IBD REVIEWS REVIEW ARTICLE

Anti-integrin antibodies as biologic therapy for patients with inflammatory bowel disease

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Abstract

The complex inflammatory cascade that forms part of the pathophysiological mechanisms underlying inflammatory bowel disease (IBD) has been subject of diverse studies since several years ago. Through time, many different molecular pathways have been elucidated and further identified as therapeutic targets for biologic therapy, which has potentially modified the classic therapeutic pyramid and consequently IBD clinical course. The current research has focused in studying and finding new therapeutic targets that allow us to maintain or improve the outcomes obtained with anti-tumor necrosis factor-α biologic agents and avoid or diminish their adverse events and related risks. Integrins and their receptors are particularly interesting and promising therapeutic targets for biologic agents under current clinical trials such as natalizumab, vedolizumab, abrilumab, etrolizumab, anti-MAdCAM-1, or alicaforsen. Here, we discuss and analyze widely the most recent advances in this regard, including the disadvantages and adverse events that we are still facing, ending with a quick look into the future of this type of therapy. (IBD Rev. 2018;4:83-91)

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Introduction

The complex inflammatory cascade that forms part of the pathophysiological mechanisms underlying inflammatory bowel disease (IBD) has been subject of diverse studies since several years ago[1]. Through time, many different molecular pathways have been elucidated and further identified as targets for biologic therapy, which has potentially modified the classic therapeutic pyramid and, consequently, IBD clinical course[2]. After the first biologic agent, infliximab (IFX, anti-tumor necrosis factor [TNF]-α)[3] showed not only promising results in clinical trials and practice[4,5] but also a considerable proportion of not responding patients[6], development of antidrug antibodies[7], some adverse events[8], and augmented risk of infections[9] and malignancies[10]; research has focused in studying and finding new therapeutic

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targets that allow us to maintain or improve the outcomes obtained with IFX and avoid or diminish adverse events and related risks[11]. Among all the different molecules that are currently under research, integrins and their receptors are particularly interesting and promising therapeutic targets for biologic agents such as natalizumab[12], vedolizumab (VLZ)[13], abrilumab[14], etrolizumab[15], anti-MAdCAM-1[16], alicaforsen[17], and others which are yet to come. The present review will briefly expose the role of integrins within the immune response of IBD and, thereafter, discuss the most recent advances in clinical trials for the already under study anti-integrin biologic agents and other molecules under research in the context of Crohn's disease (CD), ulcerative colitis (UC), and pouchitis.

Integrins and their role in IBD pathogenesis

The inflammatory response is coordinated by many different mediators that form complex regulatory networks and depending on the trigger, it can have different physiological purposes and pathological consequences[18]. The gastrointestinal tract is in direct contact with the external environment and thus continuously exposed to antigens that start physiological inflammatory reactions in the gut that by recognizing foreign and bacterial commensal antigens, mount an appropriate immune response, that is, under ideal circumstances, highly regulated, and controlled. On the other hand, pathological inflammation, as it happens in IBD, is an exaggerated immune response of the mucosal immune system to the gut environment that does not appear in the adequate context, does not have a regulated intensity, and does not limit to the necessary time, thus staying far from ending with the less damage possible to maintain the function and integrity of the tissue where it developed, as it should occur in physiological terms[19,20]. The principal gut-homing integrins are represented in figure 1 and briefly discussed hereafter.

As it has been previously stated, acute inflammation is a dysregulated mechanism in IBD, which is why the trafficking pathways of cells are potential molecular targets[21]. Integrins are a large group of adhesion receptors formed as heterodimers of α and β subunits, located on the surface of leukocytes, that play a crucial role in several immune processes from which we will mention, for the purpose of this review, the leukocyte recruitment to inflamed tissue, efferocytosis, and the egress of efferocytic macrophages from the inflamed site to lymphoid tissues, as these are the principal events that drive the onset and resolution of the acute inflammatory response[22]. The principal advantage of the use of integrins as therapeutic targets is avoiding the potential side effects we have experienced with systemic immunosuppression. This has been apparently achieved by making use, for example, of gut-tropic integrins like α4β7, which mediates migration of leukocytes specifically to the intestinal mucosa, or the mucosal vascular address in cell adhesion molecule 1 (MadCAM-1), the major ligand for α4β7, whose expression is largely restricted to the endothelium of vessels associated with Peyer's patches and the lamina propia[23]. On the other hand, the integrin αEβ7 is also targeted by one of the biologic agents currently on trials, but this is not a gut-tropic integrin because although αEβ7 shares the β7 subunit with α4β7, it interacts with E-cadherin on epithelial cells of different organs[24], which could imply a disadvantage. Other molecules targeted by one biologic agent, although not gut tropic, are intracellular adhesion molecule 1 (ICAM-1), which is a transmembrane glycoprotein of the immunoglobulin family, constitutively expressed on vascular endothelial cells and upregulated in inflamed colonic tissue[17].

The current details about biologic agents targeting integrins are discussed hereafter. In figure 2, we represent the principal biologic agents and their biologic target.

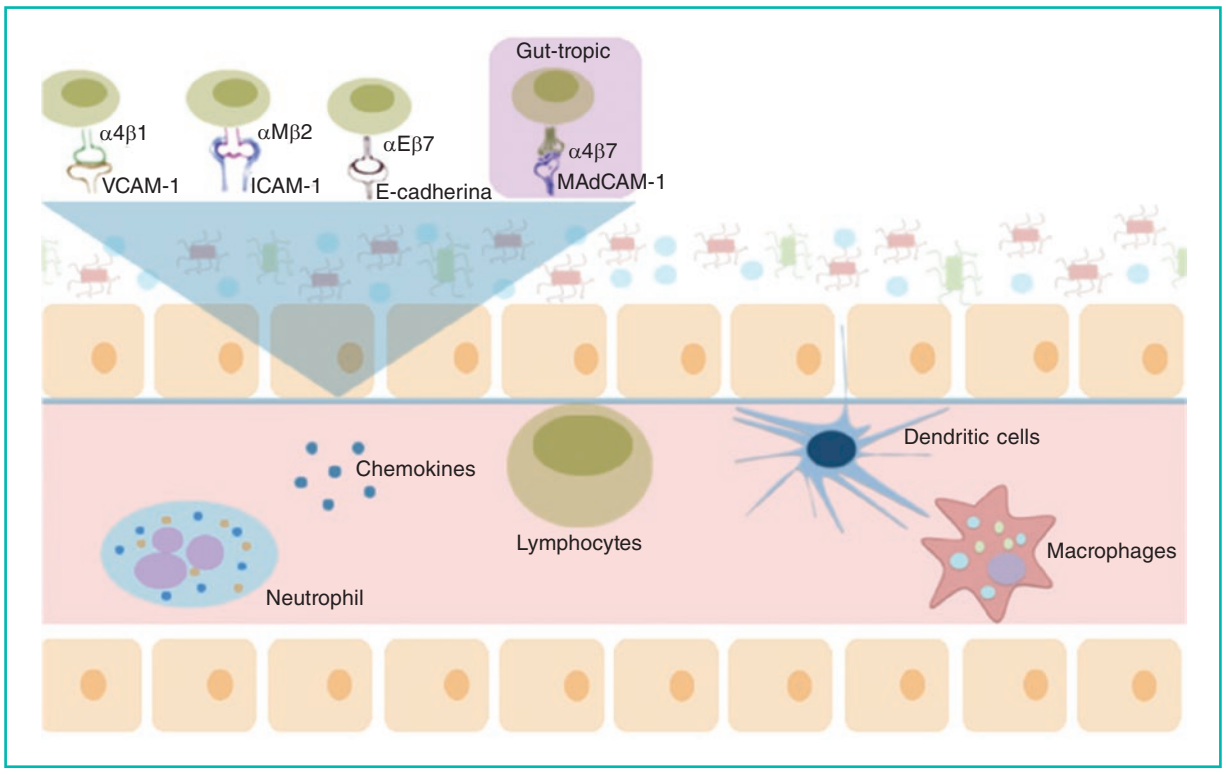

Figure 1. Principal integrins and adhesion molecules in inflammatory bowel disease.

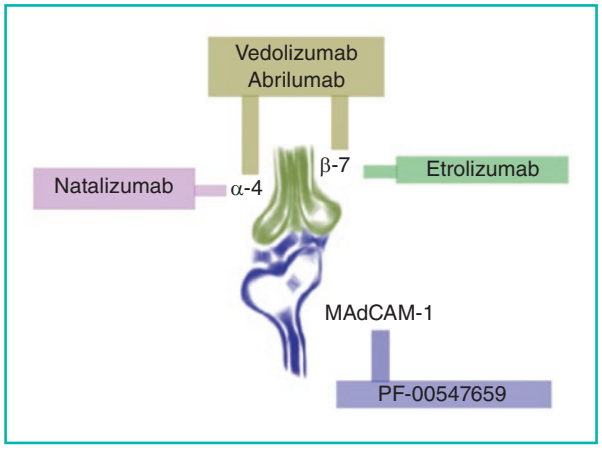

Figure 2. Anti-integrin biologic agents and their targets.

Anti-integrin biologic agents

In table 1 is summarized all biological agents blocking integrins for IBD patients.

Natalizumab

The area of anti-integrin biologic therapy started with a non-gut-specific anti-α4 antibody of intravenous administration named natalizumab. In 2003, ENCORE trials evaluated its efficacy as induction therapy for 509 patients with CD, in a dose of 300 mg at weeks 0, 4, and 8, demonstrating the early, sustained efficacy, and good tolerance of this biologic treatment as induction therapy, as it induced response and remission at week 8 that was sustained through week 12[25]. In 2005, ENACT trials evaluated its efficacy for induction and maintenance of CD remission. In the first study (NCT00032786), starting with the same dose pattern described in ENCORE and taking as a primary outcome clinical response at week 10; in the second one (NCT00032799), those who responded in the first trial, continued receiving 300 mg of natalizumab or placebo every 4 weeks through week 56, taking as a primary outcome sustained response through week 36. It was then concluded that around 10% of the patients presented serious adverse events and that one patient died from progressive multifocal leukoencephalopathy (PML) associated with the JC virus[26]. The reason of this

Table 1. Anti-integrin biologic agents and their principal characteristics

Biologic agent	Route of administration			Gut specific	Studied in the context of			Serious adverse events
	IV	SC	Topical		CD	UC	Pouchitis	
Natalizumab	X				X			X
Vedolizumab	X			X	X	X	X	
Abrilumab	X			X	X	X		
Etrolizumab		X			X	X		
Anti-MAdCAM-1		X		X	X	X		
Alicaforsen	X		X	X	X	X	X	

IV: intravenous; SC: subcutaneous; CD: Crohn's disease; UC: ulcerative colitis.

serious adverse event is that anti-α4 hinders α4β1$^+$ immune cells from not only infiltrating the gut but also the brain, hence, impeding appropriate cerebral antiviral immunity, which is why although natalizumab was approved for CD treatment in North America, this was not possible in the European Union[27]. Following this, its use has been limited, but the measurement of antibodies against JC virus in serum can be used to reduce the risk of this complication and there are successful reported cases[28] and large series that conclude its good level of efficacy and safety[12]. There are no studies regarding the use of natalizumab in the context of UC or pouchitis.

Vedolizumab (VLZ)

VLZ is a human monoclonal antibody of intravenous administration that recognizes the heterodimer α4β7 and selectively blocks leukocyte traffic in the intestine[13]. It is indicated for the treatment of moderate-to-severe CD and UC, and the favorable results it has shown in clinical trials have allowed experts to consider it as a first-line alternative therapy to anti-TNF-α agents. Even when we have evolving clinical experience with its use, the mechanisms under its efficacy continue being described and are currently under constant research. Approved by the Food and Drug Administration in 2014, it is used under a loading dose of 300 mg at weeks 0, 2, and 6, followed by maintenance doses of 300 mg every 8 weeks[29,30]. GEMINI trials have evaluated this biologic agent for the treatment of IBD and will be discussed along with their *post hoc* analysis hereafter.

Efficacy of VLZ for UC

The GEMINI I (NCT00783718) trial was completed in 2012, with the aim of evaluating the efficacy of VLZ as induction and maintenance therapy compared to placebo, in the context of patients with moderate-to-severe UC who had presented over the previous 5 years period inadequate response, loss of response or intolerance to immunomodulators (IMM), anti-TNF-α, or corticosteroids. It was then demonstrated that VLZ was superior to placebo. It evaluated VLZ as induction therapy at week 6 and maintenance at week 52. As induction therapy, it was found that at week 6 of treatment, 47.1% of the patients showed clinical response, 16.9% showed clinical remission, and 40.9% showed mucosal healing. On the other hand, as maintenance therapy, at week 52 of treatment, 41.8% of the patients who received the doses every 8 weeks and 44.8% of the ones who received it every 4 weeks presented clinical remission, all these with statistical significance when compared to placebo[29,31,32]. It was

further demonstrated that the effectiveness of VLZ persisted despite the prior exposure to anti-TNF-α[33]. From this same trial, histological healing was further evaluated and found in > 50% of the patients, with maximal effect at week 52, besides diminishing the colonic expression of many immune-related genes[34]. The long-term use of this biologic agent has been associated with clinical and life quality improvement. Besides, in those patients who do not respond adequately to the conventional bimestrial scheme, it is also recommended to apply monthly doses[35].

Efficacy of VLZ for pouchitis

A chronic antibiotic-refractory pouchitis case successfully treated with VLZ has been recently reported. It was the case of a 41-year-old female with pancolonic UC since the age of 13 years with secondary failure of IFX and mesalamine and primary failure of azathioprine and adalimumab who underwent a total proctocolectomy with ileal pouch-anal anastomosis; the dose used was 300 mg parenterally at 0, 2, and 6 weeks, then every 8 weeks. The patient reported improvement in clinical symptoms, pouchoscopy demonstrated only a single linear ulcer and healthy pouch mucosa after 6 months and biochemical inflammation markers also normalized[36]. Interestingly, a case of a patient with both pouchitis and spondylarthritis (SpA) was treated with VLZ, showing again the effectiveness of VLZ for treating pouchitis. In this case report, it was also shown that the use of VLZ in combination with etanercept appears to be safe in this type of cases[37]. Other similar cases of successful treatment of pouchitis with VLZ have been reported[38], even in scenarios where fecal microbiota transfer has not been successful[39]. As we can see, apparently, the benefit of targeting the gut-specific α4β7 can extend to these frequently challenging cases of refractory pouchitis, although further trials need to be done in this regard.

Efficacy of VLZ for CD

GEMINI II (NCT00783692)[31] and III (NCT-01224171)[40] trials have evaluated the efficacy of VLZ to induce and maintain CD remission. GEMINI II evaluated VLZ as induction therapy at week 6 and maintenance at week 52 in CD, and GEMINI III looked for the percentage of participants in clinical remission in the anti-TNF-α failure subpopulation. The results of these trials have allowed treatment guidelines to recommend the use of VLZ in CD patients who continue with disease activity despite steroids and as the first- or second-line biologic treatment, as its efficacy has been demonstrated up to week 6 in 15% of the patients and up to week 10 in 26.6% of them[41]. Posterior analysis has demonstrated that up to week 52, 48.9% of the patients who are virgin to anti-TNF-α and 27.7% of the ones who are refractory to this treatment, reach remission with VLZ, concluding that although VLZ has increased efficacy over placebo in CD patients irrespective of TNF-α antagonist treatment history, overall, rates of response and remission are numerically higher in patients receiving VLZ as a first biologic than patients who have experienced TNF failure[42]. The long-term clinical benefits of VLZ continue despite the previous history of anti-TNF-α exposure, and in those cases that do not respond to the conventional bimestrial dose, there may be a benefit from administering the biologic agent at shorter intervals[43]. A meta-analysis that included both GEMINI II and III trials showed that the clinical response and remission were significantly higher for patients with CD treated with VLZ as compared to control patients, except for the subgroup of patients with previous TNF antagonist failure, for which no significant differences in clinical remission were revealed[44].

Recently, it has been reported that, in the context of the patients who have recently undergone proctocolectomy with ileo-ano anastomosis, the use of VLZ is not associated to short-term post-operatory infectious complications[45].

Safety of the use of VLZ

Since GEMINI I trial, it was concluded that the frequency of adverse events was similar with the use of VLZ compared to placebo[31]. Due to the low incidence of infections, malignancy and infusion reactions that have been reported with the use of VLZ in comparison with other biologic agents and placebo, its use is specially recommended in elderly patients who imply greater risk of this biologic therapy complications. On the other hand, the risk of malignancy and mortality is similar to that in the general population of patients with UC, and there has not been any case of PML[13]. Nevertheless, this biologic agent has the disadvantage of developing immunogenicity, although this has not been proved to be clinically relevant, which implies a clear point that favors its use when compared with other biologic agents[10,31]. GEMINI long-term safety trial (NCT00790933), currently in Phase 3, with the aim of collecting data on the occurrence of important clinical safety events resulting from chronic VLZ administration, has shown that patients with > 1 year of VLZ therapy reach endoscopic healing in 50% of the cases for UC and 29% for CD. On the other hand, low-grade dysplasia was registered in 10% of the patients and only one patient showed high-grade dysplasia[46].

Abrilumab

This is a human monoclonal antibody of intravenous administration, anti-α4β7, studied in the context of UC with previous history of non-response to anti-TNF-α or IMM, currently under Phase II trials, where remission rates have been reported in up to 13.5% of the patients, clinical response in 49.4%, and mucosal healing in 32.2% of them. Interestingly, the appearance of antidrug antibodies has not been reported for this biologic agent[47]. It has also been studied in CD, where clinical remission has been reported in up to 21.9% of the patients at week 8 and in up to 30.8% of the patients at week 12. Specifically, in the context of patients who had history of non-response to anti-TNF-α, clinical remission has been reported in up to 16.3% of the patients at week 8 and 24.8% of the patients at week 12, and in the case of those patients who are virgin to anti-TNF-α, 26.5% of them show clinical remission at week 8 and 29.2% of them at week 12[14].

Etrolizumab

This is a humanized monoclonal antibody immunoglobulin G (IgG1) that binds selectively to the subunit β7 of the heterodimers α4β7 and αEβ7, inhibiting their interaction with MadCam-1 and E-cadherina, respectively, thus preventing lymphocyte migration and intraepithelial retention of leukocytes in the intestinal mucosa[2]. At the moment, it is under Phase II trials for the treatment of CD and UC, with the advantage of being administered subcutaneously. Clinical remission has been reported at week 10 in 20.5% of the patients[15,48]. There is still limited data regarding its efficacy as a treatment option posterior to the failure of anti-TNF-α and regarding the induction of endoscopic remission; nevertheless, a symptomatic improvement in cases of moderate-to-severe UC since week 4 of treatment has recently been reported in patients who are refractory to anti-TNF-α[49]. Regarding adverse events, no serious ones have been reported, and the ones reported are similar compared to placebo[11,29].

Anti-MAdCAM-1

It is also known as PF-00547659, this is a monoclonal human antibody IgG2K of subcutaneous administration that binds specifically to the adhesion molecule MAdCAM-1, expressed in the intestine venules and thus inhibiting the transendothelial adhesion and migration of leukocytes. At present, under TURANDOT Phase II trials, where it has been shown that up to the 54.2% of the patients

with UC present clinical remission and up to 27.8% of the patients present endoscopic remission, all these with statistically significant difference when compared with placebo. On the other hand, in the case of CD, results have not been so favorable for this biologic agent, no significant clinical response was observed compared to placebo[16]. Results of the Phase II OPERA study (NCT01276509), which studies the efficacy of anti-MAdCAM-1 antibody for CD, have shown positive pharmacology and dose-dependent changes in pharmacodynamics biomarker measurements in blood[50].

Alicaforsen

This is a highly selective antisense oligonucleotide, ICAM-1 inhibitor, that downregulates its mRNA. It has been studied in the context of UC, CD, and pouchitis. For UC, topical alicaforsen was significantly more effective than placebo in inducing remission in patients with moderate-severe distal UC, with treatment effects lasting up to 30 weeks; in the context of CD, intravenous formulation showed no significant treatment effect compared to placebo; in the context of pouchitis, results have been encouraging and continue currently in Phase 3[17]. A case series that assessed efficacy of alicaforsen for the treatment of chronic refractory pouchitis showed that clinical improvement was achieved in 11 of 13 patients, but a relapse was observed in nine of these patients. The median time from clinical improvement to relapse was 16 weeks. However, the optimal duration of alicaforsen treatment in the context of pouchitis is still not established, as due to the high proportion of patients in this case series that suffered a relapse, it has been proposed that 6 weeks are not enough[51].

Future anti-integrin biologic agents

AJM300

The promising research in this field is looking forward to diminish adverse events and risks of biologic therapy and to achieve better clinical outcomes through gut-specific targets. AJM300, an orally active antagonist of the alpha-4 integrin subunit, has been studied in the context of patients with moderately active UC who had inadequate response or intolerance to mesalamine or corticosteroids, in a dose of 960 mg, 3 times daily for 8 weeks defining as a primary end point clinical response. Results from this Phase 2a trial published in 2015 concluded a clinical response rate of 62.7% and 58.8% of mucosal healing, without any serious adverse event[52]. Nothing else has been published about AJM300.

AMG 181

Another novel anti-integrin biologic agent is AMG 181, anti-$\alpha 4\beta 7$, of subcutaneous or intravenous administration. It was designed to reduce or eliminate the immunogenic response and to avoid targeting the $\alpha_4\beta_1$-expressing leukocytes implicated in the occurrence of PML reported previously in natalizumab-treated patients. In 2015, *in vivo* pharmacology from cynomolgus monkeys was successfully translated to humans and the developed model was successfully employed to support the selection of a safe starting dose, as well as pharmacologically and clinically relevant single and multiple dose escalation schemes for clinical trials in healthy volunteers and IBD subjects[53]. Results have been reported from three UC patients, two of them reached remission at day 43 of treatment, the other one achieved clinical response, and the three of them reached mucosal healing. For CD, a clinical trial NCT01696396 is currently ongoing in Phase 2, which takes as a primary outcome remission at week 8, results are not yet available[54,55].

Conclusion

Research regarding the complex inflammatory cascade that forms part of the pathophysiological mechanisms underlying IBD has evolved fast and expansively, leading to the

identification of several molecular pathways as therapeutic targets for biologic therapy that has modified the classic therapeutic pyramid and, consequently, IBD clinical course. Despite the increasing improvement, we still have not achieved the much sought-after objective of avoiding or diminishing adverse events and related risks of immunosuppression, besides improving clinical outcomes. Within this endless research, integrins and their receptors are particularly interesting and promising therapeutic targets. Although natalizumab was the first biologic anti-adhesion agent to be introduced in the clinical field of IBD, its use has been limited due to the increased risk it implies regarding the development of PML associated with the JC virus. Even though the measurement of antibodies against JC virus in serum can be used to reduce the risk of this complication, and successful reported cases and large series that conclude its good level of efficacy and safety allow us its use if the case has been appropriately selected[12,28]. On the other hand, VLZ is probably until know the leading anti-integrin biologic agent in the context of IBD, the experience of its use and the evidence obtained from trials has allowed experts to recommend it as a first line alternative therapy to anti-TNF-α agents for moderate to severe CD and UC[13]. What we can highlight from the experience and evidence regarding its use in IBD is the persistence of its effectiveness despite the prior exposure to anti-TNF-α[33] and its association with clinical and life quality improvement[35], besides the apparently successful treatment, it can represent for chronic refractory pouchitis[36]. Abrilumab shares the same biologic target of VLZ, although it has the great advantage not developing antidrug antibodies besides being gut selective, contrary to what happens with VLZ. It is being studied in the context of UC and CD, although still in Phase II clinical trials[10,31]. Etrolizumab, of subcutaneous administration, is currently under Phase II trials for the treatment of CD and UC, as it prevents lymphocyte migration and intraepithelial retention of leukocytes in the intestinal mucosa, but it is not gut selective[2]. Unfortunately, there are still limited data regarding its efficacy as a treatment option posterior to the failure of anti-TNF-α and regarding the induction of endoscopic remission; nevertheless, results until know appear favorable[49] and no serious adverse events have been reported[11,29]. Anti-MAdCAM-1 has the advantage of inhibiting the transendothelial adhesion and migration of leukocytes specifically in the intestine venules. It is currently under Phase II trials, where results are favorable regarding UC but not as such in the case of CD[16]. Alicaforsen has been studied in the context of UC, CD, and pouchitis, with the novel and advantageous option of being topically administered, which has shown favorable results for treating distal UC. It can also be administered intravenously in the context of CD, but results in this context have not been promising. On the other hand, in the context of pouchitis, results have been encouraging and continue currently in Phase 3[17] but still uncertain about the ideal duration of the treatment[51]. The future of anti-adhesion biologic therapy points principally toward reaching the final goal of inhibiting immune response selectively and safely, but unfortunately, attempts continue in this same vein.

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