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: 2023-B-049-z Upadacitinib

Stand: Dezember 2022

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

Upadacitinib
Behandlung des mittelschweren bis schweren aktiven Morbus Crohn

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	
Upadacitinib **Behandlung des mittelschweren bis schweren aktiven Morbus Crohn** **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:	
Upadacitnib L04AA44 Rinvoq®	Anwendungsgebiet: „RINVOQ wird angewendet zur Behandlung des mittelschweren bis schweren aktiven Morbus Crohn bei erwachsenen Patienten, die auf eine konventionelle Therapie oder ein Biologikum unzureichend angesprochen haben, nicht mehr darauf ansprechen 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.
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.
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.
Integrininhibitor	

II. Zugelassene Arzneimittel im Anwendungsgebiet	
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.
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)
Methotrexat L01BA01 generisch z.B. Metex® 50mg Fertigspritze	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.
Aminosalicylsäuren	
Mesalazin A07EC02 z.B. Salofalk®	Morbus Crohn: zur Behandlung des akuten Schubs
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).

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Hydrocortison-acetat Colifoam® H02AB09 Rektalschaum	Entzündliche Erkrankungen im unteren Dickdarmbereich wie Colitis ulcerosa oder Morbus Crohn und Proktosigmoiditis.
Prednison H02A B07 generisch z.B. Prednison-ratiopharm® 5 mg Tabletten	Morbus Crohn (Dosierung: 40-80 mg/Tag)
Prednisolon H02AB06 generisch z.B. Decortin-H®,Tab	Morbus Crohn (Dosierung: 40-80 mg/Tag)
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: 2023-B-049-z (Upadacitinib)

Auftrag von:	Abteilung Arzneimittel
Bearbeitet von:	Abteilung Fachberatung Medizin
Datum:	22. November 2022

Gemeinsamer Bundesausschuss, Berlin 2023

Inhaltsverzeichnis

Abkürzungsverzeichnis

AE	Adverse Event
AGA	American Gastroenterological Association
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
AZA	Azathioprin
BSG	British Society of Gastroenterology
CAG	Canadian Association of Gastroenterology
CD	Crohn's Disease
CDAI	Clinical Disease Activity Index
CMV	Zytomegalievirus
CRP	C-reaktives Protein
DGVS	Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten
EBV	Epstein-Barr-Virus
ECCO	European Crohn's and Colitis Organisation
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	Hazard Ratio
IBD	Inflammatory Bowel Disease
IM	Immunmodulator
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
CI	Confidence Interval
CrI	Credible Interval
LoE	Level of Evidence
MCID	Minimal Clinically Important Difference
MTX	Methotrexat
NICE	National Institute for Health and Care Excellence
NMA	Netzwerk-Metaanalyse
OR	Odds Ratio
PICO	Population, Intervention, Comparator, Outcome
RCT	Randomisierte Kontrollierte Studie
ROBINS-I	Risk of Bias in non-randomized Studies – of Interventions
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network

TB	Tuberkulose
TNF	Tumornekrosefaktor
TPMT	Thiopurin-Methyltransferase
TRIP	Turn Research into Practice Database
UST	Ustekinumab
WHO	World Health Organization

1 Indikation

Behandlung von erwachsenen Patient*innen mit mittelschwerem bis schwerem aktiven Morbus Crohn, die auf eine konventionelle Therapie oder ein Biologikum unzureichend angesprochen haben, nicht mehr darauf ansprechen oder eine Unverträglichkeit gegen eine entsprechende Behandlung gezeigt haben.

Hinweis zur Synopse: Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Morbus Crohn* durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: The Cochrane Library (Cochrane Database of Systematic Reviews), PubMed. Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (https://www.google.com/) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Die Erstrecherche wurde am 06.04.2022 durchgeführt, die folgende am 26.10.2022. Die Recherchestrategie der Erstrecherche wurde unverändert übernommen und der Suchzeitraum jeweils auf die letzten fünf Jahre eingeschränkt. Die letzte Suchstrategie inkl. Angabe zu verwendeter Suchfilter ist am Ende der Synopse detailliert dargestellt. Die Recherchen ergaben insgesamt 2087 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. 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 Referenzen 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 14 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Es wurden keine relevanten Cochrane Reviews identifiziert.

3.2 Systematische Reviews

Parrot L et al., 2021 [9].

Systematic review with meta-analysis: the effectiveness of either ustekinumab or vedolizumab in patients with Crohn's disease refractory to anti-tumour necrosis factor

Zielsetzung

To compare the effectiveness of ustekinumab and vedolizumab in CD patients refractory to anti-TNF.

Methodik

Population:

patients with CD after anti-TNF failure

Intervention:

ustekinumab

Komparator:

vedolizumab

Endpunkte:

- clinical remission (Harvey Bradshaw index ≤4 or Crohn's disease activity index <150) at weeks 14 and 52
- steroid-free clinical remission at the evaluation at weeks 14 and 52
- biological remission (C-reactive protein serum concentration ≤5 mg/l or fecal calprotectin level ≤250 µg/g) at weeks 14 and 52
- persistence of treatment at week 52 (meaning that the patients were still treated by either ustekinumab or vedolizumab at 52 weeks)

Recherche/Suchzeitraum:

On March 27, 2021, we searched PubMed, EMBASE and the Cochrane Library […].

Qualitätsbewertung der Studien:

Newcastle-Ottawa Scale (high-quality studies were defined as those with a score ≥7)

Ergebnisse

Anzahl eingeschlossener Studien:

- […] six studies[18,19,20,21,22,24] were included for qualitative synthesis and quantitative meta-analysis.
- One study did not present adjusted results, and was not included in the main analysis but only in the sensitivity analysis.
- The principal analysis was based on five studies with adjusted results. Four studies were retrospective and one was prospective. A total of 1026 patients received either ustekinumab (n = 659) or vedolizumab (n = 367) and were included in the analyses.

Charakteristika der Population:

Author, Year	Study design	Number of patients	Drug dosage	Follow-up	Concomitant steroid at baseline	Concomitant immunosuppressant at baseline	Variables for adjustment
Alric 2020	Retrospective cohort	All: 239 UST: 132 VDZ: 107	UST: IV, SC at W8 then q8-q4 VDZ: W0, W2, W6 then q8-q4	48 weeks	UST: 28.0% VDZ: 48.5%	UST: 23.4% VDZ: 42.4%	Sex, age, CD duration, location and behaviour, history of perianal disease, active smoking, prior CD surgery, history of adalimumab and infliximab use, combination therapy at initiation, corticosteroids at initiation, CRP, haemoglobin and HBI
Biemans 2020	Prospective cohort	All: 213 UST: 128 VDZ: 85	UST: IV, SC at W8 then q12-q4 VDZ: W0, W2, W6 then q8-q4	52-104 weeks	UST: 11.8% VDZ: 31.3%	UST: 23.5% VDZ: 18.8%	CD duration, location and behaviour, active smoking, prior CD surgery, number of prior anti-TNF therapies, combination therapy at initiation, corticosteroids at initiation, biochemical disease activity at baseline and HBI
Manlay 2021	Retrospective cohort	All: 312 UST: 224 VDZ: 88	UST: IV, SC at W8 then q8-q4 VDZ: W0, W2, W6 then q8-q4	54 weeks	UST: 26.3% VDZ: 31.8%	UST: 14.3% VDZ: 19.3%	Sex, age, CD duration, location and behaviour, perianal disease, smoking, prior CD surgery, prior use of at least two anti-TNF, prior use of other biologics than anti-TNF, combination therapy at initiation, corticosteroids at initiation, primary nonresponse to at least one anti-TNF, CDAI >220 at baseline and CRP >5 mg/L at baseline
Rayer 2021	Retrospective cohort	All: 132 UST: 90 VDZ: 42	NA	24 weeks	NA	NA	CD location and behaviour
Townsend 2020	Retrospective cohort	All: 130 UST: 85 VDZ: 45	UST: Induction then q8-q4 VDZ: W0, W2, W6 then q8-q4	52 weeks	UST: 44.4% VDZ: 35.3%	UST: 35.6% VDZ: 47.1%	CD duration and location, disease severity, perianal disease and smoking
Kolar 2019	Retrospective cohort	All: 95 UST: 50 VDZ: 45	NA	32 weeks	UST: 32.0% VDZ: 20.0%	UST: 44.0% VDZ: 46.7%	None

Abbreviations: CD, Crohn's disease; IV, intravenous; NA, not available; q4: every 4 weeks; q8: every 8 weeks; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab.

Qualität der Studien:

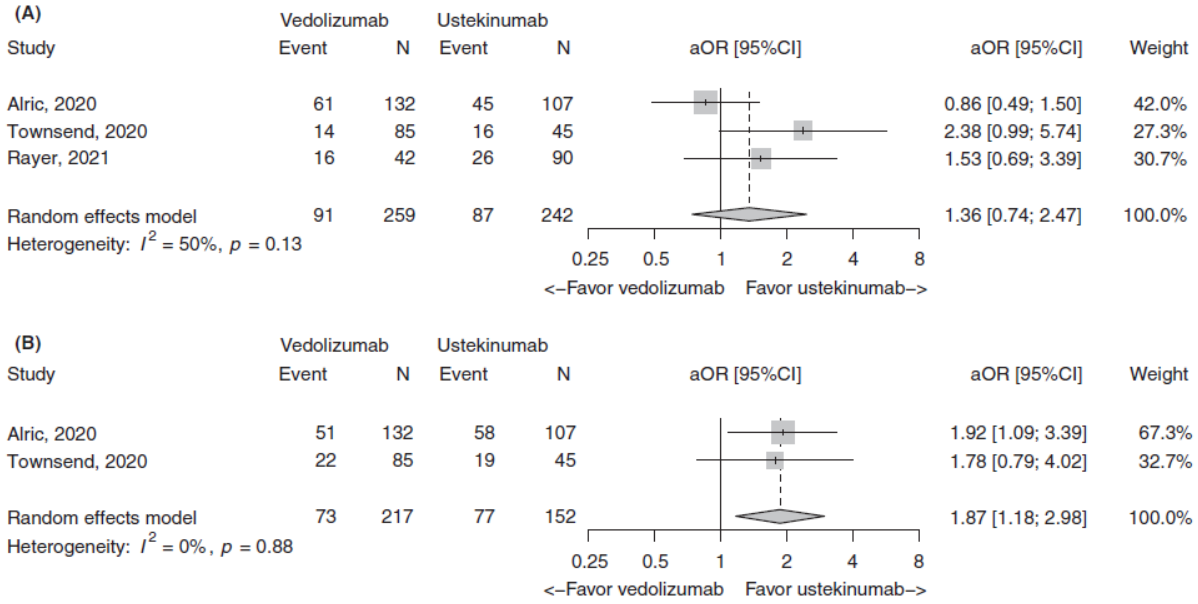
All observational studies were of high quality according to the Newcastle-Ottawa scale (siehe Anhang, Tabelle 1).

Studienergebnisse:

Clinical remission

- Comparison of the clinical remission was based on three studies at week 14 and two studies at week 52.
- At week 14, the rate of clinical remission was similar between patients treated with ustekinumab and vedolizumab (OR 1.36; 95% CI: 0.74 – 2.47; I^2 = 50%).
- At week 52, the rate of clinical remission was higher in patients treated with ustekinumab than in those treated with vedolizumab (OR 1.87; 95% CI: 1.28 – 2.98; I^2 = 0%).

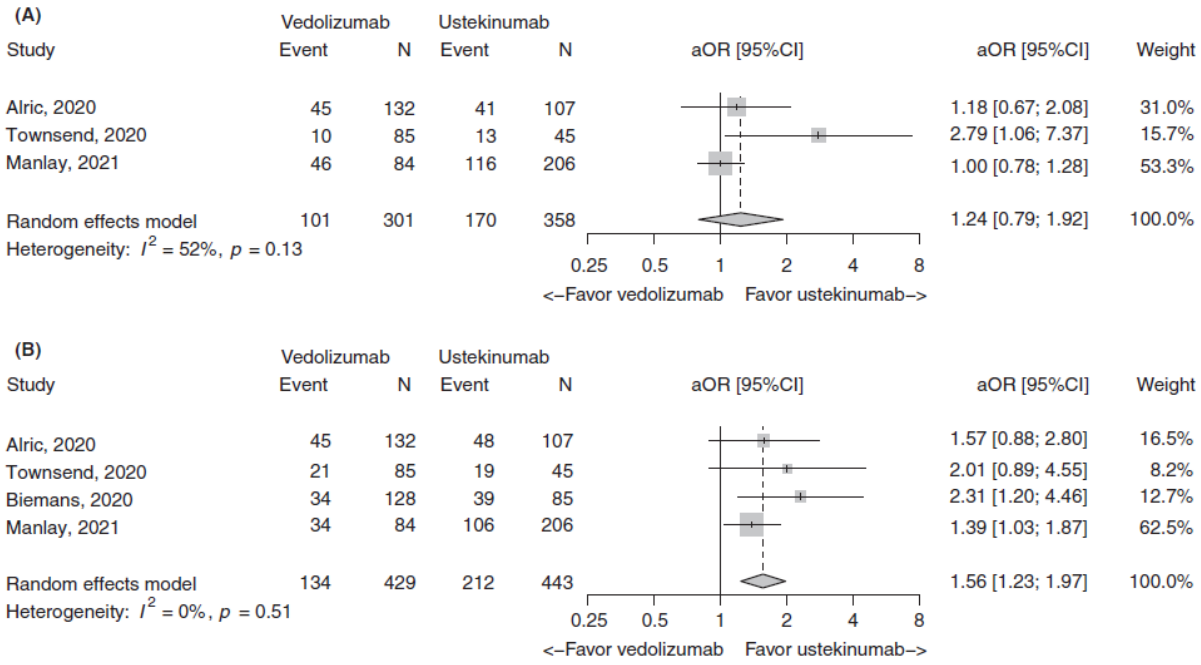
Abbildung 1: Clinical remission at week 14 (A) and week 52 (B)



Steroid-free clinical remission

- Comparison of the steroid-free clinical remission was based on three studies at week 14 and four studies at week 52.
- At week 14, the rate of steroid-free clinical remission was similar between patients treated with ustekinumab and vedolizumab (OR 1.24; 95% CI: 0.79 – 1.92; I^2 = 52%), while at week 52, it was higher in patients treated with ustekinumab than in those treated with vedolizumab (OR 1.56; 95% CI: 1.23 – 1.97; I^2 = 0%).

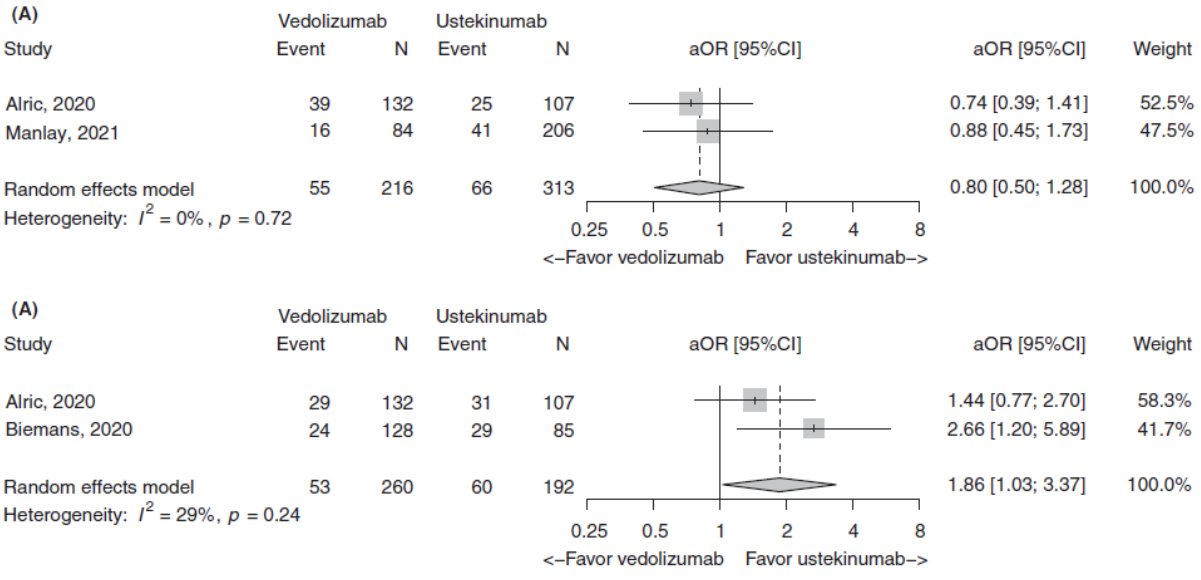
Abbildung 2: Steroid-free clinical remission at week 14 (A) and week 52 (B)



Biological remission

- Comparison of the biological remission was based on two studies at weeks 14 and 52.
- The rate of biological remission was similar between patients treated with ustekinumab and vedolizumab at week 14 (OR 0.80; 95% CI: 0.50 – 1.28; I^2 = 0%), and higher in patients treated with ustekinumab compared to those treated with vedolizumab at week 52 (OR 1.86; 95% CI: 1.03 – 3.37; I^2 = 29%).

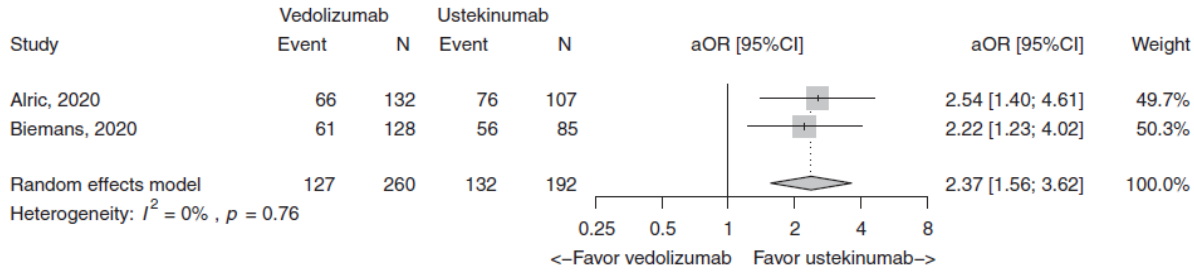
Abbildung 3: Biological remission at week 14 (A) and week 52 (B)



Persistence of treatment at week 52

- Comparison of the persistence of treatment was based on two studies.
- At week 52, more patients were still being treated with ustekinumab than with vedolizumab (OR 2.37; 95% CI: 1.56 – 3.62; I^2 = 0%).

Abbildung 3: Persistence of treatment at week 52



Sensitivity analysis

- In a sensitivity analysis based on four studies, we also included the study with unadjusted ORs for clinical remission (OR 1.47; 95% CI: 0.90 – 2.40; I^2 = 41%) and steroid-free clinical remission (OR 1.24; 95% CI: 0.87 – 1.77; I^2 = 37%) at week 14.
- The results were unchanged.

Anmerkung/Fazit der Autoren

In conclusion, our results suggest that ustekinumab was not more efficacious than vedolizumab as induction treatment, but may be more efficacious as maintenance treatment in Crohn's disease patients refractory to anti-TNF.

Kommentare zum Review

Die Studie von Kolar und Kollegen (2019) wurde anhand der Newcastle-Ottawa Scale mit 5 Punkten bewertet und entspricht, gemäß der Klassifizierung von Parrot und Kollegen (2021), somit keiner hohen Studienqualität.

Referenzen

18. Alric H, Amiot A, Kirchgesner J, Tréton X, Allez M, Bouhnik Y, et al. The effectiveness of either ustekinumab or vedolizumab in 239 patients with Crohn's disease refractory to anti-tumour necrosis factor. Aliment Pharmacol Ther 2020;51(10):948-957.
19. Biemans VBC, van der Woude CJ, Dijkstra G, van der Meulen-de Jong AE, Löwenberg M, de Boer NK, et al. Ustekinumab is associated with superior effectiveness outcomes compared to vedolizumab in Crohn's disease patients with prior failure to anti-TNF treatment. Aliment Pharmacol Ther 2020;52(1):123-134.
20. Townsend T, Razanskaite V, Dodd S, Storey D, Michail S, Morgan J, et al. Comparative effectiveness of ustekinumab or vedolizumab after one year in 130 patients with anti-TNF-refractory Crohn's disease. Aliment Pharmacol Ther 2020;52(8):1341-1352.
21. Kolář M, Ďuricová D, Bortlík M, Pudilova K, Hrubá V, Machková N, et al. Vedolizumab vs. ustekinumab as second-line therapy in Crohn's disease in clinical practice. Gastroenterol Hepatol 2019;73:25-31.
22. Rayer C, Pariente B, Fumery M, Bouguen G. Ustekinumab, vedolizumab ou second anti-TNF après échec d'un premier anti-TNF dans la maladie de Crohn: étude retrospective multicentrique. JFHOD Abstract, 2021.
24. Manlay L, Boschetti G, Pereira B, Flourié B, Dapoigny M, Reymond M, et al. Comparison of short- and long-term effectiveness between ustekinumab and vedolizumab in patients with Crohn's disease refractory to ani-tumour necrosis factor therapy. Aliment Pharmacol Ther 2021;53(12):1289-1299.

Yoshihara T et al., 2021 [14].

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

Zielsetzung

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:

CD patients in whom treatment was initiated 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:

A systematic literature search was performed using PubMed/MEDLINE, the Cochrane Library, and the *Japana Centra Revuo Medicina* from inception to October 31, 2019.

Qualitätsbewertung der Studien:

Cochrane risk-of-bias tool 2.0 (RoB 2) for RCT and Cochrane's tool, named the 'risk of bias in non-randomized studies of interventions' (ROBINS-I) tool for non-RCT

Ergebnisse

Anzahl eingeschlossener Studien:

[…] seven studies in six articles […] including a total of 1507 patients were considered in this meta-analysis.

Charakteristika der Population:

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

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:

- All included studies were non-randomized studies […], so we assessed the risk of bias in the included studies using the ROBINS-I tool.
- We judged that all studies had a serious risk of bias in the overall judgment based on the serious bias risk in their domain.
- 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.

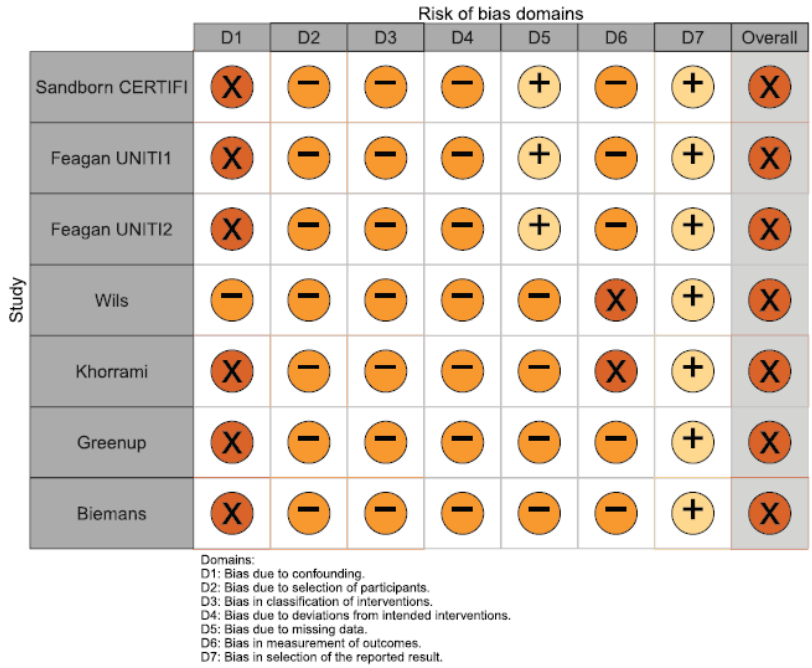


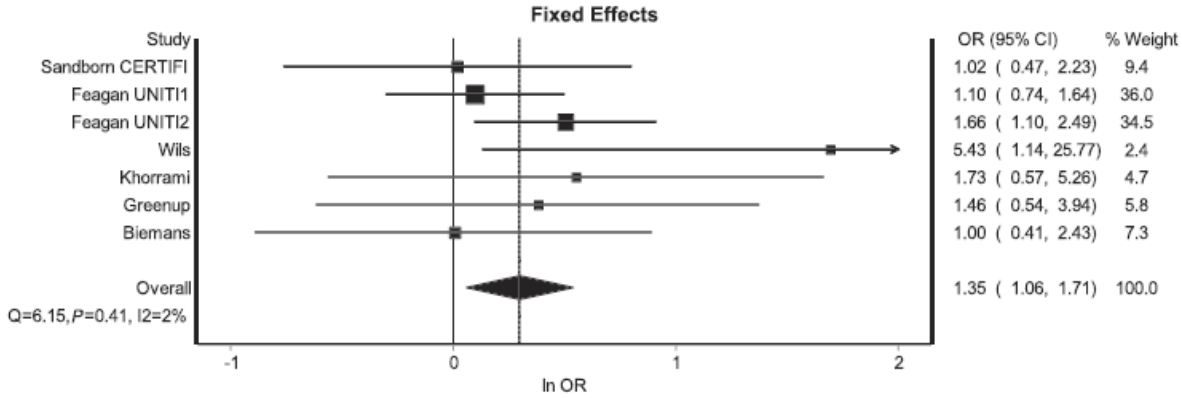
Figure 2 Risk of bias assessment for individual studies according to the risk of bias in non-randomized studies-of interventions (ROBINS-I) tool. All studies had a serious risk in the overall judgment. Judgment: x, serious; −, moderate; +, low. [Color figure can be viewed at wileyonlinelibrary.com]

Studienergebnisse:

Overall clinical efficacy

- The meta-analysis included seven studies with a total of 1507 patients. Of these patients, 1051 patients received UST monotherapy (monotherapy group) and 456 patients received concomitant use of an IM with UST (concomitant IM group).
- 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). […] the heterogeneity was considered to be low among the studies (Q = 6.16, P = 0.406, I^2 = 2.6%; 95% CI [0 – 71.5]).

Abbildung 1: Forest plot comparing the overall clinical efficacy (clinical remission, or clinical response, or clinical benefit defined as the physicians' global assessment) of UST monotherapy group and the concomitant IM group



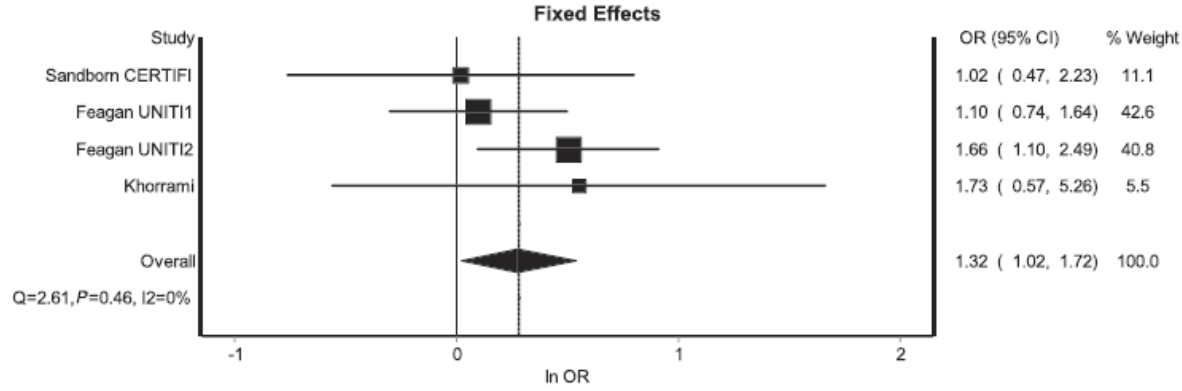
Clinical remission

- Only the prospective observational study by Biermans et al. reported the clinical remission rate of the concomitant IM group and the monotherapy group; therefore, a pooled OR regarding clinical remission could not be calculated.
- The study showed that there were no significant differences in corticosteroid-free remission between the concomitant IM group and the monotherapy group (OR: 1.004, 95% CI [0.42 – 2.43]).

Clinical response

- Four studies (the CERTIFI trial, the UNITI-1/2 trials, and the study by Khorrami et al.) were included. In these studies with a total of 1159 patients, the number of patients in the monotherapy group and the concomitant IM group were 784 and 375, respectively.
- 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 fixed-effects model). The heterogeneity was considered to be low (Q = 2.61, P = 0.456, I^2 = 0%, 95% CI [0 – 82.4] […].

Abbildung 2: Forest plot comparing the clinical response of UST monotherapy group and the concomitant IM group



Adverse events

- The adverse events in the concomitant IM group and monotherapy group were reported only in the study by Biermans et al. No other studies compared the occurrence of adverse events between the concomitant IM group and the monotherapy group.
- No statistical comparisons of the occurrence of adverse events between UST monotherapy and concomitant use of an IM with UST were performed.

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.

Referenzen
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Khorrami S, Ginard D, Marín-Jiménez I, Chaparro M, Sierra M, Aguas M, et al. Ustekinumab for the treatment of refractory Crohn's disease: The Spanish Experience in a large multicentre open-label cohort. Inflamm Bowel Dis 2016;22(7):1662-1669.
Greenup AJ, Rosenfeld G, Bressler B. Ustekinumab use in Crohn's disease: a Canadian tertiary care centre experience. Scand J Gastroenterol 2017;52(12):1354-1359.
Biemans VBC, van der Meulen-de Jong AE, van der Woude CJ, Löwenberg M, Dijkstra G, Oldenburg B, et al. Ustekinumab for Crohn's disease: results of the ICC registry, a nationwide prospective observational cohort study. J Crohns Colitis 2020;14(1):33-45.

Barberio B et al., 2022 [2]

Efficacy of biological therapies and small molecules in induction and maintenance of remission in luminal Crohn's disease: systematic review and network meta-analysis

Fragestellung

Methodik

Population:

- luminal Crohn's disease

Intervention und Komparator:

- biological therapies and small molecules

Endpunkte:

- induction of clinical remission, clinical response and maintenance of clinical remission

Recherche/Suchzeitraum:

- to 1 July 2022

Qualitätsbewertung der Studien:

- Cochrane Risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- We identified 25 induction of remission trials (8720 patients)

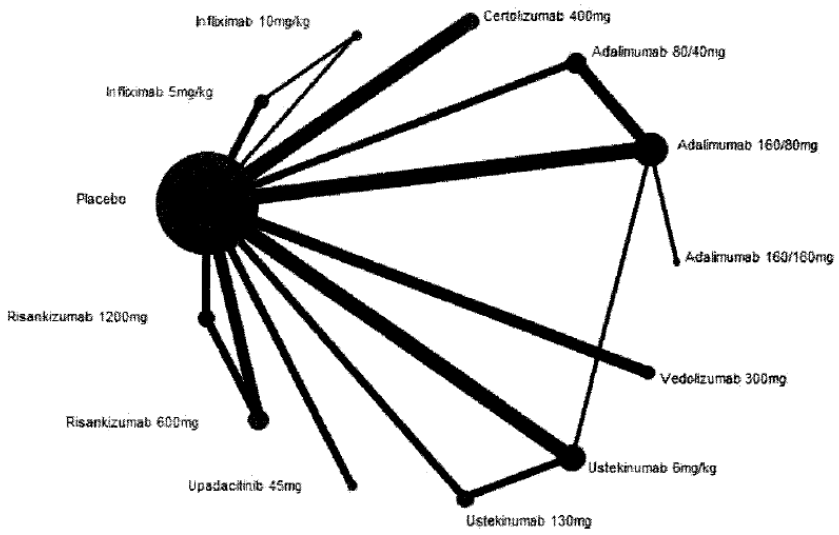


Figure 1 Network plot for failure to achieve clinical remission: all patients with moderate to severe luminal CD. Note: circle (node) size is proportional to the number of study participants assigned to receive each intervention. The line width (connection size) corresponds to the number of studies comparing the individual interventions.

-

Charakteristika der Population:

-

Qualität der Studien:

-
-
  -

Studienergebnisse:

- Achievement of clinical remission
  - When data were pooled, there was low heterogeneity, and the funnel plot appeared symmetrical All drugs, other than infliximab 10 mg/kg, adalimumab 80/40 mg and certolizumab 400 mg, were superior to placebo. Infliximab 5 mg/kg ranked. first for efficacy (RR of failure to achieve clinical remission=0.67, 95'} CI 0.56 to 0.79, p-score 0.95) (figure 2A), meaning that the probability of infliximab 5 mg/kg being most efficacious was 95%. Risankizumab 600 mg (RR=0. 73, 95% CI 0.66 to 0.80, p-score 0.85) and upadacitinib 45 mg o.d. (RR=0.75, 95%CI0.68 to 0.83, p-score 0.77) ranked second and third, respectively. After direct and indirect comparisons, infliximab 5 mg/kg was superior to ustekinumab 6 mg/kg and 130 mg, infliximab 10 mg/kg, adalimumab 80/40mg, vedolizumab 300mg and certolizumab 400 mg (table 1). Risankizumab 600mg was superior to ustekinumab 6 mg/kg and 130 mg, adalimumab 80/40 mg, vedolizumab 300 mg and certolizumab 400 mg; upadacitinib 45 mg o.d. was superior to adalimumab 80/40mg, ustekinumab 130mg, vedolizumab 300mg, and certolizumab 400mg; and risankizumab 1200mg and adalimumab 160/80mg were both superior to ustekinumab 130mg, vedolizumab 300mg and certolizumab 400 mg.

- In patients naive to biologics, all drugs, other than infliximab 10 mg/kg and certolizumab 400 mg, were superior to placebo. Risankizumab 600 mg ranked first for clinical remission (RR of failure to achieve clinical remission=0.66, 95%CI 0.52 to 0.85, p-score 0.78) (figurc 2B), with infliximab 5 mg/kg performing similarly in second (RR=0.67, 95%CI 0.55 to 0.82, p-score 0.78), risankizumab 1200mg third (RR=0.69, 95%CI 0.54 ro 0.88, p-score 0.72) and adalimumab 160/80mg fourth (RR=0.70, 95%CI 0.61 to 0.81, p-score 0.70). On direct and indirect comparison risankizumab 600mg, infliximab 5 mg/kg, and adalimumab 160/80mg were superior to certolizumab 400mg, but there were no other significant differences . After excluding the trial of infliximab that only used a single infusion of drug or placebo at week 0,9 infliximab 5 mg/kg ranked fist (RR=0.61, 95%CI 0.48 to 0.78, p-score 0.86) and risankizumab 600 mg ranked second (p-score 0.74)
- Seven RCTs reported on clinical remission in a subset of patients exposed to biological therapies previously, and six trials recruited only patients with previous exposure to these drugs. There were 3785 patients included in these 13 trials, and low heterogeneity between them. In this analysis, all drugs other than adalimumab 160/160 mg, vedolizumab 300mg, and adalimumab 80140mg were superior to placebo, with risankizumab 600 mg ranked first (RR of failure to achieve clinical remission=0.74, 95%CI 0.67 to 0.82, p-score 0.92) (figure 2C). On direct and indirect comparisons, risankizumab 600 mg was superior to ustekinumab 6 mg/kg and 13 0 mg, vedolizumab 300mg; and adalimumab 80/40mg; upadacitinib 45 mg and risankizumab 1200 mg were superior to ustekinumab 130mg, vedolizumab 300mg and adalimumab 80140mg; and adalimumab 160/160mg and ustekinumab 6 mg/kg were superior to vedolizumab 300 mg (online supplemental table 10).

- Achievement of clinical response
  - All drugs, other than infliximab 10 mg/kg and certolizumab 400 mg, were superior to placebo, but infliximab 5 mg/kg ranked first (RR of no clinical response=0.54, 95%CI 0.41 t o 0.70, p-score 0.91), followed by risankizumab 1200mg (RR=0.57, 95%CI 0.47 to 0.69, p-score 0.87) and adalimumab 160/160mg (RR=0.59, 95%CI 0.41 to 0.87, p-score 0.76). Infliximab 5 mg/kg and risankizumab 1200mg were superior to ustekinumab 130mg, vedolizumab 300mg and certolizumab 400mg risankizumab 600 mg and adalimumab ·160/80 mg were superior to vedolizumab 300 mg and certolizumab 400 mg, and ustekinumab 6 mg/kg to certolizumab 400 mg.

Anmerkung/Fazit der Autoren

Based on failure to achieve clinical remission, infliximab 5 mg/kg ranked first versus placebo (RR=0.67, 95% CI 0.56 to 0.79, p-score 0.95), with risankizumab 600 mg second and upadacitinib 45 mg once daily third. However, risankizumab 600 mg ranked first for clinical remission in biologic-naïve (RR=0.66, 95% CI 0.52 to 0.85, p-score 0.78) and in biologic-exposed patients (RR=0.74, 95% CI 0.67 to 0.82, p-score 0.92). In 15 maintenance of remission trials (4016 patients), based on relapse of disease activity, upadacitinib 30 mg once daily ranked first (RR=0.61, 95% CI 0.52 to 0.72, p-score 0.93) with adalimumab 40 mg weekly second, and infliximab 10 mg/kg 8-weekly third. Adalimumab 40 mg weekly ranked first in biologic-naïve patients (RR=0.59, 95% CI 0.48 to 0.73, p-score 0.86), and vedolizumab 108 mg 2-weekly first in biologic-exposed (RR=0.70, 95% CI 0.57 to 0.86, p-score 0.82).

Peyrin-Biroulet L, et al., 2022 [10]

Comparative efficacy and safety of infliximab and vedolizumab therapy in patients with inflammatory bowel disease: a systematic review and meta-analysis

Fragestellung

To comprehensively evaluate the comparative efficacy and safety of infliximab and vedolizumab in adult patients with moderate-to-severe CD or UC

Methodik

Population:

- adults (aged ≥ 18 years) with moderate-tosevere

CD Intervention:

- infliximab

Komparator:

- vedolizumab

Endpunkte:

- proportion of patients achieving a Crohn's Disease Activity Index (CDAI)-70 response, defined as a 70 ≥ points decrease from the baseline value,
- proportion of patients achieving a CDAI-100 response (a decrease in CDAI score of ≥ 100 points from the baseline value)
- proportion of patients achieving clinical remission (an absolute CDAI score of < 150 points)
- Safety outcomes (CD and UC) included the proportions of patients experiencing any adverse event (AE), serious adverse event (SAE), any infection or serious infection, and the proportion who discontinued due to AEs or lack of efficacy that are evaluated at any point of time in a year

Recherche/Suchzeitraum:

- 1 January 2010 through 30 April 2021

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Tool

Ergebnisse

Anzahl eingeschlossener Studien:

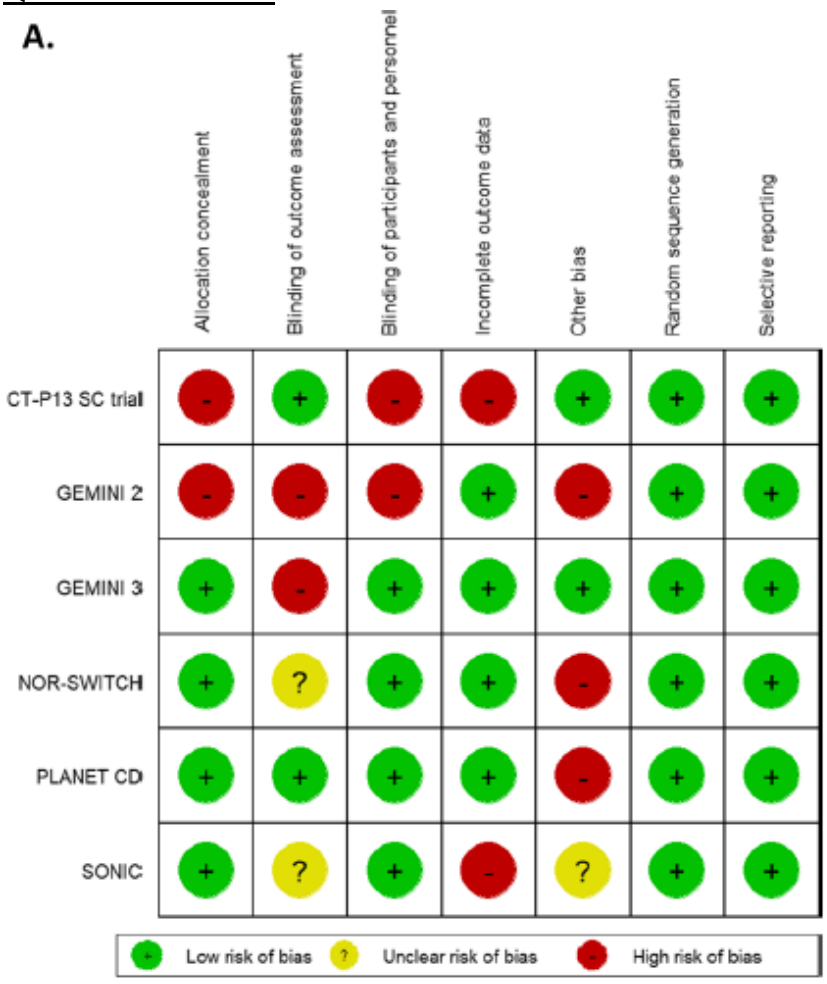
- six studies (RCTs) that contributed data to the CD analyses
- All six studies were randomised trials with a duration of ≥ 50 weeks: five studies included a double-blind period, and one study was conducted using an open-label design (CT-P13 SC trial). Two of the six studies included an open-label extension (NOR-SWITCH and GEMINI 3) and three studies (PLANET CD, NOR-SWITCH and CT-P13) included switching phases wherein participants switched between infliximab products. Five of six studies were multinational, whereas one study was conducted in Norway (NOR-SWITCH)

Charakteristika der Population:

- Across studies, inclusion criteria required participants to be adults (aged ≥ 18) with a diagnosis of CD; four of six studies required participants to have a CDAI score of 220–450, one study (GEMINI 3) specified 220–400 and another (NOR-SWITCH) did not specify a CDAI score. Prior TNFi use was not permitted in three studies (SONIC, PLANET CD, CT-P13 SC trial), stable treatment with infliximab for ≥ 6 months was an inclusion criterion in NOR-SWITCH, and treatment failure with corticosteroids, immunosuppressive agents or TNFis was an inclusion criterion for GEMINI 2 and GEMINI 3 (within the past 5 years).

- A total of 2,020 participants were initially randomised/ assigned to relevant treatment arms of the selected studies. The mean/median age ranged from 32.0 to 39.5 years, 39% to 56% of participants were female, mean/median body weight ranged from 66.1 to 72.0 kg (where reported) and mean/median disease duration ranged from 2.2 to 14.3 years
- In allen Studien waren Personen entweder mit Biologikum oder konventioneller Therapie vorbehandelt.

Qualität der Studien:



Studienergebnisse:

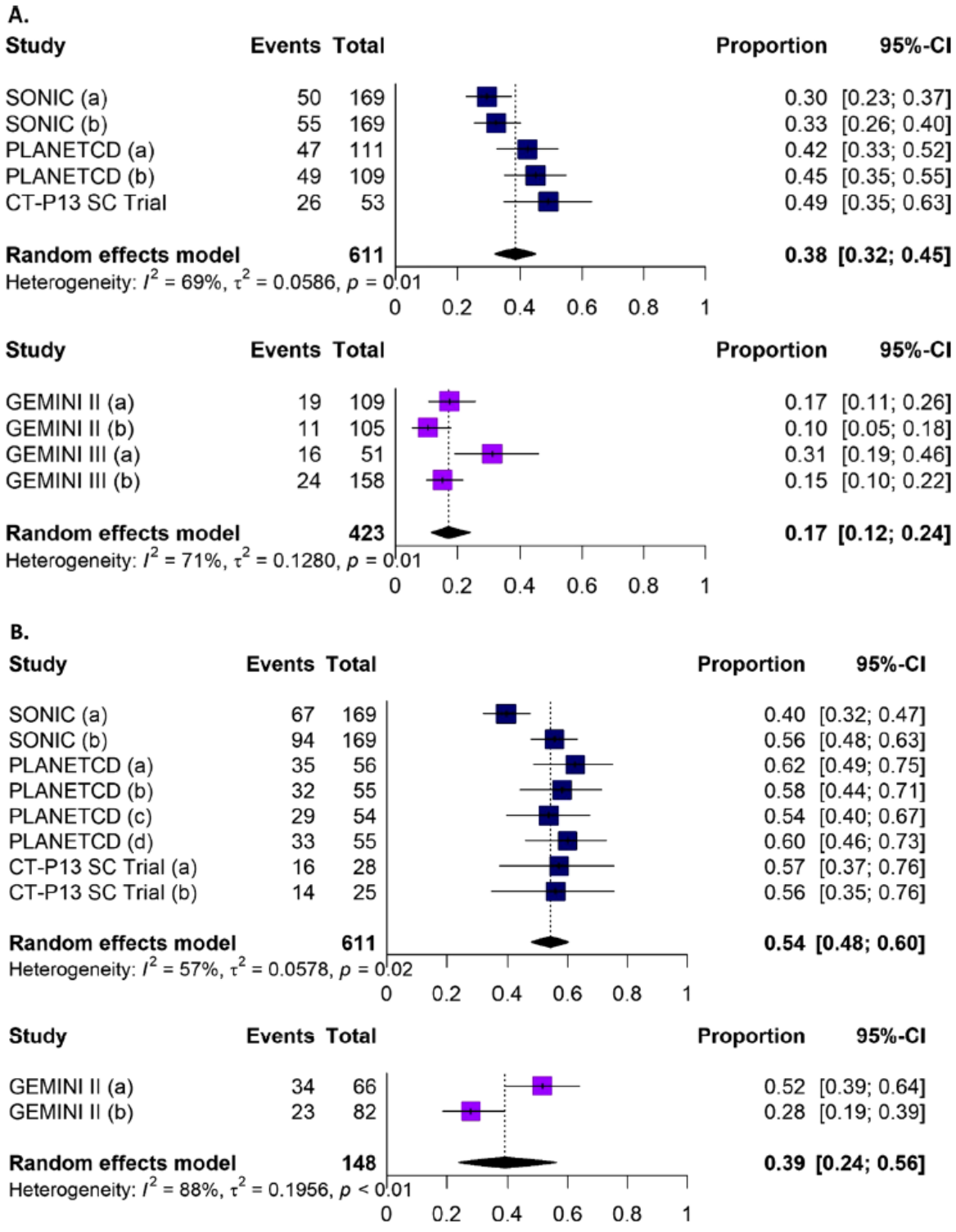


Fig. 5 Forest plots showing the proportion of patients with Crohn's disease achieving clinical remission during **A** the induction phase and **B** the maintenance phase with infliximab (upper plot) or vedolizumab (lower plot). Panel A SONIC (a): IFX IV (corticosteroid free); SONIC (b): combination therapy; PLANET CD (a): patients with CT-P13 IV only; PLANET CD (b): patients with CT-P13 IV and IFX IV; GEMINI 2 (a): VDZ before TNFi; GEMINI 2 (b): VDZ after TNFi failure; GEMINI 3 (a): VDZ IV before TNFi; GEMINI 3 (b): VDZ IV after TNFi failure. Abbreviation: CI, confidence interval; IFX, infliximab; IV, intravenous; TNFi, tumour necrosis factor-α inhibitor; VDZ, vedolizumab. Panel B SONIC (a): IFX IV (corticosteroid free); SONIC (b): combination therapy; PLANET CD (a): CT-P13 IV only; PLANET CD (b): CT-P13 IV switch to IFX IV; PLANET CD (c): IFX IV only; PLANET CD (d): IFX IV switch to CT-P13 IV; CT-P13 SC trial (a): CT-P13 SC only; CT-P13 SC trial (b): CT-P13 IV switch to CT-P13 SC; GEMINI 2 (a): VDZ before TNFi; GEMINI 2 (b): VDZ after TNFi failure. Abbreviation: CI, confidence interval; IFX, infliximab; IV, intravenous; SC, subcutaneous; TNFi, tumour necrosis factor-α inhibitor; VDZ, vedolizumab

- Induction

  - During the induction phase, pooled results for efficacy outcomes in patients with CD showed that a higher proportion of patients treated with infliximab achieved a CDAI-70 response, CDAI-100 response or clinical remission with non-overlapping 95% CIs, in comparison with patients treated with vedolizumab
- maintenance phase
  - In the maintenance phase, a CDAI-70 response was not reported for vedolizumab, so only the data for infliximab is presented (Additional file 1: Fig. 3); a numerical advantage with overlapping 95% CIs was observed with infliximab over vedolizumab for CDAI-100 and clinical remission
- Safety
  - Pooled results for safety outcomes (Fig. 6A; Additional file 1: Figs. 5–10) showed that the proportions of patients experiencing AEs, SAEs, or who discontinued due to AEs were similar in infliximab- and vedolizumab-treated patients. A higher rate of infection was reported with infliximab; however, when it comes to serious infections, similar rates between infliximab and vedolizumab are observed. Six percent of patients treated with infliximab discontinued because the treatment was ineffective (Additional file 1: Fig. 10) while one study was available for vedolizumab, where almost one-third of patients (37.7%) discontinued vedolizumab treatment due to lack of efficacy in the maintenance phase

Anmerkung/Fazit der Autoren

Our results show that infliximab yielded better efficacy than vedolizumab for all the efficacy outcomes in patients with CD or UC during the induction phase, and comparable clinical efficacies with overlapping 95% CI in both diseases during the maintenance phase. The safety profiles of infliximab and vedolizumab in both cohorts were generally similar in terms of the proportions of patients experiencing AEs, SAEs, infection, and serious infection, as well as the rates of discontinuations due to AEs in the analysed study period.

The level of heterogeneity observed within the metaanalyses was generally high, with I2 values exceeding 60% in a number of instances. This was likely influenced by the inclusion of studies with heterogeneous populations (e.g., TNFi-naïve patients and patients who had not responded adequately to prior TNFi therapy), as evidenced by the broad range of median disease durations reported across studies. It was not possible to conduct sensitivity analyses to address the source of heterogeneity due to small amount of available data. Likewise, the head-to-head trial is in need to address biases among the population and different study designs.

3.3 Leitlinien

Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten (DGVS), 2021 [3].

Diagnostik und Therapie des Morbus Crohn; S3 Leitlinie, Langfassung

Zielsetzung

- 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.

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 […] durchgeführt.

LoE

Die Literaturbewertung wurde nach der Evidenzklassifizierung des Oxford Centre for Evidence-based Medicine (2011) durchgeführt.

GoR

Tabelle 1: Schema zur Graduierung von Empfehlungen

Empfehlungsgrad	Beschreibung	Syntax
A	starke Empfehlung	soll
B	Empfehlung	sollte
0	Empfehlung offen	kann

Empfehlungen

M. Crohn – Leitlinie AG 02 akuter Schub

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

Akuter Schub, hohe Krankheitsaktivität

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

Akuter Schub, distaler Befall

Empfehlung 2.10 (modifiziert 2020)

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

Expertenkonsens, Empfehlung offen, starker Konsens

Akuter Schub, Befall des oberen Gastrointestinaltraktes

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.*

Akuter Schub, steroidrefraktärer Verlauf

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*.

Expertenkonsens, Empfehlung, Konsens

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

Empfehlung 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

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.*

M. Crohn – Leitlinie AG 03 Remissionserhaltung, einschließlich prä- und postoperativer Therapie

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

Feuerstein J et al., 2021 [4].

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: Technical Review (Singh S et al., 2021) [12] und Clinical Decision Support Tool [1]

Zielsetzung

This document presents the official recommendations of the AGA on the medical management of moderate to severe luminal and fistulizing CD in adults. This guideline addresses the outpatient medical management of moderate to severe luminal and fistulizing CD, although we anticipate that most of the recommendations would apply to inpatients as well.

Methodik

Grundlage der Leitlinie

- Multidisziplinäre Leitliniengruppe, keine Einbeziehung einer Patientenvertretung;
- 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.

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 interest was performed on July 31, 2020.

LoE / GoR

The AGA process for developing clinical practice guidelines follows the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach […].

Tabelle 1: Grading of Recommendations Assessment, Devlopment and Evaluation Definitions for Certainty of the Evidence

Quality grade	Definition
High	We are very 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.

Tabelle 2: Grading of Recommendations Assessment, Devlopment and Evaluation Definitions for 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 (siehe Anhang, Abbildung 1)

Pharmacologic Management of Adult Patients with Moderate to Severe Luminal Crohn's Disease

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-TNFα (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.

Hintergrund

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 […]. 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).

The second part of the network meta-analysis compared drug efficacy after a prioir failure of a TNFα antagonist can be categorized as primary or secondary nonresponse […].

In patients with prior TNFα antagonist exposure, 6 RCTs with 1606 patients were included in this part of the network meta-analysis. […] 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 supported by low certainty evidence rating down vor very serious imprecision related to very wide Cis and crossing unity […].

Recommendation 3A

In adult outpatients with moderate to severe CD, the AGA suggests against the use of thiopurines monotherapy over no treatment for achieving remission. *(Conditional recommendation, very low certainty evidence*).

Recommendation 3B

In adult outpatients with quiescent moderate to severe CD (or patients in corticosteroid-induced remission), the AGA suggests the use of thiopurines monotherapy over no treatment for the maintenance of remission. *(Conditional recommendation, low certainty evidence*).

Recommendation 3C

In adult outpatients with quiescent moderate to severe CD, the AGA suggests the use of subcutaneous or intramuscular methotrexate monotherapy over no treatment for the induction and maintenance of remission. *(Conditional recommendation, moderate certainty evidence*).

Recommendation 3D

In adult outpatients with quiescent moderate to severe CD, the AGA suggests against the use of oral methotrexate monotherapy over no treatment for the induction and maintenance of remission. *(Conditional recommendation, very low certainty evidence*).

Hintergrund

In adult outpatients with moderate to severe luminal CD, the Guideline Panel suggests against using thiopurines over no treatment for achieving remission because 5 trials including 380 patients treated with thiopurines did not show increased efficacy compared with placebo in achieving corticosteroid-free remission in patiwnts who were corticosteroid-dependent. The certainty of the evidence was very low due to serious bias, indirectness, and serious imprecision. However, 5 RCTs did demonstrate that thiopurines were significantly more effective than placebo or no treatment (RR, 0.62; 95% CI, 0.47–0.81) for maintaining corticosteroid-free clinical remission. The certainty of evidence was rated down for bias due to inadequate blinding and imprecision because of low OIS.

[…] Subcutaneous methotrexate doses at 25 mg/wk was evaluated in 1 trial of 141 patients and was effective for induction of remission (RR, 0.75; 95% CI 0.61–0.93). For maintenance of remission, subcutaneous methotrexate dosed at 15 mg/wk was evaluated in 1 trial of 76 patients after they had achieved remission with 16-25 weeks of 25 mg/wk subcutaneous methotrexate. Subcutaneous methotrexate was more effective than placebo for maintaining corticosteroid-free remission (RR, 0.57; 95% CI 0.34–0.94). The certainty of evidence was moderate for induction and maintenance of remission, rating down for imprecision due to the small sample size.

In contrast to subcutaneous methotrexate, oral methotrexate was evaluated in a single RCT dosed at 12.5 mg/wk and was not effective for inducing remission (RR, 1.14; 95% CI, 0.72–1.82). In the maintenance arm of the study, 12.5 mg/wk was not more effective than placebo for maintaining remission (RR, 0.30; 95% CI, 0.04–2.27). The certainty of evidence was very low due to indirectness from the lower doses of methotrexate and very serious imprecision due to the very wide 95% CI. The Guideline Panel noted that the single RCT evaluating oral methotrexate may have used a dose that is suboptimal.[13] It is not clear if a higher dose of oral methotrexate would be more effective.

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 evidence*).

Hintergrund

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 + 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.

Recommendation 5C

In adult outpatients with moderate to severe CD, the AGA makes no recommendation regarding the use of ustekinumab or vedolizumab in combination with thiopurines or methotrexate over biologic drug monotherapy for the induction and maintenance of remission. *(No recommendation, knowledge gap)*

Hintergrund

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 TNFα 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 TNFα antagonists with a thiopurine compared with 22% with TNFα 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 immunmodulator rather than delaying their use until after failure of 5-aminosalicylates and / or corticosteroids. *(Conditional recommendation, low certainty evidence*

Hintergrund

The evidence informing this recommendation was based on several RCTs. D'haens et al[20] 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 al[22] 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) […].

Recommendation 9

In adult outpatients with moderate to severe CD, the AGA recommends against the use of 5-aminosalicylates or sulfasalazine over no treatment for the induction or maintenance of remission. *(Strong recommendation, moderate certainty evidence)*

Hintergrund

Two RCTs compared 5-aminosalicylates with placebo for induction of remission but the underlying severity of CD was not clear. There was no specific subgroup with moderate to severe CD that could be extracted for our analysis. In these 2 studies, 5-aminosalicylates did not reach the MCID of 10% over placebo (RR, 0.90; 95% CI, 0.81-1.00). Sulfasalazine was evaluated in 3 RCTs, but the overall severity of CD was not clear. In these studies, sulfasalazine was more effective than placebo for induction of remission over 6-17 weeks (RR, 0.78; 95% CI, 0.65-0.93) […].

For maintenance of remission, 4 studies (415 patients) treated with sulfasalazine and 11 RCTs with 2014 patients treated with 5-aminosalicylates did not find either drug to be more effective than placebo for maintenance of remission (sulfasalazine: RR, 0.98; 95 % CI, 0,82-1,17, 5-aminosalicylates: RR, 1.02; 95 % CI, 0.92-1.16). The certainty of evidence for 5-aminosalicylates was moderate, rating down for imprecision (modest benefit and harm could not be excluded) […].

Referenzen

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Torres J et al., 2020 [13].

European Crohn's and Colitis Organisation (ECCO)

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

Zielsetzung

[…] aimed at providing evidence-based providing evidence-based guidance on critical aspects of IBD care to all health care professionals who manage patients with IBD. […]

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 has already covered in the latest ECCO Guidelines on Crohn's disease.[10]

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.

Recherche/Suchzeitraum:

[…] a comprehensive literature search on EMBASE, PubMed/Medline, and Cochrane Central databases […] (2018).

LoE

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]
- 'very low' [meaning that any estimate of effect is very uncertain]

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 – Introduction of Remission

Moderate-to-severe disease

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].

Hintergrund

[…] 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] 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 [I^2 = 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: 1.4–17.7] 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].

Hintergrund

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. 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].

Hintergrund

The SONIC [Study Of Biologic and Immunomodulator Naïve Patients In Crohn's Disease] RCT[70] 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. 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].

Hintergrund

[…] One systematic review and meta-analysis pooled the results from RCTs in which ustekinumab was compared with placebo for induction of remission in patients with moderate-to-severe active luminal CD[77]. Four trials[76,78–80] 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. The quality of evidence was high. The RR of obtaining clinical remission was 1.76 [95% CI: 1.40–2.22]. 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 trials[76,78–80] 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]. 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]; 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].

Hintergrund

[…] 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 CD[82,84,85]. 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]. 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]. 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]. 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].

Hintergrund

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 trials[76,79,82,85] involving a total of 1249 patients treated with ustekinumab or vedolizumab reported on induction of clinical response and clinical remission. 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 trials[76,79,82,85] 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 (CAG)

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

Zielsetzung

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

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;
- Weder Gültigkeit noch Verfahren zur Überwachung und Aktualisierung beschrieben.

Recherche/Suchzeitraum:

[…] performed a systematic literature search of MEDLINE (1946 on), EMBASE (1980 on), and CENTRAL (Cochrane Central Register of Controlled Trials) for trials published through February-April 2016.

LoE

The quality of evidence for each statement was graded as high, moderate, low, or very low, as described in GRADE[11,12] and used in prior Canadian Association of Gastroenterology (CAG) consensus documents.[13-16]

GoR

- 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'.[20]

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.

Empfehlungen

Antibiotics

Statement 2

In patients with CD of any severity, we suggest against the use of systemically absorbed antibiotics to induce OR maintain complete remission.

GRADE: Conditional recommendation, very low-quality evidence for induction of remission, low-quality evidence for maintenance of remission

Vote: strongly agree, 75%; agree, 25%

Hintergrund

Two systematic reviews of RTCs have evaluated the efficacy of antibiotics for induction of remission in patients with CD.[61,62] A meta-analysis of 10 trials found that antibiotics were superior to placebo,[61] but when the 2 rifaximin trials were removed from the analysis, the efficacy was no longer significant. For maintenance of remission, 1 systematic review including 3 trials found that anti-tuberculous treatments were more effective than placebo

in maintaining remission.[61] A more recent systematic review (published outside the search window), which included 1 additional study, reported similar results.[63]

5-ASA

Statement 5

In patients with CD of any severity, we suggest against the use of oral 5-ASA to induce OR maintain complete remission.

GRADE: Conditional recommendation, very low-quality evidence for induction of remission, moderate-quality evidence for maintenance of remission

Vote: strongly agree, 50%; agree, 35%; uncertain, 15%

Hintergrund

Three systematic reviews have evaluated the efficacy of oral 5-ASA for the induction of remission in patients with active CD.[65,66,73] These performed meta-analyses of various formulations and doses of non-sulfasalazine 5-ASAs (ie, mesalamine and olsalazine) and consistently reported no significant benefit with these agents over placebo for induction of remission.[65,66,73] The recent update of the Cochrane analysis (published outside our search window) also reported no significant benefit of 5-ASAs over placebo for inducing response of remission.[67]

A meta-analysis of 11 RCTs assessing the efficacy of mesalamine for maintenance therapy found a non-significant trend toward improvement over placebo (RR, 0.94; 95% CI, 0.87–1.01).[65] However, subgroup analysis of 3 RCTs that were at low risk of bias showed a significant benefit for mesalamine (RR, 0.85; 95% CI, 0.74–0.99).

Corticosteroids

Statement 9

In patients with moderate CD who have failed to respond to oral budesonide 9 mg/day, we suggest the use of prednisone 40-60 mg/day to induce complete remission.

GRADE: Conditional recommendation, low-quality evidence

Vote: strongly agree, 15%; agree, 80%; uncertain, 55%

Statement 10

In patients with moderate to severe CD, we recommend the use of oral prednisone 40-60 mg/day to induce complete remission.

GRADE: Strong recommendation, low-quality evidence

Vote: strongly agree, 50%; agree, 50%

Hintergrund

Evidence for the efficacy of oral corticosteroids over placebo is derived from 2 positive RCTs hat have been included in 2 systematic reviews.[74,80] In the analysis using induction of symptomatic remission as the outcome, corticosteroids were significantly more effective than placebo (RR, 1.99; 95% CI, 1.51–2.64).[80] Corticosteroids were associated with higher rates of adverse events than placebo (RR, 4.89; 95% CI, 1.98–12.07).[80]

These studies predate the availability of budesonide, so it is unknown whether patients with previous non-response to budesonide would respond as well as budesonide-naïve patients. Meta-analysis of 8 RCTs demonstrated that budesonide was significantly less effective than conventional steroids for induction of remission at 8 weeks (RR, 0.85; 95% CI, 0.75–0.97).[75]

The superior efficacy of conventional corticosteroids suggests that patients have a greater likelihood of responding and thus may benefit from these agents after failure of budesonide. Conversely, prednisone may be less effective in patients who have failed budesonide because these cases may be more difficult to treat, and the disease may have progressed during failure of budesonide treatment.

Immunosuppressants

Statement 15

In patients with CD of any severity, we suggest against the use of thiopurine monotherapy to induce complete remission.

GRADE: Conditional recommendation, low-quality evidence

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

Hintergrund

Two meta-analyses of the same 5 RCTs reported no significant difference in symptomatic remission rates between thiopurine monotherapy (azathioprine or 6-mercaptopurine) and placebo.[91,92] Overall, 48% of patients receiving thiopurines (95/197) achieved remission compared with 37% of placebo patients (68/183) (RR, 1.23; 95% CI, 0.97–1.55).[92] Azathioprine therapy was associated with a significant steroid-sparing effect compared with placebo (RR, 1.34; 95% CI, 1.02–1.77).[92]

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%

Hintergrund

Evidence for the efficacy of methotrexate for the induction of symptomatic remission comes from 2 systematic reviews; 1 included 2 trials[91] and the other 3 trials.[102] Only 2 trials were pooled, 1 negative trial using oral methotrexate[103] 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 favour 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%

Hintergrund

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]

Immunosuppressants

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%

Hintergrund

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). 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%

Hintergrund

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 = .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 meta-analysis 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%

Hintergrund

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.

Non-Anti-Tumor Necrosis Factor 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%

Hintergrund

Evidence for the efficacy of vedolizumab for the induction of remission in CD is available from systematic reviews[143,144] and an NMA.[111] Meta-analysis of 3 RCTs (Feagan et al,[145] GEMINI 2,[146] and GEMINI 3[147]) 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).[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%

Hintergrund

Data on the use of vedolizumab in patients who have previously failed anti-TNF therapy are available from GEMINI 2[146] 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. [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%

Hintergrund

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 2015[160] 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). Ustekinumab was effective in patients who had previously responded to anti-TNF therapy and anti-TNF-naive patients.

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British Society of Gastroenterology (BSG)

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

Zielsetzung

This aim of this document is to provide high-quality disease management guidance for health-care 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.

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.

Recherche/Suchzeitraum:

Searches of the Medline and EMBASE database were performed in March 2017 and updated in March 2018.

LoE

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 an 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 […] 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).

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 for response to the drug (*GRADE: strong recommendation, very low-quality evidence. Agreement: 95.7%).*

Hintergrund

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]

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]

4.4.3.1.1 Combination therapy of infliximab with an immunomodulator

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%).*

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%).*

Hintergrund

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).

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 this[460] and a further small open-label study[483] 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).

4.4.3.3 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 […].

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, moderate-quality evidence; GRADE for maintenance therapy: strong recommendation, high-quality evidence. Agreement: 95.5%).*

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%).*

Hintergrund

4.4.3.4 Vedolizumab

[…] 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 […].[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] […] 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

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] […] In total, 45% of those randomized to IM-UNITI were anti-TNF refractory. Of these, 41.1% were in remission at

week 44 on ustekinumab 90mg subcutaneously 8-weekly compared with 26.2% on placebo (p=0.10). 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 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%).*

Hintergrund

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 corticosteroid-dependent (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%).*

Hintergrund

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 […]. 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 […] or considering other options, including surgery.

5 Common disease considerations

5.2 Immunosuppressive therapy

5.2.1.2 Infection risk in patients on anti-TNF therapy

Statement 79

We recommend that IBD patients commencing immunomodulators or biologics treatment should undergo screening for HBV, HCV and HIV (and VZV if no history of chicken pox, shingles or varicella vaccination), unless screened already at time of diagnosis (*GRADE: strong recommendation, very low-quality evidence. Agreement: 88.9%).*

Hintergrund

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 […] should be performed if not done initially, or if new risk factors have arisen since that time.

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National Institute for Health and Care Excellence (NICE), 2012 [7].

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

Zielsetzung

This guideline covers managing 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

- 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.

Recherche/Suchzeitraum:

- All searches were conducted on core databases: Medline, Embase, Cinahl and The Cochrane Library. All searches were updated on 13th March 2012.
- Two systematic literature searches were undertaken […] in October 2015.
  [Clinical Guideline Addendum 152.1 (May 2016)]
- In 2017, a systematic literature search, which was combined with the 2013 ulcerative colitis: management guideline update, was carried out to identify randomised controlled trials. A top-up search in August 2018 […]. [Evidence review for post-surgical maintenance of remission (May 2019)]

LoE

Tabelle 1: 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

GoR

Recommendations that must (or must not) be followed

We usually use 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally we use 'must' (or 'must not') if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Recommendations that should (or should not) be followed – a 'strong' recommendation

We use 'offer' (and similar words such as 'refer' or 'advise') when we are confident that, for the vast majority of people, following a recommendation will do more good than harm, and be cost effective. We use similar forms of words (for example, 'Do not offer…') when we are confident that actions will not be of benefit for most people.

Recommendations that could be followed

We use 'consider' when we are confident that following a recommendation will do more good than harm for most people, and be cost effective, but other options may be similarly cost effective. The course of action is more likely to depend on the person's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the person.

Sonstige methodische Hinweise

May 2019: This guideline is an update of NICE guideline CG152 (published October 2012, last updated May 2016) and replaces it.

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.

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 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]

1.2.18 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] (siehe [5])

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).

Hintergrund

The committee noted that the clinical evidence for ustekinumab came from 2 induction trials (UNITI-1 and UNITI-2) and 1 maintenance trial (IM-UNITI) that included patients who had had a clinical response to ustekinumab in either of the 2 induction trials. […] In UNITI-1, patients had had a TNF-alpha inhibitor but did not respond, lost response or were intolerant to it ('the TNF-alpha inhibitor failure population'). In UNITI-2, patients had had conventional non-biological treatment that had failed ('the conventional-care failure population').

1.2.21 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] (siehe [11])

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.

Hintergrund

The company's systematic review identified 2 randomised, double-blind, placebo-controlled trials of vedolizumab, GEMINI II and GEMINI III […]. Both trials enrolled 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.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 10 of 12, October 2022) am 24.10.2022

#	Suchfrage
1	[mh "Crohn Disease"]
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 Oct 2017 to Oct 2022, in Cochrane Reviews

Systematic Reviews in PubMed am 24.10.2022

verwendete Suchfilter:
Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 02.01.2020.

#	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])

#	Suchfrage
	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 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 ("2017/04/01"[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 PubMed am 24.10.2022

verwendete Suchfilter:
Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 21.06.2017.

#	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 ("2017/04/01"[PDAT] : "3000"[PDAT])
8	(#7) NOT (retracted publication [pt] OR retraction of publication [pt])

Iterative Handsuche nach grauer Literatur, abgeschlossen am 26.10.2022

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- Nationale VersorgungsLeitlinien (NVL)

- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)

- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

Referenzen

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3. **Deutsche Gesellschaft für Gastroenterologie, Verdauungs-und Stoffwechselkrankheiten (DGVS).** Diagnostik und Therapie des Morbus Crohn; S3 Leitlinie, Langfassung [online]. AWMF-Registernummer 021-004. Berlin (GER): Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF); 2021. [Zugriff: 21.11.2022]. URL: https://register.awmf.org/assets/guidelines/021-004l_S3_Morbus_Crohn_Diagnostik_Therapie_2022-04.pdf.
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11. **Rafia R, Scope A, Harnan S, Stevens JW, Stevenson M, Lobo A.** Vedolizumab for treating moderately to severely active Crohn's disease after prior therapy: an evidence review group perspective of a NICE single technology appraisal. Pharmacoeconomics 2016;34(12):1241-1253.
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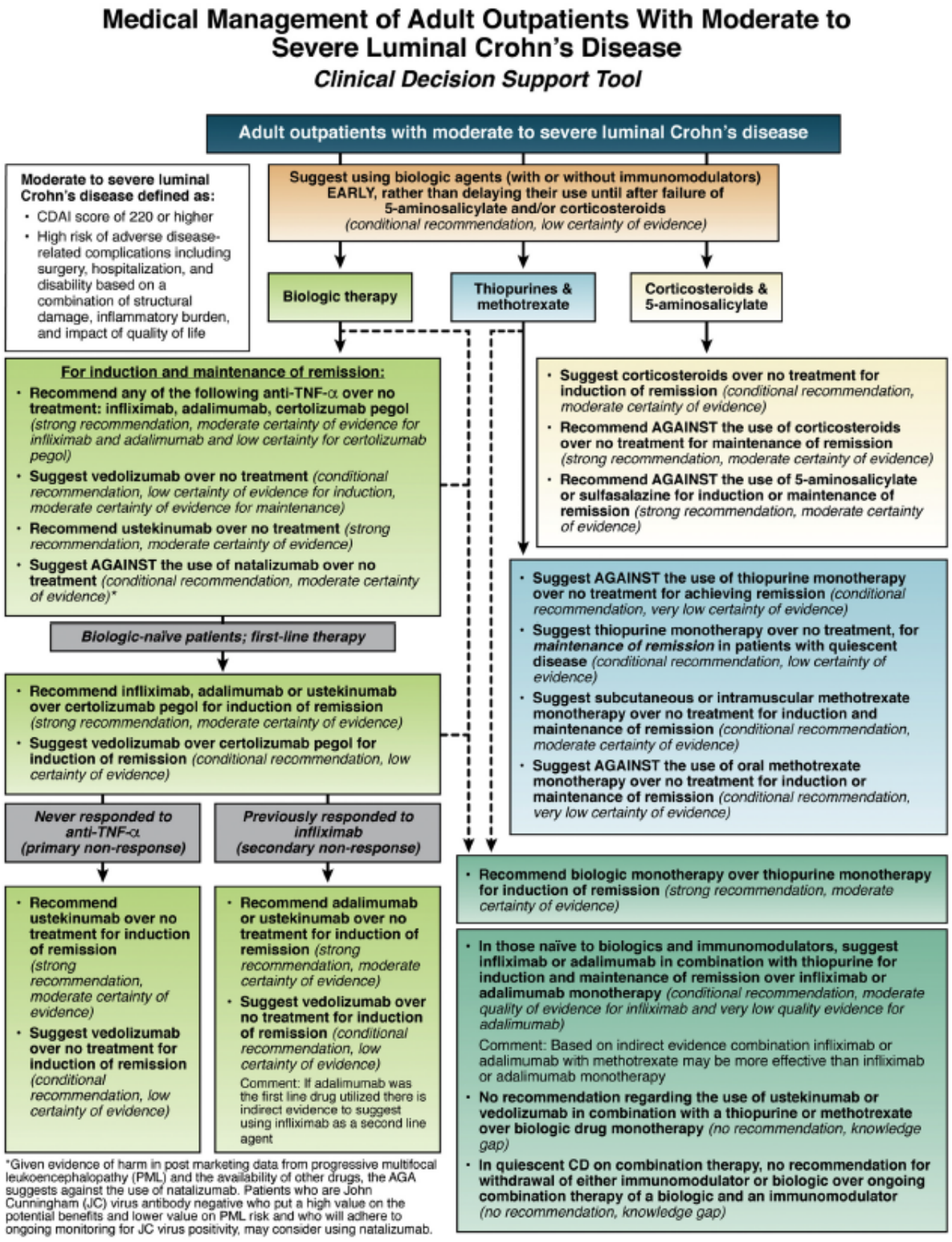
[B] **McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C.** PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol 2016;75:40-46. https://doi.org/10.1016/j.jclinepi.2016.01.021

Anhang

Abbildung 1: Clinical Decision Support Tool (American Gastroenterological Association, 2021 [1].)



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

Clinical Decision Support Tool

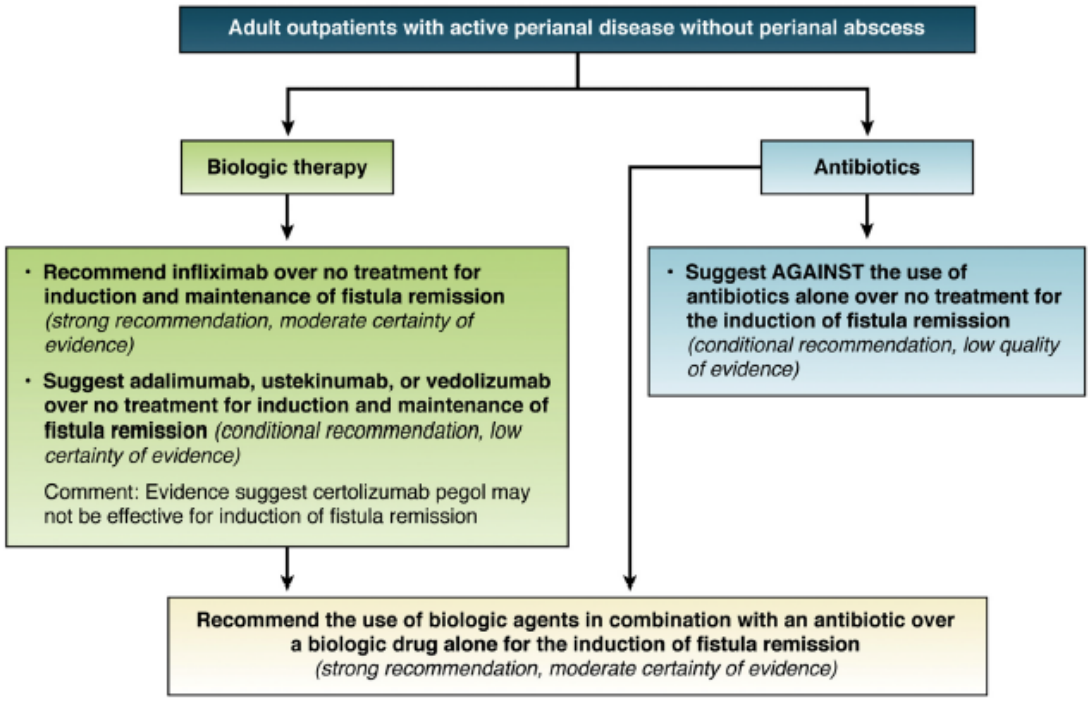


Tabelle 1: Quality Assessment (Newcastle Ottawa Scale) (Parrot L et al., 2021 [9].)

Author, Year	**Selection (maximum of 1 point for each item)**				**Comparability (maximum 2 points)**	**Outcome (maximum 1 point)**			**Score (max 9)**
	Representiveness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not presented at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up enough for outcome to occur?	Adequacy of follow-up of cohort	
Alric 2020	*	*	*		**	*	*	*	**8**
Biemans 2020	*	*	*	*	**	*	*	*	**9**
Manlay 2021	*	*	*		**	*	*	*	**8**
Rayer 2021	*	*	*	*	*	*	*	*	**8**
Townsend 2020	*	*	*		*	*	*	*	**7**
Kolar 2019	*	*	*			*	*		**5**
Color coding: a green color meaning that the study fulfilled the point and a high-quality level, a orange color meaning that the point was partially met and a red color that the study did not meet the point.									

Gemeinsamer Bundesausschuss

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

- keine eingegangenen schriftlichen Rückmeldungen gem. § 7 Absatz 6 VerfO