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EMERGING THERAPIES IN PRIMARY BILIARY CHOLANGITIS: OVERVIEW OF CLINICALTRIALS.GOV

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Background: *Primary biliary cholangitis (PBC) is an autoimmune disorder leading to different hepatic disorders. Progressive bile duct damage could result in cirrhosis. However, different clinical trials are undergone to test, evaluate and analyze t therapeutics used for management of PBC.* ***Aim:*** *Identifying the emerging therapies in primary biliary cholangitis.****Methods:*** *A comprehensive analysis of clinicaltrials.gov registry on and up to 7th November 2023. A list of included trials based on the review's inclusion and exclusion criteria was further investigated.* ***Results:*** *156 clinical trials linked to primary biliary cholangitis were found. Twenty of them are completed with result. Almost twenty chemical formula and medications were tested. These medications targeted fibrotic pathways, immune modulation, Selective farnesoid X receptor (FXR) agonist, ileal bile acid transport inhibitor and bile acid metabolism.* ***Conclusion:*** *Several promising medications were found for primary biliary cholangitis. These medications undergo different stages of trials to evaluate their tolerability, efficacy, and safety. Further investigations are extremely warranted.*

Keywords: *Primary Biliary Cholangitis, hepatology, Clinical Trials, therapeutics, metabolic disorder*

INTRODUCTION

Primary Biliary Cholangitis (PBC is an autoimmune liver disease with a distinctive pathophysiology of unknown etiology. Its chronic, cholestatic and characterized by granulomatous lymphocytic cholangitis and progressive destruction of the small bile ducts in the liver[1,2]. PBC progresses through various

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stages, typically beginning with an asymptomatic phase characterized by the presence of autoantibodies and inflammation in the bile ducts[3]. As the disease advances, stages transition through symptomatic phases, marked by increasing liver damage, fibrosis, and eventually leading to cirrhosis in later stages[4]. The final stages may involve complications like liver failure or hepatocellular carcinoma, emphasizing the importance of early detection and intervention.

PBC resulted mainly from an autoimmune response, via targeting cholangiocytes, the epithelial cells that line these ducts[5]. The autoimmune process is characterized by the presence of anti-mitochondrial antibodies (AMAs), which are detected in the majority of PBC patients[6]. Their detection through blood tests serves as a key diagnostic tool for identifying individuals at risk or experiencing early stages of PBC[7]. AMAs are not only indicative of the disease but also aid in differentiating PBC from other liver disorders, facilitating timely intervention and management strategies for patients[8,9]. While the exact triggers for this autoimmune response are not fully understood, it is believed to result from both genetic and environmental triggers[10]. The environmental triggers e.g. poisonous chemicals, infectious agents, smoking, and various xenobiotics (e.g. M. gordonae and E. coli)[11–13]. Most notably, the chronic inflammation within the bile ducts can damage to the cholangiocytes and surrounding liver tissue[14] which may leads to fibrous tissue[15]. This fibrosis gradually obstructs the bile ducts, further impeding the flow of bile from the liver to the small intestine[16].

One of the most serious complications is liver cirrhosis, which can result in liver failure and significantly reduce life expectancy[2]. Cirrhosis is often accompanied by an increased risk of other health issues, such as enlarged veins (varices) in the stomach and esophagus [17,18]. Additionally, portal hypertension, caused by the obstruction of blood flow in the liver, can lead to various complications as toxins are not filtered from the bloodstream which commences in the early stages of PBC[19,20]. Furthermore, primary biliary cholangitis can result in an enlarged spleen (splenomegaly), gallstones, and bile duct stones due to the impaired flow of bile[21,22]. It also increases the risk of liver cancer and osteoporosis[23,24]. Malabsorption of fats and fat-soluble vitamins can lead to vitamin deficiencies, affecting overall health[25,26]. This condition can also lead to high cholesterol, hepatic encephalopathy, and an increased risk of other autoimmune disorders and metabolic issues, including thyroid disorders, scleroderma, rheumatoid arthritis, and Sjogren's syndrome[27–30].

In term of diagnosis, PBC is diagnosed through a combination of blood tests and imaging procedures[31]. Blood tests primarily focus on evaluating liver health and identifying signs of autoimmune disease[32]. These tests include assessing the levels of liver enzymes, which can indicate liver disease and bile duct injury[33]. Additionally, an antibody test may be performed to check for anti-mitochondrial antibodies (AMAs), which are highly specific to PBC[34]. Cholesterol levels are also examined, as more than half of individuals with PBC exhibit significant increases in blood lipid levels, including total cholesterol[35].

Moreover, While blood tests are crucial for PBC diagnosis, imaging tests may be used to confirm the diagnosis or rule out other conditions with similar symptoms [1]. These imaging procedures include ultrasound, which employs high-frequency sound waves to create images of internal structures[36]. Fibroscan uses an ultrasound-like probe to detect liver scarring, a sign of liver damage. Magnetic resonance cholangiopancreatography (MRCP), a specialized MRI examination, provides detailed images of the organs and bile ducts[37]. Finally, magnetic resonance elastography (MRE) combines MRI with sound waves to create elastograms, revealing any liver hardening (fibrosis), which can be an early sign of cirrhosis in PBC patients[38].

The primary treatment for PBC revolves around Ursodeoxycholic acid (UDCA), which remains the cornerstone therapy[39,40]. UDCA has shown efficacy in improving liver function tests, slowing disease progression, and prolonging transplant-free survival in many patients[40,41]. However, not all individuals respond adequately to UDCA monotherapy. In cases of inadequate response or intolerance to UDCA, second-line therapies such as obeticholic acid (OCA) might be considered, particularly for patients with persistently elevated alkaline phosphatase levels [42].

Management strategies often involve a multidisciplinary approach, addressing symptom management, monitoring disease progression, and considering liver transplantation for end-stage complications. Ongoing research continues to explore new therapeutic avenues and combination therapies to improve outcomes for patients, especially those who exhibit suboptimal responses to standard treatments.

MATERIALS AND METHODS

Clinical trials

Primary biliary cholangitis was searched in the clinicaltrials.gov database on 7th November 2023. The studies related to Primary biliary cholangitis totaled 156 clinical trials. The studies related to Primary biliary cholangitis patients were screened by using database filters. Twenty studies passed the screening as they involved adults with completed clinical trials with results. Medication used, dose, scientific name, rational for use in the included clinical trials were fully explained in **table 2**.

Inclusion criteria

Only completed studies with results in adults were included. The search includes age group child (birth–17), adult (18–64) and older adult (65+). Also, female and male participants were included. Then, the therapeutics used were counted.

Exclusion criteria

Suspended, terminated, withdrawn and unknown status clinical studies were excluded from this review.

RESULTS AND DISCUSSION

Search findings

Twenty clinical trials were found with completed status and results. Description of study titles, interventions, number of patients enrolled, and their gender are tabulated in **Table1**.

Therapeutics used

A list of medication used in the selected clinical trials was summarized in **Table 2**.

Table1: Study Title, intervention, number enrolled and gender (updated 09.11.2023 from clinicaltrials.gov).

No	Study Title	Interventions	Number Enrolled	Gender
1	A Study to Assess the Safety, Tolerability, Pharmacokinetics and Efficacy of EDP-305 in Subjects with Primary Biliary Cholangitis	EDP-305 1 mg and 2.5 mg	60	All
2	ENHANCE: Seladelpar in Subjects With Primary Biliary Cholangitis (PBC) and an Inadequate Response to or an Intolerance to Ursodeoxycholic Acid (UDCA)	Seladelpar 5-10 mg	265	All
3	Study to Evaluate the Efficacy and Safety of Elafibranor in Patients with Primary Biliary Cholangitis (PBC) and Inadequate Response to Ursodeoxycholic Acid	Elafibranor 80 and 120 mg	45	All
4	Seladelpar (MBX-8025) in Subjects with Primary Biliary Cholangitis (PBC)	MBX-8025 2,5 and 10 mg	119	All
5	A Multi-part, Double Blind Study to Assess Safety, Tolerability and Efficacy of Tropifexor (LJN452) in PBC Patients	LJN452	61	All
6	Study to Assess Safety & Efficacy of GKT137831 in Patients with Primary Biliary Cholangitis Receiving Ursodiol.	GKT137831	111	All

Table 1: Continued.

7	Initial Study of Rituximab to Treat Primary Biliary Cirrhosis	Rituximab	6	Female
8	Phase 3 Study of Obeticholic Acid in Patients With Primary Biliary Cirrhosis	Obeticholic Acid	217	All
9	Study of Abatacept (Orencia) to Treat Primary Biliary Cirrhosis	Abatacept	16	All
10	Use of Fenofibrate for Primary Biliary Cirrhosis	Fenofibrate IDD-P	20	All
11	Pentoxifylline for Primary Biliary Cirrhosis	Drug: Pentoxifylline	20	All
12	A Study of Efficacy and Safety of Ustekinumab in Patients With Primary Biliary Cirrhosis (PBC) Who Had an Inadequate Response to Ursodeoxycholic Acid	Ustekinumab 45, 90 and 180 mg	20	All
13	Phase 2 Study on Effects of Obeticholic Acid (OCA) on Lipoprotein Metabolism in Participants With Primary Biliary Cirrhosis	Obeticholic Acid	27	All
14	Phase 2 Study to Evaluate LUM001 in Combination With Ursodeoxycholic Acid in Patients With Primary Biliary Cirrhosis	LUM001 and Ursodeoxycholic Acid	66	All
15	Dose Response Study of GSK2330672 for the Treatment of Pruritus in Participants With Primary Biliary Cholangitis	GSK2330672	147	All
16	Study of INT-747 as Monotherapy in Participants With Primary Biliary Cirrhosis (PBC)	Obeticholic Acid	60	All
17	Study of INT 747 in Combination With URSO in Patients With Primay Biliary Cirrhosis (PBC)	INT-747 and Ursodeoxycholic Acid (URSO)	165	All
18	Biliary Excretion of Conjugated Bile Acids in Humans Measured by 11C-cholylsarcosine PET/CT	11C-CSar and ICG	19	All
19	Linerixibat and Obeticholic Acid Drug Interaction Study in Healthy Subjects	GSK2330672 (linerixibat) Obeticholic acid	19	All
20	Gastrointestinal Microbiota in Primary Sclerosing Cholangitis and Biliary Atresia With Vancomycin	Vancomycin	32	All

Table 2: Medication used, dose, scientific name, rational for use in the included clinical trials.

No	Interventions	Dose used	Scientific name	Rational for use
	EDP-305 1	EDP-305 1 and 2.5 mg	Selective farnesoid X receptor (FXR) agonist	Safety, Tolerability, Pharmacokinetics and Efficacy of EDP-305
2	Seladelpar	Seladelpar 5-10 mg	Selective PPARδ agonist	Inadequate Response to or an Intolerance to Ursodeoxycholic Acid (UDCA)
3	Elafibranor	80-120 mg	Dual PPARα/δ agonist	Evaluate the Efficacy and Safety of Elafibranor
4	Seladelpar (MBX-8025	2, 5 and 10mg	Selective PPARδ agonist	Efficacy
5	Tropifexor (LJN452)	NA	Non-bile acid FXR agonist	Safety, Tolerability and Efficacy of Tropifexor
6	Setanaxib (GKT137831)	NA	Dual NOX1/NOX4 inhibitor	Safety & Efficacy of GKT137831
7	Rituximab	NA	monoclonal antibodies	Treatment
8	Obeticholic Acid	NA	Selective farnesoid X receptor (FXR) agonist	Phase 3 Study of Obeticholic Acid
9	Abatacept	NA	Selective costimulation modulators	Treatment
10	Fenofibrate IDD-P (Insoluble Drug Delivery-Micro Particle)	NA	Fibrates	Treatment
11	Pentoxifylline	NA	Hemorrheologic agents.	Treatment
12	Ustekinumab	45, 90 and 180	Monoclonal antibodies	Efficacy and Safety
13	Obeticholic Acid	NA	Selective farnesoid X receptor (FXR) agonist	Effects of Obeticholic Acid (OCA) on Lipoprotein Metabolism
14	Maralixibat (LUM001) Ursodeoxycholic Acid	NA	Maralixibat: ileal bile acid transporter inhibitors Ursodeoxycholic Acid: Bile acids.	Evaluate LUM001 in Combination with Ursodeoxycholic Acid in Patients
15	Linerixibat GSK2330672	NA	Ileal bile acid transport inhibitor	Treatment of Pruritus in Participants
16	Obeticholic Acid (OCA)	NA	Selective farnesoid X receptor (FXR) agonist	Treatment
17	INT-747 and Ursodeoxycholic Acid (URSO)	NA	Bile acid receptor agonists	Treatment
18	11C-CSar ICG	NA	BSEP, bile salt export pump	Biliary Excretion of Conjugated Bile Acids in Humans Measured by 11C-cholylsarcosine PET/CT
19	Linerixibat Obeticholic acid	NA	Linerixibat: Ileal bile acid transport inhibitor Obeticholic acid: Selective farnesoid X receptor (FXR) agonist	Linerixibat and Obeticholic Acid Drug Interaction Study in Healthy Subjects
20	Vancomycin	NA	Glycopeptide antibiotics	Gastrointestinal Microbiota in Primary Sclerosing Cholangitis and Biliary Atresia with Vancomycin

Discussion

Despite the availability of ursodeoxycholic acid (UDCA), a well-established therapy for PBC, a significant proportion of patients do not respond adequately to this treatment, necessitating the exploration of emerging therapies. This paper provides an overview of clinical trials registered on ClinicalTrials.gov that investigate novel treatment options for PBC. The findings presented in the above results highlight the growing interest in developing alternative therapies to improve the management of PBC, while also shedding light on the challenges and opportunities in this field.

One notable observation from the analysis of clinical trials in PBC is the diversification of therapeutic targets. Different pharmacological targets were investigated as explained in table 2. Historically, UDCA has been the primary treatment for PBC, but several trials discussed in this overview explore alternative mechanisms of action[43,44]. These include drugs targeting fibrotic pathways, immune modulation, Selective farnesoid X receptor (FXR) agonist, ileal bile acid transport inhibitor and bile acid metabolism. The emergence of novel therapies with distinct mechanisms offers a more comprehensive approach to PBC management, potentially addressing the subset of patients who do not respond to UDCA. The increased number of trials in recent years underscores the growing awareness of unmet medical needs in PBC treatment.

Nevertheless, the translation of promising results from clinical trials to clinical practice remains a substantial challenge. The paper highlights the need for rigorous study designs, large sample sizes, and long-term follow-up to establish the safety and efficacy of emerging therapies. Additionally, the complex nature of PBC necessitates a personalized medicine approach, as patient heterogeneity in terms of disease stage, genetics, and response to treatment is substantial. As a result, identifying biomarkers to predict treatment response and monitoring treatment outcomes is crucial to advancing PBC therapeutics. In summary, while the landscape of emerging therapies for PBC is promising, continued research and collaboration between the scientific community, pharmaceutical industry, and regulatory agencies are essential to ensure the successful development and implementation of new treatments for this challenging liver disease.

Conclusion

Several promising medications were found for primary biliary cholangitis. These medications undergo different stages of trials to evaluate their tolerability, efficacy and Safety. Further investigations are extremely warranted.

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العلاجات الناشئة في التهاب الأقنية الصفراوية الأولي: نظرة عامة على Clinicaltrials.gov

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الخلفية: التهاب الأقنية الصفراوية الأولي (PBC) هو اضطراب المناعة الذاتية الذي يؤدي إلى اضطرابات الكبد المختلفة. يمكن أن يؤدي تلف القناة الصفراوية التدريجي إلى تليف الكبد. ومع ذلك، يتم إجراء تجارب سريرية مختلفة لاختبار وتقييم وتحليل العلاجات المستخدمة لإدارة الـ PBC.

الهدف: التعرف على العلاجات الناشئة في التهاب الأقنية الصفراوية الأولي.

الطرق: تحليل شامل لسجل Clinicaltrials.gov في وحتى ٧ نوفمبر ٢٠٢٣. تم إجراء مزيد من التحقيق في قائمة التجارب المشمولة بناءً على معايير التضمين والاستبعاد الخاصة بالمراجعة.

النتائج: تم العثور على ١٥٦ تجربة سريرية مرتبطة بالتهاب الأقنية الصفراوية الأولي. تم الانتهاء من عشرين منهم بالنتيجة. تم اختبار ما يقرب من عشرين تركيبة كيميائية وأدوية. استهدفت هذه الأدوية المسارات الليفية، والتعديل المناعي، وناهض مستقبلات الفارنويد X الانتقائية(FXR) ، ومثبط نقل حمض الصفراء اللفائفي واستقلاب حمض الصفراء.

الاستنتاج: تم العثور على العديد من الأدوية الواعدة لعلاج التهاب الأقنية الصفراوية الأولي. تخضـــع هذه الأدوية لمراحل مختلفة من التجارب لتقييم مدى تحملها وفعاليتها وسلامتها. هناك ما يبرر إجـــراء مزيد من التحقيقات.