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Mini Review

Biologics for the Treatment of Inflammatory Bowel Disease (IBD)

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- Biologics

Abstract

Inflammatory Bowel Disease (IBD), consisting of Crohn's Disease (CD) or Ulcerative Colitis (UC), is an immune-mediated lifelong disease. In addition to biologics, 5-aminosalicylates, corticosteroids, antibiotics, immune modulators are used for the treatment of IBD. Biologics are necessary for refractory IBD to conventional therapy. In last decades, new biologics have been, and are being developed and explored rapidly in different target molecules, including Tumor Necrosis Factor alpha (TNFα). The aim of this mini-review is to summarize the biologics.

ABBREVIATIONS

IBD: Inflammatory Bowel Disease; CD: Crohn's Disease; UC: Ulcerative Colitis; TNFα: Tumor Necrosis Factor alpha; CDAI: Crohn's Disease Activity Index; IL: Interleukin; JAK: Janus Kinase

INTRODUCTION

Inflammatory Bowel Disease (IBD), consisting of Crohn's Disease (CD) or Ulcerative Colitis (UC), is an immune-mediated lifelong disease, and is refractory in some patients. Corticosteroids (prednisone, budesonide), immune modulators (azathioprine, mercaptopurine, and methotrexate), antibiotics (metronidazole, tinidazole, ciprofloxacin, and clarithromycin), 5-aminosalicylates (mesalamine, sulfasalazine, and olsalazine), in addition to biologics, are currently used for the treatment of IBD [1]. During last decades, new biologics have been, and are being developed and explored rapidly in different target molecules, including Tumor Necrosis Factor alpha (TNFα) [1-26]. Some of biologics can also be used for rheumatoid arthritis and psoriasis [27,28]. The aim of this mini-review is to summarize biologics in the treatment of IBD, using Pubmed with key words; Crohn's disease, ulcerative colitis, biologics, infliximab, adalimumab, certolizumab, golimumab, natalizumab, MLN02, vedolizumab, ustekinumub, secukinumab, AMG 827, to facitinib, and abatacept. In this mini-review, adverse events of biologics were not highlighted.

Anti–Tumor Necrosis Factor Alpha Inhibitors

TNF α promotes the inflammatory response in various diseases including CD, UC, rheumatoid arthritis, ankylosing spondylitis, and psoriasis. Symptoms of these disorders improve upon therapy with TNFα inhibitors. Four anti-TNFα molecules are used currently to treat IBD: infliximab, adalimumab, certolizumab pegol, and golimumab (Table 1) [29]. For the treatment of CD, Hanauer SB et al concluded that patients with CD who respond to an initial dose of in fliximab are more likely to be in remission at weeks 30 and 54, to discontinue corticosteroids, and to maintain their response for a longer period of time, if in fliximab treatment is maintained every 8 weeks [2]. Patients with fistulizing CD who are responsive to infliximab induction therapy have an increased likelihood of a sustained response over a 54-week period if infliximab treatment is continued every 8 weeks [3]. Patients with moderate-to-severe CD who were treated with infliximab plus azathioprine or infliximab monotherapy were more likely to have a corticosteroid-free clinical remission than those receiving azathioprine monotherapy [4]. For the treatment of UC, Rutgeerts P et al concluded that patients with moderate-to-severe active UC treated with infliximab at weeks 0, 2, and 6 and every eight weeks thereafter were more likely to have a clinical response at weeks 8, 30, and 54 than were those receiving placebo [5]. A key question is whether we should use anti-TNFα with immunomodulator. Panaccione R et al addressed this point as follows; anti–TNFα–naïve patients with moderate to severe UC treated with infliximab plus azathioprine were more likely to achieve corticosteroid-free remission at 16 weeks than those receiving either monotherapy. Combination therapy led to significantly better mucosal healing than azathioprine monotherapy [30]. Another key question is whether we should use anti-TNFα as early treatment. Walters TD et al reported at this point, recently. In children newly diagnosed with comparably severe CD, early monotherapy with anti-TNFα produced better overall clinical and growth outcomes at 1 year than early monotherapy with an immunomodulator [31].

Using adalimumab, four major studies were reported for the treatment of CD. Hanauer SB et al concluded that adalimumab was superior to placebo for induction of remission in patients

Table 1: Anti–tumor necrosis factor alpha inhibitors.

Reference number	Disease	Drug	Study	Characteristics of the patients	Evaluation points	Study design	Major results
2	CD	infliximab	ACCENT I	TN/A	1st/CRM, MIT	5 mg/kg infliximab at week 0	CRM, MIT/30 weeks
						Group 1:	**Group 1:**
						placebo at weeks 2 and 6	21%
						and then every 8 weeks	
						thereafter until week 46	
						Group 2:	**Group 2:**
						5 mg/kg infliximab at the same	39% (p=0.003)
						timepoints	
						Group 3:	**Group 3:**
						5 mg/kg infliximab at	45% (p=0.0002)
						weeks 2 and 6 followed by	
						10 mg/kg	
3	CD	infliximab	ACCENT II	TN/A	1st/response at	5 mg infliximab/kg	complete absence of
	with				14 weeks	at weeks 0, 2, and 6	draining fistulas at week
	fistulas				2nd/loss of	randomization at week 14	54
					response	**Group 1:**	**Group 1:**
						response (+)	36% (P=0.009)
						5 mg infliximab per kg	
						every eight weeks	
						Group 2:	**Group 2:**
						response (+)	19%
						placebo maintenance	
4	CD	infliximab	SONIC	TN/A	1st/	5 mg infliximab per kilogram	1st
		azathio-prine			corticosteroid-	at weeks 0, 2, and 6	mucosal healing at week
					free CRM at		26
					week 26		
						Group 1:	**Group 1:**
						infliximab every 8 weeks	44.4% (p=0.02)
						plus daily oral placebo	30.1% (p=0.06)
						capsules	
						Group 2:	**Group 2:**
						2.5 mg oral azathioprine	30.0% (p<0.01 to Group
						per kg daily plus a pla-cebo	3, p=0.006 to Group 1)
						infusion	16.5% (p<0.001 to Group
							3, p=0.02 to Group 1)
						Group 3:	**Group 3:**
						combination therapy with	56.8%
						the two drugs	43.9%

5	UC	infliximab	ACT1	TN/A	1st/CRS at		1st
					week 8		2nd
					2nd/CRS at	**Group 1:**	**Group 1:**
					week 54	placebo	37%
							20%
						Group 2:	**Group 2:**
						infliximab (5 mg per kg)	69% (p<0.001)
						at weeks 0, 2, and 6 and then	45% (p<0.001)
						every eight weeks through	
						week 46	
						Group 3:	**Group 3:**
						infliximab (10 mg per kg)	61% (p<0.001)
						at weeks 0, 2, and 6 and then	44% (p<0.001)
						every eight weeks through	
						week 46	
5	UC	infliximab	ACT2	TN/A	1st/CRS at		1st
					week 8		2nd
					2nd/CRS at	**Group 1:**	**Group 1:**
					week 30	placebo	29%
							26%
						Group 2:	**Group 2:**
						infliximab (5 mg per kg)	64% (p<0.001)
						at weeks 0, 2, and 6 and then	47% (p<0.001)
						every eight weeks through	
						week 22	
						Group 3:	**Group 3:**
						infliximab (10 mg per kg)	69% (p<0.001)
						at weeks 0, 2, and 6 and then	60% (p<0.001)
						every eight weeks through	
						week 22	
6	CD	adalimu-mab	CLASSIC-I	TN/A	1st/CRS at	**Group 1:**	**Group 1:**
					week 4	adalimumab 40 mg/20 mg at	18% (P = 0.36)
						weeks 0 and 2	
						Group 2:	**Group 2:**
						adalimumab 80 mg/40 mg at	24% (P = 0.06)
						weeks 0 and 2	
						Group 3:	**Group 3:**
						adalimumab 160 mg/80 mg at	36% (P = 0.001)
						weeks 0 and 2 with	
						Group 4:	**Group 4:**

						placebo	12%
7	CD	adalimu-mab	CLASSIC II	Patients in	1st/CRM MIT	CLASSIC-I	
				CLASSIC--I	through week	adalimumab 40 mg at weeks	
					56	0 (week 4 of CLASSIC I)	
						and 2	
						Group 1:	**Group 1:**
						remission at both weeks 0	79% (p<0.05)
						and 4	
						adalimumab 40 mg every	
						other week for 56 weeks	
						Group 2:	**Group 2:**
						remission at both weeks 0	83% (p<0.05)
						and 4	
						adalimumab 40 mg weekly	
						for 56 weeks	
						Group 3:	**Group 3:**
						remission at both weeks 0	44%
						and 4	
						placebo for 56 weeks	
						Group 4:	**Group 4:**
						not in remission at both	46%
						weeks 0 and 4	
						adalimumab 40 mg every	
						other week	
8	CD	adalimu-mab	CHARM	TN/A	1st/CRM at	adalimumab 80 mg (week 0)	1st
					week 26	followed by 40 mg (week 2)	2nd
					2nd/CRM at	randomized at week 4	
					week 56	**Group 1:**	**Group 1:**
						placebo	17%
							12%
						Group 2:	**Group 2:**
						adalimumab 40 mg every	40% (p<0.001)
						other week	36% (p<0.001)
						through week 56	
						Group 3:	**Group 3:**
						adalimumab 40 mg weekly	47% (p<0.001)
						through week 56	41% (p<0.001)
9	CD	adalimu-mab	GAIN	TT/A	1st/CRM at	**Group 1:**	**Group 1:**
					week 4	placebo	7%
						Group 2:	**Group 2:**

						adalimumab, 160 mg and	21% (p<0.001)
						80 mg, at weeks 0 and 2	
10	CD	adalimu-mab	REACH	TN/C	1st/CRS, CRM	infliximab 5 mg/kg at weeks	At week10 (1st)
					at week 10	0, 2, and 6	CRS: 88.4%
					2nd/CRS,	Patients responding to	CRM: 58.9%
					CRM	treatment at week 10 were	
					at week 54	randomized	
						Group 1:	**Group 1:**
							2nd
						infliximab 5 mg/kg every 8	CRS: 63.5% (p=0.002)
						weeks through week 46	CRM: 55.8%
							(p<0.001)
						Group 2:	**Group 2:**
							2nd
						infliximab 5 mg/kg every 12	CRS: 33.3%
						weeks through week 46	CRM: 23.5%
11	CD	adalimu-mab	IMAGINE	TN, TT/C	1st/CRM at	adalimumab	
				conventional	week 26	(160 mg and 80 mg, or	
				treatment was		80 mg and 40 mg, for body	
				unsuccessful		weight ≥40 kg or <40 kg) at	
						weeks 0 and 2	
						Group 1:	**Group 1:**
						adalimumab (40 mg or	38.7% (p=0.075)
						20 mg for body weight ≥	
						40 kg or <40 kg) every other	
						week for 48 weeks	
						Group 2:	**Group 2:**
						adalimumab (20 mg or	28.4%
						10 mg for body weight ≥	
						40 kg or <40 kg) every other	
						week for 48 weeks	
12	UC	adalimu-mab	ULTRA 1	TN, TT/A	1st/		1st
			(induction)		hospitalizations		2nd
			ULTRA 2		within the first	**Group 1:**	**Group 1/Group 3:**
			(induction		8 weeks of	placebo group switched to	7.7%
			and		adalimumab	adalimumab therapy	0.26%
			mainte-nance)		therapy	(160/80-mg induction	
					2nd/	regimen at weeks 8/10)	
					hospitalizations	followed by 40 mg every	
					during 52	other week starting at week	

					weeks	12 until 14	
					of adalimumab	**Group 2:**	**Group 2/Group 4:**
					therapy	adalimumab (ADA) induction	4.6% (p<0.05)
						therapy of 160/80 mg at	0.18%
							(p=0.03)
						weeks 0/2 followed by	
						ADA 40 mg every other week	
						starting at week 4 until 14	
						Group 3:	
						placebo	
						Group 4:	
						adalimumab (ADA) induction	
						therapy of 160/80 mg at	
						weeks 0/2 followed by	
						ADA 40 mg every other week	
						starting at week 4 until 14	
13	CD	Certolizumab	PRECISE-1	TN, TT/A	1st/CRS, CRM		CRS at week 6
					at week 6 and		CRM at week 6
					26		CRM at week 26
						Group 1:	**Group 1:**
						placebo	27%
							17%
							10%
						Group 2:	**Group 2:**
						certolizumab pegol 400 mg	35% (p=0.02)
						at weeks 0, 2, and 4 and then	22% (p=0.17)
						every 4 weeks	14% (p=0.07)
14	CD	Certolizumab	PRECISE-2	TN, TT/A	1st/CRM at	certolizumab pegol 400 mg	
					week 26	at weeks 0, 2, and 4	
						Group 1:	**Group 1:**
						placebo	29%
						Group 2:	**Group 2:**
						certolizumab pegol 400 mg	48% (p<0.001)
						every 4 weeks through week	
						24	
15	UC	Golimumab	PURSUIT-SC	TN/A	1st/CRS at		1st
					week 6		2nd/CRM
					2nd/CRM,		2nd/mucosal healing
					mucosal	**Group 1:**	**Group 1:**
					healing	placebo	30.3%

					at week 6		6.4%
							28.7%
						Group 2:	**Group 2:**
						golimumab 200 mg	51% (p<0.0001)
						and then 100mg, 2 weeks apart	17.8%
							(p<0.0001)
							42.3% (p=0.014)
						Group 3:	**Group 3:**
						golimumab 400 mg	54.9% (p<0.0001)
						and then 200mg, 2 weeks apart	17.9% (p<0.0001)
							45.1% (p<0.0001)
16	UC	Golimumab	PURSUIT-M	PURSUIT-SC	1st/CRS	Patients responding to	1st
					maintained	induction therapy with	2nd/CRM
					through week	golimumab	2nd/mucosal healing
					54	**Group 1:**	**Group 1:**
					2nd/CRM,	placebo	31.2%
					mucosal		15.6%
					healing		26.6%
					at weeks	**Group 2:**	**Group 2:**
					30 and 54	golimumab 50mg every 4	47% (p=0.10)
						weeks through week 52	23.2% (p=0.12)
							41.7% (p=0.011)
						Group 3:	**Group 3:**
						golimumab 100mg every 4	49.7% (p<0.001)
						weeks through week 52	27.8% (p=0.004)
							42.4% (p=0.002)

Abbreviations: CD: Crohn's Disease; UC: Ulcerative Colitis; TN: TNF Alpha Naïve; TT: TNF Alpha Treated; CRS: Clinical Response; CRM: Clinical Remission; MIT: Maintenance; 1st: Primary Evaluation; 2nd: Secondary Evaluation; A: Adults; C: Children

with moderate to severe CD naïve to anti-TNFα therapy. The optimal induction dosing regimen for adalimumab was 160 mg at week 0 followed by 80 mg at week 2 [6]. Clinical remission induction and maintenance with adalimumab for moderate to severe CD without anti-TNFα was reported [7]. Adalimumab responsive patients had more clinical remission than placebo in CD with adalimumab [8]. Sandborn W et al concluded that adalimumab induces remissions more frequently than placebo in adult patients with CD who cannot tolerate infliximab or have symptoms despite receiving infliximab therapy [9]. Infliximab responsive pediatric patients were more likely to be in clinical response and remission when their maintenance therapy was given every 8 weeks rather than every 12 weeks [10]. More children who received high compared with low dose adalimumab were in remission at week 26, but the difference between dose groups was not statistically significant [11]. In terms of UC treatment, Feagan BG et al reported that in patients with moderate to severe UC, the addition of adalimumab to standard of care treatment reduced the number of hospitalizations for any cause, as well as for UC-related and UC- or drug-related complications, compared with placebo [12].

With certolizumab pegol, PRECISE-1 and PRECISE-2 were major studies [13,14]. In CD patients, induction and maintenance therapy with certolizumab pegol was associated with a modest improvement in response rates, but significant improvement in remission rates was not shown [13]. Certolizumab pegol responsive patients with CD were more likely to have a maintained response and a remission with continued certolizumab pegol treatment than with a switch to placebo [14].

In 2014, two studies using golimumab for the treatment of UC have been reported. Sandborn WJ et al concluded that treatment with subcutaneous golimumab induces clinical response, remission, and mucosal healing, and increases quality of life in larger percentages of patients with active UC than placebo [15]. Golimumab responsive patients with UC who received 100 mg golimumab had clinical remission and mucosal healing at weeks 30 and 54 [16].

Selective anti-adhesion molecules

Chronic inflammation could be decreased by the following mechanism; agents that block interactions between adhesion

molecules on circulating immune cells and their endothelial cell receptors would be expected to decrease the migration of these cells through the endothelium [29]. Natalizumab, a humanized monoclonal antibody against α_4 integrin, inhibits leukocyte adhesion and migration into inflamed tissue (Table 2) [1]. Induction therapy with natalizumab for CD showed only clinical response. Natalizumab responsive patients had significantly increased rates of sustained response and remission if natalizumab was continued every four weeks [1]. Targan SR et al concluded that natalizumab induced response and remission at week 8 through week 12. Response and remission rates for natalizumab were superior to those for placebo at weeks 4 through12, demonstrating the early and sustained efficacy of natalizumab as induction therapy in active CD [17]. Use of natalizumab in CD patients has been limited by the development of progressive multifocal leukoencephalopathy [18].

Vedolizumab, a humanized immunoglobulin G1 monoclonalantibody to $\alpha_4\beta_7$ integrin, modulates gut, but not brain, lymphocyte trafficking and therefore should theoretically be less likely to confer a predisposition to progressive multifocal leukoencephalopathy [18]. Sandborn WJ et al concluded that vedolizumab-treated patients with active CD were more likely than patients receiving placebo to have a remission, but not a Crohn's Disease Activity index (CDAI)-100 response, at week 6; patients with a response to induction therapy who continued to receive vedolizumab (rather than switching to placebo) were more likely to be in remission at week 52 [18]. For UC, Feagan BG et al reported that vedolizumab was more effective than placebo as induction and maintenance therapy for UC [19].

MLN02, a humanized antibody to the $\alpha_4\beta_7$ integrin, was more effective than placebo for the induction of clinical and endoscopic remission in patients with active ulcerative colitis [20].

Table 2: Selective anti-adhesion molecules.

Reference number	Disease	Drug	Study	Characteristics of the patients	Evaluation points	Study design	Major results
1	CD	Natalizumab	ENACT1	TN/A	1st/CRS:		CRS
		(recombinant			decrease in		CRM
		humanized			the CDAI	**Group 1:**	**Group 1:**
		IgG4			score	placebo	49%
		monoclonal			of at least 70		30%
		antibody to			points, at	**Group 2:**	**Group 2:**
		alpha 4			week 10	natalizumab 300 mg at	56% (p=0.05)
		integrin)			CRM:	weeks 0, 4, and 8	37% (p=0.12)
					CDAI score		
					of less than		
					150		
					points, at		
					week 10		
			ENACT2	Responder in	1st/sustained		1st
				ENACT-1	response		
					through week	**Group 3:**	**Group 3:**
					36	placebo	28%
					2nd/CRM at		26%
					week 36		
						Group 4:	**Group 4:**
						natalizumab 300 mg of	61%
						every four weeks	(p<0.001)
						through week 56	44%
							(p=0.003)
17	CD	Natalizumab	ENCORE	TN/A	1st/CRS at		1st
					week 8		2nd
					sustained	**Group 1:**	**Group 1:**
					through week	placebo	32%
					12		16%
					2nd/CRM at		

					week 8 and 12	**Group 2:**	**Group 2:**
						natalizumab 300 mg	48%
							(p<0.001)
						at Weeks 0, 4, and 8	26% (p=0.02)
18	UC	MLN02		TN/A	1st/CRM at		1st
		(humanized			week 6		2nd
		anti–α4β7			2nd/CRS at		3rd
		integrin			week 6	**Group 1:**	**Group 1:**
		antibody)			3rd/endoscopic	placebo	14%
					remission		33%
							8%
						Group 2:	**Group 2:**
						MLN02 0.5 mg per kg	33% (p=0.02)
						on day 1 and day 29	66% (p=0.02)
							28%
							(p=0.007)
						Group 3:	**Group 3:**
						MLN02 2.0 mg per kg	32% (p=0.03)
						on day 1 and day 29	53% (p=0.02)
							12%
19	UC	Vedolizumab	GEMINI1	TN, TT/A	1st/CRS at		
		(humanized			week 6		
		anti–α4β7				**Group 1:**	**Group 1:**
		integrin				placebo	25.5%
		antibody)					
						Group 2:	**Group 2:**
						vedolizumab 300 mg at	47.1%
						weeks 0 and 2	(p<0.001)
					2nd/CRM at	**Group 3:**	**Group 3:**
					week 52	response to vedolizumab	15.9%
						at week 6	
						placebo	
						Group 4:	**Group 4:**
						response to vedolizumab	41.8%
						at week 6	(p<0.001)
						vedolizumab every 8	
						weeks	
						for up to 52 weeks	
						Group 5:	**Group 5:**
						response to vedolizumab	44.8%
						at week 6	(p<0.001)

						vedolizumab every 4	
						weeks	
						for up to 52 weeks	
20	CD	Vedolizumab	GEMINI2	TN/A	1st/CRM at		1st
		(humanized			week 6		2nd
		anti–α4β7			2nd/CDAI-100	**Group 1:**	**Group 1:**
		integrin			(≥100-point	placebo	6.8%
		antibody)			decrease) at		25.7%
					week 6	**Group 2:**	**Group 2:**
						vedolizumab 300mg at	14.5%
							(p=0.02)
						weeks 0 and 2	31.4%
							(p=0.23)
					3rd/CRM at		3rd
					week 56	**Group 3:**	**Group 3:**
						response to induction	39%
						therapy	(p<0.001)
						vedolizumab every 8	
						weeks	
						Group 4:	**Group 4:**
						response to induction	36.4%
						therapy	(p=0.04)
						vedolizumab every 4	
						weeks	
						Group 5:	**Group 5:**
						response to induction	21.6%
						therapy	

Abbreviations: CD: Crohn's Disease; UC: Ulcerative Colitis; TN: TNF Alpha Naïve; TT: TNF Alpha Treated; CRS: Clinical Response; CRM: Clinical Remission; MIT: Maintenance; 1st: Primary Evaluation; 2nd: Secondary Evaluation; 3rd: Third Evaluation; A: Adults; C: Children; CDAI: Crohn's Disease Activity Index

Table 3: Anti-interleukins.

Reference number	Disease	Drug	Study	Characteristics of the patients	Evaluation points	Study design	Major results
21	CD	Ustekinumab	CERTIFI	TT/A	1st/CRS at		1st
		(human			week 6	**Group 1:**	**Group 1:**
		monoclonal				placebo	23.5%
		antibody				**Group 2:**	**Group 2:**
		against				1 mg ustekinumab per kg	36.6% (p=0.02)
		interleukin-				at week 0	
		12/23)				**Group 3:**	**Group 3:**
						3 mg ustekinumab per kg	34.1% (p=0.06)
						at week 0	

						Group 4:	**Group 4:**
						6 mg ustekinumab per kg	39.7% (p=0.005)
						at week 0	
					2nd/CRS		2nd
					at week 22		3rd
					3rd/CRM	**Group 5:**	**Group 5:**
					at week 22	response to ustekinumab	42.5%
						at week 6	27.4%
						placebo	
						Group 6:	**Group 6:**
						response to ustekinumab	69.4% (p<0.001)
						at week 6	41.7% (p=0.03)
						90 mg ustekinumab	
						at weeks 8 and 16	
22	CD	Ustekinumab		TN, TT/A	1st/CRS at		1st
					week 4		2nd
					2nd/CRS		3rd
					at week 6		
					3rd/CRS at	**Group 1:**	**Group 1+3:**
					week 8	SC placebo at weeks 0-3,	30%
						then 90 mg ustekinumab	30%
						at weeks 8 to 11	40%
						Group 2:	**Group 2+4:**
						SC 90 mg ustekinumab	53% (p=0.02)
						at weeks 0-3, then	53% (p=0.019)
						placebo at weeks 8-11	49% (p=0.34)
						Group 3:	**Group 3:**
						IV placebo at week 0, then	
						4.5 mg/kg ustekinumab	
						at week 8	
						Group 4:	**Group 4:**
						IV 4.5 mg/kg ustekinumab	
						at week 0, then placebo	
						at week 8	
					1st/CRS at		1st
					week 8	**Group 5:**	**Group 5:**
						primary or	43%
						secondary	
						nonresponders	
						to infliximab	
						SC 90 mg ustekinumab	
						at weeks 0-3,	
						Group 6:	**Group 6:**
						primary or	54%

						secondary	
						nonresponders	
						to infliximab	
						IV 4.5 mg/kg usteki-numab	
						at week 0	
23	CD	Secukinu-mab		TN/A	1st/CDAI	**Group 1:**	**Group 1:**
		(human anti-			reduction	placebo	CDAI=
							-63.1points
		IL-17A			at week 6		(p=0.043)
		monoclonal					favor of placebo
		antibody)				**Group 2:**	**Group 2:**
						10 mg/kg secukinumab on	CDAI=
						day 1 and 22	-29.2points

Abbreviations: CD: Crohn's Disease; UC: Ulcerative Colitis; TN: TNF Alpha Naïve; TT: TNF Alpha Treated; CRS: Clinical Response; CRM: Clinical Remission; MIT: Maintenance; 1st: Primary Evaluation; 2nd: Secondary Evaluation; A: Adults; C: Children; SC: Subcutaneous; IV: Intravenous

Table 4: Janus kinases.

Reference number	Disease	Drug	Study	Characteristics of the patients	Evaluation points	Study design	Major results
25	CD	Tofacitinib		TN, TT/A	1st/CDAI		1st
		(CP-690,550)			score		2nd
		(Janus kinase			reduction of	**Group 1:**	**Group 1:**
		(JAK)			≥70 at week	placebo	43%
		inhibitor)			4		28%
					2nd/CRS	**Group 2:**	**Group 2:**
						1 mg CP BID for 4 weeks	
						Group 3:	**Group 3:**
						5 mg CP BID for 4 weeks	Difference from G1
							5%
							11%
						Group 4:	**Group 4:**
						15 mg CP BID for 4	Difference from G1
						weeks	7%
							13%
24	UC	Tofacitinib		TN, TT/A	1st/CRS at		
		(CP-690,550)			week 8		
		(Janus kinase			2nd/CRM at	**Group 1:**	**Group 1:**
		(JAK)			week 8	placebo	42%
		inhibitor)					10%
						Group 2:	**Group 2:**
						tofacitinib 0.5 mg twice	32% (p=0.39)
						daily for 8 weeks	13% (p=0.76)
						Group 3:	**Group 3:**
						tofacitinib 3 mg twice	48% (p=0.55)

						daily for 8 weeks	33% (p=0.01)
						Group 4:	**Group 4:**
						tofacitinib 10 mg twice	61% (p=0.10)
						daily for 8 weeks	48% (p<0.0019
						Group 5:	**Group 5:**
						tofacitinib 15 mg twice	78% (p,0.001)
						daily for 8 weeks	41% (p<0.001)

Abbreviations: CD: Crohn's Disease; UC: Ulcerative Colitis; TN: TNF Alpha Naïve; TT: TNF Alpha Treated; CRS: Clinical Response; CRM: Clinical Remission; MIT: Maintenance; 1st: Primary Evaluation; 2nd: Secondary Evaluation; A: Adults; C: Children

Table 5: Costimulation Modulator.

Reference	Disease	Drug	Study	Characteristics	Evaluation	Study design	Major results
number				of the patients	points		
26	CD	abatacept		TN, TT/A	1st/CRS at	**Group 1:**	**Group 1:**
		(selective			week 8 and	placebo	14.4%
		costimulation			12	**Group 2:**	**Group 2:**
		modulator)				3 mg/kg abatacept	15.5% (p=0.812)
						at weeks 0, 2, 4, and 8	
						Group 3:	**Group 3:**
						10 mg/kg abatacept	10.2% (p=0.311)
						at weeks 0, 2, 4, and 8	
						Group 4:	**Group 4:**
						30 mg/kg abatacept	17.2% (p=0.661)
						at weeks 0, 2, 4, and 8	
					2nd/CRM at	**Group 5:**	**Group 5:**
					week 52	responded to abatacept	23.8% (p=0.082)
						at week 12	
						placebo	
						Group 6:	**Group 6:**
						responded to abatacept	11.1%
						at week 12	
						abatacept 10 mg/kg every	
						4 weeks through week 52	
26	UC	abatacept		TN, TT/A	1st/CRS at	**Group 1:**	**Group 1:**
					week 8 and	placebo	29.5%
					12		
						Group 2:	**Group 2:**
						3 mg/kg abatacept	20.3% (p=0.158)
						at weeks 0, 2, 4, and 8	
						Group 3:	**Group 3:**
						10 mg/kg abatacept	19.0% (p=0.043)
						at weeks 0, 2, 4, and 8	
						Group 4:	**Group 4:**
						30 mg/kg abatacept	21.4% (p=0.124)
						at weeks 0, 2, 4, and 8	
					2nd/CRM at	**Group 5:**	**Group 5:**
					week 52	responded to abatacept	14.1% (p=0.740)

						at week 12	
						placebo	
						Group 6:	**Group 6:**
						responded to abatacept	12.5%
						at week 12	
						abatacept 10 mg/kg every	
						4 weeks through week 52	

Abbreviations: CD: Crohn's Disease; UC: Ulcerative Colitis; TN: TNF Alpha Naïve; TT: TNF Alpha Treated; CRS: Clinical Response; CRM: Clinical Remission; MIT: Maintenance; 1st: Primary Evaluation; 2nd: Secondary Evaluation; A: Adults; C: Children

Anti-Interleukins

Interleukin (IL)-12 and IL-23 have been implicated in the pathogenesis of CD [29]. TNFα resistant patients with CD had an increased rate of response to induction with ustekinumab, a human monoclonal antibody against IL-12 and IL-23. Ustekinumab responsive patients had significantly increased rates of response and remission with ustekinumab as maintenance therapy (Table 3) [21]. Ustekinumab induced a clinical response in patients with moderate-to-severe CD, especially in patients previously given infliximab [22].

Data obtained in animal models of inflammatory bowel disease suggest involvement of IL-17 in CD pathogenesis, and overexpression of IL-17 was observed in intestinal tissue from patients with active CD [23]. However, blockade of IL-17A was ineffective compared with placebo for the treatment of active CD. [23].

Janus kinases

Tofacitinib (CP-690,550) is a selective oral inhibitor of the Janus Kinase (JAK) family of kinases, including JAK1 and JAK3, a tyrosine kinase that mediates signal-transduction activity involving the common gamma chain of the surface receptors for multiple cytokines, including ILs 2, 4, 7, 9, 15, and 21. These cytokines are integral to lymphocyte activation, function, and proliferation (Table 4) [24]. Tofacitinib had no significant treatment effect within 4 weeks on clinical endpoints measured by CDAI in patients with active CD [25]. Patients with moderately to severely active UC treated with tofacitinib were more likely to have clinical response and remission than those receiving placebo [24].

Co stimulation modulator

T cells are believed to play a role in the pathogenesis of CD and UC; thus, therapies targeting T cells are highlighted. T-cell activation requires co-stimulatory signaling via T cell CD28 and CD80 or CD86 on the antigen-presenting cell. Abatacept is a recombinant fusion protein comprising a fragment of the Fc domain of human IgG1 and the extracellular domain of human cytotoxic T-lymphocyte antigen 4 (Table 5) [26]. Sand born WJ et al reported the studies using abatacept for CD and UC. The studies showed that abatacept is not efficacious for the treatment of moderate-to-severe CD or UC [26].

CONCLUSIONS AND FUTURE REMARKS

Biologics are necessary for refractory IBD to conventional therapy. In last decades, new biologics have been, and are being developed and explored rapidly in different target molecules, including TNFα. Unfortunately, some of new biologics did not work well. In this mini-review, biologics for the treatment of IBD were summarized. Further studies upon the efficacy of other biologics are waiting. The treatment of IBD is still challenging.

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