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Review

The Interleukin-17-T helper 17 axis in primary sclerosing cholangitis: A narrative review of an emerging pathogenic frontier

Amera Elzubeir [a,b,*], Meha Patel [a,b,c], Simon Rushbrook [a,b]

[a] Norwich Medical School, University of East Anglia, Bob Champion Research Centre, Norwich Research Park, Norfolk NR4 7TJ, UK
[b] Norfolk and Norwich University Hospital, Gastroenterology, Colney Lane, Norwich, NR4 7UY, UK
[c] Earlham Institute, Norwich Research Park, Colney Lane, Norwich NR4 7UZ, UK

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ABSTRACT

Interleukin-17 (IL-17) and IL-17+ secretory cells, including T helper 17 (Th17) cells play pivotal roles in autoimmune diseases such as psoriasis. Emerging evidence implicates the IL-17 pathway in primary sclerosing cholangitis (PSC), a chronic cholestatic liver disease lacking approved pharmacological therapies, for which liver transplantation remains the only life-extending option. The IL-17 pathway and Th17 biology is increasingly implicated in PSC pathogenesis through its interactions with hepatic parenchymal and non-parenchymal cells, including cholangiocytes, neutrophils and hepatic stellate cells which promote periductal fibro-inflammation, immune cell recruitment and pro-inflammatory cytokine release. Th17 cells and IL-17+ secreting lymphocytes localise to peribiliary regions, exacerbating biliary injury and fibrosis. Preclinical murine models suggest that inhibition of IL-17 signalling mitigates hepatic fibro-inflammatory responses, providing a compelling rationale for its investigation as a potential therapeutic target in PSC.

Whilst licensed IL-17 inhibitors have demonstrated efficacy and safety in a number of autoimmune and immune-mediated diseases, IL-17 has context-dependent roles in tissue homeostasis and host defence underscoring the pathway's complexity. This narrative review synthesises the biology of the IL-17 family, integrating preclinical and translational evidence relevant to PSC, and discusses the translational potential of approved anti-IL-17 agents as novel therapeutic candidates in PSC, whilst highlighting key uncertainties and gastrointestinal safety considerations.

1. Introduction

Primary sclerosing cholangitis (PSC) is a rare idiopathic cholestatic biliary disease [1,2]. It is characterised by progressive biliary inflammation and multi-focal strictures leading to cholestasis, biliary fibrosis, cirrhosis and end stage liver disease for a subset of patients [3]. Despite its devastating nature, the absence of regulatory approved pharmacological therapies renders liver transplantation as the only life extending intervention available [4].

Population-based studies estimate a PSC incidence of 0–4.39 per 100,000 person years with a prevalence of 0–31.7 per 100, 000 person years [5–8]. PSC predominantly affects young men (aged 30–40) and coexists with inflammatory bowel disease (IBD) in 70–80% of cases, most often ulcerative colitis (UC) [9–11]. Patients also have a substantially increased risk of colorectal cancer, cholangiocarcinoma and gallbladder cancer [12]. Several distinct clinical phenotypes of PSC exist, of which large-duct PSC (LdPSC) is the most common. LdPSC is characterised by cholestatic liver biochemistry and the presence of a “beaded appearance” on magnetic resonance cholangiopancreatography (MRCP) [13,14], in the absence of an alternative cause [3]. The exact aetiology of PSC has yet to be fully elucidated. Nonetheless, contributory genetic, environmental and immune dysregulatory factors are thought to be implicated in disease progression [15].

Since the discovery of T helper 17 cells (Th17) and their secretion of the signature interleukin-17 (IL-17) family of pro-inflammatory cytokines, their role in infection, tissues homeostasis and autoimmunity has been the focus of extensive research [16,17]. Emerging evidence implicates the IL-17/Th17 axis as being contributory to the immune-mediated cholangiopathy seen in PSC.

This narrative review explores the IL-17 pathway and Th17 biology, synthesises the literature (from human and murine models) that has led to our current understanding of its contributory role in PSC and provides

* Corresponding author at: Norwich Medical School, University of East Anglia, Bob Champion Research Centre, Norwich Research Park, Norfolk NR4 7JT, UK.
E-mail address: a.elzubeir@uea.ac.uk (A. Elzubeir).

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an overview of the current anti-IL-17 therapies as potentially novel repurposed therapeutic agents in PSC.

2. Methods

2.1. Search strategy and selection criteria

This narrative review was conducted and informed by structured literature searches. MEDLINE and Embase were searched from inception to February 2026 using terms [“primary sclerosing cholangitis” OR “sclerosing cholangitis” OR PSC OR “cholangitis sclerosing”] AND [“interleukin 17” OR “IL17” OR “IL-17” OR “T helper 17” OR “Th17” OR “brodalumab” OR “secukinumab” OR “ixekizumab” OR “bimekizumab” OR “anti interleukin 17” OR “anti IL 17”]. Searches were restricted to English language publications. Bibliographies of included articles were reviewed to identify additional eligible studies.

Eligible publications were those examining the IL-17 pathway and/or Th17 biology in PSC, including human clinical, translational studies (e.g., single-cell sequencing, spatial transcriptomics, tissue/bile studies) and preclinical mechanistic studies (in vitro and animal models including cholestatic murine mimics). We excluded grey literature, non-PSC/non-cholestatic related conditions and where IL-17/Th17 biology was not substantively evaluated. Given the heterogeneity of the evidence base and the mechanistic focus of this review, studies were prioritised for inclusion based on PSC relevance, PSC-specific human data, and extent to which they provided mechanistic or translational insight and corroborative preclinical evidence. As this was a narrative review we did not perform a quantitative synthesis.

2.2. T helper 17 cells & IL-17 biology

T cells are regarded as one of the principal drivers of PSC [18–20], and are classified by the expression of T cell receptors (TCR), often with the co-expression of either CD4 or CD8. T helper type 1 (Th1) and type 2 (Th2) cells were the first recognised effector subpopulations of the CD4+ T helper family [21]. This classical archetype has since expanded (Fig. 1). Th17 cells are a functionally and developmentally distinct lineage of CD4+ T helper cells [22,23]. Since their discovery in 2005 [23], Th17 cells have emerged as principal mediators of numerous autoimmune and chronic inflammatory conditions, and have become the subject of extensive research in conditions such as psoriasis, IBD, metabolic dysfunction-associated steatotic liver disease (MASLD), autoimmune hepatitis (AIH) and multiple sclerosis [16,24–29].

2.2.1. Th17 differentiation and function

Th17 differentiation is coordinated by naïve CD4+ cells' interaction with antigen presenting cells (APC) and co-stimulation by specific pro-inflammatory cytokines [23]. Th17 effector cells differentiate from naive CD4+ cells in secondary lymphoid organs under the orchestration of transforming growth factor-β (TGF-β) and pro-inflammatory cytokines IL-21, IL-6 and IL-1β. With IL-1β recognised as being one of the most potent amplifiers of IL-17 production in humans [30,31].

IL-23 also plays a critical role in expanding and stabilising Th17 phenotype subsistence [32]. IL-23 and IL-6 promote activation of the STAT3 transcription factor which in combination with retinoic acid-receptor elevated orphan receptor-γt (RORγt) signalling commences a programme of Th17 stabilisation [33]. RORγt is the lineage-defining

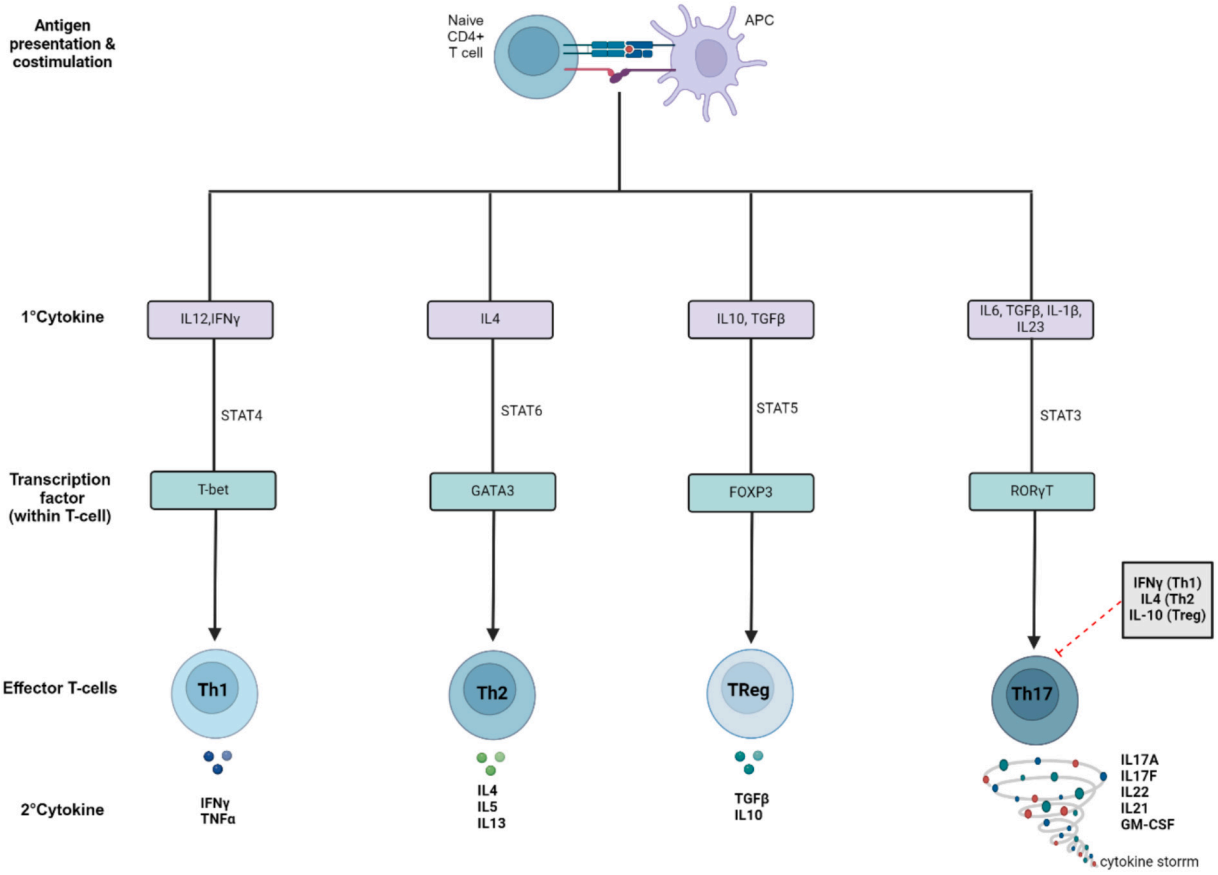

Fig. 1. Diagrammatic representation of the T cell lineage activation and associated differentiation of naïve CD4+ cells, illustrating key cytokines and transcription factors associated with lineage commitment.
APC, antigen presenting cell; IFN, interferon; IL, interleukin; GATA3, GATA binding protein 3; GM-CSF, granulocyte-macrophage colony stimulating factor; Th1, T helper 1 lymphocyte; Th2, T helper 2 lymphocyte; Th17, T helper 17 lymphocyte; Treg, T regulatory cell; TGF, tissue growth factor; STAT, signal transducer and activator of transcription; RORγT, retinoic acid receptor-related orphan receptor γT. *Created in BioRender. Elzubeir, A. (2025)* https://BioRender.com/h78x359

master transcription factor of Th17 cells, and a key regulator of Th17 development and IL-17 A/F expression [21,34]. Th17 differentiation is however antagonised by cytokines released from other Th subsets e.g., IFN-γ, IL-4 or IL-10 [35].

Effector Th17 cells characteristically secrete canonical pro-inflammatory cytokines IL-17 A and IL-17F, in addition to IL-21, IL-22, IFN-γ, TNFα, and chemokines CCL20 and GM-CSF, collectively regulating mucosal immunity, tissue inflammation and neutrophil recruitment [31,34].

2.2.2. Th17 roles and function

In health, Th17 cells are primarily enriched at mucosal sites with few circulating Th17 cells [36]. Th17 cells have two opposing, yet finely balanced roles: host defence and disease pathogenesis. Under physiological conditions Th17 cells orchestrate tissue repair, mucosal defence mechanisms and regulate epithelial barrier integrity [37–39]. Additionally, Th17 cells orchestrate chemotaxis of macrophages and neutrophils to the epithelial barrier [37]. A hosts' deficiency in Th17 cells and IL-17 signalling pathways, such as in Jobs syndrome (autosomal dominant hyper-IgE syndrome), renders them highly susceptible to bacterial and fungal infections, particularly mucocutaneous candida [22,39]. Furthermore, Th17 cells appear to be essential for pathogen clearance where Th1/2 cells have been inadequate [40], a point requiring due consideration when instituting IL-17 blocking agents in humans. Organs inherently involved in epithelial barrier integrity and host protection from external pathogens contain the largest gradient of IL-17 producing cells. Hence, it is no surprise that the skin, lungs, and intestine are abundant in IL-17 secreting cells [41].

2.2.3. Alternative sources of IL-17

Differentiation into effector Th17 cells takes days, whereas IL-17 expression can be incited hours after a stimulus [42]. Th17 cells were once considered the sole secretors of IL-17; however, it is now understood that IL-17^{+} CD8+ T cells (Tc17), natural killers (NK) cells, mucosal associated invariant T cells (MAIT), mast cells, neutrophils, Paneth cells, γδ T cells, and group 3 innate lymphoid cells (ILCs) are all capable of IL-17 production as part of an acute stress or inflammatory response [41,43]. Th17, MAIT cells and CD8+ T cells have been identified as the predominant secretors of IL-17 in several chronic liver diseases [44,45]. Providing clear evidence of an overlap in IL-17 secretion between the adaptive and innate immune system. Nonetheless, the relative contribution of these cells to IL-17 production in the differing disease models has not been fully elucidated.

2.2.4. Regulatory T cells and their reciprocal relationship with Th-17 cells

T regulatory (Tregs) cells are a unique subset of T cells present in the liver [46,47]. Tregs regulate immune responses, preventing damage to self. In homeostatic non-inflammatory states Treg differentiation is primed by STAT5, TGF-β and co-stimulatory signals and are classified into natural, peripheral and induced Tregs [33,44]. TGF-β upregulates the expression of forkhead box protein 3 (Foxp3) transcription factor, promoting Treg differentiation and reciprocally opposing Th17 differentiation [44,48]. Treg stabilisation with Foxp3+ is essential for its lineage commitment and function, promoting secretion of anti-inflammatory cytokines IL-10 and TGF-β [33,44]. Classically, Tregs and Th17 regulate one another [34]. This balance is critical for regulating homeostasis, chronic inflammation and autoimmunity. In vivo abrogation of Foxp3+ Tregs amplified Th17 activity, gene expression of IL-17 receptor A (IL-17RA) and pro-inflammatory cytokines in murine models. This upregulation correlated with liver fibrosis severity and hepatic enzyme levels [49].

2.2.5. Th17 instability & plasticity

Unlike Th1 and Th2 cells which exhibit relative lineage stability, Th17 cells (and Tregs) can exhibit functional and phenotypic environmental adaptations in vivo permitting them to deviate from their initial lineage commitment. Contingent on environmental, microbial, or pathogenic factors, Th17 cells can acquire alternative phenotypes (e.g., Treg, Th1) and effector cytokines [36]. This flexibility is often referred to as plasticity.

Functional plasticity can either be programmed during early naïve T cell differentiation or later in its development. Th17 cells can upregulate secretion of IL-10, an immune regulatory cytokine, allowing trans-differentiation of former Th17 cells towards a Treg type 1 phenotype contributing to homeostasis, restrained pathogenesis and resolving inflammation [50]. Reciprocally, Tregs can downregulate Foxp3+ expression and reprogramme towards Th17 phenotypical cells (IL-17+ Foxp3+) in animal models under the influence of IL-23, IL-1β and IL-6, however the significance of this cross over in human disease models is ill-defined [51].

2.3. IL-17 cytokine family- general principles

Whilst recognition of Th17 cells, as the third subpopulation of CD4+ effector cells, has only emerged in the last twenty years, our knowledge of IL-17 A preceded that by over a decade [21]. IL-17 A (the signature cytokine of the IL-17 family) was cloned in mice in 1993, a few years later its associated receptor IL-17RA was described [42,52].

There are six cytokine members of the IL-17 family [52]. IL-17 A, B, C, D, E (also known as IL-25) and IL-17F. Of which, our understanding of cytokines IL17 A and IL-17F is the most complete [42].

2.3.1. Cytokines IL-17 A & F

IL-17 A (originally coined CTLA-8) [53] is the founding member of the IL-17 family. Structurally IL-17 A & F are homodimers, composed of two monomers connected by a disulphide bond on a carboxyl terminal cysteine motif [54,55]. IL-17 A and IL-17F share ~50% of their structural homology and can be secreted as homodimers (IL-17 A & IL-17F) or heterodimers (IL-17 A/F) [56,57]. IL-17 A is the more potent of the two cytokines, nonetheless, in vivo the IL-17 A/F heterodimer is produced in greater magnitude than its IL-17 A homodimer by activated peripheral blood mononuclear cells (PBMCs) [58,59]. Whilst biologically similar and with overlapping functions, IL-17 A and IL-17F also carry out distinct roles [60]. IL-17 A is more strongly implicated in autoimmunity and priming of the immune system, than IL-17F [60]. Nevertheless, there is evidence of a synergistic role between IL-17 A and IL-17F. Their combined inhibition, has been found to be of greater clinical efficacy in psoriasis than inhibition of IL-17 A singularly [61].

2.3.2. Cytokines IL-17B to E

In contrast, our understanding of the remaining cytokines is incomplete. The structural overlap of IL-17B to IL-17D with IL-17 A is less than 30% [62]. IL-17B, C and D are considered proinflammatory [45,63]. IL-17C is unique as it is secreted predominantly by epithelial cells rather than haematopoietic cells [64,65]. IL-17E is the most divergent family member, with a purported anti-inflammatory role [62,66]. IL-17E has a predominant Th2 effect, inducing expression of IL-4, IL-5 and IL-13, and is considered a potential mediator of allergic airways disease [42,67]. IL-17D is the least well characterised family member. Whilst associated with health and intestinal homeostasis, it has also been implicated in tumour progression and virus surveillance [68,69].

2.4. IL-17 Receptors

There are five IL-17 receptor subunit members: IL-17RA (also known as IL-17R), RB, RC, RD, and RE [70]. IL-17RA was the first discovered. Whilst both IL-17 A and IL-17F homodimers (and heterodimers) bind to the IL-17RA/IL-17RC receptor subunits, IL-17 A binds to IL-17RA with greater affinity [70–72]. IL-17 A can additionally signal through IL-17RA/RD, whilst IL-17F can signal independently through IL-17RC/IL-17RC [58,70,73]. This is in contrast to other IL-17 cytokines whose receptors are shown in Supplementary Table 1.

IL-17RA is expressed ubiquitously throughout the body, including the liver, haemopoietic tissues, epithelium, endothelium, fibroblasts and myeloid cells. IL-17RA is present on multiple hepatic cell types including hepatocytes, Kupffer cells (KC), hepatic stellate cells (HSC), biliary epithelial cells (BECs) and liver sinusoidal endothelial cells (LSEC). Such broad expression within the liver may explain its implication in the pathogenesis of a number of liver diseases including primary biliary cholangitis (PBC), MASLD and AIH [29,74–76].

IL-17RA is also the co-receptor for IL-17RB and RE, mediating IL-17E and IL-17C activity respectively [62]. IL-17RC binds IL-17 A and IL-17F with equal affinity (unlike IL-17RA), and has greater expression in the liver, kidney, and joints, with low relative expression in haematopoietic cells [77].

2.5. IL-17 A cytokine-receptor signalling

Ligand binding of IL-17 A to its associated receptor IL-17RA/RC heteromeric complex creates a conformational change [70]. Activating the cytoplasmic protein, Act1 adaptor via the SEF/IL17R (SEFIR) domain made up of both the IL-17RA and RC subunits (Fig. 2). This engagement enables rapid recruitment of TNF receptor associated factor 6 (TRAF6) an upstream activator of the transcription factor nuclear factor kappa B (NF-κB) in addition to mitogen-activated protein kinase (MAPK) pathways [45,56,58]. NF-κB regulates gene expression of pro-inflammatory processes in the nucleus. Activation of this pathway stimulates neutrophil recruitment, cytokines, chemokines, and inflammatory genes [58] leading to a proinflammatory cascade.

2.6. IL-17 and its role in PSC pathogenesis

The IL-17 pathway and Th17 cells have complex dual roles, balancing protective immune regulation with pro-fibroinflammatory activity and disease pathogenesis. Over the past decade, a growing body of evidence has implicated the IL-17 pathway as a biologically plausible pathway contributing to the biliary fibro-inflammation exemplified in PSC. A summary of the key mechanistic evidence included within this narrative review is summarised in Supplementary Table 2.

2.6.1. Biliary epithelial cells as targets of IL-17

BECs (cholangiocytes) line the bile ducts and are responsible for transporting bile. Recent studies underscore the immunologically active role of cholangiocytes in the chronic inflammation observed in PSC. IL-17 receptors RA, RC and RE are expressed on human cholangiocytes originating from patients with and without PSC [79]. Permitting cholangiocytes to respond to IL-17 A signalling and triggering a robust biliary immune response. IL-17 stimulated BECs secrete pro-inflammatory cytokines IL-6, IL-1β, IL-23, CXCL6, CXCL9, IFN-γ & TNF further amplifying local inflammation [79,80]. Furthermore, IL-17 induces CCL20 expression by BECs, promoting recruitment of CCR6+ expressing Th17 and IL-17+ producing cells to periductal regions, thereby perpetuating chronic biliary inflammation and injury [79,80]. IL-6, IL-1β, IL-23 are essential cytokines for intrahepatic Th17 differentiation and stabilisation.

Recruitment of T cell subsets to organ-specific tissues is determined by expression of T cell chemokine receptors (CXCR3 and CCR6) as well as expression of specific chemokine ligands (CCL20) on the target tissues. In 2012, Oo et al., conducted a study on a range of chronic liver diseases utilising serum and human liver explants, including PSC [81]. BECs were confirmed as driving recruitment of Th17 and IL-17+ CD8 T cells expressing CCR6, CXCR3 and CXCR6 ligands respectively to inflamed bile ducts expressing chemokines CCL20 and CXCL9. CCL20 and CXCL9 expression by injured bile ducts, is augmented by IL-17, establishing a chronic periductal immune response and positive feedback loop [81].

2.6.2. Monocytes in IL-17 mediated inflammation

IL-17 A/F signal through IL-17RA and IL-17RC expressed on KCs and infiltrating monocytes, inducing cytokine secretion of IL-6, IL-1β and TGFβ contributing to hepatic fibro-inflammation. Human PSC studies have identified enrichment of IL-17RA+ monocytes in fibrotic PSC liver explants. Utilising spatial transcriptomics, IL-17RA+ tissue monocytes

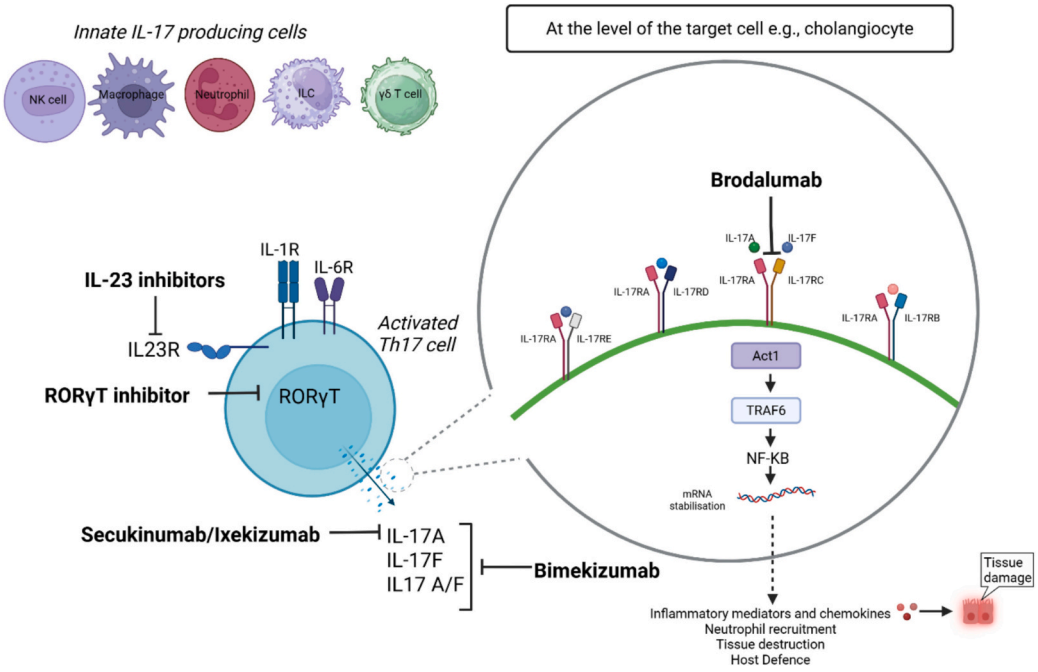

Fig. 2. Direct and indirect therapeutic targets for IL-17 axis mediated blockade [78]. Several targets are already approved for use in a number of other autoimmune conditions.
IL, interleukin; ILC, Innate lymphoid cell; NK, natural killer; γδ, gamma delta; Th17, T helper 17; IL17RA, interleukin 17 Receptor A subunit. *Created in BioRender. Elzubeir, A. (2025)* https://BioRender.com/v86d672

and IL-17RA+ T-cell subsets were identified at higher frequencies and mapped to fibrotic tissue in end-stage PSC relative to that of the parenchyma [82], supporting an association between IL-17RA+ immune cell localisation and fibrotic disease progression.

2.6.3. Neutrophils as IL-17 effectors

Neutrophils are central to acute inflammation in PSC and are heavily influenced by IL-17. Neutrophils are recruited to and perpetuate damage to bile ducts through CXCL8 (IL-8) chemotaxis, either through IL-17 or senescent BEC signalling [83]. Compared with controls, PSC has been associated with increased biliary neutrophil and $CD103^{+}CD69^{+}CD8$ tissue-resident memory (TRM) T cell infiltration, with these populations located in closer proximity to the biliary epithelium. IL-17+ biliary resident T cells are also linked to neutrophil recruitment in PSC livers [83].

Whilst our understanding of the role of neutrophils in the IL-17 axis is expanding, it has become apparent that neutrophils not only possess the proclivity to drive IL-17 secretion or skew T-cell differentiation towards a Th17 phenotype through IL-23 production and other means [1], but reciprocally Th17 cells prime and recruit neutrophils to sites of tissue damage and inflammation [1,22]. Interestingly, studies have reported a decrease in hepatic neutrophil accumulation and subsequent liver injury following IL-17 neutralisiation [84,85].

2.6.4. Th17 skewing in PSC

A single-cell atlas mapping intrahepatic T cells in PSC patients showed a developmental skewing of tissue-resident naïve T cells towards Th17 polarization as opposed to Foxp3+ Tregs. This propensity was observed to be more abundant in PSC compared to other liver diseases [86]. A complementary study, confirmed pathological biliary resident CD4+ T cells are dominated by Th17 cell aggregates in PSC and non-PSC human cholangiopathies from explanted livers [87]. Furthermore, as reported in other studies, Th17 related cytokines IL-17 A, IL-17F and associated IL-17RC were found to be upregulated in cholangiocytes after co-culture. Direct cholangiocyte-immune cell signalling facilitates pathogenic Th17 lineage expression. This pathogenic Th17 process appears to be boosted by CD100 mutations (a causal mutation in a Mendelian form of PSC), which contributes to site specific Th17 skewing and consequently localised biliary inflammation [87]. This would suggest that cholangiocytes participate in bidirectional crosstalk and are not merely passive in the ensuing biliary inflammation observed in PSC [88].

2.6.5. Bile acids as IL-17 modulators

Hepatotoxic bile acids have been implicated in driving cholestatic liver injury [89]. Pathological bile acid induced IL-23 cytokine signalling during the course of cholestasis synergistically promotes upregulation of the IL-17/Th17 axis, hepatic inflammation, neutrophil accrual and immune dysregulation. In one study bile acid induced IL-23 production in bile duct ligated (BDL) mice (a cholestatic murine mimic) and mice fed a bile acid diet, promoted Th17 expansion and IL-17 A secretion [84]. In this same model, IL-17 inhibition subdued hepatic necrosis, proinflammatory cytokines and neutrophil accumulation [84].

2.6.6. Microbial mechanisms

Th17 cells play a vital role in defending against pathogenic infections. PSC is often complicated by bacterial and/or fungal infection, which may drive IL-17 mediated inflammation. Studies postulate that fungal cholangitis in particular, may expedite disease progression [90,91]. Katt et al. demonstrated in vitro pathogenic stimulation of PBMCs with bacterial and fungal isolates cultured from PSC patient bile samples, stimulated an increase in Th17 cellular expression and IL-17 A expressing cellular aggregate in periductal regions in PSC compared to controls [92]. A later ex vivo and in vitro study by the same group corroborated their earlier findings, demonstrating amplification of Th17 cells by microbe stimulated PBMCs from patients with PSC (even in early disease stages) when compared to healthy controls and PBC, suggesting heightened Th17 differentiation in PSC [93]. This was associated with an increase in IL-17 A production and pathogen induced IL-1β secreting macrophages around BECs, which in turn promoted cholangiocyte expression of Th17 attracting chemokine CCL20 and proinflammatory cytokines IL-6 and IL-23, cytokines known to drive Th17 differentiation [93]. Th17 cell frequencies and IL-17 levels were similarly elevated in patients with PSC alone and PSC-IBD, yet notably lower in those with IBD only. Conversely, Th1 cell frequencies were comparable across PSC, PBC, and healthy controls [93].

PSC-IBD exemplifies bi-directional gut-liver axis crosstalk. A key study reported significantly greater frequencies of *Klebsiella pneumonia, Proteus mirablis* and *Enterococcus gallinarum* in PSC patients' faecal microbiota compared to healthy controls or UC alone in vivo. When gnotobiotic mice were inoculated with PSC-UC patient microbiota, they developed Th17 mediated hepatobiliary inflammation [94]. Interestingly, targeting the IL-17 pathway with an ROR-γt inverse agonist supressed Th17 numbers and hepatobiliary injury, as did antibiotics (metronidazole and vancomycin) and an intravenous-administered bacteriophage cocktail targeting *Klebsiella pneumonia* [94,95]. However, IL-17 A antibodies were less effective [94], suggesting a more complex role for the IL-17 axis. These findings support the pathogen driven IL-17/Th17 pathway as being contributory to the development of bile duct injury, while also highlighting uncertainty regarding which components of the IL-17/Th17 axis should be therapeutically targeted to ameliorate liver disease.

Genome wide association studies (GWAS) have identified polymorphisms relating to pathogen defence and Th17 differentiation. Genes such as IL-21, REL (encoding c-REL, a member of the NF-κB family) and CARD9 (encoding a protein critical for BCL10 assembly which is involved in NF-κB activation) have been identified by GWAS in PSC. These genetic variations implicate IL-17 and the dysregulated immune response as central to PSC development and progression in the presence of pathogens [96–98].

2.6.7. IL-17 driven liver fibrosis

A pivotal paper by Meng et al. [99], demonstrated an upregulation in IL-17 A and IL-17F, and their associated receptors IL-17RA and RC in fibrotic livers and serum of BDL mice ($n = 10$, $p < 0.01$ and $p < 0.05$ respectively) compared to sham counterparts. This correlated with an increase in IL-17+ expressing cells, with T cells being the chief source of IL-17 A. These findings were replicated in human disease. Meng et al. [99], report findings consistent with a role for IL-17 signalling in fibrogenesis, suggesting it may contribute to liver fibrosis. To support this hypothesis, IL-17RA−/− mice were resistant to BDL induced liver fibrosis (≈75% inhibition), as evidenced by a decrease in collagen deposition, myofibroblasts (of which HSCs are the major source) and pro-fibrogenic cytokines. As a result, liver function tests (alanine transaminase (ALT)) also improved. Conversely, administering anti-inflammatory IL-17E to BDL mice was hepatoprotective. These findings implicate IL-17 A as having a fundamental role in liver fibrosis progression in cholestatic liver disease and may serve as a biologically plausible therapeutic target in PSC.

Similar observations have been reported in other cholestatic liver disease models, in which abrogation of the IL-17 pathway either through genetic or pharmacological attenuation (e.g., IL-17RA knockout mice or via anti-IL-17 A treatment) results in attenuated hepatic fibroinflammation, as a result of downregulation of pro-inflammatory cytokines, KC, HSC, and/or hepatic neutrophil accrual [84,85,100,101]. IL-17 A neutralisation in BDL mice has shown promising anti-fibrotic effects by shifting immune polarization from Th2/Th17 towards a Th1 response, improving liver function and restoring autophagy via STAT3 suppression (a key transcription factor in the IL-17 signalling pathway) [101]. Somewhat surprisingly, IL-10 an anti-inflammatory cytokine involved in reinforcing the Treg signalling pathway and Th17 suppression, paradoxically mitigated these beneficial effects by stimulating

STAT3 activity and impairing essential autophagy [101]. Underscoring the complex interplay between immune pathways in PSC.

2.6.8. IL-17 controversies

A study investigating the effect of IL-17+ CD8 T-cells on cholangiocytes in vitro and murine cholangiocytes in vivo found that IL-17 A/F inhibition exacerbated cholangitis in autoimmune liver disease (AILD) models [102]. The proposed mechanism suggests that IL-17+ CD8+ T-cells induce programmed cell death ligand 1 (PD-L1) in cholangiocytes; which serves as a protective mechanism by supressing T-cell proliferation and limiting CD8+ T-cell mediated hepatobiliary cytotoxicity. Thus, pan-neutralisation of IL-17 cytokines may inadvertently exacerbate cholangitis [102]. However, a separate study on PD-L1 checkpoint inhibitor use in patients with cancer and concurrent autoimmune and cholestatic liver diseases reported that PD-L1 blockade was safe [103]. This suggests that PD-L1 inhibition does not universally exacerbate liver inflammation. Nonetheless, the contrasting findings highlight the need for further research in this area.

Direct human evidence for IL-17 pathway manipulation in PSC remains limited. Most mechanistic support for inhibiting the IL-17/Th17 axis is derived from preclinical cholestatic models, alongside a smaller body of PSC-specific human translational studies- often comprising advanced disease/explant tissue.

2.7. IL-17 and cancer risk in PSC

Conflicting studies implicate elevated IL-17 expression to be either pro- or anti-tumorigenic. However, recent evidence suggests its pro-tumorigenic proclivity is dependent on the tumour microenvironment and/or the cytokine milieu present. Two explanatory mechanisms have been proposed: firstly, that cells associated with the Th17 pathway either directly recruit the immunosuppressive myeloid compartment in an IL-17 mediated manner or indirectly by cancer cells in a chemokine-dependent fashion. Secondly, there is intrinsic intra-tumoral IL-17 signalling leading to enhanced in tumour cell survival, including angiogenesis promotion [104]. This pathway has been shown to be of relevance in the development of cancers in multiple organ sites, in particular the breast, lung, pancreas and skin and critically in the context of PSC: the liver, biliary tree and colon.

2.7.1. Colorectal cancer

Early evidence of the role of IL-17 in the development of cancer came from Wu et al. They demonstrated that using the murine APC^{Min} model (bearing multiple intestinal neoplasia), enterotoxigenic *Bacteroides fragilis* (ETBF) infection accelerated IL-17 A-dependent tumour development compared to mice colonised with a non-toxin producing strain and sham controls [105]. Additionally, antibody mediated blockade of IL-17 and IL-23R inhibited ETBF colitis, colonic hyperplasia and tumour formation [105].

Furthermore, abundant IL-17 A expression in early-stage colorectal tumours has been associated with rapid progression to metastasis and poor outcome when compared through quantitative real-time PCR to immune gene clusters representing Tregs, Th1/cytotoxic T cells and Th2 cells from RNA extracted from 125 colonic tumour samples [106]. This implicates IL-17 as being of potential prognostic value in colorectal cancer (CRC). Low cellular IL-17+ density, as assessed by immunohistochemistry of tissue microarrays from two regions within the primary resection tumours, was associated with significantly better 10-year disease free survival than patients with high intratumoral IL-17+ density (HR = 3.08, $p = 0.0009$) [106].

Finally, a sentinel paper by Shaw et al [107] investigated the immunopathogenesis of colorectal neoplasia in patients with PSC-IBD, IBD alone and healthy controls using single-cell RNA sequencing with T cell and B cell receptor repertoire analysis extracted from dissociated colonic biopsies via flow-assisted cell sorting (FACS) following endoscopy. Patients were clustered into four discrete groups based on histological and transcriptional markers of inflammation: two uninflamed and two inflamed (one with lower grade and the other with higher grade inflammation). PSC-IBD patients were overrepresented in the subgroup with higher grade inflammation and exhibited a greater frequency of IL-17 A+ FOXP3+ CD4+ T cells compared to those with IBD only.

2.7.2. Cholangiocarcinoma

PSC patients have a significantly increased risk of cholangiocarcinoma (CCA) [108]. In one study IL-17 A immunohistochemistry identified greater IL-17 A expression locally in PSC associated cholangiocarcinoma (CCA) tissue compared to CCA de novo [109]. In the same study, patient-derived CCA organoids were exposed to five cytokines, IL-1β, IL-6, IL-17 A, IFN-γ, TNF-α; IL-17 A was the only cytokine that demonstrated a significantly increased stimulatory effect on CCA cell proliferation rate (38% ± 16% $p < 0.05$) and organoid size (45.9% ± 16.4% $p < 0.01$). This potentially implicates IL-17 A in PSC-CCA tumour growth in vitro. Additionally, Ki-67 immunohistochemistry to assess proliferation demonstrated a significantly higher proliferation rate in PSC-CCA compared to CCA de novo (41.3% ± 5.7% vs 25.8% ± 4.1%; mean ± standard error, $p = 0.038$) [109]. Linear regression demonstrated a significant correlation between the number of Ki-67 positive cells and IL-17 A cells in PSC-CCA and sporadic CCA ($p = 0.018$) although with a low correlation co-efficient (R square = 0.14) [109]. This suggests that PSC-CCA may in part progress due to the local immune environment.

2.7.3. Hepatocellular carcinoma (HCC)

Patients with PSC also have an increased risk of HCC, linked to fibrosis. IL-17+ producing CD8+ T cells have been found to accumulate in invading tumour boundaries in HCC, co-localising with tumour-activated CD68+ monocytes secreting IL-1B, IL-6 and IL-23, triggering proliferation of IL-17+ CD8+ T cells [110]. IL-17+ cell density has been found to correlate with advanced angiogenesis and reduced survival in HCC patients [110].

Studies targeting direct or indirect neutralisation of the IL-17 pathway have demonstrated encouraging results in PSC and other liver diseases. A recent single arm, open-label pilot study in PSC ($n = 18$) of vidofludimus calcium, a dihydroorotate dehydrogenase inhibitor known to drive lymphocyte apoptosis and additionally attenuate Th17 cells and the secretion of IL-17, was found to be safe and efficacious. Just under a third of patients in the per protocol analysis ($n = 11$) met the primary outcome of reduction in alkaline phosphatase (ALP) at treatment cessation of >25% (95% CI 6.0–61.0%) [111].

Matsuda et al., observed a reduction in hepatic fibrosis markers following IL-17 blockade. In psoriasis patients treated with brodalumab (an IL-17RA antagonist), a non-invasive marker of liver fibrosis (fibrosis 4 Index (FIB-4)), was observed to significantly decline compared to both biologic naïve control patients ($p < 0.01$) and those treated with the IL-17 A inhibitor (secukinumab) ($p < 0.05$) [112]. Admittedly, this retrospective study has a small sample size ($n = 20$) and did not assess patients with concomitant PSC, with steatotic liver disease being the more likely comorbidity. A larger, recent observational study examining hepatic safety of IL-17 blockade in psoriasis and psoriatic arthritis ($n = 123$; including 22 patients with intermediate-high fibrosis scores) treated for 12 months with ixekizumab or secukinumab reported stable FIB-4 and liver enzymes, with no hepatic safety concerns [113]. While these findings are reassuring, they are again derived from non-PSC populations and longer-term real-world hepatic safety data for IL-17 inhibition particularly in cholestatic liver disease- remains limited.

2.8. An overview of therapeutic targets of the IL-17 axis

The outlined evidence points to the IL-17/Th17 axis as a key mediator of biliary fibro-inflammation pathognomonic of PSC. Given the lack of approved therapies for this orphan disease, targeting the IL-17

pathway may represent a plausible therapeutic strategy. Four IL-17 inhibitors are already approved for other chronic inflammatory and autoimmune conditions (Supplementary Table 3).

2.9. Brodalumab

In 2017 brodalumab (Kyntheum) became the first, and to date the only, IL-17RA inhibitor licensed for use. Brodalumab is a fully humanised IgG2 monoclonal antibody (mAb) which binds to the IL-17RA subunit with high affinity with resultant inhibition of IL-17 A, IL-17C, IL17E, IL-17F and IL-17 A/F heterodimer signalling. Brodalumab is approved by the European Medicines Agency for moderate to severe chronic plaque psoriasis in adults who are candidates for systemic therapy [17,114]. Brodalumab is administered subcutaneously at a dose of 210 mg weekly for the first three weeks and two weekly thereafter as maintenance therapy.

A special warning has been issued for brodalumab use in patients with a history of suicidal ideation and behaviours (SIB). Nonetheless, a causal association between brodalumab and an increased risk of SIB has not been established [115]. An updated seven year pharmacovigilance report from 5449 patients in the USA (7845 patient years) identified no completed suicides and only one attempted suicide in year 3 [116]. However, clinicians are advised to weigh the risks and benefits of brodalumab use in patients with a history of depression or SIB [117]. Brodalumab is also contraindicated in patients with active CD and clinically active important infections (e.g., active tuberculosis) [115].

2.10. Secukinumab

Secukinumab (Cosentyx) is a fully humanised IgG1κappa anti-IL17 mAb, which selectively targets a single cytokine: IL-17 A, thereby inhibiting its conformational binding with IL-17RA/RC. Its inhibition ameliorates the contribution of IL-17 A mediated inflammatory response. Secukinumab is administered subcutaneously and was the first licensed IL-17 A cytokine antagonist, having gained licensing approval in 2015 for moderate to severe plaque psoriasis. Having proven efficacious with a favourable safety profile, this approval was later extended by the U.S. Food and Drug Association (FDA) to include psoriatic arthritis, ankylosing spondylitis, hidradenitis suppurativa and non-radiographic axial spondylarthritis [17,118]. The recommended dose varies by indication. Secukinumab is recommended for patients with an inadequate response to conventional therapy or those who are candidates for systemic therapy. Similarly to brodalumab, clinically important active infections and IBD feature as contraindications and special warnings respectively [118].

2.11. Ixekizumab

Ixekizumab (Taltz) is a humanised IgG4 mAb that binds with high affinity to IL-17 A (IL-17 A and IL-17 A/F) preventing its interaction with IL-17RA/RC [119,120]. Ixekizumab received FDA approval in 2016 for use in moderate to severe plaque psoriasis, latterly it received similar approvals for psoriatic arthritis (2017) and axial spondylarthritis (2019) [17,121]. The recommended induction dose is 160 mg subcutaneously, and 80 mg thereafter as maintenance therapy either on alternative weeks or four weekly for psoriasis and psoriatic arthritis respectively [120,121].

2.12. Bimekizumab

Bimekizumab (Bimzelz) is the first bispecific IL-17 A and IL-17F IgG1 neutralising antibody, uniquely targeting IL17 A and IL-17F (homodimers and heterodimers). Thereby effectively inhibiting interaction of available IL-17 A and IL-17F hetero and homodimers with the IL-17RA/RC complex [122,123]. Bimekizumab is the latest IL-17 inhibitor to receive approval for plaque psoriasis, psoriatic arthritis, hidradenitis suppurativa and axial spondyloarthritis [122,123]. In vitro studies implicate a more significant reduction in pro-inflammatory cytokines IL-8 and IL-6 being observed with bimekizumab administration compared with a single IL-17 A cytokine inhibitor in psoriatic arthritis ($p < 0.05$) [124]. As with all IL-17 inhibitors, bimekizumab is not recommended for use in patients with known IBD.

2.13. IL-17 inhibition: Adverse events

Several of the side effects and adverse events (AEs) associated with IL-17 blockade are as a direct result of inhibition of its protective functions. The evidence to date demonstrates IL-17 inhibitors have a convincing efficacy, safety, and tolerability profile.

Whilst each IL-17 blocker has its own safety and side effect profile owing to their different modes of action, they share many commonalities. Dependent on the agent the most frequent AEs with IL-17 blockade are non-serious infections, upper respiratory tract infections (frequently nasopharyngitis), oral candidiasis (brodalumab), injection site reactions, headache and fatigue. Most AE are typically mild, self-limiting and do not require drug discontinuation. Serious adverse events are rare [115,125]. Neutropenia is a rare complication of anti-IL-17 treatment, most cases are mild, transient and reversible not requiring treatment cessation. Grade 4 neutropenia ($<0.5 \times 10^9$/l) in the trial setting was rarely reported [126].

As it stands, IL-17 blockers have not been designated a prescribing warning relating to malignancy. Greater long-term data will help to elucidate a conclusive understanding of the safety and role of IL-17 inhibitors in relation to hepatic safety and malignancy.

2.14. Liver safety with anti-IL-17 treatment

Clinically apparent liver injury appears uncommon with IL-17 antagonists. In pre-marketing clinical trials, the frequency of liver enzyme elevations with anti-IL-17 therapy was broadly comparable to placebo. Since approval, clinically apparent liver injury is rare with serum enzyme elevations reported as being no more frequent than with placebo. However, ongoing pharmacovigilance is important [127–129]. Currently, there are no associated manufacturer warnings or dose recommendation with regards to hepatic impairment as these agents have not been studied in this cohort [115,118,120,130].

The IL-17/Th17 axis has context dependent roles, as previously described, however Th17 cells also exhibits instability and plasticity, where their effects may differ by tissue compartment and disease stage. Consequently, while PSC-relevant models infer biological plausibility for IL-17 modulation, therapeutic translation should be interpreted cautiously pending PSC-specific clinical trial safety data and pharmacodynamic evidence.

2.15. Paradoxical effects in IBD following IL-17 blockade- should this be of concern in PSC?

Key studies have implicated Th17 cells in IBD pathogenesis and identified elevated IL-17 A activity within the intestinal mucosa of patients with IBD compared to controls or healthy subjects [131–135]. Nonetheless, human and animal colitis models have demonstrated contradictory results with regards to the role of IL-17 in ameliorating or exacerbating colonic inflammation [136–138]. IL-17 mAbs administered to an experimental murine model of induced colitis, (dextran sulphate sodium (DSS)) exacerbated colitis [137]. In contrast a study by Zhang et al. [138], demonstrated attenuated colonic inflammation in IL-17R knockout mice. This and other studies led to the eventual testing of both secukinumab and brodalumab in patients with moderate to severe CD. A double-blind randomised controlled trial (RCT) of 59 CD patients were randomised to intravenous secukinumab (39 patients) or placebo (20 patients) [139]. The trial was prematurely terminated due to meeting pre-specified futility criteria i.e., failure to meet their primary

efficacy outcomes (Crohn's disease activity index (CDAI) reduction of ≥50 points). Statistically significant differences in mean CDAI were found to be in favour of placebo ($p = 0.043$). The intervention arm saw more adverse events (74% vs 50%) especially with regards to infections. Four patients were noted to have experienced a worsening of their CD [139]. In 2016 a phase 2, double blind, RCT of brodalumab in moderate to severely active CD was conducted in 130 patients [25]. Patients were randomised 1:1:1:1 to 210 mg, 350 mg, 700 mg or placebo. The proportion of patients achieving clinical remission (CDAI <150) at 6 weeks was selected as the primary endpoint. The study was terminated early due to a disproportionate accrual of participants presenting with worsening of their CD in the treatment arm compared to placebo (OR 6.64, 95% CI 1.48, 29.88), in addition to failing to meet its primary efficacy outcome [25].

Despite early data suggesting a potential role for IL-17 blockade in CD, the RCT findings were surprising and disparate from those seen in other autoimmune diseases [140–142]. Such results highlight the dual functionality and plasticity of the IL-17 pathway, but also its important and perhaps distinct role in CD and the gut compared to other inflammatory conditions [25]. Whilst the rationale behind these conflicting results remains unclear, explanatory alternative hypotheses suggest a role of increased colonic pathogenic microorganisms, particularly *Candida albicans* [143], and loss of the epithelial barrier function orchestrated by drug induced inhibition of IL-17's protective functions [25]. The degree to which over-expression of IL-17 activity may be either causatory, consequential or contributory to IBD pathogenesis is undetermined. Remarkably, the attenuation of pathways slightly upstream of and synergistic with the IL-17 pathway, by ustekinamab, vidofludimus, risankizumab and mirkizumab have proven to be efficacious in IBD, whilst direct targeting of IL-17 to date has not [144–147].

To provide a more comprehensive understanding of IL-17 inhibitors paradoxical role in colitis development, a series of metanalyses evaluating the risk of development of IBD in psoriasis, psoriatic arthritis and ankylosing spondylitis during anti IL-17 treatment have been undertaken. Results concluded IBD events were rare and no detectable significant difference in risk of new IBD exists between treatment and control groups [148,149]. In one study, no difference in pooled risk of new onset IBD in the best- and worst-case scenario was observed (worst case scenario RD 0.0008, 95% CI -0.0005, 0.0022) [148].

Given that the immunology of PSC associated colitis may well be different, the above results should not discourage studies in the field of PSC-IBD.

2.16. Controversies and considerations of anti-IL-17 therapy in PSC

Several safety considerations have emerged from anti-IL-17 therapy in other autoimmune and chronic inflammatory conditions and require consideration in PSC. First, IL-17 blockade can increase susceptibility to infections, including candidiasis, which is of particularly relevance in PSC as *Candida albicans* infections not only stimulate IL-17 A expression but its persistence is associated with disease progression and reduced transplant-free survival [92,150,151]. Second, there are class concerns of paradoxical intestinal inflammation reported in studies including prior CD trials, underscoring the need for rigorous gastrointestinal safety monitoring in PSC, where concomitant IBD is common and symptoms may be discordant with mucosal activity. Third, PSC populations include individuals with advanced disease with an increased risk of infections and decompensating events- pharmacodynamics in advanced liver disease warrants careful consideration. Finally, robust evidence of clinical benefit (or harm) of IL-17 blockade in PSC beyond basic science and translational studies are required. Prospective, well designed clinical trials are required and should incorporate structured hepatic and colonic safety outcomes.

2.17. Strengths and limitations

This review synthesises emerging evidence implicating the IL-17/Th17 axis in PSC by integrating findings across human tissue studies, translational datasets and experimental models. A key strength is the focus on mechanistic plausibility- linking IL-17 biology to cholangiocyte injury, immune cell recruitment, and hepatic fibro-inflammatory pathways. We also bridge basic science and clinical translation by summarising the therapeutic landscape of the IL-17 pathway, whilst highlighting areas of uncertainty and opportunity for future investigation.

There are several inherent limitations of a narrative review. While a structured literature search was conducted, a narrative review does not aim to systematically identify all available literature, but rather selectively include studies deemed most relevant, which may introduce selection bias and limit reproducibility. Unlike systematic reviews, a formal quality assessment and quantitative synthesis was not performed, which may introduce subjectivity in synthesising results. The heterogeneity of the included studies and lack of quantitative synthesis may limit the strength of causal inferences. Mechanistic murine or preclinical models whilst capturing selected featured of PSC (e.g., cholangiocyte injury) do not faithfully recapitulate its human complexity, including gut-liver axis contributions in concomitant PSC-IBD, heterogeneity in PSC phenotype, complex cell-cell interactions, gender predilection, long disease courses and increased gastrointestinal and hepatobiliary malignancy contributions. The human evidence base remains limited by small sample sizes often weighted towards advanced disease or explant tissue, which may not represent early-stage PSC, where immune pathways and therapeutic responsiveness may differ. Additionally, IL-17 signalling has context-dependent roles. Therefore, interpretation of IL-17 blockade in PSC must remain cautious, particularly given class concerns around paradoxical intestinal inflammation with IL-17 inhibition and limited PSC-specific clinical safety data. Finally, while IL-17RA antagonism is biologically plausible, direct pharmacodynamic evidence linking IL-17 blockade to clinical benefit in PSC is not yet established; future studies should incorporate receptor engagement, IL-17 activity and downstream cytokine/chemokine readouts pre and post-treatment to strengthen mechanistic contributions.

3. Conclusion

The liver is an essential organ in immune surveillance and tolerance. Disruption of this delicately balanced immune regulation can result in pathogenic chronic inflammation. The IL-17 axis and its associated pro-inflammatory secretory cytokines and chemokines have been implicated in PSC pathogenesis, promoting fibro-inflammation, immune cells recruitment, and cytokine and chemokine production leading to liver injury. Whilst preclinical and early translational models suggest inhibition of this pathway may lead to the amelioration or abrogation of fibro-inflammatory pathways in PSC, early phase clinical trials are urgently needed to clarify its role. The IL-17 axis' complex dual roles in host defence and autoimmunity, present a therapeutic challenge. Further research is required to determine if IL-17 inhibition is a viable therapeutic intervention in PSC, particularly in those with concomitant IBD, for this we will need to explore beyond pre-clinical models. The SABR-PSC pilot study [78], is to the best of our knowledge, the first clinical study directly evaluating IL-17RA antagonism in PSC focusing primarily on safety and feasibility. Nonetheless, pharmacodynamic confirmation of IL-17 pathway suppression, together with evidence of clinically meaningful benefit in PSC remain the critical next steps.

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

No AI tools were used in the creation of this manuscript.

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Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.autrev.2026.104095.

Data availability

All data relevant to the study are included in the article.

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