National Institute for Health Research

NIHR Innovation Observatory
Evidence Briefing: February 2018

Timolumab for primary sclerosing cholangitis

NIHRIO (HSRIC) ID: 11549 NICE ID: 9623

LAY SUMMARY

Primary sclerosing cholangitis (PSC) is an uncommon chronic liver disease. In PSC the bile ducts (small tubes which allow bile to flow from the liver to the small intestine where it helps with digestion) become inflamed and scarred causing them to narrow and block. This causes bile to build up in the liver which slowly damages and scars the liver. The cause of PSC is unknown but potential causes may originate from genetics, immune system problems and bacteria or viruses. The main symptoms of PSC include itching, tiredness and yellowing of the skin and eyes. There is no cure for PSC and there are few treatments available. This means many people with PSC will require a liver transplant.

Timolumab is currently being developed to treat PSC. Timolumab is given by injection into the vein which blocks a molecule called VAP-1 from working. VAP-1 helps immune cells enter areas of inflammation (such as the bile ducts in PSC) where they can further contribute to inflammation. By blocking this process, timolumab has the potential to prevent some of the inflammation in PSC and slow the progress of the disease. Therefore if licensed, timolumab will offer an additional treatment option for patients with PSC who currently have few effective therapies available.

This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.

TARGET GROUP

Primary sclerosing cholangitis (PSC)

TECHNOLOGY

DESCRIPTION

Timolumab (BTT-1023; SI-3106; SI-636) is a fully human, monoclonal, anti-vascular adhesion protein-1 (VAP-1) antibody which works by blocking the adhesion function of VAP-1 which diminishes leucocyte entry to sites of inflammation. In primary sclerosing cholangitis (PSC), the disease progression (to liver scaring, cirrhosis and hepatobiliary cancer) is driven by a chronic inflammatory response and immune cell mediated destruction of the bile ducts. Timolumab may have the potential to impact inflammation and fibrosis.[1]

In the phase II clinical trial (NCT02239211), timolumab is administered by intravenous (IV) infusion at 8mg/kg over 1-2 hours every 14 days for a total of 7 infusions.[2]

Timolumab does not currently have Marketing Authorisation in the EU for any indication.

INNOVATION and/or ADVANTAGES

If licensed, timolumab will offer an additional treatment option for patients with PSC who currently have few effective therapies available.[7, 8] Through its mechanism of action, timolumab has the potential to reduce the inflammation and fibrosis that leads to destruction of the bile ducts in PSC and therefore slow the progression of disease.[1]

DEVELOPER

Acorda Therapeutics

REGULATORY INFORMATION/ MARKETING PLANS

Timolumab was awarded Orphan Drug status for PSC by the EMA in March 2015 and by the FDA in August 2016.[3, 4]

PATIENT GROUP

BACKGROUND

PSC is an uncommon, chronic cholestatic liver disease characterised by the inflammation and fibrosis of the bile ducts. This can result in the ducts becoming blocked, causing bile to build up in the liver which damages liver cells. This in turn causes progressive scarring which spreads through the liver which can cause cirrhosis and end-stage liver disease and failure. The cause of PSC is unknown but genetics, immunological mechanisms, bacteria and viruses have all been associated with the development of the disease. PSC is also linked to inflammatory bowel disease with around 75% of people with PSC having coexistent ulcerative colitis.[5, 8]

The main symptoms of PSC are itching, fatigue and yellowing of the skin and whites of eyes. Infections in the bile ducts can also cause chills and fever. As PSC develops slowly, a person can have the disease for years without experiencing symptoms.[6] PSC affects males and females at a ratio of 2:1. The mean age of diagnosis for PSC is 40 years.[7] PSC can lead to a number of complications including vitamin A, D, E, K deficiencies, infections of the bile ducts, cirrhosis, liver failure and bile duct cancer.[6] An estimated 44% of all PSC deaths are cancer related.[8]

CLINICAL NEED and BURDEN OF DISEASE

PSC affects approximately 1.6 per 10,000 people in the EU which is equivalent to 82,000 people.[3] The reported incidence of PSC across Europe and North America is 0.77 per 100,000 person years.[9] However incidence can significantly vary geographically with reported incidence rates as high as 1.3 per 100,000 per year in Northern Europe.[5]

There can be substantial morbidity associated with PSC. About 80% of patients with PSC also have inflammatory bowel disease (IBD) (75-80% ulcerative colitis and 10-15% crohn's disease). Other immune-related comorbidities are also associated with PSC including autoimmune hepatitis, thyroid disease, type 1 diabetes mellitus and celiac disease. Some with PSC will also develop malignancies (mainly cholangiocarcinoma) and those with IBD especially, are also at increased risk of carcinoma of the large intestine.[10]

The progression of PSC can be difficult to predict as it can be highly variable. Estimated median time from diagnosis to death for PSC has been reported as 21.3 years.[11] Progression to liver cirrhosis, liver failure and the need for liver transplantation occurs 13-21 years following diagnosis.[10] Approximately 15% patients will require a liver transplant which has a 5 year survival rate of up to 80%.[11]

In 2016-2017 there were 8,341 admissions, 16,854 finished consultant episodes and 78,134 bed days for Cholangitis (ICD10 K83.0), a category which included PSC.[12]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

No relevant guidance.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Hepatobiliary and Pancreas (adult). A02/S/a.

OTHER GUIDANCE

- American College of Gastroenterology (ACG) Clinical guideline: Primary Sclerosing Cholangitis. 2015
- EASL Clinical Practice Guidelines. Primary sclerosing cholangitis. 2009.

- American Association for the Study of Liver Diseases (AASLD) Practice Guidelines. Diagnosis and Management of Primary Sclerosing Cholangitis. 2009

CURRENT TREATMENT OPTIONS

Currently there is no cure for PSC and treatment mainly focuses on slowing the progression of disease and relieving symptoms.[13]

The most commonly prescribed drug for PSC is ursodeoxycholic acid (UDCA), a form of natural bile acid, which works by reducing the hydrophobicity of bile (thereby increasing bile flow) and may have a direct effect on adaptive immunity by inhibiting dendritic cell responses.[8, 13] Current evidence also suggests that UDCA may also act as a chemoprotective agent by modifying bile acid composition and reducing faecal levels of secondary bile acids.[8]

Additional treatments to manage symptoms can also be prescribed including cholestyramine to relieve itching and artificial tears and lozenges for dry mouth and eyes.[13]

There are also some surgical procedures for the treatment of PSC, including endoscopic retrograde cholangiopancreatography (ERCP) in which the narrowed bile ducts are stretched or dilated using stents or balloons. However the procedure is associated with a 14% complication rate and needs to be repeated often due to the short period of effectiveness. The only remaining treatment option for end stage PSC is liver transplantation.[7] PSC accounts for 10% of all UK liver transplants, although this is not a curative treatment as there is a 20% disease recurrence even after transplantation.[8]

EFFICACY and SAFETY

Trial	BUTEO, NCT02239211, ISRCTN11233255, EudraCT-2014-002393-37, 2014-002393-37, RG_13-027, MREC14/EM/1272, HE2022, 146127; timolumab only; phase I/II
Sponsor	Birmingham University, UK
Status	Ongoing
Source of Information	Publication[1], Trial registry[2]
Location	United Kingdom
Design	Non-randomised, uncontrolled study
Participants	n=59 (planned); aged 18-75 years; clinical diagnosis of primary sclerosing cholangitis
Schedule	All participants receive 8mg/kg intravenous infusion over 1-2 hours of timolumab every 14 days (for a total of 7 infusions).
Follow-up	Active treatment up to 98 days. Follow up for up to 120 days
Primary Outcomes	Activity of the anti-Vap-1 antibody timolumab in patients with PSC as measured by a decrease in alkaline phosphatase levels (primary endpoint): baseline to day 99.
Secondary Outcomes	Safety and tolerability (including treatment compliance and withdrawal, Serious Adverse Event [SAEs] and Adverse Event [AEs] frequencies) of timolumab in patients with PSC: baseline to day 120

	Change, improvement or worsening from baseline to Day 99 in: - Quality of life questionnaires: EQ-5D, Fatigue Severity Scale, Pruritus Visual Analogue Scale (VAS), Inflammatory Bowel Disease (IBD) diaries where applicable. - Tests of liver fibrosis: enhanced liver fibrosis (ELF) and Fibro scan - Individual markers of liver biochemistry and function: aspartate transaminase (AST), alanine transaminase (ALT), ALP, gamma glutamyl transferase (GGT), bilirubin, albumin, International Normalised Ratio (NR) and composite risk scores (Mayo PSC Risk score and model for end stage liver disease [MELD] score) - Liver disease assessed using LiverMultiscan MRI imaging - Changes in sVAP-1/SSAO enzyme as a biomarker of liver disease activity across the study period
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Trial end date: 1st February 2019 Intension to publish date: 1st February 2020

ESTIMATED COST and IMPACT

COST

The cost of timolumab is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☐ Other

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☒ Decreased use of existing services: potentially preventing need for other treatments

☐ Re-organisation of existing services

☐ Need for new services: services need to deliver IV infusions regularly

☐ Other

☐ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☐ Reduced drug treatment costs

☒ Other increase in costs: additional costs for IV administration in clinic

☐ Other reduction in costs

☐ Other

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

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