Digestive and Liver Disease 48 (2016) 843–850

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Review Article

Toward precision medicine in primary biliary cholangitis

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ARTICLE INFO

Article history:
Received 30 March 2016
Accepted 25 May 2016
Available online 3 June 2016

Keywords:
Primary biliary cholangitis
Precision medicine
Risk-stratification

ABSTRACT

Primary biliary cholangitis is a chronic, cholestatic liver disease characterized by a heterogeneous presentation, symptomatology, disease progression and response to therapy. In contrast, clinical management and treatment of PBC is homogeneous with a 'one size fits all' approach. The evolving research landscape, with the emergence of the -omics field and the availability of large patient cohorts are creating a unique opportunity of translational epidemiology. Furthermore, several novel disease and symptom-modifying agents for PBC are currently in development. The time is therefore ripe for precision medicine in PBC. In this manuscript we describe the concept of precision medicine; review current approaches to risk-stratification in PBC, and speculate how precision medicine in PBC might develop in the near future.

1. Introduction

Primary biliary cholangitis (PBC, formerly known as primary biliary cirrhosis) [1–3] is a chronic, cholestatic liver disease characterized by non-suppurative granulomatous cholangitis; duct destruction and ductopenia, and portal fibrosis that progresses slowly to biliary cirrhosis [4]. A substantial proportion of cases eventually develop end-stage liver disease (ESLD) with attendant need for liver transplantation (LT) [5]. PBC is an autoimmune condition, typified by auto-antibodies and auto-reactive T cells directed against mitochondrial self-antigens. However, the aetiology of PBC remains enigmatic. The disease is best described as a complex disorder, meaning that it is caused by a complex of largely unknown genetic and environmental factors [6].

Like other complex disorders, PBC is heterogeneous in its presentation, symptomatology, disease progression and response to therapy. Well-known examples of this heterogeneity include the following:

- A proportion of cases have variant syndromes. Thus, PBC – autoimmune hepatitis (AIH) overlap syndrome may be found in ~10% and the premature ductopenic variant in ~5% of cases [7].
- The autoantibody profile is variable. For example, anti-centromere antibodies (ACA) are found in ~30% [8], anti-sp100 antibodies in ~20–30% [9] and anti-gp210 antibodies in ~10% of cases [10].
- The symptom profile is variable. For example, pruritus is present in 40% and fatigue is present in 45% of cases [11].
- Distinct modes of disease progression are recognized, such as portal hypertensive-type versus hepatocellular failure-type progression [12].
- The rate of disease progression is variable, ranging from no overt progression at one end of the spectrum, to ESLD occurring within a few years of diagnosis, at the other [5].
- The biochemical response to treatment with ursodeoxycholic acid (UDCA) is variable – and strongly predicts the long-term outcome [5].

In contrast, disease-modifying treatment of PBC is homogeneous, inasmuch as almost all patients receive the same treatment. For example, current guidelines from the European Association for the Study of the Liver (EASL) [4] and the American Association for the Study of the Liver Disease (AASLD) [13] recommend that all PBC patients be treated with UDCA 13–15 mg/kg/day, irrespective of the liver biochemistry or stage of disease at baseline. It is advised that the biochemical response to UDCA be assessed, using the Paris I or Barcelona criteria (according to EASL) or the ALP and Mayo risk score (according to AASLD). The guidelines do not,

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http://dx.doi.org/10.1016/j.dld.2016.05.023
1590-8658/

however, elaborate an approach to treatment of patients with inadequate response to UDCA. The EASL guidelines recommend that patients with AI overlap receive additional treatment with immunosuppressants, while those of AASLD provide no recommendation [4].

The 'one size fits all' approach to management of PBC is unsurprising because UDCA is presently the only pharmacotherapy licensed for disease-modifying treatment of this condition. Several novel disease and symptom-modifying agents for PBC are, however, currently in development (Textbox 1). There are molecules targeting the immune-mediated response and bile-acid therapies targeting the bile acid biosynthetic and feedback processes that drive the biliary epithelial cells (BEC) injury. In addition, antifibrotic therapies are under study to tackle the downstream damage following BEC injury. In practice, these therapeutic strategies are not mutually exclusive, especially as different underlying disease mechanisms do coincide (Textbox 1) [14]. The time is ripe for precision medicine in PBC. In this manuscript we describe the concept of precision medicine; review current approaches to risk-stratification in PBC, and speculate how precision medicine in PBC might develop in the near future.

2. Precision medicine

Precision medicine (PM) is a system in which healthcare is tailored to the individual patient, based on genotypic or phenotypic characteristics correlated to a particular treatment response or disease outcome. In simple terms, the aim of PM is 'the right treatment, for the right person, at the right time'. PM is not a new concept. Wherever data are available to guide different treatment strategies, healthcare workers already practice PM. However, the concept has become fashionable of late because, owing to recent technological advances, clinically relevant sub-phenotypes may be defined (or re-defined) based on unprecedented volumes of genotype or phenotype data.

The major advantage of PM is that medical interventions – investigations or treatments – are focused on those who will benefit, sparing those who will not. This is especially cost-effective for patients, in whom the potential costs of medical interventions include the adverse effects of medication or surgery and the psychological burden of screening, surveillance or treatment. For obvious reasons, PM is also cost-effective for healthcare systems. For these reasons, PM is a global priority for healthcare providers, policy makers and industries [43].

3. Risk-stratification

Data are already available to guide PM in PBC. Using medical investigations that are widely available, it is possible to recognize variant syndromes and to stratify patients according to their risk of critical outcomes, such as chronic liver failure, variceal haemorrhage and hepatocellular carcinoma. This information can (and should) influence management. Variant syndromes and risk stratification are discussed below.

3.1. Variant syndromes

Variant syndromes may be evident at presentation. They have a different disease trajectory, which justifies efforts to clarify the diagnosis at the earliest possible stage.

3.1.1. PBC-AIH overlap

The *PBC – AIH* overlap syndrome, which may occur in 10–20% of PBC patients, is characterized by the fluctuating or persistent presence of AIH-like features [4]. The diagnosis depends on a combination of biochemical, serological and histological features, although standardization of diagnostic criteria has not been achieved. The current EASL guidelines on cholestatic liver disease advocate the diagnostic criteria proposed by Chazouilleres et al. [15] (Textbox 2). Of note, these criteria require histological confirmation of moderate to severe interface hepatitis to make the diagnosis [15]. Other experts advocate the simplified scoring system of the International Autoimmune Hepatitis Group (IAIHG) [16]. However it is defined, AI overlap is more severe than 'pure PBC', with earlier development of liver fibrosis and liver failure [7].

Box 1: Active and recently run clinical trials in PBC.

Drug's name	Class of drugs	Rationale	Phase of development
INT 767	TGR5 agonists	Dual FXR and TGR5 agonist effect shown to affect energy metabolism, glucose homeostasis, bile composition/secretion, and inflammation.	Phase 1 (recruiting)
FFP104	Anti-CD40	CD 40 plays a key role in $CD4^+$ T-cell priming, B-cell terminal maturation, and immunoglobulin (Ig) class-switch recombination. Administration of anti-CD40L in murine models of autoimmune cholangitis reduces liver inflammation significantly lowers the levels of AMA.	Phase 1–2 (recruiting)
Bezafibrate	PPAR-α	Improvement of hepatic inflammation through PPAR-α and MDR3	Phase 3 (active)
MBX-8025	PPAR-γ	Activation of PPAR-γ reduces peribiliary inflammation and reverses the activation of stellate cells and might, therefore, be involved in fibrosis regression.	Phase 2 (recruiting)
Rituximab	Anti-CD20	B-cell depleting therapy shown to reduced fatigue in pilot study in PBC.[a] Endpoint is reduction of fatigue.	Phase 2 (active)
Lopixibat	ASBT inhibitors	Apical sodium-dependent bile acid transporter inhibitor reduces bile acid accumulation in the liver. Trial endpoint is reduction of pruritus.	Phase 2 (closed)
NI-0801	Anti-CXCL-10	The chemokine CXCL10 plays an important role in T cell trafficking by binding CXCR3, highly expressed on effector T cells, that drives infiltration of inflammatory lymphocytes into the liver.	Phase 2 (closed)
Ustekinumab	Anti-IL12/IL23	Blockade of IL12/23 pathway, key player in the effector mechanisms that lead to biliary destruction, could alleviate inflammation in PBC.	Phase 2 (closed)
Obeticholic Acid (OCA)	FXR agonists	Bile acid shown anti-cholestatic, anti-inflammatory, and anti-fibrotic effects in clinical studies, through the activation of the FXR.	FDA filing Phase 3 (confirmatory trial, recruiting)
Abatacept	Chimeric CTLA4	Fusion protein of the extracellular domain of CTLA-4 and human IgG1, which binds to CD80 and CD86 molecules on the APC and prevents the co-stimulatory signal being delivered to the T cell that is needed for an immune response.	Phase 4 (recruiting)

[a] Myers RP, Shaheen AA, Swain MG, et al. Rituximab for primary biliary cirrhosis (PBC) refractory to ursodeoxycholic acid (UDCA). Hepatology 2007;46:550A.

Abbreviations: APC, antigen-presenting cells; FXR, farnesoid X receptor; IL, interleukin; TGR5, G protein-coupled bile acid receptor; MDR3, multiple drug resistance gene-3; PPAR, peroxisome proliferator-activated receptor.