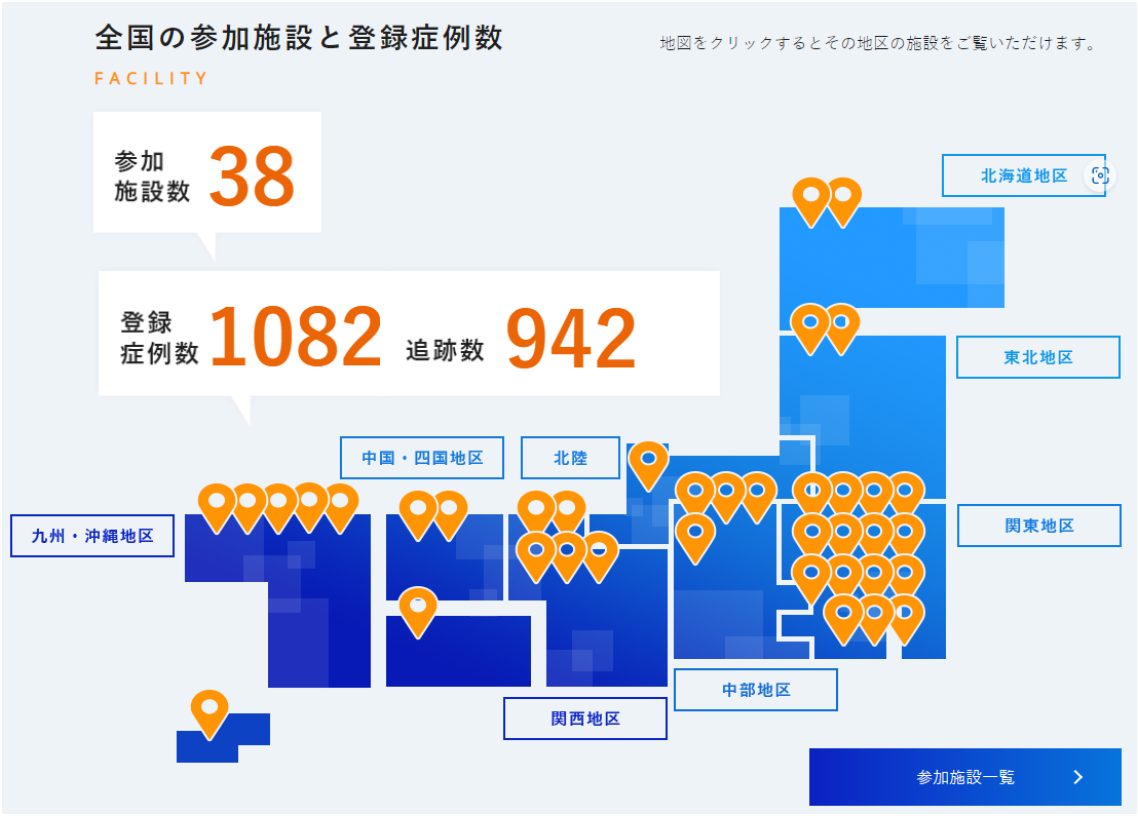
本研究の目的は CTEPH に関する全国規模のレジストリを構築して治療法に係るエビデンスを創出することである。

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、登録数 1,000 名を超える世界最大規模の CTEPH レジストリ（CTEPH AC レジストリ）を構築した。



CTEPH AC Registry ホームページより（URL: cteph-registry.jp) (2022 年 11 月 1 日)

D.考察

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。

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

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Efficacy and safety of edoxaban in patients with chronic thromboembolic pulmonary hypertension: protocol for a multicentre, randomised, warfarin-controlled, parallel group trial - KABUKI trial

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ABSTRACT

Introduction Chronic thromboembolic pulmonary hypertension (CTEPH) is a complication of prior pulmonary thromboembolism (PE), caused by incomplete clot dissolution after PE. In patients with CTEPH, lifelong anticoagulation is mandatory to prevent recurrence of PE and secondary in situ thrombus formation. Warfarin, a vitamin K antagonist, is commonly used for anticoagulation in CTEPH based on historical experience and evidence. The anticoagulant activity of warfarin is affected by food and drug interactions, requiring regular monitoring of prothrombin time. The lability of anticoagulant effect often results in haemorrhagic and thromboembolic complications. Thus, lifelong warfarin is a handicap in terms of safety and convenience. Currently, the use of direct oral anticoagulants (DOACs) in CTEPH has increased with the advent of four DOACs. The safety of DOACs is superior to warfarin, with less intracranial bleeding in patients with non-valvular atrial fibrillation and venous thromboembolism. Edoxaban, the latest DOAC, also has proven efficacy and safety for those diseases in two large clinical trials; the ENGAGE-AF trial and HOKUSAI-VTE trial. The present trial seeks to evaluate whether edoxaban is non-inferior to warfarin in preventing worsening of CTEPH.

Methods and analysis The KABUKI trial (is an investigator-initiated, multicentre, phase 3, randomised, single-blind, parallel-group, warfarin-controlled, non-inferiority trial to evaluate the efficacy and safety of edoxaban versus warfarin (vitamin K Antagonist) in subjects with chronic thromBoembolic pUlmonary hypertension taking warfarin (vitamin K antagonIst) at baseline) is designed to prove the non-inferiority of edoxaban to warfarin in terms of efficacy and safety in patients with CTEPH.

Ethics and dissemination This study is approved by the Institutional Review Board of each participating institution. The findings will be published in a peer-reviewed journal, including positive, negative and inconclusive results.

Trial registration number NCT04730037.

Strengths and limitations of this study

⇒ This study is the first multicentre randomised controlled trial comparing the efficacy and safety of edoxaban and warfarin in patient with chronic thromboembolic pulmonary hypertension (CTEPH).
⇒ The study is designed to prove non-inferiority of edoxaban to warfarin by evaluating the changes in catheter-based pulmonary vascular resistance in edoxaban and warfarin arms over 12 months.
⇒ The secondary efficacy and safety endpoints are the incidence of clinical worsening of CTEPH and the incidence of major bleeding and/or clinically relevant non-major bleeding.
⇒ The trial is conducted in accordance with International Conference on Harmonisation Good Clinical Practice guidelines.
⇒ A limitation of this study is small sample size.

Protocol version This paper was written per the study protocol V.4.0, dated 29 January 2021.

INTRODUCTION

The KABUKI trial is an investigator-initiated, multicentre, phase 3, randomised, single-blind, double-dummy, parallel-group study to evaluate the efficacy and safety of edoxaban versus warfarin (vitamin **K A**ntagonist) in subjects with chronic throm**B**oembolic p**U**lmonary hypertension taking warfarin (vitamin **K** antagon**I**st) at baseline. This trial is designed to prove the non-inferiority of edoxaban to warfarin in terms of efficacy and safety in patients with chronic thromboembolic pulmonary hypertension (CTEPH). CTEPH is a complication of prior pulmonary