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ECCO Guideline/Consensus Paper

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3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 1: Diagnosis and Medical Management

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Abstract

This paper is the first in a series of two publications relating to the European Crohn's and Colitis Organisation [ECCO] evidence-based consensus on the diagnosis and management of Crohn's disease and concerns the methodology of the consensus process, and the classification, diagnosis and medical management of active and quiescent Crohn's disease. Surgical management as well as special situations including management of perianal Crohn's disease of this ECCO Consensus are covered in a subsequent second paper [Gionchetti et al JCC 2016].

Key Words: Crohn's disease; biologics; fistulizing disease; Immunosuppressant; perianal disease; steroids; strictureplasty; thiopurine; treatment; vedolizumab

1 Introduction

Crohn's disease [CD] is a life long disease arising from an interaction between genetic and environmental factors. It is observed predominantly in developed countries,[1,2] although the landscape is quickly changing.[3] The precise aetiology is unknown and therefore a causal therapy is not yet available. It is unlikely that the precise pathogenesis of CD will be understood soon,[4,5] and therefore clinicians have to advise patients based on current knowledge.

This Consensus endeavours to address these differences. It is not meant to supersede the guidelines of different countries [such as those from the UK,[6] or Germany[7]], which reach broadly the same conclusions since they are, after all, based on the same evidence. Rather, the aim of the Consensus is to promote a European perspective on the management of CD and its dilemmas.

The Consensus[8] is based in parts on the previous evidence-based CD consensus of European Crohn's and Colitis Organisation [ECCO].[9–11] The strategy to reach agreement involved several steps and follows the standard operating procedures for consensus guidelines of ECCO. An open call for chairs and participants was made [see acknowledgements and www.ecco-ibd]. Participants were selected by the Guidelines' Committee of ECCO [GuiCom] on the basis of their publication record and a personal statement. Six working groups [WGs] were formed: WG 1 on definitions and diagnosis, WG 2 on medical management of acute disease, WG 3 on maintenance treatment, WG 4 on surgical management, WG 5 on fistulizing disease and WG 6 on extraintestinal manifestations and special situations. Participants were asked to answer relevant questions on current practice and areas of controversy related to the diagnosis and management of CD based on their experience as well as evidence from the literature [Delphi procedure].[8] In parallel, the WG members performed a systematic literature search of their topic with the appropriate key words using Medline/PubMed/ISI/Scopus and the Cochrane database, as well as their own files. The evidence level [EL] was graded according to the Oxford Centre for Evidence-Based Medicine,[12] using the 2011 version [table 1.1] [http://www.cebm.net/index.aspx?o=5653]. Provisional guideline statements [with supporting text] were then written by the WG chairs based upon answers to the questionnaire and were circulated among the WG members, prompting discussions and exchange of literature evidence. The proposed statements and the supporting text were submitted to an online platform for online discussion and two online voting procedures among all Consensus participants for the first voting procedure and including all national representatives of ECCO for the second voting procedure. The WGs finally met in Berlin on October 12, 2013 for a face-to-face discussion and to vote and consent on the statements. Consensus was defined as agreement by more than 80% of participants, termed a Consensus Statement and numbered for convenience in the document. During the process of finalizing the manuscripts, new data on vedolizumab for the treatment of CD were presented and published as a full publication and vedolizumab was approved for the treatment of CD by the European Medicines Agency [EMA] and the Food and Drug Administration [FDA]. In order to present an up-to-date consensus statement, medical treatments were revisited and the new evidence with vedolizumab was recognized. The statements were again submitted to the online platform for online discussion and two online voting procedures among all Consensus participants. A complete bibliographic review was performed and updated (up to February 2016) by AD, PG and FG. The final manuscript was written by the WG chairs in conjunction with the WG members and revised for consistency by AD, PG and FG. An update of this current consensus guideline is planned in about 3 years. This document is based on the previous European Consensus on the diagnosis and management of Crohn's Disease of ECCO from 2006[13,14] and 2010.[9–11]

1.1 Definitions

Common agreement has been previously reached about frequently used terms[15] [for details see the previous version of this CD consensus guideline].[9] The arbitrariness of some of these definitions is still recognized,[16] but the Consensus group considers it still useful to agree on a commonly used terminology.

1.1.1 Active disease

For the purposes of this Consensus, clinical disease activity is grouped into mild, moderate and severe. These are no precisely defined entities. Most clinical trials in patients with active CD recruit patients with a Crohn's Disease Activity Index [CDAI][17,18] >220. Remission [see below] is widely accepted as a CDAI <150 and response is increasingly defined as a decrease in CDAI ≥ 100 points.[15]

1.1.2 Remission
The criterion used in the majority of clinical trials when selecting CD patients in clinical remission is a CDAI <150.[19] As CDAI has clear limitations,[20,21] objective data such as C-reactive protein [CRP] <10 mg/l,[22,23] endoscopy,[24] imaging[25–29] and even histology[30] are increasingly being required to define remission, which is an evolving concept.[31–34] In keeping with the views of the International Organisation for the study of Inflammatory Bowel Disease, ECCO believes that studies evaluating the maintenance of remission in CD should last at least 12 months.[24]

1.1.3 Response
Response should be defined by a ΔCDAI ≥100 points,[16] although in some studies, including those initially evaluating the effectiveness of infliximab, a lesser end point of response with a reduction in CDAI ≥70 points[35–37]was used.

1.1.4 Relapse
The term relapse is used to define a flare of symptoms in a patient with established CD who is in clinical remission, either spontaneously or after medical treatment. Relapse should be preferably confirmed by laboratory parameters, imaging, endoscopy or imaging in clinical practice.[16] For the purposes of clinical trials, a CDAI >150 with an increase of more than 70 points has been suggested.[19] A change by 100 points would be more logical if we accept our reponse definition, but no clear consensus is available in the literature.

1.1.5 Early relapse
An arbitrary but clinically relevant period of <3 months after achieving remission with previous therapy defines early relapse. The therapeutic significance needs to be defined.

1.1.6 Pattern of relapse
Relapse may be infrequent [≤1/year], frequent [≥2/year] or continuous [persistent symptoms of active CD without a period of remission]. Although the terms are arbitrary, they are considered clinically relevant. The prognostic significance needs to be determined.

The term 'chronic active disease' has been used in the past to define a patient who is dependent on, refractory to or intolerant of steroids, or who has disease activity despite immunomodulators. Since this term is ambiguous it is best avoided. Instead, arbitrary but more precise definitions are preferred, including steroid-refractory or steroid-dependence.

1.1.7 Steroid-refractory disease
Patients who have active disease despite prednisolone up to 1 mg/kg/day for a period of 4 weeks.

1.1.8 Steroid-dependent disease
Patients who are either

[i] unable to reduce steroids below the equivalent of prednisolone 10 mg/day [or budesonide below 3 mg/day] within 3 months of starting steroids, without recurrent active disease, or
[ii] who have a relapse within 3 months of stopping steroids.

The assessment of steroid-refractoriness or -dependence should be made after careful exclusion of disease-specific complications.

This definition of steroid-dependence requires that the total duration of steroids does not exceed 3 months before a threshold equivalent to prednisolone 10 mg/day is reached. Patients are still considered steroid-dependent if they relapse within 3 months of stopping steroids. Although these limits are arbitrary, they serve as guidance for clinical practice and may be used for uniformity in clinical trials. The aim should be to withdraw steroids completely.

1.1.9 Recurrence
The term recurrence is best used to define the reappearance of lesions after surgical resection [while relapse refers to the reappearance of symptoms, as above].

1.1.10 Morphologic recurrence
This describes the appearance of new CD lesions after complete resection of macroscopic disease, usually in the neo-terminal ileum and/or at the anastomosis, detected by endoscopy, radiology or surgery.[38,39] *Endoscopic recurrence* is currently evaluated and graded according to the criteria of Rutgeerts *et al*. (0: no lesions; 1: fewer than 5 aphthous lesions; 2: more than 5 aphthous lesions with normal mucosa between the lesions, or skip areas of larger lesions, or lesions confined to the ileocolonic anastomotic lining [< 1 cm]; 3: diffuse aphthous ileitis with diffusely inflamed mucosa; 4: diffuse ileal inflammation with larger ulcers, nodules or narrowing. Hyperaemia and oedema alone are not considered as signs of recurrence].[39] Although endoscopy is still the reference investigation, imaging techniques are useful and complementary to endoscopy.[26–28]

1.1.11 Clinical recurrence
The appearance of CD symptoms after complete resection of macroscopic disease, provided [for the purposes of clinical trials] that recurrence of lesions is confirmed.[40] Symptoms suggestive of CD can be caused by motility disturbances or bile malabsorption, which underlines the need for confirmation of inflammatory, penetrating or fibrotic lesions.[41]

1.1.12 Localized disease
Intestinal CD affecting <30 cm in extent. This usually applies to an ileocaecal location [<30 cm ileum ± right colon], but could apply to isolated colonic disease, or conceivably to proximal small intestinal disease.

1.1.13 Extensive CD
Intestinal CD affecting >100 cm in extent whatever the location. This applies to the sum of inflammation in discontinuous segments. While there is clearly a 'grey area' of disease extent [between 30 and 100 cm] and the length is arbitrary, this definition of extensive disease recognizes the greater inflammatory burden and implications for medical and surgical decision-making with this extent of disease.

1.1.15 Alternative therapy
One that is used in place of conventional medicine.

1.1.16 Complementary therapies
Similar treatments used alongside conventional medicine.

2.1 Clinical features of CD

ECCO statement 2A

Symptoms of CD are heterogeneous, but commonly include abdominal pain, weight loss and chronic diarrhoea. These symptoms should raise the suspicion of CD, especially in young patients. Systemic symptoms of malaise, anorexia, or fever are common [EL5]

Chronic diarrhoea is the most common presenting symptom.[41] A decrease in faecal consistency for more than 6 weeks may be adequate to differentiate this from self-limited, infectious diarrhoea.[42] More acute presentations may occur, and acute terminal ileal CD may be mistaken for acute appendicitis. Chronic non-specific symptoms[43] mimicking irritable bowel syndrome [IBS], unexplained anaemia and growth failure in children should also be considered to avoid delayed diagnosis.[44,45] Abdominal pain and weight loss are seen in about 80 and 60%, respectively, of patients before diagnosis.[46] Although IBS is more common than CD, associated systemic symptoms, blood in stools and weight loss, should always trigger further investigations. Blood and/or mucus in the stool may be seen in up to 40–50% of patients with Crohn's colitis, but less frequently than in ulcerative colitis [UC].[47] Patients may present with extraintestinal manifestations of CD[48] before the gastrointestinal symptoms become prominent; abnormalities of the musculoskeletal system are the most common extraintestinal manifestations of irritable bowel disease [IBD].[49] Extraintestinal manifestations are most common when CD affects the colon. Perianal fistulas are present in 4–10% of patients at the time of diagnosis[50,51] and may be the presenting complaint.

2.2 Diagnosis

ECCO statement 2B

A single gold standard for the diagnosis of CD is not available. The diagnosis is confirmed by clinical evaluation and a combination of endoscopic, histological, radiological, and/or biochemical investigations. Genetic or serological testing is currently not recommended for routine diagnosis of CD [EL5]

CD is a heterogeneous entity comprising a variety of complex phenotypes in terms of age of onset, disease location and disease behaviour.[52] As there is no single way to diagnose CD, Lennard-Jones *et al.* have defined macroscopic and microscopic criteria to establish the diagnosis. The macroscopic diagnostic tools include physical examination, endoscopy, radiology and examination of an operative specimen. Microscopic features can be only partly assessed on mucosal biopsy, but more completely assessed on an operative specimen. The diagnosis depends on the finding of discontinuous and often granulomatous intestinal inflammation.[47] The current view is that the diagnosis is established by a non-strictly defined combination of clinical presentation, endoscopic appearance, radiology, histology, surgical findings and serology. This still results in diagnostic obstacles. A change in diagnosis to UC during the first year occurs in about 5% of cases. IBD restricted to the colon that cannot be allocated to CD or UC categories is best termed IBDU and the term indeterminate colitis confined to operative specimens as originally described.[53]

2.2.1 History and examination

ECCO statement 2C

A full history should include detailed questioning about the onset of symptoms, recent travel, food intolerances, medication (including antibiotics and non-steroidal anti-inflammatory drugs), and history of appendectomy [EL5]. Particular attention should be paid to well proven risk factors including smoking, family history, and recent infectious gastroenteritis [EL1]

ECCO statement 2D

Careful questioning about nocturnal symptoms, features of extraintestinal manifestations involving the mouth, skin, eye, or joints, episodes of perianal abscess, or anal fissure is needed. General examination include all the following: general wellbeing, pulse rate, blood pressure, temperature, abdominal tenderness or distension, palpable masses, perineal and oral inspection, digital rectal examination, and measurement of body mass index [EL5]

Smoking and a family history of IBD have been reproduced as risk factors for the onset of CD.[54–56] The apparent increased risk of CD after appendectomy may be due to a diagnostic bias.[54,57] Infectious gastroenteritis is followed by an increased risk [four-fold] of developing CD especially in the following year, although the absolute risk is low.[58,59] Frequent use of non-steroidal anti-inflammatory drugs is a risk factor for CD, although the absolute risk is low.[60]

2.2.2 Initial laboratory investigations

ECCO statement 2E

Check for signs of acute and/or chronic inflammatory response, anaemia, fluid depletion, and signs of malnutrition or malabsorption [EL5]. Initial laboratory investigations should include CRP [EL2], and full blood count [EL2]. Other markers of inflammation may also be used such as faecal calprotectin [EL1] or erythrocyte sedimentation rate [EL5]. Microbiological testing for infectious diarrhoea including *Clostridium difficile* toxin is recommended [EL2]. Additional stool tests may be needed for some patients, especially those who have travelled abroad [EL5]

Anaemia and thrombocytosis represent the most common changes in the full blood count of patients with CD.[61] CRP and erythrocyte sedimentation rate [ESR] are standard laboratory surrogates of the acute phase response to inflammation. CRP broadly correlates with disease activity of CD assessed by standard indices and indicates serial changes in inflammatory activity because of its short half-life of 19 h.[55,62–64] Faecal calprotectin[65–68] and lactoferrin[65,68] have proved useful in the diagnosis of active inflammation. A recent meta-analysis confirmed that low CRP and/or low calprotectin have a 99% negative predictive value for IBS when considering the diagnosis of IBD.[69] Faecal calprotectin might also be useful in deciding which patient should undergo an endoscopic investigation, especially in the paediatric setting.[70] None of the above inflammatory parameters including calprotectin is specific enough to permit differentiation from UC or enteric infection. The value of routine stool examination in patients with suspected CD or exacerbations of disease arises from both the differential diagnosis and high concordance with enteric infections such as *C. difficile*.[71]

Serological testing currently available may be used as an adjunct to diagnosis, but the accuracy of the best of the available tests [ASCA and ANCA] is such that they are unlikely to be useful in routine diagnosis, and are ineffective at differentiating colonic CD from UC.[72,73] The same holds true for anti-glycan and antimicrobial antibodies, such as anti-OmpC and CBir1.[63,74–76] Despite the major advances in the field of CD genetics there are currently no genetic tests recommended routinely for diagnosis.

New biomarkers,[77] for instance faecal volatile organic metabolites, could have a role in the future.[78]

2.2.3 Procedures recommended to establish the diagnosis

ECCO statement 2F

For suspected CD, ileocolonoscopy and biopsies from the terminal ileum as well as each colonic segment to look for microscopic evidence of CD are first line procedures to establish the diagnosis [EL1]. Irrespective of the findings at ileocolonoscopy, further investigation is recommended to examine the location and extent of CD in the small bowel [EL5]. Whether upper GI endoscopy should be routinely performed in asymptomatic adult patients is still debated [EL5]

Ileocolonoscopy with multiple biopsy specimens is well established as the first-line procedure for diagnosing CD.[79,80,81] Ileoscopy with biopsy can be achieved with practice in at least 85% of colonoscopies and increases the diagnostic yield.[80,82–84] The endoscopic hallmark of CD is the patchy distribution of inflammation, with skip lesions [areas of inflammation interposed between normal appearing mucosa]. CD ulcers tend to be longitudinal and may be associated with a cobblestone appearance of the ileum or colon, fistulous orifices and stricture. Rectal sparing is often encountered while circumferential, continuous inflammation is rare. Anatomical criteria of severity are defined as deep ulcerations eroding the muscle layer, or mucosal detachments or ulcerations limited to the submucosa but extending to more than one-third of a defined colonic segment [right, transverse, left colon].[85] When there is severe, active disease, the value of full colonoscopy is limited by a higher risk of bowel perforation. In these circumstances initial flexible sigmoidoscopy is safer and ileocolonoscopy should be postponed until the clinical condition improves.[86] Ileoscopy is superior for the diagnosis of CD of the terminal ileum[87–89] when compared with radiology techniques, including magnetic resonance imaging [MRI] and computed tomography [CT], especially for mild lesions. Capsule endoscopy and enteroscopy with biopsy are well tolerated and useful procedures for the diagnosis of CD in selected patients with suggestive symptoms after failure of radiological examinations.[90]

2.3 Extent of disease

2.3.1 Procedures recommended for establishing the extent of CD

CD may affect the ileum out of reach of an endoscope, or involve more proximal small bowel [10% of patients]. Additionally, at the time of diagnosis 15% of patients have penetrating lesions [fistulas, phlegmons or abscesses].[91] Endoscopy and radiology are complementary techniques to define the site and extent of disease, so that optimal therapy can be planned.[91–93]

ECCO statement 2G

Cross-sectional imaging (MRI and CT enterography) and trans-abdominal ultrasonography (US) are complementary to endoscopy and offer the opportunity to detect and stage inflammatory, obstructive and fistulising CD [EL1]. Radiation exposure should be considered when selecting techniques, especially to monitor follow-up [EL4]. Because of the lower sensitivity of barium studies, alternative techniques are preferred if available

Cross-sectional imaging techniques are needed after endoscopy, to allow a complete and sensitive staging of the small bowel and perineum with the unique advantage to assess mural and extramural disease. This topic has been extensively reviewed in a joint ECCO–European Society of Gastrointestinal and Abdominal Radiology [ESGAR] evidence-based consensus guideline.[26]

A meta-analysis comparing the accuracies of US, MRI, scintigraphy, CT and positron emission tomography [PET] for diagnosis in patients with suspected or known IBD, mainly CD, showed that mean sensitivity estimates for the diagnosis of IBD on a per-patient basis were high and not significantly different among the imaging modalities [90, 93, 88 and 84% for US, MRI, white blood cell scintigraphy and CT, respectively].[87] CT and MRI are the current standards for assessing the small intestine. Both techniques can establish disease extension and activity based on wall thickness and increased intravenous contrast enhancement.[94] The magnitude of these changes, along with presence of oedema and ulcerations, allows categorization of disease severity.[93,95] CT is more widely available and is less time consuming than MRI. The radiation burden from fluoroscopy and CT is appreciable.[96] Considering that these examinations need to be repeated over time and the young age of the IBD population, radiation exposure resulting from CT examination may entail an increased risk of malignancy.[97,98] Therefore, MRI should be used where possible.

CT and MRI examinations of the small intestine require oral luminal contrast to achieve adequate distension.[99] Administration of luminal contrast by enteroclysis allows better small bowel distention than simple oral ingestion. However, naso-jejunal tube placement entails radiation exposure and produces discomfort. The only study comparing both modalities in MR examinations concluded that bowel distension was inferior with MR follow-through, but diagnostic accuracy was similar using both methods.[99] Likewise, oral CT enterography has similar accuracy in the detection of active CD in comparison with CT enteroclysis with a naso-jejunal tube.[95] Oral ingestion of the luminal contrast provides adequate distension of the ileum. Enteroclysis may be necessary in selected cases in which upper CD lesions are suspected and adequate distention is not achieved following oral administration of luminal contrast.

Trans-abdominal US represents another non-ionizing, non-invasive imaging technique that is well tolerated and accepted by patients.[92,100,101] Use of contrast-enhanced abdominal US[102] and Doppler US[100,103] may increase the sensitivity and specificity of this technique for the detection of disease activity. The ileocecal region, sigmoid and often ascending and descending colon are adequately visualized in most patients. The proximal ileum and jejunum can be difficult to assess, whereas study of the transverse colon is challenging because of its variable anatomy, and the rectum for accessibility. US diagnosis of CD relies on several features, but primarily on the detection of increased bowel wall thickness, which is considered the most common and constant US finding in CD.[104] The importance of this sign for the accuracy of US diagnosis of CD has been evaluated in several studies and sensitivities of 75–94% with specificities of 67–100% have been reported.[101,105,106]

Leucocyte scintigraphy is well tolerated, non-invasive, and potentially permits assessment of the presence, extent and activity of inflammation[107] but radiation exposure and limited sensitivity, especially in patients under steroid treatment,[108] leads to reduced use of this technique.

Evidence for the diagnostic yield of the above imaging techniques for assessment of colonic CD is expanding, and seems to be highly dependent on technical details. Trans-abdominal US[100, 109–111] and

MRI[112–114] have high accuracy in assessing the activity and severity of CD colitis, while less data are available for CT.[115, 116] Direct and indirect comparisons of the relative accuracy of US, CT and MRI for diagnosis of disease activity and severity in CD show that the techniques provide similar sensitivities and specificities overall.[87,117] White blood cell scintigraphy can detect colon inflammation and can be used as an additional technique.

ECCO statement 2H

MRI, CT and US have a high accuracy for the diagnosis of small bowel stenosis [EL2], penetrating complications [EL1], and may assist differentiation between predominantly inflammatory and fibrotic strictures [EL5]

2.3.2 Procedures recommended for establishing the extent of stricturing CD

The most reliable criterion for defining a stricture is a localized, persistent narrowing, whose functional effects may be judged from prestenotic dilatation.[52,118]

Ileocolonoscopy is recommended for the detection of stenosis in the colon and distal ileum allowing tissue sampling for pathological diagnosis, as dysplasia or cancer complicates 3.5% of colonic strictures.[119] Complementary radiological techniques to rule out additional stenotic lesions are necessary when the lesion is impassable with the endoscope.

Plain film radiography may identify small bowel obstruction but cannot depict the cause, making additional diagnostic workup based on US, MRI or CT necessary. All techniques are superior to conventional barium studies for detection of stenotic lesions.[120–122] Direct comparison of CT and MRI for the diagnosis of a variety of small intestine lesions demonstrates a high sensitivity and specificity, similar in both techniques.[115,117] Comparison of enteroclysis and oral contrast administration on CT and MRI examinations resulted in similar results, showing superior bowel distension when enteroclysis was used, but a similar diagnostic accuracy for the detection of stenotic lesions,[95,99,123] although enteroclysis may be superior for the demonstration of low-grade stenosis.[124]

US is helpful in detecting pre-stenotic dilatation in small bowel strictures in severe cases that are candidates for surgery.[125,126] In experienced hands, using surgery as a reference standard, the sensitivity of US was 79% and specificity 92%.[117]

Differentiation between inflammatory and fibrostenotic strictures is crucial to the choice of therapy, but the diagnostic value of current techniques has not been fully validated. CT can detect disease activity at a stricture based on wall thickness, wall enhancement, a comb sign and the presence of enlarged lymph nodes.[125,127] Using surgical specimens as a reference standard, controversial data on signs defining fibrosis versus inflammation have been published.[126,128,129,130] Most recent data using current technology suggest that using percentage of enhancement gain MRI can discriminate between mild–moderate and severe fibrosis with 0.94 sensitivity and 0.89 specificity.[131] Contrast-enhanced US may also be valuable in determining disease activity within strictures.[127,132,133]

2.3.3 Procedures recommended for detecting extramural complications

US, CT and MRI have a high accuracy for the assessment of penetrating complications [i.e. abscess, fistulae].[95,120,133,134] In a systematic review, using surgery as a reference standard for fistulizing lesions, US demonstrated a sensitivity of 74% and specificity of 95%, CT 79% and 97%, and MRI 76% and 96%, respectively.[117] The accuracy is also similar for abdominal abscess, although in clinical practice, if an intra-abdominal abscess or deep-seated fistula is suspected, CT is usually preferred for high accuracy and availability.

2.3.4 Role of upper gastrointestinal [GI] endoscopy and biopsy in CD

CD involving the upper GI tract is almost invariably accompanied by small or large bowel involvement.[135–137] CD patients with dyspepsia, abdominal pain and vomiting benefit from an upper GI endoscopy.[138] Upper GI endoscopy may also be important in specific cases to establish the diagnosis, as focal gastritis may be a feature of CD [135].

2.3.5 Role of small bowel capsule endoscopy [SBCE] and device-assisted enteroscopy [DAE] in suspected or proven CD

ECCO statement 2I

Small bowel capsule endoscopy (SBCE) should be reserved for patients in whom the clinical suspicion for CD remains high despite negative evaluations with ileocolonoscopy and radiological examinations (SBE/SBFT or CTE or MRI) [EL2]. SBCE has a high negative predictive value for small bowel CD [EL4]

Device assisted enteroscopy may be performed in expert hands if histological diagnosis is needed [EL3] or when endoscopic therapy is indicated, including dilatation of strictures, retrieval of impacted capsules, and treatment of bleeding [EL4]

SBCE is a sensitive tool to detect mucosal abnormalities in the small bowel. The diagnostic yield [prevalence of abnormal findings] of SBCE is superior to other modalities (SBE/small bowel follow through [SBFT], CT-enteroclysis) for diagnosing small bowel CD.[139–147] In a recent meta-analysis,[148] the diagnostic yield of SBCE was compared with push enteroscopy [PE], ilecolonoscopy, SBFT or SBE, CT-enteroclysis and MRI. The incremental yield ranged from 10% against MRI [not significant] up to 22% [ileocolonscopy], 32% [SBFT/SBE] and 47% [CTE: all $p < 0.001$]. Contraindications for SBCE include gastrointestinal obstruction, strictures and swallowing disorders.[149] Activity can be measured with the Lewis score,[70] and recent data confirm the high sensitivity of SCBE in the follow-up of treated patients.[150] Second-generation colon capsule has been shown to be potentially useful for evaluating colonic activity in CD.[151]

In addition, a normal SBCE examination has a very high negative predictive value, essentially ruling out small bowel CD. However, the use of SBCE in suspected cases of small bowel CD is limited by a lack of specificity. CD-associated lesions described by SBCE need more precise definition. Indeed, over 10% of healthy subjects demonstrate mucosal breaks and erosions in their small bowel. Thus, SBCE findings of mucosal lesions of the small bowel are not alone sufficient to establish a diagnosis of CD. The International Conference on Capsule Endoscopy [ICCE][152] recommended that patients with suspected CD should be selected to undergo SBCE if they present with typical symptoms, plus either extraintestinal manifestations, inflammatory markers or abnormal small bowel imaging [small bowel series or CT scan].

The risk of capsule retention in patients with suspected CD without obstructive symptoms and without history of small bowel resection or known stenosis is low and comparable to that of obscure GI bleeding.[153–156] Cheifetz *et al*. reported a retention rate of 13% in

patients with established CD, but only 1.6% in patients with suspected CD. In this setting, routine small bowel imaging or patency capsule prior to capsule endoscopy is not mandatory.

In 43–60% of patients with established CD and suspected small bowel involvement, the lesions may not be assessed by conventional endoscopy.[157] The diagnostic yield of DAE is variable,[158–161] but recent prospective data suggest DBE is clearly superior in sensitivity to MRI.[162] However, DAE is invasive and a very demanding technique, so is indicated for obtaining biopsies for histopathology in specific cases, or for therapeutic intervention, such as dilatation of strictures, retrieval of impacted capsules or haemostatic procedures for bleeding.

3 Histological diagnosis of CD

This topic has been extensively reviewed in an ECCO and the European Society of Pathology [ESP] joint consensus. More detailed explanations, statements and references can be found in Magro *et al*.[163] In this section the procedures required for a proper diagnosis, and diagnostic criteria will be briefly reported.

3.1 Procedures for the diagnosis with endoscopic biopsies

3.1.1 Number of biopsies

ECCO statement 3

For a reliable diagnosis of CD a minimum of two biopsies from five sites around the colon (including the rectum) as well as from the ileum should be obtained [EL5]

For the initial diagnosis, analysis of a full colonoscopic biopsy series, rather than a single biopsy, produces the most reliable diagnosis of CD.[82,164–171] Samples are preferably obtained both from areas which are involved by the disease and from uninvolved areas. During follow up examinations, a smaller number of biopsy samples may be useful to confirm the diagnosis.

3.1.2 Handling of biopsies

The biopsy samples should be accompanied by clinical information including the age of the patient, duration of disease and duration and type of treatment [EL5]. Biopsies from different regions should be handled in a way that the region of origin can be identified, and orientation of the samples using filter paper may yield better results [EL5]. Routine staining with haematoxylin and eosin are appropriate for diagnosis [EL5]. At present special stains, immunohistochemistry or other techniques for diagnostic purposes are not needed routinely.

3.2 Diagnostic features

3.2.1 Microscopic features

A large variety of macroscopic and microscopic features have been identified which help to establish a diagnosis of CD. Focal [discontinuous] chronic [lymphocytes and plasma cells] inflammation and patchy chronic inflammation, focal crypt irregularity [discontinuous crypt distortion] and granulomas [not related to crypt injury] are the generally accepted microscopic features, which allow a diagnosis of CD. The same features and, in addition, an irregular villous architecture, can be used for analysis of endoscopic biopsy samples from the ileum. If ileitis is in continuity with colitis, the diagnostic value of this feature should be used with caution [EL2].

3.2.2 Granulomas

Granuloma in CD is defined as a collection of epithelioid histiocytes [monocyte/macrophage cells], the outlines of which are often vaguely defined. Multinucleated giant cells are not characteristic and necrosis is usually not apparent. Only granulomas in the lamina propria not associated with active crypt injury may be regarded as a corroborating feature of CD. Granulomas associated with crypt injury are less reliable features.[172]

3.2.3 Number of features needed for diagnosis

The following features can be identified in the mucosa and thus in endoscopic biopsy samples: granulomas and focal [segmental or discontinuous] crypt architectural abnormalities, in conjunction with focal or patchy chronic inflammation [chronic is defined as the presence of lymphocytes and plasma cells], or mucin preservation at active sites. The patchy nature of the inflammation is only diagnostic in untreated adult patients. Inflammation can become patchy in UC after treatment, and young children [age <10 years] with UC may present with discontinuous inflammation.[173–177]

The presence of a single feature is not regarded as sufficient for a firm diagnosis. For single or multiple endoscopic samples there are no data available as to how many features must be present for a firm diagnosis of CD. For surgical material, it has been suggested that a diagnosis of CD should be made when three features are present in the absence of granulomas, or when an epithelioid granuloma is present with one other feature provided that specific infections are excluded [EL5].[178]

The absence of features that are highly suggestive or diagnostic of UC, such as diffuse crypt irregularity, reduced crypt numbers and general crypt epithelial polymorphs, can also lead towards a diagnosis of CD.

In difficult cases, gastric biopsies might help to establish the diagnosis of CD, in the presence of granulomas or focally enhanced or focal-active gastritis.[179–183]

3.3 Histology and dysplasia–intra-epithelial neoplasia

3.3.1 Number of biopsies

Patients with extensive Crohn's colitis carry an increased risk of colorectal cancer. Endoscopy with biopsy can be used for secondary prevention and the detection of dysplasia [intra-epithelial neoplasia] [EL2]. The microscopic features for the diagnosis and grading of dysplasia–intra-epithelial neoplasia of the colon in CD are the same as those proposed for UC and, similarly, a second opinion is recommended for a firm diagnosis. The focal nature of inflammation in Crohn's colitis, the possibility of strictures and prevalence of segmental resection means that surveillance practice in UC cannot be transferred directly to Crohn's colitis. The use of targeted biopsies, aimed at lesions identified by chromoendoscopy or endomicroscopy, has changed the policy of taking biopsies in UC and this policy should also be considered in patients with Crohn's colitis.[26,184,185]

3.3.2 Microscopic features

Microscopic features that are used for a diagnosis of intra-epithelial neoplasia include architectural and cytological abnormalities. Architectural abnormalities are crowding of glands, thickening of the mucosa, lengthening and distortion of the crypts with excessive budding and increased size. Surface and crypts are lined by tall, high columnar cells, in which there is some mucus differentiation. Mucin tends to be in columnar cells rather than in the usual goblet cells. Nuclear changes are morphologically similar to those seen in tubular adenomas.[186,187]

3.4 Histology and disease activity

In contrast to UC, disease activity is not generally assessed by pathologists for CD. This is mainly due to the discontinuous character of the disease, inducing sampling error and the fact that the ileum may be the only area involved. The data available on histology and activity for CD are limited. Several clinical trials have shown that medical treatment can alter the mucosal histology, promoting healing and normalization of the mucosa.[188–193] There is, however, no general agreement among expert clinicians about the use of microscopy to assess disease activity.

4 Classification of CD

Disease classification is an important step to provide appropriate tools that enable us to identify differences in the features and behaviour of CD. CD has been classified by disease phenotype [Montréal classification], disease activity [mostly according to CDAI] and response to therapy [mainly steroids: 'steroid-refractory' or 'steroid-dependent', as already defined]. Since there is a strong trend toward the prescription of earlier and more aggressive maintenance therapies, some efforts are currently being made to predict at diagnosis the subsequent phenotype of the disease, in order to adapt the level of the therapy to the severity of the disease.

4.1 General recommendations

ECCO statement 4A

The use of the Montréal classification of CD is advocated, until more advanced classification is available. Genetic tests or serological markers should currently not be used to classify CD in clinical practice [EL2]

ECCO statement 4B

The course of CD may be predicted by clinical factors at diagnosis and/or endoscopic findings. This should be taken into account when determining a therapeutic strategy [EL2]

ECCO statement 4C

Serum CRP levels and faecal markers, such calprotectin or lactoferrin can be used to guide therapy and short-term follow-up [EL2] and to predict clinical relapse [EL2]. Faecal calprotectin can help to differentiate CD from IBS [EL2]

4.2 Specific components

4.2.1 Montréal phenotype classification

The Montréal revision [2005][52,194] of the Vienna classification[195] is regarded as the international standard of subtyping in CD. It describes age at diagnosis [below 16 years [A1], between 17 and 40 years [A2], above 40 years [A3]], disease location, (terminal ileum [L1], colon [L2], ileocolon [L3] and upper GI location [L4]) and disease behaviour (non-stricturing non-penetrating [B1], stricturing [B2] and penetrating [B3]) at any time during the disease course. The occurrence of perianal fistulae and abscesses is considered a 'modifier', depicted by a 'p' [for perianal] added to B1, B2 or B3. While disease location may remain stable after diagnosis, CD behaviour evolves over time, with an increasing number of patients progressing from non-penetrating, non-structuring disease to stricturing or penetrating disease.[91,196] The superiority of the Montréal classification over the Vienna classification in detecting early changes in CD behaviour phenotype, associated with the need for subsequent major surgery, has been validated in a non-Caucasian population.[197]

The concept of disease classification is evolving.[16] Given the chronically progressive destructive nature of CD, currently used classification systems appear too rigid. The hierarchical nature of the Montréal classification makes the investigation of stricturing and fistulizing disease as separate entities impossible. In addition, accumulating bowel damage might be better depicted in the future by the longitudinal 'Lemann Damage Score',[198] which has been developed and validated prospectively.[199]

4.2.2 Clinical predictors at diagnosis of subsequent phenotype

Increasing evidence suggests that early or prolonged immunosuppressive therapy in CD with immunomodulators and/or biologics is associated with an increased probability of mucosal healing, early sustained remission without steroids, and reduction in the need for surgery and hospitalizations.[200–203] Given the risks of immunosuppressive therapy, only patients with a predisposition for a severe or complicated disease course should be considered for early intensive therapy. No uniform definition for a severe disease course exists, but endpoints used in investigations include, but are not restricted to, sustained disabling symptoms and impaired quality of life, repeated flare-ups with or without hospitalization, development of irreversible penetrating and/or stricturing lesions, need for repeated courses of steroids and need for surgery. Using various combinations of these criteria, concordant data from three independent patient cohorts [two from referral centres[204,205] and one population-based[206]] suggest that the presence of perianal lesions and/or ileocolonic location and/or young age at diagnosis together with the need for treating the first flare with steroids is associated with a high risk of disabling disease within the 5-year period after diagnosis. When two or more predictors are present in an individual patient, early treatment with thiopurines and/or biologics could be considered. These predictors, however, are present in a large fraction of CD patients and might not be able to discriminate the severity of disease course well; their use in clinical practice has also been challenged in recent prospective clinical trials.[207]

Endoscopic mucosal healing appears to have an impact on the later disease course of CD, namely increased steroid-free remission rates 4 years after therapy began,[208] a longer time to relapse after drug withdrawal,[209] a lower rate of hospitalizations[210,211] and surgery.[211, 212] Hence, the absence of mucosal healing can be used as a predictor for complicated disease course.[213]

[For an extensive review and guidelines on initiating immunosuppressive and biological therapy see Section xx. in Current Management.]

4.2.3 Classification by serum CRP and faecal markers

High CRP levels are indicative of active disease or an infectious complication. In addition, there is a good correlation between clinical and endoscopic disease activity in CD and CRP level.[62,71,214] A decrease in CRP is indicative of treatment response[63] while persistently increased CRP levels are associated with diminished or loss of response to the drug.[215] Serum levels of CRP might also be useful for assessing a patient's risk of relapse[216] even though CRP appears to be less powerful than faecal markers.

Growing evidence suggests that mucosal healing is a surrogate marker of sustained controlled CD.[201,208,217] Endoscopy is still considered the standard for evaluation of mucosal healing but

is invasive and costly. The faecal concentration of calprotectin and lactoferrin reflects the migration of neutrophils through the inflamed bowel wall to the mucosa. Both calprotectin and lactoferrin are stable, degradation-resistant proteins that can be easily measured in stools using enzyme-linked immunosorbent assay.[218] Increased faecal levels of calprotectin and lactoferrin reflect intestinal inflammation of any cause.[68,219] A recent meta-analysis showed that adult as well as paediatric patients with CD have increased calprotectin levels in contrast to patients with IBS.[220] A different meta-analysis demonstrated that normal calprotectin levels could exclude IBD with high accuracy, in particular in adult patients.[221] In CD calprotectin has a >90% positive predictive value for endoscopically active disease.[222] As for serum CRP, the limit of the accuracy of faecal markers is that some patients have endoscopically active disease and faecal protein levels within the normal range, more often with ileal than colonic disease.[222, 223] However, the 60–70% sensitivity of raised faecal markers for predicting concurrent endoscopically active disease is superior to that of serum CRP and clearly superior to CDAI.[222,224–226] In addition, several studies demonstrate that faecal calprotectin is a sensitive marker that predicts relapse in patients with CD.[227–230] Weaknesses of calprotectin in CD include its diminished value in patients with CD restricted to the small bowel,[224] an imperfect correlation with transmural inflammation and an absence of uniform thresholds. In summary, faecal levels of calprotectin or lactoferrin are emerging as surrogate markers of mucosal healing, even though the predictive value of uniform thresholds at an individual level has not been clearly demonstrated.

4.2.4 Correlation between genetic and serological markers and phenotype

Genetic studies define more than 200 distinct susceptibility loci for CD.[231,232] However, none of them is associated with an individual risk for developing disease high enough to justify the routine use. Regarding genotype–phenotype correlations, only NOD2 variants and 5q31 susceptibility haplotype have been reproducibly shown to be associated with ileal location, complicated disease (including perianal disease) and need for surgery.[233,234]

A significant relationship between the severity of CD and the presence and levels of serological antimicrobial antibodies has been reported. The number and magnitude of immune responses to different microbial antigens is associated with the severity of the disease, characterized by the occurrence of stricturing/penetrating lesions and the need for surgery.[235] Predictive data, however, are limited for individual patients, and it remains unclear if patients with high levels of these markers do indeed benefit from stronger immunosuppressive therapies.[74,236] At diagnosis, the positive predictive value of antimicrobial antibodies for the subsequent disease course appears to be limited[74,236] and their routine use in clinical practice cannot be advocated at this time.

4.2.5 Need for a composite predictive index at diagnosis

Given the complex benefit–risk balance of early aggressive therapeutic strategies using immunomodulators and biologics in CD, there is an increasing need to identify at diagnosis patients who are likely to develop severe or complicated disease later on. Simple clinical predictors have been identified, but their individual accuracy and discriminatory capability remains limited. Genetic factors and serological markers of immune reactivity, considered alone or in combination, have so far been unhelpful in predicting the future course of CD at diagnosis.

5 Medical management of active CD

5.1 Introduction

ECCO statement 5A

The presence of active inflammation due to CD should be confirmed before initiating or changing medical therapy

The management plan for a patient with CD should take into account the activity, site and behaviour of disease, and should always be discussed with the patient. Determining the activity of disease may be more difficult in CD than UC, since symptoms [such as pain or diarrhoea] may be due to causes other than active disease. Therefore, alternative explanations for symptoms such as enteric infection, abscess, bacterial overgrowth, bile salt malabsorption and dysmotility [IBS] should always be considered. Experience has shown that clinicians are often poor judges of disease activity; therefore, objective evidence of disease activity should be obtained [inflammatory markers or colonoscopy as appropriate] before starting or changing medical therapy. This concept is supported by the results of the SONIC study. In this clinical trial the benefit of therapy was significantly higher in those patients with endoscopic evidence of active disease at entry.[237]

The appropriate choice of medication is influenced by various factors: the balance between drug efficacy and potential side effects, the previous response to treatment [especially when considering treatment of a relapse, or treatment for steroid-dependent or steroid-refractory disease], and the presence of extraintestinal manifestations or complications. Different preparations are released at different sites and may have local activity [such as mesalazine preparations and budesonide], so the choice is best tailored to the individual patient. It is important to remember that one option for selected patients with mild disease would be to start no active treatment, as in a systematic review of clinical trials, 18% (95% confidence interval [CI] 14–24%) of patients entered remission when receiving placebo alone.[238] Thus, it is clearly important to involve patients in all therapeutic decisions.

5.2 Treatment according to site of disease and disease activity

5.2.1 Mildly active localized ileocaecal CD

ECCO statement 5B

Oral Budesonide is the preferred treatment [EL2]

Although the stage at which immunosuppressive and biological therapy is introduced is changing, it is important to remember that an appreciable proportion of patients with CD have a mild pattern of disease. Thus, in an inception cohort of 843 patients with CD [the IBSEN cohort], diagnosed between 1990 and 1994, only a quarter of the patients were treated with immunomodulators and 4% with anti-tumour necrosis factor [TNF] agents during the first 10 years of follow-up.[212] In another cohort from Olmsted County, Minnesota, USA, 43% of patients were never treated with steroids.[239] At least one in three CD patients have a mild to moderate course in the long term, with no or little requirement for steroids, as has been shown in German[240] and French[241] cohorts. Despite this, the majority of patients with active CD have symptoms that merit treatment.

Budesonide 9 mg daily is the favoured therapy to induce remission in mildly active, localized ileocaecal CD, because it is superior to placebo (relative risk [RR] 1.93, 95% CI 1.37–2.73). Although it is inferior to conventional steroids [RR 0.85, 95% CI 0.75–0.97], especially if severe disease [CDAI > 300] is present [RR 0.52, 95% CI 0.28–0.95], it has fewer side effects [RR 0.64, 95% CI 0.54–0.76].[242] Fifty to 60% of patients with mild ileocecal CD attain remission at 8 weeks on budesonide.[243–247]

Mesalazine at 4 g/day showed a very marginal benefit [a fall in 18 points in CDAI, just reaching significance at p 0.04] in a detailed meta-analysis.[248] No definite benefit over placebo was found in another systematic review and meta-analysis,[249] and it was inferior to budesonide in a randomized clinical trial.[250] A recent trial found mesalazine equivalent to budesonide in mild ileocecal CD, which could suggest a role for the drug in mild CD.[251] However, a Bayesian meta-analysis confirmed that budesonide should be the preferred option in this clinical scenario, and found no clear evidence for mesalazine being better than placebo at any dose.[252]

Systemically acting antibiotics [metronidazole, ciprofloxacin], with or without mesalazine, are not recommended, because side effects are common, and effectiveness has not been proved in luminal CD.[253] A recent trial suggests that some doses [800 mg/day] of the non-absorbable antibiotic rifaximin could be better than placebo in inducing remission in moderate CD.[254] Given that rifaximin is well tolerated, it could be considered in selected patients.

Exclusive enteral nutrition therapy has not shown efficacy in a large randomized controlled trial in adults and is often poorly tolerated, although there are case-series or small trials that have suggested that these treatments may be modestly effective.[255]

5.2.2 Moderately active localized ileocaecal CD

ECCO statement 5C

Moderately active localised ileocaecal Crohn's disease should be treated with budesonide [EL1], or with systemic corticosteroids [EL1]. An anti-TNF based strategy should be used as an alternative for patients, who have previously been steroid-refractory or –intolerant [EL1]. For some patients who have infrequently relapsing disease restarting steroids with an immunomodulator may be appropriate [EL2]. In patients refractory to steroids and/or anti-TNF, vedolizumab is an appropriate alternative [EL1]

For moderately active CD, either budesonide or prednisolone are appropriate initial induction therapies. Prednisolone is highly effective, but more commonly causes side effects than budesonide.[242,256] In a systematic [Cochrane] review of conventional corticosteroids, two studies compared corticosteroids to placebo and six studies compared corticosteroids to 5-aminosalicylic acid [5-ASA].[257] Corticosteroids were found to be significantly more effective than placebo at inducing remission in CD [RR 1.99, 95% CI 1.51–2.64; $p < 0.00001$]. The dose of prednisolone is adjusted to the therapeutic response over a period of weeks [see below]. A more rapid dose reduction can be associated with early relapse. The Consensus does not favour sole nutritional therapy, antibiotics [unless septic complications are suspected] or surgery for moderately active ileal CD as first-line therapy.

Particular effort should be made to minimize corticosteroid exposure in CD, even though steroids still remain the mainstay for initial treatment of active disease. Part of the problem is a complete lack of efficacy for maintaining remission [see section 6]. No more than one in four patients given corticosteroids to induce symptomatic remission will still be in remission after a year, even if patients treated with immunomodulators are included.[258,259]

An effective approach to minimizing steroid therapy is the early introduction of anti-TNF agents. Selection of patients appropriate for biological therapy depends on clinical characteristics, previous response to other medical therapies, phenotype and co-morbid conditions. For some patients who have infrequently relapsing disease, restarting steroids with an immunomodulator may be appropriate [EL2]. The definition of 'infrequently relapsing disease' cannot be distilled from clinical trial evidence, although more than one full course of systemic steroids per year may be considered as the threshold for induction of steroid sparing agents. Certain patient populations may derive greater benefit from the early introduction of biological therapy, including steroid-refractory [section 5.3.3], steroid-intolerant or steroid-dependent patients.[260] However, a study of 133 patients with active CD who had not previously received glucocorticoids, anti-metabolites or infliximab also suggested benefit of early biological therapy in this relatively treatment naïve group. This trial randomized patients to either early combined immunosuppression or conventional treatment [commonly referred to as the Step Up/Top Down study].[201] At week 26, 60.0% of 65 patients in the combined immunosuppression group were in remission without corticosteroids and without surgical resection, compared with 35.9% of 64 controls, giving an absolute difference of 24.1% [95% CI 7.3–40.8, $p = 0.006$]. The SONIC study has demonstrated that combination treatment with infliximab and azathioprine is more effective than infliximab alone for achieving [and maintaining] steroid-free remission in patients at an early stage of CD.[237]

5.2.3 Severely active localized ileocaecal CD

ECCO statement 5D

Severely active localised ileocaecal Crohn's disease should initially be treated with systemic corticosteroids [EL1]. For those who have relapsed, an anti-TNF based strategy is appropriate [EL1]. Surgery is a reasonable alternative for patients with disease refractory to conventional medical treatment and should also be discussed [EL3]. For some patients who have infrequently relapsing disease restarting steroids with an immunomodulator may be appropriate [EL2]. In patients refractory to steroids and/or anti-TNF vedolizumab is an appropriate alternative [EL1]

The initial treatment of severe ileal CD still includes prednisolone or intravenous hydrocortisone. A substantial change in the therapeutic approach in the past 10 years has been the recognition that it could be possible to use clinical criteria at diagnosis to predict the subsequent course of disease. This, in turn, has affected the threshold for introducing anti-TNF and immunomodulator therapy in patients with markers of poor prognosis. Given that continued treatment with either infliximab or adalimumab has been associated with a substantial reduction [about 30% at 12 months] in surgery and hospitalization for CD,[202,261] the threshold is likely to decrease further.

Anti-TNF therapy is still best reserved for patients not responding to initial therapy and for whom surgery is considered inappropriate. However, this does not mean that surgery takes precedence over adalimumab, infliximab or certolizumab pegol [the last-named is not currently licensed for CD in Europe], and the therapeutic strategy

for an individual should be a joint decision between patient, physician and surgeon. Although anti-TNF therapy may reduce the need for surgical resection, the threshold for surgery in localized ileocaecal disease is lower than for disease elsewhere. Indeed, some experts advocate surgery [especially laparoscopic-assisted resection] in preference to anti-TNF therapy for disease in this location. Others advocate resection if medical therapy is not effective within 2–6 weeks. It is now clear when starting anti-TNF therapy in patients with CD naïve to immunosuppression that combination therapy with infliximab and azathioprine is more effective than either alone, whether for induction of remission, for maintenance of remission up to 1 year or for mucosal healing.[237] However, only patients with an elevated serum CRP or the presence of mucosal lesions at colonoscopy gained additional benefit from infliximab therapy. It is unknown whether combination therapy with anti-TNF agents other than infliximab would also improve outcome in patients naïve to immunosuppressives other than steroids.

5.2.4 Colonic disease

ECCO statement 5E

Active colonic CD should be treated with systemic corticosteroids [EL1]. For those who have relapsed, an anti-TNF based strategy is an appropriate option [EL1]. In patients refractory to steroids and/or anti-TNF vedolizumab is an appropriate alternative [EL1]

Systemic corticosteroids such as prednisolone or equivalent are effective,[262,263] whereas ileal release budesonide has no role in treating colonic disease, unless it primarily affects the proximal colon. Budesonide MMX has not yet been studied in CD. Therefore, steroids remain first-line therapy, with immunomodulators as steroid-sparing agents for those who have relapsed. As with disease in any location, the decision needs to take into account the previous response to therapy and the pattern of disease: for some patients who have infrequently relapsing disease, restarting steroids with an immunomodulator may be appropriate. As for ileocaecal disease there is no controlled evidence to define 'infrequent relapses', but it is important that the expectations of gastroenterologists and their patients are appropriate: it is no longer acceptable for patients to be subjected to recurrent cycles of steroids when effective therapy for achieving and maintaining steroid-free remission with anti-TNF therapy or vedolizumab exists. If symptoms persist in spite of steroids or when patients relapse within months of their last steroid dose [with or without immunomodulators], anti-TNF therapy should be commenced if activity is demonstrated. If patients do not respond or lose response to anti-TNF therapy, then surgery or vedolizumab are appropriate.

The Gemini II[264] and III[265] trials have demonstrated the efficacy of vedolizumab to induce and maintain remission in patients with moderate to severe CD. Vedolizumab was significantly better than placebo in obtaining remission at week 6 [14.5 vs 6.8%] although CDAI-100 response was not different, with a good safety profile.[264] Data from pivotal clinical trials and several long-term cohort studies show that vedolizumab can be effective even in patients who have been failing systemic steroids and/or immunosuppressants and/or anti-TNF therapy.[264–267] Response can take time [12–16 weeks or more], but once obtained seems to be well maintained, at least through week 52.[266] Concomitant steroid and/or immunosuppresant effectiveness is not clearly defined.[265] The safety profile seems quite favourable, as serious infections, serious infusion reactions or malignancies have low incidence even after extended periods.[268]

The use of sulfasalazine, metronidazole[269] or nutritional therapy[270] for adults with colonic CD has almost been consigned to history. Sulfasalazine 4 g daily was found to be modestly effective for active colonic disease in old trials,[262,263] but it cannot be recommended in view of a high incidence of side effects. There is no evidence that mesalazine is effective for active colonic CD, but opinion still varies about the value of topical mesalazine as adjunctive therapy in left-sided colonic CD, particularly in proctitis.

5.2.5 Extensive small bowel disease

ECCO statement 5F

Extensive small bowel Crohn's disease should initially be treated with systemic corticosteroids, but early therapy with an anti-TNF based strategy should also be evaluated [EL5]. For patients with severe disease who have relapsed, an anti-TNF based strategy is appropriate [EL5]

ECCO statement 5G

Patients who have clinical features suggesting a poor prognosis appear the most suitable for early introduction of immunosuppressive therapy. Early anti-TNF therapy [EL2] should be initiated in patients with high disease activity and features indicating a poor prognosis [EL3]

The inflammatory burden and level of malabsorption is greater in extensive [>100 cm] than in localized small bowel disease, often resulting in nutritional deficiencies. Treatment with steroids and the early introduction of concomitant immunomodulators [for their steroid-sparing effect] is considered appropriate. Nutritional support should be given as an adjunct to other treatment, and may be considered as primary therapy if disease is mild.[255,270] However, early introductiuon of anti-TNF therapy should also be considered, especially in patients who have clinical indicators of poor prognosis [section 5.3], as several analyses have shown that anti-TNF therapy is more effective when treatment is initiated early in the disease. Thus, in the CHARM trial with adalimumab, clinical remission rates approached 60% in patients who had CD for <2 years, compared to 40% [$p < 0.05$] in patients who had a longer duration of disease.[271] A similar phenomenon was observed in patients who received infliximab as first-line treatment, for whom >90% had a clinical response after first administration although no placebo-controlled data are available.[201] A post-hoc analysis of the SONIC study suggests that combined treatment is more effective in early disease.[33] The benefit of treating early in the disease course is also true for certolizumab pegol.[272] However, the most compelling evidence in favour of early intervention comes from a pilot trial in the postoperative phase of CD: 10/11 [91%] of patients treated with infliximab after ileocolonic resection had no endoscopic recurrence after 1 year,[273] compared to 2/13 [15%, $p = 0.0006$] treated with placebo infusions, a difference that seems to remain significant and relevant in the long-term.[274] The early use of immunosuppresants[275] or even more effectively adalimumab[276] seems to also be effective in this setting [preventing postoperative recurrence]. In general, common sense indicates that the management of patients with extensive small bowel disease should be more agressive given the well-documented adverse consequences.[277]

5.2.6 Oesophageal and gastroduodenal disease

ECCO statement 5H

Mild oesophageal or gastroduodenal Crohn's disease may be treated with a proton pump inhibitor only [EL5]. More severe or refractory disease requires additional systemic corticosteroids [EL4] or an anti-TNF based strategy [EL4]. Dilatation or surgery are appropriate for symptomatic stictures [EL4]

Upper GI tract inflammation in CD is increasingly diagnosed as patients more frequently undergo upper GI endoscopy. Reported incidence data vary considerably depending on the definitions used and the population studied. Paediatric data suggest that upper GI endoscopy is useful in differentiating CD from UC when inflammation is otherwise predominantly confined to the colon; however, this question has yet to be studied in adults.[278] Controlled trials of individual therapies are lacking despite CD in the proximal gut being associated with a worse prognosis.[279] Evidence-based therapy is mainly derived from case-series.[280,281] Most physicians add a proton pump inhibitor to conventional induction therapy and have a lower threshold for starting anti-TNF therapy than for disease elsewhere, given the poor prognosis.

5.3 Treatment according to the course or behaviour of disease

A novel target for both clinical trials and the management of individuals with CD is the desire to change the pattern of future disease. Therefore, a concerted effort is being made to identify those patients with a poor prognosis who might benefit most from the early introduction of immunomodulator or biological therapy. Early series showed that smoking had an adverse effect on the disease course, particularly with regard to post-operative recurrence in women.[282] Young patients and those with extensive small bowel CD were found to have a 3- to 7-fold increase in mortality in a population-based study.[277] The trouble is that these studies have neither been designed nor had sufficient power to relate outcome to the original patient phenotype.[282] In 2006, a French group reported a retrospective study of 1188 patients and identified features associated with the development of 'disabling disease'.[204] Disabling disease was defined as patients who needed treatment with more than two courses of steroids, who were hospitalized, needed immunomodulators or who came to surgery within 5 years of diagnosis. Factors *at diagnosis* that were associated with this outcome included young age [<40 years], initial need for steroid therapy and the presence of perianal disease. The authors validated their retrospective study with the prospective follow up of 302 patients from 1998. If two of the criteria were present at diagnosis, then 84% [91% in the retrospective cohort] had 'disabling disease' by 5 years and if all three risk factors were present, then the figures were 91% and 93%, respectively. The criteria for 'disabling disease' were also validated in a population-based cohort from Olmsted County, Minnesota. In this cohort of 72 patients diagnosed between 1983 and 1996 and followed for at least 5 years, 54% had disabling disease.[206] In an independent cohort, a more restrictive category of 'severe disease' was defined[205] as the development of complex perianal disease, any colonic resection, two or more small bowel resections or the construction of a definitive stoma within 5 years of diagnosis. The prevalence of 'severe disease' within 5 years of diagnosis in their series of 361 patients was 37%. Perianal disease, young age of onset and need for initial steroids were confirmed, but stricturing disease behaviour and loss of >5 kg weight before diagnosis were also independently associated with the development of severe disease.

Consequently, patients presenting at a young age, with extensive disease, needing initial treatment with steroids or with perianal disease *at diagnosis* can be considered to have a poor prognosis. This should inform discussion with the patient and is increasingly taken into account in therapeutic decision-making.

5.3.1 Treatment of relapse compared to newly diagnosed disease

The initial treatment of relapse should be based upon previously successful therapies. However, consideration should be given to other factors including patient preference [adverse effects, necessary speed of response, convenience, etc.], the time to relapse, concurrent therapy [whether a relapse occurred during treatment with immunomodulators] and adherence to therapy.

5.3.2 Early relapse

Any patient who has an early relapse [defined as an arbitrary period of <6 months] should be started on an immunomodulator to reduce the risk of a further relapse. Opinion remains divided whether to use the same treatment to induce remission and taper more slowly or use more potent induction therapy. It is important to confirm disease activity as a cause of recurrent symptoms, although unnecessary to re-evaluate the distribution of disease unless this will alter medical or surgical management. Patients who have a relapse of moderate or severe activity should be considered for anti-TNF therapy, since infliximab is more effective than azathioprine in early [duration <2 years], treatment-naïve patients with CD and there is a significant advantage in using the combination of infliximab and azathioprine.[33,237] All anti-TNF agents are more effective when introduced at an early stage. Vedolizumab may be considered in patients failing anti-TNF or in patients failing immunosuppressant moderate disease activity.[264]

5.3.3 Steroid-refractory CD

ECCO statement 5I

Patients with objective evidence of active disease refractory to corticosteroids should be treated with an anti-TNF based strategy [EL1], although surgical options should also be considered and discussed at an early stage [EL5]

For active CD refractory to steroids, local complications [such as an abscess] should be excluded by appropriate imaging and other causes of persistent symptoms considered. If active CD is confirmed, immunosuppressive, anti-TNF or vedolizumab therapy is appropriate.

It is also possible that the combination of steroids with an anti-TNF agent and an immunomodulator may improve outcome. In a randomized, double blind, placebo-controlled trial, patients who had initiated corticosteroids within the last 6 weeks were randomized 1:1 to receive infliximab and placebo [n=63], or infliximab and methotrexate 25 mg subcutaneously each week [n=63].[283] At week 14, there were no differences in the percentage of patients in steroid-free remission between the two groups [76% and 77%]. Although this can be interpreted as a failure of methotrexate to offer additional benefit to infliximab, the very high rate of steroid-free remission [twice that seen in other studies] is notable.

The timing of surgery depends on the severity of symptoms, inflammatory burden and considerations above. The patient's views and extent of disease should also be taken into account. Nutritional therapy is appropriate adjunctive, but not sole, therapy.

5.4 Therapy-specific considerations

The therapeutic goal should be to induce clinical remission for every patient, but even at diagnosis it is essential to keep in mind how remission will be maintained after medical induction therapy. In clinical practice, a 'step-up' approach of adding therapies if first-line or less toxic approaches are unsuccessful within an appropriate period is commonly used.[284] However, decisive treatment with a potent agent ['top down' approach] at an early stage may be preferred by the patient suffering symptoms from active disease.[201] Since evidence for activitiy at induction has been clearly shown for both steroids and anti-TNF-based strategies, the choice of induction agent depends on the activity, extent, location and behaviour of disease. An accelerated step-up approach has become current practice. This means rapid acceleration of therapeutic strategies, if no adequate response is seen within the expected time frame.

5.4.1 Aminosalicylates

Efficacy of aminosalicylates

Initially published trials showed oral aminosalicylates to be an effective treatment for active ileal, ileocolic or colonic CD. Sulfasalazine 3–6 g/day was effective in patients with colonic disease, but not in those with small bowel disease.[262,263] Eudragit-coated mesalazine 3.2 g/day was effective in ileocolic or colonic disease[285] and ethylcellulose-coated mesalazine 4 g/day was reported to be effective for ileitis, ileocolitis and colitis.[286] As a consequence, mesalazine became a popular treatment with limited toxicity for mild disease However, several systematic reviews and meta-analysis of clinical trial data have not shown any clinically relevant improvement with aminosalicylates over placebo[248,252,287] [see also 5.2.1].

Adverse effects of aminosalicylates

Side effects of sulphasalazine occur in 10–45% of patients, depending on the dose, but serious idiosyncratic reactions also occur.[288] Mesalazine intolerance is less frequent, and serious adverse effects are very uncommon, nephrotoxicity being the most worrisome,[289,290] (see previous document for details[10]).

5.4.2 Antibiotics and anti-mycobacterial treatment

Efficacy

Althougth data from several clinical trials suggest that metronidazole, ciprofloxacin or the combination could have some effectiveness, no conclusive superiority over placebo has been demonstrated [excluding perianal disease and septic complications].[253,291–294] A meta-analysis of six trials of anti-mycobacterial therapy showed that only the two trials including steroids for induction of remission influenced the disease.[295] A subsequent 216-patient randomized trial from Australia showed that triple therapy in conjunction with steroids improved the response at 16 weeks, although when anti-mycobacterial therapy alone was continued for 2 years in those who responded the pattern of disease was unchanged over 3 years.[296] A recent trial demonstrated that rifaximin at 800 mg/day was superior to placebo in inducing remission in mild to moderate CD,[254] although lower or higher doses were not effective, and no confirmatory trial has been reported to date.

In general, antibiotics are considered appropriate for septic complications, symptoms attributable to bacterial overgrowth or perineal disease.[253] Anti-mycobacterial therapy cannot be recommended based on the evidence from controlled trials.[294]

5.4.3 Corticosteroids

Efficacy of steroids

Two major trials established corticosteroids as effective therapy for inducing remission in CD. The National Cooperative Crohn's disease Study randomized 162 patients, achieving 60% remission with 0.5–0.75 mg/kg/day prednisone [the higher dose for more severe disease] and tapering over 17 weeks, compared to 30% on placebo (number needed to treat [NNT] = 3).[262,297] The comparable 18-week European Co-operative Crohn's Disease Study [n = 105] achieved 83% remission on 6-methylprednisolone 1 mg/kg/day compared to 38% on placebo [NNT = 2].[263] No formal dose-response trial of prednisolone has been performed. Enteric-coated budesonide 9 mg has consistently shown benefits for active ileal or ileocolic CD, but is less effective than prednisolone, especially in severe cases.[242,252]

Selection between topically and systemically acting corticosteroids At present, budesonide is advocated in preference to prednisolone if the disease distribution is appropriate [terminal ileal or ileocecal disease – section 5.2]. A standard tapering strategy for systemic steroids such as prednisolone is recommended, since this helps identify patients who relapse rapidly and therefore need thiopurines, anti-TNF-based strategies or vedolizumab. There are no trials between different steroid tapering regimens, and 'standard' regimens differ between centres. Although good at inducing remission, steroids are ineffective at maintaining remission[259,298,299] and a long-term treatment strategy to maintain steroid-induced remission should be planned at an early stage.

Adverse effects of steroids

Three groups of adverse events can be identified.[300] Budesonide is still associated with steroid side effects at a lower[244] or similar frequency,[246] although less severe than prednisolone.[242] [1] *Early effects* due to the supra-physiological doses used to induce remission in active CD include cosmetic effects [acne, moon face, oedema, skin striae], sleep and mood disturbance, dyspepsia or glucose intolerance. [2] *Effects associated with prolonged use* [usually >12 weeks, but sometimes less] include posterior subcapsular cataracts, osteoporosis, osteonecrosis of the femoral head, myopathy and susceptibility to infection. Budesonide causes less reduction in bone mineral density than prednisolone [mean –1.04% vs –3.84% over 2 years in a randomized study of 272 patients, p = 0.0084].[301] An increased risk of postoperative sepsis with steroids has been reported in 159 patients with IBD (88 with CD, odds ratio [OR] 3.7, 95% CI 1.2–11.0) which was not seen in patients receiving thiopurine therapy [OR 1.7, CI 0.7–9.6].[58] In addition, several safety cohorts indicate that steroids in combination with other immunosuppressive agents increase the risk of serious infections.[302–305]. [3] *Effects during withdrawal* include acute adrenal insufficiency [from sudden cessation], a syndrome of pseudo-rheumatism [with myalgia, malaise and arthralgia, similar to a recrudesence of CD] or raised intracranial pressure.[306]

Monitoring

Osteoprotective therapy is advisable if the duration of therapy is likely to be >6 weeks, although most advocate supplements of calcium and vitamin D for all patients based on prospective trials.[306,307]

5.4.4 Anti-TNF strategies

ECCO statement 5J

All currently available anti-TNF therapies appear to have similar efficacy in luminal Crohn's disease and similar adverse-event profiles, so the choice depends on availability, route of delivery, patient preference and cost [EL5]

ECCO statement 5K

Particular care should be taken to consider serious infections as a complication of immunosuppressive therapy, including anti-TNF [EL3]

Infliximab and adalimumab are IgG1 anti-TNF monoclonal antibodies with potent anti-inflammatory effects, possibly dependent on apoptosis of inflammatory cells. Certolizumab pegol is a pegylated anti-TNF Fab-antibody fragment with proven clinical efficacy despite the lack of pro-apoptotic effects. Numerous controlled trials have demonstrated efficacy of these anti-TNF agents for active CD.[308] Anti-TNF therapy is effective for active inflammatory CD, but should be used with care in patients with obstructive symptoms. Comparative randomized trials between different anti-TNFs, alone or in combination, and other therapies are not available, although some indirect very detailed meta-analyses are available and can give some interesting insights.[309]

Efficacy as induction therapy for inflammatory CD: infliximab

A multi-centre, double-blind study in 108 patients with moderate-to-severe CD refractory to 5-ASA and steroids[310] did show a 64% response in patients treated with 5–20 mg/kg infliximab compared with 17% given placebo [NNT = 1.6].[35] The duration of response varied, but 48% who had received 5 mg/kg still had a response at week 12. There was no dose response. In a large cohort from the University of Leuven, 89% of patients achieved response [defined by clinician's assessment] after induction therapy with infliximab.[211] Early treatment [top-down therapy] with infliximab has also been compared with a conventional approach [steroids + immunomodulators, step-up therapy].[201] One hundred and thirty steroid-naive patients with recent-onset CD were randomized to initial therapy with infliximab and azathioprine, or to steroids and later azathioprine. Although remission rates at 1 year were similar [77% vs 64%, respectively, $p = 0.15$], 19% on step-up therapy were still on steroids, compared to 0% given top-down therapy [$p < 0.001$]. Endoscopic healing was higher using the top-down approach. The SONIC study randomized 508 patients in a head-to-head, blinded, double dummy comparison of infliximab with and without azathioprine to azathioprine alone. Infliximab 5 mg/kg at 0, 2 and 6 weeks and every 8 weeks thereafter with azathioprine [2.5 mg/kg] was superior to infliximab alone for the induction of steroid-free remission after 26 weeks [57% vs. 45%, $p < 0.05$]. Azathioprine monotherapy was the least effective therapy [30% steroid-free remission after 26 weeks, $p < 0.01$ vs. both infliximab-based regimens].[33,237] Mucosal healing [defined as the disappearance of ulcers] was higher in the combined infliximab azathiopine treatment group compared to the two other groups. In contrast, preliminary data from the recent Canadian COMMIT trial showed no benefit in adding methotrexate to a combination of steroids and infliximab for the induction of clinical remission but high remission rates were achieved in both groups.[283] A network meta-analysis confirmed that infliximab or the combination of infliximab and azathioprine are more effective than placebo in the induction of remission in CD.[309] In a recent 'real-world' retrospective comparison infliximab was more effective than adalimumab and certolizumab in the induction of response in CD, with a comparable rate of serious infections.[310]

Efficacy as induction therapy for inflammatory CD: adalimumab

Adalimumab is a fully human anti-TNF monoclonal antibody given by subcutaneous injection. In the CLASSIC I trial, 299 infliximab-naïve patients with active CD were treated with adalimumab. An induction dose of 160 mg followed by 80 mg at 2 weeks was needed to achieve remission in 36% at 4 weeks compared to 12% receiving placebo [$p < 0.05$].[311] In the GAIN trial the efficacy of adalimumab as a second-line anti-TNF therapy in patients with active CD and with loss of response or intolerance to infliximab [secondary infliximab failures] was assessed. Patients [$n = 325$] were treated with adalimumab 160 then 80 mg or placebo 2 weeks apart. After 4 weeks 21% of adalimumab-treated patients versus 7% of those on placebo were in clinical remission [$p < 0.001$].[312] The remission figures were lower than those in the CLASSIC I trial and suggest that a proportion of patients losing response to a first anti-TNF agent may develop a genuine resistance against this class of agents. A post-hoc analysis of the GAIN trial indicated that concomitant steroids at baseline favoured clinical remission at 4 weeks, but the exact significance of this finding in clinical practice is unclear. After the consensus, data from the open label induction and placebo-controlled maintenance EXTEND trial exploring the efficacy of adalimumab to induce endoscopic healing indicate that, although at 12 weeks there was no benefit for endoscopic healing, adalimumab was significantly better at later time points up to 1 year at healing mucosal ulcers,[313] with better outcomes in those patients reaching mucosal healing.[314] Open data from the extension of pivotal clinical trials and clinic do suggest that flexible strategies with 'escalation' and 'de-escalation' of doses can help to obtain a high rate of long-term response.[315–318] Doses up to 80 mg/week have been reported to be effective and well tolerated in some patients.[319]

Certolizumab pegol

Certolizumab pegol [certolizumab] is a pegylated anti-TNF antibody, administered by subcutaneous injection. In a dose finding trial, 292 patients with moderately to severely active CD received placebo, certolizumab 100, 200 or 400 mg at weeks 0, 4 and 8. At week 2, 33% of patients receiving certolizumab 400 mg vs. 15% [$p = 0.01$] of those receiving placebo experienced a clinical response. Response rates were superior in patients with a baseline CRP ≥ 10 mg/l. Clinical remission rates at week 4 were 8% for placebo and 21% for certolizumab 400 mg.[272] In the Precise -1 trial 662 patients with moderately to severely active CD were randomized to receive certolizumab 400 mg or placebo at week 0, 2 and 4 then every 4 weeks until week 24. Clinical response at week 6 was 37% for certolizumab and 26% for placebo [$p < 0.05$]. Response at both weeks 6 and 26 [co-primary endpoints] was observed in 22% of patients receiving certolizumab and in 12% of patients on placebo [$p = 0.05$]. Certolizumab was superior at inducing clinical remission at week 4 and week 26 but not at other time points. The WELCOME trial explored the efficacy of certolizumab pegol in patients with previous infliximab exposure who lost response to or became intolerant of infliximab [secondary failures].[320] A total of 539 patients received open label certolizumab pegol at 0, 2 and 4 weeks and 329 were randomized to receive 400 mg every 2 or every 4 weeks through 24 weeks from baseline. After open label induction, 39.2% of patients

achieved clinical remission; remission rates for maintenance therapy were 29.2% [certolizumab every 4 weeks] and 30.4% [certolizumab every 2 weeks]. Certolizumab appears to be less effective than infliximab as induction therapy for CD.[309] Open data confirm the usefulness of certolizumab for the treatment of CD.[321]

Adverse effects of anti-TNF therapy

Most side effects associated with anti-TNF therapy in CD can be considered class effects and treatment with anti-TNF is relatively well tolerated if used for appropriate indications. Infusion reactions with infliximab [within 2 h of the infusion] are rare and respond to slowing the infusion rate or treatment with antihistamines, paracetamol and sometimes corticosteroids.[322] Anaphylactic reactions have been reported.[323] A delayed reaction of joint pain and stiffness, fever, myalgia and malaise may occur, especially if there has been an interval >1 year following a previous infusion. Pre-treatment with hydrocortisone is advised in these circumstances, but loss of response over time is common.[305] Infection is the main concern with the use of anti-TNF agents in CD. Active sepsis [such as an abscess] is an absolute contraindication given the risk of overwhelming septicaemia.[323,324] Reactivation or development of tuberculosis has been reported in 24/100 000 patients with rheumatoid arthritis given anti-TNF therapy, compared to 6/100 000 not given such treatment.[325] Because of the increased risk of infections, patients with a fever, cough, systemic symptoms or other unexplained illness should be evaluated for opportunistic infection including tuberculosis or fungal infection, if possible with advice from an infectious diseases' specialist.[326] The theoretical risk of lymphoproliferative disorders or malignancy [in view of the role of endogenous TNF in tumour suppression] has not been confirmed in post-marketing surveillance,[302,305] but follow up is short and a 2009 meta-analysis of all clinical trials with anti-TNF agents in IBD suggested an increased risk of lymphoma comparable to that of thiopurines.[327] Overall, some studies report an annual mortality of up to 1%[323] and risks may be higher in the elderly.[324] However, in a large single-centre cohort the risk of mortality with infliximab was not increased compared to that with non-biological therapy. Also, a meta-analysis of all clinical trials with infliximab in patients with IBD showed no increase in infections, malignancy or mortality over placebo with or without immunosuppressives.[328] In contrast, a post-marketing pharmacovigilance programme suggested that the infectious risk with infliximab is increased in CD.[303]

Long-term combination immunosuppressive therapy [steroids, thiopurines and anti-TNF agents] increases the risk of opportunistic infections and probably of hepato-splenic T-cell lymphoma. Careful patient selection and meticulous follow up may decrease the side effect burden associated with anti-TNF therapy and with the use of immunosuppressives in general.

5.4.5 Anti-adhesion therapy

Natalizumab, a humanized monoclonal antibody against alpha4 integrin that inhibits leukocyte adhesion and migration into inflamed tissue, has been studied in the ENACT-1 trial. In total, 905 patients were randomly assigned to receive 300 mg of natalizumab or placebo at weeks 0, 4 and 8.[329] The natalizumab and placebo groups had similar rates of response [56 and 49%, respectively, $p = 0.05$] and remission [37 and 30%, respectively; $p = 0.12$] at 10 weeks. In contrast, the ENCORE trial evaluated the efficacy of natalizumab 300 mg IV versus placebo at weeks 0, 2 and 4 in 509 patients with moderately to severly active CD and an increased baseline CRP. Clinical response was better in natalizumab patients [48 vs 32%, $p < 0.001$] as was sustained clinical remission. Of note, patients with previous exposure to infliximab responded equally well.[329,330] Natalizumab was much more effective as maintenance therapy. However, due to the risk of progressive multifocal leukoencephalopathy[331] lethal adverse effects, natalizumab is used only for very selected cases of CD in Europe, mostly patients with severe concomitant multiple sclerosis.

Vedolizumab, a more selective, drug-specific anti-integrin agent, directed against $\alpha_4\beta_7$ integrin, has shown efficacy at induction for patients with active CD. In the Gemini-II trial, 386 patients with active CD were randomly assigned to receive vedolizumab 300 mg or placebo at week 0 and week 2. At week 6 more vedolizumab-treated patients achieved CDAI remission [15 vs 7% with placebo, $p = 0.02$].[264] In the Gemini-III trial, patients with moderately to severely active CD were assigned randomly to groups given vedolizumab [300 mg] or placebo intravenously at weeks 0, 2 and 6. The primary analysis involved 315 patients with previous TNF antagonist failure. Among patients who had experienced previous TNF antagonist failure, 15.2% of those given vedolizumab and 12.1% of those given placebo were in remission at week 6 [$p = 0.433$]. At week 10, a higher proportion of the population given vedolizumab were in remission [26.6%] than those given placebo [12.1%].[265] Several cohort studies confirm the effectiveness of vedolizumab.[266,267,332]

5.4.5 Other biological therapies

Another selective anti-adhesion molecule agent, *alicaforsen* [antisense oligonucleotide to human ICAM1], has not shown benefit for active CD at the doses used in clinical trials.[333] However, the anti-*IL12/23 p40 antibody* [*ustekinumab*] has also shown efficacy for inducing clinical response and clinical remission of active CD.[334] In a placebo dose escalating controlled trial, 536 patients with active CD received 1, 3 or 6 mg/kg ustekinumab or placebo I. At 6 weeks, 40% of patients treated with the highest dose of 6 mg/kg ustekinumab achieved clinical response versus 24% of patients treated with placebo [$p = 0.005$], but no improvement in remission rates was observed. Lower doses [1 and 3 mg/kg] were not effective.[335] New confirmatory randomized trials have been presented as abstract[336] and numerous cohort studies suggest efficacy even in ultrarefractory cases [failure of immunosuppresants and anti-TNF].[337–341]

Other novel compounds such as Janus kinase inhibitors, anti-IL-6 antibodies, anti-Madcam antibodies and SMAD7 antisense oligonucleotides are being actively tested. For instance, tofacitinib, an oral Janus kinase inhibitor, has been tested with promising results in UC,[342] but failed to demonstrate better response than placebo in a phase II trial in CD.[343] Mongersen, an oral SMAD7 antisense oligonucleotide, was clearly better than placebo in obtaining clinical response, with a clear dose–response curve, in a clinical trial[344] that was criticised by lack of objective definition of response and is awaiting confirmation in other studies.

5.4.6 Thiopurines

Azathioprine [AZA] 1.5–2.5 mg/kg/day or mercaptopurine [MP] 0.75–1.5 mg/kg/day [unlicensed for use in IBD] may be used in active CD as adjunctive therapy or steroid-sparing agent. However, its slow onset of action precludes its use as a sole therapy for active disease. Purine anti-metabolites inhibit ribonucleotide synthesis, but at least one mechanism of immunomodulation is to induce T-cell apoptosis by modulating cell [Rac1] signalling,[345] and changes in T-cell subpopulations have also been demonstrated.[346] AZA is metabolized to MP and subsequently to 6-thioguanine nucleotides. Thioguanine is discussed in the section on maintenance therapy. Since the main role of thiopurine therapy resides in maintaining remission, dose,

monitoring and side effects will be discussed in the maintenance section of this paper.

Efficacy of thiopurines to induce clinical remission

A Cochrane review of the efficacy of AZA and MP for inducing remission in active CD demonstrated a benefit for thiopurine therapy compared to placebo with an OR of 2.36 [95% CI 1.57 – 3.53].[347,348] This equates to an NNT of 5 and a number needed to harm [NNH] of 14. Owing to the delayed onset of action, the response rate was higher in the studies lasting more than 16 weeks [NNT = 4]. In an attempt to accelerate the onset of action, a trial evaluating the efficacy of a high-dose 36-h infusion was no more effective than conventional oral dosing.[349] Thiopurines are clearly less effective than anti-TNF in the induction of remission in CD.[309]

5.4.7 Methotrexate

Methotrexate may be used in a similar fashion to thiopurines.[350] Polyglutamated metabolites of methotrexate inhibit dihydrofolate reductase, but this cytotoxic effect does not explain its anti-inflammatory effect and inhibition of cytokine and eicosanoid synthesis with modification of adenosine levels probably contribute more.[351]

Efficacy of methotrexate

In a controlled study, 141 steroid-dependent patients with active CD were randomized to either 25 mg/week of intramuscular methotrexate or placebo for 16 weeks, with a concomitant daily dose of prednisolone [20 mg at initiation] that was reduced over a 3-month period. More of the methotrexate-treated group were able to withdraw steroids and enter remission compared to placebo [39 vs 19%; $p = 0.025$].[352] This efficacy has been confirmed in a systematic review.[353] The same indications apply as for thiopurine therapy [see above], but at present, methotrexate is generally reserved for treatment of active or relapsing CD in those refractory to or intolerant of thiopurines or anti-TNF agents.[350,354]

Dose and monitoring

Doses of <15 mg/week are ineffective for active CD, unlike rheumatoid arthritis, and 25 mg/week is the standard induction dose. The prospective controlled trials that demonstrated efficacy in CD used an intramuscular or subcutaneous route.[352,355,356] A significant reduction of drug levels and variability in the absorption of oral methotrexate as compared to subcutaneous administration has been demonstrated,[357] which may explain why parenteral administration seems to be more effective. However, for practical reasons relating to the reconstitution of parenteral cytotoxic drugs, oral dosing is more convenient and often preferred by patients. Consequently, treatment should usually be started via the intramuscular or subcutaneous routes. A switch to oral administration may be attempted for maintenance while carefully monitoring the clinical response, although no trials are available to support this approach. Concurrent administration of folate supplementation is advisable,[358] although no data directly related to CD patients are available. Measurement of full blood count and liver tests are advisable before and within 4 weeks of starting therapy, then at longer intervals. The same caveats as for monitoring thiopurine therapy apply. Patients should remain under specialist follow up. Most agree that therapy can be continued for more than a year.[350,359]

Adverse effects of methotrexate

Early toxicity from methotrexate is primarily gastrointestinal [nausea, vomiting, diarrhoea and stomatitis] and can be limited by coprescription of folic acid 5 mg 2 or 3 days apart from methotrexate. Treatment is discontinued in 10–18% of patients because of side effects.[359] Methotrexate is contraindicated during pregnancy and conception may best be deferred for 6 months after cessation of therapy. The principal long-term concerns are hepatotoxicity and pneumonitis. However, a study of liver biopsies in IBD patients taking methotrexate showed only mild histological abnormalities, despite cumulative doses of up to 5410 mg;[360] and long-term follow-up by elastography also shows little evidence of toxicity.[361] Surveillance liver biopsy is not warranted, but if the aspartate aminotransferase doubles then it is sensible to withhold methotrexate until it returns to normal before a rechallenge. The prevalence of pneumonitis has been estimated to be 2–3 cases per 100 patient-years of exposure, but large series have not reported any cases.[350]

5.4.8 Other immunomodulators

Ciclosporin [CsA] and tacrolimus

The calcineurin inhibitors are of limited value in CD. In three placebo-controlled trials, no efficacy of oral CsA for treatment of CD was demonstrated.[191,362–364] However, three small, uncontrolled case series have reported efficacy of intravenous CsA [4–5 mg/kg/day] for both inflammatory and fistulating CD.[364–366] There are no randomized controlled studies of intravenous CsA. Consequently, oral CsA for steroid-refractory or steroid-dependent CD cannot be recommended.

In contrast, oral tacrolimus for inflammatory CD has only been reported in uncontrolled studies or case reports. These reported short- and long-term therapeutic advantages for steroid-refractory or -depedent patients.[367–372] The limited experience with tacrolimus is insufficient to recommend its general use for therapy of inflammatory luminal CD, but may be effective in perianal fistulous disease.[373]

5.4.9 Nutritional therapy

Efficacy of nutritional therapy

There have been no placebo-controlled trials of nutritional therapy for active CD in adult patients. However, elemental or polymeric diets appear less effective than corticosteroids. In a Cochrane systematic review, the four rigorously controlled trials comparing enteral therapy [in 130 patients] with prednisolone [in 123 patients] showed steroids to be more effective [OR 0.3, 95% CI 0.17–0.52].[270,374] The NNT was 4. There was no difference in efficacy between elemental and polymeric diets. A distinction must be drawn between primary therapy to induce remission and adjunctive therapy to support nutrition. Unlike the management of paediatric/adolescent CD, enteral therapy is regarded as only appropriate for adjunctive treatment to support nutrition and not for primary therapy. It is generally considered appropriate to induce remission only for patients who decline other drug therapy. It is not recommended for steroid-refractory or steroid-dependent disease. However, it is important not to underestimate the role of nutrition as supportive care in patients with CD, even if there is limited evidence to support its use as a primary therapy to induce remission.[375] Total parenteral nutrition is appropriate adjunctive therapy in complex, fistulating disease.

5.5 Complementary and alternative medicine

Complementary and alternative medicine is a group of diverse medical and healthcare systems, practices and products that are not presently considered part of conventional medicine. While evidence of benefit is commonly claimed regarding some therapies, no good quality studies show evidence of real effectiveness. Complementary and alternative therapies are different entities: *complementary*

therapy is used together with conventional medicine, while *alternative therapy* is used in place of conventional medicine. Distinctions ought to be made between alternative therapies, strategies complementary to routine practice, and frank quackery or health frauds.

ECCO statement 5L

Patients with Crohn´s disease should be asked about the use of complementary and alternative medicine [EL5]. The lack of scientific evidence, heterogeneity of the field and economic factors should be discussed with patients expressing a strong interest in CAM [EL5]

6 Management of medically induced remission

6.1 Medical management of patients in medically induced remission

6.1.1 General recommendations

In view of the adverse effects of cigarette smoking on the course of CD, smoking should be discouraged in all patients. Data from observational studies show that smoking increases the need for steroids, immunosuppressants and operations.[376–378] Conversely, smoking cessation may improve the course of the disease.[379,380] Active programmes for smoking addiction should be recommended.[381]

The absolute requirement and choice of medication for prevention of relapse in patients with medically induced remission should take into account three main factors: the course of the disease [initial presentation, frequency and severity of flares], the extent of disease and the effectiveness and tolerance of treatments previously used for induction of remission or maintenance. Other factors such as the presence of biological or endoscopic signs of inflammation and the potential for complications should also be considered. In addition, there may be other constraints [logistic, social or financial] that impact on treatment choices. Finally, patients should be encouraged to participate in the decision-making process.

Patients in remission should be clinically assessed on a regular basis. CRP or faecal calprotectin may be of help in monitoring disease activity. Routinely repeating endoscopy or imaging may help in monitoring disease progression and evolution, although supporting data are still limited and the consequences for adjusting treatment remain unclear.

6.1.2 First presentation of localized disease

ECCO statement 6A

After the first presentation if remission has been achieved with systemic steroids, a thiopurine [EL1] or methotrexate [EL3] should be considered. No maintenance treatment is an option for some patients [EL5]

There is no evidence that mesalazine is useful for maintaining medically induced remission, as the results of meta-analyses are inconsistent [see section 6.2.1]. Some consider that no maintenance treatment is an option after the first flare.[241,382] Taking into account the high risk of relapse and of steroid dependence, and the higher success rate when introduced early, AZA is favoured if remission has been achieved with systemic steroids [see section 6.2.4]. MP [1–1.5 mg/kg/day] can be tried in patients intolerant of AZA [except in cases of pancreatitis and cytopenia].[383,384] Methotrexate is an alternative, especially for patients intolerant of thiopurines [section 6.2.5].

6.1.3 Relapse of localized disease

ECCO statement 6B

If a patient has a relapse, escalation of the maintenance treatment can be considered to prevent disease progression [EL2]. Steroids should not be used to maintain remission [EL1]. Surgery should always be considered as an option in localized disease [EL4]

If a relapse occurs, AZA should be considered [see section 6.2.4]. Corticosteroids [including budesonide] are not effective for maintenance of remission, and the long-term use of corticosteroids is associated with unacceptable side effects, especially osteoporosis. Budesonide increases the time to relapse but is not effective at maintaining remission for 1 year; bone loss is less, but not eliminated [see section 6.2.3].

6.1.4 Extensive disease

ECCO statement 6C

For patients with extensive disease, thiopurines are recommended for maintenance of remission [EL1]. In patients with aggressive/severe disease course or poor prognostic factors, an anti-TNF-based strategy should be considered [EL5]

Taking into account the risks of relapse and the higher success rate when introduced early, AZA is recommended in patients with extensive CD.

6.1.5 Steroid-dependent CD

ECCO statement 6D

Immunosupressive naïve patients who are dependent on corticosteroids should be treated with a thiopurine [EL1] or methotrexate [EL2] or anti-TNF based strategy [EL1]. Surgical options should also be discussed [EL4]

Immunomodulators [AZA/MP, methotrexate] are effective in steroid-dependent CD, although the quality of evidence remains low [NNT = 3].[385–387] Ileal resection is an alternative for those with localized disease depending on other disease characteristics [see surgery section]. A very effective approach to spare steroids is the early introduction of anti-TNF agents. Selection of patients appropriate for biological therapy depends on clinical characteristics and previous response to other medical therapies. Steroid-dependent patients may derive greater benefit from the early introduction of biological therapy.[260] However, a study of 133 patients with active CD who had not previously received glucocorticoids, anti-metabolites or infliximab also suggested benefit of early biological therapy in this relatively treatment naïve group. This trial randomized patients to either early combined immunosuppression or conventional treatment [commonly referred to as the Step Up/Top Down study].[201] At week 52, 61.5% of patients in the combined immunosuppression group were in remission without corticosteroids and without surgical resection compared with 42.2% in the control group [absolute difference 19.3%, 95% CI 2.4–36.3, p = 0.028]. It has now been established [through the SONIC study] that combination treatment

with infliximab and AZA is more effective than infliximab alone for maintaining steroid-free remission in patients at an early stage of disease.[33]

6.1.5 Relapse while on AZA

ECCO statement 6E

Patients receiving thiopurines who relapse should be evaluated for adherence to therapy, and objective signs of inflammation [EL5]. Dose optimisation may improve response rates [EL4]. Where appropriate, therapy should be changed to methotrexate [EL2] or anti-TNF therapy [EL1]. Surgery should always be considered as an option in localised disease [EL4]

Patients receiving AZA or MP who relapse whilst on standard maintenance doses can have their dose escalated [>2.5 mg/kg/day or >1.5 mg/kg/day, respectively] until leucopenia occurs [EL3], or according to 6-thioguanine concentrations [EL2] [see section 5.4.6]. Methotrexate is another option [EL1] [see section 6.2.5]. Anti-TNF therapy has also proven to be effective in this setting [EL1] [see section 6.2.7].

6.1.6 Maintenance after induction of remission with anti-TNF therapy

ECCO statement 6F

If remission has been achieved with the combination of anti-TNF therapy and thiopurines in treatment naïve patients, maintenance with the same regimen is recommended [EL 1]. Thiopurines may be an option as monotherapy in selected patients who have achieved sustained remission on combination therapy [EL3]. If remission has been achieved with anti-TNF monotherapy, maintenance with anti-TNF monotherapy is appropriate [EL1]. Maintenance treatment with vedolizumab is appropriate in patients achieving remission with vedolizumab [EL1]

Patients in a scheduled-treatment strategy with regular infliximab appear to fare better for many [but not all] clinical end-points, compared to patients in an episodic [on-demand] strategy [EL1]. Concomitant immunosuppressant therapy [thiopurines, methotrexate] with anti-TNF agents is not associated with better clinical efficacy in patients who have already failed these drugs [EL1]. However, a combination of infliximab plus AZA is of greater efficacy in achieving and maintaining steroid-free remission than infliximab monotherapy or AZA monotherapy in patients naïve to both therapies [EL1] [see 6.2.7].

6.1.7 Duration of maintenance treatment

ECCO statement 6G

For patients in long term remission on thiopurine maintenance therapy, cessation of treatment may be considered in the absence of objective signs of inflammation [EL2]. No recommendation can be given for the duration of treatment with methotrexate. Prolonged use of anti-TNF agents may be considered if needed [EL3]

ECCO statement 6H

Endoscopic mucosal inflammation may be assessed, even if symptom control is maintained, as mucosal healing has been correlated with reduced hospitalisation and surgeries [EL3]

ECCO statement 6I

Confirmed loss of response to an anti-TNF agent should be first managed by dose optimisation [EL3]. Dose increase or interval shortening are equivalent strategies [EL 4]. If dose optimisation is ineffective, switching to a different anti-TNF agent is recommended [EL 2]. Where available, measurement of serum anti-TNF trough levels and anti-drug antibodies could be used to guide optimisation strategy [EL4]

ECCO statement 6K

Treatment with thiopurines is associated with an increased risk of lymphoma [EL1], non melanoma skin cancers [EL3], and cervical dysplasia [EL3]. Anti-TNF agents increase the risk of melanomas [EL3]. There is currently insufficient data to suggest that anti-TNF agents alone increase the risk of lymphoproliferative disorders or solid tumors. In contrast, their combination with thiopurines significantly increases the risk of lymphoproliferative disorders [EL3]. However, the absolute rates of these malignancies remain low and risks should always be balanced carefully against the substantial benefits associated with these treatments and discussed with the patient [EL5]

A double-blind placebo-controlled non-inferiority study comparing AZA withdrawal with its continuation in patients on AZA for more than >3.5 years found that the rates of relapse after 18 months were 21 and 8%, respectively[388] [see section 6.2.4]. Long-term evaluation of these patients has been recently reported.[389] The median follow-up time after AZA interruption was 54 months; 32 of 66 patients had a relapse. The cumulative probabilities of relapse at 1, 3 and 5 years were 14, 53 and 63%, respectively. Among the 32 relapsing patients, 23 were retreated by AZA alone, all but one achieved successful remission. Thiopurine therapy has been associated with an increased risk of non-Hogkin's lymphoma.[390, 391] Lewis *et al.*[392] conducted a decision analysis study using a Markov model. They concluded that AZA results in increased quality-adjusted life expectancy, especially in young patients who have the lowest baseline risk of lymphoma and the greatest life expectancy in the absence of CD-related death. The benefits of treatment exceed an increase in lymphoma risk postulated by the most extreme studies. A recent extensive meta-analysis confirms these results, and suggests that risk clearly disminishes after discontinuation.[393]

Long-term follow up of CD patients taking methotrexate does not demonstrate an increase risk of severe hepatotoxicity, as previously suggested in other diseases.[360,394] In two series, methotrexate withdrawal in patients maintained for several years with this drug was associated with a high proportion of relapse.[395,396]

The question of whether treatment with anti-TNF agents can be safely interrupted after a period was specifically addressed in the the 'STORI' trial.[209] In total, 115 patients with luminal CD treated for at least 1 year with scheduled infliximab combined with AZA or

methotrexate and in stable remission without steroids for at least 6 months were prospectively recruited into the study. Infliximab therapy was withdrawn, and after the last infusion immunosuppressant therapy was kept at a stable dose. After a median follow-up time of 12 months, 45 relapses were observed. A subgroup of patients with very low risk of relapse could be identified through a combination of biological and endoscopic markers. In relapsing patients, infliximab re-treatment was well tolerated and induced remission. Much more evidence has recently becomed available. To date, 27 studies have been published, one-third of patients relapsing after one year, and a half in longer follow-up; endoscopic remission is a better predictor of no relapse, but on individual terms prediction remains very difficult;[397] retreatment is successful in more than 80% of cases.[397]

6.2. Specific considerations on medications for maintenance of medically induced remission

6.2.1 Aminosalicylates

Evidence

Aminosalicylates efficacy in maintaining clinical remission in CD was extensively reviewed in the previous consensus.[10] No clinically relevant effect has been demonstrated, as confirmed in extensive recent reviews.[252] 5-ASAs are not recommended for maintenance of medically induced remission in CD.

6.2.2 Antibiotics

Evidence

Antibotics were also extensively reviewed in the previous consensus.[10] No further relevant information has been disclosed in recent years, except for a double-blind clinical trial of rifaximin in patients with moderately active CD.[254] In this trial, 800 mg rifaximin was more effective than placebo in obtaining remission in active CD, but 400 and 1200 mg failed to show significant results, and no confirmation of these data is available to date. Ciprofloxacin has been shown to significantly increase the effectiveness of adalimumab in healing perianal fistulas,[398] and other data confirm its utility in perianal disease.[399]

6.2.3 Corticosteroids

Evidence

A meta-analysis of classic corticosteroids such as prednisolone retained three out of eight studies identified in the literature, including 403 patients. The population was heterogeneous: patients had medically or surgically induced remission and had or had not been treated with corticosteroids before. No significant difference was found between steroids and placebo after 6, 12 or 24 months.[298] Budesonide in maintenance was extensively discussed in the previous version of the guideline.[10] A new Cochrane review[259] and another systematic review and meta-analysis[252] fully confirmed the conclusion that 'the modest benefits in terms of lower CDAI scores and longer time to relapse are offset by higher treatment-related adverse event rates'[10] [see previous guideline for detailed report].

6.2.4 Thiopurines

Evidence

An extensive review is available also in the previous guideline.[10] Two recent trials, GETECCU[400] and GETAID,[207] failed to demonstrate a superiority of AZA when introduced early in the evolution of CD. A very recent Cochrane review confirms that thiopurines [AZA and MP] are more effective than placebo in maintenance of remision in CD [RR 1.19, 95% CI 1.05–1.34], with an NNT of 9, although with a low quality of evidence as judged by GRADE criteria, and at the expense of an increased rate of side effects.[387] The low quality of evidence precluded any clear conclusion when comparing thiopurines with budesonide, mesalazine or other comparators.

Summary

These data show that AZA [2–2.5 mg/kg/day] is effective for the maintenance of remission in CD. A steroid-sparing effect has been shown. Recent evidence in adults[207,400] does not confirm the effectiveness of early MP previously reported in paediatric populations.[200] No specific study has been conducted for maintenance of medically induced remission with MP but this drug, used at a lower dose [1–1.5 mg/kg/day], is considered equivalent to AZA.

6.2.5 Methotrexate

Evidence

A recent Cochrane review[386] confirms that 15 mg per week of intramuscular methotrexate is significantly more effective than placebo in maintaining remission in CD [RR 1.67, 95% CI 1.05–2.67]. Combination with infliximab was not found, with limited data, to be more effective than infliximab alone in the maintenance of CD.[386] Oral methotrexate at a dose of 15 mg/week was not more effective than placebo. Although the evidence is very limited, observational data from different sources have shown that long-term toxicity is limited, suggesting that more studies with even higher doses should be considered.[350,359]

Summary

These data indicate that intramuscular methotrexate [15 mg/week] is effective for maintenance of remission in CD, at least in patients in whom remission has been achieved with this agent.

6.2.6 Other immunosuppressants

Evidence

Two placebo-controlled trials failed to show any benefit from oral ciclosporin 5 mg/kg/day given for 3–18 months to induce and maintain remission.[99,101] No controlled studies are available for maintenance of remission by mycophenolate mofetil, tacrolimus, or cyclophosphamide.

Summary

Evidence for the effectiveness of ciclosporin, mycophenolate mofetil, tacrolimus and cyclophosphamide for the maintenance of remission in CD is currently lacking.

6.2.7 Anti-TNF agents

Evidence

The effectiveness of infliximab for maintenance in CD was demonstrated in the ACCENT 1 study[37] [and ACCENT II for fistulising disease[401]] and confirmed in the SONIC study reported in two different analyses.[33,237] Adalimumab effectiveness in maintenance was proved in the CHARM study,[271] with some interesting data on mucosal healing available from the EXTEND study.[313] Certolizumab pegol was found to be effective in maintenance of CD in the PRECISE II study,[402] with some recent new data [open-label] from PRECISE III.[403] Those studies were summarized in the previous version of the guideline,[10] and have been the subject of extensive recent reviews.[308,404] In summary, all anti-TNF agents have been found to be more effective than placebo in maintaining clinical remision, and in the case of

infliximab and adalimumab even mucosal healing,[404] with scheduled treatment being considerably more effective and well tolerated than 'on demand' schedules.[308] There are seven specific points under current discussion, we will address in detail: [a] which drug is best?, [b] combination therapy with immunosuppresants or anti-TNF alone?, [c] safety isssues, [d] the role of therapeutic drug monitoring [TDM] in clinical use of anti-TNF, [e] the emergence of biosimilars, [f] anti-TNF as second-line drugs and [g] when to stop treatment.

No comparative trial is available to our knowledge. Recognizing methodological issues,[405] there are at least three recent high-quality meta-analyses.[309,406,407] Adalimumab and infliximab were found to be not different in the most recent,[309] while adalimumab showed slightly better results in the other two.[406] Adalimumab was more effective than certolizumab in the three reports, and infliximab was superior to certolizumab in two;[406,407] the combination of infliximab plus AZA was better in the other.[309] Further adding to confusion, a recent retrospective analysis of 'real-life' data in 3205 patients suggested infliximab as being superior to adalimumab and certolizumab in CD,[310] while a recent series from Austria showed equivalent efficacy of infliximab and adalimumab in CD.[408] Differences are neither consistent nor huge,[407,409] so the clinician should consider the patient's preferences, local costs and availability issues, when making a specific recommendation.

The only hard evidence favouring combination therapy comes from the SONIC study, where the combination of infliximab and AZA was superior to infliximab in clinical remission and mucosal healing.[33,237] The combination was also found to be more effective, but equivalent to adalimumab, in new network meta-analysis.[309] The combination of methotrexate and infliximab was not better than placebo and infliximab in a randomized study, although the concomitant use of steroids makes the analysis more complex [a type II error more likely]. However, another recent, extensive meta-analysis has not found any evidence of superiority of combination therapy, excluding that infusion reactions seem to be less common when an immunosuppressant is added to infliximab.[410] Combination therapy could, however, reduce immunogenicity;[411] in this case the first 6 months appear to be the most important[308], and in fact at least in children the combination, in this study especially with methotrexate, seems to prolong the effectiveness of the therapy.[412] On the contrary, combination therapy could increase the risk of neoplasia[413] or infection.[414] Considering all the data, it seems that combination therapy improves treatment efficacy in the treatment of CD,[415] and it is clear that 'one size does not fit all',[416,417] age being a key consideration as risk of lymphoma increases.[393,418] Thus, different clinical scenarios can favour combination or monotherapy.[415]

Safety issues have been raised from the very first moment of availability of anti-TNF for clinical use, and we strongly recommend following ECCO's guidelines[326] to prevent infectious complications. Curiously, when considering all the available randomized trials including more than 4000 patients, anti-TNFs did not show more side effects than placebo.[419] A retrospective but population-based study of Danish patients treated with anti-TNF during the period 1999–2012 found no evidence of increased risk of neoplasia associated with anti-TNF, either globally or in several specific subgroup analyses.[420] There are other less frequent, but sometimes very significant clinically, adverse events such as dermatological [psoriasiform lesions are common[421]], neurological, cardiac and hepatic that have been recently extensively reviewed.[422]

The pharmacokinetics of anti-TNF is rather complex, and several individual and dynamic factors can influence blood and tissue levels of the drug.[423,424] A key factor first demonstrated by Leuven's group as early as 2003[425] is immunogeniticy: antibodies against infliximab [ADA] were frequent and showed a relationship with side effects and loss of response. Although sometimes controversial, based on post-hoc analysis or with methodological problems, a considerable amount of evidence suggests that therapeutic drug monitoring could help to tailor the treatment of CD.[426] A systematic review published in 2012[427] observed a close relatinonship between trough levels of anti-TNF and maintenance of the response to these drugs, concluding that testing drug and antibody levels should be useful in helping to optimize treatment. Infliximab[428–430] and adalimumab[430–432] levels have been demonstrated having some relationship to clinical response. Local factors[433] could explain an even better correlation when tissue levels are measured instead of blood levels.[434] Some practical algorithms have been suggested for helping in clinical decisions taking into account drug and antibodies levels.[435,436] When considering dose escalation ['intensification'] an open clinical trial demonstrated that the measuring of drug levels was cost-effective.[437] However, a randomized clinical trial failed to demonstrate superiority of this strategy over expert clinical decision,[438] although some secondary analysis suggested possible utility [fewer flares, lower costs]. In summary, although many questions remain to be solved, there is general agreement that therapeutic drug monitoring can help in difficult clinical decisions, especially when evaluating primary and secondary failures or considering intensification.[426,439] Some very recent data suggest that early immunogenicity can have predictive value about the failure of anti-TNF treatment in the long term.[440]

Biosimilars have been marketed in Europe from 2006, but the very first biosimilar monoclonal antibody approved by EMA in 2014 was CT-P13 [Remsima®, Inflectra®], a biosimilar of the originator infliximab [Remicade®]. EMA defines with very stringent criteria biosimilarity,[441] but for the indication of CT-P13 in inflammatory bowel disease based its decision using 'extrapolation', a concept which was controversial for clinicians as reflected in the first ECCO position statement which asked for clinical trials in IBD populations,[442] and reflected by some experts.[443] The EMA concept was further developed and explained,[444,445] and is currently widely accepted;[446,447] a new ECCO position statement will be released in 2017. Although somewhat limited, currently available pharmacological[448] and clinical data[449,450] suggest that CT-P13 is clinically equivalent to Remicade®. Health Canada has accepted the indications of IBD for CT-P13, the FDA has approved the biosimilar for all the indications of the original infliximab, and EMA has now approved the second infliximab biosimilar [Flixabi®]. Pharmacovigilance and investigator-driven studies will be very important for defining the role of biosimilars in the future treatment of IBD.

Failure [primary, secondary or intolerance] of treatment is common even with anti-TNF drugs.[308] In these patients, a second anti-TNF can be used to try to obtain a response. In a recent systematic review including randomized controlled and observational studies, a global 43% rate of remission and 63% of response were observed.[451] Most interestingly the success rate varied according to the clinical situation. Primary failures reached remission in 30% of cases, secondary failures in 45%, and in case of intolerance to the previous anti-TNF it was 60%.[451] Much less evidence is available if a third anti-TNF is used, but a significant number of patients can be rescued, and respose can be observed in 50% of cases.[452] If an anti-TNF is adequately maintaining remission a change to another [whatever the reason] should be avoided if possible, because there is substantial probability of losing response.[453,454]

Patients' fears, stable disease, safety considerations or [in most cases] cost issues drive the decision to withdraw treatment in some

patients.[455,456] In the STORI trial 44% of patients relapsed in the first year while maintaining immunosuppresants, and several factors were found to be predictive of relapse: low haemoglobin, high faecal calprotectin, white cell count, high CRP, absence of surgical resection and male sex.[209] Perianal disease was identified as a key prognostic factor in a small series previously published.[457] However, only faecal calprotectin, young age and white cell count were identified as predictive in a recent retrospective observational study,[455] while CRP, platelet count and short exposure were identified in other clinical series.[458] In other long-term series, 52% of sustained clinical remission was maintained 10 years after discontinuation, with age >25 years as the only remaining prognostic factor after multivariant analysis.[459] In a systematic review and meta-analysis relapse rate was 38% at 6 months, 40% at 12 months and 49% at >25 months,[397] and no clear prognostic factor could be defined, although endoscopic remission had better prognosis than clinical remission. Following relapse, re-introduction of the anti-TNF achieves remission in more than 80% of cases.[460]

Summary

There is evidence that infliximab, adalimumab and certolizumab pegol are effective for maintenance of remission in patients with luminal CD who have a clinical response to induction therapy. Infliximab and adalimumab are currently approved for use in CD in many countries, while certolizumab pegol is not approved in the European Union. In the case of infliximab, combination with AZA [and probably methotrexate] is more effective, but monotherapy may be preferred in some clinical scenarios. No new relevant safety signals have been raised in recent years. Biosimilars of infliximab are probably clinically equivalent and have been made available in Europe, North America and many other countries. In some clinical scenarios measuring drug and antibodies to drug levels can help in taking clinical decisions. Comparative data between drugs are only indirect, and conflicting. Patients' preferences [route of administration being key for many] should always be considered.

6.2.8 Other biological therapies

Natalizumab, a humanized anti-α4 integrin monoclonal antibody, was investigated for maintenance of response and remission in CD [ENACT-2 study]: 339 patients with a response [ΔCDAI ≥–70] or remission after induction with natalizumab [ENACT-1, a 905-patient induction study – see section 5.4.5] were allocated to receive infusions of placebo or 300 mg natalizumab every 4 weeks for 12 months.[329] Maintenance natalizumab resulted in higher rates of sustained response [61 vs 28%, $p < 0.001$] and remission [44 vs 26%, $p = 0.003$] through week 36 than did switching to placebo.[329] Despite this promising result for maintenance, treatment with natalizumab was not approved in the European Union due to cases of progressive multifocal leucoencephalopathy that occurred in several patients with multiple sclerosis and one patient with CD.[329,331,461–464] However, taking into account JC virus status, the impressive results of natalizumab can justify its use in selected patients.[465–467]

Vedolizumab, a humanized antibody directed against the $\alpha_4\beta_7$ integrin, has shown efficacy not only in induction therapy, but also in maintenance. It has been approved for the treatment of CD by EMA and FDA.[468] In the Gemini-II trial, clinical remission was maintained in 39, 36.4 and 21.6% of patients over a year in vedolizumab every 4 weeks [$p < 0.001$ for placebo comparison], vedolizumab every 8 weeks [$p = 0.004$] and placebo arms, respectively, with significant differences in steroid-free remission rates, but no significant differences in 'durable' remission [defined as remission in >80% of the total visits].[264] In the Gemini-III trial only limited data were available from long-term follow up, but data suggested superiority over placebo.[265] Several recently published cohort studies from the USA,[469–471] Germany[472] and France[473] confirm the clinical utility of vedolizumab in the long-term treatment of patients with CD. There are, however, no comparative trials with anti-TNF and the place of vedolizumab in the CD treatment algorithm remains to be defined.[468] The most recent data available on safety indicate that vedolizumab has a favourable safety profile, with low incidence of serious infections [mild nasopharyngitis being the most common reported adverse effect] and few infusion-reactions [<5% of patients]. No signal of augmented incidence of any malignancy has been observed in the extended treatment period. As of 2016, no case of multifocal leucoencephalopathy has been associated with vedolizumab treatment.[268] The different mechanism of action raises the interesting possibility of combining two biologicals for treating IBD, which will be explored in difficult clinical cases.[474]

Ustekinumab, an anti-IL12/23 p40 antibody, has also shown effectiveness in maintenance, but data from recent trials are available only in abstract form.[336] Several cohort studies do suggest efficacy even in ultrarefractory cases [failure of immunosuppresants and anti-TNF].[337–341] Two series with more than 100 patients and long-term follow up from GÉTAID[341] and GETECCU[475] suggest that remission can be maintained in roughly 50% of patients for 12 months, with very low incidence of adverse effects. Ustekinumab can be very useful in the case of psoriasiform lesions associated with anti-TNF treatment while being also active in CD.[340,341,475,476]

There are a number of new biologics being evaluated, but they are not likely to be approved in the next 2 years, and due to limitations of space we cannot discuss them.

6.2.9 Diet therapy

Omega-3 fatty acids: evidence

A more detailed review of published evidence is available in the previous guideline.[10] A recent Cochrane Database review has been published.[477] When all six available studies were included, a marginal significant benefit was found [RR 0.77, 95% CI 0.61–0.98]. However, a GRADE analysis of the studies demonstrated considerable heterogeneity, and high risk of publication bias. There was no significant benefit when only the two studies of high methodological quality were included [RR 0.88, 95% CI 0.74–1.05]. Moreover, no serious adverse effects were observed but both diarrhoea [RR 1.36, 95% CI 1.10–1.84] and upper GI symptoms [RR 1.65, 95% CI 1.25–2.18] were significantly more common in the active arm.[477] Heterogeneity of the data also precluded firm conclusions in another very detailed systematic review.[478]

Omega-3 fatty acids: summary

For maintenance of medically induced remission in CD, high-quality studies suggest that omega-3 fatty acids are probably ineffective in maintaining remission in CD, while causing new symptoms in a significative portion of patients. The use of omega-3 fatty acids cannot be recommended for the maintenance treatment of CD [EL1].

Nutritional supplementation: evidence

In the previous guidelines[10] citing the evidence from two main studies and a Cochrane Database review[479] it was concluded that insufficient evidence to support enteral nutrional supplementation was available. A more recent and extensive systematic review and meta-analysis[480] found that elemental diet was superior to placebo in

maintaining remission at 24 months [RR 2.06, 95% CI 1.00–4.43] or preventing relapse at 12–24 months post baseline [RR 0.57, 95% CI 0.38–0.84]. However, the evidence was of very low quality in some of the analyses, mucosal healing was not found to be different [RR 2.70, 95% CI 0.62–11.72], adherence to elemental diet was less than to polymeric, and elemental diet was not different from medications, polymeric diet or combinations.[480] There was insufficient information on side effects and no cost-effectiveness data. A potential benefit of elemental diet cannot be excluded, but its use cannot be recommended based on the available evidence.

Nutritional supplementation: summary

Evidence does not support enteral nutritional supplementation as being effective for the maintenance of remission in CD [EL1].

6.2.10 Probiotics

Evidence

In the previous guideline[10] the evidence for probiotics in CD was reviewed in some detail, without evidence to justify the use of pre- and/or probiotics in the long-term treatment of CD. No recent trial has demonstrated a clinically measurable effect of probiotics in CD.[481] The title of a recent clinical trial suggested a possible effect in the prevention of recurrence, at least when considering inflammation at the anastomotic site,[482] but no difference in endoscopic or clinical recurrence was demonstrated.

Summary

There is no evidence to suggest that probiotics are beneficial for the maintenance of remission in CD [EL1].

6.2.11 Cytapheresis and autologous stem cell transplantation

The effectiveness of leukocyte apheresis has been claimed in a number of non-controlled studies,[483] with variable results[484]; but the procedure failed to show effectiveness in a double-blind controlled randomized trial.[485] Even as recent observational data continue to suggest efficacy in steroid-refractory or steroid-dependent patients,[486] the lack of evidence in controlled settings suggests that leukocyte apheresis cannot be recommended out of clinical studies.

A number of case reports and series suggest that autologous hematopoetic stem cell transplantation could be effective for refractory Crohn's disease.[487–489] However, a complex randomized clinical trial failed to show statistically significant improvement with a therapy associated with significant toxicity.[490] Improvements in treatment protocols could make this treatment adequate for ultra-refractory cases with few other options.[491]

6.2.12 General conclusion

Efficacious medications for maintaining medically-induced remission in Crohn's disease are well established [EL1], including azathioprine, infliximab, adalimumab, and vedolizumab. There is also a reasonable level of evidence [EL1] for ustekinumab, methotrexate, certolizumab and natalizumab [EL1]. The efficacy of mesalazine [EL1] and omega-3 fatty acids [EL1] remain controversial, due to inconsistent results. There is insufficient evidence to support the use of enteral nutritional supplementation, *Saccharomyces boulardii*, E. coli Nissle 1917, cytapheresis and autologous stem cell transplantation. The available evidence shows that ciclosporin, anti-mycobacterial agents, and *Lactobacillus* GG are ineffective.

Conflict of Interest

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References

References for this paper are available as supplementary data at *ECCO-JCC* online.