# Cellular immunotherapies and immune cell depleting therapies in inflammatory bowel diseases: the next magic bullet?

Markus Friedrich Neurath [1], Bruce Eric Sands,[2] Florian Rieder [3]


## ABSTRACT

Despite significant advances in biologic and small molecule treatments and the emergence of combination therapies to treat inflammatory bowel diseases (IBD) a large unmet need remains to control intestinal inflammation. New approaches targeting several pathways simultaneously with a favorable safety profile and agents that trigger anti-inflammatory pathways to drive durable resolution of inflammation are needed. This article discusses novel cellular immunotherapies and immune cell depleting therapies in IBD, including CAR-T cell approaches, Tr1 and T regulatory (Treg) cells and cell depleting antibodies such as rosnilimab. These novel approaches have the potential to overcome current therapeutic limitations in the treatment of IBD.


## BACKGROUND: CURRENT THERAPIES FOR INFLAMMATORY BOWEL DISEASES HAVE LIMITED EFFICACY

The advent of biological therapies, including anti-cytokine agents and blockers of immune cell trafficking, has led to significant advancements in the treatment of patients with inflammatory bowel diseases (IBD).[1 2] Nevertheless, recent studies indicate a largely unchanged likelihood of favourable clinical outcomes in IBD patients receiving biological treatment relative to placebo over the past decades. This suggests the existence of a 'therapeutic ceiling' for anti-inflammatory therapies,[3 4] the reasons for which are not fully understood. Potential contributing factors may include poor patient selection, treatment stratification and response monitoring, and the suboptimal selection of drugs for combination therapies.[3 4] Furthermore, it should be noted that none of the currently approved agents (biologics, small molecules) directly targets pro-resolution pathways (eg, resolvins, regulatory T cell activation, neutrophil apoptosis) that might be required to boost efficacy and induce resolution of intestinal inflammation in IBD.[5 6] Emerging evidence suggests that the limited benefit of therapy in IBD patients is associated with the presence or accumulation of numerous pro-inflammatory immune and non-immune cell types.[7] These aggressive pro-inflammatory stromal cells ('angry cells') can persist despite the use of biological therapy or can even be induced and activated under therapeutic pressure during biological therapy.[8] Such cells may include macrophages, fibroblasts, granulocytes and lymphocytes that cross-react and activate each other through multiple inflammatory signalling cascades and mediators, including cytokines.[9–12] To date, no selective therapy targeting this phenomenon is available to our patients.

Although new single anti-cytokine agents and trafficking blockers targeting single pathogenic immune mechanisms are currently in clinical development,[13–15] it appears unlikely that these molecules will significantly raise the current therapeutic ceiling in IBD. In light of the aforementioned issues, alternative therapeutic approaches are needed that simultaneously target multiple signalling pathways in order to achieve higher remission rates and are durable. Such approaches are likely to modify both immune and non-immune components of IBD pathogenesis.

One emerging concept in IBD is to combine advanced therapies of two or more therapeutic agents/classes. For example, a recent open-label phase IV study (EXPLORER) tested the combination of the anti-tumour necrosis factor (anti-TNF) antibody adalimumab, the alpha4/beta7 integrin antibody vedolizumab, and methotrexate in patients with early Crohn's disease (CD).[16] Moreover, the anti-IL-23/p19 antibody guselkumab in combination with the anti-TNF agent golimumab was recently investigated in a phase IIa study (VEGA) in patients with ulcerative colitis (UC).[17] The results of this randomised controlled clinical trial demonstrated that the combination therapy group (guselkumab plus golimumab) exhibited higher percentages of patients in clinical remission at weeks 12 and 38 (47% and 48%) in comparison to the monotherapy groups (guselkumab: 24% and 31%; golimumab: 25% and 21%). These studies show the promise of combinations of advanced therapies in achieving better efficacy as compared with advanced monotherapies.

A second approach is the use of novel therapeutic agents which block several signalling pathways simultaneously. In this context, Janus kinase (JAK) inhibitors, such as tofacitinib (target: JAK1/3), filgotinib (JAK1) and upadacitinib (JAK1), which inhibit signalling events downstream of several cytokine receptors, have been approved for clinical therapy. In addition, numerous additional JAK inhibitors are currently in clinical development for patients with IBD. These include the TYK2 inhibitor deucravacitinib, the JAK1/TYK2 inhibitor brepocitinib and the JAK3/TEC family inhibitor ritlecitinib.[18 19] Despite the promising results of the above agents observed in clinical trials and their broad anti-inflammatory drug effects, a significant proportion of patients still did not respond to these therapies. This strongly emphasises a substantial clinical need for improved therapies that can overcome the current limitations of IBD treatment. In particular, new agents targeting several pathways simultaneously with a favourable safety profile and approaches that trigger anti-inflammatory pathways to drive the resolution of inflammation are needed. In this context, cellular therapies are entering the field of IBD as a novel approach to treatment through suppression of multiple pro-inflammatory and induction of anti-inflammatory and pro-resolving signalling pathways at the same time. Moreover, new therapeutic concepts may allow selective depletion of subsets of pathogenic effector cells in the inflamed mucosa, thereby favouring resolution of inflammation with the promise of a durable effect. Here, we will discuss the hypothesis that novel cellular and cell depleting therapies may hold the potential to revolutionise

[1]Department of Medicine 1, Kussmaul Research Campus & Ludwig Demling Endoscopy Center of Excellence, Deutsches Zentrum Immuntherapie DZI, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany
[2]Dr Henry D Janowitz Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, New York, USA
[3]Department of Gastroenterology, Hepatology & Nutrition, Digestive Diseases Institute; Department of Inflammation and Immunity, Lerner Research Institute, Center for Global Translational Inflammatory Bowel Disease Research, Cleveland Clinic Foundation, Cleveland, Ohio, USA

**Correspondence to** Professor Markus Friedrich Neurath, First Department of Medicine, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany; markus.neurath@uk-erlangen.de

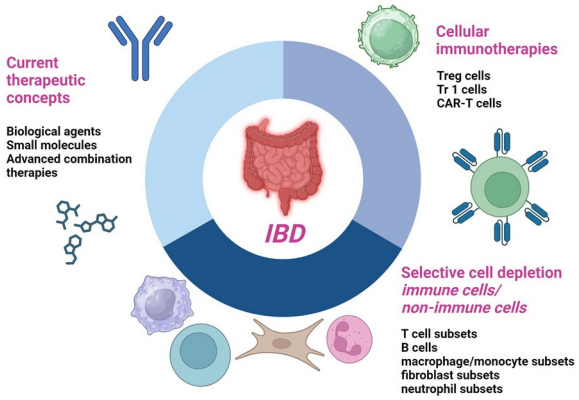


**Figure 1** Current therapies and novel possible cellular and immune-cell depleting therapies for inflammatory bowel disease therapy. Image was created with Biorender.

current IBD therapy, potentially overcoming the existing therapeutic ceiling (figure 1).

## Cellular therapies for IBD

### CAR-T cells

Initial cellular therapy studies used autologous stem cell transplantation in the presence or absence of immunotherapy with vedolizumab to induce clinical remission in refractory CD.[20 21] While this approach held the promise of an immune reset in CD, the rather non-selective approach of stem cell transplantation is associated with a potentially high burden of adverse events. This gave rise to the concept that new cellular immunotherapies that focus on immune cell subsets, and not the modulation of the entire immune system, could be more selective and well-tolerated immune interventions. Cellular immunotherapies encompass a range of treatments that employ anti-inflammatory autologous or allogeneic cells, including T lymphocytes. One of these cellular immunotherapies with innovative potential for IBD therapy is CAR-T cell therapy.

In this therapy, CD4+ or CD8+ T cells are obtained from patients via leukapheresis and genetically reprogrammed to recognise and fight target cells based on defined target structures, such as the CD19 surface molecule[22] (figure 2). Subsequently, ex vivo gene transfer is employed, during which a genetically modified virus (eg, via a lentiviral vector) is introduced into the cells, thereby enabling them to produce the chimeric antigen receptor and express this designer molecule on their surface.[22] Following the expansion of the CAR-T cells, a space is created in the patient's blood system for the transfer of the cells via lymphodepletion (eg, via cyclophosphamide and fludarabine) in preparation for infusion of the cells. Subsequently, the modified CAR-T cells are infused into the patient in a final step following lymphodepletion.[23] After administration, these CAR-T cells are capable of replicating within the body, thereby enabling long-term therapeutic effects to be achieved through the use of living CAR-T cells (figure 2). Following initial successes in the treatment of haematological tumours,[22 23] major therapeutic successes with CAR-T cell therapy have now also been achieved in chronic inflammatory and autoimmune diseases such as lupus erythematosus.[24]

A key target structure of CAR-T cell therapy in cancer is currently CD19+ B cells, which can be selectively depleted by therapy (eg, via tisagenlecleucel, lisocabtagene maraleucel, brexucabtagene autoleucel, axicabtagene ciloleucel).[22 23] Although this approach has been highly effective in B cell-mediated diseases and even led to a complete cure of the disease in individuals with lupus erythematosus,[24] the potential of a CD19+ B cell approach in IBD remains unclear. This is primarily due to the fact that studies in IBD patients have thus far failed to demonstrate a positive effect when using CD20 antibodies such as rituximab.[25] However, recent data on B cells in the pathogenesis of IBD indicate that mucosal B cells appear to play an important role in therapy resistance in IBD.[11] Activated B cells and plasma cells are enriched in therapy-refractory disease in IBD patients and are capable of producing pro-inflammatory cytokines and autoantibodies against epithelial cells, which can contribute to the inflammatory process observed in IBD.[11 26] Therefore, the effective depletion of mucosal B cells could have a greater impact on the inflammatory process in IBD than peripheral B cell depletion with rituximab. It is necessary to conduct controlled studies in order to assess the clinical benefit of CD19+ CAR-T cell therapy in IBD and to determine the extent to which target cells are depleted in different compartments.

Nevertheless, numerous additional potential targets for CAR-T cell therapies in IBD remain to be explored. A Chinese study is currently investigating the significance of CD7 CAR-T cells in

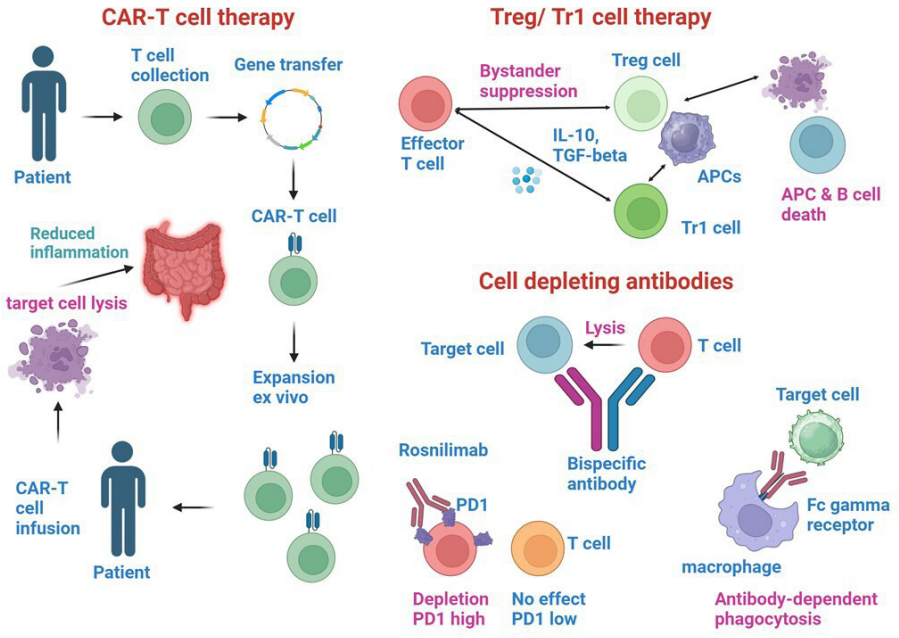


**Figure 2** New approaches for therapy: schematic of CAR-T cell therapy from cell generation to application is shown (left side). Furthermore, the mode of action of T regulatory cells (Treg) and Tr1 cells is shown (upper right side). In addition, cell depleting antibody therapies are shown (lower right side). IL, interleukin; TNF, tumour necrosis factor. Image was created with Biorender.

chronic inflammatory diseases, including CD and UC (NCT05239702). CD7 is a transmembrane glycoprotein expressed on T cells, natural killer cells and their precursors. Consequently, CAR-T cells targeting CD7 have the potential to eliminate a specific subpopulation of immune cells such as T cells, which may result in the suppression of tissue inflammation and damage in IBD. Another potential avenue for CAR-T cell therapies in IBD is the targeting of IL-23R cells.[27] In a recent study, an approach was taken to engineer regulatory T cells (Tregs) expressing an interleukin 23 receptor (IL-23R)-chimeric antigen receptor in order to create IL-23R-CAR-Tregs for the treatment of CD.[27] As IL-23R signalling and IL-23R-expressing mucosal cells play a pivotal role in IBD pathogenesis,[28 29] targeting IL-23R by CAR-T cells is a plausible new concept for IBD therapy. The study demonstrated that IL23R-CAR-Treg cells exhibited CAR-dependent suppressive activity against target cells in cell culture and protected mice from experimental colitis.[27] Furthermore, these cells demonstrated activation following exposure to intestinal biopsy-derived cells from CD, indicating the potential efficacy of IL23R-CAR cells in human disease. Despite these encouraging preclinical findings, the therapeutic efficacy of these cells in human IBD remains to be established.

Safety is important when developing new IBD treatments. CAR-T cell therapy for haematological neoplasms has been associated with the potential for life-threatening side effects, including cytokine release syndrome (CRS).[22 23] CRS is a condition that arises when CAR-T cells are activated in the human body, leading to the death of target cells and the subsequent release of cytokines. Another serious complication is immune effector cell-associated neurotoxicity syndrome (ICANS). These potentially serious complications have thus far been observed with minimal frequency in the treatment of chronic inflammatory diseases.[24] This is likely due to the significantly lower number of CD19+ target cells that are eliminated by the therapy as compared with haematological cancers. Nevertheless, further controlled studies are necessary to assess the safety of CAR-T cell therapy in inflammatory diseases. In addition, CAR-T cell therapy for the treatment of cancer has been linked to the potential for secondary cancers.[30] While these cases appear to be rare, and are still under investigation, such important adverse events would need to be weighed carefully in the risk-benefit considerations of CAR-T for IBD.

## Regulatory T cells

Studies in an experimental model of colitis have identified a protective role for regulatory CD4+CD25+FoxP3 T cells (Treg) in suppressing mucosal inflammation caused by polarised, pathogenic effector T cells.[31] In this context, the generation of additional Treg cells may provide new avenues for therapeutic intervention (figure 2). Specifically, transfer of these Treg cells has been shown to ameliorate T cell transfer colitis, which is associated with reduced production of pro-inflammatory cytokines such as interferon-gamma (IFN-γ) and TNF.[31] Moreover, it was demonstrated that the adoptive transfer of inducible Tregs generated ex vivo in cell culture in the presence of TGF-β has the capacity to ameliorate mucosal inflammation.[32] These studies provided the basis for the development of translational concepts using cellular therapies with T-regulatory cells for IBD.

A pilot study on the use of cellular therapy with autologous Tregs in patients with active CD employed ovalbumin-specific T cells (derived from peripheral blood cells on ovalbumin exposure).[33] A 12-week, open-label, single-injection, escalating-dose, phase I/IIa clinical study was conducted in 20 patients with refractory CD. The administration of Treg cells was well tolerated and exhibited a dose-related efficacy, as evidenced by a 40% reduction in Clinical Disease Activity Index scores in patients at weeks 5 and 8. However, this approach was ultimately abandoned due to manufacturing challenges associated with the cellular product. Subsequently, other research groups employed autologous, ex vivo expanded polyclonal Treg cells for cellular therapy in IBD (NCT04691232; NCT03185000). A phase I, fast-track dose-escalation clinical trial was recently completed in UC and demonstrated clinical responses in subgroups of patients with active disease following a single infusion of Treg cells[34] (Voskens *et al*, unpublished data). Treg administration was well tolerated. Ex vivo expansion of Treg cells prior to infusion may however not be necessary as shown by a recent study using low-dose subcutaneous IL-2 therapy (Proleukin) to expand Treg cells in vivo and ameliorate the activity of UC in an open-label phase Ib/IIa induction trial.[35]

T regulatory cells type 1 (Tr1) cells are a defined group of regulatory, tolerogenic T cells that are distinct from Treg cells and are characterised by the production of IL-10 and the lack of FoxP3 expression.[36 37] While FoxP3-Tr1 cells express c-Maf and Blimp-1 and produce IL-10 and TGF-β, eomesodermin-expressing Tr1-like cells produce IL-10 and IFN-γ and exhibit marked cytotoxicity. In IBD patients, a reduction in IL-10 production by mucosal Tr1-like cells was observed, suggesting a potential defect in Tr1 cells that could be overcome by the exogenous administration of these cells in order to suppress inflammation.[37 38] In experimental colitis, mucosal Tr1 cells were postulated to fill a tolerogenic niche under suboptimal conditions for Foxp3+ Treg-mediated suppression[39] and were demonstrated to suppress experimental colitis in vivo.[40]

A cell product enriched in Tr1 cells was recently employed in patients with leukaemia and allogeneic hematopoietic stem cell transplantation. In this study, Tr1 cells exhibited high expression of CTLA4 and PD1 and were detectable in the peripheral blood of patients up to 1 year after cell transfer.[41] These findings suggest that the administration of Tr1 cells could be exploited for future therapy of IBD. Indeed, a phase I programme is currently being prepared for CD therapy using polyclonal, allogeneic ex vivo expanded Tr1 cells (TRX103; www.tr1x.bio/our-programs). It is anticipated that these cells will be able to migrate to sites of mucosal inflammation via chemokine receptors, where they will suppress pro-inflammatory immune responses and stimulate the local production of antigen-specific Tr1 cells, thereby resetting the mucosal immune system and restoring homeostasis. The allogeneic nature of these Tr1 cells offers a significant advantage in that it allows for rapid cell expansion without the need to isolate and expand patient cells. This is in contrast to the previously described autologous Treg cell transfer concepts that require a significant local infrastructure, and which bear challenges of poor scaleability and significant patient burden. However, it remains to be determined whether the tolerogenic nature of these Tr1 cells is sufficient to prevent any undesired allogeneic T cell responses in the host. Controlled clinical trials are needed to ascertain the efficacy and safety of allogeneic Tr1 cell therapy in the treatment of IBD.

## Selective immune cell depleting therapies for IBD

While current therapies primarily focus on the blockade of individual cytokines or trafficking mechanisms,[1 17] selective depletion of immune cells represents an intriguing new concept for therapeutic intervention. Depletion of immune

cells has the potential for powerful and durable effects in complex immune mediated disorders such as IBD. Pathogenic subsets of immune and non-immune cells, including T cells, B cells, macrophages, granulocytes and fibroblasts, have been previously defined, particularly in patients refractory to current therapeutic concepts.[7 9] Prior attempts to deplete activated immune cells from the peripheral circulation using various techniques of apheresis have not proven to be successful in IBD.[42 43] However, new approaches to selective depletion of these cells hold promise as an emerging direction for therapy.

One example is the antibody rosnilimab, which has recently been developed for the selective targeting of PD1-high expressing immune cells.[44 45] This antibody is a novel PD1 checkpoint agonist that aims to reduce the activity of overactive T effector cells in the inflamed intestine by facilitating their removal. It is important to note that rosnilimab binds to the membrane-proximal region of PD1, and like other such antibodies is an agonist of PD1. Unlike the PD1 antagonists used in immunotherapy for cancer, rosnilimab has the potential to downregulate the immune response in inflammatory diseases.[46]

Indeed, PD1-expressing T cells are prevalent in the inflamed mucosa and in the peripheral blood of IBD patients and have been identified as a potential positive predictor of response to vedolizumab therapy.[47] Of note, rosnilimab selectively depletes PD1-high T cells and antagonises the function of PD1-intermediate T cells, while sparing the presence or function of PD1-low cells (figure 2). Such an approach may deplete or suppress highly pathogenic effector T cells in the inflamed mucosa in IBD, while maintaining immunocompetence. A phase I study in healthy volunteers demonstrated rosnilimab to be highly efficacious in the depletion of PD1 high T cells in the peripheral circulation.[45] The therapy was well tolerated, with no clinically significant safety signals. Hence, a phase II placebo-controlled study in patients with moderate to severe UC (ROSETTA; NCT06127043) has recently been initiated, with the objective to determine the efficacy and safety of rosnilimab. The study will provide first insights into the regulatory role of PD1-expressing mucosal T cells in IBD patients under in vivo conditions and should provide insight, as to whether this approach also affects cell populations within the intestinal mucosa.

A second approach to selective immunodepletion is seen with the bispecific T cell engager blinatumomab.[48] This molecule is composed of two immunoglobulin single-chain variable fragments connected via a flexible linker that permits bridging between B and T cells (figure 2). Although this concept was initially employed to facilitate T cell-mediated killing of B cells in acute lymphoblastic leukaemia,[49] recent studies have indicated that this molecule may also have therapeutic efficacy in patients with inflammatory diseases such as refractory rheumatoid arthritis through the induction of profound B cell depletion.[50] It is assumed that a single blinatumomab-driven T cell can engage several B cells and kill them serially, resulting in the depletion of B cells in the peripheral blood and inflamed tissues. In fact, in rheumatoid arthritis, blinatumomab therapy depleted autoantibody-producing memory B cells, which were replaced by non-class-switched IgD-positive naive B cells, leading to a reset of B cell immunology.[50] It can therefore be postulated that blinatumomab therapy may result in a more profound depletion of mucosal B cells than rituximab therapy.[25] Consequently, the administration of blinatumomab to patients with IBD may provide a novel approach to investigate the function of mucosal B cells. In contrast to CAR-T cell therapies targeting CD19+ B cells, the effect of blinatumomab on B cell depletion is more transient. This finding may be exploited to more tightly control mucosal B cell numbers in IBD. Nevertheless, prospective, controlled studies will be necessary to determine the efficacy and safety of this drug in the treatment of these diseases.

The third example comprises depletion of monocytes using an antibody directed against the C-C chemokine receptor type 2 (CCR2; GRT-001, GraniteBio) through antibody dependent cellular cytotoxicity (figure 2). CCR2 is mainly expressed on classical monocytes, plasmacytoid dendritic cells and basophils but can also be found on Th1 cells and Th17 cells. Monocyte chemoattractant protein-1, also known as CCL2, is its major ligand. Monocytes are multifunctional cell types central in chronic intestinal inflammation.[51] CCR2 is involved in monocyte chemotaxis and hence holds the promise of selective depletion of 'activated' or pro-inflammatory monocytes with leaving tissue resident macrophages untouched. A biological rationale is provided by CCR2+ monocyte-derived macrophages expanding in the inflamed IBD mucosa.[52] Monocyte depletion and CCR2 knock-out are protective in experimental IBD models in vivo.[51 53]

Of note, CCR2 antagonism (not depletion) failed to show an effect on clincial improvement and synovial biomarkers in active rheumatoid arthritis therapy in a phase IIa clincial trial with the human CCR2 blocking antibody MLN1202.[54] Rather than putting the monocyte depletion strategy into question, this may be due to incomplete receptor occupancy and/or redundancy of the monocyte-attracting chemokine network, in particular functional CCR1/2/5 redundancies. The first participants have now been dosed with GRT-001 in the so called MONOlith Ph1 trial in healthy volunteers and patients with IBD (EU CT 2023-507547-11-00) and outcome data is awaited. This clinical trial will provide insight into the functional relevance of CCR2 expressing monocytes in IBD patients.

## IMPLICATIONS AND CONCLUSION

Current therapeutic concepts in IBD still carry substantial limitations, with many patients failing multiple lines of therapy with biological agents or small molecules. Despite promising initial data on combination of advanced therapies with simultaneous treatment of several biologicals or small molecules, a significant unmet medical need for innovative and transformative approaches to therapy remains. We have highlighted the mechanisms and potential future clinical relevance of novel cellular and immune cell-depleting strategies for IBD therapy. In particular, novel CAR-T cell approaches, including CD19+ (B cells) and IL-23R-targeting CAR-T cells, have the potential to yield a significant impact in the treatment of patients with refractory IBD. Furthermore, cellular therapies with autologous Treg cells or allogeneic Tr1 cells hold promise for optimised treatment responses even in highly refractory patients. Finally, the opportunity to selectively target and deplete pathogenic immune effector cells, for example, via rosnilimab, blinatumomab or GRT-001, offers exciting new possibilities for IBD therapy (figures 1 and 2).

One important consideration of the therapies described here is the costs of treatment. While cell depleting antibodies may require more intense clinical and lab monitoring, CAR-T cell approaches are among the most expensive therapies in use. The wholesale price range for CAR-T cell products has been reported to be between several hundred thousand and one million US dollars.[55] This raises concerns about their affordability and access for patients, payers and healthcare systems globally. It is reasonable to speculate that, despite

their promise, the novel therapies may suffer from comparable limitations as existing therapies with only a fraction of patients responding durably. While the promise of depleting pro-inflammatory or adding regulatory cell types may be transformative, future clinical trials need to carefully explore the concept of patient stratification and personalised treatment as a 'one size fits all' approach may not be cost-effective. Furthermore, it needs to be determined if these therapies will work equally well in UC and CD, and at various disease stages, durations, locations or immunophenotypes. Finally, the clinical programme should thoroughly evaluate the tissue compartment (peripheral blood, lymphatic system, intestinal wall) in which these novel agents exert their effects. Although the efficacy and safety of these therapeutic modalities must be established through clinical development programmes, these potential new treatment options may provide insights into the role of effector immune cell subsets and offer a means of breaking through the therapeutic ceiling and overcoming resistance to therapy in IBD patients. Although the efficacy and safety of these therapeutic modalities must be established through clinical development programmes, these potential new treatment options may provide insights into the role of effector immune cell subsets and offer a means of breaking through the therapeutic ceiling and overcoming resistance to therapy in IBD patients.

**Contributors** MFN, BES and FR all contributed to the design and the content of this manuscript. All authors contributed to the writing of the manuscript.

**Funding** The work of MFN was supported by the Deutsche Forschungsgemeinschaft DFG with grant numbers TRR241, FOR2438, and GB.com as well as by the IZKF Erlangen. FR is supported by the Helmsley Charitable Trust through the Stenosis Therapy and Anti-Fibrotic Research (STAR) Consortium (No. 3081 and No. 2210-05567 to FR), the Crohn's and Colitis Foundation (No. 569125 to FR), the National Institutes of Health (NIDDK R01DK123233 and R01DK132038 to FR) and the National Institute of Health (NIDDK 2 P30 DK097948) to FR. BES is supported by the National Institutes of Health (NCATS UTR002997A).

**Competing interests** MFN has served as an advisor for MSD, Abbvie, Boehringer, PPM, Janssen, Takeda, Tr1xBio, AnaptysBio, MonteRosaTherapeutics, Pfizer and Pentax. FR is consultant to Adiso, Adnovate, Agomab, Allergan, AbbVie, Arena, Astra Zeneca, Bausch & Lomb, Boehringer-Ingelheim, Celgene/BMS, Celltrion, CDISC, Celsius, Cowen, Eugit, Ferring, Galapagos, Galmed, Genentech, Gilead, Gossamer, Granite, Guidepoint, Helmsley, Horizon Therapeutics, Image Analysis Limited, Index Pharma, Landos, Jannsen, Koutif, Mestag, Metacrine, Mirum, Mopac, Morphic, Myka Labs, Organovo, Origo, Palisade, Pfizer, Pliant, Prometheus Biosciences, Receptos, RedX, Roche, Samsung, Sanofi, Surmodics, Surrozen, Takeda, Techlab, Teva, Theravance, Thetis, Trix Bio, UCB, Ysios, 89Bio. BES reports consulting fees from Abbvie, Adiso Therapeutics, Agomab, Alimentiv, Amgen, AnaptysBio, Arena Pharmaceuticals, Artugen Therapeutics, Astra Zeneca, Biolojic Design, Biora Therapeutics, Boehringer Ingelheim, Boston Pharmaceuticals, Calibr, Celgene, Celltrion, ClostraBio, Equillium, Enthera, Envied Biosciences, Evommune, Ferring, Fresenius Kabi, Fiat, Galapagos, Genentech (Roche), Gilead Sciences, GlaxoSmithKline, Gossamer Bio, Imhotex, Index Pharmaceuticals, Innovation Pharmaceuticals, Inotrem, Kaleido, Kallyope, Merck, Microbiotica, Mitsubishi Tanabe, Mobius Care, Morphic Therapeutics, MRM Health, Nexus Therapeutics, Nimbus Discovery, Odyssey Therapeutics, Palisade Bio, Progenity, Prometheus Biosciences, Prometheus Laboratories, Protagonist Therapeutics, Q32 Bio, Rasayana Therapeutics, Recludix Therapeutics, Reistone Biopharma, Sanofi, Sorriso Therapeutics, Spyre Therapeutics, Sun Pharma, Surrozen, Target RWE,Teva, TLL Pharmaceutical, Tr1X, Union Therapeutics, Ventyx Biosciences; consulting and speaking fees from Abivax; consulting and speaking fees and other support from Lilly; research grants, consulting and speaking fees and other support from Bristol Myers Squibb, Janssen, Pfizer, Takeda; research grants and consulting fees from Theravance Biopharma; and stock/stock options from Ventyx Biopharma.

**Patient consent for publication** Not applicable.

**Ethics approval** Not applicable.

**Provenance and peer review** Commissioned; externally peer reviewed.



**To cite** Neurath MF, Sands BE, Rieder F. *Gut* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/gutjnl-2024-332919

Received 13 June 2024
Accepted 8 July 2024

*Gut* 2024;**0**:1–6.
doi:10.1136/gutjnl-2024-332919

**ORCID iDs**
Markus Friedrich Neurath http://orcid.org/0000-0003-4344-1474
Florian Rieder http://orcid.org/0000-0002-9087-1568

## REFERENCES

1 Sands BE, Irving PM, Hoops T, *et al*. Ustekinumab versus adalimumab for induction and maintenance therapy in biologic-naive patients with moderately to severely active crohn's disease: a multicentre, randomised, double-blind, parallel-group, phase 3B trial. *Lancet* 2022;399:2200–11.
2 D'Haens G, Panaccione R, Baert F, *et al*. Risankizumab as induction therapy for crohn's disease: results from the phase 3 ADVANCE and MOTIVATE induction trials. *Lancet* 2022;399:2015–30.
3 Magro F, Moreira PL, Catalano G, *et al*. Has the therapeutical ceiling been reached in crohn's disease randomized controlled trials? A systematic review and meta-analysis. *U Eur Gastroenterol J* 2023;11:202–17.
4 Raine T, Danese S. Breaking through the therapeutic ceiling: what will it take? *Gastroenterology* 2022;162:1507–11.
5 Taams LS. Inflammation and immune resolution. *Clin Exp Immunol* 2018;193:1–2.
6 Rogler G. Resolution of inflammation in inflammatory bowel disease. *Lancet Gastroenterol Hepatol* 2017;2:521–30.
7 Neurath MF. Strategies for targeting cytokines in inflammatory bowel disease. *Nat Rev Immunol* 2024.
8 Atreya R, Neurath MF. Mechanisms of molecular resistance and predictors of response to biological therapy in inflammatory bowel disease. *Lancet Gastroenterol Hepatol* 2018;3:790–802.
9 Friedrich M, Pohin M, Jackson MA, *et al*. IL-1-driven stromal-neutrophil interactions define a subset of patients with inflammatory bowel disease that does not respond to therapies. *Nat Med* 2021;27:1970–81.
10 Schmitt H, Billmeier U, Dieterich W, *et al*. Expansion of IL-23 receptor bearing Tnfr2+ T cells is associated with molecular resistance to anti-TNF therapy in crohn's disease. *Gastroenterology* 2018.
11 Martin JC, Chang C, Boschetti G, *et al*. Single-cell analysis of crohn's disease lesions identifies a pathogenic cellular module associated with resistance to anti-TNF therapy. *Cell* 2019;178:1493–508.
12 Mukherjee PK, Nguyen QT, Li J, *et al*. Stricturing crohn's disease single-cell RNA sequencing reveals fibroblast heterogeneity and intercellular interactions. *Gastroenterology* 2023;165:1180–96.
13 Kokkotis G, Bamias G. TI1A as a therapeutic target in inflammatory bowel disease. *Expert Rev Clin Immunol* 2022;18:551–5.
14 Sandborn WJ, Danese S, Leszczyszyn J, *et al*. Oral ritlecitinib and brepocitinib for moderate-to-severe ulcerative colitis: results from a randomized, phase 2B study. *Clin Gastroenterol Hepatol* 2023;21:2616–28.
15 Sandborn WJ, Feagan BG, D'Haens G, *et al*. Ozanimod as induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2021;385:1280–91.
16 Colombel J-F, Ungaro RC, Sands BE, *et al*. Vedolizumab, adalimumab, and methotrexate combination therapy in crohn's disease (EXPLORER). *Clin Gastroenterol Hepatol* 2024;22:1487–96.
17 Feagan BG, Sands BE, Sandborn WJ, *et al*. Guselkumab plus golimumab combination therapy versus guselkumab or golimumab monotherapy in patients with ulcerative colitis (VEGA): a randomised, double-blind, controlled, phase 2, proof-of-concept trial. *Lancet Gastroenterol Hepatol* 2023;8:307–20.
18 Sandborn W, Danese S, Leszczyszyn J, *et al*. Oral ritlecitinib and brepocitinib in patients with moderate to severe active ulcerative colitis: data from the VIBRATO umbrella study. *J Crohn's Colitis* 2022;15:S030–1.
19 Danese S, Panaccione R, D'Haens G, *et al*. DOP42 efficacy and safety of deucravacitinib, an oral, selective tyrosine kinase 2 inhibitor, in patients with moderately-to-severely active ulcerative colitis: 12-week results from the phase 2 LATTICE-UC study. *J Crohn's Colitis* 2022;16:i091–2.
20 Lindsay JO, Allez M, Clark M, *et al*. Autologous stem-cell transplantation in treatment-refractory crohn's disease: an analysis of pooled data from the ASTIC trial. *Lancet Gastroenterol Hepatol* 2017;2:399–406.
21 Cohen L, Gold S, Etra A, *et al*. Combination autologous stem cell transplantation and vedolizumab for refractory crohn's disease. DDW Meeting 2024 Abstract; 2024
22 Sun D, Shi X, Li S, *et al*. CAR-T cell therapy: a breakthrough in traditional cancer treatment strategies (review). *Mol Med Rep* 2024;29.

23 Willyanto SE, Alimsjah YA, Tanjaya K, *et al*. Comprehensive analysis of the efficacy and safety of CAR T-cell therapy in patients with relapsed or refractory B-cell acute lymphoblastic leukaemia: a systematic review and meta-analysis. *Ann Med* 2024;56:2349796.
24 Krickau T, Naumann-Bartsch N, Aigner M, *et al*. CAR T-cell therapy rescues adolescent with rapidly progressive lupus nephritis from haemodialysis. *Lancet* 2024;403:1627–30.
25 Leiper K, Martin K, Ellis A, *et al*. Randomised placebo-controlled trial of rituximab (anti-CD20) in active ulcerative colitis. *Gut* 2011;60:1520–6.
26 Uzzan M, Martin JC, Mesin L, *et al*. Ulcerative colitis is characterized by a plasmablast-SKEWED humoral response associated with disease activity. *Nat Med* 2022;28:766–79.
27 Cui Y, Boulakirba S, David M, *et al*. Il23R-CAR-tregs: creating a therapeutic breakthrough for crohn's. *J Crohn's Colitis* 2024;18:i3.
28 Feagan BG, Panés J, Ferrante M, *et al*. Risankizumab in patients with moderate to severe crohn's disease: an open-label extension study. *Lancet Gastroenterol Hepatol* 2018;3:671–80.
29 Neurath MF. IL-23 in inflammatory bowel diseases and colon cancer. *Cytokine Growth Factor Rev* 2019;45:1–8.
30 Ghilardi G, Fraietta JA, Gerson JN, *et al*. T cell lymphoma and secondary primary malignancy risk after commercial CAR T cell therapy. *Nat Med* 2024;30:984–9.
31 Friedrich M, Pohin M, Powrie F. Cytokine networks in the pathophysiology of inflammatory bowel disease. *Immunity* 2019;50:992–1006.
32 Fantini MC, Becker C, Tubbe I, *et al*. Transforming growth factor beta induced Foxp3+ regulatory T cells suppress Th1 mediated experimental colitis. *Gut* 2006;55:671–80.
33 Desreumaux P, Foussat A, Allez M, *et al*. Safety and efficacy of antigen-specific regulatory T-cell therapy for patients with refractory crohn's disease. *Gastroenterology* 2012;143:1207–17.
34 Voskens C, Stoica D, Rosenberg M, *et al*. Autologous regulatory T cell transfer in refractory ulcerative colitis with concomitant primary sclerosing cholangitis. *Gut* 2023;72:49–53.
35 Allegretti JR, Mitsialis V, Canavan JB, *et al*. Low-dose interleukin 2 for the treatment of moderate to severe ulcerative colitis. *Gastroenterology* 2023;165:492–5.
36 Geginat J, Vasco C, Gruarin P, *et al*. Eomesodermin-expressing type 1 regulatory (EOMES(+) Tr1)-Like T cells: basic biology and role in immune-mediated diseases. *Eur J Immunol* 2023;53:e2149775.
37 Battaglia M, Gregori S, Bacchetta R, *et al*. Tr1 cells: from discovery to their clinical application. *Semin Immunol* 2006;18:120–7.
38 Brockmann L, Soukou S, Steglich B, *et al*. Molecular and functional heterogeneity of IL-10-producing CD4(+) T cells. *Nat Commun* 2018;9:5457.
39 Zhou JY, Glendenning LM, Cavanaugh JM, *et al*. Intestinal Tr1 cells confer protection against colitis in the absence of Foxp3+ regulatory T cell-derived IL-10. *Immunohoriz* 2023;7:456–66.
40 Huber S, Gagliani N, Esplugues E, *et al*. Th17 cells express interleukin-10 receptor and are controlled by Foxp3(-) and Foxp3+ regulatory CD4+ T cells in an interleukin-10-dependent manner. *Immunity* 2011;34:554–65.
41 Chen PP, Cepika A-M, Agarwal-Hashmi R, *et al*. Alloantigen-specific type 1 regulatory T cells suppress through CTLA-4 and PD-1 pathways and persist long-term in patients. *Sci Transl Med* 2021;13:eabf5264.
42 Sands BE, Katz S, Wolf DC, *et al*. A randomised, double-blind, sham-controlled study of granulocyte/monocyte apheresis for moderate to severe crohn's disease. *Gut* 2013;62:1288–94.
43 Sands BE, Sandborn WJ, Feagan B, *et al*. A randomized, double-blind, sham-controlled study of granulocyte/monocyte apheresis for active ulcerative colitis. *Gastroenterology* 2008;135:400–9.
44 Ramírez-Marín HA, Tosti A. Emerging drugs for the treatment of alopecia areata. *Expert Opin Emerg Drugs* 2022;27:379–87.
45 Luu K, Dahl M, Hare E, *et al*. Rosnilimab, a novel PD-1 agonist monoclonal antibody, reduced T cell proliferation, inflammatory cytokine secretion, and PD-1+ expressing CD4 and CD8 T cells: results from a phase 1 healthy volunteer clinical trial. DDW Meeting 2024 Abstract; 2024
46 Suzuki K, Tajima M, Tokumaru Y, *et al*. Anti-PD-1 antibodies recognizing the membrane-proximal region are PD-1 agonists that can down-regulate inflammatory diseases. *Sci Immunol* 2023;8:eadd4947.
47 Kim MK, Jo SI, Kim S-Y, *et al*. PD-1-positive cells contribute to the diagnosis of inflammatory bowel disease and can aid in predicting response to vedolizumab. *Sci Rep* 2023;13:21329.
48 Hodder A, Mishra AK, Enshaei A, *et al*. Blinatumomab for first-line treatment of children and young persons with B-ALL. *J Clin Oncol* 2024;42:907–14.
49 Zhai Y, Hong J, Wang J, *et al*. Comparison of blinatumomab and CAR T-cell therapy in relapsed/refractory acute lymphoblastic leukemia: a systematic review and meta-analysis. *Expert Rev Hematol* 2024;17:67–76.
50 Bucci L, Hagen M, Rothe T, *et al*. Bispecific T cell engager therapy for refractory rheumatoid arthritis. *Nat Med* 2024;30:1593–601.
51 Zigmond E, Varol C, Farache J, *et al*. Ly6C hi monocytes in the inflamed colon give rise to proinflammatory effector cells and migratory antigen-presenting cells. *Immunity* 2012;37:1076–90.
52 Bernardo D, Marin AC, Fernández-Tomé S, *et al*. Human intestinal pro-inflammatory CD11c(high) CCR2(+)CX3CR1(+) macrophages, but not their tolerogenic CD11c(-)CCR2(-)CX3CR1(-) counterparts, are expanded in inflammatory bowel disease. *Mucosal Immunol* 2018;11:1114–26.
53 Platt AM, Bain CC, Bordon Y, *et al*. An independent subset of TLR expressing CCR2-dependent macrophages promotes colonic inflammation. *J Immunol* 2010;184:6843–54.
54 Vergunst CE, Gerlag DM, Lopatinskaya L, *et al*. Modulation of CCR2 in rheumatoid arthritis: a double-blind, randomized, placebo-controlled clinical trial. *Arthritis Rheum* 2008;58:1931–9.
55 Cui C, Feng C, Rosenthal N, *et al*. Hospital healthcare resource utilization and costs for chimeric antigen T-cell therapy and autologous hematopoietic cell transplant in patients with large B-cell lymphoma in the United States. *Leuk Lymphoma* 2024;65:922–31.