An international consensus on the design of clinical trials for advanced combination treatment (ACT) in inflammatory bowel disease

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Summary

Background **Advanced Combination Treatment (ACT) refers to the dual use of two advanced therapies—either two biologics, two small molecules, or one biologic and one small molecule. There is a lack of guidance regarding clinical trial design for ACT in patients with inflammatory bowel disease (IBD). Key uncertainties remain regarding aspects such as eligibility criteria, pharmacotherapy regimens, safety considerations, and standardised trial design configurations for both induction and maintenance phases. We aimed to formulate expert recommendations regarding the design of ACT clinical trials in IBD.**

Methods **A systematic search was performed in June 2023. Modified RAND/University of California, Los Angeles Appropriateness Methodology (RAM) was employed to evaluate 287 statements related to the design of ACT clinical trials in patients with IBD. A multidisciplinary panel of gastroenterologists and precision medicine scientists rated**

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statement appropriateness on a 9-point Likert scale. Statements were subsequently categorised as appropriate, uncertain, or inappropriate based on the median panel rating and the presence of disagreement. The consensus meetings were held on February 6, 2024 and June 4, 2024.

Findings ACT should consist of drugs with distinct mechanisms of action, avoiding combinations targeting the same biological pathway. Appropriate eligibility criteria included prior treatment failure and high risk for disease complications. Safety considerations were prioritised, with short-term use of high-risk regimens acceptable for induction therapy. Trial designs should compare ACT to monotherapy and allow for longitudinal evaluation. Co-primary endpoints of clinical remission and endoscopic response were endorsed, with safety outcomes including adverse events and infections. Precision medicine approaches, guided by biomarker analysis, were considered essential for further defining mechanistic pathways and monitoring treatment response.

Interpretation Implementing standardised design elements for eligibility criteria, pharmacotherapy regimens, safety considerations, and trial design configurations will facilitate the conduct of efficient clinical trials of ACT.

Funding None.

Keywords: Dual therapy; Inflammatory bowel disease

Research in context

Evidence before this study

Limited standardised guidance exists for designing clinical trials that evaluate advanced combination treatment (ACT) in inflammatory bowel disease (IBD). We conducted a systematic search of MEDLINE, Embase, and the Cochrane Library (CENTRAL) databases from inception to 25 July 2023 to identify phase 2 and 3 randomised controlled trials (RCTs) of immune mediated diseases that compared ACT to placebo or monotherapy. Ten RCTs were identified, of which two were IBD trials. ACT may offer clinical benefits in IBD, however further data are required.

Added value of this study

This modified RAND/UCLA Appropriateness Methodology study developed expert recommendations for ACT clinical trial design in IBD, and the expert panel concluded that ACT should consist of drugs with distinct mechanisms of action, avoiding combinations targeting identical biological pathways. The panel emphasised (1) the prioritisation of safety considerations, deeming short-term use of higher-risk regimens acceptable for induction therapy, (2) the comparison of ACT to monotherapy and enabling of longitudinal evaluation in trial designs, and (3) endorsed co-primary endpoints of clinical remission and endoscopic response, along with various secondary outcomes. Appropriate eligibility criteria included prior treatment failure and high risk for disease complications, and the use of precision medicine approaches, guided by biomarker analysis, were considered essential for defining mechanistic pathways and monitoring treatment response.

Implications of all the available evidence

Implementing the standardised design elements outlined in this study will facilitate the conduct of efficient and interpretable clinical trials of ACT in IBD. This guidance provides researchers with a framework to design high-quality studies, which may lead to enhanced treatment options for patients with IBD who have not adequately responded to current therapies.

Introduction

The treatment landscape for inflammatory bowel disease (IBD) has evolved substantially in recent years. Current therapies include various biologics and small molecule drugs, such as anti-TNF agents, integrin blockers, interleukin (IL) inhibitors, Janus kinase (JAK) inhibitors, and sphingosine-1-phosphate receptor (S1PR) modulators. Despite these options, short-term and 1-year clinical remission rates with monotherapy typically range between 30% and 50%.[1–3] In the SONIC trial (NCT00094458), combination therapy with infliximab and azathioprine demonstrated superior efficacy in achieving corticosteroid-free clinical remission compared to monotherapy with either agent for Crohn's disease (CD) treatment.[4] While this landmark study influenced a paradigm shift in clinical practice, the persistence of a therapeutic plateau in IBD suggests that current treatment approaches may still be insufficient.[5]

Advanced combination treatment (ACT) refers to the dual administration of two advanced therapies—either two biologics, two small molecules, or one biologic and

one small molecule to potentially enhance therapeutic outcomes.[6,7] This approach has garnered interest in the context of IBD due to the complex and varied cytokine patterns that drive inflammation. Simultaneously targeting multiple pathogenic pathways may offer additive or synergistic benefits, thereby leading to optimised outcomes in disease management. Although few controlled studies have directly compared the efficacy of different ACT strategies, preliminary data suggest promising potential. An early example—a multicentre, randomised, double-blind, placebo-controlled trial—reported that combining infliximab with natalizumab improved Crohn's Disease Activity Index scores compared to infliximab alone.[8] However, due to the serious risk of progressive multifocal leukoencephalopathy, natalizumab is no longer used in IBD. A more relevant and contemporary example is the phase 2a VEGA trial, in which the combination of guselkumab and golimumab demonstrated superior efficacy over monotherapy for inducing clinical response at 12 weeks in patients with moderate to severe ulcerative colitis (UC).[9] However, high-quality evidence supporting ACT in IBD remains limited. Further investigation is necessary to establish the role of ACT in optimising therapeutic outcomes for patients with IBD. A challenge to conducting research in this domain is the lack of standardised approaches to clinical trial design. Consequently, we conducted a two-round modified RAND/University of California Los Angeles Appropriateness Method (RAM) exercise[10,11] with the aim of generating a set of expert recommendations. This methodology applies a modified Delphi approach, integrating the best available evidence with expert clinical judgement, without forcing full consensus.

Methods

Delphi consensus process

A total of 17 gastroenterologists and precision medicine experts from 10 countries (Canada, USA, UK, Germany, France, Belgium, Slovenia, Italy, Portugal, and Spain) were invited to participate in the RAM exercise. Selection was based on their publication record, experience in clinical trial design, and/or expertise in personalised treatment strategies for IBD. Experts were identified and invited by a task force led by VS, JH, SD, and VJ, based on their scientific contributions and leadership in ACT research. All invited experts agreed to participate and completed both rounds of the RAND/UCLA process. While geographic diversity was not the primary criterion, academic expertise was prioritised. Most participants were academic gastroenterologists with a focus on clinical trials, while others had subspecialities in translational or basic science; one participant was a biologist.

The process began with development of a draft survey drawing from a previously published systematic review that identified ten randomised controlled trials (RCTs) comparing ACT with advanced monotherapy for the treatment of immune-mediated diseases.[12] In the published systematic review, we included phase 2–3 RCTs of patients with immune-mediated inflammatory disorders (IMIDs) that evaluated ACT compared with placebo or monotherapy. A comprehensive search of MEDLINE, Embase, and CENTRAL was performed from inception to July 25, 2023, without language restrictions. Two reviewers independently screened titles/abstracts and full texts, with discrepancies resolved by consensus, or if needed, by a third investigator. Reference lists of included studies and relevant systematic reviews were also hand-searched. The survey covered six domains: (1) general considerations, (2) pharmacotherapies utilised in ACT regimens, (3) trial design configurations, (4) outcome timepoints, (5) outcome measures, and (6) precision medicine considerations. ACT was defined as the concomitant administration of at least two biologics or novel small molecule drugs.

A teleconference was conducted to introduce the aims of the study and review the draft survey. Panellists were encouraged to suggest additional statements and propose modifications. Subsequently, the revised survey was distributed electronically. For both rounds of voting, panellists anonymously rated the appropriateness of statements on a nine-point Likert scale (1 = highly inappropriate, 9 = highly appropriate), and the addition of free-text comments was encouraged. Survey results from the first round of voting were shared with the panellists during a second teleconference. Statements with uncertainty or disagreement were highlighted for discussion. The survey was then revised according to feedback before final voting.

Ethics

Informed consent and approval from an ethical committee were not necessary because this study was a RAM exercise to formulate expert recommendations.

Statistics

Statements were categorised as inappropriate (median 1 to $\leq$3.5 without disagreement), uncertain (median >3.5 to <6.5 without disagreement or any median with disagreement), or appropriate (median $\geq$6.5 to 9 without disagreement).[11] Disagreement was considered present when at least five panellists scored in both the lowest (1–3) and highest (6–9) ends of the scale, indicating a clear divergence in expert opinion. For exploratory purposes, disagreement was also evaluated using the interpercentile range adjusted for symmetry (IPRAS), a statistical method that considers the spread and asymmetry of panel ratings to objectively identify disagreement.[11] These definitions and thresholds were applied consistently across both rounds. Statement appropriateness was evaluated using the criteria described above.[11,13]

Role of funding source
None.

Results

The first survey consisted of 249 statements. After the second teleconference 38 statements were added. Of the 287 statements included in the final survey, 233 (81.2%) were appropriate, 16 (5.6%) were inappropriate, and 38 (13.2%) were uncertain (Supplemental Table S1). These results were consistent regardless of the disagreement definition used. Fig. 1 illustrates the methodology employed and principal research findings. Table 1 summarises the key recommendations derived from the results.

General considerations

Panellists indicated that an antibody with two specific binding domains that blocks two separate antigens, or two epitopes of the same antigen, should be considered ACT.

Regarding inclusion criteria, failure of conventional therapy and high risk of disease-related complications were classified as appropriate. Although the panel approved of enrolling biologic-naïve participants in ACT trials, there was uncertainty about requiring participants to be ACT-naïve. Likewise, the panel expressed uncertainty regarding whether participants should be required to have failed one or two advanced monotherapies and the inclusion of participants who have previously failed therapies similar to either ACT component. Ultimately, the panel concluded that eligibility should be primarily based on a comprehensive risk-benefit analysis incorporating preclinical safety and efficacy data, rather than mandating specific prior therapies or excluding ACT as a first-line option.

Factors rated as appropriate for defining high risk of developing CD-related complications included: young diagnosis age (<30 years), deep ulcers, severe endoscopic disease activity (e.g., Simple Endoscopic Score for Crohn's Disease [SES CD] > 16), prior hospitalisation with administration of intravenous corticosteroids, fistulising disease, multiple surgical resections, upper gastrointestinal CD, and extensive ileal disease. The appropriateness of the CDPATH prognostic criteria,[14] a web-based tool developed to estimate individualised risk in adult patients with CD using clinical, serologic, and genetic variables, was considered uncertain by the panel, primarily due to the current lack of extensive external validation. Panellists deemed it acceptable for CD clinical trial participants to have active perianal fistulising disease despite receiving anti-TNF therapy, active upper gastrointestinal disease (involving the oesophagus, stomach, duodenum, or proximal small bowel i.e., proximal to the ligament of Treitz with ulceration), and extensive small bowel involvement.

Factors rated as appropriate for defining high risk of developing UC-related complications included: young diagnosis age (<40 years), persistently high C-reactive protein levels (≥50 mg/L), persistently low haemoglobin levels (<90 g/L), persistently low albumin levels (≤30 g/L), deep ulcers, severe endoscopic disease activity (e.g., Mayo Endoscopic Score [MES] = 3), and prior hospitalisation with administration of intravenous corticosteroids. Panellists highlighted the need for clearer definitions of severe endoscopic disease.

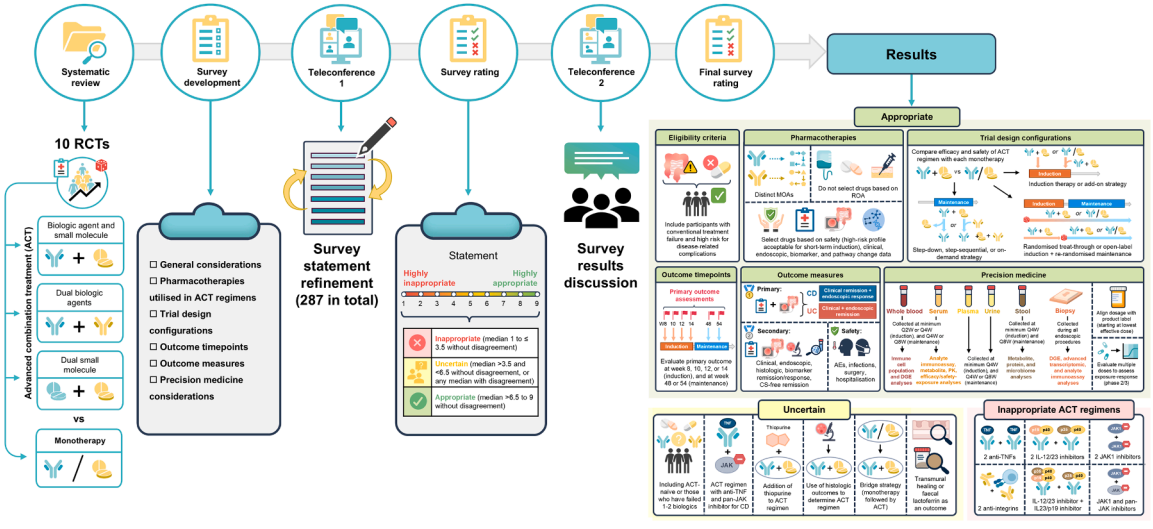

Fig. 1: Modified RAND/University of California Los Angeles Appropriateness Methodology and principal research findings. ACT, advanced combination treatment; AEs, adverse events; CD, Crohn's disease; DGE, differential gene expression; IL, interleukin; JAK, Janus kinase; MOA, mechanism of action; PK, pharmacokinetic; Q2W, every 2 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; RCTs, randomised controlled trials; ROA, route of administration; TNF, tumour necrosis factor; UC, ulcerative colitis.

Category	Finding
Eligibility criteria	• It is appropriate to include participants at high-risk for disease-related complications • It is appropriate to include participants who have failed conventional therapy • Eligibility criteria should be based on a risk-benefit analysis of safety and efficacy data
Pharmacotherapies	• The ACT regimen should include drugs with distinct mechanisms of action • Drug selection should not be based on route of administration • Drug selection should be based on safety, clinical, endoscopic, biomarker, and pathway change data
Trial design configurations	• The efficacy and safety of the ACT regimen should be compared to each monotherapy • It is acceptable to assess ACT as induction therapy, including as an add-on strategy • It is acceptable to assess ACT as maintenance therapy, including as a step-down, step-sequential, or on-demand strategy • It is acceptable to assess ACT using a treat-through, open-label induction followed by a randomised withdrawal, or re-randomised maintenance design
Outcome timepoints	
CD	• Primary (induction): Week 8, 10, 12, or 14 • Primary (maintenance): Week 48 or 52
UC	• Primary (induction): Week 6, 8, 10, 12, or 14 • Primary (maintenance): Week 48 or 52
Outcome measures CD UC	• Efficacy: clinical remission + endoscopic response (co-primary) • Efficacy: clinical remission + endoscopic remission (composite) • Safety: AEs, SAEs, withdrawal due to AEs, infections, serious infections, surgery, hospitalisation, AESIs
Precision medicine	• Whole blood: collection every 2 or 4 weeks (induction)/4 or 8 weeks (maintenance) for immune cell population and differential gene expression analyses • Serum: collection every 2 or 4 weeks (induction)/4 or 8 weeks (maintenance) for analyte immunoassay, metabolite, PK, and efficacy/safety-exposure analyses • Plasma: collection every 4 weeks (induction)/4 or 8 weeks (maintenance) for exploratory biomarker analyses • Stool: collection every 4 weeks (induction)/8 weeks (maintenance) for microbiome, protein, and metabolite analyses • Mucosal biopsies: collection at all endoscopic procedures for differential gene expression, advanced transcriptomic, and analyte immunoassay analyses

Abbreviations: ACT, advanced combination treatment; AE, adverse event; AESI, adverse event of special interest; PK, pharmacokinetic; SAE, serious adverse event.

Table 1: **Summary of key recommendations.**

Pharmacotherapies used in advanced combination treatment

Mechanism of action

Panellists recommended that ACT regimens consist of drugs with distinct mechanisms of action. For CD and UC, the use of two anti-TNF agents, two anti-integrins, two IL-12/23 inhibitors, or two JAK1 inhibitors was rated as inappropriate. Combining IL-12/23 and selective IL-23p19 inhibitors, or JAK1 and pan-JAK inhibitors, was also considered inappropriate. These combinations were seen as targeting overlapping biological pathways, which may increase the risk of adverse events without added benefit.

All other drug combinations were rated as appropriate, except for an anti-TNF agent combined with a pan-JAK inhibitor in CD trials, which was rated as uncertain due to safety concerns (e.g., opportunistic infections, major cardiovascular events, and malignancy). The use of a S1PR modulator and an α4β7 inhibitor was considered appropriate since they target different aspects of leucocyte trafficking. Adding a thiopurine to an ACT regimen was considered uncertain. Panellists emphasised careful consideration of thiopurine administration, based on the ACT regimen and study population.

Safety

Panellists indicated that drug selection should be grounded in clinical and endoscopic efficacy data, while prioritising safety. Using histologic outcomes to determine the ACT regimen was rated as uncertain. In contrast, biomarkers and pathway change data for each drug were rated as appropriate for supporting regimen choice. While it was affirmed that ACT regimens should include drugs with well-defined safety profiles, some panellists suggested limiting exposure duration to mitigate safety concerns. The panel accepted short-term use of higher-risk ACT regimens to enhance induction of clinical remission rates.

The panel concluded that non-IBD safety data are suitable for determining the ACT regimen, provided similar dosages were employed. They also deemed in vivo and in vitro models appropriate for evaluating the biological rationale for ACT. These models should compare the efficacy and toxicity profile of the ACT with its individual component drugs.

Route of administration

Panellists found it appropriate to include two intravenously administered drugs, two orally administered drugs, two subcutaneously administered drugs, or any combination thereof. While administration route should not be the primary selection criterion for determining the ACT regimen, the panel suggested that similar routes for both therapies would be optimal for practical reasons.

Trial design configurations

It was determined that the efficacy and safety of the ACT regimen should be compared with each

monotherapy used. The panel approved evaluating ACT as both an induction therapy and add-on therapy in induction trials when monotherapy fails. Continuous use of ACT throughout the induction phase was considered acceptable. Similarly, the panel found it suitable to assess ACT as a maintenance strategy, allowing for a step-down design involving withdrawal of one drug, or a step-sequential design that introduces a third agent. Continuous evaluation and on-demand approaches were also considered acceptable.

For clinical trials with induction and maintenance phases, the panel endorsed several designs: a randomised treat-through approach, an open-label induction phase followed by a randomised withdrawal phase, and re-randomisation of responders to the ACT regimen or monotherapy during the maintenance phase. The panel was uncertain about a bridge strategy using monotherapy induction, then ACT, followed by withdrawal of the initial monotherapy agent.

Outcome timepoints

The panellists determined that continuous therapy may be administered for up to 12, 24, 36, or 54 weeks in CD and UC trials. For induction trials, primary outcomes may be evaluated at 8, 10, 12, or 14 weeks. However, 6-week assessment was rated as appropriate for UC trials but uncertain for CD trials. Maintenance trials outcomes for CD and UC may be assessed at 48 or 54 weeks.

Outcome measures

Efficacy

In CD induction and maintenance trials, a co-primary endpoint combining clinical remission and endoscopic response was deemed appropriate. Appropriate secondary outcomes included clinical response, corticosteroid-free remission, endoscopic response and remission, clinical-endoscopic response, clinical-endoscopic remission, histologic remission, histologic-endoscopic response, histologic-endoscopic remission, biomarker response, and clinical-biomarker remission. Histological response and transmural healing were rated uncertain.

Combined clinical-endoscopic remission was considered a suitable primary endpoint in UC induction and maintenance trials. Appropriate secondary outcomes included clinical-endoscopic response, corticosteroid-free remission, endoscopic response, endoscopic remission, histologic response, histologic remission, histologic-endoscopic response, histologic-endoscopic remission, biomarker response, biomarker remission, and clinical-biomarker remission. In contrast, the inclusion of transmural healing as a secondary outcome was rated as uncertain.

The panellists generally endorsed remission-based endpoints, which offer high specificity, over response-based outcomes characterised by high sensitivity and low specificity, as this approach is expected to increase statistical efficiency.

Safety

Safety outcomes in both CD and UC trials should include adverse events, serious adverse events, withdrawal due to adverse events, infections, serious infections, need for surgery, and hospitalisation.

Precision medicine considerations

C-reactive protein, faecal calprotectin, faecal lactoferrin, target engagement biomarkers, and mechanism of action biomarkers were recognised as appropriate secondary endpoints in CD and UC clinical trials. However, the utility of assessing faecal lactoferrin was rated uncertain.

The panel recommended monitoring exploratory biomarkers in IBD clinical trials to identify early response or loss of response. Collection of serum, plasma, whole blood, mucosal biopsies, stool, and urine samples were considered appropriate, irrespective of expected systemic exposure with the ACT regimen. When systemic exposure is anticipated, the panel advised collecting serum samples for immunoassays of relevant analytes and metabolite analysis. Additionally, they considered it appropriate to collect whole blood samples for analysing immune cell populations and differential gene expression.

In induction trials, the panel indicated that serum samples should be collected every 2 or 4 weeks. For maintenance trials, samples should be collected every 4 or 8 weeks. When serum samples are collected and drug concentration is measured, the panellists concluded that the following should be evaluated: the pharmacokinetic profile of each drug, the pharmacokinetic profile of the ACT regimen, efficacy related to drug exposure, and safety related to drug exposure. It was also determined that if a biologic agent is included in the ACT regimen, sparse sampling throughout the trial should assess immunogenicity; this may vary depending on the biologic employed.

It was considered appropriate to collect plasma samples at a minimum frequency of every 4 weeks during induction trials. For maintenance trials, the panel supported the collection of plasma samples every 4 or 8 weeks at minimum. The panel determined that the minimum frequency of whole blood sample collection should be every 2 or 4 weeks in induction trials and every 4 or 8 weeks in maintenance trials.

The panel advised collecting mucosal biopsies during all endoscopic procedures. They also suggested performing differential gene expression analysis to identify genes and pathway signatures pertinent to the ACT regimen, the drugs used, and the disease (CD or UC), with the goal of discovering potential predictive biomarkers for treatment response. Furthermore, it was recommended to use advanced transcriptomics

technologies—including single-cell transcriptomics, spatial transcriptomics, and spatial proteogenomics—to analyse a subset of mucosal biopsies. This approach aims to confirm target engagement of the agents in the ACT regimen, assess their mechanisms of action, and facilitate biomarker discovery. If mucosal biopsies are collected, the panellists supported conducting protein analysis through immunoassays targeting analytes relevant to each agent's mechanism of action.

Urine collection every 4 weeks in induction trials and every 4 or 8 weeks in maintenance trials at minimum was considered appropriate. For stool samples, collection every 4 weeks for induction trials and every 8 weeks for maintenance trials was appropriate. When collecting stool, panellists recommended analysing proteins and metabolites relevant to the mechanism of each drug in the ACT regimen. Microbiome analysis should also be performed to identify changes relevant to the ACT regimen, its components, and the disease (CD or UC), and determine microbial signatures predicting treatment response.

If predictive biomarkers are identified for specific ACT regimens, using them to select optimal therapies for individual patients was deemed appropriate.

When determining drug dosages in ACT regimens, the panel advocated for alignment with product label recommendations, starting from the lowest effective dose. They advised considering exposure-response data for individual drugs, and potential or known drug–drug interactions affecting safety or efficacy. The panel also established that pharmacodynamic markers (e.g., molecular markers indicating target or pathway engagement, but not necessarily response) should be incorporated into ACT dosing decisions.

Evaluating multiple doses of ACT components to expand exposure ranges and assess exposure-response relationships was deemed appropriate, though more practical in small-scale or early-phase clinical trials. Exposure-response assessments were considered appropriate across phase 1 to 3 clinical trials, with emphasis on phases 2 and 3.

Discussion

As the number of studies investigating ACT strategies continues to grow, harmonising clinical trial designs becomes crucial to address knowledge gaps and refine methodologies. A systematic review of RCTs in patients with IMIDs recently highlighted key methodological limitations,[7] underscoring the need for enhanced standardisation and better integration of precision medicine into IBD research. Building on this groundwork, the RAM was employed in the current study to create a framework for clinical trials investigating ACT. By synthesising evidence from existing literature with the expertise of international specialists in clinical and precision medicine, we developed and evaluated a series of statements to guide trial design and execution.

Ratings of eligibility criteria statements emphasised including high-risk patients and those with prior failure to conventional therapy. Key high-risk features of CD and UC were established, including specific endoscopic and clinical markers of disease severity. Debate continues on whether clinical trials should exclusively enrol high-risk patients to enrich the study population and target those most in need of advanced therapies, or adopt a broader approach. While high-risk enrichment may optimise the detection of treatment efficacy and inform the management of challenging cases, broader eligibility criteria in future trials will be essential to enhance generalisability, capture real-world heterogeneity, and support regulatory and clinical adoption across the full spectrum of IBD severity. There was uncertainty about requiring failure of biologics before ACT initiation, and its use in participants who are ACT-naïve. During discussion, some panellists maintained that the latter is especially justified if robust preclinical data indicate that targeting dual pathways yields superior efficacy compared to monotherapy. This aligns with the concept of early intense treatment followed by de-escalation, ensuring that eligible patients are not excluded from potential benefits.[15,16] In the EXPLORER trial, which evaluated triple combination therapy (vedolizumab, adalimumab, and methotrexate) among biologic-naïve patients with newly diagnosed, moderate- to high-risk CD, 54.5% (30/55) and 34.5% (19/55) of patients achieved clinical and endoscopic remission at week 26, respectively.[17] This supports the use of ACT as first-line treatment, especially for high-risk patients; however, de-escalation should be considered once deep remission is achieved, which necessitates specific studies. Given the potential of ACT to be highly effective, it should not be reserved solely for patients with prior exposure to conventional therapies but rather considered for early intervention in treatment-naïve patients based on strong preclinical evidence suggesting high efficacy and low complication risks.

Panellists favoured combining therapies with distinct mechanisms of action and deemed the use of two drugs targeting the same pathway (eg, two anti-TNFs) inappropriate. Combinations such as S1PR modulators with α4β7 inhibitors were classified as appropriate, while the addition of thiopurines required case-specific consideration. Uncertainty around adding thiopurines to ACT regimens in CD and UC trials arises from safety concerns, including increased risks of opportunistic infections. Thiopurines might be considered only when an anti-TNF agent is included in the regimen to reduce immunogenicity.[18] However, no safety issues were identified with triple immunosuppressive therapy in the EXPLORER trial. According to the panel, drug selection should be guided by clinical, endoscopic, and safety data, with data from non-IBD contexts acceptable when comparable dosing is being considered.

It was determined that ACT regimens should be compared to monotherapy to assess both efficacy and safety. This approach is advantageous since it prevents potential harms associated with being allocated to placebo,[19] and it ensures that observed benefits and risks are contextualised. The panel indicated that ACT can be evaluated as induction therapy, maintenance therapy, or an add-on strategy when monotherapy fails to achieve an adequate response. Continuous evaluation of ACT was considered acceptable, and it was established that step-down and step-sequential strategies involving multiple agents are worth exploring. Administration of combination therapy followed by monotherapy is particularly attractive for addressing safety concerns. For example, in the planned VICTRIVA trial (NCT06227910), participants will be randomised to vedolizumab and upadacitinib or vedolizumab and placebo for 12 weeks. Responders will then transition to vedolizumab monotherapy for an additional 40 weeks. Rather than universally mandating exposure limits, the panel recommended tailoring ACT duration to the pharmacologic profiles of the agents, expected onset of efficacy, and patient-specific risk factors. Robust monitoring strategies—including predefined safety assessments, exposure-response evaluation, and clear criteria for step-down or discontinuation—should be integrated into all ACT trial protocols to ensure early identification and management of potential adverse events.

Randomised treat-through designs and an open-label induction phase followed by a randomised withdrawal phase were rated as appropriate. Re-randomising responders to ACT or monotherapy in the maintenance phase was also acceptable, depending on the trial objectives. Importantly, analysis must account for additive and potentially synergistic effects of combined therapy. Robust statistical modelling is crucial to accurately capture these interactions, providing reliable insights into the efficacy and safety of ACT regimens compared to monotherapy.

Precision medicine is central to optimising ACT regimens. The panel recommended detailed biospecimen collection schedules, including mucosal biopsy, stool, and urine samples, to facilitate predictive and mechanistic analyses. Urine-based metabolomic profiles have been associated with treatment response and disease activity, offering a non-invasive tool to support precision strategies. Microbiome studies were also deemed essential for individualising ACT, as baseline features such as microbial diversity, specific taxa, and functional metabolic signatures, may predict therapeutic outcomes.[20]

Gene expression profiling has already been proven to be invaluable in characterising differential responses to treatment. In the VEGA trial (NCT03662542), participants were randomised to combination therapy with golimumab and guselkumab, golimumab monotherapy, or guselkumab monotherapy. Transcriptional profiling of colonic biopsies at baseline and Week 12 revealed differential and complementary mechanisms of action for TNF and IL-23p19 blockade in UC. Combined guselkumab and golimumab exhibited greater modulation of genes that are linked to inflammatory myeloid cell activation and fibroblast activity compared to monotherapy. Additionally, the ACT regimen achieved a more substantial reduction in tissue-level inflammatory processes, which correlated with improved clinical outcomes. Future precision medicine approaches should integrate mechanistic insights with predictive biomarkers derived from biospecimens, microbiome profiles, and transcriptional data. A pragmatic approach may involve systematic biobanking of suggested biospecimens, with analyses performed as knowledge and technologies evolve.

Strengths of the current study include input of international IBD experts and translational medicine scientists, and the application of rigorous methodologies designed to minimise bias. We comprehensively addressed a wide range of issues specific to ACT, providing insights into how clinical trials can be effectively designed to assess both efficacy and safety in IBD while advancing personalised treatment strategies.

Some limitations to our study must also be acknowledged. First, panel ratings and discussion were primarily based on expert opinion due to the paucity of empirical evidence. This reliance on expert judgement highlights the need for further research to inform the design of future ACT clinical trials. Notably, the lack of comprehensive preclinical data in IBD presents a limitation, as the absence of well-established predictive models and biomarkers in early-phase research can substantially impact the design and interpretation of clinical trials. This underscores the need for continued investment in preclinical studies to improve the foundational understanding of disease mechanisms, treatment responses, and optimal trial endpoints for ACT in IBD. Additionally, while the focus of this exercise was pharmacotherapy, other combination strategies outside the scope of this study, such as using diet or timed surgery in combination with medication, may hold promise. Finally, it is important to note that the RAM is not designed to force consensus; consequently, certain areas of disagreement persisted after two rounds of voting.

In conclusion, our work highlights the importance of rationally combining ACT components based on preliminary mechanistic assessments. This approach has the potential to enhance clinical trial efficiency and clarify the position of ACT in IBD care. These findings provide a foundational framework to inform future clinical trials, ultimately advancing treatment strategies and improving patient outcomes in IBD.

Contributors

Development of the study concept and design: JH, CM, VJ; Study supervision: CM, VJ; Panellists: RB, TR, SD, BS, LPB, BV, JT, SM, GH, FU, RA, JP, RP, BES, CM, BGF, VJ; Data collection and analysis: MH,

VS; Draughting of the manuscript: VS, JH, CEP, VJ. MH and VS have verified the underlying data. All authors performed critical revision of the manuscript for intellectual content. All authors read and approved the final version of the manuscript for submission.

Data sharing statement

Data are available upon request.

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