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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- 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.

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New therapeutic avenues for treatment of fibrosis: Can we learn from other diseases?

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Abbreviations: CD: Crohn's disease; IBD: inflammatory bowel disease; IL: interleukin; UC: ulcerative colitis

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. A chronic or recurrent inflammation is generally regarded to be a necessary pre-condition 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 Crohn's disease and ulcerative colitis.

Several pharmaceutical companies now work on the therapy of fibrosis in other diseases. Strategies interfering with TGFβ expression and activation are promising. Prifenidone has been studied in several clinical trials. Further therapeutic options are second generation and wide spectrum tyrosine kinase inhibitors. The inhibit growth factor receptor signalling thus reducing fibrosis in animal models and some patients with tumor associated fibrosis. At present the development of anti-fibrotic 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 CD may develop either a structuring 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 and coworkers from the Swiss IBD Cohort group indicate that over a period of 40 years still more than 75% of patients have to undergo surgery [5]. The most frequent reason for surgery right after diagnosis of Crohn's disease is fibrosis [5]. Over the next 25 years there is almost a linear decrease in the proportion of surgery-free patients as seen from **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 also has been brought forward by Pariente [6]. In this concept surgery occurs upon a chronic subclinical inflammation and subsequent fibrosis [6]. The evidence to support this concept is weak. To some extend fibrosis might be independent from the inflammatory process. We find 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. Therefore, it is important to "think out of the box" and to learn from those areas to improve the situation of patients with Crohn's disease or ulcerative colitis. Whereas there is some progress in basic research on fibrosis in IBD, clinical research and the therapy of fibrosis is still virtually absent. An indicator for the interest on fibrosis certainly is that the 4th scientific workshop (SWS) of the European Crohn's and Colitis Foundation (ECCO) was focused on the subject of fibrosis in Crohn's disease. A series of revue articles recently have been published on a 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 it is usually done in Crohn's disease [9-12]. Several other fields of interest and research areas 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 may be the Hedgehog signalling pathway. It is a signaling pathway identified to transmit information to embryonic cells required for proper development. An involvement of this factor or pathway respectively has recently been discussed for idiopathic pulmonaty fibrosis and other fibrotic diseases [13,14]. The Hedgehog pathway was found to be activated in lungs of patients with idiopathic pulmonary fibrosis there contributing to IPF 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 TGFβ1 and TGFβ1 receptor antagonists [15-19], hepatocyte growth factor (HGF) agonist [20], angiotensin-receptor antagonists [21,22], ACE inhibitors [23], connective tissue growth factor (CTGF) antagonists [24,25], cannabinoid receptor 1 antagonist [26-28] and lysophosphatidic acid receptor type 1 (LPA1) antagonists [29,30]. In addition to direct fibrogenesis inhibitors an 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 inhibitor of metalloproteinases (TIMP) inhibitors [33], TGFβ 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 Crohn's disease 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. There are some models of intestinal fibrosis available; however, they all have certain disadvantages. Animal models of fibrosis have been recently summarized and reviewed by Theresa Pizarro [36,37]. In most of the animal models fibrosis is either induced by chemicals such as dextrane sodium sulfate (DSS) [38-40] or 2,4,6-trinitrobenzenesulfonic acid (TNBS) [41-48] or by bacterial cell wall products such as peptidoglycan (PG-PS) [49,50].

Only one spontaneous model, the SAMP1/YitFc mouse strain, which develops a Crohn's disease-like ileitis, has been studied in detail by Pizarro et.al [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 extend 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 extend.

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 (SNPs) that are relevant susceptibility factors in the pathogenesis of Crohn’s disease such as NOD2 were also shown to contribute to the risk to develop 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 is chosen because the animals are unable to scratch themselves there, avoiding mechanical irritation influencing the development of fibrosis. A 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, interleukin (IL)-13, and TGFβ [56]. Several typical histologic and molecular features of intestinal fibrosis were observed in this heterotopic intestinal grafts model. Within 3 weeks there was an almost 10-fold increase in the fibrotic layer thickness. This indicates that there is indeed a 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 prove to 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 Crohn's disease fibrosis: the lack of 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 if 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 further "marker-candidates" studied so far have not proven a sufficient correlation with the degree of intestinal fibrosis to be useful for monitoring of an anti-fibrotic therapy. Potentially 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 so far. In CT scans or MRI and also in ultrasound the evaluation of fibrosis mostly relies on subjective parameters. Contrast enhancement usually is seen as a sign of inflammation. However, active fibrosis could also lead to a 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 there is no contrast enhancement seen anymore. 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. MT generates contrast that is primarily determined by the fraction of large macromolecules or immobilized phospholipid cell membranes in tissue [50]. This means that also bone, cartilage and muscle will show a high signal in magnetization transfer. Nevertheless it is possible to identify fibrotic strictures in the gut. In a recent study we showed that in normal, non-fibrotic bowel wall segments, an intermediate magnetization transfer ratio of 25.4 +/- 3.4 % was measured [59]. In contrast, the magentization 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 as in the normal bowel wall without reaching a level of significance (22.9 +/- 2.2 %). As 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 is initiated in Europe that will investigate the usefulness of magnetization transfer as 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 and other diseases?

As mentioned the lack of a clinical endpoint is a major disadvantage for trials on intestinal fibrosis. So the question arises why there are reliable endpoints in other diseases and what those endpoints are. For liver fibrosis Fibroscan® is used, but the method so far is ideally reproducible [65]. On the other hand liver biopsy is frequently seen as 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 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 anti-fibrotic drugs for many pharmaceutical companies despite the fact that the number of patient with idiopathic pulmonary fibrosis is way lower as compared to patients with intestinal fibrosis due to Crohn’s disease.

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 PDGF, EGF, TGFα and β or enthotelin1 play an important role in promoting intestinal fibrosis and deposition of collagen [67-70]. Prostaglandin E2 seems to inhibit pulmonary fibrosis [71,72]. IL-4, IL-13, fibroblast growth factor, insulin like growth factor (IGF1) and cytokines such as IL-1 are also pro-fibrogenic [73-75]. In principal all those mediators also play a role in intestinal fibrosis indicating that probably a fibrotic stimulus is 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 requesting for more scientific interaction between pulmonologists and gastroenterologists.

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 pro-fibrotic and inflammatory mediators.

Chemically pirfenidone is 5-Methyl-1-phenylpyridin-2-one [80]. The precise mechanism of action of pirfenidone still is unknown. Pirfenidone has several effects that can be interpreted as being “anti-fibrotic”. Among others it reduces the expression of collagen in fibroblast- and muscle cells in vitro [80].In 2 out of 3 phase III trials pirfenidone significantly reduced the decline and forced vital capacity in patients with idiopathic pulmonary fibrosis [76,81]. This finally led to approval by the FDA. Recently another phase III 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 III trial studied 555 patients with idiopathic pulmonary fibrosis which were assigned to either receive oral pirfenidone (2403mg/day) or placebo over a time 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% points 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 than in the placebo group. Among the gastrointestinal side effects were abdominal pain and diarrhea. This again might limit the acceptability of pirfenidone for the treatment of Crohn’s disease patients [77].

A series of important clinical trials have recently been performed and published in idiopathic pulmonary fibrosis. In May 2014 a large trial on efficacy and safety of nintedanib (BIBF1120) in idiopathic pulmonary fibrosis has been 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 weeks, randomized, double-blind, phase III trials in altogether 1066 patients [82]. The primary endpoint was (not surprisingly) the reduction in the annual rate of decline in forced vital capacity (FVC). Both trials reached their endpoints with high significance. In INPULSIS-1 the annual rate of changed enforced vital capacity was – 114.7ml with nintedanib vs. -239.9ml in the placebo group (Δ125,3ml; $p < 0.001$) [82]. In the INPULSIS-2 trial the patients treated with nintedanib lost 113.6ml of their forced vital capacity over the 12 months trial period whereas the placebo treated patients lost 207.3ml of their FVC (Δ93.7ml; $p < 0.001$) [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 induced stop of therapy in a significant number of patients. As obvious, Crohn's disease 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 Crohn's disease 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 150mg twice daily, however, were not effective [84]. 50mg once daily, 50mg twice daily or 100mg twice daily were not significantly different to placebo with respect to the annual rate of change in forced vital capacity as published by Woodcock and co-workers [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 and co-workers [85]. As PDGF also plays a role in intestinal fibrosis this pathway could well be effective.

A number of different antibodies and compounds are tested at present in the indication of idiopathic pulmonary fibrosis (**table 1**): Centocore performs a phase II trial on the safety and effectiveness of CNTO888, compared to placebo (NCT00786201). CNTO888 is also named carlumab and is a human monoclonal antibody against the chemokine (C-C motif) ligand 2 (CCL2). CCL2 has earlier been referred to as monocyte chemotactic protein 1 (MCP1) which is known to recruit monocytes, activated and memory T cells, and dendritic cells to the sites of inflammation [86-88]. A role for MCP1 has already been shown in intestinal inflammation and fibroblast activation [89-91].

Another phase II trial studied the effect of Lebrikizumab in patients with idiopathic pulmonary fibrosis (NCT01872689). Lebrikizumab is an anti-IL13 antibody manufactured by Hoffman La Roche. IL-13 also has been associated with intestinal fibrosis and is generally believed to be a pro-fibrotic cytokine. [92-95].

Another interesting drug that is studied in the area of idiopathic pulmonary fibrosis is Simtuzumab (GS-6624) (formally AB0024). A phase I study was completed and a phase II study is active (NCT01362231; NCT01769196). This antibody targets the above mentioned lysyl oxidase-like 2 (LOXL2). The trials are performed by Gilead Sciences. Phase I and II trials seem to be promising.

Medimmune conducts a phase II 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.

Table 2 gives a list of published clinical trials in pulmonary fibrosis [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 most promising results [96]. On the other hand Interferon-γ has been studied in investigator initiated trials [97,98]. It is an attractive therapeutic candidate as it regulates both macrophages and fibroblast functions. Interferon-γ inhibits fibrogenic growth factors 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 TGFβ, insulin like growth factor (IGF)1, platelet derived growth factor (PDGF) and fibroblast growth factor (FGF). On the other hand - as most TGFβ antagonists - it delays wound healing which could be deleterious in Crohn's disease. Relaxin is another factor studied in the field of lung fibrosis. Relaxin inhibits TGFβ induced collagen and fibronection synthesis by fibroblasts and increases the expression of matrix metalloproteinase 1 (MMP1) 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 lysyl oxidase like2 is also studied in liver fibrosis in subjects with advanced liver fibrosis but not cirrhosis secondary to NASH. Two phase II trials in patients are registered. The results have not been published yet.

FibroGen studies 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 (CTGF). 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.

Summary

As obvious from the above mentioned clinical trials anti-fibrotic treatments are mainly studied in idiopathic pulmonary fibrosis and to a lesser extend in hepatic fibrosis whereas there are almost no trials going on in intestinal fibrosis. This is mainly due to two facts that we do not have animal models of intestinal fibrosis that are reliable and develop a fibrosis fast enough to do a number of screening experiments. Even more important intestinal fibrosis so far is hard to asses and there are no reliable endpoints for clinical trials. Magnetization transfer and new ultrasound techniques may provide us with those 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. Therapies successful in pulmonary fibrosis should now be studied in intestinal fibrosis. The models available so far may be a starting point.

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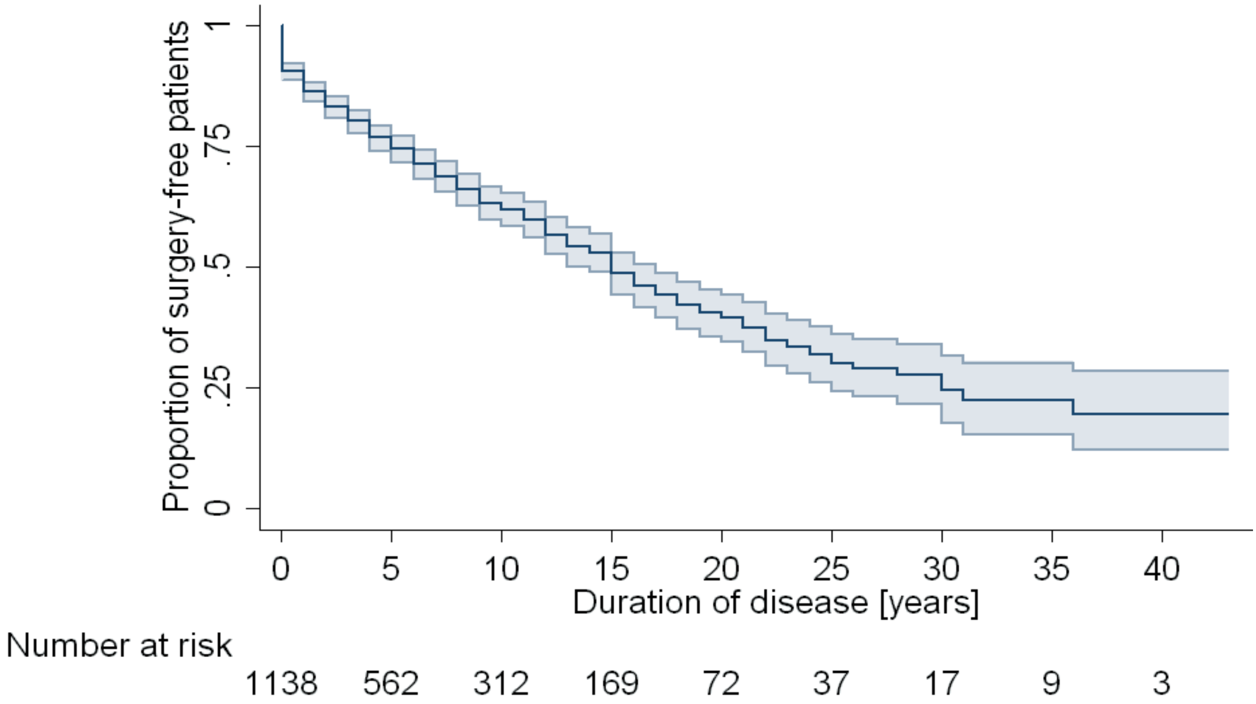
Figures:

Figure 1:



Proportion of surgery free patients the Swiss IBD cohort study over time (according to [5])

Tables:

Table 1: Clinical trials in idiopathic pulmonary fibrosis

Trial Nr	Title	Target	Sponsor
NCT01335464 and 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 1066 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 Subjects 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	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 lysyl oxidase-like 2, 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

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

Title	Drug	Mechanism of action	Reference
IFIGENIA	N-acetyl cysteine	Antioxidant	[99]
PANTHER-IPF	Prednisone Azathioprine N-acetyl cysteine	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	IFNgamma	Immunomodulation	[97]
INSPIRE	IFNgamma	Immunomodulation	[98]

Table 3: Clinical trials in liver fibrosis

Trial Nr	Title	Target	Sponsor
NCT01672866	Simtuzumab (GS-6624) in the Treatment of Liver Fibrosis in Subjects With Advanced Liver Fibrosis But Not Cirrhosis Secondary to NASH	Simtuzumab (GS-6624) (formerly AB0024): targets lysyl oxidase-like 2, 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 2 a: Simtuzumab (GS-6624) (formerly AB0024): targets lysyl oxidase-like 2, 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 (CTGF), (has been granted Orphan Drug Designation by (FDA) for the treatment of IPF	FibroGen