**Supplementary Table.** Comparison of various approaches in the treatments of IBD (**Abbreviations:** 5-ASA: 5-Aminosalicylic Acid, 6-MP: 6-Mercaptopurine, 6-TG: 6-Thioguanine, ADSCs: Adipose-Derived Stem Cells, AhR: Aryl Hydrocarbon Receptor, AZA: Azathioprine, BMSCs: Bone Marrow-Derived Mesenchymal Stem Cells, CD: Crohn's Disease, CSs: Corticosteroids, DSS-colitis: Dextran Sulfate Sodium-Induced Colitis, EGF: Epidermal Growth Factor, EVs: Extracellular Vesicles, HSCs: Hematopoietic Stem Cells, HSPs: Heat Shock Proteins, IFN-γ: Interferon-Gamma, IgG1: Immunoglobulin G1, IEC: Intestinal Epithelial Cells, IL: Interleukin, JAK: Janus Kinase, mg: Milligram, MMX: Multi-Matrix System, MSCs: Mesenchymal Stem Cells, MTX: Methotrexate, NFAT: Nuclear Factor of Activated T-Cells, NF-κB: Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells, ROS: Reactive Oxygen Species, S1PR1: Sphingosine-1-Phosphate Receptor 1, SASP: Sulfasalazine, TGF-β: Transforming Growth Factor Beta, Th17/Treg: T Helper 17 Cells/Regulatory T Cells, TNFα: Tumor Necrosis Factor-Alpha, UC: Ulcerative Colitis, UC-MSCs: Umbilical Cord Mesenchymal Stem Cells, VTE: Venous Thromboembolism.)

| Treatment Class | Examples | Molecular Target/Pathway | Mechanism of Action | Key Clinical Trials & Efficacy | Common Side Effects | Ref. |
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| **Amino salicylates** | **SASP** | Arachidonic acid metabolism, ROS, cytokines, aryl hydrocarbon receptor (AhR)/TGF-β pathway | Prodrug releasing 5-ASA (active component) and sulphapyridine (SP, carrier). 5-ASA inhibits prostaglandins/leukotrienes, scavenges ROS, modulates immune cells, induces Tregs via AhR. | Similar efficacy to other 5-ASA drugs in UC<br>Cost-effective first-line option | Infertility, hemolytic anemia, photosensitization, granulocytosis | **(1)** |
| | **5-ASA (e.g., mesalamine)** | Arachidonic acid metabolism, ROS, cytokines, AhR/TGF-β pathway | Direct anti-inflammatory effects: Inhibits arachidonic acid metabolites, scavenges ROS, modulates cytokines, induces Tregs via AhR to activate TGF-β. | Superior capability of oral 5-ASA to placebo in UC; once-daily dosing effective<br>Reduces colorectal cancer risk by 75% in UC<br>Topical use prevents UC relapse<br>Mixed evidence in CD: some long-term benefits | Mild: Flatulence, nausea, diarrhea, headache.<br>Rare: Nephrotoxicity | **(1)** |
| **CSs** | **Conventional Corticosteroids (e.g., prednisone)** | Cytoplasmic CS receptors, NF-κB, Activator Protein -1, anti-inflammatory gene promoters, membrane receptors | Bind cytoplasmic CS receptors → inhibit proinflammatory transcription factors (NF-κB, Activator Protein -1).<br>Promote anti-inflammatory gene expression<br>May act via membrane receptors for rapid anti-inflammatory effects | Effective for inducing remission in UC/CD flares<br>More effective than 5-ASA in CD<br>No efficacy in maintaining remission | Opportunistic infections, diabetes, hypertension, osteoporosis, ocular effects, VTE, steroid dependency (15–40% of patients), Frequent mood changes | **(1)** |
| | **Second-Generation CSs (e.g., budesonide)** | CS receptors (high affinity) | Targeted delivery to inflammation sites (ileum/colon for pH-dependent; entire colon for MMX)<br>Reduced systemic absorption → fewer side effects. | Budesonide MMX: Tolerability similar to placebo/mesalazine<br>9mg budesonide daily + taper effective for mild-to-moderate ileal/ascending colon CD | Altered glucose concentration, constipation, menorrhagia, UC exacerbation, headache, nausea, headache, flatulence, nausea, blood cortisol decrease | **(1)** |

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| **Thiopurines** | **AZA, 6-MP,6-TG** | DNA synthesis pathways, Rac1 activation in T lymphocytes | Prodrugs metabolized to deoxy-6-thioguanosine phosphate<br><br>Inhibits DNA synthesis → blocks lymphocyte proliferation<br><br>Binds Rac1 to form 6-TGNP-Rac1 complex → inhibits T-cell activation/survival | AZA reduces hospitalization/surgery rates in UC/CD<br><br>AZA/6-MP prevents UC recurrence<br><br>43.9% 7-year remission and 88% colectomy-free survival in UC<br><br>70% steroid-dependent CD patients achieve 60-month remission with AZA | Bone marrow suppression, Liver injury, Gastrointestinal intolerance | **(1)** |
| **MTX** | | Enzymes involved in DNA synthesis, Inflammatory cytokines (IL-1, IL-2, IL-6, IL-8) | Inhibits enzymes critical for DNA synthesis<br><br>Downregulates proinflammatory cytokines → suppresses T-cell proliferation and inflammation. | CD: 72% remission in active CD after 3 months of MTX<br><br>CD maintenance: 65% remission at 40 weeks with 15mg/week IM vs. 39% control<br><br>No efficacy in UC remission induction | Fatigue, nausea, vomiting, diarrhea, Peritoneal abscess, hypoalbuminemia, atypical pneumonia, severe rash | **(1)** |
| **calcineurin inhibitors** | **Cyclosporine A** | Calcineurin (via Cyclophilin A) | Binds to Cyclophilin A, inhibiting calcineurin → blocks NFAT dephosphorylation → reduces inflammatory cytokine production. | >80% response in severe acute refractory UC<br><br>Similar 8-day remission rates for 4 mg/kg vs. 2 mg/kg Cyclosporine A<br><br>No long-term benefit in CD | Monitoring of blood concentration/general status is required. | **(1)** |
| **Anti-TNFα** | **Tacrolimus** | Calcineurin (via FKBP12) | Binds to FKBP12, inhibiting calcineurin → blocks NFAT dephosphorylation. Also inhibits macrophage activation and promotes apoptosis. | 68.4% vs. 10% DAI improvement in refractory UC<br><br>77.8% response rate in UC | Tremor, renal damage, infections, hot flashes, hyperkalemia, headache | **(1)** |
| | **Infliximab** | TNF-α | Chimeric monoclonal antibody that neutralizes TNF-α, reducing inflammation and tissue damage. | Reduced colectomy rates by 7% in UC after 54 weeks<br><br>68% clinical response in CD; 55% fistula healing<br><br>Efficacy observed within 2 weeks | Commonly, skin eruptions, rarely pneumonia, tuberculosis, lymphoma, drug-induced lupus, and hepatotoxicity | **(1, 76, 77)** |
| | **Adalimumab** | TNF-α | Human monoclonal antibody targeting TNF-α to block inflammatory signaling. | Used for steroid-dependent or refractory IBD<br><br>Similar Efficacy to Infliximab | most common: injection site reactions, infections, rare ones: malignancies, congestive heart failure, lupus-like syndrome, and demyelinating | **(1, 75, 78, 79)** |

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| | **Golimumab** | TNF-α | Fully human IgG1 monoclonal antibody against TNF-α. | Approved for moderate-to-severe UC and CD | Pulmonary side effects, pneumonia, tuberculosis, and asthma, infusion reactions, drug-induced lupus erythematosus, and psoriasiform reactions | **(1, 80, 81)** |
| **IL-12/23 Inhibitor** | **Ustekinumab** | IL-12/IL-23 (p40 subunit) | Binds to the shared p40 subunit of IL-12/IL-23, blocking receptor interaction on T/NK cells. Inhibits downstream inflammation. | Approved for moderate-severe CD and UC<br><br>Reduced gut inflammation in CD patients vs. placebo. Higher remission rates at 6 and 44 weeks. | Tuberculosis, Mycobacterium abscesses infection during treatment, monitoring for potential adverse events | **(1, 82, 83)** |
| | **Mirikizumab** | IL-23 (p19 subunit) | Targets the unique p19 subunit of IL-23, inhibiting its pro-inflammatory effects. | 200 mg dose improved UC remission at 12 weeks vs. placebo | infections, injection-site reactions, and nasopharyngitis | **(1, 84)** |
| | **Risankizumab** | IL-23 (p19 subunit) | Humanized monoclonal antibody against IL-23 p19, blocking IL-23 signaling. | Better than placebo for CD remission.<br><br>70% of CD patients stayed in remission for 1 year. | Myocardial infarction, cataract, and pancreatitis | **(1, 85)** |
| **Anti-integrin** | **Vedolizumab** | α4β7 integrin / MAdCAM-1 interaction | Blocks α4β7 binding to MAdCAM-1, inhibiting lymphocyte migration to the gut. | Effective for inducing/maintaining remission in UC and CD<br><br>Approved for moderate-severe UC/CD refractory to anti-TNF therapy. | Infections, rheumatic disorders, and cutaneous manifestations | **(1, 86)** |
| | **Etrolizumab** | β7 subunit of α4β7 and αEβ7 integrins | Targets β7 subunit, blocking both α4β7-MAdCAM-1 (migration) and αEβ7-E-cadherin (retention). | Superior to placebo in inducing UC remission at week 10<br><br>Efficacy in maintenance unconfirmed. | No major safety issues reported. | **(1)** |
| | **Carotegrast Methyl (AJM300)** | α4 subunit (α4β7 and α4β1 integrins) | Oral small molecule inhibiting α4 subunit, blocking leukocyte adhesion. | More effective than placebo in UC at week 8 | Acceptable safety profile. | **(1)** |
| | **PF-00547659** | MAdCAM-1 | Fully human monoclonal antibody blocking MAdCAM-1, preventing | Effective in inducing remission in moderate- | Well-tolerated. | **(1)** |

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| | | | α4β7 integrin binding. | severe UC | | |
| | **PN-943** | α4β7 integrin | Oral peptide antagonist of α4β7 integrin. | Phase II trial: ongoing for moderate-severe UC | Safety data pending. | **(1)** |
| **JAK Inhibitor** | **Tofacitinib** | JAK1/JAK3 (pan-JAK inhibitor) | Blocks JAKs, reducing cytokine signaling (IL-2, IL-21, etc.). Approved for UC. | Higher remission rates vs. placebo at 8 weeks (18.5% vs. 8.2%) and 52 weeks (40.6% vs. 11.1%).<br>Effective in severe/refractory UC. | Infections, nausea, vomiting, Alopecia, Venous thromboembolism, Truncal maculopapular rash | (1, 87) |
| | **Filgotinib** | Selective JAK1 inhibitor | Targets JAK1, minimizing off-target effects. | 47% remission vs. 23% placebo at 10 weeks | nausea, upper respiratory and urinary tract infections, dizziness, and lymphopenia, potential effects on male fertility | **(1, 88, 89)** |
| | **Upadacitinib** | Selective JAK1 inhibitor | Inhibits JAK1, reducing inflammation. | Dose-dependent remission (45 mg: 19.6% vs. 0% placebo)<br>Higher endoscopic improvement (45 mg: 35.7% vs. 2.2%). | Nasopharyngitis, creatine phosphokinase elevation, headache, and anemia, herpes zoster infections, and thromboembolic events in some patients, cytomegalovirus colitis and hyperlipidemia in adolescents | **(1, 90, 91)** |
| **Sphingosie-1-Phosphate Receptor Modulators and Agonists** | **Ozanimod** | S1PR1, S1PR5 | Binds to S1PR1/5, sequestering lymphocytes in lymph nodes → reduces gut inflammation. | Higher clinical remission vs. placebo (1 mg/day)<br>18.4% vs. 6% remission (induction); 37% vs. 18.5% (maintenance)<br>23.2% endoscopic response, 39.1% clinical remission (no control group). | Levels. Infection, anemia, elevated liver enzymes, and rare instances of bradycardia, heart block, and macular edema | **(1, 92, 93)** |
| | **Etrasimod** | S1PR1, S1PR4, S1PR5 | Selective agonist for S1PR1/4/5, blocking lymphocyte egress to inflamed tissues. | 2 mg/day improved clinical (P=0.009) and endoscopic outcomes (P=0.003) vs. placebo.<br>2 mg maintained clinical benefits for up to 52 weeks, with 64% of patients achieving clinical response and 33% reaching clinical remission | headache, pyrexia, nausea, fatigue, and dizziness | **(1, 94, 95)** |
| **Stem Cell Transplantation** | **Autologous HSCs** (bone marrow, umbilical cord, peripheral blood) | CD34 glycoprotein; Immune reset via chemotherapy | Eliminates self-reactive lymphocytes and generates self-tolerant immune cells via chemotherapy-induced immune ablation. | 68% remission in refractory CD<br>38% steroid-free remission at 1 year<br>80% remission after relapse with re-treatment | infections, particularly febrile neutropenia and viral infections, mucositis, hemorrhagic complications, and potential worsening of perianal CD, Ectopic tissue formation and graft-versus-host disease | **(1, 96, 97)** |
| | **MSCs** (BMSCs, ADSCs, UC-MSCs) | Cytokines (TNF-α, IFN-γ, IL-10); Th17/Treg axis | Immunomodulation via cytokine regulation (↓ pro-inflammatory, ↑ anti-inflammatory), differentiation into mesodermal cells, tissue repair via trophic factors. | 80% clinical response in refractory CD<br>40% anal fistula healing<br>61.75% fistula healing vs. placebo (meta-analysis) | Mild adverse events (transient fever) | **(1)** |

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| | **ISCs** (intestinal organoids) | Wnt/Notch signaling; growth factors (EGF, R-spondin) | Regenerates intestinal epithelium by differentiating into functional IECs (goblet, absorptive cells) and restoring crypt-villus architecture. | Preclinical success in DSS-colitis mice (organoid engraftment)<br><br>No clinical trials yet; limited animal studies | theoretical risks: engraftment failure, immune rejection | **(1)** |
| **EVs** | **MSC-Derived Exosomes** (e.g., umbilical cord MSCs) | TGF-β, macrophage modulation | Reduce pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) and increase anti-inflammatory cytokines (IL-10)<br><br>And promote tissue repair via immunomodulatory cargo (proteins, miRNAs) | Reduced inflammation in mouse IBD models<br><br>Treating refractory perianal fistulas in CDs | Minimal immunogenicity; transient immune activation (theoretical) | **(1, 98, 99)** |
| | **Immune Cell-Derived Exosomes** (e.g., IL-10-treated dendritic cells) | IL-10 signaling; Th17/Treg axis | Suppress pro-inflammatory cytokines (IL-6, IL-17) and enhance anti-inflammatory pathways. | Inhibited colitis in mouse models | Limited data; potential immune tolerance disruption | **(1)** |
| | **IEC-Derived Exosomes** | Immune tolerance pathways | Promote IEC-mediated immune tolerance and barrier repair via<br><br>junctional proteins (e.g., PrPc). | Preclinical evidence of barrier restoration | Unknown; theoretical risk of autoimmunity | **(1)** |
| | **Food-Derived Exosomes** (e.g., coconut water, vegetables) | miRNA-mediated mRNA regulation | Deliver plant-derived miRNAs to suppress inflammation and modulate host gene expression. | Anti-inflammatory effects in vitro<br><br>No clinical trials | Generally safe; potential allergenicity (untested) | **(1)** |
| | **Parasite-Derived EVs** (e.g., hookworm EVs) | IL-6, IL-1β, IFN-γ, IL-17 inhibition | Suppress pro-inflammatory cytokines via EV cargo (e.g., immunomodulatory proteins). | Reduced colitis severity in mice | Theoretical risks: parasitic antigen exposure, immune reactions | **(1)** |
| | **ANXA1-Containing Exosomes** | Formyl peptide receptor signaling | Promote epithelial restitution and barrier repair via ANXA1-mediated signaling. | Accelerated healing in UC mouse models<br><br>Elevated in IBD patients | Unknown; synthetic ANXA1 mimetics may cause off-target effects | **(1)** |
| | **HSP-Enriched Exosomes** (e.g., HSP20, HSP70, HSP90) | Stress response pathways | Modulate inflammation and cell survival via HSP-mediated protection against mucosal damage. | Preclinical evidence in IBD models<sup>223,224</sup> | Unclear; HSP overexpression linked to autoimmunity (context-dependent) | **(1)** |