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Review

Novel therapeutics for primary biliary cholangitis: Toward a disease-stage-based approach

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ABSTRACT

Primary biliary cholangitis (PBC; previously "primary biliary cirrhosis") is a cholestatic, putatively autoimmune-mediated liver disease with a clear female preponderance affecting the intrahepatic small and medium-size bile ducts and resulting in bile duct destruction, ductopenia and portal fibrosis that progresses slowly to biliary cirrhosis. Despite suboptimal response in one third of patients treated with ursodeoxycholic acid (UDCA), this remains the only FDA-approved agent for this disease. In this review, we cover recent advances in research that have yielded numerous agents currently at different stages of the drug pipeline, some of which are expected to be approved in the near future. We also discuss accumulating evidence supporting the use of older agents (fibrates and glucocorticoids) as an adjunctive therapy to UDCA in non-responsive patients. We suggest that with the imminent expansion of the therapeutic armamentarium for PBC, a more comprehensive approach – ideally taking into account not only biochemical markers of disease stage – is needed to better select patients in whom these strategies might be most useful. Studies are also needed to compare the relative efficacy of different proposed second-line treatments not only against UDCA monotherapy.

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1. Background

The introduction of ursodeoxycholic acid (UDCA) for the treatment of primary biliary cholangitis (PBC) almost three decades ago has tremendously changed the prognosis for newly diagnosed patients, with overall survival for responders comparable to that of age-matched group [1–3]. This, along with the development of tools for early diagnosis, have changed the disease course with only a minority of UDCA responders progressing to cirrhosis and has partially driven the recent change in nomenclature [4–8]. UDCA is a hydrophilic bile acid that constitutes less than 5% of the total bile acid pool in humans [9]. Its favorable effects extend beyond protection against hydrophobic bile acid toxicity; it induces bicarbonate secretion, protects against oxidative stress, and may have anti-apoptotic and immune modulating roles [10]. It is to note that although the taurine-conjugated species of UDCA, TUDCA, has significant metabolic advantages over UDCA (it is better absorbed than UDCA and undergoes reduced biotransformation to more hydrophobic metabolites [11]) that may be of benefit for long-term therapy in PBC, no proper clinical comparative studies have been yet performed. Yet, one of three patients treated with UDCA does not achieve optimal response and this does not change with increase in dose. In the absence of FDA-approved second-line treatment, there is an urgent need to expand our therapeutic armamentarium [12].

2. Step-wise pathogenesis of primary biliary cholangitis

PBC is a chronic disease of putative autoimmune origin that results in progressive intrahepatic cholestasis that later develops into end-stage Liver Disease (ESLD) [13]. Histologically, it progresses from portal inflammation, periportal fibrosis, septal fibrosis, and finally, nodular remodeling that is characteristic of liver cirrhosis (Ludwig's Classification) [14]. The time course may be different among patients and different models have been set to predict progression [15].

A better understanding of disease progression has offered different processes along the time course at which therapeutic interventions should be aimed: from the failure of immunoregulatory checks at the incipient stages to fibrosis and parenchymal remodeling at later stages. At the outset, it should be emphasized that these therapeutic strategies are not mutually exclusive, especially as different underlying disease mechanisms do coincide. Yet, ideally, therapeutics should be tailored to the disease stage at which they are used: while therapies early in the course should be more directed toward immune tolerance breakdown, later therapies should address bile toxicity. Later on, as fibrosis becomes prominent, anti-fibrotic agents can come into play [16] (Fig. 1). In order for such strategies to be implemented, better biomarkers – both serological, biochemical, and histological – to define disease stage are needed.

3. Initiation: Breach of tolerance

Research done in the last three decades has provided important insights into the immunological mechanisms that underlie the initiation and pathogenesis of PBC. The initial breach of tolerance seems to involve immunoregulatory failure at different layers of control, including central and peripheral tolerance, liver-specific tolerance mechanisms (collectively referred to as the "liver tolerance effect"), and dysfunction of regulatory T cells [17,18]. Anti-mitochondrial antibodies (AMA), present in around 90% of PBC patients, are the serologic hallmark of PBC. The immunodominant autoantigen was later identified to be the E2 subunit of the pyruvate dehydrogenase complex (PDC-E2) [19,20]. Patients with PBC have higher prevalence rates of other autoimmune conditions, including Systemic Lupus Erythematosus (SLE), scleroderma, Sjögren's, and autoimmune thyroid disease [21,22]. An association with certain HLA alleles, including HLA DRB1*08, HLA DRB1*11, and DRB1*13, has also been documented [23]. It is thus of no surprise that great efforts have focused on targeting different immune components for potential treatment of PBC.

3.1. Glucocorticoids and classical immunosuppressants

The favorable effects of steroid treatment in PBC patients have been reported in numerous studies [24–26]. Yet, safety concerns associated with lifelong steroid treatment have limited their widespread use [24,27]. In recent years, efforts have focused on Budesonide due to its high first-pass metabolism, which would minimize these systemic side effects, with results supporting its use [28]. Indeed, two studies in patients at different disease stages have shown that adjunctive Budesonide, at 6–9 mg daily, is superior to UDCA monotherapy both in terms of

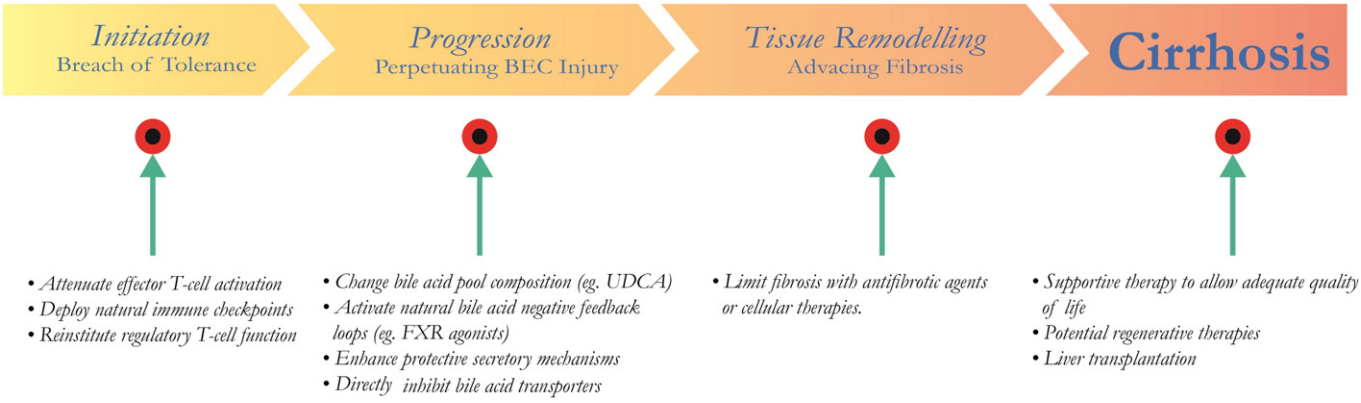

Fig. 1. Disease-stage-based approach to novel PBC therapeutics. Legend: With the expansion of our therapeutic armamentarium, the choice of agents should ideally be guided by the disease stage at which they are used.