Treatments for Crohn's Disease–Associated Bowel Damage: A Systematic Review

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BACKGROUND & AIMS: **Despite significant advances in the treatment of Crohn's disease (CD), most patients still develop stricturing or penetrating complications that require surgical resections. We performed a systematic review of mechanisms and potential treatments for tissue damage lesions in CD patients.**

METHODS: **We searched the PubMed, MBASE, and Cochrane databases from September 2016 through July 2017 for full-length articles on CD, fibrosis, damage lesions, mesenchymal stem cells, and/or treatment. We also searched published conference abstracts and performed manual searches of all reference lists of relevant articles.**

RESULTS: **Mechanisms of intestinal damage in patients with CD include fibroblast proliferation and migration, activation of stellate cells, recruitment of intestinal or extra-intestinal fibroblast, and cell trans-differentiation. An altered balance of metalloproteinases and tissue inhibitors of metalloproteinases might contribute to fistula formation. Treatment approaches that reduce excessive transforming growth factor beta (TGFB) activation might be effective in treating established intestinal damage. Stem cell therapies have been effective in tissue damage lesions in CD. Particularly, randomized controlled trials have shown local injections of mesenchymal stem cells to heal perianal fistulas.**

CONCLUSION: **In a systematic review of mechanisms and treatments of bowel wall damage in patients with CD, we found a need to test drugs that reduce TGFB and increase healing of transmural damage lesions and to pursue research on local injection of mesenchymal stem cells.**

Keywords: IBD; Inflammatory Bowel Disease; Treatment Outcomes; Inflammation.

Inflammatory bowel diseases (IBDs) are chronic inflammatory disorders that comprise Crohn's disease (CD) and ulcerative colitis (UC). The incidence of IBD is rising worldwide, increasing the burden on the patients and health care system.[1] CD is characterized by periods of clinical remission alternating with periods of relapse reflected by recurrent clinical symptoms. Persisting inflammation is believed to trigger bowel damage that, over time, culminates in the development of chronic deep ulcerations, fibrostenotic strictures, abscesses, or fistulae. These complications frequently lead to an altered intestinal function and represent the main cause for recurrent surgical resections, which in turn can lead to disability and impact social or professional life.[2]

The recent acknowledgement that CD is a progressive and destructive disease has led to the development of new disease indexes, such as the Lemann index

Abbreviations used in this paper: **AT, adipose tissue; BMP-7, bone morphogenetic protein 7; CD, Crohn's disease; CTGF, connective tissue growth factor; ECM, extracellular matrix; EMT, epithelial-to-mesenchymal transition; HGF, hepatocyte growth factor; IBD, inflammatory bowel disease; IGF, insulin-like growth factor; IL, interleukin; MMP, matrix metalloprotease; MSC, mesenchymal stem cell; PPAR-γ, peroxisome proliferator–activated receptor gamma; ROCK, rho-associated protein kinase; SMA, smooth muscle actin; TC, transitional cells; TGF-β, transforming growth factor β; TIMP, tissue inhibitor of metalloproteinase; TNF-α, tumor necrosis factor α; UC, ulcerative colitis.**

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measuring cumulative bowel damage over time[3] and the IBD Disability Index.[4,5] In parallel to this, the treatment paradigm is currently shifting in CD from pure symptom control and improvement of quality of life, toward a blockade of disease progression and the improvement of long-term disease outcomes by reducing luminal structural damage, disability, and long-term disease sequelae.

Modifying the natural history of CD remains a major clinical challenge, and the rate of fibrostenotic and fistulizing complications leading to surgery remains high.[2] As currently available CD drugs fail to effectively treat structural intestinal damage, a better understanding of the underlying pathophysiology is a necessity to further allow the identification of new therapeutic targets and the development of novel treatment options.

Methods

A literature review of the computerized databases Medline, using PubMed, Embase, and Cochrane, was conducted between September 2016 and July 2017. To increase sensitivity, searches using both free text and MeSH terms were used. MeSH terms included "Crohn's disease AND Fibrosis" OR Crohn's disease AND damage lesions" OR "Crohn's disease AND mesenchymal stem cells" OR "Crohn's disease AND fibrosis AND treatment". Abstracts judged pertinent to the review were identified; key aspects were recorded; and full-length articles were selected from relevant abstracts. A secondary bibliography was developed from the references cited in the selected full-length articles, and additional PubMed searches were performed to expand the concepts developed in these articles. The number of abstracts cited by PubMed from January 1960 to July 2017 and reviewed for pertinence to this review during the primary and secondary searches was 1406.

Additionally, we included published conference abstracts and used manual searches for all references among relevant articles and reviews. Conference abstracts from 2010 to 2016, from United European Gastroenterology Week, Digestive Disease Week, and the Congress of the European Crohn's and Colitis Organisation were screened. Furthermore, experts in the field were contacted for information regarding nonpublished studies.

Pathophysiology of Intestinal Damage in CD: A Source of New Therapeutic Targets and Strategies

The pathogenesis of stenoses and fistulizing lesions may share several common pathways, given their close clinical association. Transmural lesions and in particular fibrostenosing strictures, are the consequence of exacerbated tissue remodeling, leading to the uncontrolled production of extracellular matrix (ECM) components, ultimately resulting in obstructive lesions. More than 95% of intra-abdominal fistulae seem to develop within or at the proximal end of a stricture, and appear to traverse the muscular layer along piercing vessels, suggesting that mechanical factors (eg, intraluminal pressure) might contribute to the development of fistulae, even though prospective evaluations are missing.[6]

During chronic inflammation in CD, the epithelial and endothelial barriers are severely disrupted, leading to the activation of the innate and adaptive immune systems with release of profibrotic cytokines, growth factors, and chemokines that together result in the activation of mesenchymal cells. Once mesenchymal cells have become activated, they produce profibrotic factors in turn eliciting excessive ECM deposition and architectural distortion even in the absence of continued inflammation.[7] The main mechanisms involved in fibrosis and bowel wall damage in CD are represented in Figure 1.

Role of Epithelial Cells and the Epithelial-to-Mesenchymal Transition

An increasing amount of research indicates that injured epithelial cells are critical drivers of fibrogenic process via the acquisition of a profibrotic phenotype. Epithelial cells are characterized by an inherent plasticity. The process through which epithelial cells take on the typical mesenchymal cell morphology is known as epithelial-to-mesenchymal transition (EMT).[8,9] During this transition, epithelial cells lose typical epithelial features and gain mesenchymal morphology, markers, and function. The transition of epithelial cells to a profibrogenic phenotype is triggered by the transforming growth factor β (TGF-β)/SMAD pathway, through the tight interaction with other signaling pathways including nuclear factor-kappa B, bone morphogenetic protein 7 (BMP-7), Wnt, or Notch.[9] Overall, multiple other cytokines or growth factors, including insulin-like growth factor (IGF) 1 and IGF-2, epidermal growth factor, fibroblast growth factor 2, and tumor necrosis factor α (TNF-α), but also reactive oxygen species, fibronectin, and fibrin, may promote EMT. Moreover, animal models of tissue fibrosis have highlighted the involvement of new transcriptional factors to the already complex EMT-inducing system, such as zinc finger E-box-binding homeobox 1 or Snail.[10,11] The integrin $\alpha V\beta 6$, mainly expressed by epithelial cells,[12] is also an important in vivo activator of TGF-β in the lung and plays significant roles in the development of pulmonary fibrosis.[13] Indeed, it has been shown in murine radiation-induced lung fibrosis that $\alpha V\beta 6$-mediated TGF-β activation is required to induce lung fibrosis, and also that an anti-$\alpha V\beta 6$ therapy could be effective to prevent fibrosis.

Aside the role of EMT in fibrogenesis, studies have shown that CD-associated intestinal fistula might also be influenced by EMT.[14] In a study investigating intestinal and perianal fistulae from CD and non-CD patients,

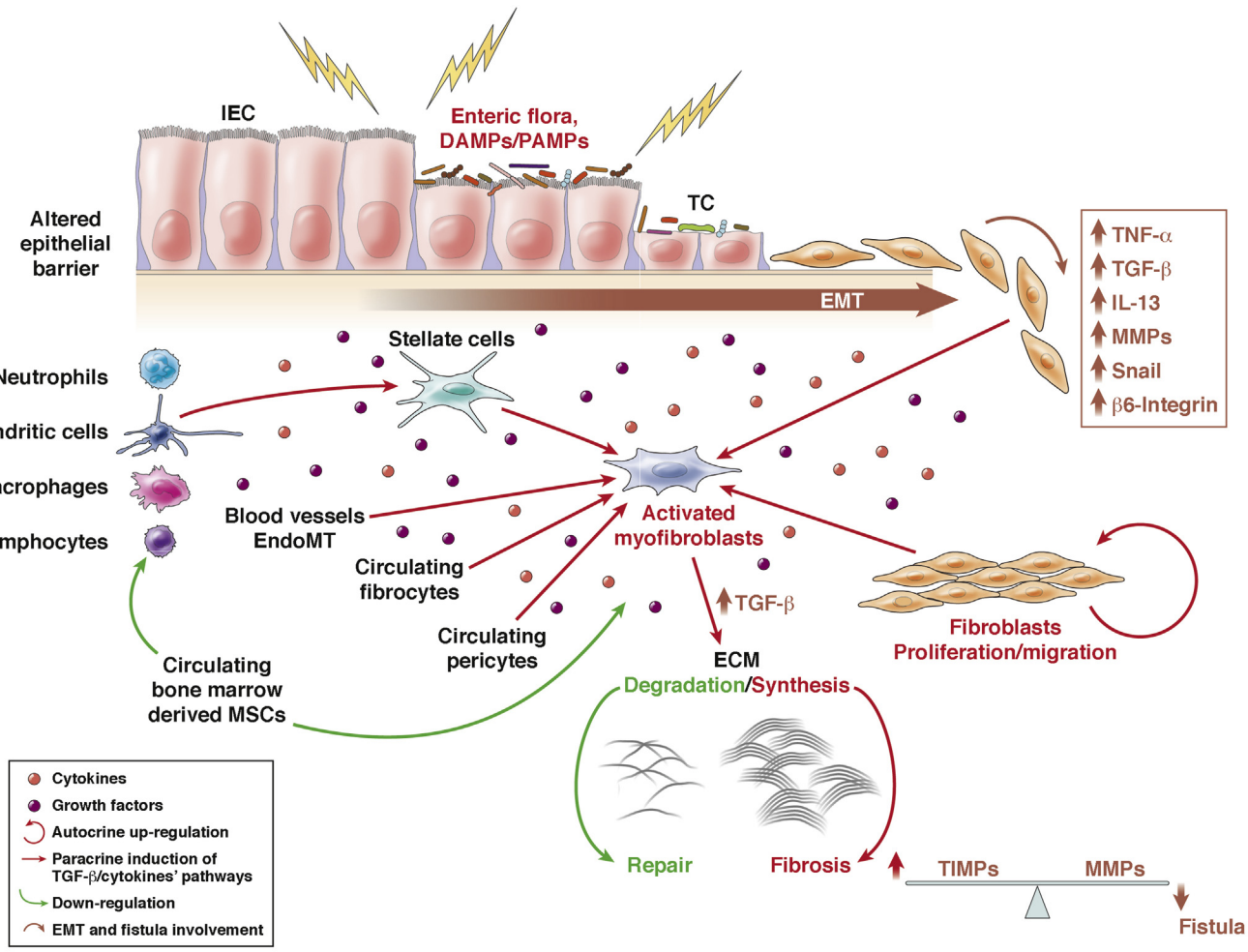

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Figure 1. Pathophysiology of transmural lesions in Crohn's disease. Fibrosis progression (red) and fistula formation (brown), and repair (green). ECM, extracellular matrix; EMT, epithelial-to-mesenchymal transition; IEC, intestinal epithelial cell; IL, interleukin; MMPs, matrix metalloproteases; MSCs, mesenchymal stem cells; TC, transitional cells; TGF-β, transforming growth factor β; TIMPs, tissue inhibitors of metalloproteinases; TNF-α, tumor necrosis factor α.

epithelialization of the fistula tract was found in a subfraction of patients. Interestingly, a novel cell type, called transitional cells (TCs), carrying mesenchymal or myofibroblast-like features, has been described,[15] suggesting epithelial-to-mesenchymal transformation.[16] These TCs express both epithelial cell markers such as cytokeratin-8 and cytokeratin-20 and mesenchymal markers such as vimentin and α-smooth muscle actin (SMA). High expression levels of Slug, TGF-β, and β6-integrin were also observed in TCs, and interleukin (IL-13) may play a central role in EMT during fistula formation.[16]

Role of Mesenchymal Cells

Mesenchymal cells can be considered the key executor of fibrogenesis given their role as potent inducer of ECM-protein production. Several cell populations may serve as precursors of myofibroblasts in CD. Increased proliferation and migration of resident fibroblasts, as well as the recruitment of bone marrow–derived fibroblasts, stellate cells, or pericytes, comprises different sources of myofibroblasts in intestinal fibrosis. In addition, cellular transdifferentiation or EMT and endothelial-to-mesenchymal transition further contributes to the enlargement of the pool of myofibroblasts (Figure 1).[17] In the intestine, there are 3 main types of resident mesenchymal cells, including smooth muscle cells, fibroblasts, and subepithelial myofibroblasts, a subtype of stromal cells located under the epithelial layer that communicate in a paracrine fashion with surrounding cells, and which play important roles in the mucosal regeneration, repair, and fibrosis.[17] In the intestine of patients with CD, myofibroblast activation can be modulated by the combined action of a wide variety of inflammatory factors, such as TNF-α, interferon gamma, TGF-β1, IGF-1, platelet-derived growth factor, connective tissue growth factor [CTGF], IGFI/II, basic Q3 fibroblast growth factor, IL-1β, IL-6, and IL-13 secreted by immune and nonimmune cells. The main mediator promoting fibrogenesis is TGF-β, exerting pleiotropic functions, such as the overexpression of α-SMA, contraction of myofibroblasts, or the excessive accumulation of ECM.

TGF-β1 signals mainly by a canonical SMAD-based pathway, supported by evidence demonstrating the effect of the disruption of the TGF-β/SMAD signaling pathway on reduced fibrosis, either by the loss of SMAD3 or the increase of the expression of the inhibitory SMAD (SMAD7). In CD patients, it has been suggested that activation of an integrin expressed on muscle cells, $\alpha V\beta 3$, could increase TGF-β1 levels in intestinal strictures.[18] Studies have explored smooth muscle cells isolated from CD strictures and normal resection margin as well as from the colon of rats after 42 days of chronic 2,4,6-trinitrobenzene sulfonic acid–induced colitis. They showed that latent TGF-β1 was activated by the $\alpha V\beta 3$ arginylglycylaspartic acid domain in human and rat intestinal smooth muscle cells.

A variety of mediators including damage-associated molecular patterns, DNA, RNA, adenosine triphosphate, high mobility group box 1 protein, microvesicles, fragments of ECM molecules as well as the Indian hedgehog (Ihh) and the Wnt/β-catenin pathways have been identified to contribute to the complexity and dynamics of myofibroblast activation.[19] Furthermore, the intestinal microbiota has been revealed to be crucially involved in the development and progression of intestinal fibrosis or fistula formation in IBD and the interaction between pathogen-associated molecular patterns and pattern recognition receptors, such as Toll-like receptors, is currently considered a possible crucial event in myofibroblast activation.[20]

Aside from excessive ECM accumulation, a dysregulation of matrix metalloproteinases (MMPs) and their inhibitors, tissue inhibitors of metalloproteinases (TIMPs), during active intestinal inflammation, by which myofibroblasts regulate tissue regeneration in IBD, has been reported. More specifically, myofibroblasts isolated from the inflamed intestine were shown to be able to express MMP-1, MMP-2, and MMP-3, as well as TIMP-1. Increased expression levels of these proteases were observed in cells isolated from fibrotic areas.[21] Early in vitro studies demonstrated that stimulation of myofibroblasts with TNF-α, a well-known IBD key player, induced the expression of TIMP-1, MMP-1, and MMP-3, and the secretion of type I and IV collagen.[22]

In a previous study in CD patients with fistulizing disease, a strong expression of MMP-3 and MMP-9 was observed in CD fistula independently of the stage of inflammation. Increased expression levels of MMP-3 and MMP-9 were detected in mononuclear cells, granulocytes and fibroblasts. Furthermore, supernatant of untreated CD fistula colonic lamina propria fibroblasts showed significantly elevated MMP-13 expression levels compared with nonfistula colonic lamina propria fibroblasts. In addition, the expression of TIMP-1, TIMP-2, and TIMP-3 was low around CD fistula.[23] Altogether, these observations suggest that an altered balance in MMP and TIMP expression levels might critically contribute to fistula formation.

Interaction Between Epithelial and Mesenchymal Cells

It is obvious that cells do not operate in isolation, but rather that their interaction is important. Recent experimental studies and clinical observations suggest that an altered crosstalk between colonic epithelial cells and adjacent subepithelial myofibroblasts may play an important role in the pathogenesis of ECM remodeling and inflammation associated fibrosis.[24] In in vitro studies on colonic epithelial cells, proinflammatory cytokines (IL-1α, TNF-α, interferon gamma) were shown to induce TGF-β and TIMP-1 expression. Moreover, the conditioned medium isolated from these cultures stimulated synthesis of MMP-9 and type I collagen and also suppressed the migration of subepithelial myofibroblasts.[24] The concept of epithelial to mesenchymal interaction has been shown in the context of idiopathic pulmonary fibrosis between alveolar epithelial cells and alveolar fibroblasts.[25] Indeed, repetitive cycles of epithelial injury and death stimulated the activation, proliferation, migration and differentiation of fibroblasts to myofibroblasts, through synthesis of TGF-β, CTGF, sonic hedgehog (Shh), and prostaglandin E2, resulting in excessive ECM deposition. In turn, these activated fibroblasts induced alveolar epithelial cell injury and death by producing angiotensin II and reactive oxygen species, therefore creating a cycle of profibrotic epithelial cell-fibroblast interactions.[26] All this evidence in idiopathic pulmonary fibrosis suggests a decisive involvement of the epithelial-fibroblast interactions in the progression of organ fibrosis that could also concern intestinal fibrosis.

Involvement of Mesenchymal Stem Cells in the Fibrotic Processes

Mesenchymal stem cells (MSCs) are pluripotent cells derived from stromal tissue such as bone marrow or adipose tissue (AT). They may migrate to the intestine and they exhibit multilineage differentiation capacity and may mediate immunomodulatory, anti-inflammatory, and regenerative properties.[27] MSCs can directly influence the fate and function of many distinct leukocyte populations, primarily through the action of soluble mediators. Lanzoni et al[28] demonstrated that intestinal-derived MSCs are able to induce differentiation and organization of intestinal epithelial Caco-2 cells in 3-dimensional collagen cultures. The potential role of these MSCs has also been studied in several experimental models of fibrosis in the lungs,[29] peritoneum,[30] skin,[31] kidneys,[31] and gastrointestinal tract.[32] These MSCs act through several distinct mechanisms including interfering with TGF-β1 pathway, secreting hepatocyte growth factor (HGF), decreasing collagen deposition, and modifying secretion of various MMPs and TIMPs.[29–40]

Existing and New Treatments as Potential Candidates for Tissue Damage Lesions in CD

Several existing drug and cell therapies have been assessed in animal or human models of pathological fibrosis, including in the intestine. These potential treatments for tissue damage lesions are summarized in Table 1 and their potential site of action on fibrosis and tissue damage pathophysiology is represented in Figure 2.

Existing Small Molecules

Tranilast. Tranilast is an antiallergic agent that blocks the release of chemical mediators such as histamine and prostaglandins from mast cells, and inhibits TGF-β–induced ECM production and transformation of epithelial cells.[33–35] It has been shown that tranilast, aside from its role in EMT, has antifibrotic actions in an experimental model of diabetic rats by reducing TGF-β activity. Furthermore, it was capable to inhibit fibroproliferative airway changes and was beneficial in preventing bronchiolitis obliterans after lung transplantation in a rat model of heterotopic tracheal transplantation.[35]

A case report on a patient with inflammatory endobronchial stenosis that was successfully treated by tranilast further corroborated the therapeutic efficacy of long-term tranilast administration.[36] In CD, Oshitani et al[37] evaluated the drug in 24 patients with nonsymptomatic intestinal strictures. Patients were followed-up prospectively after being allocated either to 200-mg tranilast 3 times daily or to the control group not receiving the agent. The primary study endpoint was the development of symptomatic strictures requiring endoscopic balloon dilatation, which was performed in 1 patient in the tranilast group and in 5 patients in the control group ($P = .0034$). However, the observed change in stricture diameter during the follow-up period was not significantly different between both groups.

Spironolactone. Spironolactone is a competitive aldosterone receptor antagonist that is commonly used as an antifibrotic medication in heart patients, and has proven to be protective in several rodent models of fibrosis.[38] Johnson et al[39] have shown that spironolactone mediated antifibrotic actions in isolated human colonic myofibroblasts and repressed TGF-β–mediated induction of profibrotic genes and proteins. The same group recently reported, that spironolactone treatment blocked TGF-β–induced profibrotic gene expression, including fibronectin, and α-SMA protein production in a novel model of human intestinal organoids.[40]

Pirfenidone. Pirfenidone is an orally bioavailable small molecule that exhibits well-documented antifibrotic and anti-inflammatory properties in a variety of animal and in vitro models in different organs, including fibrosis of the lungs, kidneys, heart, liver, and skin.[41] Meier et al[42] have investigated the impact of pirfenidone treatment on development of fibrosis in a mouse model of intestinal fibrosis. After administration of pirfenidone, a significantly decreased collagen layer thickness was revealed as compared with control. In intestinal fibroblasts TGF-β and MMP-9 were significantly decreased after treatment with pirfenidone as confirmed by real-time polymerase chain reaction and by Western blotting.

Cilengitide. Li et al[18] showed that increased activation of TGF-β1 in human CD patients and in TNBS-induced colitis caused increased collagen production and that fibrosis could be inhibited by cilengitide, an arginylglycylaspartic acid–containing $\alpha V\beta 3$ integrin inhibitor. Q8

Newly Developed Small Molecules

Peroxisome Proliferator–Activated Receptor Gamma Agonists. Peroxisome proliferator–activated receptor gamma (PPAR-γ) is a member of ligand-activated transcription factors of nuclear hormone receptor superfamily, which present pleiotropic effects on lipid metabolism, inflammation, and cell proliferation.[43] Stimulation of PPAR-γ with specific ligands downregulates the CTGF expression, promoting TGF-induced synthesis of collagen.[44] Along this, experimental studies have shown that PPAR-γ agonists attenuate fibrosis in various organs including the lungs, kidneys, pancreas, liver, and intestine. These antifibrotic effects are abolished by the use of PPAR-γ selective antagonists.[45–47] Concerning intestinal inflammation, the antifibrotic effect of a novel aminosalicyate analog able to activate PPAR-γ, named GED-0507-34, was evaluated in mice with colonic fibrosis induced by dextran sulfate sodium administration.[48] GED-0507-34 improved macroscopic and microscopic intestinal lesions and reduced the profibrotic gene expression of α-SMA, collagen, and fibronectin. It also reduced the main TGF-β/SMAD pathway components and inhibited TGF-β–induced activation of both fibroblast and intestinal epithelial cell lines. Finally, GED-0507-34 treatment also reduced the TGF-β expression in primary human intestinal fibroblasts isolated from 1 UC patient. Q9

Rho-Associated Protein Kinase Inhibitors. Holvoet et al[49] showed that rho-associated protein kinases (ROCKs), which play multiple roles in TGF-β1–induced myofibroblast activation, could be therapeutic targets. They evaluated the effects of a locally acting ROCK inhibitor, named AMA0825 (a highly selective inhibitor of ROCK 1 and ROCK 2), on intestinal fibrosis using mouse models of fibrosis (dextran sulfate sodium and adoptive T cell transfer), and biopsy cultures from CD patients. ROCK inhibition reversed established fibrosis by inhibiting myofibroblast accumulation, expression of profibrotic factors, and accumulation of fibrotic tissue without affecting clinical disease activity and histological inflammation in 2 mouse models of fibrosis. Moreover

Table 1. Studies Evaluating Potential Treatment Options for Intestinal Damage in Crohn's Disease

Molecule	Mechanism of Action	Study Design	n	Efficacy	Safety
Tranilast[37]	Antiallergic agent inhibited chemical mediators and TGF-β release	Case control	24 CD patients with small bowel strictures	There was less hydrostatic balloon dilatation in tranilast group ($P = .003$).	Reduced white blood cell count in 1 patient receiving tranilast
Spironolactone[39]	Competitive aldosterone receptor antagonist	Intestinal model of fibrosis using human intestinal organoids	NA	Spironolactone repressed induction of the fibronectin 1 and α-SMA proteins genes.	NA
GED-0507-34[48]	PPAR-γ modulator	DSS colitis mice model	110 mice	GED-0507-34 downregulates colonic expression of α-SMA, type I–III collagen, TGF-β, SMAD3, IL-13, and CTGF.	NA
Cilengitide[18]	αVβ3 integrin inhibitor	Intestine cells from ileal/ileocolonic resection	18 CD patients with stricturing lesions	Cilengitide decreased TGF-β1-activation and collagen production.	NA
AMA0825[49]	Highly selective inhibitor of ROCK 1 and ROCK 2	Mouse models of fibrosis (DSS and adoptive T cell transfer)	NA	AMA0825 reversed myofibroblast accumulation, expression of profibrotic factors, and accumulation of fibrotic tissue in 2 mouse models of fibrosis.	NA
		Biopsy cultures from CD patients		ROCK inhibitor reduced activation of myocardin-related transcription factor and p38 mitogen-activated protein kinase, and increased autophagy in fibroblasts, in intestinal fibrosis from stenotic CD biopsies.	

CD, Crohn's disease; CTGF, connective tissue growth factor; DSS, dextran sulfate sodium; NA, not applicable; PPAR, peroxisome proliferator–activated receptor; ROCK, rho-associated protein kinases; SMA, smooth muscle actin.

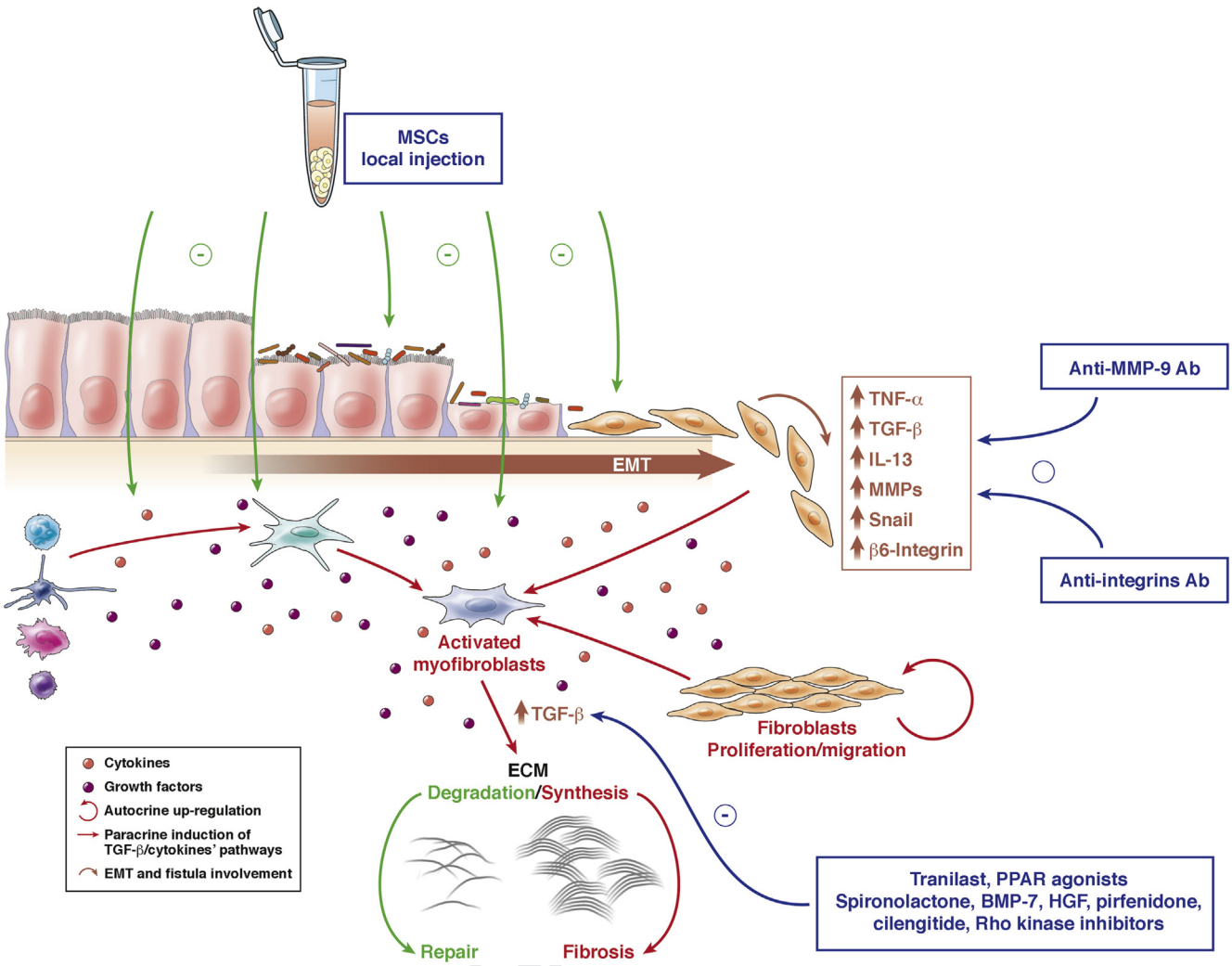

Figure 2. Potential treatment options for intestinal damage in Crohn's disease and their mechanisms of action. Several molecules have multiple mechanisms of action. Only the most prominent has been highlighted. BMP-7, bone morphogenetic protein 7; ECM, extracellular matrix; EMT, epithelial-to-mesenchymal transition; HGF, hepatocyte growth factor; IL, interleukin; MMPs, matrix metalloproteases; MSCs, mesenchymal stem cells; PPAR, peroxisome proliferator–activated receptor; TGF-β, transforming growth factor β; TNF-α, tumor necrosis factor α.

ROCK inhibition reversed intestinal fibrosis from stenotic CD biopsies, by reducing TGF-β1–induced activation of myocardin-related transcription factor and p38 mitogen-activated protein kinase, and by increasing autophagy in fibroblasts.

Recombinant Factors and Biologics

BMP7 and HGF. EMT can be reverted by the administration of BMP-7 and HGF.[50] In a mouse model of chronic renal injury, it has been shown that systemic administration of recombinant human BMP-7 reverses TGF-β1–induced EMT and leads to repair of severely damaged renal tubular epithelial cells, in association with reversal of chronic renal injury.[50] HGF is also a potent antifibrotic cytokine that blocks tubular epithelial to EMT. It has been reported in human kidney epithelial cells that HGF blocks EMT by antagonizing TGF-β1's action via upregulating SMAD transcriptional co-repressor SnoN expression.[50]

Anti-MMP-9 Antibody. C3M, an MMP-9 degradation product of type III collagen, have been shown to be associated with penetrating CD and differentiated penetrating CD from other CD subgroups and healthy control subjects.[51] Goffin et al[51] have recently assessed the effect of MMP-9 inhibition in the heterotopic transplant mouse model of intestinal fibrosis by using anti-MMP-9 antibody treatment, CALY-001. Compared with isotype control–treated group, the anti-MMP-9 antibody–treated mice presented only partially obstructed intestinal lumen, with a collagen layer only slightly thicker than that observed in freshly isolated intestinal samples. Quantification of collagen-specific amino acid hydroxyproline confirmed lower collagen amounts in grafts from mice treated with anti-MMP-9 antibodies compared with those treated with isotype control.

Anti-αVb6 Monoclonal Antibodies. Hahm et al[52] showed that anti-αVb6 monoclonal antibodies were able to inhibit accumulation of activated fibroblasts and deposition of interstitial collagen matrix in a renal

fibrosis model in Alport mice. Madala et al[13] showed that inhibition of the β6 integrin led to a significant effect on the pleural thickening and lung function decline observed in pulmonary fibrosis of TGF transgenic mice. STX-100, a humanized monoclonal antibody against αV-b6 integrin is currently tested in a phase 2 trial in idiopathic pulmonary fibrosis (NCT01371305).

MSC Therapy

As highlighted in a previous paragraph, recent studies demonstrate the potential of MSCs to be used as a new therapeutic strategy to address chronic inflammation–associated tissue damage, including fibrosis. Autologous and allogeneic MSCs have been tested in clinical trials in 2 different modalities: local injections of MSCs to treat fistulizing CD and intravenous infusion to treat luminal inflammation.[53]

Local perianal injections of autologous or allogeneic AT-MSCs or bone marrow MSCs have shown some efficacy and reassuring safety in several phase I, II, and III trials.[54–56] Until now, more than 200 CD patients with refractory fistulas have been treated with local injections of MSCs, resulting in complete response in more than half of these.[54,55] However, only 2 randomized controlled trials demonstrated the superiority of autologous and allogeneic MSCs over placebo. The first study, a phase II multicenter, randomized, controlled trial, evaluated stem cell–based therapy with expanded AT-MSCs in 49 patients with complex perianal fistulas.[57] Patients with complex perianal fistulas were randomly assigned to intralesional treatment with fibrin glue or fibrin glue plus 20 million AT-MSCs. At 8 weeks, fistula healing was observed in 71% of patients who received AT-MSCs in addition to fibrin glue, compared with 16% of patients who received fibrin glue alone (relative risk for healing, 4.43; 95% confidence interval, 1.74–11.27). At 1-year follow-up, the recurrence rate in patients treated with AT-MSCs was 18%. Importantly, among the 49 patients included, 35 had complex perianal fistulae with a cryptoglandular origin and only 14 patients had CD, but the proportion of patients with healing was similar in CD and non-CD subgroups. Over the long term, with a mean follow-up of 38 months, among the 12 patients with a complete fistula closure, 7 remained free of recurrence. Only 1 adverse event unrelated to the original treatment was reported.[58] The second trial was a randomized double-blind, parallel-group, placebo-controlled study, conducted in 49 hospitals in 7 European countries and Israel.[56] A total of 212 CD patients with refractory complex perianal fistulas were randomly assigned to receive a single intralesional injection of 120 million allogeneic AT-MSCs (Cx601) or placebo. A significantly greater proportion of patients treated with Cx601 vs placebo achieved combined remission at week 24, defined by clinical assessment of closure of all treated external openings and absence of collections >2 cm confirmed by magnetic resonance imaging (53 of 107 [49.5%] vs 36 of 105 [34.3%]; $P = .024$). A higher proportion of placebo vs Cx601 patients experienced treatment-related adverse events, mostly anal abscesses and proctalgia. Recently, authors reported efficacy and safety of patients treated with Cx601 vs placebo 1 year after AT-MSCs administration.[59] A significantly greater proportion of patients receiving Cx601 vs placebo achieved combined remission (56.3% vs 38.6%; $P = .010$) and clinical remission (59.2% vs 41.6%; $P = .013$) at week 52. Rates and types of treatment-related adverse events were similar in both groups (20.4% for Cx601 vs 26.5% for placebo). All these results underline that autologous and allogeneic MSCs administration represents an effective and safe therapy for complex fistulas in CD that failed to respond to conventional or biological treatments.

A lower number of trials have been performed with intravenous injections of MSCs.[60,61] These trials have provided conflicting results. No data are currently available reporting on the specific effect of intravenous MSCs injection on stricturing or fistulizing CD. Similarly, there is no trial available investigating the efficacy of local MSCs injection in CD lesions other than perianal fistulae, such as intestinal strictures or chronic unhealed ulcers.

Conclusion

Persistent high rates of stricturing and fistulizing complications leading to significant bowel damage, surgical resection, and disability in CD patients may lead physicians to modify their management of CD. There is an urgent need to develop novel medical treatment options to stop and reverse profibrotic mechanisms, to improve transmural damage lesions and change the chronic progressive disease course. Several small molecules, recombinant factors, monoclonal antibodies, or MSC therapies targeting TGF-β1–induced pathways, ECM deposition, and EMT are currently tested in animal models and clinical trials. Among these, tranilast, PPAR-γ agonists, rho kinase inhibitors, and especially MSC therapy have provided interesting results in CD patients with irreversible damage lesions, and thus represent the most promising and available therapies that could be evaluated in the near future in clinical trials. They may represent the future treatment of stricturing and fistulizing CD.

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Reprint requests

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Conflicts of interest

These authors disclose the following: Benjamin Pariente has served a speaker or consultant, and/or on the advisory board for Abbvie, Ferring, MSD, Takeda, Hospira, Janssen, Pfizer, Biogaran; and received funding from Abbvie, Janssen. Silvio Danese has served as a speaker or consultant, and/or on the advisory board for Abbvie, Ferring, Hospira, Johnson and Johnson, Janssen, Merck, MSD, Takeda, Mundipharma, Pfizer, Tigenix, UCB Pharma, Vifor, Biogen, Celgene, Allergan, Celltrion, Sandoz, and Boehringer Ingelheim. Florian Rieder has served as a speaker or consultant, and/or on the advisory board for UCB, Celgene, Samsung, Roche, Pliant, Thetis, Boehringer-Ingelheim, Helmsley, RedX, Abbvie, and Receptos; and has received funding from NIH, ECCO, Pliant, UCB, and Receptos. Edouard Louis has served as a speaker or consultant, and/or on the advisory board for Abbott, Abbvie, AstraZeneca, Ferring, MSD, Chiesi, Falk, Takeda, Hospira, Janssen, Pfizer, Mitsubishi Pharma, Celltrion, and Celgene; and has received funding from Takeda, Pfizer, Abbvie, and MSD. The remaining authors disclose no conflicts. Q11