Lysophosphatidic acid receptor 1 inhibition: a potential treatment target for pulmonary fibrosis

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This review discusses how novel pharmaceuticals target lysophosphatidic acid signalling in pulmonary fibrosis and summarises clinical trials of these investigational drugs within select fibrotic lung diseases. https://bit.ly/4cUcumz

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Abstract

Lysophosphatidic acid (LPA)-mediated activation of LPA receptor 1 (LPAR1) contributes to the pathophysiology of fibrotic diseases such as idiopathic pulmonary fibrosis (IPF) and systemic sclerosis (SSc). These diseases are associated with high morbidity and mortality despite current treatment options. The LPA-producing enzyme autotaxin (ATX) and LPAR1 activation contribute to inflammation and mechanisms underlying fibrosis in preclinical fibrotic models. Additionally, elevated levels of LPA have been detected in bronchoalveolar lavage fluid from patients with IPF and in serum from patients with SSc. Thus, ATX and LPAR1 have gained considerable interest as pharmaceutical targets to combat fibrotic disease and inhibitors of these targets have been investigated in clinical trials for IPF and SSc. The goals of this review are to summarise the current literature on ATX and LPAR1 signalling in pulmonary fibrosis and to help differentiate the novel inhibitors in development. The mechanisms of action of ATX and LPAR1 inhibitors are described and preclinical studies and clinical trials of these agents are outlined. Because of their contribution to numerous physiologic events underlying fibrotic disease, ATX and LPAR1 inhibition presents a promising therapeutic strategy for IPF, SSc and other fibrotic diseases that may fulfil unmet needs of the current standard of care.

Introduction

Fibrosis is a pathologic hallmark of diverse diseases and disease processes, including interstitial lung diseases (ILDs) such as idiopathic pulmonary fibrosis (IPF) and systemic sclerosis (SSc)-ILD [1–4]. Although their distinct disease aetiologies are not completely understood, IPF and SSc-ILD share the common pathologic features of low-grade inflammation and excessive extracellular matrix (ECM) deposition within the lung. Patients with SSc are also affected by fibrosis in other organ systems, including the skin, as well as by vasculopathy in different organs [2, 5, 6]. Processes that contribute to fibrosis are necessary for several physiologic events, including wound healing. However, uncontrolled, excessive ECM deposition and inflammation are pathogenic and may lead to a chronic profibrotic state, culminating in fibrotic disease [1, 5, 7, 8]. Among the multiple mechanisms that contribute to fibrosis, lipid mediators such as lysophosphatidic acid (LPA) that primarily activate LPA receptors (LPARs) and are predominantly produced by autotaxin (ATX) may play a central role in the convergence of inflammation and fibrosis [3, 4, 9–13].

This review will focus on the roles of ATX and LPAR1 in IPF and SSc-ILD, diseases in which the leading causes of death are progression of pulmonary fibrosis and respiratory failure [14, 15]. Therapeutic options for these diseases are limited and may be tolerated poorly by patients [16, 17]. Thus, several mechanisms that underly fibrosis are currently pursued as targets for the development of novel therapies such as LPAR1 and ATX inhibition [12]. Activation of LPAR1 by LPA contributes to fibrosis, with some preclinical studies suggesting LPAR1 may disproportionally contribute to fibrosis more so than other LPAR family members [12, 18, 19]. The ATX/LPA/LPAR1 signalling axis also contributes to inflammation through mechanisms such as macrophage survival and activation [20, 21]. Numerous inhibitors of the ATX/LPA/LPAR1 signalling axis have entered clinical trials for fibrotic diseases [22–25]. Inhibitors of ATX and LPAR1 signalling in clinical development have varying mechanisms of action (MOA) and are emerging as potential therapies for IPF and SSc-ILD. This review describes these investigational therapies and their potential to intervene with these disease processes. The main objectives of this review include the following: 1) review ATX and LPAR1 signalling and their roles in fibrotic disease with a focus on IPF and SSc-ILD; 2) discuss ATX and LPAR1 inhibition as a potential therapy for fibrotic disease and differentiate the MOA of ATX and LPAR1 pathway inhibitors; and 3) review ongoing clinical trials of ATX and LPAR1 inhibitors.

Physiologic role of ATX/LPA/LPAR1 signalling

ATX

ATX is an enzyme with lysophospholipase D activity and is the predominant enzyme that converts lysophosphatidylcholine (LPC) to LPA in the plasma [26, 27]. LPA is a bioactive phospholipid that mediates a host of physiologic processes (*e.g.* cell migration, proliferation and differentiation, cytoskeleton regulation, macrophage survival, inflammation, and alteration of cell–cell adhesions) and signals through a six-member family of G-coupled protein receptors, LPAR1–6 [21, 28]. Because ATX largely contributes to LPA availability, ATX activity is associated with outcomes of LPA signalling independent and dependent of LPAR, including LPAR-mediated fibrosis and inflammation [9, 11, 21, 28–30]. In ATX-dependent LPA synthesis, phospholipase A-1 or A-2 removes a fatty acid from the sn-1 or sn-2 position, respectively, from membrane phospholipids resulting in LPC, which is subsequentially hydrolysed by the lysophospholipase D activity of ATX to produce LPA [27, 28]. However, ATX is not the sole LPA producer, as LPA is also produced *via* ATX-independent mechanisms, albeit to a lesser extent. At least four intracellular ATX-independent pathways are capable of LPA production [28].

A recent study encompassing biochemical, cellular, and murine assays suggests that ATX also acts as an LPA chaperone to facilitate delivery of LPA to LPAR, independent of its catalytic activity [31]. This study revealed that ATX bound to LPA favours activation of LPAR6 more than LPAR1. Although *in vitro* and *in vivo* studies support the notion that LPA species and ATX-mediated chaperoning may influence LPAR isoform binding preference, questions remain regarding how ATX/LPA/LPAR signalling specificity affects biologic functions.

LPAR1 pathway

LPAR1 belongs to a six-member family of LPARs, each with numerous and sometimes redundant physiologic effects, including cell migration, proliferation and differentiation, cytoskeleton regulation, inflammation, and alteration of cell–cell adhesions, all of which are processes that contribute to fibrosis [8, 28]. LPA, the primary ligand of LPAR1, contains a glycerol backbone with a fatty acid chain at the sn-1 or sn-2 and a phosphate group at the sn-3 position [28]. Species of LPA are differentiated by the degree of saturation and length of the fatty acid chain and have varying affinities for LPA receptor isoforms [28]. LPAR1 has broad LPA species selectivity and binds both saturated and unsaturated LPA [32].

LPAR1, expressed by macrophages and fibroblasts amongst others cell types, promotes inflammation and fibrosis in various tissues (*e.g.* kidney, skin and lung) [4, 11, 12, 33–35]. After tissue injury (*e.g.*, bleomycin exposure) or during blood clotting, LPA levels increase locally to activate LPAR1 and promote a profibrotic state [4, 36]. The LPAR1-associated G-protein ($G\alpha_i$, $G\alpha_q$ or $G\alpha_{12/13}$) is activated upon binding of LPA to LPAR1 and this activation is associated with the aforementioned cellular events that contribute to fibrosis [3, 12, 37–42]. Preclinical evidence also suggests that LPAR1 indirectly increases ECM deposition through activation of fibroblast migration [4]. Additionally, LPAR1 increases activity of key inflammatory players such as NF-κB and c-jun N-terminal kinase; it also increases expression of chemoattractants and proinflammatory cytokines (*e.g.* interleukin-6 (IL-6), IL-8, chemokine C-X-C motif ligand 1 (CXCL1), CXCL8, C-C motif chemokine ligand 2 (CCL2) and CCL3) [12, 20, 33, 34, 43, 44].

Role of ATX and LPAR1 signalling in fibrotic diseases

IPF

IPF is characterised by progressive loss of lung function, dyspnoea and poor prognosis [1]. Approximately 70% of patients with IPF are males, with disease presentation usually occurring at an age of >60 years [16]. Risk factors for IPF include cigarette smoking, air pollution, other environmental exposures, genetics and older age [16]. An analysis of IPF survival in the literature estimates a median IPF survival of 3.2 years, with the majority of studies included in the analysis reporting median survival rates of 2–5 years [45]. Real-world data, although inconsistent, have demonstrated that approved IPF therapies (*i.e.* pirfenidone and nintedanib) are associated with improvements in survival [46–49]. For example, one study of 457 patients reported transplant-free survival rates of 3.4 *versus* 2.2 years with approved treatment *versus* without, respectively (p=0.005) [46]. However, although current pharmacologic therapies slow the decline of lung function in IPF, they do not halt disease progression and may have poor tolerability (table 1) [50, 51]. Further, the failure and termination of recent phase 3 clinical trials (Zephyrus-1 and ISABELA-1/2) that evaluated promising antifibrotic molecules (pamrevlumab (anti–connective tissue growth factor) and ziritaxestat (ATX inhibitor)) highlights challenges in drug development for IPF [24, 52, 53]. Thus, there remains an urgent need for better treatments for IPF with several phase 2 and 3 trials currently ongoing [54–59].

Preclinical and clinical studies have implicated ATX and LPA/LPAR1 signalling in IPF pathogenesis (figure 1). In one study, increased protein levels of ATX were observed in lung tissue and alveolar macrophages of the fibrotic interstitium from patients with IPF and in bronchoalveolar lavage fluid (BALF) from mice with bleomycin-induced lung fibrosis. Moreover, conditional ATX knockout in bronchiolar epithelial cells and macrophages protected mice from bleomycin-induced lung fibrosis [60]. Another study in a mouse model of bleomycin-induced lung fibrosis found that ATX protein levels and activity increased in BALF and lung homogenates (but not plasma) after bleomycin challenge and that the increase was dependent on vascular leak rather than increased mRNA expression of ATX [29]. Therefore, lung LPA production *via* ATX may be primarily dependent on ATX localisation *via* vascular leak and not local production of ATX. Collectively, these data suggest that ATX may contribute to pulmonary fibrosis and inflammation.

Regarding LPAR1 specifically, in a study of mice with bleomycin-induced pulmonary fibrosis, LPAR1 deficiency reduced fibroblast chemotaxis, vascular leakage and mortality [4]. Although LPAR1 deficiency did not affect fibroblast to myofibroblast differentiation, LPAR1-deficient mice exhibited reduced collagen accumulation following bleomycin injury, suggesting that LPAR1 indirectly drives collagen accumulation through fibroblast chemotaxis [4]. In another study of bleomycin-induced pulmonary fibrosis, LPAR1 knockout mice exhibited less bronchial epithelial cell apoptosis than LPAR1 wild-type mice. Additionally, serum-deprived primary mouse lung fibroblasts treated with LPA were more resistant to apoptosis than were untreated cells and inhibitors targeting LPAR1 attenuated this apoptotic resistance [3]. Collectively, these *in vivo* and *in vitro* observations suggest that LPAR1 contributes to vascular leakage, epithelial cell apoptosis and fibroblast chemotaxis and survival, all of which are contributory mechanisms of pulmonary fibrosis [3, 4] Further, LPAR1 mRNA expression is the highest among the LPAR family in pulmonary fibroblasts, supporting the importance of this isoform in LPA signalling outcomes in pulmonary fibrosis [4]. Clinically, elevated levels of LPA have been observed in BALF and plasma from patients with IPF [4, 12, 61]. Further, higher levels of plasma LPA associated with greater fibrosis in the lower lung and decline in lung function as measured by diffusing capacity of carbon monoxide (D_{LCO}) [61]. These observations suggest that LPA/LPAR signalling is also relevant for human pathology.

In a study using the bleomycin-induced pulmonary fibrosis mouse model, LPAR1 deficiency did not attenuate the inflammatory leukocyte response or leukocyte activation in BALF [4]. However, in humans with IPF, serum LPA levels positively correlate with inflammation-related biomarkers (*i.e.* CCL17 and CCL18) that also have profibrotic properties [61]. Thus, LPA may contribute to pathogenic fibrosis and inflammation within IPF.

SSc and SSc-associated ILD

SSc is a chronic connective tissue disease characterised by autoimmunity, vasculopathy and fibrosis of the skin and internal organs [5]. Categorised into two clinical subsets on the basis of cutaneous involvement (limited cutaneous SSc (lcSSc) and diffuse cutaneous SSc (dcSSc)), SSc is a heterogeneous disease and no therapeutic regimen has been found to be effective across various SSc phenotypes [5]. Patients with dcSSc experience profound skin fibrosis that is proximal as well as distal to the elbows/knees and generally progresses at a more rapid rate than those with lcSSc. However, both cutaneous subtypes are associated with serious internal organ involvement [62, 63]. Further, patients with dcSSc have a poor prognosis and low survival rate, estimated at 88 and 74% at 5 and 10 years, respectively [64].

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TABLE 1 Positive trials for idiopathic pulmonary fibrosis (IPF), systemic sclerosis (SSc), SSc-interstitial lung disease (ILD) and ILDs including SSc-ILD

Medication	Trial name; identifier	Patient population	Primary outcome	Relevant secondary outcome(s)	Safety
Positive phase 3 trials and currently ongoing phase 3 trials for IPF					
Pirfenidone *versus* placebo [110]	NA; JAPICCTCI-050121	IPF (n=267)	Significantly less decline in FVC with pirfenidone (p=0.04)	PFS time increased with high-dose pirfenidone (p=0.03); no significant change in lowest oxygen saturation measured by pulse oximetry during exercise test	Photosensitivity, anorexia, dizziness, elevated γ-glutamyl-transpeptidase
Pirfenidone *versus* placebo [103]	CAPACITY-004 and 006; NCT00287729, NCT00287716	IPF (n=779)	004: significantly less FVC% decline at week 72 006: no significant change in FVC% decline at week 72	Categorical change in FVC ⩾10%, PFS time and mean change in 6MWT distance significantly favoured pirfenidone *versus* placebo in the pooled data of both studies	Nausea, dyspepsia, vomiting, rash, dizziness, abdominal distension, stomach discomfort, abdominal pain, photosensitivity, anorexia, arthralgia, insomnia, weight reduction, asthenia, pharyngolaryngeal pain, pruritus, hot flush
Pirfenidone *versus* placebo [50]	ASCEND; NCT01366209	IPF (n=555)	Significant change in FVC% at week 52 (p<0.001)	Significant improvement in 6MWT (p=0.04) and risk of death (p<0.001)	Nausea, dyspepsia, vomiting, gastro-oesophageal reflux, headache, rash, dizziness, anorexia, decrease in weight, insomnia
Nintedanib *versus* placebo [51]	INPULSIS-1 and 2; NCT01335464, NCT01335477	IPF (n=1066)	Adjusted annual rate of change in FVC favoured nintedanib *versus* placebo (p<0.001)	Significant increase in time to first acute exacerbation with nintedanib in INPULSIS-2 but not INPULSIS-1; no significant change in SGRQ in INPULSIS-1 and significant improvement in INPULSIS-2 (p=0.02)	Diarrhoea, nausea, vomiting
Positive and pivotal phase 2 and 3 trials and currently ongoing phase 3 trials for SSc, SSc-ILD and ILDs including SSc-ILD					
CYC *versus* MMF [111–113]	SLSII; NCT00883129	SSc-ILD (n=142)	Significant improvement in FVC% in both arms at 12, 18, 21 and 24 months; no significant difference between arms	Significant improvements in TDI, SGRQ and radiologic fibrosis	Leukopenia and thrombocytopenia were more common in CYC arm (p<0.05); anaemia occurred similarly in both arms (CYC, 26; MMF, 18)
CYC *versus* placebo [114, 115]	The Scleroderma Lung Study; NCT00004563	SSc-ILD (n=158)	Improved FVC% at 12 months in CYC *versus* placebo group (p<0.05)	At 12 months, significant improvements in TLC%, TDI, radiologic fibrosis and HAQ-DI in CYC *versus* placebo (all p<0.05); no significant difference in D_{LCO} or D_L:VA All improvements (CYC *versus* placebo) besides dyspnoea waned 12 months post-treatment	Leukopenia and neutropenia
RTX *versus* CYC [116]	RECITAL; NCT01862926	CTD-ILD[#] (n=101; SSc-ILD: n=37)	Significant improvement in FVC in both arms, similar between arms (weeks 24 and 48)	No significant difference in D_{LCO}, 6MWT or disease and QoL assessments, with exception of improved GDA score at week 48 favouring the CYC arm (p=0.025)	GI disorders, general disorders, administration site reactions, neurologic disorders in CYC *versus* RTX arm
RTX/MMF *versus* placebo/MMF [117]	EvER-ILD; NCT02990286	ILD[¶] (n=122; SSc-ILD: n=23)	CFB to 6 months in FVC% favoured RTX/MMF *versus* placebo/MMF groups (p=0.027)	PFS was greater in RTX/MMF *versus* placebo/MMF group (p=0.03) No between-group differences for SF-36, glucocorticoid doses, 6MWT, D_{LCO}, dyspnoea, cough, HRCT ILD extent or bronchiectasis scores	Infection, infusion-related reaction, cardiac disorders

Continued

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TABLE 1 Continued

Medication	Trial name; identifier	Patient population	Primary outcome	Relevant secondary outcome(s)	Safety
RTX *versus* placebo [118]	DESIRES; NCT04274257	SSc (n=56; SSc-ILD: n=48)	CFB to week 24 in mRSS was improved in RTX (−5.81) *versus* placebo (2.14)	SSc-ILD subset: improved FVC% with RTX (week 24: +0.02%; week 48: +0.46%)	Adverse drug reaction, pulmonary valve disease[+], diarrhoea, mucositis oral, decreased neutrophil count, decreased white blood cell count
Tocilizumab *versus* placebo [67]	focuSSced; NCT02453256	dcSSc (n=210; SSc-ILD: n=136)	No significant difference in CFB to week 48 in mRSS score between tocilizumab and placebo groups	Significant CFB to week 48 in FVC% and median HRCT QLF-LM favoured tocilizumab *versus* placebo (p=0.0002, p=0.02, respectively); no significant change in patient- or physician-assessed VAS or HAQ-DI	Injection site reactions
Nintedanib *versus* placebo [119]	INBUILD; NCT02999178	Progressive ILD (n=663; SSc-ILD: n=39)	Adjusted annual rate of decline in FVC was improved in nintedanib *versus* placebo group (p<0.001)	Adjusted annual rate of decline for patients with UIP-like fibrotic patterns in FVC was improved in nintedanib *versus* placebo group (p<0.001)	Diarrhoea and abnormal liver function
Nintedanib *versus* placebo [66]	SENSCIS; NCT02597933	SSc-ILD (n=576)	Adjusted annual rate of decline in FVC was better in nintedanib *versus* placebo group (p=0.04)	No significant change in mRSS or SGRQ score between treatment groups	Diarrhoea
MMF/pirfenidone *versus* MMF/ placebo [120]	SLS III	SSc-ILD (n=51)	Similar improvement in FVC% over 18 months between arms (p=0.93)	No significant differences in treatment arms	Higher GI disorders and photosensitivity with pirfenidone
HSCT *versus* CYC [121]	Autologous Stem Cell Transplantation International; Scleroderma trial (ASTIS); ISRCTN54371254	Early dcSSc (n=156; lung involvement: n=135)	Event-free and overall survival time-varying hazard ratios favoured HSCT- *versus* CYC-treated patients (p=0.04 and 0.03, respectively)	CFB to 2-year follow-up showed improvements in the HSCT *versus* CYC treatment groups in mRSS, FVC%, TLC%, HAQ-DI, physical component score of SF-36 and EQ-5D (all p<0.05)	Death and viral infections were more common in the HSCT group *versus* CYC (each p<0.01)
mHSCT *versus* CYC [122]	SCOT; NCT00114530	SSc with pulmonary or renal involvement (n=75; lung involvement: n=36)	Global rank composite score favoured mHSCT *versus* CYC at month 54 (p=0.01)	Global rank composite score favoured mHSCT *versus* CYC at month 48 (p=0.008)	Myelodysplastic syndrome, death Percentage of patients with serious AEs and rates of serious infections were higher in mHSCT group (*p*<0.01 each)

[#]: including SSc, idiopathic inflammatory myositis (including polymyositis or dermatomyositis) or mixed connective tissue disease with associated severe or progressive ILD. [¶]: CTD-ILD or idiopathic interstitial pneumonia; 23 participants (53% of the CTD-ILD group) had SSc. [+]: all patients with pulmonary valve disease in this study had physiologic pulmonary valve regurgitation that was not pathologic. 6MWT: 6-min walk test; AE: adverse event; CFB: change from baseline; CTD-ILD: connective tissue disease-associated interstitial lung disease; CYC: cyclophosphamide; dcSSc: diffuse cutaneous systemic sclerosis; D_{LCO}: diffusing capacity for carbon monoxide; D_L:VA: diffusing capacity adjusted for alveolar volume; EQ-5D: Euro Quality of Life; FVC: forced vital capacity; FVC%: FVC as a percentage of predicted value; GDA: global disease activity; GI: gastrointestinal; HRCT: high-resolution computed tomography; HAQ-DI: Health Assessment Questionnaire Disability Index; HSCT: haematopoietic stem cell transplantation; mHSCT: myeloablative autologous HSCT; MMF: mycophenolate mofetil; mRSS: modified Rodnan skin score; NA: not applicable; PFS: progression-free survival; QLF-LM: quantitative lung fibrosis–most affected lobe; QoL: quality of life; RTX: rituximab; SF-36: 36-Item Short Form Health Survey; SGRQ: St. George's Respiratory Questionnaire; SLS: Scleroderma Lung Study; TDI: translational dyspnoea index; TLC%: total lung capacity as a percentage of predicted value; UIP: usual interstitial pneumonia; VAS: visual analogue scale.

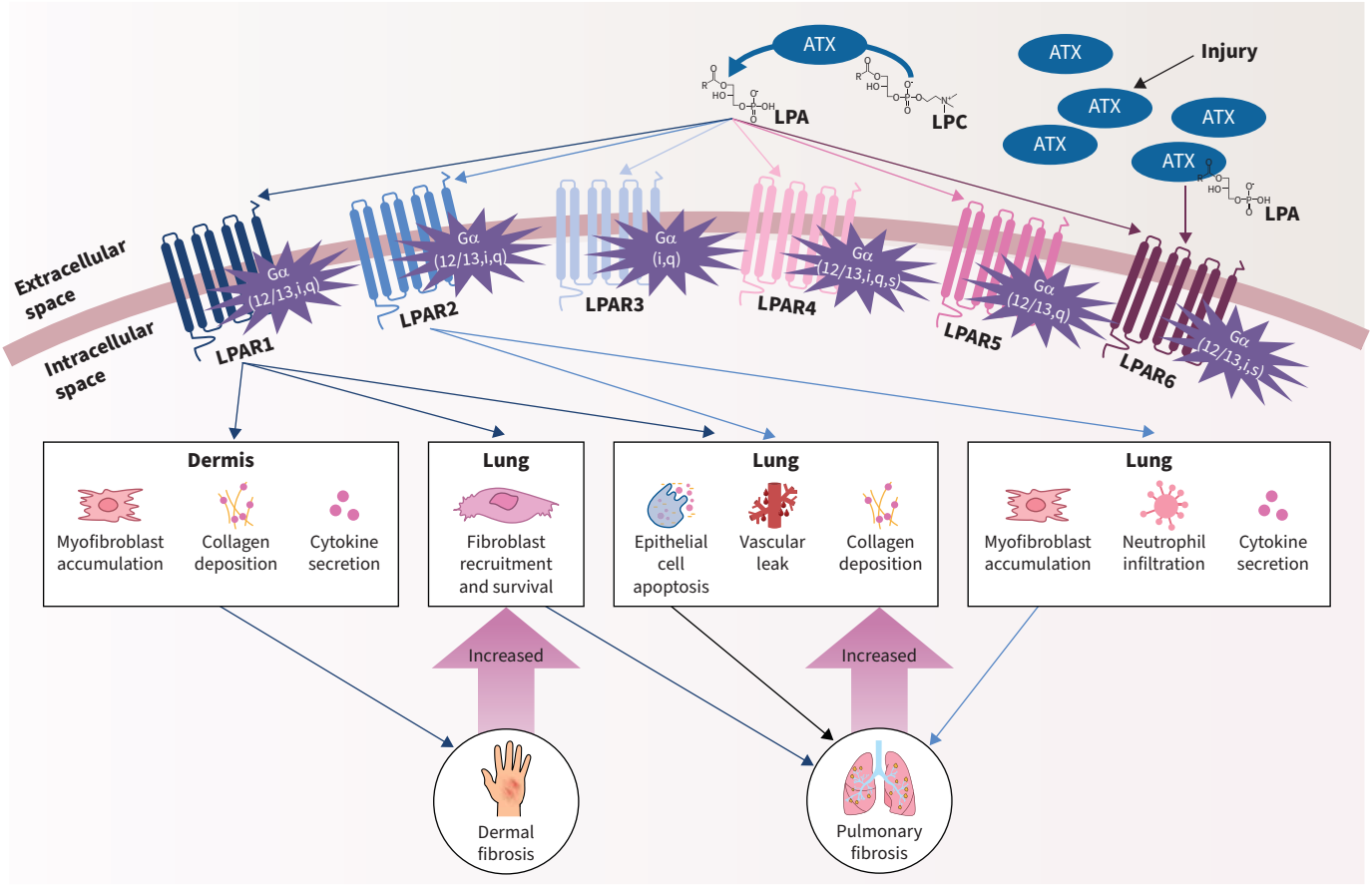

FIGURE 1 Model of autotaxin (ATX) and lysophosphatidic acid receptor (LPAR) 1 in systemic sclerosis and pulmonary fibrosis. Model is derived from empirical data collected from preclinical dermal and pulmonary fibrotic models. After injury, local levels of ATX rise. In the extracellular space, ATX catalytically converts lysophospholipids such as lysophosphatidylcholine (LPC) to lysophosphatidic acid (LPA), thus elevating local levels of LPA. LPA activates the LPAR family of G protein-coupled receptors. Additionally, ATX can chaperone LPA to LPARs, with heightened specificity for LPAR6 compared with LPAR1. Activation of LPAR1/2 and their G protein-coupled receptors leads to downstream signalling that results in cellular processes involved in fibrosis. Bleomycin-induced dermal fibrotic mouse models support that LPAR1, but not LPAR2, contributes to cellular events that culminate in dermal fibrosis. Bleomycin-induced pulmonary fibrotic mouse models support that LPAR1 and LPAR2 contribute to cellular events that culminate in pulmonary fibrosis. The effect of LPAR3–6 is not as well characterised in the development of dermal and pulmonary fibrosis.

Positive clinical trials of therapies for SSc and SSc-ILD are reviewed in table 1. Although these therapies may slow disease progression and improve symptoms and certain organ manifestations, treatments are not generally curative and do not arrest fibrosis [5, 17, 65]. Further, current treatments are ineffective in comprehensively treating the broad spectrum of SSc clinical manifestations. For example, the IL-6 receptor antagonist tocilizumab and the antifibrotic, nintedanib, are both approved for slowing the rate of pulmonary function decline in adults with SSc-ILD; however, neither was associated with improvement in skin fibrosis compared with placebo [66–69]. To fulfil the unmet need of the current treatment landscape, novel agents that target underlying mechanisms of both inflammation and fibrosis are being developed as potential therapies for SSc (*e.g.* ATX and LPAR1 inhibitors).

Pulmonary involvement is a potentially severe SSc manifestation that may manifest as ILD and is associated with high rates of morbidity and mortality [1, 70, 71]. An estimated prevalence of ILD in patients with SSc (n=1168) from the Canadian Scleroderma Research Group registry was 52% (95% CI 46–59%) [71]. Although ILD is common in patients with dcSSc, ILD occurs in patients with lcSSc, as well (dcSSc: 70%; lcSSc: 39% (Registry of the Spanish Network for SSc)) [72]. These estimates are possibly underestimated due to lack of uniform screening for early SSc for ILD [73]. The prevalence of progressive pulmonary fibrosis (PPF) among patients with SSc-ILD varies by patient population, but studies report that approximately 27–39% of SSc-ILD cases can be classified as PPF [74, 75].

As previously described, two studies of bleomycin-challenged pulmonary fibrotic mice have demonstrated an association between ATX and pulmonary fibrosis [29, 60]. Because bleomycin mouse models are used for both SSc-ILD and IPF, these studies suggest a link between ATX and SSc-ILD, while another study demonstrated that ATX is additionally involved in dermal fibrosis. In a bleomycin-induced dermal fibrosis mouse model, dermal ATX mRNA and protein levels were enhanced compared with saline-injected mice [76]. Inhibition of ATX reduced collagen and myofibroblast accumulation in the dermis as well as dermal thickening after bleomycin challenge [76]. This involvement of ATX in dermal fibrosis is also observed in humans. Messenger RNA ATX levels are elevated in skin from patients with dcSSc compared with healthy skin [76]. Further, ATX, LPA and IL-6 participate in an amplification loop in dermal fibroblasts, wherein LPA produced by ATX increases IL-6 expression and IL-6, in turn, enhances ATX expression [76]. This feedback mechanism is more pronounced in SSc *versus* healthy fibroblasts *in vitro* and implicates ATX in fibrotic-related inflammation [76]. Therefore, ATX may contribute to both dermal and pulmonary fibrosis and may thus be a mediator in SSc and SSc-ILD pathogenesis (figure 1).

Preclinical and clinical evidence also support LPAR1 as a contributor to SSc. Two studies involving bleomycin-induced pulmonary fibrotic mice with LPAR1 deficiency, one of which also involved primary mouse lung fibroblasts treated with LPAR1 inhibitors, concluded that LPAR1 contributes to physiologic mechanisms associated with pulmonary fibrosis and thus SSc-ILD (reviewed in the IPF section) [3, 4]. Mice with bleomycin-induced dermal fibrosis and LPAR1 knockout have reduced dermal thickening as well as collagen and myofibroblast accumulation compared with wild-type bleomycin-induced dermal fibrotic mice. Skin fibroblasts from patients with SSc had elevated LPA-activated Cl^- current activity, a phenomenon involved in lung fibroblast differentiation [77]. Dermal fibroblasts and skin biopsies from patients with SSc contain more LPAR1 mRNA than mRNA encoding other LPAR isoforms [12]. Inhibition of LPAR1 in SSc dermal fibroblasts led to decreased CCL2, CXCL1 and IL-6 protein secretion in response to LPA, supporting a proinflammatory role of LPAR1 [12]. Moreover, patients with SSc have elevated total serum LPA:lypophosphatidylcholine ratios compared with healthy controls [78]. Together, these observations associate LPAR1 activity with SSc.

In addition to its fibrotic and immunomodulatory effects, LPAR1 activation exerts vascular effects such as intimal hyperplasia in response to vascular injury due to interactions with smooth muscle and vasoconstriction [79, 80]. Therefore, LPAR1 activity may also contribute to SSc-related vasculopathy, which may be improved with LPAR1 inhibition. In summary, evidence of ATX and LPAR1 involvement in fibrotic disease and potential involvement in vasculopathy suggests that modulation of ATX or LPAR1 may attenuate fibrosis and that this antagonism may be an effective strategy in the development of therapies for IPF and SSc.

Preclinical and phase 1 clinical trials of ATX and LPAR1 inhibitors

ATX inhibition

The contribution of ATX in pathological fibrosis has motivated the design of multiple ATX inhibitors that have been reviewed extensively elsewhere [81, 82]. Although ATX inhibition may decrease activation of LPAR1 (*via* LPA depletion), because LPA engages LPARs 1–6, ATX inhibition is not specific to LPAR1 and may indirectly inhibit LPARs 2–6, as well (figure 2) [28]. Several ATX inhibitors are under preclinical development and three ATX inhibitors have entered clinical trials for IPF, namely BLD-0409 (cudetaxestat) [55], GLPG1690 (ziritaxestat) [83] and BBT-877 [84, 85]. In mice with bleomycin-induced lung fibrosis, all three inhibitors reduced the fibrosis *versus* vehicle [85–87].

In bleomycin-challenged mice, cudetaxestat reduced expression of ATX/LPA target genes in RNAseq experiments, plasma LPA levels, mRNA expression of key drivers of lung fibrosis and eventually lung fibrosis in a dose-dependent manner [86]. The safety of cudetaxestat was evaluated in four phase 1 clinical trials of healthy volunteers (n>200) [88]. A single/multiple ascending dose study of oral cudetaxestat solution reported only transient, mild gastrointestinal treatment-emergent adverse events (TEAEs), while a bioavailability study of oral cudetaxestat tablets reported no gastrointestinal TEAEs. A drug–drug interaction study reported that cudetaxestat is safe to use in combination with nintedanib or pirfenidone with no significant changes in drug exposure during concomitant use. No serious adverse events (AEs) were reported in the phase I studies [88].

Ziritaxestat inhibits ATX catalytic and chaperone function and has higher selectivity for LPAR6 than for LPAR1 [31]. Ziritaxestat was shown to be more efficient at protecting mice from radiation-induced pulmonary fibrosis than was an ATX catalytic inhibitor that did not inhibit chaperone activity, supporting the premise that ATX chaperone inhibition may contribute to pulmonary fibrosis protection [31]. Ziritaxestat also reduced LPA 18:2 levels in BALF of bleomycin-challenged mice [85]. In the first

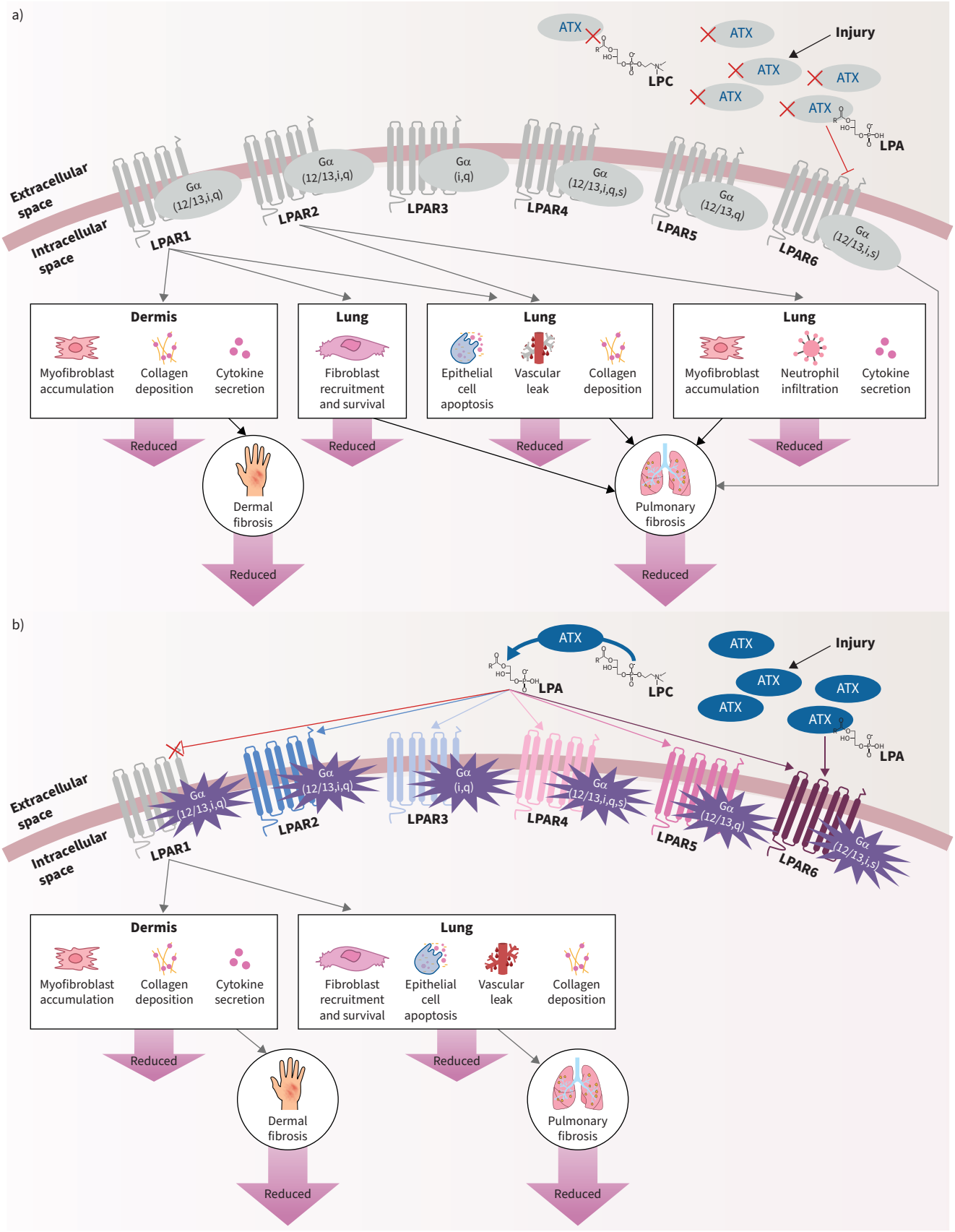

FIGURE 2 Theoretical mechanism of action of a) autotaxin (ATX) and b) selective lysophosphatidic acid receptor (LPAR) 1 inhibitors. In panel a), inhibition of ATX leads to decreased LPA and thus decreased activation of all LPARs. Decreased LPAR1 signalling leads to decreased dermal and

lung fibrosis, while decreased LPAR2 signalling leads to decreased pulmonary fibrosis. Inhibition of LPAR3–6 is not as well characterised because data for LPAR3–6 signalling in dermal and pulmonary fibrotic models are lacking. Inhibition of ATX chaperone function may lead to a more pronounced inactivation of LPAR6 and thus decreased pulmonary fibrosis. In panel b), during LPAR1 selective inhibition, upstream signalling and activation of LPAR2–6 is maintained. Inhibition of LPAR1 leads to decreased cellular events that improve dermal and pulmonary fibrosis. Because LPAR1 is expressed at higher levels compared with other LPARs in pulmonary fibroblasts and systemic sclerosis dermal fibroblasts, this selective inhibition targets cell types involved in dermal and pulmonary fibrosis. LPA: lysophosphatidic acid; LPC: lysophosphatidylcholine.

in-human study of ziritaxestat in healthy men, headache was the only reported TEAE and no serious AEs were reported [89].

BBT-877 reduced LPA 18:2 and 20:4 with higher potency than GLP1690 in *ex vivo* enzymatic assays that used human plasma. BBT-877 also reduced body weight loss, lung weight, Ashcroft score and collagen content in bleomycin-challenged mice compared with the vehicle. A phase I trial of BBT-877 in 80 healthy volunteers resulted in only mild AEs and no serious AEs [87].

LPAR1 inhibition

Although ATX and LPAR1 inhibitors both reduce fibrosis *via* inhibition of LPA signalling, their MOA vary considerably. Unlike ATX inhibitors, which deplete LPA production, LPAR1 inhibitors bind LPAR1 and specifically inhibit its activation by LPAs [12, 90]. Hence, LPAR1 inhibitors may have no or a limited effect on LPARs 2–6, depending on binding specificity for LPAR1 within the LPAR family (figure 2) [12]. Examples of LPAR1 inhibitors are fipaxalparant (HZN-825), BMS-986020 and BMS-986278 [23, 54, 91]. Although these inhibitors target the same receptor, *in vitro* and *in vivo* evidence suggests that their binding mechanisms differ, which may lead to differences in efficacy and safety profiles in the clinic [90, 92].

Fipaxalparant behaves as a selective allosteric LPAR1 inhibitor [12, 90]. *In vitro*, fipaxalparant inhibited LPAR1-mediated activation by five different LPA species, including 20:4 LPA, which is increased in serum of patients with SSc [12, 78]. In cellular assays, fipaxalparant blocked calcium response in Chinese hamster ovary cells treated with serum from patients with SSc, prevented LPA-mediated differentiation of IPF fibroblasts, decreased Wnt signalling and decreased secretion of inflammatory markers (IL-6, CCL2 and CXCL1) in SSc dermal fibroblasts [12]. Additionally, in Tsk1 mice, fipaxalparant reduced hypodermal thickening, myofibroblast accumulation, hydroxyproline content and secretion of CCL2 and CXCL1 [12]. Notably, fipaxalparant was inactive on LPAR2, 3 and 5 and had some activity with LPAR6 [12]. Thus, fipaxalparant exerts its effect primarily on LPAR1, but it has limited effect on other LPARs, whose contributions to dermal and pulmonary fibrosis are not as well established [3, 4, 12, 19]. For example, evidence from mice subcutaneously injected with bleomycin indicates that LPAR2 does not contribute to dermal fibrosis, while evidence from a bleomycin-induced fibrotic mouse model supports that LPAR2 does contribute to pulmonary fibrosis [19, 93]. Together, these data suggest that fipaxalparant selectively inhibits LPAR1 and attenuates fibrotic processes in preclinical models. Five phase 1 safety trials of fipaxalparant in healthy volunteers (n=94) reported no severe AEs. The most frequently reported TEAEs were headache, orthostatic hypotension, postural dizziness, flatulence and abdominal pain (unpublished data, Horizon Theraputics).

BMS-986020 and BMS-986278 are structurally related yet distinct inhibitors of LPAR1 [92, 94]. An *in vitro* study suggested that BMS-986020 binds LPAR1 differently than fipaxalparant [90]. BMS-986020 also inhibits hepatic resident transporters, particularly bile salt export pump (BSEP) and mitochondrial function in hepatic cells and, therefore, has off-target effects that likely caused the hepatobiliary toxicity observed in a phase 2 clinical trial [23, 92]. Conversely, BMS-986278 inhibition of BSEP was weak in *in vitro* assays, suggesting that BMS-986278 may have a better safety profile than BMS-986020 [92]. BMS-986278 did not cause hepatobiliary toxicity in rat or monkey models [95]. In addition, a phase 1 trial of BMS-986278 in healthy individuals did not report hepatic toxicity. Most AEs were mild and the most frequent one was headache. Decreased blood pressure was also reported (ClinicalTrials.gov identifier: NCT03429933) [96, 97].

Phase 2/3 clinical trials of ATX and LPAR1 inhibitors

Phase 2 and 3 clinical trials of ATX and LPAR1 inhibitors are reviewed in this section. Notably, the eligibility criteria pertaining to background therapy have not been uniform throughout trials and use of background therapy may have influenced outcomes [22, 83]. Therefore, the ability to holistically interpret results may be limited.

ATX inhibitors

Three ATX inhibitors have entered phase 2 of clinical development: BBT-877, cudetaxestat and ziritaxestat (table 2) [55, 83, 84]. ISABELA 1 and 2 were phase 3, double-blind, placebo-controlled, global, randomised clinical trials that evaluated the safety and efficacy of ziritaxestat in participants with IPF (n=525; n=781) [24]. Participants were randomised 1:1:1 to receive ziritaxestat 600 mg, ziritaxestat 200 mg or placebo for at least 52 weeks. Participants were permitted, but not required, to receive standard-of-care treatment (nintedanib, pirfenidone) during the study. Both trials were terminated early after a review by an independent data safety monitoring committee that concluded there was increased mortality in the 600 mg ziritaxestat group and lack of efficacy in all treatment groups [24]. Despite early termination, most patients were included in the analysis (1300/1306) and mean (SD) total treatment duration for ISABELA-1 and ISABELA-2 were 345 (188) and 339 (161) days, respectively. Ziritaxestat treatment did not result in benefits in the primary end-point (annual rate of forced vital capacity (FVC) decline *versus* placebo) or in key secondary end-points *versus* the placebo group. Outcomes for time to first respiratory-related hospitalisation were worse in the ziritaxestat groups *versus* placebo. Pooled all-cause mortality rates for ziritaxestat 600 mg, ziritaxestat 200 mg and placebo were 8.9, 7.0 and 5.5%, respectively, and respiratory-specific mortality rates were 3.6, 3.5 and 1.8%, respectively. The most common TEAEs were gastrointestinal disorders. Serious AEs were reported similarly across treatment groups (ISABELA 1: 22, 22 and 21%; ISABELA 2: 25, 24 and 16%; for 600 mg, 200 mg and placebo, respectively). Of participants treated with ziritaxestat, 74% had reduced LPA C18:2 plasma levels and 26% had increased LPA C18:2 levels, indicative of target engagement by ziritaxestat in a portion of participants [24]. Clinical development of ziritaxestat was stopped after termination of the ISABELA trials [83].

NOVESA was a randomised, double-blind, placebo-controlled phase 2A clinical trial for ziritaxestat in participants with dcSSc (n=33). This trial included patients with early dcSSc (first manifestation of SSc other than Raynaud's phenomenon within the last 5 years) and excluded patients with FVC ⩽45%. Most participants (90%) were receiving background immunosuppressant standard-of-care therapy. The NOVESA trial met its primary end-point of reduced mean modified Rodnan skin thickness score (mRSS) at week 24 ($p=0.04$; ziritaxestat *versus* placebo groups), with no significant differences in the change from baseline in FVC between groups. Diarrhoea and headaches were the most frequently reported TEAEs in the ziritaxestat group and 9.5 and 8.3% of patients experienced serious AEs in the ziritaxestat and placebo groups, respectively. In ziritaxestat-treated participants, circulating LPA C18:2 was significantly reduced ($p<0.0001$ *versus* placebo group), demonstrating ATX inhibition. Multiple fibrosis biomarkers in the blood were stabilised in the ziritaxestat group and increased in the placebo group (between-group difference ($p<0.04$)), while no differential gene expression was observed in the skin of ziritaxestat *versus* placebo groups. Further, membrane-spanning 4-domains A4A RNA, a biomarker of M2 macrophages, was significantly reduced 1.9-fold in blood samples from patients treated with ziritaxestat compared with placebo ($p=0.03$) [83].

31 of the 33 participants enrolled in the NOVESA trial entered the 104-week open-label extension study. However, premature termination of the NOVESA study following results from ISABELA trials precluded analysis of the NOVESA open-label extension beyond week 52. At week 52 of the open-label extension, the mean (standard error) change from baseline in mRSS was −11.6 (3.0) and −12.2 (1.6) units in the ziritaxestat–ziritaxestat and placebo–ziritaxestat groups, respectively. All participants experienced at least one TEAE and serious AEs were reported in 29% of all participants [83].

LPAR1 inhibitors

The clinical profile of fipaxalparant is being investigated in two ongoing phase 2 trials in individuals with IPF and dcSSc (NCT05032066 and NCT04781543) (table 2). The safety and tolerability of fipaxalparant were demonstrated in 32 participants with dcSSc in a phase 2a study wherein participants were treated with fipaxalparant or placebo for 8 weeks, followed by a 16-week extension during which all participants received treatment. Most patients (24/32) were receiving background immunosuppressive therapy. Headache was the most commonly reported TEAE in the fipaxalparant-treated group and one (6.7%) participant in the fipaxalparant-treated group experienced a serious AE [22].

At the end of the extension period, participants treated with fipaxalparant for the entire 24-week study duration experienced a clinically meaningful decrease in mean total mRSS from baseline (mean: −7.36; median: −7.5) [98]. Participants treated with placebo for 8 weeks and fipaxalparant for 16 weeks also experienced a clinically meaningful decrease in mRSS from baseline (mean: −7.31; median: −7.00) [22, 99]. Clinically meaningful improvements in Health Assessment Questionnaire Disability Index were observed in fipaxalparant-treated participants at week 8 (−0.14) and week 24 (−0.15) and in placebo/fipaxalparant–treated participants at week 24 (−0.23) [22]. The most commonly reported TEAEs were infection and headache. Two (6.7%) serious AEs were reported, one in each treatment group.

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TABLE 2 Agents targeting autotaxin (ATX) and lysophosphatidic acid receptor 1 (LPAR1) in phase 2–3 of clinical development

Agent	Identifier	Patient population	Primary end-point	Secondary efficacy end-points	Estimated completion date
ATX inhibitors					
BBT-877 [84]	NCT05483907	IPF (n=120)	CFB to week 24 in FVC	CFB to week 24 in FVC%, D_{LCO}, 6MWT, SGRQ and L-IPF	November 2024
Cudetaxestat [55]	NCT05373914	IPF (n=200)	CFB to week 26 in FVC	Time to disease progression, CFB to week 26 in QLF	March 2024
LPAR1 inhibitors					
Fipaxalparant [123]	NCT04781543	dcSSc (n=300)	CFB to week 52 in FVC%	CFB to week 52 in HAQ-DI, MDGA, PtGA and physical effects and limitations subscales of the SSPRO-18; proportion of patients with improved mRSS, HAQ-DI, PtGA, MDGA and FVC% from baseline to week 52	July 2025
Fipaxalparant [54]	NCT05032066	IPF (n=153)	CFB to week 52 in FVC%	CFB to week 52 in 6MWT, K-BILD, L-IPF and LCQ; proportion of participants with a decline in FVC% from baseline to week 52; time to first hospitalisation and first onset of PFS	July 2025
BMS-986278 [25, 91, 100, 124]	NCT04308681	IPF (n=276)	Mean FVC% improvement=1.4% (60 mg twice daily *versus* placebo)	Results of secondary end-points to be reported	Completed
		ILD cohort (n=125)	Mean FVC% improvement=1.6% (30 mg twice daily *versus* placebo); 3.2% (60 mg twice daily *versus* placebo)	Results of secondary end-points to be reported	Completed

6MWT: 6-min walk test; CFB: change from baseline; dcSSc: diffuse cutaneous systemic sclerosis; D_{LCO}: diffusing capacity for carbon monoxide; FVC: forced vital capacity; FVC%: FVC as a percentage of predicted value; HAQ-DI: Health Assessment Questionnaire Disability Index; ILD: interstitial lung disease; IPF: idiopathic pulmonary fibrosis; K-BILD: King's Brief Interstitial Lung Disease; LCQ: Leicester Cough Questionnaire; L-IPF: Living with IPF; MDGA: Physician Global Assessment; mRSS: modified Rodnan skin score; PFS: progression-free survival; PtGA: patient's global assessment of disease activity; QLF: quantitative lung fibrosis; SGRQ: St. George's Respiratory Questionnaire; SSPRO-18: Skin Patient-reported Outcome-18 items.

Once-daily and twice-daily BMS-986020 were evaluated in a phase 2, multicentre, three-group, randomised, double-blind, placebo-controlled clinical trial in individuals with IPF. Twice-daily BMS-986020 significantly decreased FVC decline compared with placebo at week 26 (p=0.49). BMS-986020 caused hepatobiliary toxicity in participants with IPF, inciting early termination of the study after three cases of cholecystitis occurred. Of the 143 participants, 108 completed the 26-week dosing phase and 35 participants withdrew from the study, 13 because of AEs [23].

A phase 2, randomised, double-blind, placebo-controlled clinical trial evaluated BMS-986278 in patients with IPF (n=276; ClinicalTrials.gov identifier: NCT04308681). Participants were permitted background therapy (pirfenidone or nintedanib) and/or immunosuppressive therapy if they were receiving a stable dose before screening [91]. The primary end-point was rate of change in FVC% over 26 weeks. Patients randomised to receive placebo, 30 mg or 60 mg of BMS-986278 twice daily exhibited a mean rate of change in FVC of −2.7, −2.8 and −1.2%, respectively. Thus, the mean FVC% difference of 60 mg twice daily compared with placebo was +1.4%. A subgroup analysis concluded that 60 mg of BMS-986278 had an effect regardless of background antifibrotic therapy use. Serious AEs occurred in 17, 11 and 11% of patients receiving placebo, 30 mg and 60 mg, respectively. The most frequently reported AEs were diarrhoea, cough and orthostatic hypotension [25]. A parallel cohort including 123 patients with PPF (defined as having fibrotic ILD with prior progression within 2 years) exhibited a mean rate of change in FVC of −4.3, −2.7 and −1.1%, for those treated with placebo, 30 mg and 60 mg, respectively. The mean FVC difference between the BMS-986278 and placebo groups was 1.6% for 30 mg and 3.2% for 60 mg. Treatment differences in the PPF cohort were independent of background antifibrotics and usual interstitial pneumonia pattern. AEs occurred in 78, 83 and 67% of the placebo, 30 mg and 60 mg groups, respectively [100]. Findings from both the IPF and PPF cohorts of this phase 2 trial support progression to phase 3 [25, 100].

The future of ATX and LPAR1 inhibitors

The failure of ISABELA-1/2 may trigger concerns regarding ATX and LPAR1 inhibitors. However, lessons from ISABELA-1/2 and positive phase 2 data for BMS-986278 provide optimism for future trials of therapies targeting the ATX/LPA/LPAR1 axis.

Clinical trial design challenges

Background therapy has been inconsistent throughout IPF/ILD trials and may affect trial outcomes. ISABELA-1/2 were the first phase 3 trials in IPF to allow pirfenidone (n=454/1281) and nintedanib (n=444/1281) background therapy [24, 101]. A drug–drug interaction between ziritaxestat and nintedanib caused elevated plasma levels of nintedanib and may have contributed to high rates of AEs (*e.g.* diarrhoea and nausea overall; nondiarrhoeal TEAEs (600 mg ziritaxestat arm)) [24]. Moreover, greater rates of annual FVC decline were observed in the placebo arm for patients with background therapy *versus* without (least squares mean, nintedanib: −163.1 mL; pirfenidone: −189.0 mL; neither: −149.1 mL) [24]. Comparatively, nintedanib and pirfenidone pivotal trials reported a greater decline for placebo-treated patients (adjusted annual rate: −207 and −240 mL; linear rate at week 52: −280 mL, respectively) [50, 51], suggesting an enrolment bias for patients with poor response to antifibrotic therapy or with less progressive disease that has also occurred in smaller IPF trials [101, 102]. Prior to nintedanib and pirfenidone trials, low rates of FVC decline in the placebo arm have proved challenging (*e.g.* CAPACITY 006 failure) [103]. Future trial designs should consider novel strategies to overcome these challenges, such as leveraging precision medicine or biomarkers (*e.g.* phase 3 PRECISIONS trial) [104] to increase the likelihood of success.

Despite permitted background antifibrotic use, a 26-week phase 2 trial of BMS-986278 in patients with IPF (n=276) and ILD (n=125) yielded positive results [25, 100]. Comparatively, the phase 2a study of ziritaxestat in IPF was smaller (n=23) and shorter (12 weeks); rapid progression into ISABELA-1/2 had uncertain risks because drug–drug interactions may not have been fully characterised [105]. Therefore, the BMS-986278 trial provides optimism for its phase 3 trial despite persisting challenges.

MOA: ATX versus *LPAR1 inhibitors*

The failure of the ISABELA-1/2 phase 3 trials stand in contrast to the promising results of the BMS-986278 phase 2 trial, suggesting an association between MOA and clinical outcomes. Increased levels of plasma ATX were detected in participants in ISABELA-1/2, indicative of disease progression or a regulatory feedback loop that has previously been observed in mice treated with an ATX inhibitor [106, 107]. Raised ATX levels suggest that the broad effect of ATX inhibition (*e.g.* cellular responses *via* ATX substrate accumulation and LPAR1–6 inhibition) may cause unwanted upstream effects, whereas LPAR1 selective inhibition may confer a more regulated effect. Furthermore, LPAR1 inhibitors may initially cause increased LPA levels that could trigger a feedback mechanism, resulting in reduced levels of ATX and LPA [107]. Therefore, LPAR1 inhibitors may attenuate ATX activity more than that of ATX inhibitors

(*i.e.* reduced expression *versus* pharmacological inhibition). To date, no drug–drug interactions between BMS-986278 or fipaxalparant and nintedanib or pirfenidone have been reported [108]. Although association of MOA and clinical outcome is not currently confirmed, the MOA of LPAR1 inhibitors may contribute to success in forthcoming trials of BMS-986278 and fipaxalparant. Moreover, synergy between LPAR1 inhibitors and antifibrotic therapies may occur due to distinct MOAs. Forthcoming trials will assist in testing these hypotheses.

Conclusions

Despite current therapeutic approaches, pulmonary fibrotic diseases such as IPF and SSc-ILD are associated with high morbidity and mortality [109]. Current therapies are not universally effective across the spectrum of pulmonary fibrosis and some have poor tolerability. An unmet need remains for therapies that improve quality of life, stabilise or even improve lung function, and are safe and well tolerated.

Although the pathology of fibrotic diseases is multifactorial, evidence to date indicates that the ATX/LPA/LPAR axis plays an important role in contributing to pathogenic fibrosis and inflammation. Therefore, inhibition of LPA production *via* ATX inhibition or more selective inhibition of LPAR1 may decrease fibrosis and inflammation and, thus, disease pathology. Because studies do not confirm the ATX/LPA/LPAR1 axis as the sole driver of fibrosis, combination of treatments with additive effects may be required for optimal treatment of fibrotic diseases. Developing ATX- or LPAR1-targeted therapies may be a promising avenue for stabilising lung function decline and improving outcomes in patients with SSc, IPF and other ILDs, and thereby have the potential to reduce disease burden, improve quality of life and increase long-term survival.

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