Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2021-B-230 Risankizumab

Stand: September 2021

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Risankizumab

Behandlung des mittelschweren bis schweren aktiven Morbus Crohn bei Erwachsenen und Jugendlichen ab 16 Jahren

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	Patientenindividuell: Operation
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Verfahren nach § 35a SGB V: - Vedolizumab (Beschluss vom 08.01.2015) Verfahren nach § 35 Abs.1 SGB V: Arzneimittel-Richtlinie/Anlage IX: Festbetragsgruppenbildung Infliximab, Gruppe 1, in Stufe 1 (Beschluss vom 17.11.2017) Arzneimittel-Richtlinie/Anlage IX und X: Festbetragsgruppenbildung und Vergleichsgrößenaktualisierung – TNF-alpha-Inhibitoren, Gruppe 1, in Stufe 2 (Beschluss vom 20.11.2020) Verfahren nach § 92 Abs. 1 Satz 2 Nummer 6 und Absatz 6 in Verbindung mit § 138 des Fünften Buches Sozialgesetzbuch SGB V: Heilmittel-Richtlinie/2.Teil Heilmittelkatalog: 4 Sonstige Erkrankungen: vorrangige Heilmittel: Bindegewebsmassage, Colonmassage; ergänzendes Heilmittel: Wärmetherapie (Beschluss vom 19.05.2011)

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Risankizumab **Behandlung des mittelschweren bis schweren aktiven Morbus Crohn bei Erwachsenen und Jugendlichen ab 16 Jahren** **Kriterien gemäß 5. Kapitel § 6 VerfO**	
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	Siehe systematische Literaturrecherche

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Risankizumab L04AC18 Skyrizi	Geplantes Anwendungsgebiet laut Beratungsanforderung: Risankizumab wird angewendet zur Behandlung des mittelschweren bis schweren aktiven Morbus Crohn bei Erwachsenen und Jugendlichen ab 16 Jahren, die auf eine konventionelle Therapie unzureichend angesprochen, das Ansprechen verloren haben oder diese nicht vertragen haben.
Tumornekrosefaktor alpha (TNF-alpha)-Inhibitoren	
Infliximab L04AB02 generisch z.B. REMICADE®	Remicade ist indiziert zur: -Behandlung eines mäßig- bis schwergradig aktiven Morbus Crohn bei erwachsenen Patienten, die trotz eines vollständigen und adäquaten Therapiezyklus mit einem Kortikosteroid und/oder einem Immunsuppressivum nicht angesprochen haben oder die eine Unverträglichkeit oder Kontraindikationen für solche Therapien haben. -Behandlung von aktivem Morbus Crohn mit Fistelbildung bei erwachsenen Patienten, die trotz eines vollständigen und adäquaten Therapiezyklus mit einer konventionellen Behandlung (einschließlich Antibiotika, Drainage und immunsuppressiver Therapie) nicht angesprochen haben. <u>Morbus Crohn bei Kindern und Jugendlichen</u> Remicade ist indiziert zur Behandlung eines schwergradigen, aktiven Morbus Crohn bei Kindern und Jugendlichen im Alter von 6 bis 17 Jahren, die nicht auf eine konventionelle Therapie einschließlich einem Kortikosteroid, einem Immunmodulator und einer primären Ernährungstherapie angesprochen haben oder die eine Unverträglichkeit oder Kontraindikationen für solche Therapien haben. Remicade wurde nur in Kombination mit einer konventionellen immunsuppressiven Therapie untersucht.
Adalimumab L04AB04 Humira®	Humira ist indiziert zur Behandlung des mittelschweren bis schweren, aktiven Morbus Crohn bei erwachsenen Patienten, die trotz einer vollständigen und adäquaten Therapie mit einem Glukokortikoid und/oder einem Immunsuppressivum nicht ausreichend angesprochen haben oder die eine Unverträglichkeit gegenüber einer solchen Therapie haben oder bei denen eine solche Therapie kontraindiziert ist. <u>Morbus Crohn bei Kindern und Jugendlichen</u> Humira wird angewendet zur Behandlung des mittelschweren bis schweren, aktiven Morbus Crohn bei Kindern und Jugendlichen (ab dem Alter von 6 Jahren), die nur unzureichend auf eine konventionelle Therapie, einschließlich primärer Ernährungstherapie und einem Kortikosteroid und/oder einem Immunsuppressivum, angesprochen haben oder die eine Unverträglichkeit gegenüber einer solchen Therapie haben oder bei denen eine solche Therapie kontraindiziert ist.

II. Zugelassene Arzneimittel im Anwendungsgebiet

Interleukin-Inhibitor	
Ustekinumab L04AC05 STELARA® Konzentrat, Injektionslösung, Fertigspritze	Stelara ist indiziert für die Behandlung erwachsener Patienten mit mittelschwerem bis schwerem aktiven Morbus Crohn, die entweder auf eine konventionelle Therapie oder einen der Tumornekrosefaktor-alpha (TNFα)-Antagonisten unzureichend angesprochen haben, nicht mehr darauf ansprechen oder eine Unverträglichkeit oder eine Kontraindikation gegen eine entsprechende Behandlung aufweisen. <u>Kinder und Jugendliche</u> Die Sicherheit und Wirksamkeit von STELARA zur Behandlung des Morbus Crohn oder Colitis ulcerosa bei Kindern und Jugendlichen unter 18 Jahren sind bisher noch nicht erwiesen. Es liegen keine Daten vor.
Integrininhibitor	
Vedolizumab L04AA33 ENTYVIO®	Vedolizumab (Entyvio®) ist indiziert für die Behandlung von erwachsenen Patienten mit mittelschwerem bis schwerem aktiven Morbus Crohn, die entweder auf konventionelle Therapie oder einen der Tumornekrosefaktor-alpha (TNFα)-Antagonisten unzureichend angesprochen haben, nicht mehr darauf ansprechen oder eine Unverträglichkeit gegen eine entsprechende Behandlung aufweisen. <u>Kinder und Jugendliche</u> Die Sicherheit und Wirksamkeit von Vedolizumab bei Kindern im Alter von 0 bis 17 Jahren ist nicht erwiesen. Es liegen keine Daten vor.
Immunsupressiva	
Azathioprin L04AX01 generisch z.B. Azathioprin-ratiopharm®	Azathioprin ist in Fällen der folgenden Erkrankungen bei Patienten, die Steroide nicht vertragen, die steroidabhängig sind oder bei denen trotz hochdosierter Behandlung mit Steroiden keine ausreichende oder nachhaltige therapeutische Wirkung erzielt werden kann, angezeigt: – schwere oder mittelschwere entzündliche Darmerkrankungen (Morbus Crohn oder Colitis ulcerosa) <u>Kinder und Jugendliche</u> Für den Einsatz von Azathioprin bei der Behandlung der juvenilen idiopathischen Arthritis (JIA), des systemischen Lupus erythematodes, einer Dermatomyositis oder einer Polyarteriitis nodosa bei Kindern und Jugendlichen unter 18 Jahren liegen keine ausreichenden Daten vor. In Bezug auf die anderen Indikationen gelten die Dosisempfehlungen gleichermaßen für Kinder, Jugendliche und Erwachsene.
Methotrexat L01BA01 generisch	Behandlung von leichtem bis mittelschwerem Morbus Crohn, entweder allein oder in Kombination mit Kortikosteroiden bei erwachsenen Patienten, die auf Thiopurine nicht ansprechen oder diese nicht vertragen.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
z.B. Metex® 50mg/ ml Inj.lsg, FS	Aufgrund mangelnder Erfahrung bei Kindern und Jugendlichen wird Metex zur Behandlung von Morbus Crohn bei dieser Patientengruppe nicht empfohlen.
Aminosalicylsäuren	
Mesalazin A07EC02 z.B. Salofalk®	Morbus Crohn: zur Behandlung des akuten Schubs <u>Kinder und Jugendliche:</u> Die Wirksamkeit bei Kindern (6 – 18 Jahre) ist nur in begrenztem Umfang belegt.
Sulfasalazin A07EC01 z.B. Azulfidine®	Akutbehandlung des milden bis moderaten Morbus Crohn bei Befall des Kolon
Kortikosteroide	
Budenosid A07EA06 generisch z.B. Budenofalk®, Tab	Akuter Morbus Crohn leichten bis mittelschweren Grades mit Beteiligung des Ileums (Krummdarm) und/oder des Colon ascendens (Teil des Dickdarms). <u>Jugendliche</u> Die Sicherheit und Wirksamkeit von Budenofalk® 3mg bei Kindern von 12 bis 18 Jahren wurden bisher nicht nachgewiesen. Gegenwärtig verfügbare Daten zu jugendlichen Patienten (12 bis 18 Jahre) mit Morbus Crohn oder mit Autoimmunhepatitis werden in den Abschnitten 4.8 und 5.1 beschrieben. Es können jedoch keine Dosierungsempfehlungen gegeben werden.
Hydrocortison-acetat Colifoam® H02AB09 Rektalschaum	Entzündliche Erkrankungen im unteren Dickdarmbereich wie Colitis ulcerosa oder Morbus Crohn und Proktosigmoiditis. <u>Kinder und Jugendliche</u> Es liegen keine Daten vor.
Prednison H02A B07 generisch z.B. Prednison-ratiopharm® 5 mg Tabletten	Morbus Crohn (Dosierung: 40-80 mg/Tag)
Prednisolon	Morbus Crohn (Dosierung: 40-80 mg/Tag)

II. Zugelassene Arzneimittel im Anwendungsgebiet	
H02AB06 generisch z.B. Decortin-H®,Tab	
Methylprednisolon H02AB04 generisch z.B. Methylprednisolon JENAPHARM®	Morbus Crohn (Dosierung: 40-80 mg/Tag)
Quellmittel	
Indische Flohsamen und Flohsamenschalen A06AC51 Agiocur Madaus	Stuhlunregelmäßigkeiten beim irritablen Kolon, bei Divertikulose, beim Anus praeter und unterstützend beim Morbus Crohn.

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2021-B-230 (Risankizumab)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	1. September 2021

Inhaltsverzeichnis

Abkürzungsverzeichnis

ADA	adalimumab
AE	adverse events
AGA	American Gastroenterological Association
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
ATA	antibodies to adalimumab
AZA	Azathioprine
BNF	British national formulary
BNFC	British national formulary for children
BSG	British Society of Gastroenterology
CD	Crohns' disease
CDAI	Crohn's disease activity index
ECCO	European Crohn's and Colitis Organisation
ECRI	ECRI Guidelines Trust
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GL	guideline
GoR	Grade of Recommendations
HBI	Harvey Bradshaw Index
HR	Hazard Ratio
IFX	infliximab
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
IMM	immunomodulators
KI	Konfidenzintervall
LoE	Level of Evidence
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
RR	Relatives Risiko
SAE	serious adverse events
SIGN	Scottish Intercollegiate Guidelines Network
TPMP	thiopurine methyltransferase
TRIP	Turn Research into Practice Database
UST	ustekinumab
VDZ	vedolizumab
WHO	World Health Organization

1 Indikation

Zur Behandlung des mittelschweren bis schweren aktiven Morbus Crohn bei Erwachsenen und Jugendlichen ab 16 Jahren, die auf eine konventionelle Therapie unzureichend angesprochen, das Ansprechen verloren haben oder diese nicht vertragen haben.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Morbus Crohn* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 02.08.2021 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, ECRI, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Die Recherche ergab 1404 Quellen. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 17 Quellen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

G-BA, 2020 [5].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage IX (Festbetragsgruppenbildung) und Anlage X (Vergleichsgruppenaktualisierung) – TNF-alpha-Inhibitoren, Gruppe 1, in Stufe 2 vom 20. November 2020

I. Die Arzneimittel-Richtlinie wird wie folgt geändert:

1. In Anlage IX wird folgende Festbetragsgruppe „TNF-alpha-Inhibitoren, Gruppe 1“ in Stufe 2 eingefügt:

Stufe: 2

Wirkstoffgruppe: TNF-alpha-Inhibitoren

Festbetragsgruppe Nr.: 1

Status: verschreibungspflichtig

Wirkstoffe und Vergleichsgrößen:
Adalimumab – Vergleichsgröße 231
Certolizumab pegol – Vergleichsgröße 1156
Etanercept – Vergleichsgröße 625
Golimumab – Vergleichsgröße 166

Gruppenbeschreibung: subkutane Darreichungsformen (Adalimumab >20mg, Etanercept >10mg, Golimumab >45mg)

Darreichungsformen: Injektionslösung, Pulver und Lösungsmittel zur Herstellung einer Injektionslösung

G-BA, 2017 [6].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage IX – Festbetragsgruppenbildung Infliximab, Gruppe 1, in Stufe 1 nach §35 Abs. 1 SGB V vom 17. November 2017

I. In Anlage IX der Arzneimittel-Richtlinie wird folgende Festbetragsgruppe „Infliximab, Gruppe 1“ in Stufe 1 eingefügt:

Stufe: 1

Wirkstoffgruppe: Infliximab

Festbetragsgruppe Nr.: 1

Status: verschreibungspflichtig

Gruppenbeschreibung: parenterale Darreichungsformen

Darreichungsformen: Pulver für ein Konzentrat zur Herstellung einer Infusionslösung

G-BA, 2015 [7].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 8. Januar 2015 – Vedolizumab

Anwendungsgebiet

Colitis ulcerosa

Vedolizumab (Entyvio®) ist indiziert für die Behandlung von erwachsenen Patienten mit mittelschwerer bis schwerer aktiver Colitis ulcerosa, die entweder auf konventionelle Therapie oder einen der Tumornekrosefaktor-alpha (TNFα)-Antagonisten unzureichend angesprochen haben, nicht mehr darauf ansprechen oder eine Unverträglichkeit gegen eine entsprechende Behandlung aufweisen.

Morbus Crohn

Vedolizumab (Entyvio®) ist indiziert für die Behandlung von erwachsenen Patienten mit mittelschwerem bis schwerem aktiven Morbus Crohn, die entweder auf konventionelle Therapie oder einen der Tumornekrosefaktor-alpha (TNFα)-Antagonisten unzureichend angesprochen haben, nicht mehr darauf ansprechen oder eine Unverträglichkeit gegen eine entsprechende Behandlung aufweisen.

Zweckmäßige Vergleichstherapie und Ausmaß des Zusatznutzens

a) Patienten mit mittelschwerer bis schwerer aktiver Colitis ulcerosa, die auf konventionelle Therapie unzureichend angesprochen haben, nicht mehr darauf ansprechen oder eine Unverträglichkeit gegen eine entsprechende Behandlung aufweisen.

Zweckmäßige Vergleichstherapie:

Ein TNF-alpha-Antagonist (Adalimumab oder Infliximab)

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Adalimumab:

Ein Zusatznutzen ist nicht belegt.

b) Patienten mit mittelschwerer bis schwerer aktiver Colitis ulcerosa, die auf einen der Tumornekrosefaktor-alpha (TNFα)-Antagonisten unzureichend angesprochen haben, nicht mehr darauf ansprechen oder eine Unverträglichkeit gegen eine entsprechende Behandlung aufweisen.

Zweckmäßige Vergleichstherapie:

Ein TNF-alpha-Antagonist (Adalimumab oder Infliximab unter Berücksichtigung der Vortherapien)

(Hinweis: Bei Versagen der Therapie mit einem TNF-alpha-Antagonisten (Adalimumab oder Infliximab) ist eine Dosisanpassung oder ein Wechsel auf jeweils den anderen TNF-alpha-Antagonisten möglich.)

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Adalimumab:

Ein Zusatznutzen ist nicht belegt.

c) Patienten mit mittelschwerem bis schwerem aktiven Morbus Crohn, die auf konventionelle Therapie unzureichend angesprochen haben, nicht mehr darauf ansprechen oder eine Unverträglichkeit gegen eine entsprechende Behandlung aufweisen.

Zweckmäßige Vergleichstherapie:

Ein TNF-alpha-Antagonist (Adalimumab oder Infliximab)

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Adalimumab:

Ein Zusatznutzen ist nicht belegt.

d) Patienten mit mittelschwerem bis schwerem aktiven Morbus Crohn, die auf einen der Tumornekrosefaktor-alpha (TNFα)-Antagonisten unzureichend angesprochen haben, nicht mehr darauf ansprechen oder eine Unverträglichkeit gegen eine entsprechende Behandlung aufweisen.

Zweckmäßige Vergleichstherapie:

Ein TNF-alpha-Antagonist (Adalimumab oder Infliximab unter Berücksichtigung der Vortherapien)

(Hinweis: Bei Versagen der Therapie mit einem TNF-alpha-Antagonisten (Adalimumab oder Infliximab) ist eine Dosisanpassung oder ein Wechsel auf jeweils den anderen TNFalpha-Antagonisten möglich.)

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Adalimumab:

Ein Zusatznutzen ist nicht belegt.

G-BA, 2011 [4].

Verfahren nach § 92 Abs. 1 Satz 2 Nummer 6 und Absatz 6 in Verbindung mit § 138 des Fünften Buches Sozialgesetzbuch SGB V: Heilmittel-Richtlinie/2.Teil Heilmittelkatalog: 4 Sonstige Erkrankungen: vorrangige Heilmittel: Bindegewebsmassage, Colonmassage; ergänzendes Heilmittel: Wärmetherapie (Beschluss vom 19.05.2011)

4 Sonstige Erkrankungen

Diagnosengruppe:

SO1 Störung der Dickdarmfunktion (z.B. neurogene Darmlähmungen bei ZNS-Erkrankungen/Rückenmarkserkrankungen, Colon irritable, Colitis ulcerosa, Morbus Crohn, Megakolon)

Leitsymptomatik: Funktionelle/strukturelle Schädigung

a) Vorübergehende oder dauerhafte chronische Schädigung der intestinalen Funktion mit Schmerzen, Durchfall, Obstipation oder Flatulenz

Ziel der Physikalischen Therapie:

Besserung des Stoffwechsels, Regulierung der Darmmotilität

Heilmittelverordnung im Regelfall

Vorrangiges Heilmittel: Colonmassage, Bindegewebsmassage

Ergänzendes Heilmittel: Wärmetherapie

Verordnungsmengen je Diagnose; weitere Hinweise

Erst-Verordnung: bis zu 6x/Verordnung

Folge-Verordnung: bis zu 6x/Verordnung

Gesamtverordnungsmenge des Regelfalls: bis zu 12 Einheiten

Frequenzempfehlung: mindestens 2x wöchentlich

3.2 Cochrane Reviews

Es wurden keine relevanten Cochrane Reviews identifiziert.

3.3 Systematische Reviews

Yoshihara T et al., 2021 [17].

Concomitant use of an immunomodulator with ustekinumab as an induction therapy for Crohn's disease: a systematic review and meta-analysis.

Fragestellung

This study aimed to provide a systematic review and meta-analysis comparing the efficacy and safety of concomitant use of an IM with UST as an induction therapy for CD patients.

Methodik

Population:

- patients who were diagnosed as CD and treated with UST

Intervention:

- concomitant use of an IM (thiopurines or methotrexate) with UST

Komparator:

- UST monotherapy

Endpunkte:

- clinical efficacy at weeks 6–12 defined as clinical remission (CDAI score ≤150 points or HBI score ≤4 points), or clinical response (decrease from baseline in CDAI score of at least 100 points or a total CDAI score less than 150 or reduction of 3 points of HBI score from the baseline), or clinical benefit defined as physician's global assessment
- clinical remission at weeks 6–12
- clinical response at weeks 6–12
- adverse events

Recherche/Suchzeitraum:

- until October 31, 2019

Qualitätsbewertung der Studien:

RoB 2 and ROBINS-I for bias assessment, GRADE for assessment of the certainty of the evidence

Ergebnisse

Anzahl eingeschlossener Studien:

- n= 7 studies in six articles with a total of 1507 patients

Charakteristika der Population:

Table 1 Characteristics of included studies

Author (year)	Study design	Country	Sample	Patients	UST regimen	Type of IMs	No. of patients in the concomitant IM group and monotherapy group	Outcome	Outcome definition	OR	95% CI	Serious adverse events	
												Concomitant IM group	Monotherapy group
Sandborn *et al.* (2012, CERTIFI)	Prospective observational study†	12 countries	526 patients at 153 centers	Moderate-to-severe CD that was resistant to anti-TNF treatment (CDAI: 220 to 450)	UST was administered in doses of 6 mg/kg of body weight at week 0	Thiopurines or methotrexate	35, 96	Clinical response at week 6	Clinical response: decrease from baseline in CDAI score of at least 100 points or a total CDAI score less than 150	1.018	0.466–2.225	NA	NA
Feagan *et al.* (2016, UNITI-1)	Prospective observational study†	23 countries	741 patients at 175 centers	Moderate-to-severe CD that was resistant to anti-TNF treatment (CDAI: 220 to 450)	UST initial intravenous infusion using weight-based dose (260 mg < 55 kg, 390 mg between 55 and 85 kg, 520 mg > 85 kg) or single intravenous infusion of 130 mg of UST at week 0	Thiopurines or methotrexate	152, 342	Clinical response at week 6	Clinical response: decrease from baseline in CDAI score of at least 100 points or a total CDAI score less than 150	1.102	0.739–1.644	NA	NA
Feagan *et al.* (2016, UNITI-2)	Prospective observational study†	23 countries	628 patients at 175 centers	Moderate-to-severe CD that was resistant to IMs or glucocorticoids treatment (CDAI: 220 to 450)	UST initial intravenous infusion using weight-based dose (260 mg < 55 kg, 390 mg between 55 and 85 kg, 520 mg > 85 kg) or single intravenous infusion of 130 mg of UST at week 0	Thiopurines or methotrexate	146, 272	Clinical response at week 6	Clinical response: decrease from baseline in CDAI score of at least 100 points or a total CDAI score less than 150	1.655	1.100–2.490	NA	NA
Wils *et al.* (2016)	Retrospective observational study	France	122 patients at 20 centers	CD patients who were failed to one or more anti-TNF treatment	13 different UST induction regimens were used. The most common regimen was UST 90-mg SC at weeks 0 and 4	Thiopurines or methotrexate	18, 104	Clinical benefit at 3 months	Clinical benefit was defined as a significant improvement in CD-related clinical symptoms and laboratory tests	5.43‡	1.14–25.77	NA	NA
Khorrami *et al.* (2016)	Retrospective observational study	Spain	116 patients at 42 centers	CD patients who were refractory, or intolerant to one or more anti-TNF treatment	Different induction regimens were used. The most f requent induction regimen was UST 90-mg SC at weeks 0, 1, 2, and 3	No information	42, 74	Clinical response or remission at 8–12 weeks	Clinical response: reduction of 3 points of HBI score from the baseline, clinical remission: HBI score ≤4 points	1.73	0.57–5.26	NA	NA
Greenup *et al.* (2017)		Canada		Anti-TNF experienced	UST 90-mg SC at weeks 0, 1 and 2,		30, 43		Symptomatic response was	1.46	0.54–3.94	NA	NA

(Continues)

Table 1 (Continued)

Author (year)	Study design	Country	Sample	Patients	UST regimen	Type of IMs	No. of patients in the concomitant IM group and monotherapy group	Outcome	Outcome definition	OR	95% CI	Serious adverse events	
												Concomitant IM group	Monotherapy group
	Retrospective observational study		73 patients at a single center	CD patients who required alternative therapy	or UST 270-mg SC at week 0 and UST 180-mg SC at weeks 1 and 2	Azathioprine or methotrexate		Symptomatic response at 3 months	defined as physicians documentation of resolution or reduction of CD-associated symptoms				
Biemans *et al.* (2019)	Prospective observational study	Netherlands	153 patients by a nationwide registry	CD patients who were failed to anti-TNF or vedolizumab therapy, the median HBI of participants was 7 (IQR: 4–11)	Initial UST intravenous infusion using weight-based dose (260 mg < 55 kg, 390 mg between 55 and 85 kg, 520 mg > 85 kg) at week 0 and UST 90-mg SC at week 8	Thiopurines or methotrexate	33, 120	Clinical remission at week 12	Clinical remission: HBI score ≤4 points	1.004	0.42–2.43	6.5 per 100 PY	2.9 per 100 PY

CD, Crohn's disease; CDAI, Crohn's disease activity index; CI, confidence interval; HBI, Harvey Bradshaw index; IM, immunomodulator; NA, not assessed; OR, odds ratio; SC, subcutaneous injection; PY, patient-years; UST, ustekinumab.
†These studies were conducted as randomized control trial, but concomitant use of an IM was not the target of randomization.
‡The OR was adjusted by the confounder (C-reactive protein >5 mg/L).

Qualität der Studien:

- We considered the quality of this meta-analysis to be "low" based on the GRADE assessment because these studies were non-randomized studies and had a serious risk of bias.

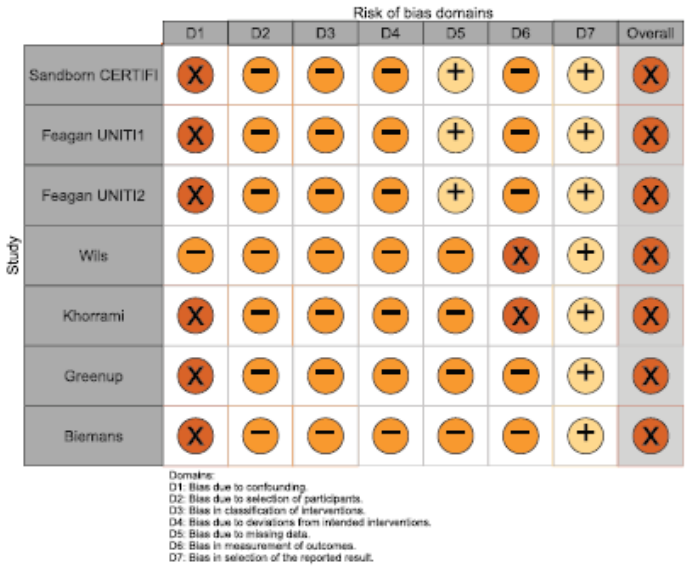

Figure 2 Risk of bias assessment for individual studies according to the risk of bias in non-randomized studies-of interventions (ROBINS-I) tool. All studies had a serious risk in the overall judgment. Judgment: serious; moderate; low. [Color figure can be viewed at wileyonlinelibrary.com]

Studienergebnisse:

Overall clinical efficacy

In this meta-analysis, concomitant use of an IM with UST was significantly effective than UST monotherapy as an induction therapy (a pooled OR: 1.35; 95% CI [1.06–1.71], P = 0.015 in the fixed-effects model: Fig. 3a). (n=1501 patients)

Clinical remission

n=1 study → therefore, a pooled OR could not be calculated

Clinical response

Concomitant use of an IM with UST was also significantly effective than UST monotherapy in this analysis (a pooled OR: 1.32; 95% CI [1.02–1.72], P = 0.036 in the fixedeffects model: Fig. 3b). (n= 1159 patients in four studies)

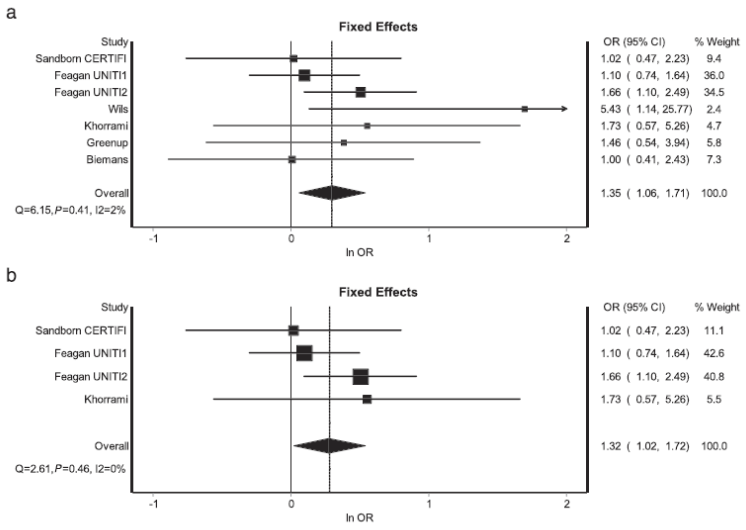

Figure 3 Forest plots for each outcome comparing the clinical efficacy of ustekinumab (UST) monotherapy group and the concomitant immunomodulator (IM) group as an induction therapy in a fixed-effects model using the inverse variance (IV) method. The concomitant use of IM with UST was significantly effective than the UST monotherapy in both the analyses. (a) Overall clinical efficacy (clinical remission, or clinical response, or clinical benefit defined as the physicians' global assessment): a pooled odds ratio (OR); 1.35; 95% confidence interval CI [1.06–1.71], P = 0.015. (b) Clinical response: a pooled OR: 1.32; 95% CI [1.02–1.72], P = 0.036.

Adverse events

n=1 study → therefore, a pooled OR could not be calculated

Anmerkung/Fazit der Autoren

In conclusion, this meta-analysis showed that concomitant use of an IM with UST is more effective than UST monotherapy for an induction therapy to CD patients. There is no RCT regarding with or without an IM in therapy with UST; in addition, the data for safety of the therapy with concomitant use of an IM and UST are limited. Therefore further studies are necessary to clarify whether or not the concomitant use of an IM may benefit CD patients who have induction therapy with UST.

Kommentare zum Review

- Endpunkt "overall efficacy" setzt sich sowohl aus objektiven Kriterien (clinical remission (CDAI score ≤150 points or HBI score ≤4 points), or clinical response (decrease from baseline in CDAI score of at least 100 points or a total CDAI score less than 150 or reduction of 3 points of HBI score from the baseline)) als auch aus der Bewertung der Behandelnden zusammen

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Kawalec P et al., 2017 [9].

An indirect comparison of ustekinumab and vedolizumab in the therapy of TNF-failure Crohn's disease patients.

Fragestellung

The objective of this indirect comparison was to evaluate the clinical efficacy and safety of two immunosuppressive monoclonal antibodies: ustekinumab and vedolizumab, in patients with active Crohn's disease who were intolerant or nonresponsive to previous TNF-antagonist treatment.

Methodik

<u>Population:</u>

Patients with active CD and intolerant or nonresponsive to TNF-therapy

Intervention und Komparator:

Ustekinumab; Vedolizumab (indirekter Vergleich)

Endpunkte:

- Clinical response in induction and maintenance phase: ≥100-point decrease in CDAI at week 6 of therapy
- Clinical remission in induction and maintenance phase: CDAI of 150 or less
- Frequency of any AEs and SAEs, AEs associated with infusion or injection-site reactions/ infusion reactions and infections

Recherche/Suchzeitraum:

- until 30 April 2017

Qualitätsbewertung der Studien:

- Cochrane RoB

Hinweise zum indirekten Vergleich:

- The studies were homogeneous enough to perform an indirect comparison for the induction phase. For the maintenance phase, only two trials occurred eligible for the indirect comparison (IM-UNITI/ UNITI-1 and GEMINI-2)
- According to the recommendations of European network for Health Technology Assessment, the choice of indirect comparison method should be considered based on available evidence. In our opinion, the available RCTs and relevant data placed Bucher's method over NMA so we used a more transparent way to provide the best available evidence for the comparison of considered biological drugs in CD therapy.

Ergebnisse

Anzahl eingeschlossener Studien:

- N= 5
  - 2 RCTs (in 2 publications) regarding ustekinumab and 2 RCTs (in 3 publications) regarding vedolizumab eligible for indirect comparison

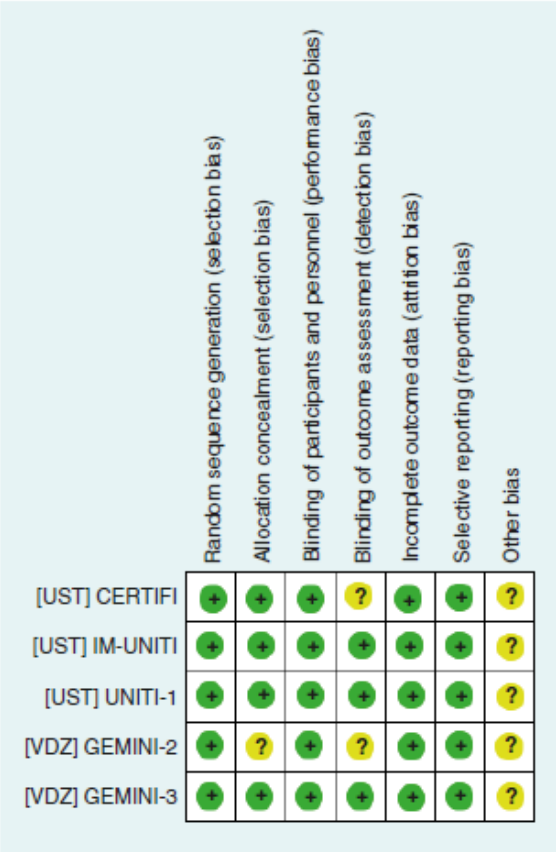
Charakteristika der Population:

Table S1. Analysis of homogeneity of the included studies

Analysis of homogeneity						
Reference	**Methodology**	**Patients**	**End points**	**Intervention**	**Follow up period (efficacy)**	**Follow up period (safety)**
Ustekinumab						
Sandborn 2012 [13] CERTIFI	RCT, multinational, multicenter, phase 3, parallel-group, double-blind, placebo-controlled	Patients at age of at least 18 years and at least a 3-month history of CD with a score of 220 to 450 points on the CDAI	Clinical response (≥100-point decrease from the baseline CDAI score) at week 6 Clinical remission (CDAI score <150 points) at week 6	UST 1, 3, or 6 mg per kg or placebo during the induction phase (weeks 0 to 8); patients were randomly assigned to receive intravenous UST 6 mg per kg (n=131) or placebo (n=132) UST (90 mg) or placebo at weeks 8 and 16, with efficacy assessed at week 22 during the maintenance phase (weeks 8 to 36), patients who had a response to UST as induction therapy and those who did not have a response underwent separate randomization to receive *s.c.*	6 weeks – induction phase 22 weeks – maintenance phase	6 weeks – induction phase 22 weeks – maintenance phase
Feagan 2016 [14] UNITI-1 and IM-UNITI	RCT, multinational, multicenter, phase 3, parallel-group, double-blind, placebo-controlled	Patients 18 years of age or older who had had CD for at least 3 months and had a score on the CDAI of 220 to 450 out of a possible range of 0 to 600 patients were required to have received one or more TNF	Clinical response at week 6 (decrease from baseline in CDAI score of at least 100 points or a total CDAI score less than 150)	UST *i.v.* 130 mg or 6 mg per kg, or placebo during the induction phase patients were randomly assigned to receive intravenous UST 6 mg per kg (n=249) or placebo (n=247)	6 weeks – induction phase 52 weeks maintenance phase (44 weeks of maintenance and 8 weeks of	6 weeks – induction phase 52 weeks maintenance phase (44 weeks of maintenance and 8 weeks of therapy in induction phase)

Analysis of homogeneity						
Reference	**Methodology**	**Patients**	**End points**	**Intervention**	**Follow up period (efficacy)**	**Follow up period (safety)**
		antagonists at approved doses and to have met the criteria for primary nonresponse (the absence of a response) or secondary nonresponse (a response that was not maintained) or to have had unacceptable side effects	Clinical remission at week 8 (CDAI score <150) Clinical response at week 8 (decrease from baseline in CDAI score of at least 70 points at weeks 3 and 6)	UST *s.c.* 90 mg every 8 or 12 weeks, or placebo through week 44	therapy in induction phase) –	
Sandborn 2013 [15] GEMINI-2	RCT, multinational, multicenter, phase 3, parallel-group, double-blind, placebo-controlled	Patients (age 18–80 years) with CD for at least 3 months (score of 220 to 450 on the CDAI) and with no response to or unacceptable side effects from one or more of the following: glucocorticoids, immunosuppressive agents or TNF antagonists	Clinical remission (CDAI score of ≤150 points) Clinical response (CDAI-100 response: ≥100-point decrease in the CDAI score)	patients were randomly assigned to receive: VDZ 300 mg *i.v.* (n=105) or placebo (n=70) treatment was given at weeks 0 and 2 for induction therapy	6 weeks – induction phase 52 weeks – maintenance phase	6 weeks – induction phase 52 weeks – maintenance phase
Sands 2014 [16] GEMINI-3	RCT, multinational, multicenter, phase 3, double-blind, placebo-controlled	Patients (age 19–77 years) with CD for at least 3 months (score of 220 to 400 on the CDAI) and with no response to or unacceptable side effects from one or more of the following: glucocorticoids, immunosuppressive agents or TNF antagonists	Clinical remission (CDAI score of ≤150 points) Clinical response (CDAI-100 response: ≥100-point decrease in the CDAI score)	patients were randomly assigned to receive VDZ 300 mg *i.v.* (n=158) or placebo (n=157) treatment was given at weeks 0, 2 and 6 for induction therapy	6 weeks – induction phase	6 weeks – induction phase

Qualität der Studien:



Studienergebnisse:

Clinical response

- […] revealed **no significant difference** between ustekinumab and vedolizumab with regard to achieving clinical response at week 6 during induction phase of therapy.

Clinical remission

- The overall results of the indirect comparison demonstrated that ustekinumab (for dosing regimen including 6 mg/kg) was **as effective as** vedolizumab (300 mg) for induction of clinical remission at week 6.
- In the maintenance phase, there was **no significant difference** between ustekinumab and vedolizumab for clinical remission after a total of 52 weeks of treatment in a subpopulation of patients who were intolerant or refractory to TNF-antagonist treatment

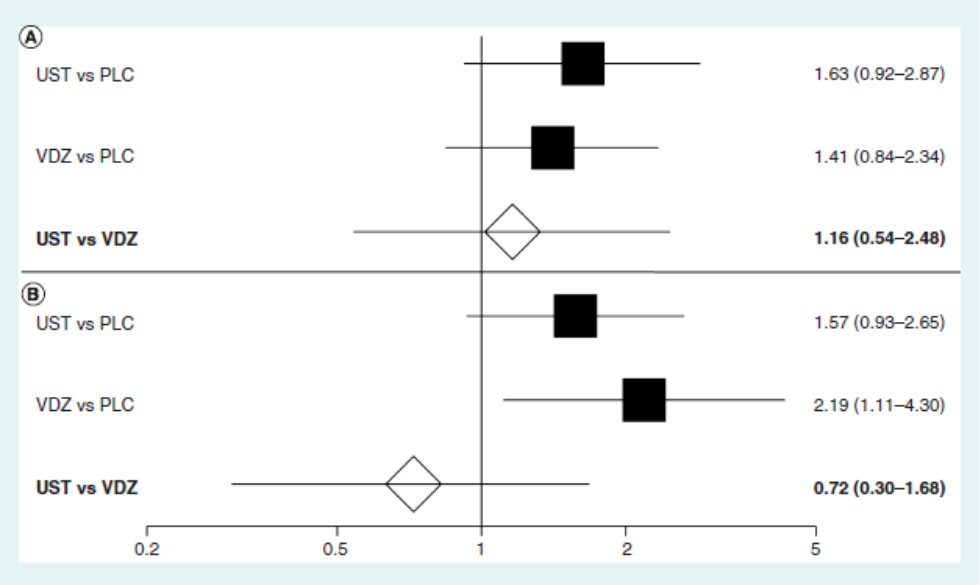


Figure 4. Indirect comparison of ustekinumab and vedolizumab for clinical remission in a subpopulation of Crohn's disease patients with TNF treatment failure or intolerance. (A) Induction phase of therapy; **(B)** Maintenance phase of therapy.
PLC: Placebo; UST: Ustekinumab; VDZ: Vedolizumab.

Safety outcomes in induction and maintenance phase

- In regard to the risk of any AEs during short-term induction phase of treatment (6–10 weeks) **no significant difference** between ustekinumab and vedolizumab was revealed; there were also **no significant differences** in the frequency of any SAEs, serious infections or infusion-related reactions in the induction phase of therapy.
- An indirect comparison revealed **no statistically significant** differences between ustekinumab and vedolizumab in the frequency of any AEs and SAEs in the maintenance phase. […] risk of any infections or probability of serious infections occurred similar […].

Anmerkung/Fazit der Autoren

- No statistically significant differences between ustekinumab and vedolizumab in clinical response and clinical remission for induction and remission in maintenance phase of therapy were revealed in the TNF-antagonist failure population as well as in primary and secondary nonresponders. In addition, a similar safety profile was revealed for the considered drugs.

Kommentare zum Review

- Vergleich der Ergebnisse zur Erhaltungsphase beruht auf lediglich zwei Studien

3.4 Leitlinien

Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF), 2021 [2].

Deutsche Gesellschaft für Gastroenterologie, Verdauungs-und Stoffwechselkrankheiten (DGVS)

Diagnostik und Therapie des Morbus Crohn; S3 Leitlinie, Langfassung.

Zielsetzung/Fragestellung

Ziel der Leitlinie soll sein, in der hausärztlichen, internistischen, chirurgischen, pädiatrischen und gastroenterologischen Praxis einfach anwendbar zu sein. Die Behandlung besonders schwerer oder komplizierter Fälle, wie sie in Spezialambulanzen und spezialisierten Praxen erfolgt, kann durch diese Leitlinie nicht vollständig abgebildet werden. Patientenzielgruppe sind Patient*innen mit M. Crohn jeden Alters.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert: Die Gültigkeit wird auf fünf Jahre geschätzt (2026)

Recherche/Suchzeitraum:

- Die systematische Recherche nach Literatur schließt an die Vorgängerversion an und wurde in der Zeit vom 02. Juni 2012 bis 12. Mai 2020 in der Medline-Datenbank über die PubMed-Suchoberfläche für 16 Schlüsselfragen

LoE/GoR

Tabelle 4: Schema zur Graduierung von Empfehlungen

Empfehlungsgrad (nur S3)[1]	Beschreibung	Syntax
A	starke Empfehlung	soll
B	Empfehlung	sollte
0	Empfehlung offen	kann

Die Konsensusstärke wurde gemäß Tabelle 5 festgelegt.

Tabelle 5: Einteilung der Konsensstärke

Konsens	% Zustimmung
Starker Konsens	> 95
Konsens	> 75 - 95
Mehrheitliche Zustimmung	> 50 - 75
Kein Konsens	≤ 50

Empfehlungen, die unverändert aus der letzten Leitlinie übernommen wurden, wurden mit „geprüft 2020“ gekennzeichnet. Die mit „modifiziert 2020“ gekennzeichneten Empfehlungen wurden im Vergleich zur vorherigen Version von 2014 verändert.

Empfehlungen

Empfehlung 2.1 (neu 2020)

Vor Einleitung oder Änderungen der medikamentösen Therapie sollte die entzündliche Aktivität objektiviert werden.

Expertenkonsens, Empfehlung, starker Konsens

Empfehlung 2.3 (neu 2020)

Nach Therapiebeginn oder -wechsel sollten zur Evaluation des Therapieansprechens innerhalb der ersten drei Monate neben klinischen Parametern biochemische Marker wie CRP und/oder fäkales Calprotectin sowie eine Darmsonographie herangezogen werden.

Expertenkonsens, Empfehlung, Konsens

Klug Entscheiden

Empfehlung 2.4 (neu 2020)

Vor der Einleitung einer Therapie mit Immunsuppressiva oder Biologika sollte eine chirurgische Intervention als Alternative geprüft werden.

Evidenzgrad 4, Empfehlungsgrad B, starker Konsens

Empfehlung 2.5 (neu 2020)

Bei persistierender oder erneuter Aktivität eines M. Crohn sollte die bisherige Therapie optimiert werden (Prüfung der Adhärenz, Dosis, Dosierungsintervalle, Komedikation) bevor eine Umstellung der Therapie erfolgt.

Expertenkonsens, Empfehlung, Konsens

Empfehlung 2.6 (neu 2020)

Bei Versagen der bisherigen Therapie sollten die Diagnosesicherheit geprüft, eine Re-Evaluierung der Erkrankungsaktivität und ein Ausschluss anderer Ursachen einer klinischen Verschlechterung erfolgen, sowie der Einsatz anderer, bisher nicht verwendeter Wirkprinzipien oder chirurgischer Therapieoptionen interdisziplinär diskutiert werden.

Expertenkonsens, Empfehlung, starker Konsens

Empfehlung 2.9 (geprüft 2020)

M. Crohn-Patient*innen mit Befall der Ileozökalregion und/oder des rechtsseitigen Colons und hoher Entzündungsaktivität sollen initial mit systemisch wirkenden Steroiden behandelt werden.

Evidenzgrad 1, Empfehlungsgrad A, starker Konsens

Patient*innen mit aktiver Colitis-Crohn sollen initial mit systemischen Glukokortikoiden behandelt werden.

Expertenkonsens, starke Empfehlung, Konsens

Empfehlung 2.10 (modifiziert 2020)

Bei distalem Colon-Befall können Suppositorien, Klysmen oder Schäume (Mesalazin, Budesonid, Steroide) eingesetzt werden.

Expertenkonsens, Empfehlung offen, starker Konsens

Empfehlung 2.11 (neu 2020)

M. Crohn-Patient*innen mit ausgedehntem Dünndarmbefall und/oder Befall des oberen GI-Traktes sollten initial mit systemisch wirkenden Steroiden behandelt werden. Eine frühzeitige immunsuppressive Therapie oder Therapie mit TNF-α-Antikörpern (im Falle von Infliximab ist die Kombination mit Thiopurinen zu erwägen), Ustekinumab oder Vedolizumab sollten erwogen werden*.

Expertenkonsens, Empfehlung, starker Konsens

**Die Medikamente sind alphabetisch gereiht. Wenn nicht anders angegeben, impliziert diese Reihung keine Priorisierung für den klinischen Einsatz.*

Empfehlung 2.12 (neu 2020)

Der steroidrefraktäre M. Crohn mit mittlerer bis hoher Krankheitsaktivität sollte primär mit TNF-α-Antikörpern (im Falle von Infliximab ggf. kombiniert mit einem Thiopurin) oder Ustekinumab oder Vedolizumab behandelt werden*.

Expertenkonses, Empfehlung, Konsens

**Die Medikamente sind alphabetisch gereiht. Wenn nicht anders angegeben, impliziert diese Reihung keine Priorisierung für den klinischen Einsatz.*

Statement 2.13 (neu 2020)

Bei einem isolierten Befall der Ileozökalregion, kurzer Anamnese und fehlendem Ansprechen auf Steroide ist das operative Vorgehen (Ileozökalresektion) verglichen mit der Therapie mit Infliximab als gleichwertig anzusehen.

Expertenkonsens, Konsens

Klug Entscheiden

Empfehlung 2.14 (neu 2020)

Bei einer elektiv geplanten Operation sollte präoperativ eine Beurteilung des Ernährungszustandes erfolgen und bei der Feststellung von Defiziten ein Ausgleich mit enteraler oder parenteraler Zusatzernährung vorgenommen werden.

Expertenkonsens, Empfehlung, starker Konsens

Empfehlung 2.15 (neu 2020)
Eine präoperative Steroidtherapie sollte zur Senkung des perioperativen Komplikationsrisikos reduziert oder wenn möglich beendet werden. *Expertenkonsens, Empfehlung, starker Konsens*

Empfehlung 2.16 (neu 2020)
Über den Einfluss einer präoperativen Therapie mit Thiopurinen oder Biologika auf perioperative Komplikationen kann keine sichere Aussage getroffen werden. Eine präoperative Fortsetzung der Therapie sollte daher gegen das Risiko der Therapiepause vor einer elektiven Operation wegen eines damit verbundenen Risikos für das Auftreten einer vermehrten Aktivität abgewogen werden. *Expertenkonsens, Empfehlung, starker Konsens*

Empfehlung 2.17 (neu 2020)
Patient*innen mit einem steroidabhängigen M. Crohn sollten mit einem Thiopurinen, MTX oder einem TNF-α-Antikörper (im Falle von Infliximab ggf. kombiniert mit Thiopurinen), Ustekinumab oder Vedolizumab behandelt werden*. *Expertenkonsens, Empfehlung, starker Konsens*

**Die Medikamente sind alphabetisch gereiht. Wenn nicht anders angegeben, impliziert diese Reihung keine Priorisierung für den klinischen Einsatz.*

Kinder und Jugendliche:

Empfehlung 2.18 (modifiziert 2020)
Bei Kindern und Jugendlichen soll zur Remissionsinduktion des M. Crohn primär eine exklusive, enterale Ernährungstherapie statt einer Therapie mit Steroiden durchgeführt werden. *Evidenzgrad 1, Empfehlungsgrad A, starker Konsens*

Empfehlung 2.19 (modifiziert 2020)
Bei Kindern mit mittelschweren oder schweren M. Crohn soll eine frühzeitige immunsuppressive Therapie und/ oder Therapie mit Biologika erfolgen. *Evidenzgrad 1, Empfehlungsgrad A, starker Konsens*

Empfehlung 2.20 (modifiziert 2020)

Bei Wachstumsverzögerung, umschriebenem Befall oder anhaltender Krankheitsaktivität trotz optimierter konservativer Therapie soll eine elektive Operation frühzeitig erwogen werden.

Evidenzgrad 4, Empfehlungsgrad A, starker Konsens

Empfehlung 2.21 (geprüft 2020)

Pubertätsentwicklungsverzögerungen sollten bei heranwachsenden M. Crohn-Patient*innen nicht mit wachstumsfördernden Hormonen behandelt werden.

Evidenzgrad 4, Empfehlungsgrad B, starker Konsens

Remissionserhaltung

Empfehlung 3.2 (modifiziert 2020)

Die Indikation zur remissionserhaltenden Therapie, die Wahl des anzuwendenden Medikamentes und die Dauer der Therapie sollte unter Berücksichtigung des individuellen Krankheitsverlaufs, des spezifischen Risikoprofils, der Vortherapien und der Patient*innenpräferenz festgelegt werden.

Expertenkonsens, Empfehlung, starker Konsens

Empfehlung 3.3 (geprüft 2020)

Bei für Kinder und Jugendliche prinzipiell gleich geltenden Therapieprinzipien, wie für Erwachsene, sollte allerdings beachtet werden, dass zusätzlich Wachstumsretardierung und verzögerte Pubertät als besondere Zeichen der Krankheitsaktivität für die Therapieentscheidung bedeutsam sind.

Evidenzgrad 4, Empfehlungsgrad B, starker Konsens

Empfehlung 3.5 (modifiziert 2020)

Systemische Steroide sollen nicht zur Remissionserhaltung eingesetzt werden.

Expertenkonsens, starke Empfehlung, starker Konsens
Klug Entscheiden

Empfehlung 3.6 (neu 2020)
Nach einer Remissionsinduktion sollte in Abhängigkeit von der remissionsinduzierenden Substanz und der Krankheitsvorgeschichte eine remissionserhaltende Therapie mit Azathioprin / 6-Mercaptopurin, MTX, TNF-α-Antikörpern, Ustekinumab oder Vedolizumab durchgeführt werden*. *Expertenkonsens, Empfehlung, starker Konsens* Bei mildem Verlauf kann ein abwartendes Verhalten ohne remissionserhaltende Therapie erwogen werden. *Expertenkonsens, Empfehlung offen, starker Konsens*

**Die Medikamente sind alphabetisch gereiht. Wenn nicht anders angegeben, impliziert diese Reihung keine Priorisierung für den klinischen Einsatz.*

Empfehlung 3.7 (neu 2020)
Erleidet ein*e Patient*in ein Rezidiv der entzündlichen Aktivität soll eine Re-Evaluation der Krankheitssituation vorgenommen werden, um über die weitere Therapie zu entscheiden. Dabei soll auch eine chirurgische Option bedacht werden. *Expertenkonsens, Empfehlung, starker Konsens*

Empfehlung 3.8 (neu 2020)
Bei einem steroidabhängigen Verlauf sollte unter Berücksichtigung einer Nutzenrisikoabwägung eine remissionserhaltende Therapie mit Thiopurinen, MTX oder eine Therapie mit TNF-α-Antikörpern, Ustekinumab oder Vedolizumab durchgeführt werden*. *Expertenkonsens, Empfehlung, starker Konsens*

**Die Medikamente sind alphabetisch gereiht. Wenn nicht anders angegeben, impliziert diese Reihung keine Priorisierung für den klinischen Einsatz.*

Empfehlung 3.9 (neu 2020)
Bei Risikofaktoren wie beispielsweise jungem Erkrankungsalter, langstreckigem Dünndarmbefall oder perianalem M. Crohn kann unter Nutzen-/Risikoabwägung eine Kombinationstherapie von Infliximab und Thiopurinen gegenüber einer Infliximab-Monotherapie auch zur Remissionserhaltung eingesetzt werden. *Expertenkonsens, Empfehlung offen, starker Konsens*

Empfehlung 3.10 (modifiziert 2020)
Bei einer dualen Immunsuppression mit Azathioprin/6-Mercaptopurin und TNF-α-Antikörpern sollte nach Erreichen einer stabilen Remission wegen der erhöhten Nebenwirkungsrate eine Monotherapie entweder mit Thiopurinen oder mit TNF-α-Antikörpern angestrebt werden. *Expertenkonsens, Empfehlung, starker Konsens*

Empfehlung 3.13 (neu 2020)
Eine generelle Empfehlung zur Dauer einer remissionserhaltenden Therapie mit Immunsuppressiva oder Biologika kann aufgrund fehlender Evidenz nicht gegeben werden. *Expertenkonsens, Empfehlung offen, starker Konsens*

Empfehlung 3.14 (neu 2020)
Bei einer länger bestehenden, stabilen klinischen Remissionsphase unter einer Thiopurin- oder Biologika-Therapie ohne begleitende Steroidmedikation und ohne nachweisbare Entzündungszeichen kann eine Beendigung der immunsuppressiven Therapie erwogen werden. *Expertenkonsens, Empfehlung offen, starker Konsens*

Feuerstein J et al., 2021 [3].

American Gastroenterological Association (AGA)

AGA clinical practice guidelines on the medical management of moderate to severe luminal and perianal fistulizing Crohn's disease;

→ siehe auch das dazugehörige Technical Review [15] und Clinical Decision Support Tool [1]

Zielsetzung/Fragestellung

This guideline "focuses on drugs and treatment strategies for the management of adult (18 years and older) outpatients with moderate to severe luminal and/or fistulizing (including perianal) CD. Patients with moderate to severe luminal CD are those with moderate to severe disease activity based on the Crohn's Disease Activity Index (CDAI), patients who are corticosteroid-dependent or have corticosteroidrefractory CD, and/or patients with severe endoscopic disease activity (large and/or deep ulcers). Although we intended to address management of fistulizing CD, most of the evidence for fistulizing disease is reported for perianal CD".

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium: trifft teilweise zu
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt: trifft teilweise zu
- Systematische Suche, Auswahl und Bewertung der Eviden: trifft zu
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt: trifft zu
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt: trifft zu
- Regelmäßige Überprüfung der Aktualität gesichert: trifft zu

Recherche/Suchzeitraum:

The search was initially conducted on August 4, 2019. A focused update using PubMed for new randomized controlled trials (RCTs) on PICOs of interestwas performed on July 31, 2020.

LoE und GoR:

- Certainty of the evidence was assessed using the GRADE framework:
  - ‘High’: We are confident that the true effect lies close to the estimate of the effect.
  - ‘Moderate’: We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
  - ‘Low’: Our confidence in the estimate is limited. The true effect may be substantially different from the estimate of effect.
  - ‘Very low’: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.
  - ‘Evidence gap’: Available evidence is insufficient to determine true effect.

Table 2. Grading of Recommendations Assessment, Development and Evaluation Definitions on Strength of Recommendation and Guide to Interpretation

Strength of recommendation	Wording in the guideline	For the patient	For the clinician
Strong	“The AGA recommends…”	Most individuals in this situation would want the recommended course and only a small proportion would not.	Most individuals should receive the recommended course of action. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.
Conditional	“The AGA suggests…”	The majority of individuals in this situation would want the suggested course, but many would not.	Different choices would be appropriate for different patients. Decision aids may be useful in helping individuals in making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working towards a decision.
No recommendation	“The AGA makes no recommendation…”		The confidence in the effect estimate is so low that any effect estimate is speculative at this time.

Empfehlungen

Recommendation 2A: In adult outpatients with moderate to severe CD who are naïve to biologic drugs, the AGA recommends the use of infliximab, adalimumab, or ustekinumab, over certolizumab pegol for the induction of remission *(Strong recommendation, moderate certainty evidence)* and suggests the use of vedolizumab over certolizumab pegol for the induction of remission. *(Conditional recommendation, low certainty evidence)*

Recommendation 2B. In adult outpatients with moderate to severe CD who never responded to anti-TNFa (primary nonresponse), the AGA recommends the use of ustekinumab *(Strong recommendation, moderate certainty evidence)* and suggests the use of vedolizumab over no treatment for the induction of remission. *(Conditional recommendation, low certainty evidence)*

Recommendation 2C. In adult outpatients with moderate to severe CD who previously responded to infliximab (secondary nonresponse), the AGA recommends the use of adalimumab or ustekinumab *(Strong recommendation, moderate certainty evidence)* and suggests the use of vedolizumab over no treatment for the induction of remission. *(Conditional recommendation, low certainty evidence)*

Comment: If adalimumab was the first-line drug used, there is indirect evidence to suggest the option of using infliximab as a second-line agent.

There were no head-to-head trials comparing the efficacy of different agents for induction and maintenance of remission. Therefore, indirect evidence was derived using network meta-analysis from drug trials with similar study designs and outcomes. Network meta-analysis can help assess comparative efficacy of several interventions and synthesize evidence across a network of RCTs, especially if there is weak (or absent) direct evidence.12 The analysis included 8 RCTs with a total of 1458 biologic-naïve patients with moderate to severe luminal CD. On network metaanalysis, infliximab was more effective than certolizumab pegol (OR, 4.33; 95% CI, 1.83–10.27) with moderate confidence in estimates (rated down for imprecision) and low confidence in estimates supporting its use over vedolizumab (OR, 2.20; 95% CI, 0.79–6.07) or ustekinumab (OR, 2.14; 95% CI, 0.89–5.15) rated down for imprecision. There was moderate confidence in estimates for the use of ustekinumab (OR, 2.02; 95% CI, 1.09–3.75) or adalimumab (OR, 2.97; 95% CI, 1.16–6.70) over certolizumab pegol with low confidence in estimates (rated down for very serious imprecision). There was low confidence in the estimates for the use of vedolizumab over certolizumab pegol (OR 1.97; 95% CI, 0.88–4.41). There was no significant difference in the efficacy of adalimumab, ustekinumab, or vedolizumab as a first-line agent (very low certainty evidence). […]

In patients with prior TNFa antagonist exposure, 6 RCTs with 1606 patients were included in this part of the network meta-analysis. Three studies were performed exclusively in those with prior TNFa antagonist exposure (1 trial adalimumab and 2 trials of ustekinumab), 2 subgroup analyses of phase 2 trials (1 for adalimumab and 1 for vedolizumab), 1 trial of vedolizumab (GEMINI-II) in which 75% of patients had prior TNFa antagonist exposure, and 1 trial of adalimumab (GAIN) that only included patients with prior response or intolerance to infliximab. On network metaanalysis, ustekinumab was superior to placebo (OR, 2.58; 95% CI, 1.50–4.44) with moderate certainty evidence rating down for imprecision. Using adalimumab in patients with prior intolerance or secondary nonresponse to infliximab (OR, 3.57; 95% CI, 1.66–7.65) was moderate certainty evidence rating down for imprecision. Vedolizumab (OR, 1.53; 95% CI, 0.77–3.06) was supported by low certainty evidence rating down for very serious imprecision related to the very wide CIs and crossing unity). […]

Recommendation 4. In adult outpatients with moderate to severe CD, the AGA recommends the use of biologic drug monotherapy over thiopurine monotherapy for the induction of remission. *(Strong recommendation moderate certainty of evidence)*

The Panel recommends the use of biologic drug monotherapy over thiopurine monotherapy for induction of remission. A separate recommendation for maintenance of remission was not provided because corticosteroid-sparing drugs that are started for induction of remission are typically continued for maintenance of remission. The SONIC (Study of Biologic and Immunomodulator Naïve Patients in Crohn's Disease) study design was a 3-arm RCT including biologic and immunomodulator-naïve patients comparing infliximab vs azathioprine vs infliximab þ azathioprine.14 Infliximab was more effective than azathioprine for induction of clinical remission (RR, 0.79; 95% CI, 0.67–0.94) and endoscopic remission (65 of 93 vs 91 of 109; P < .01). The certainty of evidence was moderate, rating down for imprecision due to low OIS. Data on other biologics compared with thiopurines for induction of remission were lacking. However, given the overall efficacy of other biologics compared with placebo, and thiopurines failing to show efficacy compared with placebo for induction of remission, indirect evidence suggests that other biologics would also be more effective than thiopurines for induction of remission. Similarly, no RCTs compared biologic monotherapy with methotrexate monotherapy and data are therefore lacking.

Recommendation 5A. In adult outpatients with moderate to severe CD who are naïve to biologics and immunomodulators, the AGA suggests the use of infliximab in combination with thiopurines for the induction and maintenance of remission over infliximab monotherapy. *(Conditional recommendation, moderate certainty evidence)*

Comment: Based on indirect evidence, combination infliximab with methotrexate may be more effective over infliximab monotherapy.

Recommendation 5B. In adult outpatients with moderate to severe CD who are naïve to biologics and immunomodulators, the AGA suggests the use of adalimumab in combination with thiopurines for the induction and maintenance of remission over adalimumab monotherapy. *(Conditional recommendation, very low certainty evidence)*

Comment: Based on indirect evidence, combination adalimumab with methotrexate may be more effective over adalimumab monotherapy.

Two trials compared infliximab with a thiopurine to infliximab monotherapy. Combination therapy was more effective for induction of remission (RR, 0.77; 95% CI, 0.64– 0.92). Although there were no direct maintenance trials, both of these studies included follow-up of patients with active disease up to 50 of 52 weeks with combination therapy showing greater efficacy than infliximab monotherapy for maintenance of remission (RR, 0.74; 95% CI, 0.60–0.90). The certainty of evidence for induction of remission was moderate, rating down for imprecision, given the low OIS. Maintenance of remission certainty of evidence was low. This was rated down for indirectness (entering the maintenance with active disease and not specifically quiescent disease) and imprecision due to the low OIS.

Combination therapy using infliximab and methotrexate vs infliximab monotherapy was compared in 1 RCT with 126 patients. There was no difference in achieving corticosteroid-free remission at week 14 (RR, 1.07; 95% CI, 0.57–2.03) and at week 50 there was no difference in failure to maintain corticosteroid-free clinical remission (RR, 1.18; 95% CI, 0.68–2.03). The certainty of evidence for induction and maintenance of remission using infliximab with methotrexate was rated low due to very serious imprecision.

A single open-label RCT (DIAMOND study group) compared adalimumab and azathioprine to adalimumab monotherapy for 52 weeks. There was no difference between the 2 groups for induction of remission (RR, 1.31; 95% CI, 0.80–2.14) or maintenance of remission (RR, 1.13; 95% CI, 0.72–1.78).15 However, combination therapy was associated with higher rates of endoscopic remission at week 26 compared with adalimumab monotherapy (48 of 57 [84.2%] vs 37 of 58 [63.2%]; P = .02). The certainty of evidence was very low, rating down for risk of bias (unblinded study with high rates of drug discontinuations due to treatment intolerance), indirectness of outcomes, and imprecision from the low OIS.

Importantly, use of combination therapy may be even more important in the subset of patients who have developed secondary nonresponse to TNFa antagonists. Roblin et al16 noted that combination therapy resulted in improved outcomes without clinical failure or unfavorable pharmacokinetics at 24 months, with improvements of 77%–78% for TNFa antagonists with a thiopurine compared with 22% with TNFa antagonists monotherapy (P < .001).

There were no RCTs to provide data on combination therapy using vedolizumab or ustekinumab with a thiopurine or methotrexate. […]

Recommendation 7. In adult outpatients with moderate to severe CD, the AGA suggests early introduction with a biologic with or without an immunomodulator rather than delaying their use until after failure of 5-aminosalicylates and/or corticosteroids. *(Conditional recommendation, low certainty evidence)*

The evidence informing this recommendation was based on several RCTs. D'haens et al20 randomized patients to early combination therapy with an immunosuppressant and infliximab compared with conventional step therapy in which patients were first given corticosteroids followed by azathioprine and infliximab. At 52 weeks, 61.5% of patients in the early combined immunosuppression group were in corticosteroid- and surgery-free remission compared with 42.2% in the step-up therapy arm (RR for failure to achieve remission, 0.67; 95% CI, 0.46–0.97). A long-term extension arm of this trial to 8 years suggested lower rates of clinical relapse, and

corticosteroid use in the patients randomized to early combination therapy. The certainty of the evidence was low due to risk of bias (open label trial) and imprecision (low OIS).

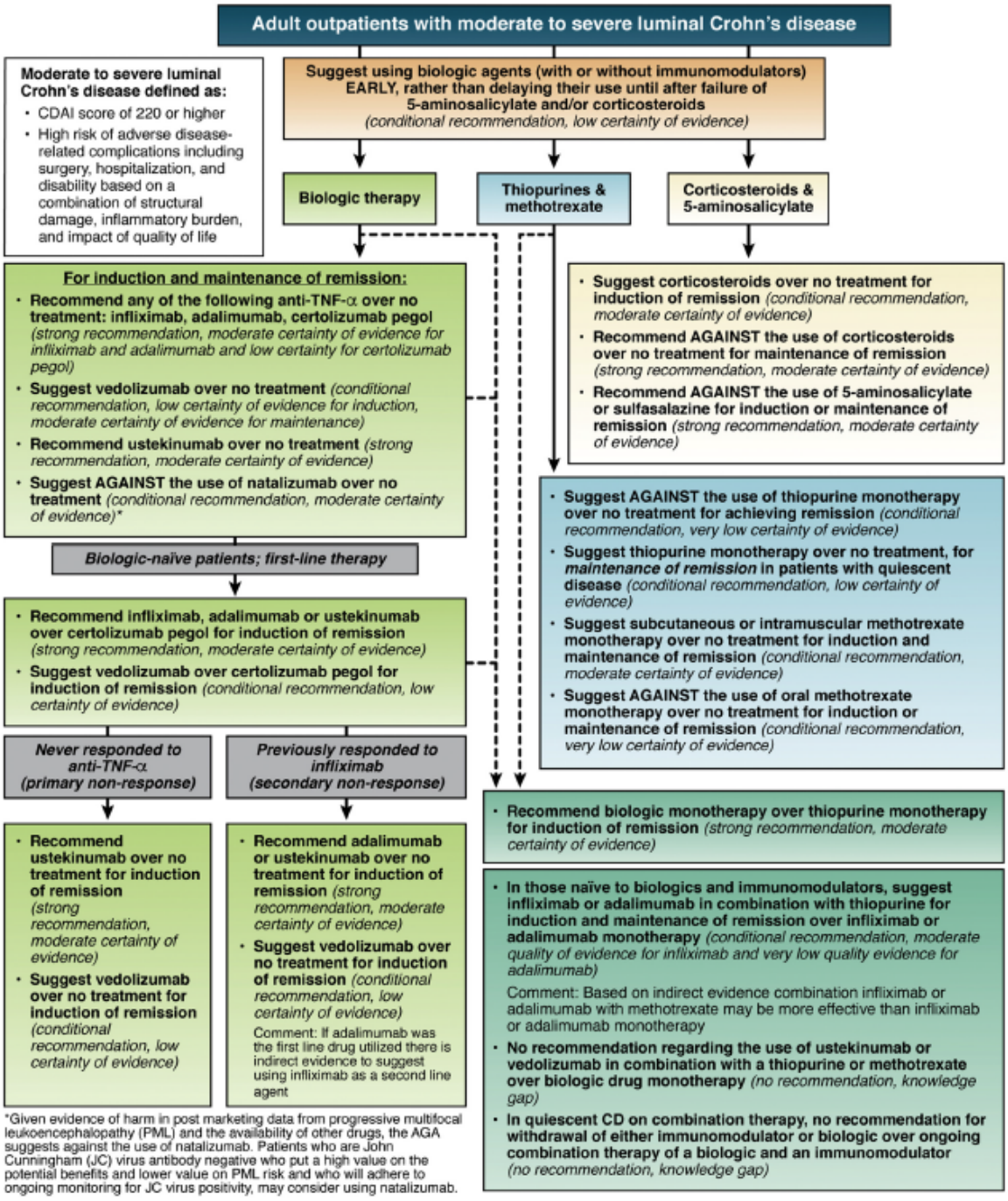
The REACT (Randomised Evaluation of an Algorithm for Crohn's Treatment) study was an open-label cluster randomized trial that compared an algorithmic approach of early combination therapy with an immunomodulator and biologic drug or conventional management of CD in 1982 patients.21 At 12 months, there was no significant difference in rates of corticosteroid-free remission (66% early combination therapy vs 62% in usual care). However, at 24 months, patients in the early combination therapy arm had lower rates of major adverse disease-related complications compared with conventional management (hazard ratio, 0.73; 95% CI, 0.62–0.86).

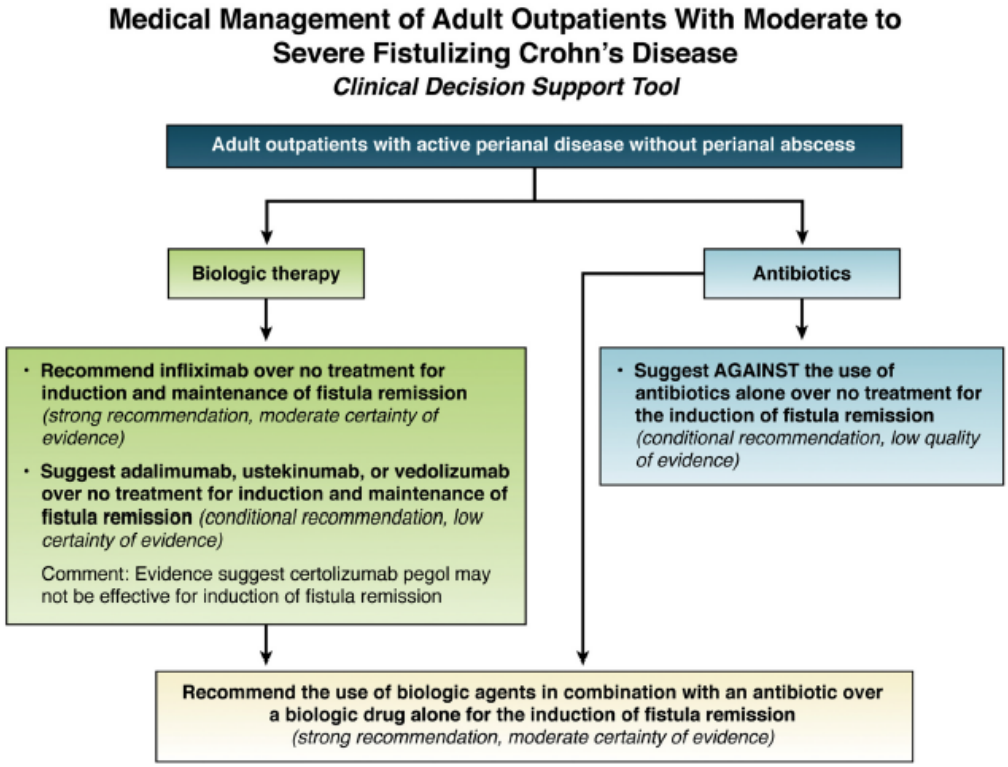
Data for early use of thiopurines alone was evaluated by Cosnes et al22 in an RCT of 122 patients in which patients were randomized to early azathioprine (within 6 months of CD diagnosis) vs conventional management in which azathioprine was only used in cases of corticosteroid dependency, in those not responding to corticosteroids, or those with perianal disease.22 During a 3-year follow-up, no significant differences were observed in the risk of corticosteroid-requiring flare (58 of 65 [89%] vs 61 of 67 [91%]; P =.73), hospitalization (22 of 65 [34%] vs 26 of 67 [39%]; P = .74), or CD-related surgery (5 of 65 [8%] vs 4 of 67 [6%]; P = .68). Evidence was rated low due to risk of bias (open-label trial) and imprecision (very wide CI).

Data for 5-aminosalicylates indicate that these drugs are not effective for the management of moderate to severe CD (see question 9 below). […]

Medical Management of Adult Outpatients With Moderate to Severe Luminal Crohn's Disease

Clinical Decision Support Tool





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European Crohn's and Colitis Organisation (ECCO)

ECCO Guidelines on therapeutics in Crohn's disease: medical treatment.

Zielsetzung/Fragestellung

The European Crohn's and Colitis Organisation [ECCO] produces and regularly updates several guidelines aimed at providing evidence-based guidance on critical aspects of IBD care to all health care professionals who manage patients with IBD. […]

Therefore ECCO reviewed the available high-quality evidence on the medical management of CD and developed evidence-based recommendations on the medical treatment of adult patients with CD. These guidelines do not cover specific situations, such as postoperative

management of adult patients with CD, which was already covered in the latest ECCO Guidelines on Crohn's disease.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium: trifft zu
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt: trifft zu
- Systematische Suche, Auswahl und Bewertung der Evidenz: trifft zu
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt: trifft zu
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt trifft zu
- Regelmäßige Überprüfung der Aktualität gesichert: trifft teilweise zu

Recherche/Suchzeitraum:

- up to July 2018

LoE/ quality of evidence:

- The quality of evidence was classified into the following four categories in accordance with the GRADE approach: 'high' [meaning that further research is unlikely to change our confidence in the effect estimates], 'moderate' [further research may change our confidence in the effect estimates], 'low' [further research likely to change our confidence in the effect estimates], and 'very low' [meaning that any estimate of effect is very uncertain]. For each PICO question, the quality of evidence was equal to the lowest quality of evidence among those outcomes graded as 'critical'.

GoR

The strength of each recommendation was graded as either 'strong' [meaning the desirable effects of an intervention clearly outweigh the undesirable effects, or vice versa] or as 'weak' [meaning the balance is less certain], considering also the quality of evidence, values or preferences, and resource use.

Empfehlungen

4. Medical management of Crohn's disease

Section 1 – Induction of Remission

Moderate-to-severe disease – monoclonal antibodies

Recommendation 1.5. ECCO CD Treatment GL [2019]
We recommend the use of TNF inhibitors [infliximab, adalimumab, and certolizumab pegol] to induce remission in patients with moderate-to-severe Crohn's disease who have not responded to conventional therapy [strong recommendation, moderate-quality evidence].

[…] Data on anti-TNF agents versus placebo [infliximab, adalimumab, and certolizumab pegol] from several meta-analyses of RCTs 62–64 support their efficacy for induction of clinical remission [RR: 1.6; 95% CI: 1.17–2.36] and clinical response [RR: 1.43; 95% CI: 1.17–1.73] [Supplementary Material, SoF Table 8, available as Supplementary data at ECCO-JCC online] in patients who did not achieve adequate response or were intolerant to corticosteroids and/ or immunosuppressants. Limited endoscopic data were available for the induction period; two studies showed a non-significant trend towards enhanced mucosal healing [RR: 3.25; 95% CI: 0.53–19.8].65,66 However, the evidence was downgraded due to imprecision. Data on clinical remission were highly heterogeneous [I2 = 63%], and data on endoscopic improvement were affected by high imprecision due to the low number of patients included in the meta-analysis [n = 35]. Data on patient-reported

outcomes [PRO] response and remission, biochemical and radiological improvement, and quality of life are insufficient. There was no difference in terms of AEs [RR: 0.99; 95% CI: 0.90–1.08].

The choice of anti-TNF agent depends on patient preference, availability, cost, and accessibility. However, in a 2015 network meta-analysis, pairwise comparison revealed that infliximab with AZA [OR: 3.1; 95% CI: 1.4–7.7] and adalimumab monotherapy [OR: 2.1; 95% CI: 1–4.6] were superior to certolizumab pegol for induction of remission.67

The timing of introduction of biologic agents is a matter of debate. It has been suggested that patients presenting with poor prognostic factors [e.g. fistulising perianal disease, extensive disease, deep ulcerations, complicated phenotype] would benefit from the early introduction of anti-TNF to achieve a reduced risk of surgery, hospitalisation, or development of disease-related complications.15 Furthermore, anti-TNF agents might be more effective if introduced earlier [in the first 2 years] in disease course,68–72 although these results are based on post-hoc analyses from clinical trials.

Recommendation 1.6. ECCO CD Treatment GL [2019]
We suggest against the combination of adalimumab and thiopurines over adalimumab alone to achieve clinical remission and response [weak recommendation, moderate quality evidence].

Only one RCT [the DIAMOND trial]73 studied the use of combination therapy of adalimumab with thiopurine as compared with adalimumab monotherapy for the induction of clinical remission in patients naïve to both therapies [Supplementary Material, SoF Table 9, available as Supplementary data at ECCO-JCC online]. In this trial, combination therapy was not superior to adalimumab monotherapy for inducing clinical remission [RR: 0.95; 95% CI: 0.78–1.15]. However, combination therapy was associated with endoscopic improvement at Week 26 [RR: 1.32; 95% CI: 1.06–1.65], although this benefit was lost at the end of 1 year. There was no increase in AEs leading to discontinuation associated with combination therapy [RR: 1.03; 95% CI: 0.60–1.78]. Of note, the dose of AZA used in this trial was lower than the usual dose used in CD patients [25–100 mg/day instead of 2–2.5 mg/kg/day].

Recommendation 1.7. ECCO CD Treatment GL [2019]
We recommend combination therapy with a thiopurine when starting infliximab to induce remission in patients with moderate-to-severe Crohn's disease, who have had an inadequate response to conventional therapy [strong recommendation, moderate-quality evidence].

The SONIC [Study Of Biologic and Immunomodulator Naïve Patients In Crohn's Disease] RCT70 compared the efficacy of infliximab combined with AZA over infliximab monotherapy in patients naïve to both therapies, who failed to respond to steroids or 5-ASA [Supplementary Material, SoF Table 10, available as Supplementary data at ECCO-JCC online]. Combination therapy resulted in higher rates of clinical remission at Week 26 as compared with infliximab monotherapy [RR: 1.64; 95% CI: 1.07–2.53]. Combination therapy was also more likely to result in mucosal healing at this timepoint [RR: 1.82; 95% CI: 1.01–3.26]. There was no difference in AEs for those receiving combination therapy. Rather, there were significantly lower rates of serious AEs in those receiving combination therapy [RR: 0.56; 95% CI: 0.32–0.97].

A commonly encountered scenario in clinical practice is patients who have failed or have had an inadequate response to thiopurines and in whom anti-TNF therapy is planned. No RCT has directly compared whether in such cases thiopurine maintenance in combination with the anti-TNF would carry additional benefits in terms of efficacy. A post-hoc analysis of RCTs has shown no added benefit of the continued use of immunomodulator therapy after starting anti- TNF therapy in this setting.74 However, immunogenicity should be considered and, in the absence of direct evidence, an individualized approach should be considered.74

Recommendation 1.8. ECCO CD Treatment GL [2019]
We recommend ustekinumab for induction of remission in patients with moderate-to-severe Crohn's disease with inadequate response to conventional therapy and/or to anti-TNF therapy [strong recommendation, high-quality evidence].

[…] One systematic review and metaanalysis pooled the results from RCTs in which ustekinumab was compared with placebo for induction of remission in patients with moderate-to-severe active luminal CD77[Supplementary Material, SoF Table 11, available as Supplementary data at ECCO-JCC online]. Four trials76,78–80 involving 1947 patients treated with different ustekinumab intravenous doses or equivalent placebo reported induction of clinical response and induction of clinical remission at Week 6. Data were extracted and a meta-analysis was performed, yielding an RR of obtaining clinical response of 1.56 [95% CI: 1.38–1.77] versus placebo [Supplementary Figure 13, available as Supplementary data at ECCO-JCC online]. The quality of evidence was high. The RR of obtaining clinical remission was 1.76 [95% CI: 1.40–2.22] [Supplementary Figure 14, available as Supplementary data at ECCO-JCC online]. The quality of evidence was high. An endoscopic substudy involving 252 CD patients revealed that 47.7% of patients receiving ustekinumab achieved endoscopic improvement at 8 weeks as compared with 29.9% of those receiving placebo [RR: 1.60; 95% CI: 1.13–2.26]. The quality of evidence was moderate. Four trials76,78–80 reported on AEs [2024 patients] or serious AEs [1947 patients] after induction. The pooled RR of any AEs was not significantly different between ustekinumab and placebo [62.0% vs 63.9%; RR: 0.96; 95% CI: 0.90–1.03] [Supplementary Figure 15, available as Supplementary data at ECCO-JCC online]. Similarly, the pooled RR of any serious AEs was not significantly different between ustekinumab and placebo [5.2% vs 6.4%; RR: 0.79; 95% CI: 0.54–1.15] [Supplementary Figure 16, available as Supplementary data at ECCO-JCC online]; the quality of evidence was high. The rate of antibody drug formation seems to be low [under 5%].81

Recommendation 1.9. ECCO CD Treatment GL [2019]
We recommend vedolizumab for induction of response and remission in patients with moderate-to-severe Crohn's disease with inadequate response to conventional therapy and/or to anti-TNF therapy [strong recommendation, moderate-quality evidence].

[…] Patients who do not achieve response at Week 6 can benefit from an additional administration at Week 10.83 Three randomised trials involving 969 patients treated with vedolizumab or placebo reported on induction of clinical response, induction of clinical remission, and serious AEs in adult patients with moderate-to-severe active CD82,84,85[Supplementary Material, SoF Table 12, available as Supplementary data at ECCO-JCC online]. Patients in these studies were followed up for 6 to 10 weeks. Clinical remission was more common in patients receiving vedolizumab compared with placebo [RR: 2.01; 95% CI: 1.50–2.71] [Supplementary Figure 17, available as Supplementary data at ECCO-JCC online]. Likewise, clinical response was also more common in patients receiving vedolizumab compared with placebo [40.8% vs 25.7%; RR: 1.55; 95% CI: 1.14–2.11] [Supplementary Figure 18, available as Supplementary data at ECCO-JCC online]. The quality of evidence for these outcomes was high. Rates of serious AEs with vedolizumab were not significantly different with placebo [RR: 0.94; 95% CI: 0.61–1.45] [Supplementary Figure 19, available as Supplementary data at ECCO-JCC online]. The quality of evidence for this outcome was moderate due to serious imprecision arising from sparse data.

Recommendation 1.10. ECCO CD Treatment GL [2019]
We equally suggest the use of either ustekinumab or vedolizumab for the treatment of moderate-to-severe active luminal Crohn's disease in patients who have previously failed anti-TNF therapy [weak recommendation, very low-quality evidence].

One systematic review and meta-analysis performed an indirect comparison of ustekinumab and vedolizumab for induction of remission in patients with moderate-to-severe active luminal CD who were non-responsive or intolerant to previous anti-TNF agents.86

Four trials76,79,82,85 involving a total of 1249 patients treated with ustekinumab or vedolizumab reported on induction of clinical response and clinical remission [Supplementary Material, SoF Table 13, available as Supplementary data at ECCO-JCC online]. The pooled RR of clinical response [35.8% vs 33.1%; RR:1.14; 95% CI: 0.65–1.99] and clinical remission [16.3% vs. 13.3%; RR: 1.16; 95% CI: 0.54–2.48] were not significantly different between ustekinumab and vedolizumab, but the quality of evidence was very low for both outcomes.

Four trials76,79,82,85 involving a total of 1541 patients treated with ustekinumab or vedolizumab reported on AEs or serious AEs after induction. The pooled RR of any AEs was not significantly different between ustekinumab and vedolizumab [64.2% vs 56.2%; RR: 1.00; 95% CI: 0.82–1.23]. Finally, the pooled RR of any serious AEs was not significantly different between ustekinumab and vedolizumab [7.1% vs 7.7%; RR: 0.95; 95% CI: 0.43–2.12]; the quality of evidence was very low. However, surgery should always be considered as an option in refractory patients.

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Canadian Association of Gastroenterology clinical practice guideline for the management of luminal Crohn's disease

Zielsetzung/Fragestellung

The purpose of these consensus statements is to review the literature relating to the medical management of luminal CD and to develop specific statements regarding the various therapies available for ambulatory patients with mild to severe active disease. Furthermore, we offer practical guidance for the practicing clinician given the evidence.

Methodik

At the time the literature searches were conducted […] the most recent clinical practice guideline on the treatment of CD was the second European evidence-based consensus from the European Crohn's and Colitis Organisation (ECCO), which incorporated data published until 2008. […] However, there are differences between the present consensus guidelines and the ECCO consensus with respect to the methods for grading the level of evidence, the conclusions reached, the recommendations made, and the presentation of the discussions. As such, both guidelines are likely to be relevant to clinicians and their patients when managing CD.

<u>Grundlage der Leitlinie:</u>

- Repräsentatives Gremium: trifft zu
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt: trifft zu
- Systematische Suche, Auswahl und Bewertung der Evidenz: trifft zu
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt: trifft zu
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt: trifft zu
- Regelmäßige Überprüfung der Aktualität gesichert: trifft nicht zu

Recherche/Suchzeitraum:

- systematic search through April 2016, focused (non-systematic) searches up to September 2016

LoE und GoR:

- certainty of the evidence was assessed using GRADE
- A statement was accepted if >75% of participants voted 4 (agree) or 5 (strongly agree) on a scale of 1–5 (with 1, 2, and 3 indicating disagree strongly, disagree, and uncertain, respectively).
- A level of agreement of ≥75% of participants was needed to classify a statement as **"strong" (we recommend**); if this threshold was not met, the statement defaulted to **"conditional" (we suggest).**
  - As per the GRADE method, a strong recommendation is indicative of a more broadly applicable statement ("most patients should receive the recommended course of action"), whereas a conditional recommendation suggests that clinicians should "…recognize that different choices will be appropriate for different patients and that they must help each patient to arrive at a management decision consistent with her or his values and preferences".

Sonstige methodische Hinweise

- The consensus group defined "**corticosteroid resistance"** as a lack of a symptomatic response despite a course of oral prednisone of 40–60 mg/day (or equivalent) for a minimum of 14 days. "Corticosteroid dependence" was defined as the inability to withdraw oral corticosteroid therapy (within 3 months of initiation) without recurrence of symptoms, a symptomatic relapse within 3 months of discontinuing corticosteroid therapy, or the need for more than 1 course of corticosteroid therapy within 1 year.
- Obwohl die Figure 2 (siehe unten) im obersten Kasten mit „mild to moderate Crohns's disease" beginnt, trägt die Abbildung den Titel „Consensus guided algorithm for management **of moderate to severe active CD**". Der dargestellte Algorithmus entspricht ebenfalls den Empfehlungen für die Behandlung eines moderaten bis schweren aktiven Morbus Crohn, sodass hier davon ausgegangen wird, dass es sich um einen Fehler in der Beschriftung des Kastens handelt.

Empfehlungen

Immunosuppressants

Statement 17. In patients with moderate to severe corticosteroid-dependent/resistant CD, we suggest parenteral methotrexate to induce complete remission.
GRADE: Conditional recommendation, very low-quality evidence.
Vote: strongly agree, 10%; agree, 65%; uncertain, 10%; disagree, 15%.

Evidence for the efficacy of methotrexate for the induction of symptomatic remission comes from 2 systematic reviews; 1 included 2 trials91 and the other 3 trials.102 Only 2 trials were pooled, 1 negative trial using oral methotrexate103 and 1 positive trial using intramuscular methotrexate,104 and the resulting RR expressed as the risk of having ongoing active disease was not statistically significant (RR, 0.82; 95% CI, 0.65–1.03).91 However, the trial assessing the intramuscular formulation in corticosteroid-dependent patients demonstrated a significant benefit in favor of methotrexate over placebo, with symptomatic remission being achieved by 39% of patients with methotrexate, as compared with 19% with placebo (RR, 1.95; 95% CI, 1.09–3.48; P =.025). In

addition, methotrexate therapy was associated with a significant steroid-sparing effect compared with placebo (P = .026).104

A review of RCTs of methotrexate therapy versus active comparators reported that methotrexate was as effective as azathioprine or 6-mercaptopurine and more effective than 5-ASA for induction therapy.102

Most of the trials assessing the efficacy of methotrexate have included relatively small numbers of patients and may have lacked power to show a benefit of this therapy.102

Statement 19. We suggest that patients with CD receiving thiopurine or methotrexate who do not achieve corticosteroid-free remission within 12–16 weeks should have therapy modified.
GRADE: Conditional recommendation, very low-quality evidence.
Vote: strongly agree, 40%; agree, 55%; uncertain, 5%.

In the meta-analysis of RCTs of thiopurines for induction therapy, patients evaluated at 17 weeks or later were significantly more likely to be in remission than those taking placebo (RR, 1.59; 95% CI, 1.05–2.41), whereas those evaluated before 17 weeks were not.92

In the methotrexate induction RCT, there were significant differences in disease activity scores between methotrexate and placebo from week 6 through the 16- week study. Corticosteroid use was significantly lower in the methotrexate group by week 4 in high-dose patients and by week 12 in those taking lower prednisone doses.104

Anti-TNF biologics

Statement 20. In patients with moderate to severe luminal CD with risk factors of poor prognosis, we recommend anti-TNF therapy (infliximab, adalimumab) as first-line therapy to induce complete remission.
GRADE: Strong recommendation, moderate-quality evidence.
Vote: strongly agree, 60%; agree, 40%.

Statement 21. In patients with moderate to severe CD who fail to achieve complete remission with any of corticosteroids, thiopurines, or methotrexate, we recommend anti-TNF therapy (infliximab, adalimumab) to induce complete remission.
GRADE: Strong recommendation, high-quality evidence.
Vote: strongly agree, 80%; agree, 20%.

Anti-TNF therapies have been extensively evaluated in RCTs and systematic reviews.110–112 One meta-analysis included 10 trials evaluating the anti-TNF therapy alone or with concomitant therapies.110 Using the outcome of failure to achieve symptomatic remission, anti-TNF therapy was significantly more effective than placebo (RR, 0.87; 95% CI, 0.80–0.94; P =.0004) (Figure 3). Positive results were reported with infliximab and adalimumab but not with certolizumab pegol.110 When certolizumab pegol was removed from the analysis, the benefits of anti-TNF therapy were more robust (RR, 0.82; 95% CI, 0.73–0.91). The NMA also found significantly greater odds of induction of remission with infliximab (OR, 2.8; 95% CrI, 1.4–7.2) and adalimumab (OR, 2.9; 95% CrI, 1.6–5.5) but not certolizumab pegol (OR, 1.4; 95% CrI, 0.95–2.0) compared with placebo.111

In most of the studies, patients had previously received other treatments; therefore, the quality of evidence for statement 20 (first-line anti-TNF therapy) was downgraded for indirectness of the patient population (treatment-naive patients with risk factors for poor prognosis).

Statement 22. In patients with active CD, when starting anti-TNF therapy, we suggest it be combined with a thiopurine over monotherapy to induce complete remission.

GRADE: Conditional recommendation, low-quality evidence.

Vote: strongly agree, 45%; agree, 50%; uncertain, 5%.

Statement 23. In patients with active CD, when starting anti-TNF therapy, we suggest it be combined with a thiopurine or methotrexate over monotherapy to improve pharmacokinetic parameters.

GRADE: Conditional recommendation, low-quality evidence for infliximab, very low-quality evidence for adalimumab.

Vote: strongly agree, 35%; agree, 55%; uncertain, 5%; disagree, 5%.

Evidence for the efficacy of combination therapy with an anti-TNF therapy plus a thiopurine (infliximab plus azathioprine) is available from 2 meta-analyses.111,125 In 1 analysis, the combination of infliximab plus azathioprine was more effective than either therapy alone,125 whereas in the other the combination was more effective than placebo or azathioprine alone but not more effective than infliximab alone.111 However, the SONIC trial is the only RCT directly comparing these 3 strategies.115 At 26 weeks, combination therapy was more effective in inducing corticosteroid-free symptomatic remission (56.8%) compared with either infliximab (44.4%) or azathioprine (30.0%) monotherapies (P < .001 vs azathioprine and P ¼ .02 vs infliximab; OR vs infliximab, 1.65; 95% CI, 1.07–2.54). Significantly higher rates of mucosal healing were also seen.115 Patients who received combination therapy were less likely to develop anti-TNF antibodies (0.9% vs 14.6%) and had higher median serum infliximab trough levels (3.5 mg/ mL vs 1.6 mg/mL; P < .001).115

Evidence for the efficacy of the combination of adalimumab plus azathioprine is available from a metaanalysis of observational data from RCTs and cohort studies.126 Adalimumab alone was inferior to combination therapy (OR, 0.78; 95% CI, 0.64–0.96; P =.02) for induction of symptomatic remission. However, a more recent pooled analysis of data from 4 RCTs published outside of the search window for these guidelines found no advantage with the combination of adalimumab plus an immunosuppressant over adalimumab alone.127 An open-label, randomized study in patients who had not previously received immunosuppressants or biologics found no difference in symptomatic remission rates between the combination of adalimumab plus azathioprine (68.1%) and adalimumab monotherapy (71.8%; P = .63).128 However, the rate of endoscopic improvement was significantly higher with combination therapy at 6 months (84.2% vs 63.8%; P = .019) but not 12 months (79.6% vs 69.8%; P = .36).128

One RCT, the COMMIT study, compared the efficacy of combination therapy with an anti-TNF (infliximab) plus methotrexate to infliximab alone and found no difference in rates of symptomatic remission between the 2 treatment groups (HR, 1.16; 95% CI, 0.62–2.17;

P = .63).129 There appeared to be a pharmacokinetic advantage, with patients receiving combination infliximab plus methotrexate being less likely to develop antibodies to infliximab (4% vs 20%; P =.01) than those who received infliximab alone. In addition, there was a trend to higher median serum trough infliximab concentrations in patients who received combination therapy (6.35 vs 3.75 mg/mL; P = .08).129

Statement 26. In patients with CD who have a suboptimal response to anti-TNF induction therapy, we suggest dose intensification to achieve complete remission.
GRADE: Conditional recommendation, very low-quality evidence.
Vote: strongly agree, 10%; agree, 75%; uncertain, 15%.

Statement 27. In patients with CD who lose response to anti-TNF maintenance therapy, we suggest dose optimization to recapture complete remission.
GRADE: Conditional recommendation, very low-quality evidence.
Vote: strongly agree, 35%; agree, 55%; uncertain, 10%.

Data on the efficacy of dose intensification in patients who did not respond to anti-TNF induction therapy (primary non-response, statement 26) and those who had an initial response (secondary loss of response, statement 27) are available from 2 systematic reviews of case series.136,137 In a meta-analysis of 23 studies, the annual rate of non-response or loss of response was about 21% in the pooled data for patients who did or did not respond to adalimumab induction therapy.136 Of those who underwent dose intensification for whom data were available, 71% achieved a symptomatic response and 40% symptomatic remission. Subgroup analysis revealed that about 20% of patients who had initially responded subsequently lost response annually, and among those for whom data were available, about 25% underwent dose intensification annually. Efficacy in this subgroup was not reported.136

A review of 16 studies calculated the annual incidence of loss of response to infliximab to be 13%.137 In the studies included in this review, rates of response to dose intensification were 54%–90%, with 1 study reporting that 31% achieved symptomatic remission.

Statement 29. We suggest against switching between anti-TNF therapies in patients who are doing well on anti-TNF therapy.
GRADE: Conditional recommendation, low-quality evidence.
Vote: strongly agree, 55%; agree, 45%.

The open-label, randomized SWITCH trial demonstrated that elective switching from one anti- TNF therapy to another was associated with a loss of tolerance and loss of efficacy within 1 year.141 Although the study was small and open-label, it did demonstrate a strong effect. Among patients with CD controlled on infliximab, 16% of those randomized to stay on infliximab compared with 47% switched to adalimumab required dose optimization or interruption of treatment (P =.006). Among the patients who interrupted adalimumab treatment, most were for loss of tolerance. A meta-analysis of observational studies found the rates of clinical remission were higher when the reason for switching was intolerance (61%) rather than secondary (45%) or primary failure (30%).142

Non-anti TNF biologics

Statement 30. In patients with moderate to severe CD who fail to achieve complete remission with any of corticosteroids, thiopurines, methotrexate, or anti-TNF therapy, we recommend vedolizumab to induce complete remission.

GRADE: Strong recommendation, moderate-quality evidence.

Vote: strongly agree, 60%; agree, 40%.

Evidence for the efficacy of vedolizumab for the induction of remission in CD is available from systematic reviews143,144 and an NMA.111 Meta-analysis of 3 RCTs (Feagan et al,145 GEMINI 2,146 and GEMINI 3147) found that vedolizumab was significantly more effective than placebo in the overall patient population (OR, 1.93; 95% CI, 1.33–2.81; P = .0006).111 Among patients who were anti-TNF-naive (see statement 31 for patients who have been previously treated with anti-TNF therapy), meta-analyses have shown that vedolizumab was significantly superior to placebo for the outcome of symptomatic remission (OR, 1.76; 95% CI, 1.11–2.78)143 or failure to achieve symptomatic remission (RR, 0.86; 95% CI, 0.79–0.94; P = .001) (Figure 5).144

Statement 31. In patients with CD who fail to achieve or maintain corticosteroid-free symptomatic remission with anti-TNF therapy, we suggest vedolizumab to induce complete remission.

GRADE: Conditional recommendation, low-quality evidence.

Vote: strongly agree, 20%; agree, 70%; uncertain, 5%; disagree 5%.

Data on the use of vedolizumab in patients who have previously failed anti-TNF therapy are available from GEMINI 2146 and GEMINI 3.147 In a meta-analysis of the patients previously treated with anti-TNF therapy, the RR of failure to induce symptomatic remission was 0.89 (95% CI, 0.78–1.01), but in the study with low risk of bias (GEMINI 3) the RR was 0.84 (95% CI, 0.75–0.93) with vedolizumab compared with placebo (Figure 5).144 Among the previously treated patients in GEMINI 3 the rate of symptomatic remission with vedolizumab was not significantly greater than placebo at week 6 but was at week 10 (26.6% vs 12.1%; P = .001; RR, 2.2; 95% CI, 1.3–3.6).147

Statement 34. In patients with moderate to severe CD who fail to achieve complete remission with any of corticosteroids, thiopurines, methotrexate, or anti-TNF therapy, we recommend ustekinumab to induce complete remission.

GRADE: Strong recommendation, moderate-quality evidence.

Vote: strongly agree, 70%; agree, 30%.

Evidence for the efficacy of ustekinumab for the induction of symptomatic remission of CD is available from 4 RCTs.157–159 A Cochrane systematic review conducted in 2015160 included 2 of the RCTs,157,158 and we added the 2 more recently published UNITI trials, UNITI-1 and UNITI-2,159 to the meta-analysis. Ustekinumab was significantly superior to placebo for the outcome of failure to achieve symptomatic remission at week 6 (RR, 0.88; 95% CI, 0.85–0.92) (Figure 6). Ustekinumab was effective in patients who had previously responded to anti-TNF therapy and anti-TNF-naive patients.

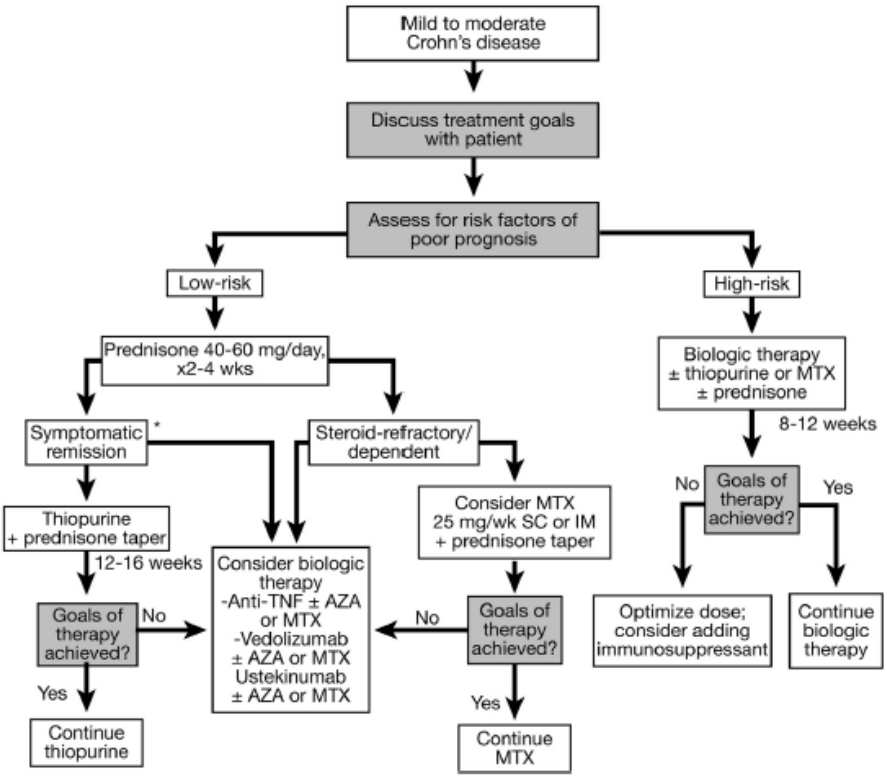

Figure 2. Consensus guided algorithm for management of moderate to severe active CD. *Initiation of biologic therapy may be an alternative pathway to thiopurines. Despite the fact that certolizumab is FDA approved and used in the United States, it is not licensed for the treatment of CD in Canada or Europe and therefore was not included in this CPG. AZA, azathioprine; IM, intramuscular; MTX, methotrexate; SC, subcutaneous; TNF, tumor necrosis factor.

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NICE, 2012 (last Update: 2019) [11].

NICE guideline 129

Crohn's disease: management in adults, children and young people.

Zielsetzung/Fragestellung

This guideline covers the management of Crohn's disease in children, young people and adults. It aims to reduce people's symptoms and maintain or improve their quality of life.

Methodik

Grundlage der Leitlinie

This guideline is an update of NICE guideline CG152 (published October 2012, last updated May 2016) and replaces it.

- Repräsentatives Gremium: trifft zu
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt: trifft zu
- Systematische Suche, Auswahl und Bewertung der Evidenz: trifft zu

- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt: trifft zu
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt: trifft teilweise zu
- Regelmäßige Überprüfung der Aktualität gesichert: trifft zu

Recherche/Suchzeitraum:

- NICE guideline CG152: Recherchedatum 13. März 2012, danach Aktualisierung der Empfehlungen im Mai 2016 und Mai 2019 – hierzu fehlen allerdings konkrete Daten bzgl. des Recherchedatums

LoE und GoR:

- The software (GRADEpro) developed by the GRADE working group was used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results.

Table 3: Levels of quality elements in GRADE

Level	Description
None	There are no serious issues with the evidence
Serious	The issues are serious enough to downgrade the outcome evidence by one level
Very serious	The issues are serious enough to downgrade the outcome evidence by two levels

Table 4: Overall quality of outcome evidence in GRADE

Level	Description
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

Empfehlungen

1.2 Inducing remission in Crohn's disease

Monotherapy

1.2.3 Consider budesonide for a first presentation or a single inflammatory exacerbation in a 12-month period for people:

- who have one or more of distal ileal, ileocaecal or right-sided colonic disease (see the recommendations on when to consider surgery early in the course of the disease in the section on Crohn's disease limited to the distal ileum) and
- if conventional glucocorticosteroids are contraindicated, or if the person declines or cannot tolerate them. Explain that budesonide is less effective than a conventional glucocorticosteroid, but may have fewer side effects. [2012]

1.2.4 Consider aminosalicylate treatment for a first presentation or a single inflammatory exacerbation in a 12-month period if conventional glucocorticosteroids

are contraindicated, or if the person declines or cannot tolerate them. Explain that aminosalicylates are less effective than a conventional glucocorticosteroid or budesonide but may have fewer side effects than a conventional glucocorticosteroid. [2012]

1.2.5 Do not offer budesonide or aminosalicylate treatment for severe presentations or exacerbations. [2012]

1.2.6 Do not offer azathioprine, mercaptopurine or methotrexate as monotherapy to induce remission. [2012]

Add-on treatment

1.2.7 Consider adding azathioprine or mercaptopurine to a conventional glucocorticosteroid or budesonide to induce remission of Crohn's disease if:

• there are 2 or more inflammatory exacerbations in a 12-month period or

• the glucocorticosteroid dose cannot be tapered. [2012]

1.2.8 Assess thiopurine methyltransferase (TPMT) activity before offering azathioprine or mercaptopurine. Do not offer azathioprine or mercaptopurine if TPMT activity is deficient (very low or absent). Consider azathioprine or mercaptopurine at a lower dose if TPMT activity is below normal but not deficient (according to local laboratory reference values). [2012]

1.2.9 Consider adding methotrexate (follow British national formulary [BNF]/British national formulary for children [BNFC] cautions) to a conventional glucocorticosteroid or budesonide to induce remission in people who cannot tolerate azathioprine or mercaptopurine, or in whom TPMT activity is deficient, if:

• there are 2 or more inflammatory exacerbations in a 12-month period or

• the glucocorticosteroid dose cannot be tapered. [2012]

Infliximab and adalimumab

The recommendations in the following section (except for the recommendation on discussing the options of monotherapy or combined therapy) are from the NICE technology appraisal guidance on infliximab and adalimumab for the treatment of Crohn's disease. [12]

1.2.12 Infliximab and adalimumab, within their licensed indications, are recommended as treatment options for adults with severe active Crohn's disease (see recommendation 1.2.18) whose disease has not responded to conventional therapy (including immunosuppressive and/or corticosteroid treatments), or who are intolerant of or have contraindications to conventional therapy. Infliximab or adalimumab should be given as a planned course of treatment until treatment failure (including the need for surgery), or until 12 months after the start of treatment, whichever is shorter. People should then have their disease reassessed (see recommendation 1.2.16) to determine whether ongoing treatment is still clinically appropriate. [2010]

1.2.14 When a person with Crohn's disease is starting infliximab or adalimumab (in line with recommendations 1.2.12, 1.2.15, 1.2.17 and 1.2.20), discuss options of: • monotherapy with one of these drugs or • combined therapy (either infliximab or adalimumab, combined with an immunosuppressant). Tell the person there is uncertainty about the comparative effectiveness and long-term adverse effects of monotherapy and combined therapy. [2016]

1.2.15 Infliximab, within its licensed indication, is recommended as a treatment option for people with active fistulising Crohn's disease whose disease has not responded to conventional therapy (including antibiotics, drainage and immunosuppressive treatments), or who are intolerant of or have contraindications to conventional therapy. Infliximab should be given as a planned course of treatment until treatment failure (including the need for surgery) or until 12 months after the start of treatment, whichever is shorter. People should then have their disease reassessed (see recommendation 1.2.16) to determine whether ongoing treatment is still clinically appropriate. [2010]

1.2.16 Treatment with infliximab or adalimumab (see recommendations 1.2.12 and 1.2.15) should only be continued if there is clear evidence of ongoing active disease as determined by clinical symptoms, biological markers and investigation, including endoscopy if necessary. Specialists should discuss the risks and benefits of continued treatment with patients and consider a trial withdrawal from treatment for all patients who are in stable clinical remission. People who continue treatment with infliximab or adalimumab should have their disease reassessed at least every 12 months to determine whether ongoing treatment is still clinically appropriate. People whose disease relapses after treatment is stopped should have the option to start treatment again.[2010]

1.2.17 Infliximab, within its licensed indication, is recommended for the treatment of people aged 6 to 17 years with severe active Crohn's disease whose disease has not responded to conventional therapy (including corticosteroids, immunomodulators and primary nutrition therapy), or who are intolerant of or have contraindications to conventional therapy. The need to continue treatment should be reviewed at least every 12 months. [2010]

1.2.18 For the purposes of this guidance, severe active Crohn's disease is defined as very poor general health and one or more symptoms such as weight loss, fever, severe abdominal pain and usually frequent (3 to 4 or more) diarrhoeal stools daily. People with severe active Crohn's disease may or may not develop new fistulae or have extra-intestinal manifestations of the disease. This clinical definition normally, but not exclusively, corresponds to a Crohn's Disease Activity Index (CDAI) score of 300 or more, or a Harvey-Bradshaw score of 8 to 9 or above. [2010]

Ustekinumab and vedolizumab

1.2.21 For guidance on using ustekinumab, see the NICE technology appraisal guidance on ustekinumab for moderately to severely active Crohn's disease after previous treatment. [2019] [8]

➔ 1.1 Ustekinumab is recommended, within its marketing authorisation, as an option for treating moderately to severely active Crohn's disease, that is, for adults who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNF-alpha inhibitor or have medical contraindications to such therapies.

➔ 1.2 The choice of treatment between ustekinumab or another biological therapy should be made on an individual basis after discussion between the patient and their clinician about the advantages and disadvantages of the treatments available. If more than 1 treatment is suitable, the least expensive should be chosen (taking into account administration costs, dosage and price per dose).

Evidence: two induction trials (UNITI-1: TNF-alpha-inhibitor failure population; and UNITI-2: conventional-care failure population) and 1 maintenance trial (IM-UNITI) that included patients who had had a clinical response to ustekinumab in either of the two induction trials

1.2.22 For guidance on using vedolizumab, see the NICE technology appraisal guidance on vedolizumab for treating moderately to severely active Crohn's disease after prior therapy. [2019] [14]

➔ 1.1 Vedolizumab is recommended as an option for treating moderately to severely active Crohn's disease only if: a tumour necrosis factor-alpha inhibitor has failed (that is, the disease has responded inadequately or has lost response to treatment) or a tumour necrosis factor-alpha inhibitor cannot be tolerated or is contraindicated. Vedolizumab is recommended only if the company provides it with the discount agreed in the patient access scheme.

Evidence: two randomised, double-blind, placebo-controlled trials of vedolizumab, GEMINI II and GEMINI III (adults with moderately to severely active Crohn's disease (Crohn's Disease Activity Index [CDAI] score 220–450) that had shown inadequate response to, loss of response to, or intolerance to at least 1 of the following: immunomodulators, TNF-alpha inhibitors or corticosteroids (outside the USA only) within the last 5 years)

Lamb CA et al., 2019 [10].

British Society of Gastroenterology (BSG)

British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults

Zielsetzung/Fragestellung

- The aim of this document is to provide high-quality disease management guidance for healthcare professionals managing IBD, to ensure that investigation, treatment and monitoring decisions are based on the best available evidence, and to promote and improve best accepted practice.
- Comprehensive up-to-date guidance is provided regarding indications for, initiation and monitoring of immunosuppressive therapies, nutrition interventions, pre-, peri- and postoperative management, as well as structure and function of the multidisciplinary team and integration between primary and secondary care.
- The guideline is of relevance to adults aged 16 years and over and was developed according to Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology, in accordance with the principles of the AGREE II tool, and in compliance with the BSG Guidelines Advice Document.

Methodik

<u>Grundlage der Leitlinie</u>

- Repräsentatives Gremium: trifft zu;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt: trifft zu;
- Systematische Suche, Auswahl und Bewertung der Evidenz: trifft zu;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt: trifft zu;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt: trifft zu;
- Regelmäßige Überprüfung der Aktualität gesichert: trifft zu.

Recherche/Suchzeitraum:

Searches of the Medline and EMBASE databases were performed in March 2017 and updated in March 2018. Focused top-up searches using keywords were performed until June 2019

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- […] Following two rounds of anonymised voting, statements conforming to PICO/PEO which achieved consensus of 80% agreement or higher were categorised according to the GRADE system for grading quality of evidence and strength of recommendations.
- The quality of evidence ranged from **'high'** (further research is very unlikely to change confidence in the estimate of effect), **'moderate'** (further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate), **'low' (**further research is very likely to have important impact on confidence in the estimate of effect and is likely to change the estimate), and **'very low'** (any estimate of effect is very uncertain).

GoR

- The strength of each recommendation was then recorded as '**strong'** (meaning that benefits clearly outweigh risks and burdens or vice versa) and **conditional** recommendations as '**weak'** (where benefits, risks and burdens are conditional, closely balanced or uncertain).
- Where statements did not conform to PICO/PEO (such as subjective interventions or where outcomes were multiple) and evidence was indirect or of low quality, recommendations to inform clinical practice were presented as **Good Practice** Recommendations and listed separately to GRADE recommendations, but still underwent consensus voting.

Empfehlungen

4. CROHN´S DISEASE

4.4 Maintenance treatment in ileocolonic Crohn's disease

4.4.3 Biological therapy with anti-TNF drugs, vedolizumab or ustekinumab

Statement 43.

We recommend that patients refractory to immunomodulator therapy despite dose optimisation should be considered for biological therapy. **Choice between anti-TNF therapy, ustekinumab and vedolizumab should be made on an individual basis**, considering patient preference, cost, likely adherence, safety data and speed of response to the drug (GRADE: strong recommendation, very low-quality evidence. Agreement: 95.7%).

4.4.3.1 Infliximab

Infliximab is a monoclonal antibody to tumour necrosis factor alpha (TNF) and was the first in class to be used in IBD, demonstrating definitive benefit in luminal Crohn's disease in the ACCENT I study. 573 patients with active luminal disease received a single 5 mg/kg intravenous dose, and after assessment of response at week 2, were randomly assigned to infusions of placebo at weeks 2, 6 and then 8-weekly (group 1), or infliximab 5 mg/kg at the same time points, or 5 mg/kg at weeks 2 and 6, then 10 mg/kg 8-weekly. At week 2, 58% responded to the initial infusion, and of these responders: at week 30, 39% treated with 5 mg/kg maintenance and 45% on 10 mg/kg were in clinical remission, with similar remission rates observed at week 54.474 In routine clinical practice reported results are significantly

better, with a large single-centre cohort of 614 Crohn's disease patients (treated for luminal, perianal or extraintestinal manifestations) showing that 89.1% had clinical improvement after initial treatment and 63.4% showing sustained clinical benefit.475 This study included a significant proportion of patients receiving episodic therapy, whereas regular scheduled therapy is of proven superiority.476

Statement 44.

We recommend that **combination therapy of infliximab with a thiopurine** should be used as it is more effective than monotherapy infliximab in induction and maintenance of remission in active Crohn's disease (GRADE: strong recommendation, high-quality evidence. Agreement: 97.7%).

[…] The SONIC study showed that combined infliximab and azathioprine was superior to infliximab in achieving clinical remission and mucosal healing.477 A network meta-analysis of published data shows that combination therapy was more effective than azathioprine monotherapy, as was adalimumab monotherapy. 456 Similar benefits of combination therapy are seen in children.478 479 Addition of an immunosuppressant has also been shown to reduce the need for dose escalation of infliximab and also reduces the rate of drug switching.480 In the PANTS 3-year observational cohort of 1601 Crohn's patients treated with infliximab or adalimumab, 751 patients were treated with infliximab.481 At week 54 the immunogenicity rates for Remicade and biosimilar infliximab (Inflectra/ Remsima) were 26% and 28%, respectively. Immunomodulator use reduced the risk of immunogenicity in infliximab therapy (HR=0.37, p<0.0001).

Statement 45.

We suggest that **combination therapy of infliximab with methotrexate therapy** may be used in Crohn's disease to reduce immunogenicity (GRADE: weak recommendation, moderate-quality evidence. Agreement: 90.5%).

A study of patients who had recently started prednisolone treatment for active disease showed that combination therapy with infliximab and methotrexate was no more effective

that infliximab monotherapy in maintaining remission up to 50 weeks, although equally safe.482 A recent Cochrane systematic literature review evaluating this460 and a further small openlabel study483 reached the same conclusion. Immunogenicity to infliximab may, however, be reduced by the addition of methotrexate, 480 suggesting that some clinical benefit might have been observed beyond the 1 year timeframe of the study. A paediatric

registry study of 502 Crohn's disease patients studied the impact of concomitant immunomodulator therapy on the duration of infliximab therapy.484 Concomitant methotrexate, taken for more than 6 months, increased likelihood of remaining on infliximab, both compared with non-use of immunomodulators and compared with thiopurine use. Due to the small number of girls given methotrexate, only boys were included in this analysis.

In order to maximise the benefit of infliximab therapy and reduce treatment failure, combination therapy with immunomodulator should always be preferred (with stronger evidence for azathioprine than methotrexate). For those intolerant to thiopurines and methotrexate, alternatives to infliximab should be used unless there are other compelling reasons (such as the presence of perianal disease).

4.4.3.2 Adalimumab

The CLASSIC I study in moderate to severe Crohn's disease naïve to anti-TNF therapy showed that the optimum dose for induction therapy was 160 mg followed by 80 mg at week 2, with remission (CDAI <150) achieved in 36% (p=0.001 against placebo) compared with 24% (80 mg/40 mg), 18% (40 mg/20 mg) and 12% on placebo.485 In the CHARM study of maintenance therapy, responders to induction therapy with 80 mg subcutaneously and 40 mg at 2 weeks were given placebo, 40 mg every 2 weeks or 40 mg weekly, with 12%, 36% and 41%, respectively, in clinical remission at week 56.486 The GAIN

trial showed efficacy of adalimumab in patients with active Crohn's disease and loss of response or intolerance to infliximab (secondary infliximab failures).487 Data from the EXTEND trial demonstrated adalimumab to be effective in inducing and maintaining endoscopic mucosal healing over the longer term,488 and with improved outcomes in those who achieved deep remission.489

The signal for the importance of combination therapy with an immunomodulator is not as strong in studies of adalimumab as it is for infliximab. A meta-analysis suggested that combination therapy with an immunomodulator was slightly better than adalimumab monotherapy for induction of remission, but remission rates at 1 year were no different, and there was no reduction in rates of dose escalation compared with monotherapy.490 Likewise, the DIAMOND trial comparing adalimumab monotherapy to combination therapy with azathioprine in 176 Japanese Crohn's disease patients naïve to biologics and immunomodulators showed similar remission rates at weeks 26 and 52,491 and another study has shown efficacy of monotherapy with adalimumab in maintaining clinical remission for up to 4 years.492[…]

4.4.3.3 Choice of anti-TNF agent in Crohn's disease

There is little to choose between adalimumab and infliximab in efficacy in luminal Crohn's disease, and practical considerations regarding mode and frequency of administration are the main factors as well as consideration of the relative need for combination therapy with an immunomodulator (see Section 5.2.4.1: Choice of anti-TNF agent).

4.4.3.4 Vedolizumab

Statement 46.

We recommend that in Crohn's disease, **vedolizumab** can be used in both anti-TNF naïve patients and in those where anti-TNF treatment fails. Choice of treatment in biologics-naïve patients should be individualised (GRADE for induction therapy: strong recommendation, moderatequality evidence; GRADE for maintenance therapy: strong recommendation, high-quality evidence. Agreement: 95.5%).

[…] It has been demonstrated as effective in inducing remission in the GEMINI-2 trial.497 […] A systematic review has also demonstrated that vedolizumab was superior to placebo in induction and maintenance of remission in IBD and has an acceptable safety profile over the short term.499 Vedolizumab responders also appear to have persistence of benefit, with long-term follow-up data from the GEMINI-2 study showing that, of responders at week 6 for whom data were available, 83% were in remission after 2 years and 89% after

3 years.500 Observational studies have shown consistent findings— for example, a Scottish retrospective study of 153 patients had 1 year steroid-free remission of 28.6%.501 The Swedish SWIBREG study reported 147 patients with active Crohn's disease (86% of whom had previously failed anti-TNF therapy) showed 1 year clinical remission of 54%.502 Recently reported real-world data suggest that higher rates of response with vedolizumab are more likely in patients with Crohn's disease of ≤2 years duration in comparison to those with later stage disease >2 years.503 This study did not identify an association or response to vedolizumab with disease duration in UC. […]

There are currently no head-to-head comparative trials published of anti-TNF therapy versus anti-integrin therapy. Due to heterogeneity in trial design and patient characteristics, results of network meta-analyses comparing different agents should be treated with some caution, and are no substitute for head-to-head comparisons.504 Using propensity score matching, 269 patients with active Crohn's disease in the VICTORY consortium were matched 1:1 with anti-TNF treated patients. At 1 year remission was observed in vedolizumab and anti-TNF treated patients in 38% and 34% respectively, HR 1.27 (95% CI 0.91 to 1.27), steroid-free remission in 26% and 18%, HR 1.75 (95% CI 0.90 to 3.43), endoscopic healing in 50% and 41% respectively, HR 1.67 (95% CI 1.13 to 2.47).505 Side effects of vedolizumab are discussed in the Section 5.2.5 Drug management: vedolizumab and ustekinumab. In biologics-naïve patients, anti-TNF therapy is currently likely to be an initial biologic choice, but there

are situations where vedolizumab may be preferred (such as where there is an advantage of gut-specific immunosuppression, or use in older patients where infection and malignancy are a concern), but there are few data to support a clear benefit of anti-integrin therapy in any particular subgroup in Crohn's disease as yet.

4.4.3.5 Ustekinumab

Statement 47.

We recommend that **ustekinumab** can be used in the induction and maintenance of remission of Crohn's disease, both in anti-TNF naïve patients and in those where anti-TNF treatment fails. No direct comparison data are available with other biological therapies (GRADE: strong recommendation, high-quality evidence. Agreement: 97.7%).

Ustekinumab is an anti-IL12/23 p40 antibody and has been evaluated in the UNITI and IM-UNITI studies in patients with Crohn's disease. UNITI-1 enrolled patients who had prior anti-TNF failure (primary or secondary loss of response or intolerance). Clinical response at week 8 was 37.8% in those receiving ustekinumab 6 mg/kg ($p<0.001$ vs placebo), 33.5% with 130 mg ($p=0.001$ vs placebo) and 20.2% with placebo.506 […]

[…] Efficacy has been demonstrated in a retrospective observational GETAID study of 122 Crohn's disease patients refractory anti-TNF drugs. 65% had clinical benefit within 3 months, and in 68% of these, benefit was maintained at 12 months.507 A growing real-world experience confirms the benefit of ustekinumab. 508–512 […]

4.4.3.6 Choice of biological therapy after anti-TNF failure

Statement 48.

We suggest that, where a switch from anti-TNF therapy to a different drug class is required in Crohn's disease, the choice to use vedolizumab or ustekinumab may be made on an individual basis. Factors to be included in the decision-making process should include patient preference, cost, likely adherence, safety data and speed of response to the drug. The potential for surgery as an alternative to further drug therapy should also be considered (GRADE: weak recommendation, very low-quality evidence. Agreement: 97.8%).

To date there are no head-to-head studies comparing ustekinumab and vedolizumab in patients with IBD who have failed anti-TNF therapy, but indirect comparisons suggest no difference in efficacy in this relatively treatment-refractory group.513 A consistent theme across multiple clinical trials in Crohn's disease is that response rates are generally lower in patients with a longer disease duration,514 515 or who have proven refractory to other therapies.506 Given the reduced likelihood of response to therapies in patients who have medically refractory but surgically tractable disease (eg, limited ileocaecal inflammation), surgical approaches should be actively considered to restore quality of life and reduce the risk of complications resulting either from prolonged uncontrolled inflammation or from the use of multiple drug therapies often interspersed with multiple courses of corticosteroid therapy.

4.4.3.7 Corticosteroid use and infection risk while on anti-TNF therapy

Statement 49.

Patients with Crohn's disease treated with a biological therapy in optimal dose who remain corticosteroiddependent (particularly if on triple immunosuppression with immunomodulator therapy) are at significant risk of opportunistic infections. We recommend that alternative

medical treatments or surgery should be explored (GRADE: strong recommendation, moderate-quality evidence. Agreement: 97.8%).

Conventional immunomodulator therapies and anti-TNF therapies were associated with an increased risk of infection, including serious and opportunistic infections. Nonetheless the greatest risk of infection, and with it an associated increase in mortality, was seen in patients on corticosteroid therapy (see Section 5.2.1.2: Common Disease Considerations, Infection risk in patients on anti-TNF therapy). Requirement for continuous corticosteroid therapy or repeated short courses in patients on biologics suggests that treatment may be failing, and consideration should be given to switching to an alternative (see Section 5.2.4.6: Common Disease Considerations, Secondary loss of response to anti-TNF therapy) or considering other options, including surgery.

5.2.1.2 Infection risk in patients on anti-TNF therapy

Meta-analysis of clinical trial data of 4135 patients receiving anti-TNF therapy as part of randomised clinical trials found a 0.9% incidence of opportunistic infection.708 This represented a two-fold increased risk of infections including TB, herpes simplex, oral or oesophageal candidiasis, herpes zoster, CMV, EBV and Nocardia in IBD patients (RR 2.05; 95% CI 1.10 to 3.85). The relative risk for TB was 2.52 (95% CI 0.62 to 10.21). Pooled analysis of 2266 patients receiving adalimumab as part of clinical trials found that higher disease activity was associated with an increased risk of opportunistic infection, with a 31% (HR 1.31; 95% CI 1.04 to 1.64) increase accompanying every 100 point rise in CDAI.709 IBD patients over 50 years of age receiving immunosuppression are at highest risk of opportunistic infection.710 711 For patients starting biologics or immunosuppressive drugs, the viral screen (as recommended at diagnosis, see box 4) should be performed if not done initially, or if new risk factors have arisen since that time.

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 08 of 12, August 2021) am 02.08.2021

#	Suchfrage
1	MeSH descriptor: [Crohn Disease] explode all trees
2	(crohn OR crohns OR crohn's):ti,ab,kw
3	(inflammatory NEXT bowel NEXT disease*):ti,ab,kw OR IBD:ti,ab,kw
4	((granulomatous AND (enteritis OR colitis)) OR (regional AND (enteritis OR ileitis)) OR (terminal AND ileitis) OR ileocolitis):ti,ab,kw
5	#1 OR #2 OR #3 OR #4
6	#5 with Cochrane Library publication date from Jul 2016 to present

Systematic Reviews in Medline (PubMed) am 02.08.2021

#	Suchfrage
1	Crohn Disease/therapy[MeSH Major Topic]
2	crohn[ti] OR crohns[ti] OR crohn's[ti]
3	"inflammatory bowel disease*"[ti] OR IBD[ti]
4	(granulomatous[ti] AND (enteritis[ti] OR colitis[ti])) OR (regional[ti] AND (enteritis[ti] OR ileitis[ti])) OR terminal ileitis[ti] OR ileocolitis[ti]
5	(#2 OR #3 OR #4) AND ((treatment*[tiab] OR treating[tiab] OR treated[tiab] OR treat[tiab] OR treats[tiab] OR treatab*[tiab] OR therapy[tiab] OR therapies[tiab] OR therapeutic*[tiab] OR monotherap*[tiab] OR polytherap*[tiab] OR pharmacotherap*[tiab] OR effect*[tiab] OR efficacy[tiab] OR management[tiab] OR drug*[tiab]))
6	#1 OR #5
7	(#6) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR

#	Suchfrage
	bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
8	((#7) AND ("2016/08/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
9	(#8) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in Medline (PubMed) am 02.08.2021

#	Suchfrage
1	Crohn Disease[mh]
2	crohn[tiab] OR crohns[tiab] OR crohn's[tiab]
3	"inflammatory bowel disease*"[tiab] OR IBD[tiab]
4	(granulomatous[tiab] AND (enteritis[tiab] OR colitis[tiab])) OR (regional[tiab] AND (enteritis[tiab] OR ileitis[tiab])) OR terminal ileitis[tiab] OR ileocolitis[tiab]
5	#1 OR #2 OR #3 OR #4
6	(#5) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] *OR recommendation*[ti])*
7	(#6) AND ("2016/08/01"[PDAT] : "3000"[PDAT])
8	(#7) NOT (retracted publication [pt] OR retraction of publication [pt])

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Beteiligung von AkdÄ und Fachgesellschaften nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

2021-B-230

Kontaktdaten

Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ), Herbert-Lewin-Platz 1, 10623 Berlin (www.akdae.de);
Stand: 15.09.2021

Indikation gemäß Beratungsantrag

zur Behandlung des mittelschweren bis schweren aktiven Morbus Crohn bei Erwachsenen und Jugendlichen ab 16 Jahren, die auf eine konventionelle Therapie unzureichend angesprochen, das Ansprechen verloren haben oder diese nicht vertragen haben

Was ist der Behandlungsstandard in o. g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus?

Unter dem Begriff „konventionelle Therapie“ werden bei Morbus Crohn eine Behandlung mit Mesalazin, Kortikosteroiden und/oder Immunsuppressiva (Azathioprin, 6-Mercaptopourin, Tacrolimus, Cyclosporin, Mycophenolat) verstanden. Im nachfolgenden Text wird also davon ausgegangen, dass diese Substanzen einschließlich der Immunsuppressiva bereits eingesetzt wurden.

Sind diese Therapeutika bei aktiver Erkrankung trotz optimierten Einsatzes (Dosierung, Intervall, Compliance) nicht oder nicht mehr wirksam oder werden nicht vertragen, wird in nationalen und internationalen Leitlinien die Einleitung einer Behandlung mit Biologika empfohlen.

Zu den Biologika zählen die TNF-alpha-Antikörper (einschließlich der sogenannten Biosimilars), der Interleukin-Antikörper Ustekinumab, und der Integrin-Antagonist Vedolizumab. Mangels direkter Vergleiche (head-to-head) zwischen diesen Substanzen/Substanzgruppen, ist keine Priorisierung unter diesen Medikamenten möglich. Der Nutzen eines gleichzeitigen Einsatzes eines Biologikum und eines Immunsuppressivums ist ausschließlich für die Kombination Infliximab/Azathioprin bei Patienten belegt, die zuvor nicht mit einem Immunsuppressivum oder einem Biologikum behandelt wurden. Dieser Option kommt also in der hier adressierten Patientengruppe keine Bedeutung zu.

Vor Therapieänderung ist zu prüfen, ob andere Faktoren zu einer Verschlechterung führen oder sich die Erkrankungsmanifestation geändert hat. Die Bewertung der Erkrankungsaktivität hat klinische Faktoren (z. B. Aktivitätsindizes), bildgebende Verfahren (Endoskopie, Sonographie, MRT) und laborchemische Parameter (z. B. CRP i.S., Calprotectin i. Stuhl) zu berücksichtigen. Ferner ist zu prüfen, ob durch eine chirurgische Maßnahme (z. B. Strikturoplastik, chirurgische Fisteltherapie) die Therapieumstellung vermieden werden kann. Bei Morbus Crohn mit ausschließlich ileozökalem Befall kann eine Resektion des befallenen Darmabschnittes eine passagere Therapiefreiheit (teilweise über mehrere Jahre) ermöglichen.

Die hier getroffenen Aussagen finden ihre Begründung in Ausführungen zu den Empfehlungen der Konsultationsfassung der deutschen S3-Leitlinie der AWMF zum Morbus Crohn (1). Auf der Basis der darin kritisch bewerteten Literatur ist sie in manchen Formulierungen zurückhaltender als die ECCO Guideline von 2019 (2), aus Sicht der AkdÄ zurecht. Der Umsetzungsgrad im klinischen Alltag kann für Fachpraxen und spezialisierten Kliniken als sehr hoch angenommen werden.

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zur Behandlung des mittelschweren bis schweren aktiven Morbus Crohn bei Erwachsenen und Jugendlichen ab 16 Jahren, die auf eine konventionelle Therapie unzureichend angesprochen, das Ansprechen verloren haben oder diese nicht vertragen haben

Zusätzlich bitten wir Sie um eine Einschätzung zu folgendem Anwendungsgebiet „Erwachsene und Jugendliche ab 16 Jahren mit mittelschwerem bis schwerem aktivem Morbus Crohn, die auf ein Biologikum (TNF-α-Antagonist oder Integrin-Inhibitor oder Interleukin-Inhibitor) unzureichend angesprochen, das Ansprechen verloren oder diese nicht vertragen haben". Was ist hier der Behandlungsstandard unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus?

Ein Wirkverlust einer initial wirksamen Therapie mit einem Biologikum tritt mit 15–50 % per anno auf. Auch ist die Ansprechrate auf ein anderes Biologikum in dieser Situation oft reduziert (40–80 %) und durch einen erneuten Wirkverlust im weiteren Verlauf beeinträchtigt. Somit gibt es im klinischen Alltag regelhaft Patienten mit wiederholtem Therapiewechsel. Üblicherweise wechselt man die Substanzgruppe (TNF-α-Antagonist vs. Integrin-Inhibitor vs. Interleukin-Inhibitor). Ein Wechsel innerhalb der TNF-α-Antagonisten ist unüblich, wenn die beiden anderen Gruppen noch nicht eingesetzt wurden. Eine Rückkehr zu den TNF-α-Antagonisten ist Standard, wenn die beiden anderen Gruppen bereits eingesetzt wurden. Es wird aber nicht die gleiche Substanz, die bereits einmal versagt hat, ein zweites Mal eingesetzt. Nachfolgender, bereits im letzten Statement enthaltener Passus gilt auch hier:

„Vor Therapieänderung ist zu prüfen, ob andere Faktoren zu einer Verschlechterung führen oder sich die Erkrankungsmanifestation geändert hat. Die Bewertung der Erkrankungsaktivität hat klinische Faktoren (z. B. Aktivitätsindizes), bildgebende Verfahren (Endoskopie, Sonographie, MRT) und laborchemische Parameter (z. B. CRP i.S., Calprotectin i. Stuhl) zu berücksichtigen. Ferner ist zu prüfen, ob durch eine chirurgische Maßnahme (z. B. Strikturoplastik, chirurgische Fisteltherapie) die Therapieumstellung vermieden werden kann. Bei Morbus Crohn mit ausschließlich ileozökalem Befall kann eine Resektion des befallenen Darmabschnittes eine passagere Therapiefreiheit (teilweise über mehrere Jahre) ermöglichen."

Zusammenfassend: Der Wirkverlust bei Biologika ist häufig, wenn man nur eine Einzelsubstanz betrachtet. Patienten, die alle Biologika mit fehlendem oder verlorenem Ansprechen bereits erhalten haben und für die keine therapierbare Infektion oder operative Behandlungsoption mehr besteht, sind in der Zahl selten, in der Behandlung aber ein echtes Problem.

Die nachfolgende **Literatur** bezieht sich auf o. g. Ansprechraten und Wirkverlust im ersten Absatz in Ergänzung zur früheren Literaturangabe:

(1) Ma C, Fedorak RN, Kaplan GG et al.: Clinical, endoscopic and radiographic outcomes with ustekinumab in medically-refractory Crohn's disease: real world experience from a multicentre cohort. Aliment Pharmacol Ther 2017; 45: 1232-1243.
(2) Ma C, Fedorak RN, Kaplan GG et al.: Long-term maintenance of clinical, endoscopic, and radiographic response to ustekinumab in moderate-to-severe crohn's disease: real-world experience from a multicenter cohort study. Inflamm Bowel Dis 2017; 23: 833-839.
(3) Lindsay JO, Armuzzi A, Gisbert JP et al.: Indicators of suboptimal tumor necrosis factor antagonist therapy in inflammatory bowel disease. Dig Liver Dis 2017; 49: 1086-1091.
(4) Chaparro M, Garre A, Ricart E et al.: Short and long-term effectiveness and safety of vedolizumab in inflammatory bowel disease: results from the ENEIDA registry. Aliment Pharmacol Ther 2018; 48: 839-851.

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zur Behandlung des mittelschweren bis schweren aktiven Morbus Crohn bei Erwachsenen und Jugendlichen ab 16 Jahren, die auf eine konventionelle Therapie unzureichend angesprochen, das Ansprechen verloren haben oder diese nicht vertragen haben

(5) Rutgeerts P, Gasink C, Chan D et al.: Efficacy of ustekinumab for inducing endoscopic healing in patients with crohn's disease. Gastroenterology 2018; 155: 1045-1058.

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen bei der Behandlung von „mittelschwerem bis schwerem aktiven Morbus Crohn bei Erwachsenen und Jugendlichen ab 16 Jahren“, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?

Im Grundsatz ist diese Frage mit einem Nein zu beantworten. Die Auswahl des Biologikums erfolgt patientenindividuell anhand bisherigem Erkrankungsverlauf, Art der Vorbehandlung (inklusive möglicher Nebenwirkungen wie allergischen Reaktionen, Antikörperbildung oder Infektionen unter Therapie), Ausdehnung/Manifestation der Erkrankung inklusive perianaler Erkrankung, Erwartungen an den weiteren Verlauf.

Nur bei Risikofaktoren für einen schweren Verlauf wie beispielsweise jungem Erkrankungsalter, langstreckigem Dünndarmbefall oder perianalem M. Crohn gibt es in der deutschen Leitlinie eine Empfehlung für den kombinierten Einsatz von Infliximab und Azathioprin (1). Diese Patientengruppe sollte und wird im klinischen Alltag jedoch bereits frühzeitig intensiviert immunsupprimierend unter Einsatz von Biologika therapiert und sollte somit eigentlich nicht in die hier adressierte Gruppe fallen.

Literatur

1. Sturm A, Atreya R, Bettenworth D et al.: Aktualisierte S3-Leitlinie „Diagnostik und Therapie des Morbus Crohn“ der Deutschen Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten (DGVS): https://www.dgvs.de/wissen/leitlinien/leitlinien-dgvs/morbus-crohn/ (letzter Zugriff: 16. August 2021). Konsultationsfassung vom Juni 2021.
2. Torres J, Bonovas S, Doherty G et al.: ECCO guidelines on therapeutics in crohn's disease: medical treatment. J Crohns Colitis 2020; 14: 4-22.

Beteiligung von AkdÄ und Fachgesellschaften nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

2021-B-230

Indikation gemäß Beratungsantrag

zur Behandlung des mittelschweren bis schweren aktiven Morbus Crohn bei Erwachsenen und Jugendlichen ab 16 Jahren, die auf eine konventionelle Therapie unzureichend angesprochen, das Ansprechen verloren haben oder diese nicht vertragen haben

Was ist der Behandlungsstandard in o.g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus?

Die aktualisierte Fassung der S3-Leitlinie zur Diagnostik und Therapie der Morbus Crohn (MC), steht als Konsultationsfassung zur Verfügung und beschreibt in verschiedenen Empfehlungen die Behandlungsstandards bei diesen Patientengruppen[1]. Aus inhaltlichen Gründen wird die formal noch gültige Leitlinie, die 2014 publiziert wurde, bei der Beantwortung der Fragen nicht berücksichtigt.

Bei Therapieversagen auf eine konventionelle Therapie (Budesonid, Steroidstoßtherapie) im akuten Schub wird zwischen einem **a) steroidabhängigem** und einem **b) steroidrefraktären** Verlauf unterschieden. Bezüglich der Therapie der steroidabhängigen Form des Morbus Crohn wird in der Leitlinie aufgeführt:

a) Steroidabhängiger M. Crohn:

Empfehlung 2.17 (neu)
Patient*innen mit einem steroidabhängigen M. Crohn sollten mit einem Thiopurinen, MTX oder einem TNF-α-Antikörper (im Falle von Infliximab ggf. kombiniert mit Thiopurinen), Ustekinumab oder Vedolizumab behandelt werden*. *Expertenkonsens, Empfehlung, starker Konsens*

**Die Medikamente sind alphabetisch gereiht. Wenn nicht anders angegeben, impliziert diese Reihung keine Priorisierung für den klinischen Einsatz.*

Aufgrund fehlender Evidenzen priorisieren die Autoren der Leitlinie keines der genannten Medikamente im Absatz beim steroidabhängigen MC und stellen die verfügbaren Medikamente gleichwertig nebeneinander. So ist sowohl der Einsatz von Azathioprin bzw. 6-Mercaptopurin (Thioipurine), Methotrexat (MTX) wie auch Biologika möglich. Azathioprin (2,0 – 2,5 mg/kg KG/Tag) bzw. 6-Mercaptopurin (1,0 – 1,5 mg/kg KG/Tag) sind zur Remissionsinduktion mangels Effektivität nicht geeignet, wirken jedoch remissionserhaltend und weisen einen steroideinsparenden Effekt auf. Methotrexat stellt bei einem steroidabhängigen Erkrankungsverlauf eine geeignete Alternative zu Thiopurinen dar. Studien mit Biologika, die ausschließlich Patient*innen mit einem MC mit einem steroidabhängigen Verlauf eingeschlossen haben, liegen nicht vor.

Indikation gemäß Beratungsantrag

zur Behandlung des mittelschweren bis schweren aktiven Morbus Crohn bei Erwachsenen und Jugendlichen ab 16 Jahren, die auf eine konventionelle Therapie unzureichend angesprochen, das Ansprechen verloren haben oder diese nicht vertragen haben

Die Wirksamkeit von Adalimumab, Infliximab, Ustekinumab und Vedolizumab wurde jedoch bei Patient*innen mit moderatem bis schwerem M. Crohn mit unzureichendem Ansprechen oder bei Intoleranz einer konventionellen Therapie (Steroide u./o. Immunsuppressiva) gezeigt. Die genannten Substanzen waren bzgl. der Remissionsinduktion und -erhaltung sowohl bei Biologika-naiven als auch Biologika-erfahrenen Patient*innen effektiv. Direkte Vergleichsstudien der hier dargestellten Präparate (Immunsuppressiva und Biologika) liegen derzeit ebenfalls nicht vor.

Bezüglich der Therapie der steroidabhängigen Form des Morbus Crohn werden in der aktuellen MC-Leitlinie folgende Empfehlungen aufgeführt:

b) steroidrefraktärer M. Crohn

Empfehlung 2.12 (neu)

Der steroidrefraktäre M. Crohn mit mittlerer bis hoher Krankheitsaktivität sollte primär mit TNF-α-Antikörpern (im Falle von Infliximab ggf. kombiniert mit einem Thiopurin) oder Ustekinumab oder Vedolizumab behandelt werden*.

Expertenkonses, Empfehlung, Konsens

**Die Medikamente sind alphabetisch gereiht. Wenn nicht anders angegeben, impliziert diese Reihung keine Priorisierung für den klinischen Einsatz*

Um ein rasches Therapieansprechen zu erreichen, sollten Patient*innen mit einem steroidrefraktären Erkrankungsverlauf mit Biologika behandelt werden. Mehrere Metaanalysen von randomisierten klinischen Studien belegen die Wirksamkeit von TNF-α-Antikörpern bei Patient*innen, die unzu-reichend auf Steroide oder Immunsuppressiva angesprochen haben oder diese nicht vertragen haben. Ein aktueller, bei der Erstellung der Leitlinie noch nicht berücksichtigter systematischer Review mit Netzwerkwerkmetaanalyse konnte keinen Unterschied in der Wirksamkeit der in Deutschland zur Behandlung des MC zugelassenen Biologika finden, sodass eine Gleichwertigkeit angenommen wird und die Auswahl des Präparates nach individuellen Kriterien getroffen werden muss (2).

Zusätzlich bitten wir Sie um eine Einschätzung zu folgendem Anwendungsgebiet „Erwachsene und Jugendliche ab 16 Jahren mit mittelschwerem bis schwerem aktivem Morbus Crohn, die auf ein Biologikum (TNF-α-Antagonist oder Integrin-Inhibitor oder Interleukin-Inhibitor) unzureichend angesprochen, das Ansprechen verloren oder diese nicht vertragen haben". Was ist hier der Behandlungsstandard unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus?

In dieser Situation sind folgende Empfehlungen wichtig:

Indikation gemäß Beratungsantrag

zur Behandlung des mittelschweren bis schweren aktiven Morbus Crohn bei Erwachsenen und Jugendlichen ab 16 Jahren, die auf eine konventionelle Therapie unzureichend angesprochen, das Ansprechen verloren haben oder diese nicht vertragen haben

Empfehlung 2.5 (neu 2020)

Bei persistierender oder erneuter Aktivität eines M. Crohn sollte die bisherige Therapie optimiert werden (Prüfung der Adhärenz, Dosis, Dosierungsintervalle, Komedikation) bevor eine Umstellung der Therapie erfolgt.

Expertenkonsens, Empfehlung, Konsens

Empfehlung 2.6 (neu 2020)

Bei Versagen der bisherigen Therapie sollten die Diagnosesicherheit geprüft, eine Re-Evaluierung der Erkrankungsaktivität und ein Ausschluss anderer Ursachen einer klinischen Verschlechterung erfolgen, sowie der Einsatz anderer, bisher nicht verwendeter Wirkprinzipien oder chirurgischer Therapieoptionen interdisziplinär diskutiert werden.

Expertenkonsens, Empfehlung, starker Konsens

Sollte durch eine Dosisoptimierung keine Remission erreicht werden, sollte der Einsatz eines bisher nicht verwendeten Wirkprinzips zum Einsatz kommen. Auf Grund von fehlenden randomisierten Studien, welche die Wirksamkeit der verschiedenen Wirkprinzipien (TNF-α-Antikörper, Ustekinumab, Vedolizumab) direkt miteinander vergleichen, gibt es keine klare Empfehlung über die zu verwendende Therapiesequenz.

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen bei der Behandlung von „mittelschwerem bis schwerem aktiven Morbus Crohn bei Erwachsenen und Jugendlichen ab 16 Jahren“ die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?

Neben dem Schweregrad des akuten Schubes (Behandlung von „mittelschwerem bis schwerem aktiven Morbus Crohn bei Erwachsenen und Jugendlichen ab 16 Jahren“) besitzt das Befallsmuster, das Erkrankungsalter und das Vorhandensein von extraintestinalen Komplikationen in der Behandlungsentscheidung eine Bedeutung. So wird z. B. bei Patienten mit einem auf das terminale Ileum beschränkten MC die Operation der Behandlung mit Infliximab gleichgestellt.

Empfehlung 2.13 (neu)

Bei einem isolierten Befall der Ileozökalregion, kurzer Anamnese und fehlendem Ansprechen auf Steroide ist das operative Vorgehen (Ileozökalresektion) verglichen mit der Therapie mit Infliximab als gleichwertig anzusehen.

Expertenkonsens, Empfehlung, Konsens

Klug Entscheiden

Indikation gemäß Beratungsantrag

zur Behandlung des mittelschweren bis schweren aktiven Morbus Crohn bei Erwachsenen und Jugendlichen ab 16 Jahren, die auf eine konventionelle Therapie unzureichend angesprochen, das Ansprechen verloren haben oder diese nicht vertragen haben

Die Evidenz zur früh-elektiven Ileozökalresektion bei der limitierten Ileitis terminalis Crohn („auf den Endteil des Dünndarms beschränkter MC“) konnte in jüngster Vergangenheit durch prospektive randomisierte Studien weiter ausgebaut werden. Eine hohe Aussagekraft hat eine im Jahre 2017 publizierte randomisierte Multicenter-Studie (LIR!C Trial), die die laparoskopische Ileozökalresektion mit einer Monotherapie mit Infliximab bei der Ileitis terminalis Crohn verglich (3, 4.) Auf Grundlage dieser neuen Evidenzlage sollte bei einem isolierten Crohn-Befall in der Ileozökalregion die chirurgische Resektion als gleichwertige Alternative zur medikamentösen Therapie betrachtet werden und Patient*innen dementsprechend über beide Therapiemöglichkeiten aufgeklärt werden.

Weitere Risikofaktoren bzw. Kriterien für unterschiedliche Behandlungsentscheidungen ergeben sich wie folgt:

Empfehlung 2.11 (neu)

M. Crohn-Patient*innen mit ausgedehntem Dünndarmbefall und/oder Befall des oberen GI-Traktes sollten initial mit systemisch wirkenden Steroiden behandelt werden. Eine frühzeitige immunsuppressive Therapie oder Therapie mit TNF-α-Antikörpern (im Falle von Infliximab ist die Kombination mit Thiopurinen zu erwägen), Ustekinumab oder Vedolizumab sollten erwogen werden*.

Expertenkonsens, Empfehlung, starker Konsens

**Die Medikamente sind alphabetisch gereiht. Wenn nicht anders angegeben, impliziert diese Reihung keine Priorisierung für den klinischen Einsatz.*

Empfehlung 3.9 (neu)

Bei Risikofaktoren wie beispielsweise jungem Erkrankungsalter, langstreckigem Dünndarmbefall oder perianalem M. Crohn kann unter Nutzen-/Risikoabwägung eine Kombinationstherapie von Infliximab und Thiopurinen gegenüber einer Infliximab-Monotherapie auch zur Remissionserhaltung eingesetzt werden.

Expertenkonsens, Empfehlung offen, starker Konsens

Ein ausgedehnter Befall des Dünndarmes oder des oberen Gastrointestinaltraktes ist ein Prädiktor für einen ungünstigen Verlaufes. Aufgrund der Langzeitfolgen eines ausgedehnten Dünndarmbefalls mit resultierender Malabsorption und der Gefahr eines Kurzdarmsyndroms nach (wiederholten) chirur-gischen Eingriffen sowie des Risikos wiederholter Steroidtherapie wird bei betroffenen Patient*innen eine frühzeitige intensivierte Therapie mit Biologika und Immunsuppressiva empfohlen. Ebenso gilt ein junges Erkrankungsalter sowie perianale Manifestation als Risikofaktoren für einen ungünstigen Verlauf. Bei einer hohen Krankheitsaktivität kann eine Kombinationstherapie von Infliximab und Thiopurinen angewendet

Indikation gemäß Beratungsantrag

zur Behandlung des mittelschweren bis schweren aktiven Morbus Crohn bei Erwachsenen und Jugendlichen ab 16 Jahren, die auf eine konventionelle Therapie unzureichend angesprochen, das Ansprechen verloren haben oder diese nicht vertragen haben

werden. Diese Empfehlung basiert ganz wesentlich auf den Ergebnissen der SONIC-Studie in der die Kombination von Infliximab und Azathioprin gegenüber der Monotherapie von Azathioprin und Infliximab untersucht wurde (5).

Empfehlung 5.16 (modifiziert 2020)
Zur Behandlung der peripheren Arthritiden sollten Sulfasalazin, Methotrexat oder TNF-α-Antikörper eingesetzt werden. *Evidenzgrad 2, Empfehlungsgrad B, starker Konsens*

Empfehlung 5.17 (neu)
Axiale Spondylarthritiden sollten mit TNF-α-Antikörpern behandelt werden. *Expertenkonsens, Empfehlung, starker Konsens*

Periphere Spondyloarthritiden sprechen sehr gut auf Sulfasalazin, Methotrexat und TNF-α-Antikörper an, während Sulfasalazin und Methotrexat bei axialen Spondyloarthritiden unwirksam sind und daher TNF-α-Antikörper empfohlen werden. Studien zur Therapie von Arthritiden bei CED liegen nur für Infliximab, aber nicht für Basistherapeutika vor. Sulfasalazin, Methotrexat und TNF-α-Antikörper und haben ihre Wirksamkeit bei rheumatoider Arthritis gezeigt. Als Extrapolation können diese Medikamente auch bei CED-assoziierten Arthritiden eingesetzt werden.

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