Monoclonal antibody BTT1023 targeting vascular adhesion protein 1 for treating primary sclerosing cholangitis: BUTEO single-arm Phase II trial

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Declared competing interests of authors: The industry partner Acorda Therapeutics, Inc. (Ardsley, NY, USA) (formerly known as Biotie Therapies Ltd, Helsinki, Finland), funded the study drug and magnetic resonance imaging. David Smith is a company representative of Acorda Therapeutics, Inc., and was involved in the preclinical and clinical development of the investigational medicinal product and is an expert on vascular adhesion protein 1 (VAP-1) function. David Smith reports personal fees from Biotie Therapies Ltd (now part of Acorda Therapeutics, Inc.) outside the submitted work. Christopher Weston reports grants from the Medical Research Council (London, UK), the National Institute for Health Research Efficacy and Mechanism Evaluation programme and Biotie Therapies Ltd during the conduct of the study, and grants from C.H. Boehringer Sohn AG & Co. KG (Ingelheim am Rhein, Germany), Novo Nordisk A/S (Bagsværd, Denmark) and Pharmaxis Ltd (Frenchs Forest, NSW, Australia) outside the submitted work. In addition, Christopher Weston has a patent, Use of VAP-1 inhibitors for treating fibrotic conditions (WO2011029996A1), issued. Gideon Hirschfield reports consultancy from Acorda Therapeutics, Inc., CymaBay Therapeutics (Newark, CA, USA), GlaxoSmithKline plc (Brentford, UK), GENFIT (Loos, France), Intercept Pharmaceuticals, Inc. (New York, NY, USA), F. Hoffmann-La Roche Ltd (Basel, Switzerland), Pliant Therapeutics (South San Francisco, CA, USA) and Mirum Pharmaceuticals (Foster City, CA, USA) outside the submitted work.

Published March 2022
DOI: 10.3310/ZPNF4670

Scientific summary

BUTEO single-arm phase II trial

Efficacy and Mechanism Evaluation 2022; Vol. 9: No. 1
DOI: 10.3310/ZPNF4670

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Scientific summary

Background

Primary sclerosing cholangitis (PSC) is a progressive inflammatory biliary and liver disease that is characterised by progressive biliary structuring and liver fibrosis. There is a high unmet need for new therapies. PSC has a population incidence of 1.3 per 100,000 people annually, with a prevalence of 16.2 per 100,000 people. It affects both men and women, with a median age at presentation of 41 years, and is frequently associated with inflammatory bowel disease. More than 50% of patients require liver transplantation within 10–15 years of symptomatic presentation, reflecting an absence of medical therapies. In clinical practice, risk of disease progression is determined in a multitude of ways. Bile duct inflammation and obstruction is frequently reflected by elevated serum activity of alkaline phosphatase (ALP). Although the correlation between ALP values and disease severity is complicated, this marker remains a frequent surrogate of disease activity used in determining the efficacy of interventions.

The aetiology of PSC remains debated, and collectively it is believed that a combination of genetic and environmental risk factors contribute. Mechanistic themes for disease initiation and progression span aberrant immune regulation/autoimmunity, changes in biliary tree function and bile acid metabolism, the microbiome having an impact on mucosal immunology of the colon and bile duct, as well as the consequences of progressive fibrogenic and pre-neoplastic pathways in the biliary tree, liver and colon. In particular, the close association with colitis has generated several hypotheses linking inflammation in the gut and liver, one of which centres on aberrant lymphocyte homing. Ordinarily, the gut and liver harbour distinct endothelial phenotypes, which provide a mechanism to compartmentalise tissue-specific lymphocyte recruitment. In the gut, expression of mucosal addressin cell adhesion molecule 1 on mucosal endothelium is responsible for recruiting intestinal lymphocytes that are imprinted with tissue-specific tropism, specifically those that express the mucosal addressin cell adhesion molecule 1 receptor, $\alpha4\beta7$. Under normal circumstances, expression of mucosal addressin cell adhesion molecule 1 is restricted to the gut, but in PSC can also be detected on hepatic endothelium, where it promotes recruitment of mucosal $\alpha4\beta7^{+}$ T cells to the liver. These T cells are predominantly effector memory lymphocytes, which on reactivation result in a T-cell-rich portal infiltrate within the liver and an iterative inflammatory response.

Vascular adhesion protein 1 (VAP-1) is a 170-kDa homodimeric type 2 transmembrane sialoglycoprotein with a short cytoplasmic tail of no known signal sequence, a single transmembrane segment and a large extracellular domain. VAP-1 is constitutively expressed on human hepatic endothelium and supports lymphocyte adhesion and transendothelial migration. Cloning of VAP-1 revealed it to be a copper-dependent semicarbazide-sensitive amine oxidase (SSAO) that catalyses the oxidative deamination of exogenous and endogenous primary amines, resulting in the generation of aldehyde, ammonia and hydrogen peroxide (H_2O_2). These products activate nuclear factor kappa B (NF-κB)-dependent chemokine secretion and adhesion molecule expression in liver endothelium and may initiate and propagate oxidative stress following the conversion of H_2O_2 to hydroxyl free radicals. A soluble form of VAP-1 accounts for nearly all of the circulating amine oxidase activity in humans.

The progression of PSC to scarring, cirrhosis and hepatobiliary cancer is driven by a chronic inflammatory response and immune cell-mediated destruction of bile ducts. Prior studies implicate VAP-1 in the inflammation that drives fibrogenesis in liver disease. VAP-1 also acts as an adhesion receptor to support leucocyte recruitment in liver inflammation, a function that is critical in the formation of fibrosis in animal models. Therefore, inhibition of VAP-1 is predicted to have an impact on both inflammation and fibrosis. Treatment with an antibody against VAP-1 prevents fibrosis in murine models of liver injury. Data also

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show that there are particularly high levels of circulating serum vascular adhesion protein 1 (sVAP-1) in patients with PSC, and there is a strong correlation between sVAP-1/SSAO activity in serum and histological fibrosis scores in patients.

Timolumab (BTT1023) is a fully human monoclonal anti-VAP-1 antibody that blocks the adhesion function of VAP-1, thereby diminishing leucocyte entry into sites of tissue inflammation. In vivo, blocking VAP-1 function with an anti-mouse anti-VAP-1 antibody significantly alleviates inflammation in mouse models of arthritis and liver fibrosis. BTT1023 appears to be safe and well tolerated in humans. BTT1023 has been given in doses of up to 8 mg/kg in patients with rheumatoid arthritis and psoriasis after oral premedication (with cetirizine and ibuprofen), and also appears safe and well tolerated in repeated intravenous (i.v.) dosing. No cytokine release syndrome has been reported.

BTT1023 is produced in a Chinese hamster ovary cell culture and purified with appropriate methods, including specific viral inactivation and removal procedures.

Objectives

In this study, we sought to test the hypothesis that inhibiting VAP-1 with a neutralising antibody (BTT1023) would reverse or delay fibrogenesis in patients with PSC. Our trial design, incorporating a dose-confirmatory stage and a safety stage (based on the traditional 3 + 3 design), was followed by a Phase II Simon's two-stage design that aimed to determine a safe and well-tolerated dose of BTT1023 and the efficacy of this treatment in a new disease group.

Dose-confirmatory stage

The objective of the dose-confirmatory stage was to determine a dose of BTT1023 that provides an acceptable level of pharmacokinetic (PK) activity and was deemed to be safe, meeting the acceptable dose-limiting toxicity (DLT) level.

This was to be achieved by evaluating:

- the number of DLTs per dose level of BTT1023
- PK data per dose level of BTT1023.

Phase II

Primary objectives

- To determine the activity of the anti-VAP-1 antibody BTT1023 in patients with PSC as measured by a decrease in ALP activity (i.e. the primary end point), with secondary end points to include various measures of liver injury and fibrosis.
- To evaluate the safety, effective dosage and tolerability of BTT1023 in patients with PSC.

Secondary objectives

- To determine the mechanisms of action of BTT1023 through in vivo assessment of VAP-1/SSAO enzyme activity and immune cell function.
- To evaluate the potential of a novel magnetic resonance imaging-based assessment of liver fibrosis and biliary strictures for assessing therapeutic response in patients with PSC.
- To assess the use of sVAP-1/SSAO as a biomarker to monitor disease progression in patients with PSC.

Methods

Six UK academic hospital centres were involved, with four actively recruiting. (Those centres that were actively recruiting were based in Birmingham, Nottingham, Oxford and London, and the centres that failed to recruit were based in Newcastle and Cambridge.)

Informed consent was obtained by appropriately trained members of the research team at each site. The baseline measurements were recorded at the pre-infusion visit 3, on day 1 of treatment and on day 99 (i.e. 21 days following the last infusion). During screening, patients had routine blood screens and were tested for other non-invasive markers of liver fibrosis. These tests were repeated during treatment and in the follow-up period to assess for any change. During all seven treatment visits, patients received premedication [10 mg of cetirizine + 400 mg of ibuprofen orally (in the absence of any contraindications) plus 100 mg of hydrocortisone intravenously, 1–2 hours pre infusion (the last for the first three doses only)]. The first infusion was given over 2 hours, with a 4-hour monitoring period post infusion. Provided that no adverse reactions were seen, the infusion time dropped to 1 hour with an initial 3-hour observation period (for the second dose) and then down to 2 hours' monitoring post infusion (for all subsequent doses). Safety investigations were completed pre and post infusion, and included samples being taken for haematological/biochemical analysis, electrocardiography, clinical assessment and physical examination. An aliquot (0.5–1.0 ml) of the BTT1023 infusion solution was taken at the end of every infusion and refrigerated. These samples could be used for analysis of BTT1023 concentration if anomalies in PK data that could be due to errors in BTT1023 preparation were observed.

The trial began with the recruitment of six patients all receiving the starting dose of 8 mg/kg of BTT1023. Recruitment was paused while awaiting the results of trough blood serum levels of circulating BTT1023 at visit 7 (i.e. day 50) from all six patients and until the DLT reporting period was completed for each patient [at visit 10 (i.e. day 99)]. The trial was to be stopped at any stage if patient safety was compromised. Once a confirmed dose had been established, the trial was expanded until a total of 37 patients had received treatment with the confirmed dose, including those patients who have previously received this dose during the confirmatory period. Those patients not receiving the confirmed dose were not included in the final evaluation.

The two-stage design incorporated an interim analysis of the accumulating data after 18 patients had received the trial treatment. At this point, the design required that at least 3 of the 18 patients had a successful response (i.e. a reduction in ALP activity of ≥ 25%) to allow the trial to continue. If the stage 1 criterion was not met, and fewer than three evaluable patients had a successful response, the trial was to stop early. However, if the criterion was met, then further patient recruitment was to continue until 37 evaluable patients were recruited. The final design required at least 9 of 37 patients to have a successful response to conclude that the trial treatment successfully met the trial's primary outcome.

A response was considered to be a reduction in inflammation, indicated by a reduction in serum ALP activity of ≥ 25% (a comparison of measured ALP from baseline to day 99).

Results

Toxicity of the treatment was indicated if a patient experienced a DLT, as defined in the trial protocol. It was concluded that no DLTs were experienced during the dose-confirmatory period. The dose-confirmatory stage of the trial showed that the dose was well tolerated.

In accordance with the Simon's two-stage design of the trial, there needed to be at least three successful, out of 18 evaluable, responses to BTT1023 at the interim assessment to continue the trial onto stage 2. Only 2 of the 18 evaluable patients (11.11%) achieved a decrease and, therefore, the trial did not continue after the interim analysis.

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Discussion

It is clear that this study is limited in its design. The limitations were well recognised at the outset and relate, in large part, to the defined budget with which to test this new agent. In the absence of an unlimited opportunity to test a new agent in large numbers of patients and over a prolonged period, it was necessary to aim to see efficacy in a small cohort over a short period of time. Given the absence of any proven biochemical surrogate of disease activity in PSC, in keeping with multiple prior trials in PSC over the last 20 years, ALP activity was chosen as an end point. This is an inherently difficult end point and well known by those working in the field to be challenging.

Trial registration

This trial is registered as ISRCTN11233255, EudraCT 2014-002393-37 and NCT02239211.

Funding

This project was funded by the Efficacy and Mechanism Evaluation programme, a Medical Research Council and National Institute for Health Research (NIHR) partnership. This will be published in full in *Efficacy and Mechanism Evaluation*; Vol. 9, No. 1. See the NIHR Journals Library website for further project information.

Efficacy and Mechanism Evaluation

ISSN 2050-4365 (Print)

ISSN 2050-4373 (Online)

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The EME programme is funded by the Medical Research Council (MRC) and the National Institute for Health Research (NIHR), with contributions from the Chief Scientist Office (CSO) in Scotland and National Institute for Social Care and Health Research (NISCHR) in Wales and the Health and Social Care Research and Development (HSC R&D), Public Health Agency in Northern Ireland.

This report

The research reported in this issue of the journal was funded by the EME programme as project number 12/165/31. The contractual start date was in January 2015. The final report began editorial review in September 2020 and was accepted for publication in July 2021. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The EME editors and production house have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the final report document. However, they do not accept liability for damages or losses arising from material published in this report.

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