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New Therapeutic Avenues for Treatment of Fibrosis: Can We Learn from Other Diseases?

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Key Words
IBD · Environmental factors · Pathogenesis · Induction of flares

Abstract
Crohn's disease (CD) is characterized by the frequent occurrence of complications, such as fibrotic strictures and subsequently the need for CD-related surgery. Chronic or recurrent inflammation is generally regarded to be a necessary precondition for the initiation of intestinal fibrosis. In this view, fibrosis is a pathologically augmented healing response to inflammation-induced mucosal tissue destruction and injury. At present, there are no approved or effective medical therapies aimed specifically at fibrosis or stricture in IBD. Indirect benefits may occur from anti-inflammatory therapies, although there is no consensus on this. Therapy for fibrosis is complicated by the fact that a wound-healing response is essential in CD and ulcerative colitis. Several pharmaceutical companies are now working on the therapy of fibrosis in other diseases. Strategies interfering with TGF-β expression and activation are promising. Pirfenidone has been studied in several clinical trials. Further therapeutic options are second-generation and wide-spectrum tyrosine kinase inhibitors. These inhibit growth factor receptor signaling, thus reducing fibrosis in animal models and some patients with tumor-associated fibrosis. At present, the development of antifibrotic therapies takes place in other diseases such as lung and liver fibrosis. This is partially due to a lack of experimental models for gut fibrosis and the fact that reliable readouts (MRI, serum markers) in patients are lacking. It will be important to test the above-mentioned newly available treatment strategies in IBD to profit from progress in other fibrotic diseases.

Introduction

Up to two thirds of patients with Crohn's disease (CD) may develop either a stricturing or penetrating disease course within 10 years after diagnosis [1]. Up to 80% of all CD patients undergo surgery at least once during the course of their disease [2–4]. In half of these patients, intestinal obstructions and strictures are the indication for surgery.

Recent data by Pittet et al. [5] from the Swiss IBD Cohort group indicate that over a period of 40 years more than 75% of patients have to undergo surgery. The most frequent reason for surgery right after diagnosis of CD is

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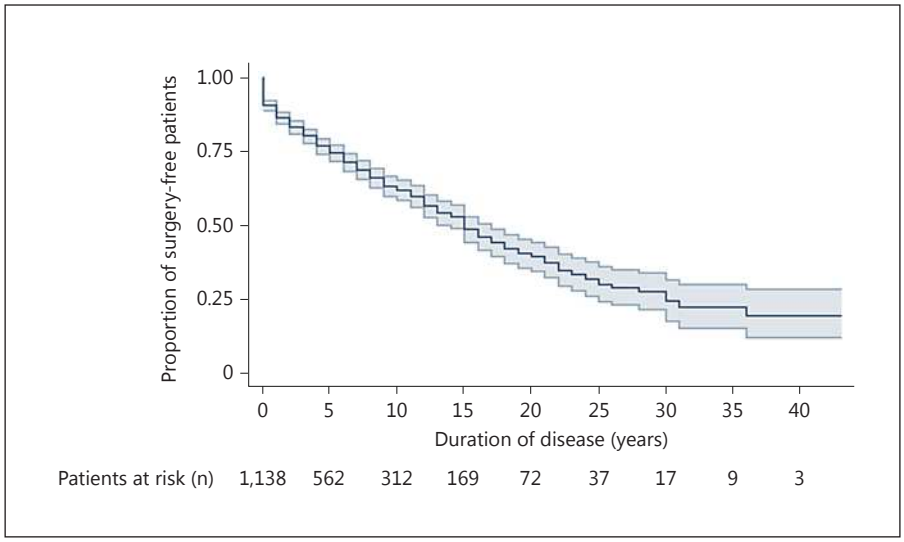

Fig. 1. Proportion of surgery-free patients in the Swiss IBD cohort study over time (according to [5]).

fibrosis [5]. Over the next 25 years there is almost a linear decrease in the proportion of surgery-free patients as seen in figure 1.

Whereas we are able to control for inflammation better and better, an effective preventive therapy for fibrosis or a pharmacological approach that even could reduce fibrosis is virtually absent. Most gastroenterologists believe that surgery can be avoided by preventing or reducing inflammation. This concept has also been brought forward by Pariente et al. [6]. In this concept, surgery occurs upon a chronic subclinical inflammation and subsequent fibrosis [6]. The evidence, however, to support this concept is weak. To some extent fibrosis might be independent from the inflammatory process. We find fibrotic strictures also in patients fibrotic strictures also in patients without IBD at surgical anastomosis, indicating that fibrosis might occur completely without any basic inflammation.

It is obvious that fibrosis research and development of potential therapeutic avenues is much more advanced in other fibrotic diseases when compared to IBD. Therefore, it is important to think 'out of the box' and to learn from those areas to improve the situation of patients with CD or ulcerative colitis. Whereas there is some progress in basic research on fibrosis in IBD, clinical research and fibrosis therapy is still virtually absent. An indicator for the interest in fibrosis certainly is that the 4th Scientific Workshop of the European Crohn's and Colitis Foundation (ECCO) was focused on the subject of fibrosis in CD. A series of review articles have recently been published on the subject, featuring pathogenesis, markers and potential treatment [7, 8].

Which Therapeutic Targets Have Been Identified in Other Fibrotic Diseases?

Basic research in liver fibrosis not only focuses on the anti-inflammatory agents and the reduction of injury as is usually done in CD [9–12]. Several other fields of interest have been introduced in liver fibrosis research. Inhibitors of proliferation and angiogenesis have been shown to be successful in prevention of liver fibrosis. An example is the Hedgehog signaling pathway. It is a signaling pathway identified to transmit information to embryonic cells required for proper development. An involvement of this factor or pathway has recently been discussed also for idiopathic pulmonary fibrosis and other fibrotic diseases [13, 14]. The Hedgehog pathway was found to be activated in lungs of patients with idiopathic pulmonary fibrosis, thereby contributing to idiopathic pulmonary fibrosis pathogenesis by increasing the proliferation, migration, extracellular matrix production and survival of pulmonary fibroblasts [13].

Fibrogenesis inhibitors also have been tested in animal models of fibrotic disease. Among those direct fibrogenesis inhibitors are TGF-β1 and TGF-β1 receptor antagonists [15–19], hepatocyte growth factor agonist [20], angiotensin-receptor antagonists [21, 22], ACE inhibitors [23], connective tissue growth factor antagonists [24, 25], cannabinoid receptor 1 antagonist [26–28] and lysophosphatidic acid receptor type 1 antagonists [29, 30]. In addition to direct fibrogenesis inhibitors, enhanced degradation of extracellular matrix proteins has proven to be promising in a number of experimental models [31, 32].

Tested substances in those models were tissue inhibitors of metalloproteinases [33], TGF-β antagonists, cell modulation therapy and inhibitors of lysyl oxidase-like 2 (LOXL2) [34]. The LOX enzyme also plays an important role in therapeutic trials in lung fibrosis. Therefore, this interesting molecule that is not studied in CD could be of future interest. Lysyl oxidase-like (LOX) refers to a group of copper-dependent amine oxidases that catalyze the covalent cross-link of collagens and elastin in the extracellular environment [35]. LOXL2 as a prototypic member of the group plays an essential role in the formation of connective tissue. It thus influences the mechanical properties of the extracellular matrix [35]. A dysregulation of LOXL2 has been discussed to play an important role in the pathogenesis of fibrosis in different organs.

Why Is Fibrosis Research in IBD Not More Advanced?

Fibrosis research, especially with respect to the development of therapeutic targets, is hampered by two major problems. While there are some models of intestinal fibrosis available, they all have certain disadvantages. Animal models of fibrosis have been recently summarized and reviewed by Pizarro and colleagues [36, 37]. In most of the animal models, fibrosis is either induced by chemicals such as dextran sodium sulfate [38–40] or 2,4,6-trinitrobenzenesulfonic acid [41–48], or by bacterial cell wall products such as peptidoglycan [49, 50].

Only one spontaneous model, the SAMP1/YitFc mouse strain, which develops CD-like ileitis, has been studied in detail by Pizarro and colleagues [37, 51]. Certainly this mouse model has the great advantage that intestinal fibrosis indeed develops spontaneously without any chemical induction that may not reflect natural pathophysiology and that there is additional inflammation in the terminal ileum similar to what is seen in humans. On the other hand, the model is not very stable and seems to depend to some extent on the bacterial flora [52]. Also, fibrosis in the chemically induced models is variable and only occurs after a long time. Therefore, for the study of intestinal fibrosis, new models would be highly warranted that develop fibrosis rapidly and reliably to a constant extent.

To develop such a model of intestinal fibrosis with the advantages mentioned above, we adapted a heterotopic tracheal transplant model that was developed a long time ago for the investigation of bronchiolitis obliterans (BO) after lung transplantation [53, 54]. BO also occurs after allogeneic stem cell transplantation. Single nucleotide polymorphisms that are relevant susceptibility factors in the pathogenesis of CD such as NOD2 were also shown to contribute to the risk of developing BO [55].

To study therapeutic prevention of BO, a piece of trachea was transplanted heterotopically into the neck fold of rats where it developed fibrosis with a constant time course [53, 54]. We adopted this rat model and transplanted small parts of the small intestine also in the neck fold of isogenic animals [56]. Donor (Brown Norway or Lewis rats) small bowel resections were transplanted subcutaneously into the neck of recipients (Lewis rats) [56]. Grafts were explanted 2, 7, 14 and 21 days after transplantation. The neck fold was chosen because the animals are unable to scratch themselves there, avoiding mechanical irritation that can influence the development of fibrosis. Rapid fibrosis occurred similar to the BO model. Collagen expression was increased with time [56]. Lumen obliteration was associated with increased expression of fibrosis-mediators such as $\alpha_V\beta_6$ integrin, IL-13 and TGF-β [56]. Several typical histologic and molecular features of intestinal fibrosis were observed in this heterotopic intestinal graft model. Within 3 weeks there was an almost tenfold increase in fibrotic layer thickness. This indicates that there is indeed rapid and stable fibrosis development. mRNA expression of collagen-1 was increased 100-fold after 3 weeks as compared to baseline [56]. This model may to some extend solve the problem of a lack of a rapid and reliable model of intestinal fibrosis. It will be possible to study and screen a number of agents on their ability to prevent intestinal fibrosis, thus identifying promising drug candidates for the prevention/treatment of intestinal fibrosis.

Why Do We Have No Clinical Trials on the Prevention of Intestinal Fibrosis?

There is a second aspect that prevents the development of successful therapies for CD fibrosis: the lack of a reliable endpoint for clinical trials. So far we do not have any reliable biomarker that would fulfill the criteria for a good endpoint in a respective clinical study. There are no reliable serum markers of intestinal fibrosis that would nicely correlate with the process of fibrosis or the degree of collagen deposition. YKL-40 has been reported to be a marker for liver fibrosis [57]. It is also increased when intestinal strictures are present, but the correlation coefficient is only r = 0.457 and serum levels are also increased during active inflammation [58] making this

marker not a good candidate for a surrogate marker in clinical trials.

All of the other 'marker-candidates' studied so far have not proven a sufficient correlation with the degree of intestinal fibrosis to be useful for monitoring antifibrotic therapy. It could be that the volume of the fibrotic area is too small in intestinal fibrosis to be represented reliably by a serum marker.

On the other hand, imaging techniques have not been developed to a state where they can be used as clinical endpoints. In CT scans or MRI as well as ultrasound, the evaluation of fibrosis mostly relies on subjective parameters. Contrast enhancement is usually seen as a sign of inflammation. However, active fibrosis could also lead to contrast enhancement because it is a biologically and metabolically highly active process. Only when fibrosis is already established and a full scar or sclerosis has developed is contrast enhancement no longer seen. A recently developed technique developed for the detection of intestinal fibrosis in MRI is 'magnetization transfer' [49, 50]. MR magnetization transfer imaging has several advantages as compared to conventional MRI. Magnetization transfer generates contrast that is primarily determined by the fraction of large macromolecules or immobilized phospholipid cell membranes in tissue [50]. This means that bone, cartilage and muscle will also show a high signal in magnetization transfer. Nevertheless, it is possible to identify fibrotic strictures in the gut. In a recent study in normal nonfibrotic bowel wall segments, an intermediate magnetization transfer ratio of 25.4 ± 3.4% was measured [59]. In contrast, the magnetization transfer ratio was significantly increased in bowel wall segments with fibrotic areas (35.3 ± 4.0%, $p < 0.0001$) [59]. In bowel segments with acute inflammation and no fibrosis, the mean magnetization transfer ratio was slightly lower than in the normal bowel wall without reaching a level of significance (22.9 ± 2.2%). As is obvious from the above numbers, it is possible to quantify magnetization transfer and give a ratio to have a quantification of tissue fibrosis. If magnetization transfer in MRI is further developed, this may be a promising technique to quantify intestinal fibrosis and to provide a quantitative endpoint for clinical trials on intestinal fibrosis. Currently, a large trial has been initiated in Europe that will investigate the usefulness of magnetization transfer as an endpoint for clinical trials of intestinal fibrosis. On the other hand, new ultrasound techniques and FibroScan® may be promising [60–64]. New developments have taken place that could allow quantification of fibrosis with ultrasound in the near future.

Which Endpoints Are Used in Clinical Trials on Fibrosis in Clinical Trials on Fibrosis in Other Diseases?

As mentioned earlier, the lack of a clinical endpoint is a major disadvantage for trials on intestinal fibrosis. So, why are there reliable endpoints in other diseases and what are those endpoints? FibroScan is used for liver fibrosis, but the method so far is not perfectly reproducible [65]. On the other hand, liver biopsy is frequently seen as the gold standard, but has the disadvantage of a patchy distribution of fibrosis in many patients. Results might be hampered by this fact and therefore patient numbers included in those studies must be rather high to avoid a bias by the patchiness of the tissue sample.

In contrast, there is a very reliable endpoint for clinical trials in idiopathic pulmonary fibrosis. This is the reason why most clinical fibrosis trials are done in this indication. The endpoint in all those trials is the 'forced vital capacity' [66]. The vital capacity is the maximum amount of air a person can expel from the lungs after maximum inhalation. A patient's vital capacity of course can easily be measured by a spirometer in a regular setting. This endpoint for clinical trials can be measured without any invasive methods, can be easily repeated, and is not of any disadvantage or risk for the patient [66]. Therefore, idiopathic pulmonary fibrosis is the main indication of the development of antifibrotic drugs for many pharmaceutical companies despite the fact that the number of patients with idiopathic pulmonary fibrosis is much lower as compared to patients with intestinal fibrosis due to CD.

The factors that have been identified to play a role in the pathogenesis of idiopathic pulmonary fibrosis are similar to those identified to be relevant during intestinal fibrosis. Data show that growth factors such as platelet-derived growth factor (PDGF), epidermal growth factor, TGF-α and -β, or endothelin-1 play an important role in promoting intestinal fibrosis and deposition of collagen [67–70]. Prostaglandin E_2 seems to inhibit pulmonary fibrosis [71, 72]. IL-4, IL-13, fibroblast growth factor, insulin-like growth factor and cytokines such as IL-1 are also profibrogenic [73–75]. In principal all of those mediators also play a role in intestinal fibrosis, indicating that a fibrotic stimulus is probably locally active and that the mechanisms are very similar in lung and intestinal fibrosis. This indicates that results derived from animal studies and clinical trials in idiopathic pulmonary fibrosis may be transferable to intestinal fibrosis, which calls for more scientific interaction between pulmonologists and gastroenterologists.

Table 1. Clinical trials in idiopathic pulmonary fibrosis

Trial No.	Title	Target	Sponsor
NCT01335464, NCT01335477	Efficacy and Safety of Nintedanib (BIBF 1120) in Idiopathic Pulmonary Fibrosis; two replicate 52-week, randomized, double-blind trials (INPULSIS-1 and INPULSIS-2) in 1,066 patients	Phase 3: intracellular tyrosine kinase inhibitor	Boehringer Ingelheim
NCT00786201	A Study to Evaluate the Safety and Effectiveness of CNTO 888 Administered Intravenously (IV) in Participants With Idiopathic Pulmonary Fibrosis (IPF)	Phase 2: this study tests the safety and effectiveness of CNTO 888 compared to placebo; CNTO 888 (carlumab) is a human monoclonal antibody against CC-chemokine ligand 2 (CCL2)	Centocor Inc.
NCT01872689	A Study of Lebrikizumab in Patients With Idiopathic Pulmonary Fibrosis	Phase 2: lebrikizumab is an anti-IL-13 antibody	Hoffmann-La Roche
NCT01366209	Efficacy and Safety of Pirfenidone in Patients With Idiopathic Pulmonary Fibrosis (IPF)	PIPF-016 (ASCEND) is a randomized, double-blind, placebo-controlled, phase 3 study	InterMune
NCT00262405	Zileuton for the Treatment of Idiopathic Pulmonary Fibrosis	5-Lipoxygenase inhibitor	University of Michigan
NCT01362231, NCT01769196	A Study to Evaluate the Safety and Efficacy of GS-6624 (Formerly AB0024) in Patients With Idiopathic Pulmonary Fibrosis	Phase 1 study completed, phase 2 study active: simtuzumab (GS-6624; formerly AB0024) targets LOXL2, which is an enzyme that promotes cross-linking of type 1 collagen in all types of fibrosis	Gilead Sciences
NCT01629667	A Phase 2, Randomized Dose-ranging Study to Evaluate the Efficacy of Tralokinumab in Adults With Idiopathic Pulmonary Fibrosis	Tralokinumab is a human recombinant monoclonal antibody that specifically binds human IL-13	MedImmune LLC

Clinical Trials in Idiopathic Pulmonary Fibrosis

Despite the prototypic role of idiopathic lung fibrosis for fibrotic disease and the above-mentioned clear clinical endpoint, so far only one substance is approved for the treatment of idiopathic pulmonary fibrosis and one has an orphan drug status.

The only currently approved drug for lung fibrosis is pirfenidone [76–79]. It is an orally active, small molecule that inhibits the synthesis of profibrotic and inflammatory mediators. Chemically, pirfenidone is 5-methyl-1-phenylpyridin-2-one [80]. The precise mechanism of action of pirfenidone is still unknown. Pirfenidone has several effects that can be interpreted as being 'antifibrotic'. Among others, it reduces the expression of collagen in fibroblast and muscle cells in vitro [80]. In 2 out of 3 phase 3 trials, pirfenidone significantly reduced the decline of the forced vital capacity in patients with idiopathic pulmonary fibrosis [76, 81]. This finally led to approval by the FDA. Recently another phase 3 trial on pirfenidone was published in *The New England Journal of Medicine* [77] (in the same issue where the study on nintedanib was published). This phase 3 trial studied 555 patients with idiopathic pulmonary fibrosis who were assigned to receive either oral pirfenidone (2,403 mg/day) or placebo over a period of 52 weeks [77]. The primary endpoint of this trial was again the change in forced vital capacity or death at week 52. In the pirfenidone group, a relative reduction of 47.9% in the proportion of patients who had an absolute decline of 10% or more in the percentage of the predicted forced vital capacity or who died was observed [77]. Thus, the whole trial achieved significance and confirmed that pirfenidone successfully prevents progress of idiopathic pulmonary fibrosis [77]. Unfortunately, gastrointestinal and skin-related adverse events were more common in the pirfenidone group

than in the placebo group. Pain and diarrhea were among the gastrointestinal side effects. This might limit the acceptability of pirfenidone for the treatment of CD patients [77].

In May 2014 an also large trial on the efficacy and safety of nintedanib (BIBF1120) in idiopathic pulmonary fibrosis was published in *The New England Journal of Medicine* [82] (table 1). Nintedanib is an intracellular tyrosine kinase inhibitor. INPULSIS-1 and INPULSIS-2 were two replicate 22-week, randomized, double-blind, phase 3 trials in altogether 1,066 patients [82]. The primary endpoint was (not surprisingly) the reduction in the annual rate of decline in forced vital capacity. Both trials reached their endpoints with high significance. In INPULSIS-1 the annual rate of changed enforced vital capacity was –114.7 ml with nintedanib versus –239.9 ml in the placebo group (Δ125.3 ml, $p < 0.001$) [82]. In INPULSIS-2 the patients treated with nintedanib lost 113.6 ml of their forced vital capacity over the 12-month trial period, whereas the placebo-treated patients lost 207.3 ml of their forced vital capacity (Δ93.7 ml, $p < 0.001$) [82]. It is striking that in those two studies the effect of the drug was so similar. Obviously, this tyrosine kinase inhibitor effectively reduces the progress of pulmonary fibrosis. However, application in intestinal fibrosis may be hampered by the most important side effect reported in those two trials: the most frequent adverse event in the nintedanib groups was diarrhea which occurred in 61.5% of the patients in INPULSIS-1 and in 63.2% in INPULSIS-2 [82]. It caused therapy to be discontinued in a significant number of patients. As is obvious, CD patients would be even more affected by an induction of diarrhea by the study drug.

However, it might be possible to use lower dosages of nintedanib in patients with CD fibrosis. The dosage for idiopathic pulmonary fibrosis has been determined in earlier studies such as the TOMORROW trial [83, 84]. In the TOMORROW trial, dosages of nintedanib (BIBF1120) less than 150 mg twice daily, however, were not effective [84]. 50 mg once daily, 50 mg twice daily or 100 mg twice daily were not significantly different to placebo with respect to the annual rate of change in forced vital capacity as published by Woodcock et al. [84].

With respect to the pathophysiological targets, nintedanib could also work in intestinal fibrosis. It dose-dependently inhibits the phosphorylation of several receptors of growth factors such as the phosphorylation of PDGF receptor by PDGF-BB as shown by Wollin et al. [85]. As PDGF also plays a role in intestinal fibrosis, this pathway could well be effective.

A number of different antibodies and compounds are being tested at present for the indication of idiopathic pulmonary fibrosis (table 1): Centocore is performing a phase 2 trial on the safety and effectiveness of CNTO 888 compared to placebo (NCT00786201). CNTO 888 is also named carlumab and is a human monoclonal antibody against the chemokine (C-C motif) ligand 2, which has earlier been referred to as monocyte chemotactic protein 1, which is known to recruit monocytes, activated and memory T cells, and dendritic cells to the sites of inflammation [86–88]. A role for monocyte chemotactic protein 1 has already been shown in intestinal inflammation and fibroblast activation [89–91].

Another phase 2 trial studied the effect of lebrikizumab in patients with idiopathic pulmonary fibrosis (NCT01872689). Lebrikizumab is an anti-IL-13 antibody manufactured by Hoffmann-La Roche. IL-13 also has been associated with intestinal fibrosis and is generally believed to be a profibrotic cytokine [92–95].

Another interesting drug that is being studied in the area of idiopathic pulmonary fibrosis is simtuzumab (GS-6624; formerly AB0024). A phase 1 study was completed and a phase 2 study is active (NCT01362231; NCT01769196). This antibody targets the above-mentioned LOXL2. The trials are being performed by Gilead Sciences, and the phase 1 and 2 trials seem to be promising.

MedImmune is conducting a phase 2 trial in idiopathic pulmonary fibrosis which is a randomized, dose-ranged study to evaluate the efficacy of tralokinumab in adults. Tralokinumab is a human recombinant monoclonal antibody that specifically binds human IL-13.

A list of published clinical trials in pulmonary fibrosis can be seen in table 2 [96]. It shows that endothelin receptor antagonists have been studied with some success and that at the moment tyrosine kinase inhibitors and pirfenidone have demonstrated the most promising results [96]. On the other hand, IFN-γ has been studied in investigator-initiated trials [97, 98]. It is an attractive therapeutic candidate as it regulates both macrophages and fibroblast functions. IFN-γ inhibits fibrogenic growth factors (FGFs), namely FGF2 and basic FGF, and a variety of neutrophil-derived cytokines.

Other substances also have shown some effects in models of pulmonary fibrosis. Suramin is a sulfonated naphthyl-urea that antagonizes the effects of certain growth factors including TGF-β, insulin-like growth factor-1, PDGF and FGF. On the other hand – as most TGF-β antagonists – it delays wound healing which could

Table 2. Completed trials in idiopathic pulmonary fibrosis (modified according to [96])

Trial	Drug	Mechanism of action	Reference
IFIGENIA	N-acetylcysteine	antioxidant	99
PANTHER-IPF	prednisone azathioprine N-acetylcysteine	antioxidant immunosuppression	100
Taniguchi	pirfenidone	antifibrotic	101
CAPACITY 1 CAPACITY 2	pirfenidone	antifibrotic	102
ACE-IPF	warfarin	anticoagulant	103
TOMORROW	BIBF1120	tyrosine kinase inhibitor	104
Daniels	imatinib mesylate	tyrosine kinase inhibitor	105
STEP-IPF	sildenafil	phosphodiesterase-5 inhibitor	106
BUILD-1	bosentan	endothelin receptor antagonist	107
BUILD-2	bosentan	endothelin receptor antagonist	108
ARTEMIS-IPF	ambrisentan	endothelin receptor antagonist	109
MUSIC-IPF	macitentan	endothelin receptor antagonist	110
Raghu	IFN-γ	immunomodulation	97
INSPIRE	IFN-γ	immunomodulation	98

Table 3. Clinical trials in liver fibrosis

Trial No.	Title	Target	Sponsor
NCT01672866	Simtuzumab (GS-6624) in the Treatment of Liver Fibrosis in Subjects With Advanced Liver Fibrosis But Not Cirrhosis Secondary to Non-Alcoholic Steatohepatitis (NASH)	simtuzumab (GS-6624; formerly AB0024) targets LOXL2, which is an enzyme that promotes cross-linking of type 1 collagen in all types of fibrosis	Gilead Sciences
NCT01707472	A Phase 2a Study of Simtuzumab in HIV and/or Hepatitis C-Infected Subjects With Liver Fibrosis	phase 2a: simtuzumab (GS-6624; formerly AB0024) targets LOXL2, which is an enzyme that promotes cross-linking of type 1 collagen in all types of fibrosis	Gilead Sciences
NCT01217632	A Study of FG-3019 in Subjects With Liver Fibrosis Due to Chronic Hepatitis B Infection	human monoclonal antibody against connective tissue growth factor; has been granted orphan drug designation by the FDA for the treatment of idiopathic pulmonary fibrosis	FibroGen

be deleterious in CD. Relaxin is another factor studied in the field of lung fibrosis. Relaxin inhibits TGF-β-induced collagen and fibronectin synthesis by fibroblasts, and increases the expression of matrix metalloproteinase 1, which is able to degrade collagen.

Clinical Trials in Other Fibrotic Diseases

A number of clinical trials also have been finished or are currently ongoing in liver fibrosis (table 3). Simtuzumab (GS-6624; formerly AB0024), the antibody that

targets LOXL2, is also being studied in liver fibrosis in subjects with advanced liver fibrosis, but not cirrhosis secondary to NASH. Two phase 2 trials are registered. The results have not been published yet.

FibroGen is studying FG-3019 in subjects with liver fibrosis due to chronic hepatitis B infection. FG-3019 is a human monoclonal antibody against connective tissue growth factor. The drug has been granted orphan drug designation by the FDA for the treatment of idiopathic pulmonary fibrosis due to promising data from a clinical trial there.

Conclusion

As is obvious from the clinical trials mentioned above, antifibrotic treatments are mainly studied in idiopathic pulmonary fibrosis and to a lesser extent in hepatic fibrosis, whereas there are almost no trials ongoing in intestinal fibrosis. This is mainly due to two factors. First, we do not have animal models of intestinal fibrosis that are reliable and develop fibrosis fast enough to do a number of screening experiments. Even more importantly, intestinal fibrosis is hard to assess and there are no reliable endpoints for clinical trials. Magnetization transfer and new ultrasound techniques may provide us with these endpoints; however, they need financial support to be further developed in the near future. At present a new European-wide clinical trial has been started to validate MRI for the assessment of intestinal fibrosis.

We should also join in efforts to develop new animal models for intestinal fibrosis. Therapies successful in pulmonary fibrosis should now be studied in intestinal fibrosis. The models available so far may be a starting point.

Disclosure Statement

The author has no conflicts of interest to declare.

References

1 Louis E, Collard A, Oger AF, Degroote E, Aboul Nasr El Yafi FA, Belaiche J: Behaviour of Crohn's disease according to the Vienna classification: changing pattern over the course of the disease. Gut 2001;49:777–782.
2 Whelan G, Farmer RG, Fazio VW, Goormastic M: Recurrence after surgery in Crohn's disease. Relationship to location of disease (clinical pattern) and surgical indication. Gastroenterology 1985;88:1826–1833.
3 Farmer RG, Whelan G, Fazio VW: Long-term follow-up of patients with Crohn's disease. Relationship between the clinical pattern and prognosis. Gastroenterology 1985;88:1818–1825.
4 Andres PG, Friedman LS: Epidemiology and the natural course of inflammatory bowel disease. Gastroenterol Clin North Am 1999;28:255–281, vii.
5 Pittet V, Rogler G, Michetti P, Fournier N, Vader JP, Schoepfer A, Mottet C, Burnand B, Froehlich F; Swiss Inflammatory Bowel Disease Cohort Study G: Penetrating or stricturing diseases are the major determinants of time to first and repeat resection surgery in Crohn's disease. Digestion 2013;87:212–221.
6 Pariente B, Cosnes J, Danese S, et al: Development of the Crohn's disease digestive damage score, the Lemann score. Inflamm Bowel Dis 2011;17:1415–1422.
7 Latella G, Rogler G, Bamias G, Breynaert C, Florholmen J, Pellino G, Reif S, Speca S, Lawrance IC: Results of the 4th scientific workshop of the ECCO (I): pathophysiology of intestinal fibrosis in IBD. J Crohns Colitis 2014, Epub ahead of print.
8 Rieder F, de Bruyn JR, Pham BT, Katsanos K, Annese V, Higgins PD, Magro F, Dotan I: Results of the 4th Scientific Workshop of the ECCO (Group II): markers of intestinal fibrosis in inflammatory bowel disease. J Crohns Colitis 2014, Epub ahead of print.
9 Pellicoro A, Ramachandran P, Iredale JP, Fallowfield JA: Liver fibrosis and repair: immune regulation of wound healing in a solid organ. Nat Rev Immunol 2014;14:181–194.
10 Karsdal MA, Krarup H, Sand JM, Christensen PB, Gerstoft J, Leeming DJ, Weis N, Schaffalitzky de Muckadell OB, Krag A: Review article: the efficacy of biomarkers in chronic fibroproliferative diseases – early diagnosis and prognosis, with liver fibrosis as an exemplar. Aliment Pharmacol Ther 2014;40:233–249.
11 Elpek GO: Cellular and molecular mechanisms in the pathogenesis of liver fibrosis: an update. World J Gastroenterol 2014;20:7260–7276.
12 Schuppan D, Kim YO: Evolving therapies for liver fibrosis. J Clin Invest 2013;123:1887–1901.
13 Bolanos AL, Milla CM, Lira JC, Ramirez R, Checa M, Barrera L, Garcia-Alvarez J, Carbajal V, Becerril C, Gaxiola M, Pardo A, Selman M: Role of sonic Hedgehog in idiopathic pulmonary fibrosis. Am J Physiol Lung Cell Mol Physiol 2012;303:L978–L990.
14 Yang JJ, Tao H, Li J: Hedgehog signaling pathway as key player in liver fibrosis: new insights and perspectives. Expert Opin Ther Targets 2014;18:1011–1021.
15 Gressner AM, Weiskirchen R, Breitkopf K, Dooley S: Roles of TGF-beta in hepatic fibrosis. Front Biosci 2002;7:d793–d807.
16 Arribillaga L, Dotor J, Basagoiti M, Riezu-Boj JI, Borras-Cuesta F, Lasarte JJ, Sarobe P, Cornet ME, Feijoo E: Therapeutic effect of a peptide inhibitor of TGF-beta on pulmonary fibrosis. Cytokine 2011;53:327–333.
17 de Gouville AC, Boullay V, Krysa G, Pilot J, Brusq JM, Loriolle F, Gauthier JM, Papworth SA, Laroze A, Gellibert F, Huet S: Inhibition of TGF-beta signaling by an ALK5 inhibitor protects rats from dimethylnitrosamine-induced liver fibrosis. Br J Pharmacol 2005;145:166–177.
18 Fu K, Corbley MJ, Sun L, et al: SM16, an orally active TGF-beta type I receptor inhibitor prevents myofibroblast induction and vascular fibrosis in the rat carotid injury model. Arterioscl Thromb Vasc Biol 2008;28:665–671.
19 Liu Y, Wang Z, Kwong SQ, Lui EL, Friedman SL, Li FR, Lam RW, Zhang GC, Zhang H, Ye T: Inhibition of PDGF, TGF-beta, and Abl signaling and reduction of liver fibrosis by the small molecule Bcr-Abl tyrosine kinase antagonist Nilotinib. J Hepatol 2011;55:612–625.
20 Iekushi K, Taniyama Y, Azuma J, Sanada F, Kusunoki H, Yokoi T, Koibuchi N, Okayama K, Rakugi H, Morishita R: Hepatocyte growth factor attenuates renal fibrosis through TGF-β1 suppression by apoptosis of myofibroblasts. J Hypertens 2010;28:2454–2461.

21 Moreno M, Gonzalo T, Kok RJ, et al: Reduction of advanced liver fibrosis by short-term targeted delivery of an angiotensin receptor blocker to hepatic stellate cells in rats. Hepatology 2010;51:942–952.
22 Kim MY, Baik SK, Park DH, Jang YO, Suk KT, Yea CJ, Lee IY, Kim JW, Kim HS, Kwon SO, Cho MY, Ko SB, Chang SJ, Um SH, Han KH: Angiotensin receptor blockers are superior to angiotensin-converting enzyme inhibitors in the suppression of hepatic fibrosis in a bile duct-ligated rat model. J Gastroenterol 2008; 43:889–896.
23 Yoshiji H, Noguchi R, Fukui H: Combined effect of an ACE inhibitor, perindopril, and interferon on liver fibrosis markers in patients with chronic hepatitis C. J Gastroenterol 2005;40:215–216.
24 Li G, Xie Q, Shi Y, Li D, Zhang M, Jiang S, Zhou H, Lu H, Jin Y: Inhibition of connective tissue growth factor by siRNA prevents liver fibrosis in rats. J Gene Med 2006;8:889–900.
25 Yokoi H, Mukoyama M, Sugawara A, Mori K, Nagae T, Makino H, Suganami T, Yahata K, Fujinaga Y, Tanaka I, Nakao K: Role of connective tissue growth factor in fibronectin expression and tubulointerstitial fibrosis. Am J Physiol Renal Physiol 2002;282:F933–F942.
26 Wei Y, Kang XL, Wang X: The peripheral cannabinoid receptor 1 antagonist VD60 efficiently inhibits carbon tetrachloride-intoxicated hepatic fibrosis progression. Exp Biol Med (Maywood) 2014;239:183–192.
27 Patsenker E, Stoll M, Millonig G, Agaimy A, Wissniowski T, Schneider V, Mueller S, Brenneisen R, Seitz HK, Ocker M, Stickel F: Cannabinoid receptor type I modulates alcohol-induced liver fibrosis. Mol Med 2011;17: 1285–1294.
28 Wasmuth HE, Trautwein C: CB1 cannabinoid receptor antagonism: a new strategy for the treatment of liver fibrosis. Hepatology 2007;45:543–544.
29 Rancoule C, Pradere JP, Gonzalez J, Klein J, Valet P, Bascands JL, Schanstra JP, Saulnier-Blache JS: Lysophosphatidic acid-1-receptor targeting agents for fibrosis. Expert Opin Investig Drugs 2011;20:657–667.
30 Tager AM, LaCamera P, Shea BS, et al: The lysophosphatidic acid receptor LPA1 links pulmonary fibrosis to lung injury by mediating fibroblast recruitment and vascular leak. Nat Med 2008;14:45–54.
31 Iredale JP, Thompson A, Henderson NC: Extracellular matrix degradation in liver fibrosis: biochemistry and regulation. Biochim Biophys Acta 2013;1832:876–883.
32 Unemori EN, Pickford LB, Salles AL, Piercy CE, Grove BH, Erikson ME, Amento EP: Relaxin induces an extracellular matrix-degrading phenotype in human lung fibroblasts in vitro and inhibits lung fibrosis in a murine model in vivo. J Clin Invest 1996;98:2739–2745.
33 Hemmann S, Graf J, Roderfeld M, Roeb E: Expression of MMPs and TIMPs in liver fibrosis – a systematic review with special emphasis on anti-fibrotic strategies. J Hepatol 2007;46: 955–975.
34 Wakasaki H, Ooshima A: Synthesis of lysyl oxidase in experimental hepatic fibrosis. Biochem Biophys Res Commun 1990;166:1201–1204.
35 Rodriguez C, Rodriguez-Sinovas A, Martinez-Gonzalez J: Lysyl oxidase as a potential therapeutic target. Drug News Perspect 2008; 21:218–224.
36 Lopetuso LR, Scaldaferri F, Pizarro TT: Emerging role of the interleukin (IL)-33/ST2 axis in gut mucosal wound healing and fibrosis. Fibrogenesis Tissue Repair 2012;5:18.
37 Pizarro TT, Pastorelli L, Bamias G, Garg RR, Reuter BK, Mercado JR, Chieppa M, Arseneau KO, Ley K, Cominelli F: SAMP1/YitFc mouse strain: a spontaneous model of Crohn's disease-like ileitis. Inflamm Bowel Dis 2011; 17:2566–2584.
38 Yamaguchi H, Suzuki K, Nagata M, et al: Irsogladine maleate ameliorates inflammation and fibrosis in mice with chronic colitis induced by dextran sulfate sodium. Med Mol Morphol 2012;45:140–151.
39 Ding S, Walton KL, Blue RE, McNaughton K, Magness ST, Lund PK: Mucosal healing and fibrosis after acute or chronic inflammation in wild type FVB-N mice and C57Bl6 procollagen α1(I)-promoter-GFP reporter mice. PloS One 2012;7:e42568.
40 Suzuki K, Sun X, Nagata M, Kawase T, Yamaguchi H, Sukumaran V, Kawauchi Y, Kawachi H, Nishino T, Watanabe K, Yoneyama H, Asakura H: Analysis of intestinal fibrosis in chronic colitis in mice induced by dextran sulfate sodium. Pathol Int 2011;61:228–238.
41 Zhu MY, Lu YM, Ou YX, Zhang HZ, Chen WX: Dynamic progress of 2,4,6-trinitrobenzene sulfonic acid induced chronic colitis and fibrosis in rat model. J Dig Dis 2012;13:421–429.
42 Wengrower D, Zanninelli G, Latella G, Necozione S, Metanes I, Israeli E, Lysy J, Pines M, Papo O, Goldin E: Losartan reduces trinitrobenzene sulphonic acid-induced colorectal fibrosis in rats. Can J Gastroenterol 2012;26: 33–39.
43 Stidham RW, Xu J, Johnson LA, Kim K, Moons DS, McKenna BJ, Rubin JM, Higgins PD: Ultrasound elasticity imaging for detecting intestinal fibrosis and inflammation in rats and humans with Crohn's disease. Gastroenterology 2011;141:819–826.e1.
44 Peterson TC, Peterson MR, Raoul JM: The effect of pentoxifylline and its metabolite-1 on inflammation and fibrosis in the TNBS model of colitis. Eur J Pharmacol 2011;662:47–54.
45 Koon HW, Shih D, Karagiannides I, Zhao D, Fazelbhoy Z, Hing T, Xu H, Lu B, Gerard N, Pothoulakis C: Substance p modulates colitis-associated fibrosis. Am J Pathol 2010;177: 2300–2309.
46 Mahavadi S, Flynn RS, Grider JR, Qiao LY, Murthy KS, Hazelgrove KB, Kuemmerle JF: Amelioration of excess collagen IαI, fibrosis, and smooth muscle growth in TNBS-induced colitis in IGF-I(+/–) mice. Inflamm Bowel Dis 2011;17:711–719.
47 Flier SN, Tanjore H, Kokkotou EG, Sugimoto H, Zeisberg M, Kalluri R: Identification of epithelial to mesenchymal transition as a novel source of fibroblasts in intestinal fibrosis. J Biol Chem 2010;285:20202–20212.
48 Ma Y, Guan Q, Bai A, Weiss CR, Hillman CL, Ma A, Zhou G, Qing G, Peng Z: Targeting TGF-beta1 by employing a vaccine ameliorates fibrosis in a mouse model of chronic colitis. Inflamm Bowel Dis 2010;16:1040–1050.
49 Adler J, Rahal K, Swanson SD, Schmiedlin-Ren P, Rittershaus AC, Reingold LJ, Brudi JS, Shealy D, Cai A, McKenna BJ, Zimmermann EM: Anti-tumor necrosis factor α prevents bowel fibrosis assessed by messenger RNA, histology, and magnetization transfer MRI in rats with Crohn's disease. Inflamm Bowel Dis 2013;19:683–690.
50 Adler J, Swanson SD, Schmiedlin-Ren P, Higgins PD, Golembeski CP, Polydorides AD, McKenna BJ, Hussain HK, Verrot TM, Zimmermann EM: Magnetization transfer helps detect intestinal fibrosis in an animal model of Crohn disease. Radiology 2011;259:127–135.
51 Rivera-Nieves J, Bamias G, Vidrich A, Marini M, Pizarro TT, McDuffie MJ, Moskaluk CA, Cohn SM, Cominelli F: Emergence of perianal fistulizing disease in the SAMP1/YitFc mouse, a spontaneous model of chronic ileitis. Gastroenterology 2003;124:972–982.
52 Bamias G, Okazawa A, Rivera-Nieves J, Arseneau KO, De La Rue SA, Pizarro TT, Cominelli F: Commensal bacteria exacerbate intestinal inflammation but are not essential for the development of murine ileitis. J Immunol 2007;178:1809–1818.
53 Gomez-de-Antonio D, Campo-Canaveral de la Cruz JL, Gonzalez-Lois C, Santos M, Millan I, Varela de Ugarte A: Heterotopic tracheal transplantation animal model of bronchiolitis obliterans: a reproducible model. Ann Transplant 2013;18:661–670.
54 Atanasova S, Hirschburger M, Jonigk D, Obert M, Petri K, Evers A, Hecker A, Schmitz J, Kaufmann A, Wilhelm J, Chakraborty T, Warnecke G, Gottlieb J, Padberg W, Grau V: A relevant experimental model for human bronchiolitis obliterans syndrome. J Heart Lung Transplant 2013;32:1131–1139.
55 Hildebrandt GC, Granell M, Urbano-Ispizua A, Wolff D, Hertenstein B, Greinix HT, Brenmoehl J, Schulz C, Dickinson AM, Hahn J, Rogler G, Andreesen R, Holler E: Recipient NOD2/CARD15 variants: a novel independent risk factor for the development of bronchiolitis obliterans after allogeneic stem cell transplantation. Biol Blood Marrow Transplant 2008;14:67–74.
56 Hausmann M, Rechsteiner T, Caj M, Benden C, Fried M, Boehler A, Rogler G: A new heterotopic transplant animal model of intestinal fibrosis. Inflamm Bowel Dis 2013;19:2302–2314.

57 Tao H, Yang JJ, Shi KH, Huang C, Zhang L, Lv XW, Li J: The significance of YKL-40 protein in liver fibrosis. Inflamm Res 2014;63: 249–254.
58 Erzin Y, Uzun H, Karatas A, Celik AF: Serum YKL-40 as a marker of disease activity and stricture formation in patients with Crohn's disease. J Gastroenterol Hepatol 2008; 23:e357–e362.
59 Pazahr S, Blume I, Frei P, Chuck N, Nanz D, Rogler G, Patak M, Boss A: Magnetization transfer for the assessment of bowel fibrosis in patients with Crohn's disease: initial experience. MAGMA 2013;26:291–301.
60 Wong GL: Update of liver fibrosis and steatosis with transient elastography (Fibroscan). Gastroenterol Rep (Oxf) 2013;1:19–26.
61 Kim D, Kim WR, Talwalkar JA, Kim HJ, Ehman RL: Advanced fibrosis in nonalcoholic fatty liver disease: noninvasive assessment with MR elastography. Radiology 2013;268: 411–419.
62 Rockey DC: Noninvasive assessment of liver fibrosis and portal hypertension with transient elastography. Gastroenterology 2008; 134:8–14.
63 Pinzani M, Vizzutti F, Arena U, Marra F: Technology insight: noninvasive assessment of liver fibrosis by biochemical scores and elastography. Nat Clin Pract Gastroenterol Hepatol 2008;5:95–106.
64 Friedrich-Rust M, Ong MF, Martens S, Sarrazin C, Bojunga J, Zeuzem S, Herrmann E: Performance of transient elastography for the staging of liver fibrosis: a meta-analysis. Gastroenterology 2008;134:960–974.
65 Verveer C, de Knegt RJ: Non-invasive measurement of liver fibrosis: application of the FibroScan in hepatology. Scand J Gastroenterol Suppl 2006;243:85–88.
66 Wells AU: Forced vital capacity as a primary end point in idiopathic pulmonary fibrosis treatment trials: Making a silk purse from a sow's ear. Thorax 2013;68:309–310.
67 Wolters PJ, Collard HR, Jones KD: Pathogenesis of idiopathic pulmonary fibrosis. Annu Rev Pathol 2014;9:157–179.
68 Spagnolo P, Rossi G, Cavazza A: Pathogenesis of idiopathic pulmonary fibrosis and its clinical implications. Exp Rev Clin Immunol 2014; 10:1005–1017.
69 Camelo A, Dunmore R, Sleeman MA, Clarke DL: The epithelium in idiopathic pulmonary fibrosis: breaking the barrier. Front Pharmacol 2014;4:173.
70 Steele MP, Schwartz DA: Molecular mechanisms in progressive idiopathic pulmonary fibrosis. Annu Rev Med 2013;64:265–276.
71 Maher TM, Evans IC, Bottoms SE, Mercer PF, Thorley AJ, Nicholson AG, Laurent GJ, Tetley TD, Chambers RC, McAnulty RJ: Diminished prostaglandin E_2 contributes to the apoptosis paradox in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2010;182:73–82.
72 Wilborn J, Crofford LJ, Burdick MD, Kunkel SL, Strieter RM, Peters-Golden M: Cultured lung fibroblasts isolated from patients with idiopathic pulmonary fibrosis have a diminished capacity to synthesize prostaglandin E_2 and to express cyclooxygenase-2. J Clin Invest 1995;95:1861–1868.
73 Murray LA, Zhang H, Oak SR, Coelho AL, Herath A, Flaherty KR, Lee J, Bell M, Knight DA, Martinez FJ, Sleeman MA, Herzog EL, Hogaboam CM: Targeting interleukin-13 with tralokinumab attenuates lung fibrosis and epithelial damage in a humanized SCID idiopathic pulmonary fibrosis model. Am J Respir Cell Mol Biol 2014;50:985–994.
74 Smith DR, Kunkel SL, Standiford TJ, Rolfe MW, Lynch JP 3rd, Arenberg DA, Wilke CA, Burdick MD, Martinez FJ, Hampton JN, et al: Increased interleukin-1 receptor antagonist in idiopathic pulmonary fibrosis. A compartmental analysis. Am J Respir Crit Care Med 1995;151:1965–1973.
75 Coffey E, Newman DR, Sannes PL: Expression of fibroblast growth factor 9 in normal human lung and idiopathic pulmonary fibrosis. J Histochem Cytochem 2013;61:671–679.
76 Xaubet A, Serrano-Mollar A, Ancochea J: Pirfenidone for the treatment of idiopathic pulmonary fibrosis. Expert Opin Pharmacother 2014;15:275–281.
77 King TE Jr, Bradford WZ, Castro-Bernardini S, et al: A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med 2014;370:2083–2092.
78 King TE Jr, Albera C, Bradford WZ, Costabel U, du Bois RM, Leff JA, Nathan SD, Sahn SA, Valeyre D, Noble PW: All-cause mortality rate in patients with idiopathic pulmonary fibrosis. Implications for the design and execution of clinical trials. Am J Respir Crit Care Med 2014;189:825–831.
79 Potts J, Yogaratnam D: Pirfenidone: a novel agent for the treatment of idiopathic pulmonary fibrosis. Ann Pharmacother 2013;47: 361–367.
80 Kreuter M, Kardos P, Hoffstein V: Management of idiopathic pulmonary fibrosis: selected case reports. Eur Respir Rev 2014;23:239–248.
81 Okuda R, Hagiwara E, Baba T, Kitamura H, Kato T, Ogura T: Safety and efficacy of pirfenidone in idiopathic pulmonary fibrosis in clinical practice. Respir Med 2013;107:1431–1437.
82 Richeldi L, du Bois RM, Raghu G, Azuma A, et al: Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med 2014;370:2071–2082.
83 Antoniu SA: Nintedanib (BIBF 1120) for IPF: a tomorrow therapy? Multidiscip Respir Med 2012;7:41.
84 Woodcock HV, Molyneaux PL, Maher TM: Reducing lung function decline in patients with idiopathic pulmonary fibrosis: potential of nintedanib. Drug Des Devel Ther 2013;7: 503–510.
85 Wollin L, Maillet I, Quesniaux V, Holweg A, Ryffel B: Antifibrotic and anti-inflammatory activity of the tyrosine kinase inhibitor nintedanib in experimental models of lung fibrosis. J Pharmacol Exp Ther 2014;349:209–220.
86 Rafei M, Galipeau J: A CCL2-based fusokine as a novel biopharmaceutical for the treatment of CCR2-driven autoimmune diseases. Crit Rev Immunol 2010;30:449–461.
87 Conductier G, Blondeau N, Guyon A, Nahon JL, Rovere C: The role of monocyte chemoattractant protein MCP1/CCL2 in neuroinflammatory diseases. J Neuroimmunol 2010; 224:93–100.
88 Daly C, Rollins BJ: Monocyte chemoattractant protein-1 (CCL2) in inflammatory disease and adaptive immunity: therapeutic opportunities and controversies. Microcirculation 2003;10:247–257.
89 Herfarth H, Goke M, Hellerbrand C, Muhlbauer M, Vogl D, Scholmerich J, Rogler G: Polymorphism of monocyte chemoattractant protein 1 in Crohn's disease. Int J Colorectal Dis 2003;18:401–405.
90 Leeb SN, Vogl D, Falk W, Schölmerich J, Rogler G, Gelbmann CM: Regulation of migration of human colonic myofibroblasts. Growth Factors 2002;20:81–91.
91 Spoettl T, Hausmann M, Herlyn M, Gunckel M, Dirmeier A, Falk W, Herfarth H, Schoelmerich J, Rogler G: Monocyte chemoattractant protein-1 (MCP-1) inhibits the intestinal-like differentiation of monocytes. Clin Exp Immunol 2006;145:190–199.
92 Fichtner-Feigl S, Fuss IJ, Young CA, Watanabe T, Geissler EK, Schlitt HJ, Kitani A, Strober W: Induction of IL-13 triggers TGF-beta1-dependent tissue fibrosis in chronic 2,4,6-trinitrobenzene sulfonic acid colitis. J Immunol 2007;178:5859–5870.
93 Fichtner-Feigl S, Young CA, Kitani A, Geissler EK, Schlitt HJ, Strober W: IL-13 signaling via IL-13R alpha2 induces major downstream fibrogenic factors mediating fibrosis in chronic TNBS colitis. Gastroenterology 2008;135: 2003–2013, 2013 e1–7.
94 Kaviratne M, Hesse M, Leusink M, Cheever AW, Davies SJ, McKerrow JH, Wakefield LM, Letterio JJ, Wynn TA: IL-13 activates a mechanism of tissue fibrosis that is completely TGF-beta independent. J Immunol 2004;173: 4020–4029.
95 Scharl M, Frei S, Pesch T, Kellermeier S, Arikkat J, Frei P, Fried M, Weber A, Jehle E, Ruhl A, Rogler G: Interleukin-13 and transforming growth factor beta synergise in the pathogenesis of human intestinal fistulae. Gut 2013;62: 63–72.
96 Antoniou KM, Margaritopoulos GA, Siafakas NM: Pharmacological treatment of idiopathic pulmonary fibrosis: from the past to the future. Eur Respir Rev 2013;22:281–291.

97 Raghu G, Brown KK, Bradford WZ, Starko K, Noble PW, Schwartz DA, King TE Jr, Idiopathic Pulmonary Fibrosis Study G: A placebo-controlled trial of interferon gamma-1b in patients with idiopathic pulmonary fibrosis. N Engl J Med 2004;350:125–133.
98 King TE Jr, Albera C, Bradford WZ, Costabel U, Hormel P, Lancaster L, Noble PW, Sahn SA, Szwarcberg J, Thomeer M, Valeyre D, du Bois RM, Group IS: Effect of interferon gamma-1b on survival in patients with idiopathic pulmonary fibrosis (INSPIRE): a multicentre, randomised, placebo-controlled trial. Lancet 2009;374:222–228.
99 Demedts M, Behr J, Buhl R, et al: High-dose acetylcysteine in idiopathic pulmonary fibrosis. N Engl J Med 2005;353:2229–2242.
100 Idiopathic Pulmonary Fibrosis Clinical Research Network, Raghu G, Anstrom KJ, King TE Jr, Lasky JA, Martinez FJ: Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. N Engl J Med 2012;366:1968–1977.
101 Taniguchi H, Ebina M, Kondoh Y, et al: Pirfenidone in idiopathic pulmonary fibrosis. Eur Respir J 2010;35:821–829.
102 Noble PW, Albera C, Bradford WZ, Costabel U, Glassberg MK, Kardatzke D, King TE Jr, Lancaster L, Sahn SA, Szwarcberg J, Valeyre D, du Bois RM, Group CS: Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. Lancet 2011;377:1760–1769.
103 Noth I, Anstrom KJ, Calvert SB, de Andrade J, Flaherty KR, Glazer C, Kaner RJ, Olman MA, Idiopathic Pulmonary Fibrosis Clinical Research Network: A placebo-controlled randomized trial of warfarin in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2012;186:88–95.
104 Richeldi L, Costabel U, Selman M, et al: Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. N Engl J Med 2011;365:1079–1087.
105 Daniels CE, Lasky JA, Limper AH, Mieras K, Gabor E, Schroeder DR, Imatinib-IPF Study Investigators: Imatinib treatment for idiopathic pulmonary fibrosis: randomized placebo-controlled trial results. Am J Respir Crit Care Med 2010;181:604–610.
106 Idiopathic Pulmonary Fibrosis Clinical Research Network, Zisman DA, Schwarz M, Anstrom KJ, Collard HR, Flaherty KR, Hunninghake GW: A controlled trial of sildenafil in advanced idiopathic pulmonary fibrosis. N Engl J Med 2010;363:620–628.
107 King TE Jr, Behr J, Brown KK, du Bois RM, Lancaster L, de Andrade JA, Stahler G, Leconte I, Roux S, Raghu G: Build-1: a randomized placebo-controlled trial of bosentan in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2008;177:75–81.
108 King TE Jr, Brown KK, Raghu G, du Bois RM, Lynch DA, Martinez F, Valeyre D, Leconte I, Morganti A, Roux S, Behr J: BUILD-3: A randomized, controlled trial of bosentan in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2011;184:92–99.
109 Raghu G, Behr J, Brown KK, et al: Treatment of idiopathic pulmonary fibrosis with ambrisentan: a parallel, randomized trial. Ann Intern Med 2013;158:641–649.
110 Raghu G, Million-Rousseau R, Morganti A, et al: Efficacy and safety of macitentan in idiopathic pulmonary fibrosis: results of a prospective, randomized, double-blind, placebo-controlled trial. Clin Trials Idiopath Pulmonary Fibrosis Sarcoidosis 2012, p A3631.