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Review

Modulation of sphingosine-1-phosphate in inflammatory bowel disease

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ABSTRACT

Inflammatory bowel diseases (IBD), including ulcerative colitis and Crohn's disease, involve an inappropriate immune reaction in the digestive tract, causing a variety of disabling symptoms. The advent of monoclonal antibodies (anti-tumor necrosis factor, anti-integrin, anti-interleukin −23) has revolutionized IBD management. Nevertheless, these agents, with potential for immunogenicity, are associated with high rates of response loss and disease relapse over time. They are also associated with high production costs.

Sphingosine-1-phosphate (S1P), a membrane-derived lysophospholipid signaling molecule, is implicated in a vast array of physiological and pathophysiological processes, primarily via extracellular activation of S1P1-S1P5 receptors. S1P1, S1P4 and S1P5 are involved in regulation of the immune system, while S1P2 and S1P3 may be associated with cardiovascular, pulmonary, and theoretical cancer-related risks. Targeting S1P receptors for inflammatory conditions has been successful in clinical trials leading to approval of the non-selective S1P modulator, fingolimod, for relapsing forms of multiple sclerosis. However, the association of this non-selective S1P modulator with serious adverse events provides the rationale for developing more selective S1P receptor modulators. Until recently, three S1P modulators with differing selectivity for S1P receptors were in clinical development for IBD: ozanimod (RPC1063), etrasimod (APD334) and amiselimod (MT-1303). The development of amiselimod has been stopped as Biogen are currently focusing on other drugs in its portfolio. Following encouraging results from the Phase 2 TOUCHSTONE trial, a Phase 3 trial of the S1P modulator ozanimod in patients with moderate-to-severe ulcerative colitis is ongoing. Etrasimod is also being tested in a phase 2 trial in ulcerative colitis. These pipeline medications can be administered orally and may avoid the formation of anti-drug antibodies that can lead to treatment failure with injectable biologic therapies for IBD. Data from ongoing clinical trials will establish the relationship between the selectivity of S1P modulators and their safety and efficacy in IBD, as well as their potential place in the clinical armamentarium for IBD.

Contents

Abbreviations: IBD, inflammatory bowel disease; MS, multiple sclerosis; PML, progressive multifocal leukoencephalopathy; RBS, rectal bleeding subscore; S1P, sphingosine-1-phosphate; TNF, tumor necrosis factor; ULN, upper limit of normal.

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1. Introduction

Inflammatory bowel diseases (IBD), including ulcerative colitis and Crohn's disease, are chronic, disabling conditions [1] that can cause progressive damage to the lining of the digestive tract [2]. Medical therapy for IBD aims to suppress the inappropriate inflammatory response, heal the lining of the digestive tract, maintain corticosteroid-free remission, and improve quality of life [2,3]. Pharmacotherapies for IBD include glucocorticoids, aminosalicylates, immunomodulators (thiopurines and methotrexate), as well as relatively newer biologic therapies, e.g. tumor necrosis factor (TNF) inhibitors, gut-selective integrin antagonists, and the recently Food and Drug Administration (FDA)-approved interleukin-12 and -23 inhibitor, ustekinumab [4–7]. However, these treatment options for IBD have limitations in terms of patient response, efficacy, side effects, and routes of administration, as well as being costly to use.

Poor efficacy with conventional therapies was highlighted in a recent, multicenter, European cohort study assessing disease burden and unmet clinical needs in adults with moderate-to-severe ulcerative colitis (Mayo score ≥ 6, treatment excluding biologic therapies and surgery). Among the study population, 75% were receiving aminosalicylates and 63% were receiving thiopurines. A high proportion of the patients (87%) had uncontrolled ulcerative colitis and one quarter reported unmet clinical needs [3]. Almost half (48%) were dissatisfied with their current treatment, and moderate-to-severe symptoms were a predictor of this dissatisfaction [8].

Intravenously or subcutaneously administered biologic therapies, introduced nearly two decades ago [4], show good initial clinical response rates but are associated with high rates of response loss and disease relapse over time [9]. All monoclonal antibodies have the potential for immunogenicity and anti-drug antibodies are associated with an increased risk of losing response to therapy [9]. Costs associated with the biologics are also limiting the use of these agents [10]. A recent web-based survey of 1315 patients with Crohn's disease or ulcerative colitis, across 14 hospitals in the Netherlands, identified anti-TNF use as being the main driver behind healthcare costs in IBD, accounting for 64% and 31% of total costs among these respective patient groups [11].

Small molecule drugs, with molecular weights of <1 kDa (often below 500 Da), are able to diffuse easily through cell membranes, therefore providing potential advantages over the larger biologics in terms of route of administration, pharmacokinetic features, and antigenicity [12]. Furthermore, these small molecules are also simpler to produce, compared with the more complex production of biologics, and overall drug costs are expected to be lower [12]. Sphingosine-1-phosphate (S1P) receptor modulators are among these small molecule therapies currently in clinical development for IBD [4]. These novel, oral pipeline medications not only have the advantage of a more convenient route of administration, but also have the potential to avoid the formation of anti-drug antibodies, which requires the need for frequent testing and often leads to treatment failure.

This article reviews the physiological and pathophysiological roles of S1P and S1P1–5 receptor subtypes, and discusses how these may relate to the efficacy and safety of S1P modulators. It also offers perspectives on the development of the clinical armamentarium for IBD.

2. Molecular aspects of S1P action

S1P is a membrane-derived lysophospholipid signaling molecule [13]. Although intracellular roles for S1P have been described, it acts primarily as an extracellular signaling molecule, activating five different subtypes of G protein-coupled receptors, S1P1–5 [13,14]. The expression, downstream signaling molecules, and functions of these five receptors are summarized in Fig. 1 [13,15–24]. S1P1–3 are widely expressed, whereas the expression of S1P4 and S1P5 is restricted to distinct cell types [13]. These receptors are involved in many physiological processes, and are particularly important for the regulation of the immune, cardiovascular, and nervous systems [13]. They have also been implicated in pathological conditions, and preclinical work has implicated theoretical risks such as cancer pathogenesis [13].

2.1. S1P1

In the immune system, S1P1 regulates the trafficking of lymphocytes out of the secondary lymphoid organs into the blood and lymph (Fig. 2; panel A) [13,25]. Naïve T-cells enter lymph nodes and egress in an S1P/S1P1-dependent mechanism through the sinus-lining endothelium via the efferent lymph into the blood [25]. However, when a productive antigen encounter occurs, the T-cells become activated and transiently down-modulate S1P1. This renders the cells unresponsive to the egress signal provided by S1P and the proliferating cells remain in the lymph node. Therefore, S1P1 activation leads to the sequestration of lymphocyte subpopulations in the peripheral lymphoid organs, preventing them from being trafficked to inflamed tissues, thereby modulating immunity [26].

Dendritic and endothelial cells also express S1P1, which may mediate effects on dendritic cell migration and vascular barrier function [15].

S1P1 may also play a role in nociception, acute bradycardia and proliferation [19,20–22,27]. In estrogen receptor-positive breast cancer cells, high expression of S1P1 has been linked with poor prognosis and decreased expression of pro-apoptotic markers [22,28].

2.2. S1P2 and S1P3

S1P2 often exerts cellular functions that are opposed to the functions of the S1P1 receptor, and the pro-inflammatory roles of the S1P2 receptor are well documented in the literature [13,29]. Nevertheless, the manner by which S1P2 regulates the underlying migratory events of the different cell types is complicated, and evidence can appear to be contradictory [29].

In addition to a pro-inflammatory role, the S1P2 receptor is involved in smooth muscle contraction and fibrosis. S1P2 induces contraction of diverse types of smooth muscle (including vascular, bronchial, intestinal, and bladder smooth muscle) by increasing intracellular Ca^{2+} concentrations and by activation of the Rho/Rho kinase [29–32]. Both S1P2 and S1P3 receptors mediate vasoconstriction in the vascular system, with differential responses in different vascular beds [29]. Notably, S1P2 may play an injurious role in renal ischemia-reperfusion injury [33] and S1P3 receptor may be responsible for the hypertension associated with the non-selective S1P receptor agonist, fingolimod (FTY720) [19].

Both S1P2 and S1P3 receptors are involved in pro-fibrotic pathways induced by S1P and fingolimod-phosphate (the active metabolite of fingolimod) in normal human lung fibroblasts [23]. Activation of the S1P2/Rho/ROCK pathway by fingolimod-phosphate leads to contraction of human lung myofibroblasts [24]. Fibroblast contraction is observed in many fibrotic disorders, and contributes to tissue stiffness and organ