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Supplementary Table 1A. Currently used immunomodulatory therapies for IBD that do not primarily target leukocyte homing receptors (inhibitors of leukocyte traffic molecules were summarized separately in Table 2).

Pharmacological Agent		Indication	Advantages	Disadvantages/Side effects	Ref.
Classic anti-inflammatory/immunosuppressive drugs					
Aminosalicylates	sulphasalazine 5-aminosalicylic acid (5-ASA)	Mild to-moderate UC and CD (?)	Availability of oral and topical formulations selected principally on the basis of disease location	Maintenance of remission controversial in CD. Therapeutic effecacy for 5-ASA may depend on the mucosal concentration	1, 2
Coticosteroids		Moderated to-severe UC and CD	Available in topical formulations. Suppress active inflammation in the acute setting	Side-effect profile does not allow long-term treatment. Possible high relapse rate.	3
Immunomodulation and/or inhibition of lymphocyte activation					
Thiopurines	azathioprine 6-mercaptopurine	Mild to-moderate UC and CD	Effective maintenance immunosuppressant agents indicated for steroid-dependent patients	Slow onset of action and potential serious adverse events and toxicity (toxic hepatitis, pancreatitis and lymphopenia, opportunistic infections)	4
Cyclosporin A		Severe UC and CD refractory to conventional therapy	Rapidly acting therapeutic agent	Use restricted to hospitalized patients. Potential risks of hypertension, nephrotoxicity, electrolyte imbalance, encephalopathy, tremors, myelosuppression, opportunistic infections, and seizures.	5, 6
Methotrexate		Steroid-dependent CD	Mainteinance of remission after successful induction	Potential myelosuppression, hepatotoxicity, and teratogenic and abortigenic effects.	7, 8

Inhibitors of pro-inflammatory cytokines

Target	Biological agent	Indication	Mechanism	Advantages	Disadvantages/Side effects	Ref.

TNF-α blockers	Infliximab	Moderate to-severe UC/CD refractory to conventional therapy.	Chimeric mAb targeting human TNF-α. Binds soluble bioactive TNF in the intestinal mucosa neutrolizing its effect. Binds to membrane-bound TNF, leading to T cell apoptosis	Long-term clinical benefit; permits the tapering of corticosteroids; effective in the treatment of extraintestinal IBD manifestations	Drug-induced lupus acute infusion Reactions; delayed hypersensitivity reactions, demyeliniation; limited but real risk of infections, lymphoma, cardiac failure.	9-12
	Adalimumab	CD refractory to conventional therapy	Fully human IgG1 anti-TNF-α mAb	Well tolerated; decrease in immunogenicity compared to Infliximab	Injection site reactions	13

Supplementary Table 1B. Promising immunomodulatory therapies in IBD.

Target	Biological agent	Indication	Mechanism	Clinical Phase	Advantages	Disadvantages/Side effects	Ref.
Inhibitors of pro-inflammatory cytokines							
TNF-α blockers	RDP58 (delmitide acetate)	Mild-to-moderate active UC	Protease resistant decapeptide; inhibits synthesis of pro-inflammatory cytokines (TNF, IFN-γ, IL-2, and IL-12) by blocking the formation of the MyD88-IL-1 receptor-associated kinase (IRAK)-TRAF6 cell signaling protein complex	Phase III/IIIb	oral solution; no systemic bioavailability; not immunogenic	No major adverse events reported	14
	Certolizumab pegol	CD	Humanized TNF-α Fab' mAb fragment linked to polyethylene glycol	Phase III (only in USA)	Increased drug plasma half-life	Modest improvement in response rates; Risk of infections	15, 16

Supplementary Table 1C. Unsuccessful immunomodulatory therapies in IBD.

Target	Biologic Agent	Indication	Mechanism	Clinical Phase	Advantages	Disadvantages/Side effects	Ref.
Inhibitor of T cell activation							
Anti-CD4 therapy	IDEC-131	CD	Anti-CD40Ligand	Phase II discontinued		Thromboembolism	17
	cM-T412	CD/UC	Anti-CD4 depleting mAb	Phase I discontinued	Short-term clinical improvement/remission	CD4 lymphopenia	18, 19
	MAX.16H5 and B-F5	CD/UC	Anti-CD4 non-depleting mAb	Phase I discontinued	Clinical improvement in UC	CD4 lymphopenia	20

Anti-CD3 therapy	Visilizumab (UhM291)	Severe and refractory UC	Humanized IgG2 Anti-CD3e mAb; induces T cell apoptosis and enhances IL-10 secretion	Phase III suspended	Clinical response observed in the majority of patients	Dose-limiting toxicities; Transient decrease in T lymphocyte counts; liver injury; cytokine-release symptoms	21, 22
Anti-inflammatory cytokines							
	rHuIL-10	Refractory CD	Down-regulates lymphocytes activation	Failed phase II/III	Safe and well tolerated	Ineffective even in oral formulation	23
	rhIL-11	Mild to moderate active CD	Enhance epithelial integrity	Phase II/III	Subcutaneous administration safe and well tolerated	Minor injection site reactions	24, 25
	Adalimumab	CD refractory to conventional therapy	Fully human IgG1 anti-TNF-α mAb	Phase IV	Well tolerated; decrease in immunogenicity compared to Infliximab	Injection site reactions	13
Inhibitors of pro-inflamatory cytokine receptor							
	MRA	Active CD	Humanised IgG1 monoclonal antibody to iIL-6 receptor; increases apoptosis of mononuclear cells.	Phase II	Well tolerated	Efficacy not-definitely proven	26
Inhibitors of Th1 polarization							
	Fontolizumab	Moderate-to-severe active CD	Humanized anti-IFN-g mAb	Phase II	Well tolerated, with a good safety profile.	Efficacy not-definitely proven	27, 28
	ABT-874	Active CD	Human anti-IL12/23 p40 mAb	Phase II		Limited clinical response; Injection site reactions; antidrug antibodies development	29
Inhibitors of T cell proliferation							
Anti-IL-2 receptor therapy	Daclizumab	UC	humanized IgG1 anti-IL-2 receptor (CD25) mAb	Phase II	Clinical benefit	Efficacy not-definitely proven	
	Basiliximab	UC	chimeric monoclonal anti-CD25 mAb	Phase II	Clinical remission in combination with steroid treatment	Efficacy not-definitely proven	
Growth hormone and growth factors							
	Somatropin (growth hormon)	CD	Stimulates production of insulin-like growth factor 1; trophic for intestinal mucosa	Phase II	Clinical benefit with decreased disease score; improved diarrhea and overall well-being	Efficacy not-definitely proven	30
	Keratinocyte growth factor (Repifermin, KGF-2)	Active UC	Stimulates epithelial proliferation and repair through activation of PI3k/ AKT and MAPK pathway	Phase II	Safe and well tolerated	No adverse effects; no proven efficacy over placebo	
	Epidermal growth factor (EGF)	UC	Induces epithelial growth through activation of PI3k/ AKT and MAPK pathway	Phase II	Highly efficacious in patients with active distal UC	Risk of malignant transformation in predisposed patients	31
	Sargramostim (recombinant human GM-CSF)	Steroid-dependent CD	Activates Jak/STAT pathway, PI3k/AKT, and MAPK; Immunostimulant effect on neutrophils;	Phase II	Well tolerated	No clear benefit over placebo; Irritation at the injection site; bone pain; dyspnea	32, 33

Filgrastim (recombinant human G-CSF)	CD	Immunostimulant effect on neutrophils; prevents apoptosis in epithelial cells	Phase II	Clinical remission and mucosal healing	Transient bone pain	34

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