Journal of Crohn's and Colitis, 2024, **18**, 1531–1555
https://doi.org/10.1093/ecco-jcc/jjae091
Advance access publication 15 June 2024
ECCO Guideline/Consensus Paper

ECCO Guidelines on Therapeutics in Crohn's Disease: Medical Treatment

Hannah Gordon,[a] Silvia Minozzi,[b] Uri Kopylov,[c] Bram Verstockt,[d,e] María Chaparro,[f] Christianne Buskens,[g] Janindra Warusavitarne,[h] Manasi Agrawal,[i,j] Mariangela Allocca,[k] Raja Atreya,[l] Robert Battat,[m] Dominik Bettenworth,[n] Gabriele Bislenghi,[o] Steven Ross Brown,[p] Johan Burisch,[q] María José Casanova,[f] Wladyslawa Czuber-Dochan,[r] Joline de Groof,[s] Alaa El-Hussuna,[t] Pierre Ellul,[u] Catarina Fidalgo,[v,w] Gionata Fiorino,[x] Javier P Gisbert,[f] João Guedelha Sabino,[d] Jurij Hanzel,[y,z] Stefan Holubar,[aa] Marietta Iacucci,[ab] Nusrat Iqbal,[ac] Christina Kapizioni,[ad] Konstantinos Karmiris,[ae] Taku Kobayashi,[af] Paulo Gustavo Kotze,[ag] Gaetano Luglio,[ah] Christian Maaser,[ai] Gordon Moran,[aj,ak] Nurulamin Noor,[al] Konstantinos Papamichael,[am] Georgios Peros,[an] Catherine Reenaers,[ao] Giuseppe Sica,[ap] Rotem Sigall-Boneh,[aq,ar] Stephan R. Vavricka,[as] Henit Yanai,[at] Pär Myrelid,[au] Michel Adamina,[av] Tim Raine[aw]

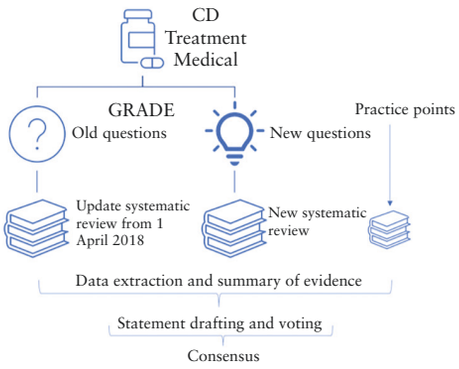
[a]Translational Gastroenterology and Liver Unit, University of Oxford, Oxford, UK
[b]Department of Epidemiology, Lazio Regional Health Service, Rome, Italy
[c]Department of Gastroenterology, Sheba Medical Center, Ramat Gan, Israel
[d]Department Gastroenterology & Hepatology, University Hospitals Leuven, KU Leuven, Leuven, Belgium
[e]Department of Chronic Diseases and Metabolism, KU Leuven, Leuven, Belgium
[f]Gastroenterology Department. Hospital Universitario de La Princesa, Instituto de Investigación Sanitaria Princesa [IIS-Princesa], Universidad Autónoma de Madrid [UAM], Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas [CIBEREHD], Madrid, Spain
[g]Department of Surgery, Amsterdam UMC, Location VUMC, Amsterdam, The Netherlands
[h]Department of Colorectal Surgery, St Mark's Hospital London, United Kingdom
[i]Dr Henry D. Janowitz Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, NY, USA
[j]Center for Molecular Prediction of Inflammatory Bowel Disease [PREDICT], Department of Clinical Medicine, Aalborg University, Copenhagen, Denmark
[k]IRCCS Hospital San Raffaele and University Vita-Salute San Raffaele, Gastroenterology and Endoscopy, Milan, Italy
[l]First Department of Medicine, Friedrich-Alexander-University Erlangen-Nürnberg, Erlangen, Germany.
[m]Division of Gastroenterology, Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada
[n]CED Schwerpunktpraxis, Münster and Medical Faculty of the University of Münster, Münster, Germany
[o]Department of Abdominal Surgery, University Hospitals Leuven, Leuven, Belgium
[p]Department of Surgery, Sheffield Teaching Hospitals, Sheffield, UK
[q]Gastrounit, Medical Division, Copenhagen University Hospital - Amager and Hvidovre, Hvidovre, Denmark; Copenhagen Center for Inflammatory Bowel Disease in Children, Adolescents and Adults; Copenhagen University Hospital - Amager and Hvidovre, Hvidovre, Denmark; Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark
[r]Florence Nightingale Faculty of Nursing, Midwifery and Palliative Care, King's College London, London, UK
[s]Colorectal Surgery, Royal Surrey NHS Foundation Trust, Guildford, UK
[t]Department of Surgery, OpenSourceResearch Organization [OSRC.Network], Aalborg, Denmark
[u]Division of Gastroenterology, Mater Dei Hospital, L-Imsida, Malta
[v]Division of Gastroenterology, Hospital Beatriz Ângelo, Loures, Portugal
[w]Division of Gastroenterology, Hospital da Luz, Lisboa, Portugal
[x]IBD Unit, San Camillo-Forlanini Hospital, Rome, Italy
[y]Department of Gastroenterology, University Medical Centre Ljubljana, Ljubljana, Slovenia
[z]Department of Internal Medicine, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia
[aa]Department of Colon & Rectal Surgery, Cleveland Clinic, Cleveland, OH, USA
[ab]APC Microbiome Ireland, College of Medicine and Health, University College of Cork, Cork, Ireland
[ac]Department of Surgery, Worcestershire Acute Hospitals NHS Trust, Worcester, UK
[ad]Department of Gastroenterology, Attikon University Hospital, Athens, Greece
[ae]Department of Gastroenterology, Venizeleio General Hospital, Heraklion, Greece
[af]Center for Advanced IBD Research and Treatment, Kitasato University Kitasato Institute Hospital, Tokyo, Japan

[ag]Health Sciences Postgraduate Program, Pontificia Universidade Católica do Paraná [PUCPR], Curitiba, Brazil
[ah]Department of Public Health, University of Naples Federico II, Naples, Italy
[ai]Outpatients Department of Gastroenterology, University Teaching Hospital Lueneburg, Lueneberg, Germany
[aj]National Institute of Health Research Nottingham Biomedical Research Centre, University of Nottingham and Nottingham University Hospitals, Nottingham, UK
[ak]Translational Medical Sciences, School of Medicine, Faculty of Medicine and Health Sciences, University of Nottingham, Nottingham, UK
[al]Department of Medicine, University of Cambridge, School of Clinical Medicine, Cambridge, UK
[am]Center for Inflammatory Bowel Diseases, Division of Gastroenterology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA
[an]Department of Surgery, Cantonal Hospital Winterthur, Winterthur, Switzerland
[ao]Gastroenterology Department, Chu Liege, Liege, Belgium
[ap]Department of Surgery, Università Tor Vergata, Roma, Italy
[aq]Pediatric Gastroenterology and Nutrition Unit, E. Wolfson Medical Center, Holon, Israel
[ar]Tytgat Institute for Liver and Intestinal Research, Amsterdam Gastroenterology Endocrinology and Metabolism, University of Amsterdam, Amsterdam, The Netherlands
[as]Department of Gastroenterology and Hepatology, University Hospital Zürich, Zürich, Switzerland
[at]IBD Center, Division of Gastroenterology, Rabin Medical Center, Petah Tikva; Faculty of Medical & Health Sciences, Tel Aviv University, Tel Aviv, Israel
[au]Department of Surgery and Department of Biomedical and Clinical Sciences, Linköping University, Linköping, Sweden
[av]Department of Surgery, Cantonal Hospital of Fribourg & Faculty of Science and Medicine, University of Fribourg, Fribourg, Switzerland
[aw]Department of Gastroenterology, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK

Corresponding author: Hannah Gordon, Translational Gastroenterology and Liver Unit, John Radcliffe Hospital, Headley Way, Headington, Oxford, OX3 9DU. Email: hannahgordon@doctors.org.uk

Graphical Abstract

The ECCO GRADE CD treatment guidelines were updated



We provide practical guidance on choice and optimisation of medical therapy

	Induction i	Maintenance i	Perianal disease ii	Peripheral Spondylo-arthropathy	Axial Spondylo-arthropathy	Pregnancy iii	Over 65 years
Systemic corticosteroids	iv			iv	iv	iv	iv
Enteral release corticosteroids						v	v
Enteral Nutrition							
Thiopurines monotherapy						vi	vii
Methotrexate							
Infliximab							
Adalimumab							
Certolizumab							
Vedolizumab							
Ustekinumab							
Risankizumab				vii	ix		
Upadacitinib			x	xi	xii		xiii

Recommended
Can be considered
Not recommended
Insufficient evidence

DRUGS SHOULD BE CONSIDERED BY MERIT, NOT SEQUENCED AS CONVENTIONAL TO ADVANCED

We recommend a holistic approach to management of CD

GRADE statements on medical therapy

GRADE statements and practice points on nutritional therapy

Practice points on the role of the multidisciplinary team

Drug selection should factor efficacy, safety, patient characteristics and preferences, disease characteristics and cost or access to therapies

GRADE statements and practice points on therapeutic drug monitoring, drug sequencing and combination, including ACT

1. Introduction

Crohn's disease [CD] is a chronic inflammatory bowel disease [IBD] that can result in progressive bowel damage and disability.[1] CD can affect individuals of any age, from children to the elderly,[2,3] and may cause significant morbidity and impact on quality of life [QoL]. The precise aetiology of CD remains unknown and a curative therapy is not yet available. Contemporary therapy therefore is focused on control of inflammation, using medications along with timely surgical interventions to alleviate the symptoms of bowel damage.

The European Crohn's and Colitis Organisation [ECCO] produces several guidelines aimed at providing evidence-based

guidance on critical aspects of IBD care. In 2020, ECCO published new guidelines on the management of CD in two manuscripts focused on the medical and surgical management of disease.[4,5] For the 2020 CD guidelines, ECCO adopted the Grading of Recommendations Assessment, Development, and Evaluation [GRADE] approach, a systematic process for developing guidelines that addresses how to frame the health care questions, summarise the evidence, formulate the recommendations, and grade their strength and quality of associated evidence.[6] The present manuscript represents an update to the 2020 guidelines and is focused specifically on medical management of CD, and a companion manuscript developed as part of the same process addresses optimal surgical management.[5] We take a drug-by-drug approach to review the evidence for various medical and dietary strategies used in the management of CD.

For this iteration of the guidelines, we have introduced several new, clinically relevant questions as chosen by members of the guidelines group, a systematic approach to reviewing and updating previous topics to incorporate any new evidence, and a reappraisal of all evidence in the context of contemporary practice. We have also introduced several 'practice points' to summarise evidence, and expert recommendations in certain key areas of practice where the evidence base is limited but where clinicians and patients need to make decisions nonetheless. Here, where application of the GRADE methodology might be impractical, we have used an approach based on systematic literature review, expert discussion, and voting to form consensus recommendations outside the formal GRADE process.

It is important to remember that achieving optimal outcomes in CD relies not just on knowledge of the appropriate use of current medical and surgical therapies but also on careful attention to wider aspects of management, including early diagnosis, prompt initial management,[7] close monitoring of treatment response, and psychological and dietary support.[8]

2. Methods

The development of these guidelines followed the GRADE workflow, as adopted in previous ECCO guidelines.[9] A panel of 46 experts were selected from an open call according to criteria based on IBD expertise, scientific background, knowledge of GRADE methodology, and prior contribution to ECCO projects. Additionally, six patients with CD selected by the European Federation of Crohn's and Colitis Associations [EFFCA] were invited to participate in discussions. The group was supported in their work by a team of professional methodologists and librarians.

The panellists first agreed on a list of questions using the Population, Intervention, Comparator, Outcomes [PICO] format. PICO questions addressed as part of the 2020 ECCO CD guidelines were reviewed and considered for retention with regards to ongoing relevance, and new PICO questions were formulated, discussed, and added to the list. The relevant outcomes for all PICO questions were graded according to importance using a Delphi consensus process. Note that for PICO questions retained from 2020, the importance of the outcomes was nonetheless revised according to the results of this new consensus.

The professional librarians next performed a comprehensive literature search on EMBASE, PubMed/Medline, and Cochrane Central databases, using specific search strings developed for each PICO question [Supplementary files available as Supplementary data at ECCO-JCC online]. For PICO questions retained from the 2020 guidelines, the same search string was used as during the prior literature search, and the start date of database queries set to the same as the end search date for the previous guidelines 1 April 2018. For all new PICO questions, the search start date was unlimited. Two independent consensus group members assessed the relevance of each abstract to the PICO and included or excluded all the relevant papers for the final data extraction and analysis. Subsequently, group members systematically reviewed and summarised the evidence on every outcome voted as 'important' or 'critical', to compile a Summary of Findings [SoF] table for each question, or updated the prior SoF tables from 2020 [including revision according to any changes to outcomes deemed critical or important]. We adopted a standard hierarchical approach, searching for recent, high-quality systematic reviews and meta-analyses of clinical trials to use in preference to individual randomised clinical trials [RCTs] or observational studies. Results of individual studies were pooled using random-effects meta-analysis as appropriate and when needed. The quality of evidence was then classified and used to inform draft recommendations according to the GRADE methodology.[6] GRADE evidence levels for safety data tended to be low, due to downgrading for sparsity of events, reflecting the overall relative safety of the interventions under consideration. Therefore, whereas the evidence for all 'important' and 'critical' outcomes was considered in the drafting of a recommendation, we decided to base the overall assessment of evidence quality used to inform the strength of each recommendation upon the lowest quality of evidence obtained for the clinical or endoscopic outcomes for each PICO question. Where evidence was not available for an outcome of critical importance, this was reflected in the overall assessment of the quality of the evidence. The assessment of evidence for all individual outcomes was available to all panel members and is presented in the Supplementary materials.

During initial discussions and based on feedback from previous ECCO guidelines, we recognised that in certain areas of CD management there are limited high-quality sources of evidence available, but that clinicians and patients must make decisions nonetheless. There are also broad, overarching themes relating to approaches to care that cannot be readily formulated into a PICO question. Use of the GRADE approach in these areas can be resource intensive and lead to recommendations of limited clinical utility. We therefore decided to frame a separate series of 'practice points' for such common areas of importance. For these, the systematic literature review and data extraction exercise were followed and the findings used to inform drafting of an expert recommendation. We recognise that the resulting practice points are based upon a different level of evidence compared with the GRADE recommendations, but hope that they will be of practical use to readers nonetheless. These are clearly delineated in the text as distinct from GRADE recommendations.

All recommendations and practice points were subject to two rounds of online voting by the panel members, the ECCO National Representatives [two for each country affiliated with ECCO], and 37 additional reviewers from a list of ECCO members who applied to the open call but were not selected to be part of the Working Groups [see Acknowledgements

section]. The pre-final versions of all recommendations and practice points were discussed among panel members during a series of final virtual consensus meetings before being put to a vote; final versions were approved only if at least 80% of the panellists agreed with the statement. The resulting statements and draft of this manuscript were critically reviewed by two external Guideline Committee members and by the ECCO Governing Board members, who also approved the final version of these guidelines. Statements and practice points are ordered by drug, with statements concerning induction and maintenance therapy presented together where relevant. All statements should be read in the context of the supporting text that follows. A brief summary of the statements and text is presented at the start of each section of supporting text.

The literature search strategies, the relevant definitions of patient populations and outcomes, a detailed description of the process, and the SoF tables on the evidence can be found in the Supplementary material, available as Supplementary data at ECCO-JCC online.

3. Medical Management of CD

3.1. 5-Aminosalicylates in the treatment of CD

3.1.1. 5-Aminosalicylates for the induction of remission in CD

Statement 1.1. We recommend against the use of 5-aminosalicylic acid for induction of remission of CD [strong recommendation, moderate-quality evidence]. [Consensus: 100%]

3.1.2. 5-Aminosalicylates for the maintenance of remission in CD

Statement 1.2. We recommend against the use of oral 5-aminosalicylic acid as maintenance therapy in CD [strong recommendation, low-quality evidence]. [Consensus: 100%]

5-aminosalicylic acid has no role in contemporary management of CD, regardless of disease location, based on a consistent lack of evidence of efficacy.

There have been no new studies on 5-aminosalicylic acid [5-ASA] in induction of remission published since the previously published ECCO guidelines on therapeutics in CD.[4] A meta-analysis was performed by the ECCO working group on seven RCTs that compared induction therapy with oral mesalazine[10–14] or sulphasalazine[15,16] with placebo in patients with active CD. 5-ASA doses of 1–3.2 g/day were for mild-to-moderate ileal, ileo-colonic, or colonic CD. There, clinical remission rates between 5-ASA therapy and placebo were similar (relative risk [RR]: 1.28; 95% confidence interval [CI]: 0.97–1.69) and these data are consistent with other meta-analyses.[17] Adverse event [AE]-related treatment withdrawals were similar between treatment and placebo groups [RR: 1.13; 95% CI: 0.73–1.84].

When excluding sulphasalazine trials, similar conclusions were reached for lack of benefit compared with placebo for induction of clinical remission [RR: 1.27; 95% CI: 0.79–2.03] and similar AE-related treatment withdrawal [RR: 1.0; 95% CI: 0.58–1.71]. Contradictory network meta-analysis data exist on the impact of higher dose [> 2.4 g/day] mesalazine therapy on clinical remission.[18,19] To assess for impact of delivery mechanism, pooled data from three trials for a slow-release preparation of mesalazine reported a significantly greater reduction in the absolute value of the Crohn's Disease Activity Index [CDAI] compared with placebo [weighted mean difference of 18 points]. However, the clinical significance of this difference is not meaningful.[20]

Data comparing sulphasalazine with placebo as induction therapy in CD are derived from RCTs performed prior to 1985. Pooled data showed borderline significantly higher clinical remission rates favouring sulphasalazine [RR: 1.38; 95% CI: 1.00–1.89] and similar AE-related treatment withdrawal rates between sulphasalazine and placebo [RR: 1.88; 95% CI: 0.65–5.47]. Importantly, analysis stratified by disease location showed sulphasalazine benefited only patients with colonic disease, whereas those with small-bowel involvement did not have higher clinical remission rates compared with placebo.[15,16] There are no RCT data on the use of topical 5-ASA [enema or suppository] as induction therapy in CD.

Oral 5-ASA has been extensively studied for the maintenance of medically induced remission in patients with CD. Overall, 11 placebo-controlled clinical trials assessed doses between 1 and 4 g per day.[21] Treatment durations varied between 4 and 36 months, with a 12-month evaluation most commonly assessed. No statistically significant benefit has been demonstrated for clinical outcomes with oral 5-ASA [risk ratio for relapse 0.98; 95% CI: 0.91–1.07]. No statistically significant benefit was demonstrated based on disease location, such as for patients with colonic-only involvement or with proctitis. However, given the relatively small nature of all the studies conducted in CD, none of the 11 placebo-controlled trials were adequately powered to assess efficacy in different sub-phenotypes. No significant differences were reported in AEs [RR: 1.05; 95% CI: 0.95-1.17] or serious adverse events [SAEs] [RR: 1.43; 95% CI: 0.24–8.44] between 5-ASA and placebo. However, no definitive statements about safety can be made, given the limited available safety data in CD [10 AEs in 1814 patients, and three SAEs in 576 patients].[21]

3.2. Steroids in the treatment of CD

3.2.1. Locally acting steroids in the treatment of CD

3.2.1.1. Budesonide for the induction of remission in CD

Statement 2.1. We recommend budesonide for the induction of clinical remission in patients with active, mild-to-moderate CD limited to the ileum and/or ascending colon [strong recommendation, moderate-quality evidence]. [Consensus: 100%]

Locally acting oral steroids are effective in induction of remission in CD and have a more favourable side-effect profile than systemic steroids. They have a role in induction of remission of mild-to-moderate CD but have no role as maintenance therapy.

A 2015 systematic review and meta-analysis[22] compared the efficacy and safety of induction therapy with budesonide with placebo. This analysis included three RCTs of patients with mild CD with disease location in the small intestine, ascending colon, or both.[23–25] Budesonide 9 mg was superior to placebo for inducing clinical remission [CDAI ≤ 150] at Week

8 [RR: 1.93; 95% CI: 1.37–2.73]. In addition, withdrawals due to AEs [RR: 1.14; 95% CI: 0.46–2.79] and corticosteroid-related AEs [RR: 0.97; 95% CI: 0.76–1.23] were similar between budesonide 9 mg and placebo.[22] An updated meta-analysis in 2018 contained no new induction RCTs.[26]

Meta-analyses from 2015 and 2018 reviewed two RCTs[27,28] comparing budesonide 9 mg daily with mesalazine < 4.5 g daily for mild-to-moderate CD. Another RCT in 2018 also compared budesonide 9 mg daily with mesalazine 1 g three times daily in patients with mild CD and disease location in the small intestine, ascending colon, or both.[29] Budesonide had similar clinical remission [CDAI ≤ 150] rates at Week 8 [RR: 1.30; 95% CI: 0.98–1.72] as compared with mesalazine. However, clinical response [decrease in CDAI ≥ 100 or total CDAI ≤ 150] rates were higher among budesonide-treated patients [RR: 1.22; 95% CI: 1.03–1.45]. Further data are needed regarding the impact of budesonide on mucosal healing.

AE [RR: 0.91; 95% CI: 0.79–1.05] and SAE [RR: 0.94; 95% CI: 0.24–3.75] rates were similar between budesonide and mesalazine-treated patients. Budesonide does not appear to be more effective than placebo for the maintenance of remission in CD.[30]

3.2.2. Systemic corticosteroids in the treatment of CD

3.2.2.1. Systemic corticosteroids for the induction of remission in CD

Statement 2.2. We suggest systemic corticosteroids can be used as induction therapy in patients with active, moderate-to-severe CD [weak recommendation, moderate-quality evidence]. [Consensus 100%]

Although systemic steroids are effective in induction of remission in CD, they are associated with significant morbidity and mortality. Therefore, they should only be used as induction therapy when there is no alternative agent available for timely administration. Steroids should never be used as maintenance therapy.

The efficacy of systemic corticosteroids [oral methylprednisolone or oral prednisolone] compared with placebo for the treatment of moderately-to-severely active CD was assessed in two RCTs.[15,16] Data from these studies were synthesised in a Cochrane systematic review.[15] Oral methylprednisolone was administered at a dose of 48 mg/day and tapered on a weekly basis to 32 mg, 24 mg, and 4 mg weekly thereafter to 12 mg, resulting in a 6-week induction period.[15] Doses of oral prednisolone ranged from 0.50 to 0.75 mg/kg with a maximum daily dose of 60 mg, dependent on baseline CDAI. Induction lasted for 17 weeks, with tapering to a dose of 0.25 mg/kg based on the CDAI.[16]

One trial involving 105 patients reported on induction of clinical response.[15] Clinical response was more common in patients receiving methylprednisolone compared with placebo [93.6% vs 53.4%, RR: 1.75; 95% CI: 1.36–2.25]. Corticosteroids were twice as effective in inducing clinical remission than placebo in the two studies[15,16] involving 267 patients [RR: 1.99; 95% CI: 1.51–2.64].[31]

Data on AEs were available from one trial involving 162 patients treated with oral prednisolone.[16,32] The frequency of AEs was 5-fold higher in patients receiving corticosteroids compared with placebo [31.8% vs 6.5%, RR: 4.89; 95% CI: 1.98–12.07]. Steroid-related AEs included Cushing syndrome, acne, hirsutism, infection, ecchymoses, hypertension, diabetes mellitus, osteoporosis, cataracts, and glaucoma. A non-negligible proportion of patients experienced corticosteroid dependency or excessive exposure to these drugs, which is preventable.[33] In addition to the aforementioned AEs, there is substantial evidence on the association of corticosteroid use with increased incidence of infection[34] and death.[35,36]

Imprecision associated with a low number of events for all efficacy and safety outcomes led to the downgrading of evidence to moderate quality. The availability of induction agents with a more favourable risk-benefit profile led to the recommendation being classed as 'weak'. Clinicians should seek to minimise steroid usage in their practice. In instances where steroids are used, the need for more than a single course of corticosteroids in 1 year or the presence of corticosteroid dependency [the inability to taper and stop steroids without a clinical flare or relapse] should warrant a steroid-sparing strategy.

3.3. Immunomodulators in the treatment of CD

3.3.1. Thiopurines in the treatment of CD

3.3.1.1. Thiopurines for the induction of remission in CD

Statement 3.1. We recommend against the use of thiopurine monotherapy as induction therapy for CD [strong recommendation, very low-quality evidence]. [Consensus: 100%]

3.3.1.2. Thiopurines for the maintenance of remission in CD

Statement 3.2. We suggest thiopurine monotherapy can be used as maintenance therapy in CD [weak recommendation, low-quality evidence]. [Consensus: 95%]

Thiopurines may be effective in maintenance of remission in CD after induction has been achieved by other means, but clinicians should consider their side-effect profile and the availability of other therapies.

Several studies have evaluated thiopurines compared with placebo for induction of remission and response in CD[16,37–43]; the data have been synthesied in a Cochrane systematic review.[44] Five trials evaluated thiopurines for induction of clinical remission [12–17 weeks] in comparison with placebo; four used azathioprine[16,37,38,41] and one mercaptopurine.[40] The trials differed in the definition of remission and the time of endpoint assessment, and most allowed concomitant corticosteroids [except for Summers *et al.*[16]]. There was no significant difference in clinical remission compared with placebo (48% [95/197] vs 37% [68/183], RR: 1.23; 95% CI: 0.97–1.55).

Three trials reported clinical response using non-standardised disease activity measures based on physician assessment.[39,42,43] There was no significant difference compared with placebo (42.9% [12/28] vs 26.9% [7/26], RR: 1.87; 95% CI: 0.44–7.96]). Heterogeneity and sparse data led to downgrading the quality of evidence to very low.

A single trial reported on AEs during induction[41] with no significant difference between thiopurines and placebo (69% [36/52] vs 86% [24/28], RR: 0.81; 95% CI: 0.64–1.02]). SAEs were reported in two trials[16,41]; 13.5% of those receiving azathioprine [AZA] versus 3.8% of those receiving placebo developed SAEs [pooled RR: 2.57; 95% CI: 0.92–7.13]. The quality of evidence was deemed low due to a very low number

of events [*n* = 19] and wide confidence intervals. In conjunction with ample data supporting the delayed onset of action of thiopurines,[45] a strong recommendation against thiopurine use as induction therapy was made despite the very low quality of evidence.

When considering thiopurines as maintenance therapy, one meta-analysis consisting of six studies [489 participants] reported the efficacy and safety in patients with steroid-dependent CD [and thus was judged to provide indirect evidence in patients without steroid dependency].[46] Azathioprine [1.0–2.5 mg/kg/day] was significantly superior to placebo for maintaining clinical remission over a 6–18 month period [73% vs 62%, RR: 1.19; 95% CI: 1.05–1.34].[46] This meta-analysis also demonstrated that a significantly higher proportion of azathioprine-treated patients [9%] withdrew due to AEs compared with placebo [2%, RR: 3.12; 95% CI: 1.59–6.09] and experienced more SAEs [azathioprine 9% vs placebo 3%, RR: 2.45; 95% CI: 1.22–4.90]. The most prevalent AEs included pancreatitis, leukopenia, nausea, allergic reactions, and infections.[46] The frequent dose-limiting haematopoietic toxicity that is seen in thiopurine-treated patients can be decreased by thiopurine methyltransferase analysis [enzymatic activity or genotype] prior to commencing thiopurine therapy. Loss-of-function variants of the nucleoside diphosphate linked moiety X [Nudix]-type motif 15 [NUDT15] genotype, common in Asian populations, also predispose to myelosuppression and can also be analysed prior to treatment initiation.[47,48] Large cohort studies have also suggested limited efficacy as maintenance therapy in CD.[49]

A nationwide French cohort study confirmed an increased adjusted hazard ratio [HR] for serious infections [HR: 1.32; 95% CI: 1.23–1.42] in thiopurine-treated patients when compared with unexposed patients.[50] Patients on thiopurines are at increased risk for lymphoproliferative disorders and myeloproliferative disorders, with older patients and those without a previous Epstein–Barr virus infection at highest risk.[51] A systematic review and meta-analysis [four studies] on the risk of lymphoma in patients exposed to thiopurine monotherapy versus patients unexposed to anti-tumour necrosis factor [TNF] agents or thiopurines demonstrated that the pooled incidence rate [IRR] of lymphoma was 2.23 [95% CI: 1.79–2.79].[52] Patients on thiopurine monotherapy are also at an increased risk of non-melanoma skin cancer [NMSC] and may have an increased risk of cervical high-grade dysplasia and cancer.[51]

The SONIC trial showed thiopurine monotherapy to be inferior to infliximab monotherapy or combination therapy.[53] Along with the lack of efficacy in induction and the adverse safety profile, this limits the use of thiopurines as maintenance therapy and is reflected in the weak recommendation given by the consensus group.

3.3.2. Methotrexate in the treatment of CD

3.3.2.1. Methotrexate for the induction of remission in CD

Statement 4.1. We suggest parenteral methotrexate can be used as induction therapy in moderate-to-severe CD [weak recommendation, moderate-quality evidence]. [Consensus: 94%]

3.3.2.2. Methotrexate for the maintenance of remission in CD

Statement 4.2. We suggest parenteral methotrexate monotherapy can be used as maintenance therapy in moderate-to-severe CD [weak recommendation, low-quality evidence]. [Consensus: 97%]

Parenteral methotrexate may be effective in the treatment of CD, whereas studies of oral methotrexate have failed to demonstrate efficacy.

In the single eligible, placebo-controlled, RCT,[54] 141 steroid-dependent patients with active CD were randomised to either 25 mg/week of intramuscular methotrexate or placebo for 16 weeks, with a concomitant daily dose of prednisone [20 mg at initiation] that was tapered over 10 weeks. At Week 16, a significantly larger proportion of patients treated with methotrexate were in clinical remission than those reveiving placebo (39% [37/94] vs 19% [9/47], RR: 2.06; 95% CI: 1.09–3.89]). The rate of treatment discontinuation for AEs [mainly elevated liver enzymes and nausea] was significantly higher when compared with placebo (17% [16/94] versus 2% [1/47], RR: 8.00; 95% CI: 1.09–58.51). The effect size estimates for remission are imprecise and the results may be confounded by the concomitant use of corticosteroids. There were no studies comparing methotrexate without concurrent steroid use with placebo, for the induction of remission, resulting in indirectness of evidence when considering patients without steroid dependency.

Two further studies evaluated the efficacy of oral methotrexate at lower doses [12.5 mg weekly or 15 mg weekly][55,56] compared with placebo in steroid-dependent patients with CD, and found no significant difference for induction of clinical remission.

Methotrexate may be considered as an option for steroid-dependent patients when alternative options [including surgery] cannot be used. The teratogenicity of the drug must be considered and patients counselled appropriately.[9] Retrospective data suggest that methotrexate has some efficacy in peripheral arthritis in IBD.[57]

Evidence on the use of parenterally administered methotrexate as maintenance therapy is derived from a single, double-blind, placebo-controlled RCT where patients with steroid-dependent CD were administered weekly intramuscular injections of 15 mg methotrexate or placebo for 40 weeks. Patients with previously active CD, who had entered remission after 16–24 weeks of treatment with 25 mg methotrexate given intramuscularly once weekly, were randomly assigned to receive either methotrexate 15 mg intramuscularly once weekly or placebo for 40 weeks. No other treatments for CD were permitted. After 40 weeks, the proportion of patients who remained in clinical remission was higher in the methotrexate group [65% vs 39%, RR: 1.67; 95% CI: 1.05–2.67].[58] No differences in SAEs were observed, although nausea and vomiting occurred numerically more frequently among patients in the methotrexate group [40% vs 25%]. Patients treated with methotrexate may be at increased risk of NMSC, as demonstrated in a single, nested, case-control study (odds ratio [OR]: 8.55; 95%: CI 2.55–31.8).[59] However, other studies exploring NMSC in patients with IBD failed to demonstrate such an association.[51,60,61] Low-dose oral methotrexate [12.5–15 mg/week] as monotherapy

does not appear to be effective for maintenance of remission in CD.[62]

3.4. TNFα antagonists in treatment of CD

3.4.1. Infliximab in the treatment of CD

3.4.1.1. Infliximab monotherapy for the induction of remission in CD

Statement 5.1. We recommend infliximab as induction therapy with moderate-to-severe active CD [strong recommendation, moderate-quality evidence]. [Consensus: 100%]

3.4.1.2. Infliximab monotherapy for the maintenance of remission in CD

Statement 5.2. We recommend infliximab as maintenance therapy in moderate-to-severe CD [strong recommendation, low-quality evidence]. [Consensus: 100%]

3.4.1.3. Infliximab combination therapy for the induction of remission in CD

Statement 5.3. We recommend combination therapy with a thiopurine when starting infliximab as induction therapy in patients with moderate-to-severe CD [strong recommendation, moderate-quality evidence]. [Consensus: 100%]

3.4.1.4. Infliximab combination therapy for the maintenance of remission in CD

Statement 5.4. We recommend combination therapy with infliximab and thiopurines for a minimum of 6–12 months when using infliximab as maintenance therapy in patients with CD [strong recommendation, moderate-quality evidence]. [Consensus: 100%]

3.4.1.5. Withdrawal of immunomodulator in patients with long-term remission when using infliximab to treat CD

Statement 5.5. In patients with CD who have achieved long-term remission with the combination of anti-TNF and thiopurines, we suggest de-escalation to anti-TNF monotherapy and withdrawal of thiopurines [weak recommendation, moderate-quality evidence]. [Consensus: 100%]

Infliximab is effective for the induction and maintenance of remission in CD. Combination therapy used during induction and for the first 6–12 months can improve efficacy and reduce immunogenicity; data to support this practice are largely derived from studies evaluating combination with a thiopurine. Once long-term remission has been established, the immunomodulator can be withdrawn in most patients, although caution may be exercised in patients with prior immunogenicity to an anti-TNF.

Infliximab is monoclonal antibody targeting TNFα, which is administered intravenously [IV] at a dose of 5 mg/kg at 0, 2, and 6 weeks during induction and every 8 weeks thereafter when continued IV. The efficacy of infliximab monotherapy for induction therapy in patients with active CD was evaluated in one small [n = 108], randomised, placebo-controlled trial comparing a single infusion of infliximab 5 mg/kg [n = 27], 10 mg/kg [n = 28], or 20 mg/kg [n = 28] with placebo [n = 25]. In this trial, standard dosing of infliximab [5 mg/kg] was superior to placebo for inducing clinical response at Week 12 [RR: 4.01; 95% CI: 1.29–12.44]. Superiority of infliximab was not observed for clinical remission at Week 12 [RR: 3.70; 95% CI: 0.87–15.80]. Endoscopic endpoints were not reported. Although safety was evaluated in this study, AEs were pooled for all dosing schemes of infliximab, precluding any conclusion on the safety profile of standard dosing of infliximab, with the level of certainty further affected by sparse data.[63] Following the pivotal trial of Targan *et al*., the ACCENT I trial established the induction dosing time points of Week 0 followed by Week 2 and Week 6.[64]

No separate meta-analysis has focused primarily on the outcomes of infliximab maintenance therapy in patients with CD. Two landmark RCTs were published more than 20 years ago, and were pooled for the purpose of this guideline.[64,65] In total, 408 patients who clinically responded to one dose of infliximab [CDAI decrease ≥ 70] were included. After 44 weeks, the overall likelihood of achieving clinical remission with infliximab [5 or 10 mg/kg every 8 weeks] over placebo was 2.15 [95% CI: 1.52–3.05]. Mucosal healing [defined as absence of mucosal ulceration] was assessed at 54 weeks in one RCT,[66] showing superiority of infliximab over placebo [RR: 7.00; 95% CI: 1.02–48.10]. However, patients in the placebo group received episodic doses of infliximab.

In the pivotal trials, AEs [RR: 0.97; 95% CI: 0.88–1.07], SAEs [RR: 0.86; 95% CI: 0.65–1.14], and serious infections [RR: 0.85; 95% CI: 0.36–2.00] were not different between infliximab and placebo.[64,65] In a network analysis performed in the framework of a Cochrane collaboration, the dose-adjusted OR for severe AEs for infliximab was 1.13 [95% CI: 0.79–1.62].[67] Evidence for clinical and endoscopic outcomes for infliximab maintenance therapy was downgraded due to imprecision [sparse events] and indirectness [since the 10 mg/kg dose is higher than the standard maintenance dose of 5 mg/kg] in the two pivotal RCTs. This led to an overall assessment of the level of evidence as low. Nevertheless, consensus participants decided to make a strong recommendation for use in maintenance therapy based on extensive real-world experience relating to efficacy and safety of standard dosing, and the widespread availability of infliximab as biosimilars with relatively low acquisition costs.

The SONIC RCT[53] compared the efficacy of infliximab combined with azathioprine over infliximab monotherapy in patients naïve to both therapies, who failed to respond to steroids or 5-ASA. Combination therapy resulted in higher rates of clinical remission at Week 26 when compared with infliximab monotherapy [RR: 1.64; 95% CI: 1.07–2.53]. Combination therapy was also more likely to result in mucosal healing at this time point [RR: 1.82; 95% CI: 1.01–3.26]. There were significantly lower rates of SAEs in those receiving combination therapy [RR: 0.56; 95% CI: 0.32–0.97],[53] with no difference in total AEs. In addition, several prospective[68] and retrospective observational studies[69–71] and a network meta-analysis have also suggested the benefit of combination therapy with azathioprine over infliximab monotherapy.[72] Combination therapy with azathioprine

appears to improve efficacy by enhancing pharmacokinetic features of infliximab.[73]

For patients who achieved clinical remission after induction with combination therapy with infliximab and immunomodulator, two RCTs provide data on combination therapy versus monotherapy within the maintenance period; these are the SONIC trial[53] for combination of infliximab with azathioprine, and the COMMIT trial[74] for combination of infliximab with methotrexate. Meta-analysis of these data revealed higher rates of mucosal healing [RR: 1.46; 95% CI: 1.00–2.13] and improved patient-reported outcomes, measured as change in Inflammatory Bowel Disease Questionnaire [IBDQ] score from baseline (mean difference [MD]: 4.8; 95% CI: 2.23–11.83]) Although resulting in numerically higher efficacy rates, combination therapy was not superior in clinical response [RR: 1.21; 95% CI: 0.96–1.53], clinical remission [RR: 1.25; 95% CI: 0.97–1.61], or steroid-free clinical remission [RR: 1.15; 95% CI: 0.85–1.55]. SAEs were less frequent with combination therapy [RR: 0.66; 95% CI: 0.41–0.98], whereas total AEs [RR: 1.01; 95% CI: 0.94–1.09] were similar between groups.

More recently, infliximab has been licensed for subcutaneous [SC] maintenance administration after intravenous [IV] induction dosing. This decision was based on pharmacokinetic and safety data comparing maintenance SC dosing every 2 weeks with IV dosing.[75] Subsequent RCT data have demonstrated the superiority of maintenance SC infliximab versus placebo for clinical and endoscopic endpoints among responders to IV infliximab induction therapy, demonstrating that this formulation is an effective option for responders to IV induction.[76] Multiple cohort studies have reported the effectiveness and safety of switching patients already established on standard doses of IV maintenance infliximab to SC maintenance dosing.[77] Future recommendations on infliximab combination therapy may change with emerging evidence on the efficacy, pharmacokinetics, and immunogenicity of SC infliximab.[78]

The combination of anti-TNF therapy with a thiopurine is associated with adverse long-term safety signals in terms of risk of both serious infection and malignancy.[50,51] This raises questions regarding potential de-escalation of treatment for patients in stable remission. The recent SPARE trial investigated clinical relapse in CD patients in steroid-free clinical remission for a minimum 8 months under combined infliximab and immunomodulator therapy, who either continued combination therapy or stopped infliximab or immunosuppressive therapy.[79] In this study with 211 randomised CD patients, clinical remission was significantly more often maintained over 2 years of follow-up when combination therapy was de-escalated to infliximab monotherapy [63/69; 91%] when compared with immunomodulator monotherapy [46/71; 65%] [RR: 1.41; 95% CI: 1.17-1.7]. There were no significant differences in clinical relapse rates, endoscopic outcomes, or pharmacokinetic outcomes between the group continuing combination therapy and those discontinuing immunomodulator therapy. AEs occurred at a similar frequency across treatment groups.

In general, a higher risk of lymphoma exists when anti-TNF agents are combined with conventional immunosuppression, although the absolute rates remain very low and are estimated at 1.9 per 10 000 patient-years in a meta-analysis consisting of almost 9000 patients included in the SEER database.[80] In clinical practice, the decision to de-escalate should be discussed individually with the patient, and risk factors for disease progression and residual disease activity should be considered. Finally, in patients with immunogenic failure towards a first anti-TNF agent, the addition of thiopurines during switch to a second anti-TNF agent increases efficacy and reduces immunogenicity.[81] In these patients, evaluation of thiopurine discontinuation should be done with special caution, with de-escalation considered predominantly in patients without prior immunogenicity.

3.4.2. Adalimumab in the treatment of CD

3.4.2.1. Adalimumab monotherapy for the induction of remission in CD

Statement 6.1. We recommend adalimumab as induction therapy in patients with moderate-to-severe CD [strong recommendation, moderate-quality evidence]. [Consensus: 100%]

3.4.2.2. Adalimumab monotherapy for the maintenance of remission in CD

Statement 6.2. We recommend adalimumab monotherapy as maintenance therapy in moderate-to-severe CD [strong recommendation, moderate-quality evidence]. [Consensus: 100%]

3.4.2.3. Adalimumab combination therapy for the induction of remission in CD

Statement 6.3. We suggest adalimumab monotherapy should be used over combination therapy with thiopurines as induction therapy in patients with moderate-to-severe CD naïve to biologics [weak recommendation, moderate-quality evidence]. [Consensus: 100%]

3.4.2.4. Adalimumab combination therapy for the maintenance of remission in CD

Statement 6.4. We suggest adalimumab monotherapy should be used over combination with an immunomodulator as maintenance therapy in patients with moderate-to-severe CD naïve to biologics [weak recommendation, low-quality evidence]. [Consensus: 98%]

Adalimumab is effective for the induction and maintenance of remission in CD. Available evidence does not support combination with an immunomodulator in biologic-naïve patients, although combination therapy may be considered in patients with prior immunogenicity to an alternative anti-TNF.

Adalimumab is a fully humanised IgG1 monoclonal antibody directed against TNFα, approved for the treatment of moderate-to-severe CD. Adalimumab is administered SC at a dose of 160 mg and then 80 mg 2 weeks after induction, followed by 40 mg SC every 2 weeks. A meta-analysis of pooled data on adalimumab versus placebo from three RCTs[82–84] involving 680 patients with moderate-to-severe CD, who did not achieve adequate response or were intolerant to corticosteroids and/or immunosuppressants, demonstrated efficacy

for induction of clinical remission [RR: 3.58; 95% CI: 2.42–5.29] and clinical response [RR: 1.98; 95% CI: 1.47–2.67] within 4 weeks of therapy initiation. Limited endoscopic data were available for the induction period only in one study; the data showed a significant trend towards enhanced mucosal healing [RR: 30.51; 95% CI: 1.87–498.81]. However, this evidence was downgraded due to high imprecision arising from sparse data.[85] There was no difference in AEs between those receiving adalimumab or placebo during the induction period [RR: 0.91; 95% CI: 0.75–1.11].[82–84] Rates of SAEs with adalimumab were also not significantly different from placebo [RR: 0.29; 95% CI: 0.09–0.96], but evidence was downgraded due to imprecision from sparse data.[82–84] Data revealed improved QoL based on the IBDQ within 4 weeks of therapy initiation[RR: 0.91; 95% CI: 0.75–1.11]. A Cochrane review based on three RCTs revealed similar results for clinical remission, response, improvement in QoL, and AEs during the first 4 weeks of therapy.[86]

Data from three RCTs in individuals with moderate-to-severe CD, who responded to induction therapy [CHARM, EXTEND 1, CLASSIC-II], demonstrated efficacy of adalimumab 40 mg SC every 2 weeks over placebo for maintenance of clinical remission [RR: 2.70; 95% CI: 1.75–4.19] at 52–56 weeks of follow-up.[85,87,88] Outcomes of clinical response [RR: 2.01; 95% CI: 1.14–3.55], but not corticosteroid-free remission [RR: 2.32; 95% CI: 0.62-8.63], were also improved with adalimumab.[87,88] RCT data on endoscopic outcomes are more limited, but suggest efficacy of adalimumab relative to placebo in endoscopic remission [RR: 9.14; 95% CI 2.21–37.80], endoscopic response [RR: 14.22; 95% CI: 1.93–104.98], and mucosal healing [RR: 31.00; 95% CI: 1.90–506.95].[85] Based on a post-hoc analysis of a single, placebo-controlled trial, QoL improvement was greater with adalimumab [RR: 1.32; 95% CI: 1.11–1.62].[89]

Regarding safety during the maintenance period, pooled clinical trial data indicated that adalimumab was associated with fewer SAEs than placebo [RR: 0.57; 95% CI: 0.39–0.83], and associations with any AE [RR: 1.00; 95% CI: 0.86–1.15] and serious infections were comparable [RR: 0.79; 95% CI: 0.34–1.79].[85,87,88] In a network analysis performed in the framework of a Cochrane collaboration, the dose-adjusted OR for SAEs for adalimumab was 1.01 [95% CI: 0.64–1.59].[67]

Only one open-label RCT [the DIAMOND trial][90] studied the use of combination therapy of adalimumab with a thiopurine when compared with adalimumab monotherapy for the induction of clinical remission in patients naïve to both therapies. In this trial, combination therapy was not superior to adalimumab monotherapy for inducing clinical remission at Week 26 [primary endpoint] [RR: 0.95; 95% CI: 0.78–1.15]. However, combination therapy was associated with endoscopic improvement at Week 26 [RR: 1.32; 95% CI: 1.06–1.65], although this benefit was lost by Week 52. There was no increase in AEs leading to discontinuation associated with combination therapy [RR: 1.03; 95% CI: 0.60–1.78].

The Week 52 maintenance outcomes of the DIAMOND trial demonstrated no clinical benefit of combination therapy in clinical remission [RR: 1.07; 95% CI: 0.91–1.25], clinical response [RR: 0.95; 95% CI: 0.78–1.15],[90,91] steroid-free clinical remission [RR: 0.97; 95% CI: 0.85–1.12],[91] endoscopic response [RR: 1.20; 95% CI: 0.89–1.62],[92] mucosal healing [RR: 1.77; 95% CI: 0.82–3.82],[92] SAEs [RR: 0.25; 95% CI: 0.01–5.00], or any AE [RR: 0.81; 95% CI: 0.47–1.38].[90,91] Likewise, a meta-analysis that included retrospective studies also revealed that combination therapy was not superior to monotherapy for maintenance of remission [OR: 1.08; 95% CI: 0.79–1.48, $p = 0.48$].[93] More recently, post-hoc analysis of six RCTs [CLASSIC-I, GAIN, CHARM, EXTEND, ULTRA 1, and ULTRA 2] demonstrated no efficacy benefits with immunomodulator and adalimumab combination therapy when compared with adalimumab monotherapy in CD patients with inadequate disease control on immunomodulatory therapy.[94]

The DIAMOND study included patients naïve to adalimumab. In the case of immune-mediated loss of response to a first anti-TNF, RCT evidence suggests that combination therapy is of benefit with the second anti-TNF.[81] Additionally, the observational PANTS study demonstrated a significant reduction in anti-adalimumab antibody development with adalimumab combination therapy in anti-TNF-naïve patients [HR: 0.44; 95% CI: 0.31–0.61],[68] suggesting that some patients may benefit from combination therapy with adalimumab and a thiopurine, depending on genetic predisposition.[95] Therefore, combining adalimumab with an immunomodulator should be considered in high-risk groups, including those with prior immunogenic failure to other anti-TNFs.

3.4.3. Certolizumab in the treatment of CD

3.4.2.1. Certolizumab for the induction of remission in CD

Statement 7.1. We suggest certolizumab can be used as induction therapy in patients with moderate-to-severe CD [weak recommendation, moderate-quality evidence]. [Consensus: 97%]

3.4.3.2. Certolizumab for the maintenance of remission in CD

Statement 7.2. We suggest certolizumab can be used as maintenance therapy in moderate-to-severe CD [weak recommendation, moderate-quality evidence]. [Consensus: 100%]

Certolizumab may be an effective treatment for the induction and maintenance of remission in CD. Availability varies between regions; it is not approved by the European Medicines Agency.

Certolizumab pegol [herein termed certolizumab] is a humanised polyethylene glycol [PEG]ylated F[ab] fragment of a monoclonal antibody directed against TNFα. Although certolizumab is not approved by the European Medicines Agency [EU] for the treatment of CD, it is commercially available elsewhere, including in Switzerland and Russia. The efficacy and safety of certolizumab for induction therapy in patients with moderately to severely active CD was evaluated in four randomised, placebo-controlled trials including a total of 1485 patients.[96–98] A Cochrane review from 2019 evaluated the efficacy and safety of certolizumab as induction therapy for CD.[99] Certolizumab was superior to placebo for induction of clinical response [RR: 1.29; 95% CI: 1.09–1.53] and clinical remission [RR: 1.36; 95% CI: 1.11–1.66]. Endoscopic outcomes were not reported. The rates of any SAEs [RR: 1.35;

95% CI: 0.93–1.97] were not different between certolizumab and placebo.

Two RCTs assessed the efficacy and safety of certolizumab as maintenance therapy [400 mg every 4 weeks] in patients with moderate-to-severe CD [PRECISE I and II].[97,100] A total of 1088 patients [30% had previous infliximab failure] were included and followed for only 26 weeks. Compared with placebo, certolizumab maintained a higher clinical response rate [reduction ≥ 100 points from baseline CDAI, OR: 1.64; 95% CI: 1.38–1.95] and resulted in greater rates of clinical remission [CDAI score ≤ 150 points, OR: 1.55; 95% CI: 1.23–1.95]. Furthermore, QoL as assessed by a minimum 16-point increase in the IBDQ from baseline showed a significant improvement in patients treated with certolizumab, with a relative effect of 1.35 [95% CI: 1.17–1.55]. Endoscopic outcomes were not measured. The incidence of SAEs did not differ significantly between patients treated with certolizumab and those who received placebo, with a relative effect of 1.19 [95% CI: 0.70–2.02]. In a network analysis performed in the framework of a Cochrane collaboration, the dose-adjusted OR for severe AEs for certolizumab was 1.57 [95% CI: 0.96–2.57].[67]

The reporting of all maintenance endpoints at the early time points of Week 26 resulted in downgrading the evidence quality of clinical maintenance endpoints. When combined with the absence of endoscopic endpoints, the consensus group decided that the strength of recommendation should be weak. Consistent with the weak recommendation for certolizumab as a maintenance therapy, and the widespread availability and suitability of other anti-TNF therapies, including biosimilar options, the consensus group agreed that the recommendation for use of certolizumab as induction therapy should also be weak.

3.4.4. Drug monitoring when using anti-TNF therapy

3.4.4.1. Proactive and reactive drug monitoring compared with standard of care

Statement 8.1. There is insufficient evidence to recommend the use of proactive therapeutic drug monitoring. compared with reactive therapeutic drug monitoring or standard of care. when using anti-TNF agents [weak recommendation, very low-quality evidence]. [Consensus: 100%]

Practice Point 1: Therapeutic drug monitoring may be used when optimising dose in patients with CD treated with anti-TNF therapy. [Consensus: 94%]

The use of therapeutic drug monitoring for anti-TNF therapy was evaluated with both a GRADE evaluation and development of a practice point. GRADE evaluation of trial data did not demonstrate superiority of proactive drug monitoring compared with reactive monitoring or no drug monitoring, when considering our predefined GRADE outcomes. However, further assessment of the literature during development of the practice point highlighted several ways in which therapeutic drug monitoring can be useful when optimising dose of anti-TNF therapy, which is reflected in widespread use in clinical practice as discussed in the text.

Numerous prospective studies and post-hoc analysis of RCTs have shown that higher anti-TNF drug concentrations during maintenance therapy are associated with higher rates of favourable therapeutic outcomes in patients with CD.[101] Low drug concentrations are also associated with primary non-response [PNR], loss of response [LOR], and development of anti-drug antibodies.[68] A key question is whether dose optimisation in clinical practice, based on prospective measurement of drug levels [proactive therapeutic drug monitoring, or TDM] can confer clinical benefit.

Pooled data from RCTs showed no statistically significant difference between proactive TDM and standard-of-care anti-TNF therapy in clinical remission [three studies, RR: 1.12; 95% CI: 0.90–1.39], steroid-free clinical remission [three studies, RR: 1.00; 95% CI: 0.77–1.31], endoscopic remission [two studies, RR: 0.96; 95% CI: 0.72–1.27], biochemical remission [two studies, RR: 1.08; 95% CI: 0.87–1.33], SAEs [two studies, RR: 1.27; 95% CI: 0.76–2.14], or serious infections [two studies, RR: 1.47; 95% CI: 0.10–21.20].[102–106] However, these RCTs had some important methodological issues regarding study design, including a rather low cut-off drug concentration for dose escalation, heterogeneity of study populations, and the fact that proactive TDM did not start early during induction.

In a recent systematic review and meta-analysis, there was no significant difference in the risk of failing to maintain clinical remission in patients who underwent proactive TDM versus clinically driven dose adjustments in patients with CD treated with anti-TNF therapy [RR: 0.87; 95% CI: 0.66-1.15].[107] Similarly, another meta-analysis showed no superiority of proactive TDM compared with conventional management in maintaining clinical remission with anti-TNF agents [RR: 1.16; 95% CI: 0.98–1.37].[108] On this basis, there was insufficient evidence to recommend the use of proactive therapeutic monitoring for patients with CD undergoing treatment with anti-TNF therapy.

However, the consensus group noted that there was evidence for additional important outcomes outside the remit of our voted GRADE outcomes, which may confer benefit to the patient. A meta-analysis including both retrospective studies and RCTs found that proactive TDM of anti-TNF therapy was associated with a significantly decreased risk of treatment failure compared with either standard of care [RR: 0.64; 95% CI: 0.48–0.85] or reactive TDM [RR: 0.46; 95% CI: 0.21–0.98]. Moreover, proactive TDM was associated with a significant reduction in hospitalisation [RR: 0.33; 95% CI: 0.21–0.54].[109] These findings were replicated in another meta-analysis that also highlighted potential cost efficiency of proactive TDM.[108]

Proactive TDM may also be useful in other clinical scenarios, such as anti-TNF therapy de-escalation,[110] restarting infliximab following a pause in scheduled drug administration, and optimising infliximab monotherapy when combination therapy with an immunomodulator is not possible due to patient preference or high risk of SAEs.[111] Recent data from two studies, including mainly patients with CD, suggest that proactive TDM can also mitigate risk of immunogenicity to anti-TNF therapy and treatment cessation in patients with a positive HLA-DQA1*05 genotype, previously found to predispose to development of anti-drug antibodies against infliximab and adalimumab.[95,112,113]

Data from paediatric studies were not included in the GRADE analysis. However, cumulative evidence from RCTs suggests that proactive TDM of anti-TNF therapy is associated with better outcomes compared with clinically based

dosing or reactive TDM in CD in paediatric populations.[114,115] In particular, the PAILOT RCT, including children with CD naïve to biological therapy who responded to adalimumab induction therapy, showed that sustained corticosteroid-free clinical remission was significantly higher in the proactive compared with the reactive TDM arm [82% vs 48%, respectively, $p = 0.002$].[114] Moreover, a recent RCT on a biologic-naïve paediatric population with CD, who responded to infliximab induction therapy, showed that proactive TDM compared with clinically based dosing was superior regarding sustained corticosteroid-free clinical remission [89.5% vs 70.9%, $p = 0.025$] and endoscopic healing [85% vs 57.1%, $p = 0.025$].[115]

Reactive TDM, defined as the evaluation of drug concentrations and antidrug antibody titres when PNR or LOR occur, may help identify the mechanisms underlying these undesirable outcomes, which in turn may shape future drug selection.[116] Observational study data suggest that this may be a cost-effective strategy associated with potential for better therapeutic outcomes.[117–119]

Consequently, while recognising the problems with the evidence base reflected in the GRADE statement, the consensus group recognises a place for TDM in clinical care, when available. Nonetheless, several problems concerning TDM for anti-TNF therapy remain, including identification of optimal drug concentration targets, assay variability, and feasibility of timely dosing interventions. Importantly, although there is some evidence of dose-response relationships for non-anti-TNF biologics in CD, there is much less evidence to suggest a potential benefit for TDM-guided dosing, and use of TDM in the routine care of patients treated with non-anti-TNF biologics is not supported.[120,121]

3.5. IL-12/IL-23 inhibitors in the treatment of CD

3.5.1. Ustekinumab in the treatment of CD

3.5.1.1. Ustekinumab for the induction of remission in CD

Statement 9.1. We recommend ustekinumab as induction therapy in moderate-to-severe CD [strong recommendation, moderate-quality evidence]. [Consensus: 100%]

3.5.1.2. Ustekinumab for the maintenance of remission in CD

Statement 9.2. We recommend ustekinumab as maintenance therapy in moderate-to-severe CD [strong recommendation, moderate-quality evidence]. [Consensus: 100%]

Ustekinumab is effective for the induction and maintenance of remission in CD.

Ustekinumab is an IgG1 monoclonal antibody that binds to the p40 subunit shared by the pro-inflammatory interleukins 12 and 23. In CD, induction is given IV using a weight-based regimen of approximately 6 mg/kg. One systematic review and meta-analysis pooled the results from RCTs in which ustekinumab was compared with placebo for induction of remission in adult patients with moderately to severely active luminal CD.[122] Four trials[123–126] involving 1947 patients treated with different ustekinumab IV doses or equivalent placebo reported on induction outcomes at 6 weeks. Data were extracted and a meta-analysis was performed, demonstrating efficacy in clinical response [RR: 1.56; 95% CI: 1.38–1.57] and clinical remission [RR: 1.76; 95% CI: 1.40–2.22]. Two substudies[125,127] involving 252 patients revealed that more patients receiving ustekinumab achieved endoscopic improvement compared with placebo [47.7% vs 29.9%, RR: 1.60; 95% CI: 1.13–2.26] and a reduction in the mean global histology activity scores [from 10.4 ± 7.0 to 7.1 ± 5.9; $p < 0.001$] at 8 weeks. A more recent RCT[128] investigating the efficacy and safety of guselkumab in CD, in which ustekinumab was administered in a reference arm [63 patients], reported similar results at 12 weeks. Two studies[129,130] reported on the effect of ustekinumab on health-related QoL. The RR was 2.42 [95% CI: 1.27–4.61] for achieving PRO-2 remission, 2.14 [95% CI: 1.27–3.62] for IBDQ remission, and 1.86 [95% CI: 1.33–2.59] for IBDQ response at 12 weeks.[128] Similarly, significantly greater proportions of patients receiving ustekinumab had clinically meaningful IBDQ and SF-36 score improvement at 8 weeks compared with placebo in a pooled analysis of two pivotal RCTs. One study reported pooled safety results of phase 2/3 RCTs on any AEs or SAEs after induction [1653 patients].[129] The pooled RR of any AEs was not significantly different between ustekinumab and placebo [53.8% vs 56.1%, RR: 0.96; 95% CI: 0.89–1.03]. Similarly, the pooled RR of any SAEs and of any serious infection were not significantly different between ustekinumab and placebo [4.5% vs 6.2%, RR: 0.72; 95% CI: 0.51–1.02; and 1.1% vs 1.2%, RR: 0.95; 95% CI: 0.45–2.01, respectively]. The rate of antidrug antibody formation was < 5%.[131] Finally, a meta-analysis[132] of 63 observational studies [8529 patients] reported that 60% [95% CI: 54–67%, $I^2 = 93\%$] of patients who received ustekinumab achieved clinical response, 37% [95% CI: 28–46%, $I^2 = 97\%$] achieved clinical remission, and 33% [95% CI: 27–40%, $I^2 = 86\%$] achieved corticosteroid-free clinical remission at 8–14 weeks, replicating the results of RCTs in a real-world setting of refractory patients with CD.

Maintenance outcomes were also evaluated. One RCT included patients with moderate-to-severe CD who responded to ustekinumab induction therapy. Patients were re-randomised to receive ustekinumab 90 mg [either every 8 weeks or every 12 weeks] or placebo. More patients receiving ustekinumab when compared with those receiving placebo were in clinical remission over a 44-week follow-up [51% vs 35.9%, RR: 1.42; 95% CI: 1.10–1.84],[124] and at Week 56 [50.2% vs 27.7%; RR: 1.83; 95% CI: 1.35–2.47].[131,133] The same study showed that more patients receiving ustekinumab were also in corticosteroid-free clinical remission over a 44-week follow-up [44.7% vs 29.8%, RR: 1.50; 95% CI: 1.12–2.02] and after 56 weeks of treatment [44.7% vs 22.1%; RR: 2.02; 95% CI: 1.43–2.86].[124,131,133] Similar results were shown for clinical response. There are limited placebo-controlled trial data from a subgroup analysis on endoscopic remission [total SES-CD score ≤ 2] and mucosal healing [complete absence of any mucosal ulcerations among patients who presented with ulceration in at least one ileocolonic segment at induction]. There was no statistically significant difference in mucosal healing [RR: 3.13; 95% CI: 0.40–24.53] or endoscopic remission [RR: 2.61; 95% CI: 0.32–21.08] between ustekinumab and placebo.[125] Nevertheless, outcome data from a large randomised trial comparing treatment with ustekinumab every 8 weeks with adalimumab every 2 weeks showed similar endoscopic outcomes between the two groups.[134] In addition, post-hoc analyses showed that ustekinumab improved health-related QoL compared with placebo.[129] A

pooled safety analysis from phase 2/3 studies showed that there was no statistically significant difference between placebo- or ustekinumab-treated patients for SAEs [RR: 1.03; 95% CI: 0.85–1.26] and serious infections [RR: 1.57; 95% CI: 0.98–2.51] for a mean follow-up of 48 weeks.[130]

3.5.2. Ustekinumab compared with adalimumab for induction of remission in CD

Statement 10.1. We suggest adalimumab or ustekinumab are equally as effective as induction therapy in biologic-naïve patients with moderate-to-severe CD [weak recommendation, moderate-quality evidence]. [Consensus: 100%]

3.5.2.1. Ustekinumab compared with adalimumab for maintenance of remission in CD

Statement 10.2. We suggest adalimumab and ustekinumab are equally as effective as maintenance therapy in biologic-naïve patients with moderate-to-severe CD [weak recommendation, moderate-quality evidence]. [Consensus: 100%]

RCT evidence suggests that ustekinumab and adalimumab may be equally effective for the induction and maintenance of remission in CD in patients without prior biologic exposure.

The SEAVUE trial [phase 3b][134] was an active comparator randomised trial that used a 'treat-through' design to compare the effectiveness and safety of ustekinumab and adalimumab monotherapy in biologic-naïve adult patients with moderately to severely active CD. Of note, the threshold of endoscopic disease required for trial inclusion was lower compared with several other studies [requiring at least one, single ulcer of any size]. The primary endpoint was the proportion of patients in clinical remission [CDAI score < 150] at Week 52. A total of 386 patients were enrolled and randomly assigned to receive ustekinumab [n = 191] or adalimumab [n = 195]. Ustekinumab induction was approximately 6 mg/kg IV on Day 0, followed by maintenance of 90 mg SC at Week 8, and then 90 mg SC once every 8 weeks. Adalimumab induction was 160 mg SC on Day 0, 80 mg SC at Week 2, followed by maintenance of 40 mg SC at Week 4, and then once every 2 weeks. Study treatments were administered as monotherapy and without dose modifications. Both monotherapies were effective for induction of remission at Week 16 [ustekinumab 57% vs adalimumab 60%, difference -3%, 95% CI: -13 to 7; nominal p = 0.55] and demonstrated comparative efficacy [RR: 0.95, 95% CI: 0.80–1.13]. Response rates at 16 weeks were similar between agents [72% vs 73%, respectively], with moderate-quality evidence. Safety outcomes for both groups did not show significant differences.

When considering maintenance outcomes at Week 52, 64.9% [124/191] of patients receiving ustekinumab every 8 weeks versus 61.0% [119/195] of patients receiving adalimumab every 2 weeks were in clinical remission [RR: 1.06, 95% CI: 0.91–1.24].[134] Similarly, corticosteroid-free clinical remission was achieved in 61% of the ustekinumab group and 57% of the adalimumab group [RR: 1.06, 95% CI: 0.90–1.25]. Both treatment groups showed similar endoscopic response [ustekinumab 42% vs adalimumab 37%, RR: 1.14, 95% CI: 0.88–1.47] and endoscopic remission rates [ustekinumab 29% vs adalimumab 31%, RR: 0.93, 95% CI: 0.67–1.28] at Week 52.[134]

Overall, the safety profile was similar between groups for AEs [RR: 1.03, 95% CI 0.93–1.14] and SAEs [RR: 0.82, 95% CI 0.22–3.00]. However, the numerical proportions of patients in the ustekinumab group [34%] who experienced infections was lower than in the adalimumab group [41%], although rates of serious infections were similar.[134]

Overall, the consensus group noted that data from this single RCT suggested similar efficacy and safety outcomes, with moderate evidence quality. Nonetheless, the study used doses of drugs that did not entirely align with licensed doses within Europe, and dose escalation was not permitted. The findings may not apply to patients with previous biologic therapy failure or longer disease history. Furthermore, longer-term follow-up beyond 1 year would be required to determine if efficacy and safety are sustained similarly with each drug. Overall, this led to a decision to make a weak recommendation, reflecting the strength of the evidence and these additional concerns.

3.5.3. Risankizumab in the treatment of CD

3.5.3.1. Risankizumab for the induction of remission in CD

Statement 11.1. We recommend risankizumab as induction therapy in moderate-to-severe CD [strong recommendation, high-quality evidence]. [Consensus: 100%]

3.5.3.2. Risankizumab for the maintenance of remission in CD

Statement 11.2. We recommend risankizumab as maintenance therapy in moderate-to-severe CD [strong recommendation; high-quality evidence]. [Consensus: 100%]

Risankizumab is effective for the induction and maintenance of remission in CD.

Risankizumab is a humanised, monoclonal IgG1 class antibody that binds to the p19 subunit of IL-23. Two placebo-controlled RCTs were identified.[135] The two studies included a total of 889 patients with moderately to severely active CD, with evaluable outcome data after exposure to either three IV doses of 600 mg risankizumab [Weeks 0, 4, and 8] or placebo, with primary outcome measures captured at Week 12. Clinical response and clinical remission were achieved more often in patients receiving risankizumab compared with placebo [RR: 1.79, 95% CI: 1.47–2.17 and RR: 1.95, 95% CI:1.57–2.43, respectively]. Endoscopic response and endoscopic remission were achieved with risankizumab more often than placebo [RR: 2.96, 95% CI: 2.17–4.05 and RR: 3.22, 95% CI: 1.93–5.38, respectively]. Rates of any AEs in patients treated with risankizumab occurred statistically less often than in patients receiving placebo [RR: 0.85, 95% CI: 0.62–1.17]. SAEs and serious infections occurred less often in risankizumab-treated patients [RR: 0.45, 95% CI: 0.3–0.67 and RR: 0.21, 95% CI: 0.07–0.65, respectively].

Clinical responders to risankizumab from the two phase 3 induction trials were re-randomised in a single maintenance therapy trial. A total of 141 evaluable participants received 360 mg risankizumab SC every 8 weeks, and 164 participants received SC placebo.[136] Compared with placebo, more

patients treated with risankizumab achieved clinical remission [51.8% vs 39.6%, RR: 1.31, 95% CI: 1.02–1.67] or endoscopic response [46.8% vs 22.0%, RR: 2.13, 95% CI: 1.52–2.99] at Week 52.[136,137] A higher proportion of patients on risankizumab maintenance also achieved clinical response, endoscopic remission, and ulcer-free endoscopy after 1 year of therapy. The overall incidence of any SAEs or serious infections were similar across study groups.

3.6. Anti-integrin therapies in the treatment of CD

3.6.1. Vedolizumab in the treatment of CD

3.6.1.1. Vedolizumab for the induction of remission in CD

Statement 12.1. We recommend vedolizumab as induction therapy in moderate-to-severe CD [strong recommendation, moderate-quality evidence]. [Consensus: 100%]

3.6.1.2. Vedolizumab for the maintenance of remission in CD

Statement 12.2. We recommend vedolizumab as maintenance therapy in moderate-to-severe CD [strong recommendation, moderate-quality evidence]. [Consensus: 100%]

Vedolizumab is effective for the induction and maintenance of remission in CD.

Vedolizumab is a monoclonal IgG1 antibody that acts by blocking the α4β7 integrin, resulting in disruption of lymphocyte trafficking and anti-inflammatory activity. It is administered IV at a fixed dose of 300 mg at 0, 2, and 6 weeks for induction. Patients who do not achieve response at Week 6 can benefit from an additional administration at Week 10.[138] Four RCTs involving 1126 patients treated with vedolizumab or placebo reported on clinical and safety outcomes in adult patients with moderately to severely active luminal CD at 6–10 weeks.[139–142] Data were extracted and a meta-analysis was performed. Vedolizumab was superior to placebo in induction of clinical response [RR: 1.59, 95% CI: 1.32–1.91] and clinical remission [RR: 2.00, 95% CI: 1.51–2.66]. Endoscopic outcome data were not assessed. The pooled RR of any AEs was not significantly different between vedolizumab and placebo [62% vs 53.8%, RR: 1.15, 95% CI: 0.88–1.51]. Similarly, the pooled RR of SAEs was not significantly different between vedolizumab and placebo [9.0% vs 9.2%, RR: 0.99, 95% CI: 0.68–1.44].

A meta-analysis[143] of 74 observational studies [13 663 patients] reported that 56% [95% CI: 51–61%, I^2 = 89%] of the patients who received vedolizumab exhibited clinical response, 36% [95% CI: 32–40%, I^2 = 85%] achieved clinical remission, 30% [95% CI: 25–34%, I^2 = 87%] achieved corticosteroid-free clinical remission, and 29% [95% CI: 19–42%, I^2 = 58%] achieved mucosal healing at 6–16 weeks, replicating the results of RCTs in a real-world setting of refractory patients with CD.

Maintenance therapy with vedolizumab was investigated in three RCTs in patients with moderate-to-severe CD who had responded to induction therapy. Vedolizumab was administered IV at 300 mg every 8 weeks in two studies[139,142] and SC at 108 mg every 2 weeks in one study.[144] Following 52–60 weeks of maintenance therapy, vedolizumab was superior to placebo in achieving clinical remission [RR: 1.55, 95% CI: 1.25–1.91], with 44.7% [197/441] of patients receiving vedolizumab in clinical remission when compared with 27.1% [81/299] of patients receiving placebo. Moreover, vedolizumab was effective at maintaining steroid-free clinical remission [RR: 2.23, 95% CI: 1.44–3.44]; this endpoint was achieved in 39.0% [71/182] of patients receiving vedolizumab compared with 16.3% [21/129] of patients receiving placebo. Again, no endoscopic data were generated during the registrational trials, although endoscopic outcomes have been collected during open-label clinical trials and cohort studies.[145] Vedolizumab showed a similar incidence of AEs [RR: 0.96, 95% CI: 0.86–1.08], SAEs [RR: 0.98, 95% CI: 0.67–1.44], and serious infections [RR: 0.32, 95% CI: 0.09–1.13] compared with placebo through Week 52–60. Similar safety signals were observed in the GEMINI long-term safety study that followed CD patients exposed to IV vedolizumab every 4 weeks for a median of 32 months [range 0.03–100.3].[146]

3.7. Janus kinase inhibitors in the treatment of CD

3.7.1. Upadacitinib in the treatment of CD

3.7.1.1. Upadacitinib for the induction of remission in CD

Statement 13.1. We recommend upadacitinib as induction therapy in moderate-to-severe CD [strong recommendation; high-quality evidence]. [Consensus: 100%]

3.7.1.2. Upadacitinib for the maintenance of remission in CD

Statement 13.2. We recommend upadacitinib as maintenance therapy in moderate-to-severe CD [strong recommendation; moderate-quality evidence]. [Consensus: 100%]

Upadacitinib is the only JAK inhibitor recommended for the induction and maintenance of remission in CD.

Upadacitinib is an oral Janus kinase [JAK] inhibitor with relatively increased selectivity for JAK-1. Two RCTs[147] reported outcomes for a total 1021 patients who were randomised in a 2:1 ratio to receive either 45 mg/day of upadacitinib or placebo for 12 weeks. We meta-analysed outcomes from these trials. A significantly higher percentage of patients receiving upadacitinib achieved clinical remission than those who received placebo [44.4% vs 25.1%, $p < 0.001$] and endoscopic response [40.2% vs 8.4%, $p < 0.001$]. Significantly higher proportions of patients on upadacitinib achieved clinical response, steroid-free remission, and endoscopic remission when compared with placebo. The overall incidence of safety outcomes was similar between patients exposed to upadacitinib and placebo.

Clinical responders from the induction RCTs were re-randomised to receive daily upadacitinib 15 mg [n = 169], upadacitinib 30 mg [n = 168], or placebo [n = 165].[148] When compared with placebo, maintenance therapy with upadacitinib, 15 mg once daily and 30 mg once daily by Week 52, resulted in significantly higher rates of clinical remission [37.3% and 47.6% vs 15.1%, respectively, $p < 0.001$ for both comparisons], endoscopic response [35.5% and 40.1% vs 7.3%, respectively, $p < 0.001$ for both], and remission [19.1% and 28.6% vs 5.5%, respectively, $p < 0.001$ for both].

A higher proportion of patients on upadacitinib maintenance achieved clinical response and steroid-free clinical remission with improved QoL. Efficacy outcomes were all numerically higher in the group receiving higher doses of maintenance therapy, although this should be viewed against safety and cost considerations. The overall incidence of any SAEs or serious infections were similar across study groups. Herpes zoster infection was reported in 4.0% of patients receiving maintenance treatment with 15 mg upadacitinib and 7.2% of patients receiving 30 mg upadacitinib, compared with 4.7% in the placebo group. No adjudicated cardiovascular events were reported. One case of hepatic vein thrombosis concurrent with exacerbation of CD was reported in a patient receiving 30 mg upadacitinib.

3.8. Nutritional therapy in the treatment of CD

3.8.1. Exclusive enteral nutrition for the induction of remission in CD

Statement 14.1. We suggest exclusive enteral nutrition can be used as induction therapy in patients with mild-to-moderate CD who are motivated to adhere to dietary therapy, have access to dietetic support, and prefer to avoid corticosteroids. [Weak recommendation, very low-quality evidence.] [Consensus: 100%]

Exclusive enteral nutrition [EEN] is suggested for induction of remission in CD. A meta-analysis of available data for adult patients demonstrated inferiority to steroids in intention-to-treat analysis; however, similar rates of induction of remission were found when restricting analysis to patients who were able to adhere to therapy. As steroid use is associated with high morbidity, we suggest EEN as an alternative to steroids in motivated patients with appropriate dietetic support.

EEN is a therapeutic approach involving the consumption of a liquid medical formula as the sole food source, usually for 6–8 weeks. In children with luminal mildly to moderately active CD, EEN is the first-line therapy for inducing clinical remission according to ECCO-ESPGHAN guidelines, with data showing superiority over corticosteroids in achieving mucosal healing.[149] In adults, several studies show that in patients who are able to tolerate the diet, EEN can be effective for induction of remission,[150] even in complicated diseases,[151] and as preoperative optimisation therapy.[152] An age subgroup analysis [> 18] conducted in the most recent Cochrane review, including six trials with very low-quality evidence, indicated that 45% [87/194] of EEN patients achieved remission compared with 73% [116/158] of patients treated with corticosteroids [RR: 0.65, 95% CI: 0.52–0.82].[150] However, a per-protocol analysis did not reveal a significant difference in inducing remission between EEN and corticosteroids. This suggests that the disparity in the success of EEN between children and adults is primarily attributed to compliance. AE rates did not significantly differ between EEN and corticosteroids during the trial period, although milder AEs were reported with EEN.

Consequently, where clinicians and patients wish to attempt use of EEN as a therapeutic alternative to corticosteroids for induction of remission in CD, it is important to focus on strategies to enhance compliance and improve palatability. The effectiveness of EEN does not appear to be influenced by the type of formula, including protein [elemental, semi-elemental, and polymeric] and fat composition or method of administration [nasogastric or oral].[150] Using EEN effectively requires a multidisciplinary team [MDT], with dietitian support playing a pivotal role.[153]

3.8.2. Dietary therapies in the management of CD

3.8.2.1. Dietary therapy for the induction of remission in CD

Practice Point 2A. There is emerging evidence that dietary therapies may be beneficial in reducing the inflammatory burden in CD. However, currently no universally applicable diet will benefit all patients with CD. Dietary intervention should primarily be considered based on disease activity, the patient's motivation, the current evidence, and the availability of dietetic support. All patients with CD should have access to dietary services, especially during disease flare. [Consensus: 97%]

3.8.2.2. Dietary therapy for the maintenance of remission in CD

Practice Point 2B. Partial enteral nutrition might be considered as a strategy for maintaining remission, with or without additional medication, in a subset of patients who are willing and able to tolerate the formula with routine monitoring. [Consensus: 100%]

Recently, food-based diets have gained attention as a potential adjunct or monotherapy for reducing inflammation in active CD, offering a more palatable alternative to EEN.[154] The Crohn's Disease Exclusion Diet [CDED] is currently the most studied approach with accumulating supportive data for its use in adult patients with CD.[155–157] A recent pilot RCT, involving adult patients with active mild-to-moderate disease, showed that CDED, either alone or in combination with partial enteral nutrition [PEN] as monotherapy, resulted in a 62% remission rate at Week 6, with 50% of patients maintaining remission up to Week 24 and 35% achieving endoscopic remission.[157] Based on the currently available evidence, the recent ESPEN guidelines recommended considering using CDED as an alternative to EEN in adults with mild-to-moderate CD.[158]

Another noteworthy study investigated the Specific Carbohydrate Diet [SCD] alongside the Mediterranean diet as an adjunct to licensed medical therapy. Both diets exhibited approximately 40% symptomatic remission rates, with no significant difference observed. Consequently, the authors concluded that the Mediterranean diet, given its ease of adherence, should be preferred over SCD.[159] An additional diet derivative from the SCD is the IBD anti-inflammatory diet, with one case series in IBD showing an improvement in Harvey–Bradshaw Index [HBI] and potential as an adjunct dietary therapy with ongoing studies.[160–162]

Additional interventions, such as CD-TREAT, aim to replicate EEN's nutritional composition and effects on the intestinal microbiota, with ongoing studies in adults exploring efficacy with promising preliminary data.[163] Last, the low fermentable oligosaccharides, disaccharides, monosaccharides, and polyols [FODMAP] diet has shown promise in alleviating intestinal symptoms without significant impact on

inflammation. Therefore, the low FODMAP diet is recommended primarily for patients with quiescent CD experiencing functional symptoms.[164]

Numerous studies, particularly within the Japanese population, suggest that Partial Enteral Nutrition (PEN) may be effective as a long-term strategy to maintain remission. In a meta-analysis including eight studies, patients receiving PEN [420–1800 kcal/d] had a significantly lower clinical relapse rate [RR: 0.67, 95% CI: 0.54–0.82, $p < 0.01$] over 0.5 to 2 years compared with those not receiving nutritional therapy. The authors concluded that PEN may be more effective than the absence of enteral nutrition therapy for the maintenance of remission in CD, with a good safety profile.[165] Another meta-analysis showed that adding PEN to infliximab led to 74.5% remission at 1 year compared with 49.2% using infliximab alone [OR: 2.93, $p < 0.01$].[166] The use of PEN for maintenance of remission was suggested as a treatment option to prolong remission, by the paediatric ECCO-ESPGHAN guidelines in the case of low-risk patients.[149]

3.9. Sequencing and combination of therapies in CD

3.9.1. Sequencing of advanced therapies in CD

Practice Point 3. There is currently insufficient evidence to direct how advanced therapies should be positioned in a therapeutic algorithm for luminal CD. Decisions should consider efficacy, safety, patient preferences and characteristics, disease characteristics, and cost or access to therapies. [Consensus: 97%]

Positioning of therapies in CD is one of the main challenges in daily clinical practice. This is particularly true of agents commonly termed advanced therapies: biologic therapies and targeted small molecules. All approved drugs can be effective for patients with CD, but data enabling direct comparison between drugs are largely absent. Limited, head-to-head RCT data exist, such as the SEAVUE trial, which compared adalimumab and ustekinumab in CD[134] and the SEQUENCE trial, which compared risankizumab and ustekinumab.[167] Even with these large and well-conducted RCTs, it is important to consider that they apply to specific comparisons made in specific populations. For example, in SEAVUE, the finding of broadly comparable efficacy between ustekinumab and adalimumab relates to the treatment of patients without prior biologic exposure and without the option of dose escalation. Likewise, the SEQUENCE trial, presented in abstract form only during the preparation of these guidelines, showed significantly higher rates of response and remission for clinical and endoscopic outcomes in patients treated in an open-label manner with risankizumab over those treated with ustekinumab, specifically among a population of patients with failure of prior anti-TNF therapy.[167,168]

Even with other head-to-head RCTs in progress, there will still be insufficient direct evidence to address many questions that arise in routine clinical practice. In this context, clinicians can and should try to make treatment recommendations based upon understanding of the available evidence. This includes the consideration as to what extent evidence from populations that differ slightly from the patient under consideration may be used to inform decision making for the individual patient. Clinicians may also wish to consider indirect comparisons based on network meta-analyses.[169–171] However, it is important to note that these are sensitive to differences between trial populations, definitions and timing of outcome measures, and design of maintenance studies. Cohort studies can provide complementary evidence on real-world populations, often including groups that might otherwise be excluded from clinical trials, with use of statistical methodologies to correct for baseline differences in measured confounders.[71] These studies should be considered alongside assessment of potential sources of bias, unmeasured confounding factors, and difficulties inherent in the lack of randomisation. Additionally, understanding of safety data may be improved with analysis of similar data that may be available for patients exposed to a drug for a different licensed indication, although again, clinicians should consider to what extent the risk profile of the external population matches the patient under consideration.

Ultimately, whereas it is not appropriate to form firm conclusions from indirect methodologies such as network meta-analyses or large cohort studies, taken in isolation, these can provide valuable insight. Where alternative sources of indirect evidence are discrepant, it is not possible to form clear predictions of relative drug performance. When the findings are congruent, this may provide some confidence in the application of the results to clinical practice.

Given the potential for uncertainty in many of these comparisons, it is also important to understand the factors important in decision making for an individual patient. Different patients may apply different priority to, for example, efficacy, safety, or other aspects of the therapeutic profile. Clinicians should also consider disease-related factors [such as perianal disease and extraintestinal manifestations[57]] and patient-related factors [such as comorbidity, including concurrent immune-mediated disorders, age, desire to become pregnant, and susceptibility to infection], all of which may have implications for the risk-benefit profile of any given therapy. Finally, short-term, long-term, direct, and indirect costs should be considered in the decision process, which may differ from region to region. We have summarised the situations in which specific therapies may be beneficial in CD [Figure 1].

3.9.2. Advanced combination therapies in treatment of CD

Practice Point 4. Advanced combination therapy may be necessary when there are uncontrolled extraintestinal manifestations or symptomatic immune-mediated disorders needing more than one agent to achieve remission. Advanced combination therapy may also be an option for refractory CD. There is currently no evidence to support advanced combination therapy in patients naïve to advanced therapies, even in high-risk patients. [Consensus: 100%]

Despite important progress in therapy for CD, up to 60% of patients fail to achieve long-term remission.[179] Advanced combination therapy [ACT] refers to the combination of biologic agents, targeted small molecules, or both, and can be considered for the following three different settings: uncontrolled extraintestinal manifestations, patients with concomitant immune-mediated diseases, and patients with a refractory IBD phenotype where no surgical options are feasible.[180] When considering refractory disease, it is reasonable to combine agents that have resulted at least in a

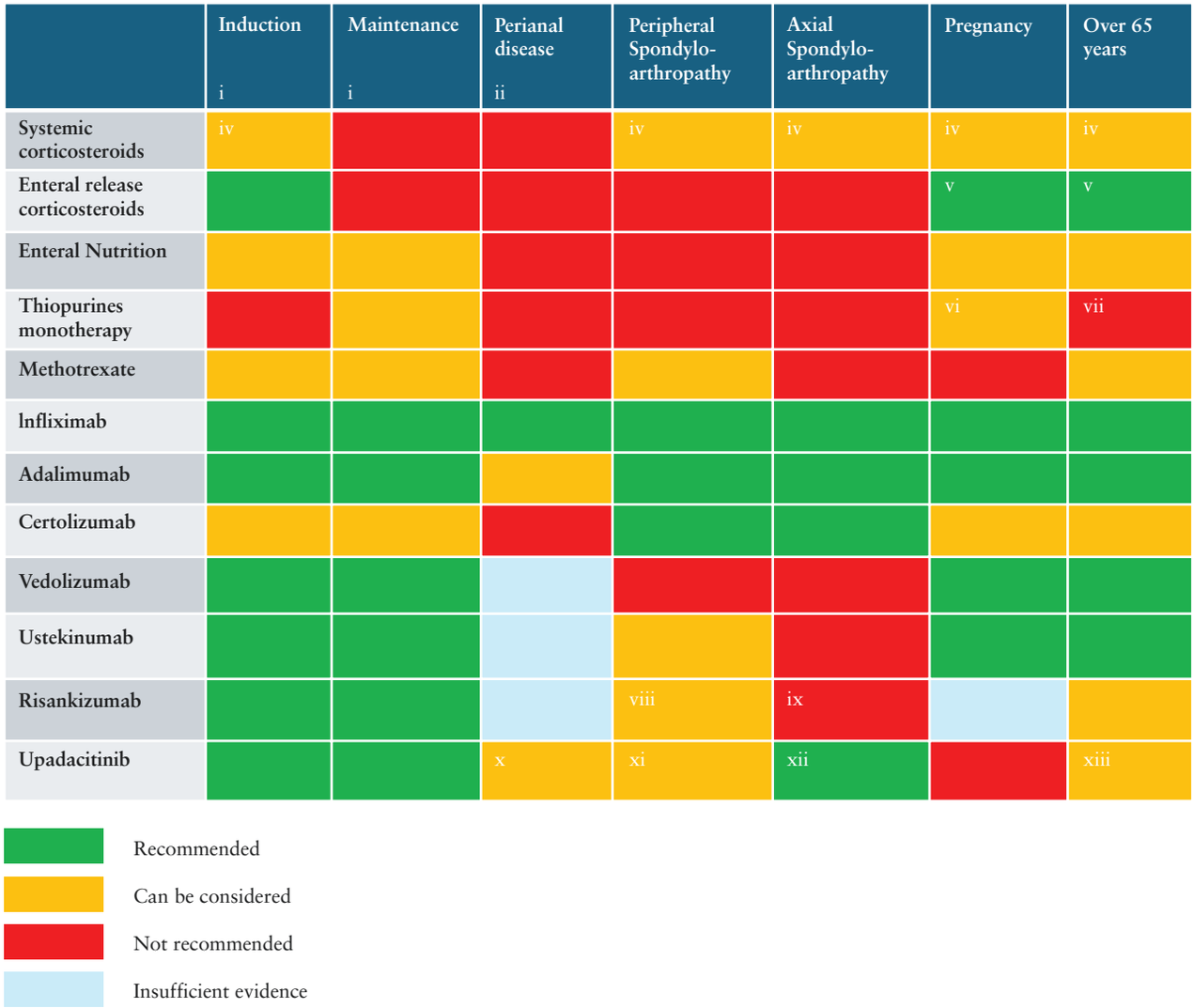


Figure 1. Medical therapy in the management of CD. i. This figure summarises a complex area with limitations to much of the available data, it is not intended to replace individualised decision making. Please see the main text of these guidelines for discussion of the evidence base; recommendations and considerations are derived from GRADE recommendations and suggestions, respectively, for induction and maintenance outcomes. ii. Recommendations on the medical management of perianal disease are adapted from the CD Treatment Guideline surgical manuscript[5]. iii. Recommendations on the safe medical management of CD during pregnancy are taken from the ECCO guidelines on sexuality, fertility, pregnancy and lactation,[9] with strength of recommendation aligned to the GRADE recommendations of this guideline. iv. Systemic corticosteroids should only be used if there are no available alternatives, particularly in patients over the age of 65, or as a bridge to the initiation of an effective maintenance therapy. v. Enterally acting corticosteroids can only be considered as induction agents in pregnancy and in the over-65s, and are not recommended for maintenance of remission. vi. Thiopurines can be continued as maintenance therapy in pregnancy, but should not be newly started as monotherapy nor used as induction agents.[9] vii. Can be considered case by case if there are no available alternatives. viii. Inferred from positive trial data in psoriatic arthritis.[172–174] ix. Inferred from negative trial data in axial spondyloarthritis.[175] x. Upadacitinib may represent a therapeutic alternative in patients with prior anti-tumour necrosis factor [TNF] failure, intolerance, or contraindications. This is based upon post-hoc analysis of randomised controlled trial [RCT] data showing a significant benefit over placebo across a range of relevant fistula endpoints[176]. xi. Inferred from positive trial data in psoriatic arthritis.[177] xii. Inferred from positive trial data in axial spondyloarthritis.[178] xiii. EMA recommend reserving for when no alternatives are available in patients over the age of 65.

partial response before, without adverse side effects. When ACT is aimed at controlling extraintestinal manifestations or immune-medicated diseases, the preferred combination should be based on the specific clinical setting, including any prior evidence of partial response to a particular agent, availability of evidence suggesting potential efficacy from other relevant indications, and safety considerations. Whereas targeting more than one mechanistic pathway in patients naïve to advanced therapies may make sense, particularly if the underlying biology is better characterised, there is currently no evidence to support ACT upfront, even in patients judged to be at high risk of disease progression or complications.

Evidence on ACT in IBD is mostly retrospective with limited quality, and has recently been gathered in two systematic reviews with meta-analyses that include studies reporting on outcomes in both UC and CD.[179,181] Table 1 summarises the single RCT and the cohorts that have reported outcomes with ACT specifically for CD patients. The use of ACT for CD was the focus of the phase 4 single-arm EXPLORER trial [NCT02764762], which was designed to investigate the safety and efficacy of the combination of vedolizumab,

Table 1 Available evidence for advanced combined therapy in CD.

Author [year]	Study design	Population	Outcomes	Combination [*n* exposed]	Safety	Efficacy	Notes
Sands [2007][182]	Randomised controlled trial	79 adult patients with active CD despite infliximab	Safety, tolerability clinical remission, quality of life; CRP	Infliximab + natalizumab [52] Infliximab + placebo [27]	AEs reported in 48/52 vs 17/27 SAEs reported in 1/52 vs 1/27	CDAI decrease [38 vs 3.5 points; $p = 0.085$]	Steroids, antibiotics, and immunomodulators allowed
Yang [2020][183]	Retrospective cohort	22 adult patients with refractory CD [with total of 24 different ACT exposures]	Endoscopic improvement Endoscopic remission, clinical response, clinical remission, CRP	Vedolizumab + ustekinumab [8] Vedolizumab + anti-TNF [13] Ustekinumab + anti-TNF [3]	AEs in 3/24 trials [13%]	Endoscopic improvement [43%] Endoscopic remission [26%] Clinical response [50%] Clinical remission [41%] Steroid-free clinical remission [36%] Significant CRP decline [17 to 9 mg/dL, $p = 0.02$]	Assessment at 32 weeks
Lee [2020][184]	Retrospective cohort	19 adult patients with CD	Clinical response Clinical remission Endoscopic response Endoscopic remission Biochemical remission AEs SAEs	Tofacitinib + ustekinumab [11/19] Tofacitinib + vedolizumab [7/19] Tofacitinib + certolizumab [1/19]	0/19 SAEs 7/19 AEs	8/19 clinical response 6/19 clinical remission 2/19 endoscopic response 2/19 endoscopic remission 3/19 biochemical remission	3/19 patients added the second treatment for pyoderma gangrenosum 16/19 added the second treatment for CD Assessment between Weeks 30 and 36 Steroids and methotrexate allowed
Colombel [2022][185] Open-label clinical trial Interim analysis	55 biologic-naïve adult patients with moderate-to- severe newly diagnosed CD [prior 24 months] at high risk of complications	Endoscopic remission Clinical remission AEs SAEs	Vedolizumab + adalimumab + methotrexate	48/55 AEs 6/55 SAEs	19/55 endoscopic remission 34/55 clinical remission	Assessment at Week 26	

CDAI, Crohn's disease activity index; CRP, C-reactive protein; SAE, severe adverse event.

adalimumab, and methotrexate in patients newly diagnosed with CD with the presence of features predictive of an increased risk of disease complications. There was no comparator arm, although post-hoc Bayesian analysis suggested a high degree of probability that the combination treatment was more effective than benchmark estimates for the efficacy of adalimumab or vedolizumab monotherapy.[185] Ongoing RCTs of ACT, including a trial of guselkumab with golimumab [NCT05242471], may improve understanding of potential efficacy and safety. Cost-effectiveness analyses will be important prior to any more widespread adoption of these approaches.

3.10. Optimisation of the delivery of care in the treatment of CD

3.10.1. The role of the MDT and governance around decision making in the treatment of CD

Practice Point 5. We recommend involvement of an MDT in clinical management and joint decision making in managing care of patients with CD. [Consensus: 97%]

Health care organisations and clinicians should be continuously improving and safeguarding the quality of care. Shared decision making [SDM] practised by MDT members is fundamental to attaining this goal and delivering patient-centred care. Data from two systematic reviews [62 and 28 manuscripts, respectively, number of patients not stated] suggested that using an integrated care model and MDT consisting of health care professionals across specialties [eg, gastroenterologists, IBD nurses, colorectal surgeons, psychologists or counsellors, dietitians, radiologists, pathologists, pharmacists] achieved the most effective management of IBD. This was reflected in reduced hospital admissions and IBD-related surgery and comorbidities, with associated reductions in direct and indirect costs of care compared with a more traditional patient-physician model.[186,187] A cross-sectional survey conducted in the USA, with 306 patients with autoimmune conditions including 102 with IBD, examined the impact of SDM for biologic treatment selection and treatment outcomes.[188] Among the SDM participants, the mean number of treatments discussed with the physician was significantly higher than for the non-SDM group [2.8 vs 2.2, $p < 0.05$], more SDM participants reported thinking about the impact of a medication on the future than non-SDM participants [83.2% vs 72.6%, $p < 0.05$], and more SDM patients self-reported a likelihood of adherence to treatment compared with patients managed without SDM [$p = 0.001$].

Measuring the impact of changes in systems of care delivery can be challenging, and data are largely limited to observational studies. A Norwegian cross-sectional survey examined health-related QoL outcomes among patients living with IBD who received solely physician-delivered care [$n = 164$], compared with those receiving care delivered by a team including physicians and IBD nurses [$n = 140$]. QoL outcomes were significantly better in the group receiving MDT care, although the magnitude of difference fell short of an a priori-defined threshold of clinical significance.[189] A Belgian study [$n = 1313$ patients] reported that IBD nurse involvement in starting immunosuppressive therapy, follow-up care, flare management, and providing disease information and psychosocial support to patients, systematically increased contact with patients, resulting in avoidance of emergency room and unscheduled outpatient visits.[190] In the UK, care of CD patients in a centre with an active MDT was associated with reduced excess exposure to corticosteroids.[191]

In recent years, dietitians have assumed a prominent role in the treatment of patients with CD, specifically in guiding the implementation of therapeutic diets, such as EEN, conducting assessments of nutritional status, and enhancing overall quality of care.[153] A real-world prospective study from Israel reported favourable outcomes among a cohort of newly diagnosed CD patients [$n = 76$] treated by MDT, including dietitian input.[192] Other innovations in care delivery include increased use of remote monitoring and telemedicine. Two studies in paediatric populations[193,194] revealed that telemedicine can support improved access to IBD services and improved attendance at follow-up appointments. An RCT of 909 patients in The Netherlands found that use of telemedicine to support patient self-management improved outcomes for patients with IBD compared with standard care, including reductions in the number of outpatient visits and number of hospital admissions.[195] In a similar manner, a retrospective multicentre cohort study revealed increased treatment success among 69 patients managed through a virtual clinic while undergoing dose optimisation of anti-TNF therapy for CD, when compared with 80 patients receiving standard outpatient care.[196]

It is recognised that not all centres have health care professionals across all the different MDT specialties. Nonetheless, efforts should be made to build an MDT with the widest range of specialties available. More research is needed on the role of different MDT members and different care delivery models to understand long-term value for patients. In particular, better understanding of cost-effectiveness may help manage funding for implementation.

3.10.2. The role of 'treat-to-target' and early treatment in the management of CD

Practice Point 6. We recommend a tight control and treat-to-target approach for management of patients with CD. [Consensus: 97%]

'Treat-to-target' describes an approach where a treatment goal is set and agreed upon following discussions between individual patients and treating clinicians, with one or more targets specified to measure progress towards that goal.[197] Following initiation of any therapy, these targets are then assessed, with modification of treatment considered if a target is missed.[198] Significant improvement in medium- and long-term outcomes has been reported for patients when targeting more objective£ measures of inflammation (such as normalisation of faecal calprotectin or serum C-reactive protein [CRP]) when compared with subjective measures [such as clinical symptoms alone].[199,200] Moreover, early combined immunosuppression followed by a treat-to-target approach is associated with reduced occurrence of surgery, reduced hospital admissions, and lower risk of serious disease-related complications.[201] Notably, the majority of evidence to date for a treat-to-target approach has been with anti-TNF therapy. Indeed, a treat-to-target strategy trial to guide ustekinumab dose escalation failed to show a benefit of more aggressive dose escalation driven by early endoscopy and more frequent clinical monitoring, although arguably the intensity of clinical monitoring was not substantially different between

treatment arms.[202] There is still debate about what should be the optimal treatment target[s] in CD. There is also a lack of evidence to reassure patients and clinicians contemplating a change in treatment in the event of a partial response that falls short of meeting a target and where dose optimisation has already occurred. Unlike in clinical trials, treatment targets should be individualised where possible and should be agreed upon as part of a SDM process between clinicians and patients. In addition, targets and goals of treatment should be regarded as dynamic and a decision can be made to change treatment targets over time.

Regardless of the monitoring strategy chosen, it is increasingly clear that early effective treatment should be a focus of management in CD, with emphasis on avoidance of diagnostic delays and any delays in initiation of treatment. Chronic, untreated inflammation, even if asymptomatic, ultimately results in poor outcomes, whiereas early control of inflammatory burden reduces the risk of long-term complications of disease.[199,203] Typically, effectiveness of the drugs discussed in these guidelines appears to be greater when used earlier in disease course.[204] Consequently, clinicians should work to ensure rapid access for patients with suspected CD to appropriate diagnostic tests and clinical expertise, with urgent consideration of early treatment. Previous trials have hinted at the effectiveness of such an approach,[134,205] and the recently reported UK PROFILE trial provides important evidence in favour of early aggressive treatment of CD. PROFILE enrolled patients with moderate-to-severe CD at a median of just 12 days after diagnosis.[7] Patients received initial corticosteroid therapy and were randomised. A total of 193 patients received 'accelerated step-up' care, with steroid taper alongside protocol-defined follow-up, further corticosteroids and initiation of immunomodulator therapy in the event of a flare, and then anti-TNF therapy in the event of a further flare. In the other arm, 193 patients received 'top-down' combination therapy with IV infliximab and immunomodulator therapy and could taper the initial corticosteroid course more rapidly. The primary endpoint of sustained steroid- and surgery-free remission to Week 48 was more frequent in the 'top-down' than in the 'accelerated step-up' arm [79% vs 15%, $p < 0.001$]. Endoscopic remission was more frequent in the 'top-down' arm [67% vs 44%, $p < 0.001$], with similarly positive data for QoL endpoints, avoidance of admissions, and reduction in CD-related surgery.

When patients are started on any treatment, clear definitions should be set as to how and when treatment success will be defined and assessed, with a focus on prompt actions in the event of treatment non-response. Notably, for these guidelines the consensus group chose to remove from all recommendations a need for patients to have 'failed', proven intolerant to, or have contraindications to 'conventional' therapy. This decision reflects a growing unease with the term 'conventional therapy', as many of the treatments discussed in these guidelines can now be regarded as forming an established part of the 'conventional' management of CD. Therefore, whereas these guidelines have appraised the available evidence for a range of treatments used in the management of CD, it remains for local payers to consider the health economic impacts, the disease burden, and the impact on long-term outcomes, of mandating treatment cycles with treatments receiving only a weak recommendation in these guidelines.

Funding

This project was initiated, funded, and supported by ECCO.

Conflict of Interest

ECCO has diligently maintained a disclosure policy of potential conflicts of interests [CoI]. The conflict-of-interest declaration is based on a form used by the International Committee of Medical Journal Editors [ICMJE]. The CoI disclosures are not only stored at the ECCO Office and the editorial office of JCC, but are also open to public scrutiny on the ECCO website [https://www.ecco-ibd.eu/about-ecco/ecco-disclosures.html], providing a comprehensive overview of potential conflicts of interest of the authors.

Acknowledgements

We would like to thank and acknowledge the ECCO Office for logistical and coordination support: Dr Fadi Ifram for project management, Dr Paul Freudenberger for the literature search, and Torsten Karge for support with informatics and the online Guidelines platform. We gratefully thank the EFCCA patient representatives who proactively collaborated in the development of these Guidelines: Bastien Corsat, Xavier Donnet, Evelyn Gross, Janek Kapper, Lucie Lastikova, and Antonio Valdivia. We would also like to thank Ibrahim Ethem Gecim for his work in the abstract screening process. We would like to thank and acknowledge the ECCO National Representatives and additional reviewers, who acted as external reviewers and provided suggestions on the recommendations and supporting text to this document: Pascal Juillerat, Allesandra Soriano, Mark Samaan, Tiago Cúrdia Gonçalves, Edoardo Savarino, Federica Furfaro, Davide Giuseppe Ribaldone, Gulustan Babayeva-Sadiqova, Aurelien Amiot, Gianmichele Meucci, Iago Rodríguez Lago, Mathieu Uzzan, Gerassimos Mantzaris, Beatriz Gros Alcalde, Vito Annese, Eduard Brunet Mas, Maria Jose Garcia, Eirini Zach, John Marshall, Carla Felice, Maha Maher, Paul Pollack, Andreas Blesl, Negreanu Lucian, Ferdinando D'Amico, Dimitrios Karagiannis, Patrick Allen, Oliver Bachmann, Imerio Angriman, Anna Kagramanova, Dahham Alsoud, Natália Queiroz, Usha Chauhan, Petra Golovics, Chen Sarbagili, Lorenzo Bertani, Ulf Helwig, Clas-Göran af Björkesten, Ante Bogut, Anthony Buisson, Ignacio Catalan-Serra, Aslı Çifcibaşı Örmeci, Marco Daperno, Mihai Mircea Diculescu, Dana Duricová, Piotr Eder, Magdalena Gawron-Kiszka, Ayal Hirsch, Ondrej Hradsky, Hendrik Laja, Sara Onali, Samuel Raimundo Fernandes, Christian Philipp Selinger, Helena Tavares de Sousa, Svetlana Turcan, Sophie Vieujean, and Yamile Zabana.

Disclaimer

The ECCO Guidelines are targeted at health care professionals only and are based on an international consensus process. This process includes intensive literature research as explained in the methodology section, and may not reflect subsequent scientific developments, if any, until the next Guidelines update is prepared. Readers of the Guidelines acknowledge that research about medical and health issues is constantly evolving and diagnoses, treatments, and dose schedules for medications are being revised continually. Therefore, the European Crohn´s and Colitis Organisation [ECCO] encourages all readers to

also consult the most up-to-date published product information and data sheets provided by the manufacturers, as well as the most recent codes of conduct and safety regulations. Any treatment decisions are to be made at the sole discretion and within the exclusive responsibility of the individual clinician and should not be based exclusively on the content of the ECCO Guidelines. The European Crohn´s and Colitis Organisation [ECCO] and/or any of its staff members and/or any consensus contributor may not be held liable for any information published in good faith in the ECCO Consensus Guidelines. ECCO makes no representations or warranties, express or implied, as to the accuracy or completeness of the whole or any part of the Guidelines. ECCO does not accept, and expressly disclaims, responsibility for any liability, loss, or risk that may be claimed or incurred as a consequence of the use or application of the whole or any part of the Guidelines. When the Guidelines mention trade names, commercial products, or organisations, this does not constitute any endorsement by ECCO and/or any consensus contributor.

Data Availability

Summary of findings tables [SOFs] produced for GRADE meta-analyses are as Supplementary material at *ECCO-JCC*.

Supplementary Data

Supplementarydata are available online at *ECCO-JCC* online.

References

1. Torres J, Mehandru S, Colombel JF, Peyrin-Biroulet L. Crohn's disease. *Lancet* 2017;**389**:1741–55.
2. Keyashian K, Dehghan M, Sceats L, Kin C, Limketkai BN, Park KT. Comparative incidence of inflammatory bowel disease in different age groups in the United States. *Inflamm Bowel Dis* 2019;**25**:1983–9.
3. Jones GR, Lyons M, Plevris N, *et al*. IBD prevalence in Lothian, Scotland, derived by capture-recapture methodology. *Gut* 2019;**68**:1953–60.
4. Torres J, Bonovas S, Doherty G, *et al*. ECCO guidelines on therapeutics in Crohn's disease: medical treatment. *J Crohns Colitis* 2020;**14**:4–22.
5. Adamina M, Bonovas S, Raine T, *et al*. ECCO guidelines on therapeutics in Crohn's disease: surgical treatment. *J Crohns Colitis* 2020;**14**:155–68.
6. Atkins D, Eccles M, Flottorp S, *et al*.; GRADE Working Group. Systems for grading the quality of evidence and the strength of recommendations I: critical appraisal of existing approaches. The GRADE Working Group. *BMC Health Serv Res* 2004;**4**:38.
7. Noor NM, Lee JC, Bond S, *et al*. A biomarker-stratified comparison of top-down versus accelerated step-up treatment strategies for patients with newly diagnosed Crohn's disease [PROFILE]: a multicentre, open-label randomised controlled trial. *Lancet Gastroenterol Hepatol* 2024;**9**:415–27.
8. Raine T, Danese S. Breaking through the therapeutic ceiling: what will it take? *Gastroenterology* 2022;**162**:1507–11.
9. Torres J, Chaparro M, Julsgaard M, *et al*. European Crohn's and Colitis guidelines on sexuality, fertility, pregnancy, and lactation. *J Crohns Colitis* 2023;**17**:1–27.
10. Ford AC, Kane SV, Khan KJ, *et al*. Efficacy of 5-aminosalicylates in Crohn's disease: systematic review and meta-analysis. *Am J Gastroenterol* 2011;**106**:617–29.
11. Rasmussen S, Lauritsen K, Tage-Jensen U, *et al*. 5-aminosalicylic acid in the treatment of Crohn's disease: a 16-week double-blind, placebo-controlled, multicentre study with Pentasa®. *Scand J Gastroenterol* 1987;**22**:877–83.
12. Singleton JW, Hanauer SB, Gitnick GL, *et al*. Mesalamine capsules for the treatment of active Crohn's disease: results of a 16-week trial. *Gastroenterology* 1993;**104**:1293–301.
13. Tremaine WJ, Schroeder KW, Harrison JM, Zinsmeister AR. A randomized, double-blind, placebo-controlled trial of the oral mesalamine [5-ASA] preparation, Asacol, in the treatment of symptomatic Crohn's colitis and ileocolitis. *J Clin Gastroenterol* 1994;**19**:278–82.
14. Ferring Pharmaceuticals. *PEACE Study: A Study with Pentasa in Patients with Active Crohn's Disease*. 2012. https://clinicaltrials.gov/study/NCT00862121 Accessed November 2023.
15. Malchow H, Ewe K, Brandes J, *et al*. European Cooperative Crohn's Disease Study [ECCDS]: results of drug treatment. *Gastroenterology* 1984;**86**:249–66.
16. Summers RW, Switz DM, Sessions JT Jr, *et al*. National Cooperative Crohn's Disease Study: results of drug treatment. *Gastroenterology* 1979;**77**:847–69.
17. Lim WC, Wang Y, MacDonald JK, Hanauer S. Aminosalicylates for induction of remission or response in Crohn's disease. *Cochrane Database Syst Rev* 2016;**7**:CD008870.
18. Coward S, Kuenzig ME, Hazlewood G, *et al*. Comparative effectiveness of mesalamine, sulfasalazine, corticosteroids, and budesonide for the induction of remission in Crohn's disease: a Bayesian network meta-analysis. *Inflamm Bowel Dis* 2017;**23**:461–72.
19. Moja L, Danese S, Fiorino G, Del Giovane C, Bonovas S. Systematic review with network meta-analysis: comparative efficacy and safety of budesonide and mesalazine [mesalamine] for Crohn's disease. *Aliment Pharmacol Ther* 2015;**41**:1055–65.
20. Hanauer SB, Strömberg U. Oral Pentasa in the treatment of active Crohn's disease: a meta-analysis of double-blind, placebo-controlled trials. *Clin Gastroenterol Hepatol* 2004;**2**:379–88.
21. Akobeng AK, Zhang D, Gordon M, MacDonald JK. Oral 5-aminosalicylic acid for maintenance of medically-induced remission in Crohn's disease. *Cochrane Database Syst Rev* 2016;**9**:CD003715.
22. Rezaie A, Kuenzig ME, Benchimol EI, *et al*. Budesonide for induction of remission in Crohn's disease. *Cochrane Database Syst Rev* 2015:**CD000296**.
23. Greenberg GR, Feagan BG, Martin F, *et al*. Oral budesonide for active Crohn's disease. *N Engl J Med* 1994;**331**:836–41.
24. Tremaine WJ, Hanauer SB, Katz S, *et al*.; Budesonide CIR United States Study Group. Budesonide CIR capsules [once or twice daily divided-dose] in active Crohn's disease: a randomized placebo-controlled study in the United States. *Am J Gastroenterol* 2002;**97**:1748–54.
25. Suzuki Y, Motoya S, Takazoe M, *et al*. Efficacy and tolerability of oral budesonide in Japanese patients with active Crohn's disease: a multicentre, double-blind, randomized, parallel-group Phase II study. *J Crohns Colitis* 2013;**7**:239–47.
26. Kuenzig ME, Rezaie A, Kaplan GG, *et al*. Budesonide for the induction and maintenance of remission in Crohn's disease: systematic review and meta-analysis for the Cochrane Collaboration. *J Can Assoc Gastroenterol* 2018;**1**:159–73.
27. Thomsen OO, Cortot A, Jewell D, *et al*. A comparison of budesonide and mesalamine for active Crohn's disease. *N Engl J Med* 1998;**339**:370–4.
28. Tromm A, Bunganič I, Tomsová E, *et al*.; International Budenofalk Study Group. Budesonide 9 mg is at least as effective as mesalamine 4.5 g in patients with mildly to moderately active Crohn's disease. *Gastroenterology* 2011;**140**:425–34.e1; quiz e13.
29. Yokoyama T, Ohta A, Motoya S, *et al*. Efficacy and safety of oral budesonide in patients with active Crohn's disease in Japan: a multicenter, double-blind, randomized, parallel-group phase 3 study. *Inflamm Intest Dis* 2018;**2**:154–62.

30. Greenberg GR, Feagan BG, Martin F, *et al*. Oral budesonide as maintenance treatment for Crohn's disease: a placebo-controlled, dose-ranging study. Canadian Inflammatory Bowel Disease Study Group. *Gastroenterology* 1996;**110**:45–51.
31. Benchimol EI, Seow CH, Steinhart AH, Griffiths AM. Traditional corticosteroids for induction of remission in Crohn's disease. *Cochrane Database Syst Rev* 2008;**2008**:CD006792.
32. Singleton JW, Law DH, Kelley ML Jr, Mekhjian HS, Sturdevant RA. National Cooperative Crohn's Disease Study: adverse reactions to study drugs. *Gastroenterology* 1979;**77**:870–82.
33. Dorrington AM, Selinger CP, Parkes GC, Smith M, Pollok RC, Raine T. The historical role and contemporary use of corticosteroids in inflammatory bowel disease. *J Crohns Colitis* 2020;**14**:1316–29.
34. Stuck AE, Minder CE, Frey FJ. Risk of infectious complications in patients taking glucocorticosteroids. *Rev Infect Dis* 1989;**11**:954–63.
35. Lichtenstein GR, Feagan BG, Cohen RD, *et al*. Serious infection and mortality in patients with Crohn's disease: more than 5 years of follow-up in the TREAT registry. *Am J Gastroenterol* 2012;**107**:1409–22.
36. D'Haens G, Reinisch W, Colombel JF, *et al*.; ENCORE investigators. Five-year safety data from ENCORE, a European Observational Safety Registry for adults with Crohn's disease treated with infliximab [Remicade] or conventional therapy. *J Crohns Colitis* 2017;**11**:680–9.
37. Candy S, Wright J, Gerber M, Adams G, Gerig M, Goodman R. A controlled double blind study of azathioprine in the management of Crohn's disease. *Gut* 1995;**37**:674–8.
38. Ewe K, Press AG, Singe CC, *et al*. Azathioprine combined with prednisolone or monotherapy with prednisolone in active Crohn's disease. *Gastroenterology* 1993;**105**:367–72.
39. Klein M, Binder HJ, Mitchell M, Aaronson R, Spiro H. Treatment of Crohn's disease with azathioprine: a controlled evaluation. *Gastroenterology* 1974;**66**:916–22.
40. Present DH, Korelitz BI, Wisch N, Glass JL, Sachar DB, Pasternack BS. Treatment of Crohn's disease with 6-mercaptopurine. A long-term, randomized, double-blind study. *N Engl J Med* 1980;**302**:981–7.
41. Reinisch W, Panes J, Lemann M, *et al*. A multicenter, randomized, double-blind trial of everolimus versus azathioprine and placebo to maintain steroid-induced remission in patients with moderate-to-severe active Crohn's disease. *Am J Gastroenterol* 2008;**103**:2284–92.
42. Rhodes J, Bainton D, Beck P, Campbell H. Controlled trial of azathioprine in Crohn's disease. *Lancet* 1971;**2**:1273–6.
43. Willoughby JM, Beckett J, Kumar PJ, Dawson AM. Controlled trial of azathioprine in Crohn's disease. *Lancet* 1971;**2**:944–7.
44. Chande N, Townsend CM, Parker CE, MacDonald JK. Azathioprine or 6-mercaptopurine for induction of remission in Crohn's disease. *Cochrane Database Syst Rev* 2016;**10**:CD000545.
45. Sahasranaman S, Howard D, Roy S. Clinical pharmacology and pharmacogenetics of thiopurines. *Eur J Clin Pharmacol* 2008;**64**:753–67.
46. Chande N, Patton PH, Tsoulis DJ, Thomas BS, MacDonald JK. Azathioprine or 6-mercaptopurine for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev* 2015;**2015**:CD000067.
47. Relling MV, Schwab M, Whirl-Carrillo M, *et al*. Clinical Pharmacogenetics Implementation Consortium Guideline for Thiopurine Dosing Based on TPMT and NUDT15 Genotypes: 2018 Update. *Clin Pharmacol Ther* 2019;**105**:1095–105.
48. Pratt VM, Cavallari LH, Fulmer ML, *et al*. CYP3A4 and CYP3A5 Genotyping recommendations: a Joint Consensus Recommendation of the Association for Molecular Pathology, Clinical Pharmacogenetics Implementation Consortium, College of American Pathologists, Dutch Pharmacogenetics Working Group of the Royal Dutch Pharmacists Association, European Society for Pharmacogenomics and Personalized Therapy, and Pharmacogenomics Knowledgebase. *J Mol Diagn* 2023;**25**:619–29.
49. Stournaras E, Qian W, Pappas A, *et al*. Thiopurine monotherapy is effective in ulcerative colitis but significantly less so in Crohn's disease: long-term outcomes for 11 928 patients in the UK inflammatory bowel disease bioresource. *Gut* 2021;**70**:677–86.
50. Kirchgesner J, Lemaitre M, Carrat F, Zureik M, Carbonnel F, Dray-Spira R. Risk of serious and opportunistic infections associated with treatment of inflammatory bowel diseases. *Gastroenterology* 2018;**155**:337–46.e10.
51. Gordon H, Biancone L, Fiorino G, *et al*. ECCO guidelines on inflammatory bowel disease and malignancies. *J Crohns Colitis* 2023;**17**:827–54.
52. Chupin A, Perduca V, Meyer A, Bellanger C, Carbonnel F, Dong C. Systematic review with meta-analysis: comparative risk of lymphoma with anti-tumour necrosis factor agents and/or thiopurines in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2020;**52**:1289–97.
53. Colombel JF, Sandborn WJ, Reinisch W, *et al*.; SONIC Study Group. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med* 2010;**362**:1383–95.
54. Feagan BG, Rochon J, Fedorak RN, *et al*. Methotrexate for the treatment of Crohn's disease. The North American Crohn's Study Group Investigators. *N Engl J Med* 1995;**332**:292–7.
55. Oren R, Moshkowitz M, Odes S, *et al*. Methotrexate in chronic active Crohn's disease: a double-blind, randomized, Israeli multicenter trial. *Am J Gastroenterol* 1997;**92**:2203–9.
56. Arora S, Katkov W, Cooley J, *et al*. Methotrexate in Crohn's disease: results of a randomized, double-blind, placebo-controlled trial. *Hepatogastroenterology* 1999;**46**:1724–9.
57. Gordon H, Burisch J, Ellul P, *et al*. ECCO guidelines on extraintestinal manifestations in inflammatory bowel disease. *J Crohns Colitis* 2023;**18**:1–37.
58. Feagan BG, Fedorak RN, Irvine EJ, *et al*. A comparison of methotrexate with placebo for the maintenance of remission in Crohn's disease. North American Crohn's Study Group Investigators. *N Engl J Med* 2000;**342**:1627–32.
59. Kopylov U, Vutcovici M, Kezouh A, Seidman E, Bitton A, Afif W. Risk of lymphoma, colorectal and skin cancer in patients with IBD treated with immunomodulators and biologics: a Quebec Claims Database Study. *Inflamm Bowel Dis* 2015;**21**:1847–53.
60. Long MD, Herfarth HH, Pipkin CA, Porter CQ, Sandler RS, Kappelman MD. Increased risk for non-melanoma skin cancer in patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2010;**8**:268–74.
61. Singh H, Nugent Z, Demers AA, Bernstein CN. Increased risk of nonmelanoma skin cancers among individuals with inflammatory bowel disease. *Gastroenterology* 2011;**141**:1612–20.
62. Patel V, Wang Y, MacDonald JK, McDonald JW, Chande N. Methotrexate for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev* 2014;**2014**:CD006884.
63. Targan SR, Hanauer SB, van Deventer SJ, *et al*. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. *N Engl J Med* 1997;**337**:1029–35.
64. Hanauer SB, Feagan BG, Lichtenstein GR, *et al*.; ACCENT I Study Group. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002;**359**:1541–9.
65. Rutgeerts P, D'Haens G, Targan S, *et al*. Efficacy and safety of retreatment with anti-tumor necrosis factor antibody [infliximab] to maintain remission in Crohn's disease. *Gastroenterology* 1999;**117**:761–9.
66. Rutgeerts P, Diamond RH, Bala M, *et al*. Scheduled maintenance treatment with infliximab is superior to episodic treatment for the healing of mucosal ulceration associated with Crohn's disease. *Gastrointest Endosc* 2006;**63**:433–42; quiz 464.
67. Singh JA, Wells GA, Christensen R, *et al*. Adverse effects of biologics: a network meta-analysis and Cochrane overview. *Cochrane Database Syst Rev* 2011;**2011**:CD008794.
68. Kennedy NA, Heap GA, Green HD, *et al*.; UK Inflammatory Bowel Disease Pharmacogenetics Study Group. Predictors of anti-TNF

treatment failure in anti-TNF-naive patients with active luminal Crohn's disease: a prospective, multicentre, cohort study. *Lancet Gastroenterol Hepatol* 2019;**4**:341–53.
69. Luber RP, Dawson L, Munari S, *et al*. Thiopurines and their optimisation during infliximab induction and maintenance: A retrospective study in Crohn's disease. *J Gastroenterol Hepatol* 2021;**36**:990–8.
70. Targownik LE, Benchimol EI, Bernstein CN, *et al*. Combined biologic and immunomodulatory therapy is superior to monotherapy for decreasing the risk of inflammatory bowel disease-related complications. *J Crohns Colitis* 2020;**14**:1354–63.
71. Kapizioni C, Desoki R, Lam D, *et al*. Biologic therapy for inflammatory bowel disease: Real-world comparative effectiveness and impact of drug sequencing in 13,222 patients within the UK IBD BioResource. *J Crohns Colitis* 2024;**18**:790–800.
72. Rui M, Fei Z, Wang Y, *et al*. Will the inducing and maintaining remission of non-biological agents and biological agents differ for Crohn's disease? The evidence from the network meta-analysis. *Front Med [Lausanne]* 2021;**8**:679258.
73. Colombel JF, Adedokun OJ, Gasink C, *et al*. Combination therapy with infliximab and azathioprine improves infliximab pharmacokinetic features and efficacy: a Post Hoc Analysis. *Clin Gastroenterol Hepatol* 2019;**17**:1525–32.e1.
74. Feagan BG, McDonald JW, Panaccione R, *et al*. Methotrexate in combination with infliximab is no more effective than infliximab alone in patients with Crohn's disease. *Gastroenterology* 2014;**146**:681–8.e1.
75. Schreiber S, Ben-Horin S, Leszczyszyn J, *et al*. Randomized controlled trial: subcutaneous vs intravenous infliximab CT-P13 maintenance in inflammatory bowel disease. *Gastroenterology* 2021;**160**:2340–53.
76. Colombel JF, SB H, Sandborn W, Sands BE, *et al*. CT-P13 SC 3.8. DOP86 Subcutaneous infliximab [CT-P13 SC] as maintenance therapy for Crohn's disease: a phase 3, randomised, placebo-controlled study [LIBERTY-CD]. *J Crohns Colitis* 2023;**17**:i161–2.
77. Smith PJ, Critchley L, Storey D, *et al*. Efficacy and safety of elective switching from intravenous to subcutaneous infliximab [CT-P13]: a multicentre cohort study. *J Crohns Colitis* 2022;**16**:1436–46.
78. D'Haens G, Reinisch W, Schreiber S, *et al*. Subcutaneous infliximab monotherapy versus combination therapy with immunosuppressants in inflammatory bowel disease: a Post Hoc Analysis of a Randomised Clinical Trial. *Clin Drug Investig* 2023;**43**:277–88.
79. Louis E, Resche-Rigon M, Laharie D, *et al*.; GETAID and the SPARE-Biocycle research group. Withdrawal of infliximab or concomitant immunosuppressant therapy in patients with Crohn's disease on combination therapy [SPARE]: a multicentre, open-label, randomised controlled trial. *Lancet Gastroenterol Hepatol* 2023;**8**:215–27.
80. Siegel CA, Marden SM, Persing SM, Larson RJ, Sands BE. Risk of lymphoma associated with combination anti-tumor necrosis factor and immunomodulator therapy for the treatment of Crohn's disease: a meta-analysis. *Clin Gastroenterol Hepatol* 2009;**7**:874–81.
81. Roblin X, Williet N, Boschetti G, *et al*. Addition of azathioprine to the switch of anti-TNF in patients with IBD in clinical relapse with undetectable anti-TNF trough levels and antidrug antibodies: a prospective randomised trial. *Gut* 2020;**69**:1206–12.
82. Chen B, Gao X, Zhong J, *et al*. Efficacy and safety of adalimumab in Chinese patients with moderately to severely active Crohn's disease: results from a randomized trial. *Therap Adv Gastroenterol* 2020;**13**:1756284820938960.
83. Hanauer SB, Sandborn WJ, Rutgeerts P, *et al*. Human anti-tumor necrosis factor monoclonal antibody [adalimumab] in Crohn's disease: the CLASSIC-I trial. *Gastroenterology* 2006;**130**:323–33; quiz 591.
84. Sandborn WJ, Rutgeerts P, Enns R, *et al*. Adalimumab induction therapy for Crohn disease previously treated with infliximab: a randomized trial. *Ann Intern Med* 2007;**146**:829–38.
85. Rutgeerts P, Van Assche G, Sandborn WJ, *et al*; EXTEND Investigators. Adalimumab induces and maintains mucosal healing in patients with Crohn's disease: data from the EXTEND trial. *Gastroenterology* 2012;**142**:1102–11.e2.
86. Abbass M, Cepek J, Parker CE, *et al*. Adalimumab for induction of remission in Crohn's disease. *Cochrane Database Syst Rev* 2019;**2019**:CD012878.
87. Colombel JF, Sandborn WJ, Rutgeerts P, *et al*. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology* 2007;**132**:52–65.
88. Sandborn WJ, Hanauer SB, Rutgeerts P, *et al*. Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. *Gut* 2007;**56**:1232–9.
89. Panaccione R, Colombel JF, Sandborn WJ, *et al*. Adalimumab sustains clinical remission and overall clinical benefit after 2 years of therapy for Crohn's disease. *Aliment Pharmacol Ther* 2010;**31**:1296–309.
90. Matsumoto T, Motoya S, Watanabe K, *et al*.; DIAMOND study group. Adalimumab monotherapy and a combination with azathioprine for Crohn's disease: a prospective, randomized trial. *J Crohns Colitis* 2016;**10**:1259–66.
91. Hisamatsu T, Matsumoto T, Watanabe K, *et al*.; DIAMOND study group . Concerns and side effects of azathioprine during adalimumab induction and maintenance therapy for Japanese patients with Crohn's disease: a subanalysis of a prospective randomised clinical trial [DIAMOND Study]. *J Crohns Colitis* 2019;**13**:1097–104.
92. Watanabe K, Matsumoto T, Hisamatsu T, *et al*.; DIAMOND study group. Clinical and pharmacokinetic factors associated with adalimumab-induced mucosal healing in patients with Crohn's disease. *Clin Gastroenterol Hepatol* 2018;**16**:542–9.e1.
93. Kopylov U, Al-Taweel T, Yaghoobi M, *et al*. Adalimumab monotherapy versus combination therapy with immunomodulators in patients with Crohn's disease: a systematic review and meta-analysis. *J Crohns Colitis* 2014;**8**:1632–41.
94. Colombel JF, Jharap B, Sandborn WJ, *et al*. Effects of concomitant immunomodulators on the pharmacokinetics, efficacy and safety of adalimumab in patients with Crohn's disease or ulcerative colitis who had failed conventional therapy. *Aliment Pharmacol Ther* 2017;**45**:50–62.
95. Sazonovs A, Kennedy NA, Moutsianas L, *et al*.; PANTS Consortium. HLA-DQA1*05 carriage associated with development of anti-drug antibodies to infliximab and adalimumab in patients with Crohn's disease. *Gastroenterology* 2020;**158**:189–99.
96. Sandborn WJ, Schreiber S, Feagan BG, *et al*. Certolizumab pegol for active Crohn's disease: a placebo-controlled, randomized trial. *Clin Gastroenterol Hepatol* 2011;**9**:670–8.e3.
97. Sandborn WJ, Feagan BG, Stoinov S, *et al*.; PRECISE 1 Study Investigators. Certolizumab pegol for the treatment of Crohn's disease. *N Engl J Med* 2007;**357**:228–38.
98. Schreiber S, Rutgeerts P, Fedorak RN, *et al*.; CDP870 Crohn's Disease Study Group. A randomized, placebo-controlled trial of certolizumab pegol [CDP870] for treatment of Crohn's disease. *Gastroenterology* 2005;**129**:807–18.
99. Yamazaki H, So R, Matsuoka K, *et al*. Certolizumab pegol for induction of remission in Crohn's disease. *Cochrane Database Syst Rev* 2019;**8**:CD012893.
100. Schreiber S, Khaliq-Kareemi M, Lawrance IC, *et al*.; PRECISE 2 Study Investigators. Maintenance therapy with certolizumab pegol for Crohn's disease. *N Engl J Med* 2007;**357**:239–50.
101. Papamichael K, Afif W, Drobne D, *et al*.; International Consortium for Therapeutic Drug Monitoring. Therapeutic drug monitoring of biologics in inflammatory bowel disease: unmet needs and future perspectives. *Lancet Gastroenterol Hepatol* 2022;**7**:171–85.
102. D'Haens GR, Sandborn WJ, Loftus EV Jr, *et al*. Higher vs standard adalimumab induction dosing regimens and two maintenance strategies: randomized SERENE CD trial results. *Gastroenterology* 2022;**162**:1876–90.
103. Vande Casteele N, Ferrante M, Van Assche G, *et al*. Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease. *Gastroenterology* 2015;**148**:1320–9.e3.

104. Strik AS, Lowenberg M, Mould DR, *et al*. Efficacy of dashboard driven dosing of infliximab in inflammatory bowel disease patients; a randomized controlled trial. *Scand J Gastroenterol* 2021;**56**:145–54.
105. Syversen SW, Jorgensen KK, Goll GL, *et al*. Effect of therapeutic drug monitoring vs standard therapy during maintenance infliximab therapy on disease control in patients with immune-mediated inflammatory diseases: a randomized clinical trial. *JAMA* 2021;**326**:2375–84.
106. D'Haens G, Vermeire S, Lambrecht G, *et al*.; GETAID. Increasing infliximab dose based on symptoms, biomarkers, and serum drug concentrations does not increase clinical, endoscopic, and corticosteroid-free remission in patients with active luminal Crohn's disease. *Gastroenterology* 2018;**154**:1343–51.e1.
107. Nguyen NH, Solitano V, Vuyyuru SK, *et al*. Proactive therapeutic drug monitoring versus conventional management for inflammatory bowel diseases: a systematic review and meta-analysis. *Gastroenterology* 2022;**163**:937–49.e2.
108. Mancenido Marcos N, Novella Arribas B, Mora Navarro G, Rodriguez Salvanes F, Loeches Belinchon P, Gisbert JP. Efficacy and safety of proactive drug monitoring in inflammatory bowel disease treated with anti-TNF agents: a systematic review and meta-analysis. *Dig Liver Dis* 2024;**56**:421–8.
109. Sethi S, Dias S, Kumar A, Blackwell J, Brookes MJ, Segal JP. Meta-analysis: the efficacy of therapeutic drug monitoring of anti-TNF-therapy in inflammatory bowel disease. *Aliment Pharmacol Ther* 2023;**57**:1362–74.
110. Gisbert JP, Chaparro M. De-escalation of biological treatment in inflammatory bowel disease: a comprehensive review. *J Crohns Colitis* 2023;**18**:642–58. doi:10.1093/ecco-jcc/jjad181
111. Papamichail K, Cheifetz A. Mistakes in therapeutic drug monitoring of biologics in IBD and how to avoid them. *UEG Education* 2023;**23**:12–8.
112. Spencer EA, Stachelski J, Dervieux T, Dubinsky MC. Failure to achieve target drug concentrations during induction and not HLA-DQA1 *05 carriage is associated with antidrug antibody formation in patients with inflammatory bowel disease. *Gastroenterology* 2022;**162**:1746–8.e3.
113. Fuentes-Valenzuela E, Garcia-Alonso FJ, Maroto-Martin C, *et al*. Influence of HLADQA1*05 genotype in adults with inflammatory bowel disease and anti-TNF treatment with proactive therapeutic drug monitoring: a retrospective cohort study. *Inflamm Bowel Dis* 2023;**29**:1586–93.
114. Assa A, Matar M, Turner D, *et al*. Proactive monitoring of adalimumab trough concentration associated with increased clinical remission in children with Crohn's disease compared with reactive monitoring. *Gastroenterology* 2019;**157**:985–96.e2.
115. Kang B, Moon J, Lee Y, *et al*. DOP83 Proactive dosing is superior to clinically based dosing in terms of endoscopic healing in paediatric patients with Crohn's disease receiving maintenance infliximab: a randomised controlled trial. *J Crohns Colitis* 2023;**17**:i159.
116. Fine S, Papamichael K, Cheifetz AS. Etiology and management of lack or loss of response to anti-tumor necrosis factor therapy in patients with inflammatory bowel disease. *Gastroenterol Hepatol [N Y]* 2019;**15**:656–65.
117. Marquez-Megias S, Nalda-Molina R, Sanz-Valero J, *et al*. Cost-effectiveness of therapeutic drug monitoring of anti-TNF therapy in inflammatory bowel disease: a systematic review. *Pharmaceutics* 2022;**14**:1009.
118. Papamichael K, Cheifetz AS. Therapeutic drug monitoring in patients on biologics: lessons from gastroenterology. *Curr Opin Rheumatol* 2020;**32**:371–9.
119. Steenholdt C, Brynskov J, Thomsen OO, *et al*. Individualised therapy is more cost-effective than dose intensification in patients with Crohn's disease who lose response to anti-TNF treatment: a randomised, controlled trial. *Gut* 2014;**63**:919–27.
120. Alsoud D, Vermeire S, Verstockt B. Monitoring vedolizumab and ustekinumab drug levels in patients with inflammatory bowel disease: hype or hope? *Curr Opin Pharmacol* 2020;**55**:17–30.
121. Restellini S, Khanna R, Afif W. Therapeutic drug monitoring with ustekinumab and vedolizumab in inflammatory bowel disease. *Inflamm Bowel Dis* 2018;**24**:2165–72.
122. MacDonald JK, Nguyen TM, Khanna R, Timmer A. Anti-IL-12/23p40 antibodies for induction of remission in Crohn's disease. *Cochrane Database Syst Rev* 2016;**11**:Cd007572.
123. Sandborn WJ, Gasink C, Gao LL, *et al*.; CERTIFI Study Group. Ustekinumab induction and maintenance therapy in refractory Crohn's disease. *N Engl J Med* 2012;**367**:1519–28.
124. Feagan BG, Sandborn WJ, Gasink C, *et al*.; UNITI–IM-UNITI Study Group. Ustekinumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med* 2016;**375**:1946–60.
125. Rutgeerts P, Gasink C, Chan D, *et al*. Efficacy of ustekinumab in inducing endoscopic healing in patients with Crohn's disease. *Gastroenterology* 2018;**155**:1045–58.
126. Sandborn WJ, Feagan BG, Fedorak RN, *et al*.; Ustekinumab Crohn's Disease Study Group. A randomized trial of Ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with moderate-to-severe Crohn's disease. *Gastroenterology* 2008;**135**:1130–41.
127. Li K, Friedman JR, Chan D, *et al*. Effects of ustekinumab on histologic disease activity in patients with Crohn's disease. *Gastroenterology* 2019;**157**:1019–31.e7.
128. Sandborn WJ, D'Haens GR, Reinisch W, *et al*. Guselkumab for the treatment of Crohn's disease: induction results from the Phase 2 GALAXI-1 Study. *Gastroenterology* 2022;**162**:1650–64.e8.
129. Sands BE, Han C, Gasink C, *et al*. The effects of ustekinumab on health-related quality of life in patients with moderate to severe Crohn's disease. *J Crohns Colitis* 2018;**12**:883–95.
130. Sandborn WJ, Feagan BG, Danese S, *et al*. Safety of ustekinumab in inflammatory bowel disease: pooled safety analysis of results from phase 2/3 studies. *Inflamm Bowel Dis* 2021;**27**:994–1007.
131. Hanauer SB, Sandborn WJ, Feagan BG, *et al*. IM-UNITI: three-year efficacy, safety, and immunogenicity of ustekinumab treatment of Crohn's disease. *J Crohns Colitis* 2020;**14**:23–32.
132. Rubín de Célix C, Chaparro M, Gisbert JP. Real-world evidence of the effectiveness and safety of ustekinumab for the treatment of Crohn's disease: systematic review and meta-analysis of observational studies. *J Clin Med* 2022;**11**:4202.
133. Sandborn W, Sands B, Colombel JF, *et al*. Efficacy of ustekinumab in Crohn's disease at maintenence Week 56: IM-UNITI study. *J Crohns Colitis* 2019;**13**:S274.
134. 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.
135. 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.
136. Ferrante M, Panaccione R, Baert F, *et al*. Risankizumab as maintenance therapy for moderately to severely active Crohn's disease: results from the multicentre, randomised, double-blind, placebo-controlled, withdrawal phase 3 FORTIFY maintenance trial. *Lancet* 2022;**399**:2031–46.
137. Ferrante M, Irving PM, Abreu MT, *et al*. Maintenance risankizumab sustains induction response in patients with Crohn's disease in a randomised phase 3 trial. *J Crohns Colitis* 2023;**18**:416–23.
138. Sands BE, Van Assche G, Tudor D, Akhundova-Unadkat G, Curtis RI, Tan T. Vedolizumab in combination with corticosteroids for induction therapy in Crohn's disease: a Post Hoc analysis of GEMINI 2 and 3. *Inflamm Bowel Dis* 2019;**25**:1375–82.
139. Sandborn WJ, Feagan BG, Rutgeerts P, *et al*.; GEMINI 2 Study Group. Vedolizumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med* 2013;**369**:711–21.
140. Feagan BG, Greenberg GR, Wild G, *et al*. Treatment of active Crohn's disease with MLN0002, a humanized antibody to the

alpha4beta7 integrin. *Clin Gastroenterol Hepatol* 2008;**6**:1370–7.
141. Sands BE, Feagan BG, Rutgeerts P, *et al*. Effects of vedolizumab induction therapy for patients with Crohn's disease in whom tumor necrosis factor antagonist treatment failed. *Gastroenterology* 2014;**147**:618–27.e3.
142. Watanabe K, Motoya S, Ogata H, *et al*. Effects of vedolizumab in Japanese patients with Crohn's disease: a prospective, multicenter, randomized, placebo-controlled Phase 3 trial with exploratory analyses. *J Gastroenterol* 2020;**55**:291–306.
143. Macaluso FS, Ventimiglia M, Orlando A. Effectiveness and safety of vedolizumab in inflammatory bowel disease: a comprehensive meta-analysis of observational studies. *J Crohns Colitis* 2023;**17**:1217–27.
144. Vermeire S, D'Haens G, Baert F, *et al*. Efficacy and safety of subcutaneous vedolizumab in patients with moderately to severely active Crohn's disease: results from the vISIBLE 2 Randomised Trial. *J Crohns Colitis* 2022;**16**:27–38.
145. Danese S, Sandborn WJ, Colombel JF, *et al*. Endoscopic, radiologic, and histologic healing with vedolizumab in patients with active Crohn's disease. *Gastroenterology* 2019;**157**:1007–18.e7.
146. Loftus EV, Feagan BG, Panaccione R, *et al*. Long-term safety of vedolizumab for inflammatory bowel disease. *Aliment Pharmacol Ther* 2020;**52**:1353–65.
147. Loftus EV Jr, Panés J, Lacerda AP, *et al*. Upadacitinib induction and maintenance therapy for Crohn's disease. *N Engl J Med* 2023;**388**:1966–80.
148. Loftus EV Jr, Panes J, Lacerda AP, *et al*. Upadacitinib induction and maintenance therapy for Crohn's disease. *N Engl J Med* 2023;**388**:1966–80.
149. van Rheenen PF, Aloi M, Assa A, *et al*. The medical management of paediatric Crohn's Disease: an ECCO-ESPGHAN guideline update. *J Crohns Colitis* 2020;**15**:171–94.
150. Narula N, Dhillon A, Zhang D, Sherlock ME, Tondeur M, Zachos M. Enteral nutritional therapy for induction of remission in Crohn's disease. *Cochrane Database Syst Rev* 2018;**4**:CD000542.
151. Yang Q, Gao X, Chen H, *et al*. Efficacy of exclusive enteral nutrition in complicated Crohn's disease. *Scand J Gastroenterol* 2017;**52**:995–1001.
152. Adamina M, Gerasimidis K, Sigall-Boneh R, *et al*. Perioperative dietary therapy in inflammatory bowel disease. *J Crohns Colitis* 2020;**14**:431–44.
153. Fitzpatrick JA, Melton SL, Yao CK, Gibson PR, Halmos EP. Dietary management of adults with IBD: the emerging role of dietary therapy. *Nat Rev Gastroenterol Hepatol* 2022;**19**:652–69.
154. Limketkai BN G-BG, Parian AM, Noorian S, *et al*. Dietary interventions for the treatment of inflammatory bowel diseases: an updated systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2023;**21**:2508–25.
155. Szczubelek M, Pomorska K, Korolczyk-Kowalczyk M, Lewandowski K, Kaniewska M, Rydzewska G. Effectiveness of Crohn's disease exclusion diet for induction of remission in Crohn's disease adult patients. *Nutrients* 2021;**13**:4112.
156. Fliss-Isakov N, Aviv Cohen N, Bromberg A, *et al*. Crohn's disease exclusion diet for the treatment of Crohn's disease: real-world experience from a tertiary center. *J Clin Med* 2023;**12**:5428.
157. Yanai H, Levine A, Hirsch A, *et al*. The Crohn's disease exclusion diet for induction and maintenance of remission in adults with mild-to-moderate Crohn's disease [CDED-AD]: an open-label, pilot, randomised trial. *Lancet Gastroenterol Hepatol* 2022;**7**:49–59.
158. Bischoff SC, Bager P, Escher J, *et al*. ESPEN guideline on Clinical Nutrition in inflammatory bowel disease. *Clin Nutr* 2023;**42**:352–79.
159. Lewis JD, Sandler RS, Brotherton C, *et al*.; DINE-CD Study Group. A randomized trial comparing the specific carbohydrate diet to a Mediterranean diet in adults with Crohn's disease. *Gastroenterology* 2021;**161**:837–52.e9.
160. Peter I, Maldonado-Contreras A, Eisele C, *et al*. A dietary intervention to improve the microbiome composition of pregnant women with Crohn's disease and their offspring: The MELODY [Modulating Early Life Microbiome through Dietary Intervention in Pregnancy] trial design. *Contemp Clin Trials Commun* 2020;**18**:100573.
161. Rojas Correa M, Estremera L, Yap Y, *et al*. DietaAnti-Inflamatoria or DAIN: a Crohn's disease management strategy tailored for Puerto Ricans. *Contemp Clin Trials Commun* 2023;**34**:101162.
162. Olendzki B. An anti-inflammatory diet as treatment for IBD. *Nutr J* 2014;**13**:5.
163. Svolos V, Hansen R, Nichols B, *et al*. Treatment of active Crohn's disease with an ordinary food-based diet that replicates exclusive enteral nutrition. *Gastroenterology* 2019;**156**:1354–67.e6.
164. Cox SR, Lindsay JO, Fromentin S, *et al*. Effects of low FODMAP diet on symptoms, fecal microbiome, and markers of inflammation in patients with quiescent inflammatory bowel disease in a randomized trial. *Gastroenterology* 2020;**158**:176–88.e7.
165. Yang H, Feng R, Li T, *et al*. Systematic review with meta-analysis of partial enteral nutrition for the maintenance of remission in Crohn's disease. *Nutr Res* 2020;**81**:7–18.
166. Nguyen DL, Palmer LB, Nguyen ET, McClave SA, Martindale RG, Bechtold ML. Specialized enteral nutrition therapy in Crohn's disease patients on maintenance infliximab therapy: a meta-analysis. *Therap Adv Gastroenterol* 2015;**8**:168–75.
167. *Study Comparing Intravenous [IV]/Subcutaneous [SC] Risankizumab to IV/SC Ustekinumab to Assess Change in Crohn's Disease Activity Index [CDAI] in Adult Participants With Moderate to Severe Crohn's Disease [CD] [SEQUENCE]*. 2023. https://classic.clinicaltrials.gov/ct2/show/NCT04524611 Accessed March 2024.
168. Thomas H. UEG Week 2023. *Lancet Gastroenterol Hepatol*. 2023;**8**:1076.
169. Barberio B, Gracie DJ, Black CJ, Ford AC. Efficacy of biological therapies and small molecules in induction and maintenance of remission in luminal Crohn's disease: systematic review and network meta-analysis. *Gut* 2023;**72**:264–74.
170. Singh S, Murad MH, Fumery M, *et al*. Comparative efficacy and safety of biologic therapies for moderate-to-severe Crohn's disease: a systematic review and network meta-analysis. *Lancet Gastroenterol Hepatol* 2021;**6**:1002–14.
171. Wu G, Yang Y, Liu M, Wang Y, Guo Q. Systematic review and network meta-analysis: comparative efficacy and safety of biosimilars, biologics and JAK1 inhibitors for active Crohn disease. *Front Pharmacol* 2021;**12**:655865.
172. Kristensen LE, Keiserman M, Papp K, *et al*. Efficacy and safety of risankizumab for active psoriatic arthritis: 52-week results from the KEEPsAKE 1 study. *Rheumatology [Oxford]* 2023;**62**:2113–21.
173. Ostor A, Van den Bosch F, Papp K, *et al*. Efficacy and safety of risankizumab for active psoriatic arthritis: 52-week results from the KEEPsAKE 2 study. *Rheumatology [Oxford]* 2023;**62**:2122–9.
174. Kristensen LE, Keiserman M, Papp K, *et al*. Efficacy and safety of risankizumab for active psoriatic arthritis: 24-week results from the randomised, double-blind, phase 3 KEEPsAKE 1 trial. *Ann Rheum Dis* 2022;**81**:225–31.
175. Baeten D, Ostergaard M, Wei JC, *et al*. Risankizumab, an IL-23 inhibitor, for ankylosing spondylitis: results of a randomised, double-blind, placebo-controlled, proof-of-concept, dose-finding phase 2 study. *Ann Rheum Dis* 2018;**77**:1295–302.
176. Colombel JF, Irving P, Rieder F, *et al*. P491 Efficacy and safety of upadacitinib for the treatment of fistulas and fissures in patients with Crohn's disease. *J Crohns Colitis* 2023;**17**:i620–3. doi:10.1093/ecco-jcc/jjac190.0621
177. Mease P, Setty A, Papp K, *et al*. Upadacitinib in patients with psoriatic arthritis and inadequate response to biologics: 3-year results from the open-label extension of the randomised controlled phase 3 SELECT-PsA 2 study. *Clin Exp Rheumatol* 2023;**41**:2286–97.
178. Deodhar A, Van den Bosch F, Poddubnyy D, *et al*. Upadacitinib for the treatment of active non-radiographic axial spondyloarthritis

[SELECT-AXIS 2]: a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2022;**400**:369–79.
179. Ahmed W, Galati J, Kumar A, *et al*. Dual biologic or small molecule therapy for treatment of inflammatory bowel disease: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2022;**20**:e361–79.
180. Raine T, Verstockt B, Kopylov U, *et al*. ECCO topical review: refractory inflammatory bowel disease. *J Crohns Colitis* 2021;**15**:1605–20.
181. Alayo QA, Fenster M, Altayar O, *et al*. Systematic review with meta-analysis: safety and effectiveness of combining biologics and small molecules in inflammatory bowel disease. *Crohns Colitis 360* 2022;**4**:otac002.
182. Sands BE, Kozarek R, Spainhour J, *et al*. Safety and tolerability of concurrent natalizumab treatment for patients with Crohn's disease not in remission while receiving infliximab. *Inflamm Bowel Dis* 2007;**13**:2–11.
183. Yang E, Panaccione N, Whitmire N, *et al*. Efficacy and safety of simultaneous treatment with two biologic medications in refractory Crohn's disease. *Aliment Pharmacol Ther* 2020;**51**:1031–8.
184. Lee SD, Singla A, Harper J, *et al*. Safety and efficacy of tofacitinib in combination with biologic therapy for refractory Crohn's disease. *Inflamm Bowel Dis* 2022;**28**:309–13.
185. Colombel JF, Ungaro RC, Sands BE, *et al*. Vedolizumab, adalimumab, and methotrexate combination therapy in Crohn's disease [EXPLORER]. *Clin Gastroenterol Hepatol* 2023. doi: 10.1016/j.cgh.2023.09.010.
186. Fiorino G, Allocca M, Chaparro M, *et al*. 'Quality of Care' standards in inflammatory bowel disease: a systematic review. *J Crohns Colitis* 2019;**13**:127–37.
187. Schoenfeld R, Nguyen GC, Bernstein CN. Integrated care models: optimising adult ambulatory care in inflammatory bowel disease. *J Can Assoc Gastroenterol* 2020;**3**:44–53.
188. Lofland JH, Johnson PT, Ingham MP, Rosemas SC, White JC, Ellis L. Shared decision-making for biologic treatment of autoimmune disease: influence on adherence, persistence, satisfaction, and health care costs. *Patient Prefer Adherence* 2017;**11**:947–58.
189. Alvestad L, Jelsness-Jørgensen LP, Goll R, *et al*. Health-related quality of life in inflammatory bowel disease: a comparison of patients receiving nurse-led versus conventional follow-up care. *BMC Health Serv Res* 2022;**22**:1602.
190. Coenen S, Weyts E, Vermeire S, *et al*. Effects of introduction of an inflammatory bowel disease nurse position on the quality of delivered care. *Eur J Gastroenterol Hepatol* 2017;**29**:646–50.
191. Selinger CP, Parkes GC, Bassi A, *et al*. Assessment of steroid use as a key performance indicator in inflammatory bowel disease: analysis of data from 2385 UK patients. *Aliment Pharmacol Ther* 2019;**50**:1009–18.
192. Yanai H, Sharar Fischler T, Goren I, *et al*. A real-world prospective cohort study of patients with newly diagnosed Crohn's disease treated by a multidisciplinary team: 1-year outcomes. *Crohns Colitis 360* 2023;**5**:otad064.
193. Carlsen K, Jakobsen C, Houen G, *et al*. Self-managed eHealth disease monitoring in children and adolescents with inflammatory bowel disease: a randomized controlled trial. *Inflamm Bowel Dis* 2017;**23**:357–65.
194. Michel HK, Maltz RM, Boyle B, Donegan A, Dotson JL. Applying telemedicine to multidisciplinary pediatric inflammatory bowel disease care. *Children [Basel]* 2021;**8**:315.
195. de Jong MJ, van der Meulen-de Jong AE, Romberg-Camps MJ, *et al*. Telemedicine for management of inflammatory bowel disease [myIBDcoach]: a pragmatic, multicentre, randomised controlled trial. *Lancet* 2017;**390**:959–68.
196. Srinivasan A, van Langenberg DR, Little RD, Sparrow MP, De Cruz P, Ward MG. A virtual clinic increases anti-TNF dose intensification success via a treat-to-target approach compared with standard outpatient care in Crohn's disease. *Aliment Pharmacol Ther* 2020;**51**:1342–52.
197. Turner D, Ricciuto A, Lewis A, *et al*.; International Organization for the Study of IBD. STRIDE-II: an update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease [STRIDE] Initiative of the International Organization for the Study of IBD [IOIBD]: determining therapeutic goals for treat-to-target strategies in IBD. *Gastroenterology* 2021;**160**:1570–83.
198. Colombel JF, D'Haens G, Lee WJ, Petersson J, Panaccione R. Outcomes and strategies to support a treat-to-target approach in inflammatory bowel disease: a systematic review. *J Crohns Colitis* 2020;**14**:254–66.
199. Colombel JF, Panaccione R, Bossuyt P, *et al*. Effect of tight control management on Crohn's disease [CALM]: a multicentre, randomised, controlled phase 3 trial. *Lancet* 2017;**390**:2779–89.
200. Ungaro RC, Yzet C, Bossuyt P, *et al*. Deep remission at 1 year prevents progression of early Crohn's disease. *Gastroenterology* 2020;**159**:139–47.
201. Khanna R, Bressler B, Levesque BG, *et al*.; REACT Study Investigators. Early combined immunosuppression for the management of Crohn's disease [REACT]: a cluster randomised controlled trial. *Lancet* 2015;**386**:1825–34.
202. Danese S, Vermeire S, D'Haens G, *et al*.; STARDUST study group. Treat to target versus standard of care for patients with Crohn's disease treated with ustekinumab [STARDUST]: an open-label, multicentre, randomised phase 3b trial. *Lancet Gastroenterol Hepatol* 2022;**7**:294–306.
203. Oh EH, Oh K, Han M, *et al*. Early anti-TNF/immunomodulator therapy is associated with better long-term clinical outcomes in Asian patients with Crohn's disease with poor prognostic factors. *PLoS One* 2017;**12**:e0177479.
204. Ben-Horin S, Novack L, Mao R, *et al*. Efficacy of biologic drugs in short-duration versus long-duration inflammatory bowel disease: a systematic review and an individual-patient data meta-analysis of randomized controlled trials. *Gastroenterology* 2022;**162**:482–94.
205. D'Haens G, Baert F, van Assche G, *et al*.; Belgian Inflammatory Bowel Disease Research Group. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. *Lancet* 2008;**371**:660–7.