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: D-1090 Risankizumab

Stand: Juni 2024

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

Risankizumab
Mittelschwere bis schwere aktive Colitis Ulcerosa

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	Escherichia coli: - ausgenommen vom Verordnungsausschluss nach AM-RL; Anlage III; Nr. 22: Escherichia coli Stamm Nissle 1917 nur zur Behandlung der Colitis ulcerosa in der Remissionsphase bei Unverträglichkeit von Mesalazin - E. coli Stamm Nissle 1917 (Mutaflor®) gem. Anlage I d. AM-RL (Zugelassene Ausnahmen zum gesetzlichen Verordnungsausschluss nach § 34 Abs. 1 Satz 2 SGB V (OTC-Übersicht)), Ziffer 16: „E. coli Stamm Nissle 1917 nur zur Behandlung der Colitis ulcerosa in der Remissionsphase bei Unverträglichkeit von Mesalazin Verfahren nach § 35a SGB V: - Vedolizumab (Beschluss vom 08.01.2015) - Tofacitinib (Beschluss vom 21.02.2019) - Filgotinib (Beschluss vom 19.05.2022) - Ozanimod (Beschluss vom 16.06.2022) - Upadacitinib (Beschluss vom 16.02.2023) - Mirikizumab (Beschluss vom 18.01.2024)

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Risankizumab **Mittelschwere bis schwere aktive Colitis Ulcerosa** **Kriterien gemäß 5. Kapitel § 6 VerfO**	
	Verfahren nach § 35 Abs.1 SGB V: - Arzneimittel-Richtlinie/Anlage IX: Anlage IX – Festbetragsgruppenbildung Infliximab, Gruppe 1, in Stufe 1 nach § 35 Abs. 1 SGB V (Beschluss vom 17.11.2017) 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)
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	Siehe systematische Literaturrecherche

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Risankizumab L04AC18 Skyrizi®	Anwendungsgebiet laut Zulassung: „Skyrizi wird angewendet zur Behandlung von erwachsenen Patienten mit mittelschwerer bis schwerer aktiver Colitis ulcerosa, die auf eine konventionelle Therapie oder eine Biologikatherapie unzureichend angesprochen, diese nicht vertragen haben oder nicht mehr darauf ansprechen."
Tumornekrosefaktor alpha (TNF-alpha)-Inhibitoren	
Infliximab L04AB02 Biosimilar z.B. REMICADE®	[…] Colitis ulcerosa Remicade [oder Remsima®; Inflectra®] ist indiziert zur Behandlung der mittelschweren bis schweren aktiven Colitis ulcerosa bei erwachsenen Patienten, die auf eine konventionelle Therapie, einschließlich Kortikosteroide und 6-Mercaptopurin (6-MP) oder Azathioprin (AZA), unzureichend angesprochen haben oder die eine Unverträglichkeit oder Kontraindikation für solche Therapien haben. Kinder und Jugendliche Remicade ist indiziert zur Behandlung der schweren aktiven Colitis ulcerosa bei Kindern und Jugendlichen im Alter von 6 bis 17 Jahren, die auf eine konventionelle Therapie, einschließlich Kortikosteroide und 6-MP oder AZA, unzureichend angesprochen haben oder die eine Unverträglichkeit oder Kontraindikation für solche Therapien haben. [Stand FI: September 2019]
Adalimumab L04AB04 Biosimilar z.B. Amgevita®	[…] Colitis ulcerosa AMGEVITA wird angewendet zur Behandlung des mittelschweren bis schweren, aktiven Morbus Crohn bei erwachsenen Patienten, die trotz einer vollständigen und adäquaten Therapie mit einem Kortikosteroid 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 Kinder und Jugendliche AMGEVITA wird angewendet zur Behandlung des mittelschweren bis schweren, aktiven Morbus Crohn bei Kindern und Jugendlichen (ab dem Alter von 6 Jahren), die nur unzureichend auf eine konventionelle Therapie, einschließlich primärer Ernährungstherapie und einem Kortikosteroid und/oder einem Immunsuppressivum, angesprochen haben oder die eine Unverträglichkeit gegenüber einer solchen Therapie haben oder bei denen eine solche Therapie kontraindiziert ist.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	[Stand FI: Januar 2023]
Golimumab L04AB04 Simponi®	[…] Colitis ulcerosa (CU) Simponi ist indiziert zur Behandlung der mittelschweren bis schweren aktiven Colitis ulcerosa bei erwachsenen Patienten, die auf eine konventionelle Therapie, einschließlich Kortikosteroide und 6-Mercaptopurin (6-MP) oder Azathioprin (AZA), unzureichend angesprochen haben oder die eine Unverträglichkeit oder Kontraindikation für solche Therapien haben. „Therapieansprechen:“ Den verfügbaren Daten zufolge wird ein klinisches Ansprechen auf die Therapie üblicherweise innerhalb von 12 bis 14 Behandlungswochen (d. h. nach 4 Dosen) erzielt. Die Fortführung der Behandlung ist bei Patienten, bei denen innerhalb dieser Zeit kein therapeutischer Nutzen belegt werden kann, zu überdenken. [Stand FI: Feb 19]
Integrininhibitoren	
Vedolizumab L04AA33 ENTYVIO®	Entyvio ist indiziert für die Behandlung von erwachsenen Patienten mit mittelschwerer bis schwerer aktiver Colitis ulcerosa, die entweder auf konventionelle Therapie oder einen der Tumornekrosefaktor-alpha (TNFα)-Antagonisten unzureichend angesprochen haben, nicht mehr darauf ansprechen oder eine Unverträglichkeit gegen eine entsprechende Behandlung aufweisen. *„Therapieansprechen:“* Bei Patienten mit Colitis ulcerosa sollte die Fortsetzung der Therapie sorgfältig überdacht werden, wenn bis Woche 10 keine Hinweise für einen therapeutischen Nutzen zu beobachten sind. [Stand FI: Feb 19]
JAK-Inhibitoren	
Tofacitinib L04AA29 Xelianz®	Tofacitinib ist indiziert zur Behandlung erwachsener Patienten mit mittelschwerer bis schwerer aktiver Colitis ulcerosa (CU), die auf eine konventionelle Therapie oder ein Biologikum unzureichend angesprochen haben, nicht mehr darauf ansprechen oder diese nicht vertragen haben. [Stand FI: Januar 2020]
Filgotinib L04AA45 Jyseleca®	Jyseleca ist angezeigt zur Behandlung von mittelschwerer bis schwerer aktiver Colitis ulcerosa bei erwachsenen Patienten, die auf eine konventionelle Therapie oder auf ein Biologikum unzureichend angesprochen haben, nicht mehr darauf ansprechen oder eine Unverträglichkeit gegen eine entsprechende Behandlung gezeigt haben. [Stand FI: Nov. 2021]
Upadacitinib L04AA44 Rinvoq®	[…] Colitis ulcerosa RINVOQ wird angewendet zur Behandlung der mittelschweren bis schweren aktiven Colitis ulcerosa bei erwachsenen Patienten, die auf eine konventionelle Therapie oder ein Biologikum unzureichend angesprochen haben, nicht mehr darauf ansprechen oder diese nicht vertragen haben.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Interleukin-Inhibitoren	
Ustekinumab L04AC05 Stelara®	STELARA ist indiziert für die Behandlung erwachsener Patienten mit mittelschwerer bis schwerer aktiver Colitis ulcerosa, die entweder auf eine konventionelle Therapie oder auf ein Biologikum unzureichend angesprochen haben, nicht mehr darauf ansprechen oder eine Unverträglichkeit oder eine Kontraindikation gegen eine entsprechende Behandlung aufweisen. [Stand FI: Februar 2020]
Mirikizumab L04AC24 Omvoh®	Omvoh ist angezeigt für die Behandlung von erwachsenen Patienten mit mittelschwerer bis schwerer aktiver Colitis ulcerosa, die auf eine konventionelle Therapie oder eine Biologika-Behandlung unzureichend angesprochen haben, nicht mehr darauf ansprechen oder eine Unverträglichkeit zeigen. [Stand FI: Juli 2023]
Weitere	
Ozanimod L04AA38 Zeposia®	Zeposia ist indiziert zur Behandlung erwachsener Patienten mit mittelschwerer bis schwerer aktiver Colitis ulcerosa (CU), die auf eine konventionelle Therapie oder ein Biologikum unzureichend angesprochen haben, nicht mehr darauf ansprechen oder diese nicht vertragen haben. [Stand FI: Nov. 2021]
5- Aminosalicylsäuren	
Mesalazin A07EC02 generisch z.B. Asacol Tab.	Asacol wird angewendet bei Erwachsenen, Jugendlichen und Kindern ab 6 zur: • Behandlung akuter Schübe der Colitis ulcerosa. • Langzeitbehandlung der Colitis ulcerosa zur Vermeidung eines Rezidivs. [Stand FI: Jan 19]
Sulfasalazin A07EC01 Colo-Pleon® Tabl.	Akutbehandlung und Rezidivprophylaxe der Colitis ulcerosa […] [Stand FI: März 16]
Olsalazin A07EC03 Dipentum® Tabl.	Leichte und mittelschwere Schübe der akuten Colitis ulcerosa. Rezidivprophylaxe der Colitis ulcerosa. […][Stand FI: Sept 14]
Immunsupressiva	
Azathioprin L04AX01 generisch	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: […]

II. Zugelassene Arzneimittel im Anwendungsgebiet	
z.B. Azathioprin-ratiopharm®	– schwere oder mittelschwere entzündliche Darmerkrankungen (Morbus Crohn oder Colitis ulcerosa) [Stand FI: Juni 18]
Kortikosteroide	
Budesonid A07EA06 Generisch z.B. Budenofalk® Rektalschaum	(topisch) Akutbehandlung der Colitis ulcerosa, die auf das Rektum und das Colon sigmoideum beschränkt ist. [Stand FI: Mai 17]
Budesonid A07EA09 Generisch z.B. Cortiment® Retardtabl.	(systemisch) Einleitung der Remission bei erwachsenen Patienten mit leichter bis masig schwerer Colitis ulcerosa, wenn die Behandlung mit 5-ASA nicht ausreicht. [Stand FI: Feb 18]
Hydrocortison-acetat Colifoam® H02AB09 Rektalschaum	(topisch) Entzündliche Erkrankungen im unteren Dickdarmbereich wie Colitis ulcerosa oder Morbus Crohn und Proktosigmoiditis. [Stand FI: Dez 17]
Prednison H02A B07 generisch z.B. Prednison-ratiopharm® 5 mg Tabletten	Prednison-ratiopharm ® 5 mg Tabletten ist angezeigt zur Behandlung von Erkrankungen, die einer systemischen Therapie mit Glucocorticoiden bedürfen. Hierzu gehören je nach Erscheinungsform und Schweregrad: (Dosierungsschemata [DS]: a – d siehe Abschnitt 4.2). […] <u>Gastroenterologie/Hepatologie:</u> • Colitis ulcerosa (DS: b – c)
Prednisolon H02AB06	Prednisolon acis ist angezeigt zur Behandlung von Erkrankungen, die einer systemischen Therapie mit Glucocorticoiden bedürfen. Hierzu gehören je nach Erscheinungsform und Schweregrad: (Dosierungsschemata [DS]: a – d siehe Abschnitt 4.2).

II. Zugelassene Arzneimittel im Anwendungsgebiet	
generisch z.B. Prednisolon acis Tab.	[…] <u>Gastroenterologie/Hepatologie:</u> • Colitis ulcerosa (DS: b – c)
Methylprednisolon H02AB04 generisch z.B. Methylprednisolon JENAPHARM®	Erkrankungen, die einer systemischen Therapie mit Glukokortikoiden bedürfen. Hierzu gehören je nach Erscheinungsform und Schweregrad zum Beispiel: […] Magen-Darm-Erkrankungen: – Colitis ulcerosa,
Betamethason A07EA04 generisch z.B. Betnesol Rektal-Instillation	(topisch) Linksseitige Colitis ulcerosa im unteren Darmbereich

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	9. Januar 2024

Inhaltsverzeichnis

Abkürzungsverzeichnis

5-ASA	5-aminosalicylic acid
6-MP	6-mercaptopurine
ASUC	Acute severe ulcerative colitis
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CD	Crohn's disease
CI	Konfidenzintervall
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
IFX	Infliximab
IPAA	Ileal pouch anal anastomosis
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
JAK	Janus kinase
KI	Konfidenzintervall
LoE	Level of Evidence
MS-IBD	Moderate to severe inflammatory bowel disease
MTX	Methotrexate
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
PRESS	Peer Review of Electronis Search Strategies
RCT	Randomized controlled trial/s
RoB	Risk of bias
RR	Relatives Risiko
(S)AE	(Serious) adverse event/s
SIGN	Scottish Intercollegiate Guidelines Network
SR	Systematic Review
TNF	Tumornekrosefaktor
TRIP	Turn Research into Practice Database
UC	ulcerative colitis
WHO	World Health Organization

1 Indikation

Behandlung von erwachsenen Patienten mit mittelschwerer bis schwerer aktiver Colitis ulcerosa, die auf eine konventionelle Therapie oder eine Biologikatherapie unzureichend angesprochen, diese nicht vertragen haben oder nicht mehr darauf ansprechen.

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 *Colitis ulcerosa* 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.ecosia.org/*) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Der Suchzeitraum wurde auf die letzten fünf Jahre eingeschränkt und die Recherche am 05.12.2023 abgeschlossen. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Angabe durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherche ergab 1308 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 16 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Davies SC et al., 2020 [6].

Oral Janus kinase inhibitors for maintenance of remission in ulcerative colitis.

Fragestellung

The primary objective was to assess the efficacy and safety of oral JAK inhibitors for the maintenance of remission in participants with quiescent UC.

Methodik

Population:

- Participants of all ages with quiescent UC, as defined by a combination of clinical, endoscopic, radiographic or histological criteria, were considered for inclusion.

Intervention:

- JAK inhibitor

Komparator:

- placebo or an active comparator

Endpunkte:

- the proportion of participants who failed to maintain clinical remission (as defined by the included studies).
- proportion of participants who failed to maintain clinical response (as defined by the included studies)
- the proportion of participants who failed to maintain endoscopic remission (as defined by the included studies)
- the proportion of participants who failed to maintain endoscopic response (as defined by the included studies)
- disease-specific quality of life, adverse events (AEs), serious adverse events (SAEs), and withdrawal due to AEs

Recherche/Suchzeitraum:

- We searched the following databases from inception to 20 September 2019: MEDLINE, Embase, CENTRAL, and the Cochrane IBD Group Specialized Register, WHO trials registry and clinicaltrials.gov. References and conference abstracts were searched to identify additional studies.

Qualitätsbewertung der Studien:

- Cochrane approach / GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

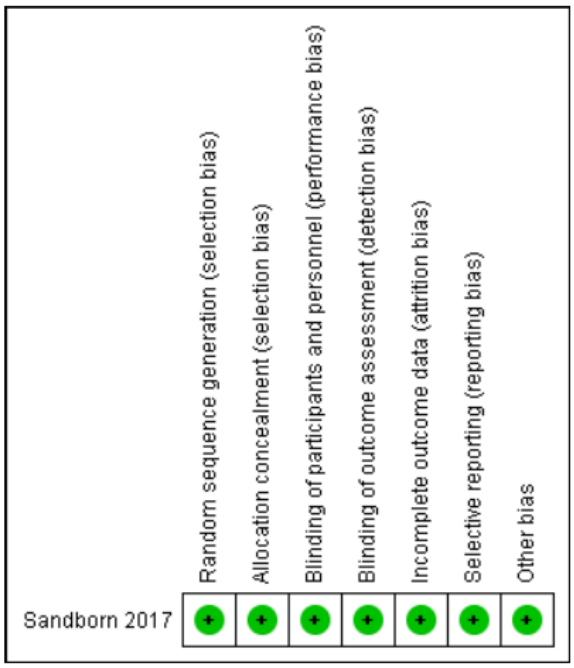
- 1 study

Charakteristika der Population:

- Sandborn 2017 included three phase 3, randomized, doubleblind, placebo-controlled trials of tofacitinib in the treatment of adults with moderate-to-severe ulcerative colitis (UC) (N = 593 participants). Participants were required to have an overall Mayo score of 6 to 12, with a rectal bleeding sub-score of 1 to 3 and an endoscopic sub-score of 2 or 3. OCTAVE 1 and OCTAVE 2 randomly assigned patients with active UC to receive induction therapy with 10 mg twice daily of tofacitinib or placebo for eight weeks. Patients who responded to treatment then had the opportunity to take part in the OCTAVE SUSTAIN trial where they were randomly assigned to receive maintenance therapy of tofacitinib (5 mg or 10 mg twice daily) or placebo for 52 weeks.

Qualität der Studien:

Figure 2. 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included study.



Studienergebnisse:

- One RCT (593 participants) including patients with moderately to severely active UC met the inclusion criteria. Patients were randomly assigned in a 1:1:1 ratio to receive maintenance therapy with tofacitinib at 5 mg twice daily, 10 mg twice daily or placebo for 52 weeks. The primary endpoint was remission at 52 weeks and the secondary endpoints included mucosal healing at 52 weeks, sustained remission at 24 and 52 weeks and glucocorticosteroid-free remission. This study was rated as low risk of bias. The study reported on most of the prespecified primary and secondary outcomes for this review including clinical remission, clinical response, endoscopic remission, AEs, SAEs and withdrawal due to AEs. However, the included study did not report on endoscopic response or disease-specific quality of life.
- Sixty-three per cent (247/395) of tofacitinib participants failed to maintain clinical remission at 52 weeks compared to 89% (176/198) of placebo participants (RR 0.70, 95% CI 0.64 to 0.77; high-certainty evidence). Forty-three per cent (171/395) of tofacitinib participants failed to maintain clinical response at 52 weeks compared to 80% (158/198) of placebo participants (RR 0.54, 95% CI 0.48 to 0.62; high-certainty evidence). Eighty-four per cent (333/395) of tofacitinib participants failed to maintain endoscopic

remission at 52 weeks compared to 96% (190/198) of placebo participants (RR 0.88, 95% CI 0.83 to 0.92; high-certainty evidence).

- AEs were reported in 76% (299/394) of tofacitinib participants compared with 75% (149/198) of placebo participants (RR 1.01, 95% CI 0.92 to 1.11; high-certainty evidence). Commonly reported AEs included worsening UC, nasopharyngitis, arthralgia (joint pain)and headache. SAEs were reported in 5% (21/394) of tofacitinib participants compared with 7% (13/198) of placebo participants (RR 0.81, 95% CI 0.42 to 1.59; low-certainty evidence). SAEs included non-melanoma skin cancers, cardiovascular events, cancer other than non-melanoma skin cancer, Bowen's disease, skin papilloma and uterine leiomyoma (a tumour in the uterus). There was a higher proportion of participants who withdrew due to an AE in the placebo group compared to the tofacitinib group. Nine per cent (37/394) of participants taking tofacitinib withdrew due to an AE compared to 19% (37/198) of participants taking placebo (RR 0.50, 95% CI 0.33 to 0.77; moderate-certainty evidence). The most common reason for withdrawal due to an AE was worsening UC. The included study did not report on endoscopic response or on mean disease-specific quality of life scores.

Summary of findings for the main comparison. Tofacitinib compared to placebo for maintenance of remission in ulcerative colitis

Tofacitinib compared to placebo for maintenance of remission in ulcerative colitis

Patient or population: participants with quiescent ulcerative colitis
Setting: outpatient
Intervention: tofacitinib (5 mg/10 mg)
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with Tofacitinib				
Failure to maintain clinical remission (5 mg/10 mg) Follow-up: 52 weeks	Study population 889 per 1,000	622 per 1,000 (569 to 684)	RR 0.70 (0.64 to 0.77)	593 (1 study)	⊕⊕⊕⊕ HIGH	Clinical remission was defined as a total Mayo score of ≤2, with no sub score ≥1 and a rectal bleeding sub score of 0
Failure to maintain clinical response (5 mg/10 mg) Follow-up: 52 weeks	Study population 798 per 1,000	431 per 1,000 (375 to 495)	RR 0.54 (0.47 to 0.62)	593 (1 study)	⊕⊕⊕⊕ HIGH	Clinical response was defined as a decrease from induction-trial baseline in the total Mayo score of at least 3 points and at least 30%, with an accompanying decrease in the rectal bleeding sub score or 0 or 1
Failure to maintain endoscopic remission (5 mg/10 mg) Follow-up: 52 weeks	Study population 960 per 1,000	844 per 1,000 (796 to 883)	RR 0.88 (0.83 to 0.92)	593 (1 study)	⊕⊕⊕⊕ HIGH	Endoscopic remission was defined as a Mayo endoscopic sub score of 0
Adverse events (5 mg/10 mg) Follow-up: 52 weeks	Study population 753 per 1,000	760 per 1,000 (692 to 835)	RR 1.01 (0.92 to 1.11)	592 (1 study)	⊕⊕⊕⊕ HIGH	Adverse events include worsening of ulcerative colitis, nasopharyngitis, arthralgia and headache
Serious adverse events (5 mg/10 mg) Follow-up: 52 weeks	Study population 66 per 1,000	53 per 1,000 (28 to 104)	RR 0.81 (0.42 to 1.59)	592 (1 study)	⊕⊕⊖⊖ LOW[1]	Serious adverse events include cancer, intestinal perforation and cardiovascular events
Withdrawals due to adverse events (5 mg/10 mg) Follow-up: 52 weeks	Study population 187 per 1,000	93 per 1,000 (62 to 144)	RR 0.50 (0.33 to 0.77)	592 (1 study)	⊕⊕⊕⊖ MODERATE[2]	Adverse events leading to withdrawal include worsening of ulcerative colitis

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[1] Downgraded two levels due to very serious imprecision (34 events)
[2] Downgraded one level due to serious imprecision (74 events)

Fazit der Autoren

High-certainty evidence suggests that tofacitinib is superior to placebo for maintenance of clinical and endoscopic remission at 52 weeks in participants with moderate-to-severe UC in remission. The optimal dose of tofacitinib for maintenance therapy is unknown. High-certainty evidence suggests that there is no increased risk of AEs with tofacitinib compared to placebo. However, we are uncertain about the effect of tofacitinib on SAEs due to the low number of events. Further studies are required to look at the long-term effectiveness and safety of using tofacitinib and other oral JAK inhibitors as maintenance therapy in participants with moderate-to-severe UC in remission.

3.2 Systematische Reviews

Attauabi M et al., 2023 [2].

Comparative onset of effect of biologics and small molecules in moderate-to-severe ulcerative colitis: a systematic review and network meta-analysis

Es liegen weitere SRs zu dieser Fragestellung mit derselben Schlussfolgerung vor:

- Panaccione R et al., 2023 [13]
- Ahuja D et al., 2023 [1]
- Gao J et al., 2023 [8]

Fragestellung

We aimed to assess the comparative onset of efficacy of biological therapies and small molecules for this patient population.

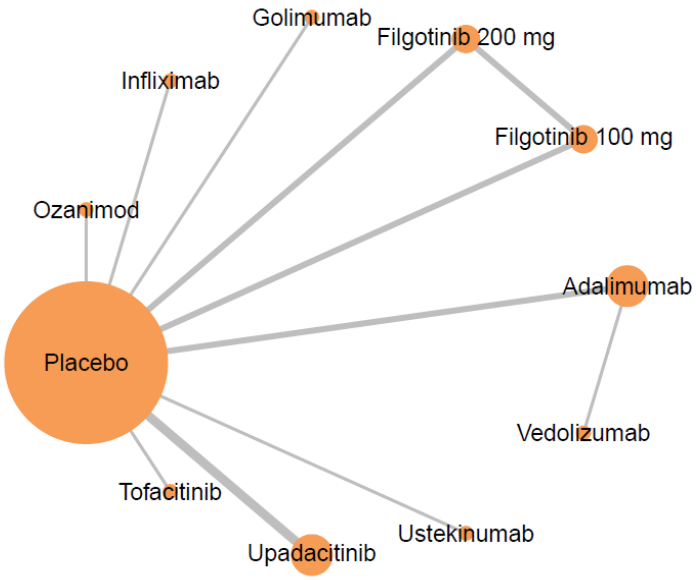
Methodik

Population:

- Patients with moderate-to-severe ulcerative colitis

Intervention/Komparator:

- biological therapies and small molecules and placebo



Endpunkte:

- co-primary outcomes were the overall clinical response and clinical remission of biological therapies or small molecules for UC at week 2 after treatment initiation, compared with placebo or each other
- Secondary outcomes included clinical response, clinical remission, biochemical response, biochemical remission, and endoscopic remission at weeks 2 and 6.

Recherche/Suchzeitraum:

- inception to 24 August 2022

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 25 studies comprising 11,074 patients

Charakteristika der Population/Studien:

- patients with moderate-to-severe UC

Qualität der Studien:

- Low risk of bias: N=21 studies; Some concerns: N=3 studies; high risk of bias: N=1 study

Studienergebnisse:

Key findings

- Upadacitinib ranked highest for induction of clinical response and clinical remission at week 2 and was significantly superior to all agents but tofacitinib, which ranked second highest.
- Although the rankings remained consistent, no differences between upadacitinib and biological therapies were demonstrated in the sensitivity analyses of partial Mayo clinic score response or resolution of rectal bleeding at week 2.
- Tumor necrosisfactor-α (TNF) inhibitors were significantly superior to vedolizumab and ustekinumab for patient-reported outcome-2 (PRO-2) remission at week 2 in bio-naïve patients.
- Filgotinib 100 mg, ustekinumab, and ozanimod ranked lowest across all endpoints.

Clinical response within two weeks of treatment

- Clinical response within two weeks of treatment has only been reported in three studies on moderate-to severe UC, which precluded statistical analysis.
- The post hoc analysis on the OCTAVE trials demonstrated separation of tofacitinib and placebo within three days in terms of achieving Mayo rectal bleeding Subscore = 0 (130/905 (14.4%) vs. 19/234 (8.2%), $p < 0.05$) and seven days in terms of achieving Mayo stool score = 0 (83/905 (9.2%) vs. 5/234 (2.3%), $p < 0.01$).11 A post hoc analysis on the U-ACHIEVE trial demonstrated significantly higher clinical response at day 8 among patients treated with upadacitinib as compared to placebo in terms of Mayo stool score = 0 (21/53 (39.6%) vs. 6/43 (14.0%), $p = 0.01$) and Mayo rectal bleeding Subscore = 0 (33/53 (62.3%) vs. 9/43 (20.9%), $p < 0.01$).43
- A post hoc analysis on the SELECTION trial demonstrated that filgotinib 200 mg induced significantly more often rectal bleeding subscore of 0 than placebo by day 6 in biologic-naive patients (20.8% vs 12.4%, $p = 0.04$), and day 5 in biologic-experienced patients (17.2% vs 9.2%, $p = 0.02$).

Clinical response at week 2

- The first systematic assessment of clinical response in patients with moderate-to-severe UC across the majority of biological therapies and small molecules was found to be two weeks after treatment initiation with no sign of funnel asymmetry (Egger's $p = 0.37$).

- All agents were significantly superior to placebo for the induction of clinical response at week 2 in the direct, pair-wise metaanalysis
- No comparison between vedolizumab and placebo at week 2 was identified; however, data from the VARSITY trial indicated no difference between vedolizumab and adalimumab (RR = 0.93 (95% CI 0.80–1.09) The overall heterogeneity was high (I2 = 78%).
- When comparing the active medications, upadacitinib was significantly superior to all agents (high confidence) but tofacitinib (moderate confidence) in the overall analysis.
- Further, tofacitinib was significantly superior to filgotinib 100 mg and ozanimod. Accordingly, upadacitinib and tofacitinib ranked highest for this endpoint, while filgotinib 100 mg, ozanimod, and ustekinumab ranked lowest.

Clinical response at week 6

- In a direct, pair-wise meta-analysis, all agents apart from intravenous golimumab were significantly superior to placebo for the induction of clinical response at week 6 (Supplementary Fig. S8, I2 = 76%) (Egger's p = 0.84). In network meta-analysis, upadacitinib, which ranked highest, was significantly superior to infliximab, adalimumab, and filgotinib 100 mg but not vedolizumab or filgotinib 200 mg

Anmerkung/Fazit der Autoren

In this network meta-analysis, we found upadacitinib to be significantly superior to all agents but tofacitinib for the induction of clinical response and clinical remission two weeks after treatment initiation. In contrast, ustekinumab and ozanimod ranked lowest. Our findings help to establish the evidence regarding the onset of efficacy of advanced therapies.

Lu X et al., 2023 [11].

Comparative efficacy of advanced treatments in biologic-naïve or biologic-experienced patients with ulcerative colitis: a systematic review and network meta-analysis

Fragestellung

The relative treatment effects of filgotinib and adalimumab, golimumab, infliximab, tofacitinib, ustekinumab and vedolizumab were estimated using a network meta-analysis (NMA).

Methodik

Population:

- Patient with moderately to severely active UC

Intervention:

- filgotinib

Komparator:

- key comparators: adalimumab, golimumab, infliximab, tofacitinib, ustekinumab and vedolizumab

Endpunkte:

- clinical response (MCS ≤ 2 points with no individual subscore of > 1), clinical remission (≥ 30% and ≥ 3-point decrease from baseline MCS and rectal bleeding subscore of 0–1, or ≥ 1-point decrease in baseline rectal bleeding subscore), and endoscopic mucosal healing (MCS endoscopic subscore of 0–1) during the induction or maintenance phases, as defined in the studies.

Recherche/Suchzeitraum:

- MEDLINE, Embase and Cochrane Library; searched: inception–May 2019, updated November 2020

Qualitätsbewertung der Studien:

- Studies were assessed for heterogeneity

Ergebnisse

Anzahl eingeschlossener Studien:

- Seventeen trials (13 induction; 9 maintenance)

Charakteristika der Population/Studien:

- biologic-naïve or biologic-experienced

Qualität der Studien:

- A summary of potential bias including direction, magnitude and approach and details of the re-weighting calculations are outlined in Supplementary Material 2

Studienergebnisse:

Induction phase analyses

- MCS response/remission: biologic-experienced
  - The analysis network for MCS response/remission in biologic-experienced patients comprised seven treatment groups (adalimumab 160/80/40 mg, filgotinib 100 mg, filgotinib 200 mg, placebo, tofacitinib 10 mg, ustekinumab 6 mg/kg and vedolizumab 300 mg) across seven studies.
  - All interventions were statistically superior to placebo, with the exception of adalimumab 160/80/40 mg.
  - Treatment effects were similar between filgotinib 200 mg and all other comparators except for adalimumab 160/80/40 mg, over which filgotinib 200 mg was statistically superior (mean relative effect filgotinib 200 mg vs adalimumab 160/80/40 mg [95% CrI], – 0.75 [– 1.16, – 0.35].
- Endoscopic mucosal healing: biologic-experienced
  - In the biologic-experienced population, the analysis network for endoscopic mucosal healing comprised seven treatment groups (adalimumab 160/80/40 mg, filgotinib 100 mg, filgotinib 200 mg, placebo, tofacitinib 10 mg, ustekinumab 6 mg/kg and vedolizumab 300 mg) across 6 studies.
  - Adalimumab 160/80/40 mg and vedolizumab 300 mg were similar to placebo, and filgotinib 200 mg, tofacitinib 10 mg and ustekinumab 6 mg/kg were statistically superior to placebo.
  - Treatment effects were similar between filgotinib 200 mg and all other interventions.

Maintenance phase analyses

- MCS response/remission: biologic-experienced
  - The analysis network for MCS response/remission in biologic-experienced patients comprised 11 treatment groups (adalimumab 160/80/40 mg, filgotinib 100 mg, filgotinib 200 mg, placebo, tofacitinib 5 mg, tofacitinib 10 mg, ustekinumab 90 mg Q8W, ustekinumab 90 mg Q12W, vedolizumab 108 mg SC, vedolizumab 300 mg Q4W and vedolizumab 300 mg Q8W) across 7 studies.
  - All interventions were statistically superior to placebo, except for ustekinumab 90 mg Q12W (Fig. 5e). Treatment effects were similar between filgotinib 200 mg and all interventions.
- Endoscopic mucosal healing: biologic-experienced
  - In the biologic-experienced population, the analysis network for endoscopic mucosal healing comprised 8 treatment groups (adalimumab 160/80/40 mg, filgotinib 100 mg, filgotinib 200 mg, placebo, ustekinumab 90 mg Q8W, ustekinumab 90 mg Q12W, vedolizumab 300 mg Q4W and vedolizumab 300 mg Q8W) across five studies.
  - All comparators were statistically superior to placebo with the exception of ustekinumab 90 mg Q12W (Fig. 5a). Treatment effects were similar between filgotinib 200 mg and all other interventions.

Anmerkung/Fazit der Autoren

The current treatment landscape benefits patients with moderately to severely active UC, improving key outcomes; filgotinib 200 mg was similar to current standard of care in most outcomes.

Kommentare zum Review

- Im Ergebnisteil wurden ausschließlich Daten der „biologic-experienced“ dargestellt.

Chu X et al., 2023 [5].

Network meta-analysis on efficacy and safety of different biologics for ulcerative colitis

Es liegen weitere SRs zu dieser Fragestellung mit derselben Schlussfolgerung vor:
  - Chae K et al., 2023 [3]

Fragestellung

This study aimed to compare the efficacy and safety of biologics in treating ulcerative colitis.

Methodik

Population:

- patients with UC

Intervention:

- different biological agents

Komparator:

- placebo, conventional drugs or other biologics, which were used as a comparative measure

Endpunkte:

- Efficacy metrics were clinical remission (Mayo score ≤ 2, no single subscore > 1), clinical response (Mayo score ≥ 3 points lower and ≥ 30% lower than baseline, rectal bleeding subscore ≥ 1 point or ≤ 1), endoscopic remission (Mayo score ≥ 0 or 1), and mucosal healing (Mayo score ≥ 0 or 1).
- The safety outcome was the number of patients with any adverse events (AEs), recurrence of ulcerative colitis, infections, discontinuation due to AEs, serious AEs and serious infections.

Recherche/Suchzeitraum:

- Retrieved 1 June 2023, from inception.

Qualitätsbewertung der Studien:

- Cochrane Bias Risk Tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 26 studies

Charakteristika der Population/Studien:

- adult patients diagnosed with ulcerative colitis who were aged 18 years or older.

Qualität der Studien:

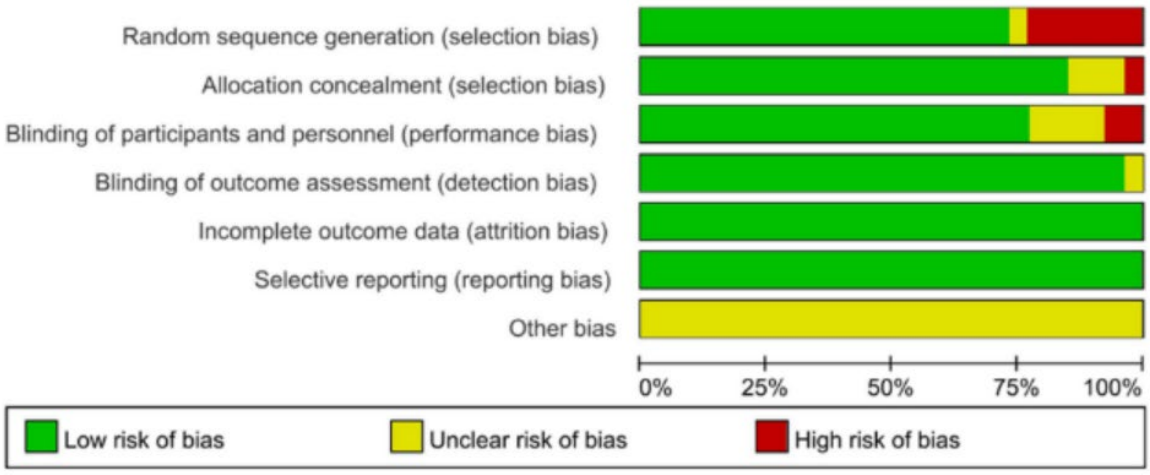


Fig. 2 Risk of bias assessment for randomized controlled trials

Studienergebnisse:

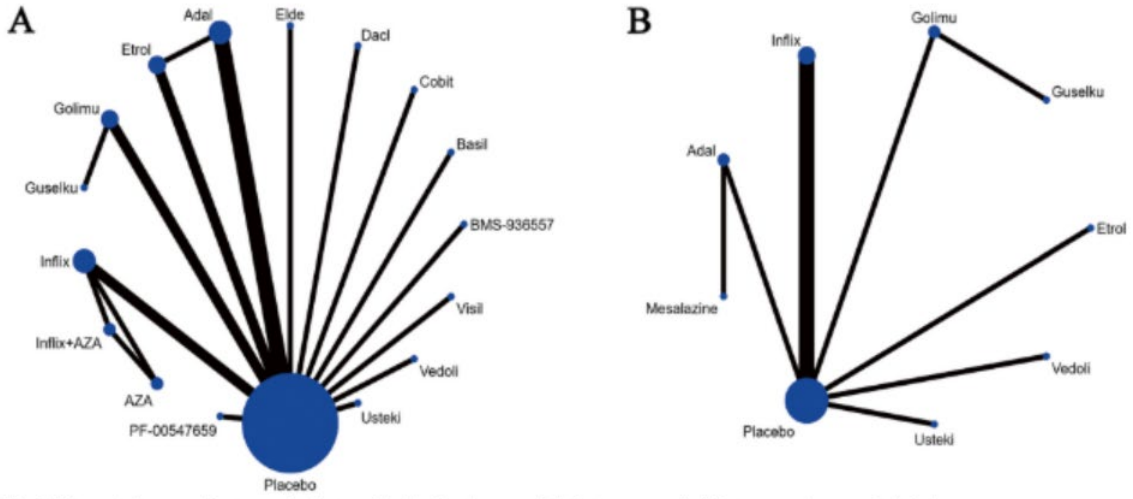


Fig. 3 Network diagram of outcome indicators. A Induction therapy of clinical response; A Maintenance therapy of clinical response

- Induction Therapy:
  - Among the biologic therapies evaluated for induction therapy, vedolizumab demonstrated the highest efficacy in achieving clinical remission (OR vs daclizumab, 9.09; 95% CI, 1.01–81.61; SUCRA 94.1) and clinical response.
  - Guselkumab showed the lowest risk of recurrence of UC (SUCRA 94.9%), adverse events resulting in treatment discontinuation (SUCRA 94.8%), and serious infections (SUCRA 78.0%).
- Maintenance Therapy:
  - For maintenance therapy, vedolizumab ranked highest in maintaining clinical remission (OR vs mesalazine 4.36; 95% CI, 1.65–11.49; SUCRA 89.7) and endoscopic improvement (SUCRA 92.6).
  - Infliximab demonstrated the highest efficacy in endoscopic improvement (SUCRA 92.6%).
  - Ustekinumab had the lowest risk of infections (SUCRA 92.9%), serious adverse events (SUCRA 91.3%), and serious infections (SUCRA 67.6%).

Anmerkung/Fazit der Autoren

Our network meta-analysis suggests that vedolizumab is the most effective biologic therapy for inducing and maintaining clinical remission in UC patients. Guselkumab shows promise in reducing the risk of recurrence and adverse events during induction therapy. Infliximab is effective in improving endoscopic outcomes during maintenance therapy. Ustekinumab appears to have a favorable safety profile. These findings provide valuable insights for clinicians in selecting the most appropriate biologic therapy for UC patients.

Kommentare zum Review

Zulassung der in der NMA untersuchten Wirkstoffe beachten.

Peyrin-Biroulet, L et al., 2022 [14].

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

Fragestellung

We conducted a systematic review and meta-analysis to compare the efficacy and safety of infliximab and vedolizumab in adult patients with moderate-to-severe Crohn's disease or ulcerative colitis.

Methodik

Population:

- Patient with moderately to severely active UC

Intervention:

- infliximab (reference product or biosimilar)

Komparator:

- vedolizumab

Endpunkte:

- proportion of patients achieving clinical response (defined as a decrease from baseline in total Mayo score of ≥ 3 points and ≥ 30%, with an accompanying decrease in rectal bleeding subscore of ≥ 1 point or an absolute rectal bleeding subscore of 0 or 1),
- proportion of patients achieving clinical remission (a total Mayo score of ≤ 2 points with no individual subscore exceeding 1 point) and proportion of patients achieving mucosal healing (an absolute endoscopic subscore of 0 or 1 per the Mayo Scoring System).
- Safety outcomes 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:

- All searches were performed for the period of 1 January 2010 through 30 April 2021 to ensure the inclusion of recently published data.

Qualitätsbewertung der Studien:

- Risk of bias and generalisability for the included studies were evaluated according to criteria defined in the Cochrane Handbook for Systematic Reviews of Interventions

Ergebnisse

Anzahl eingeschlossener Studien:

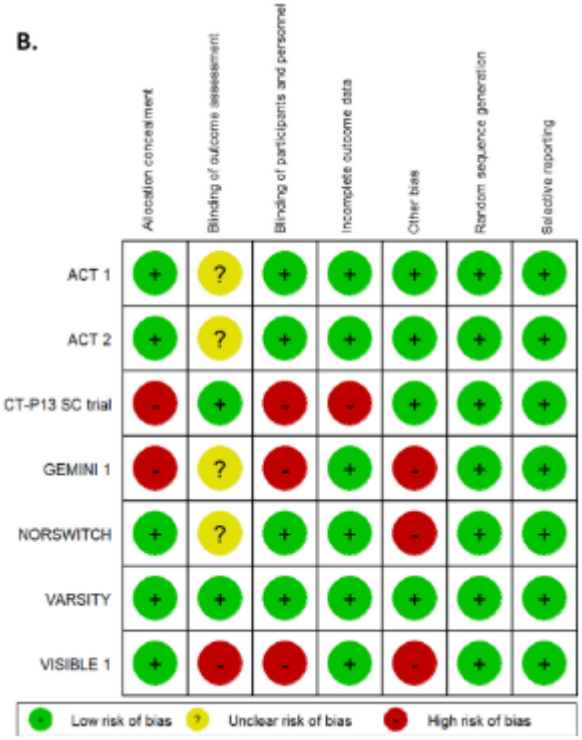
- Seven studies (reported in 13 articles)

Charakteristika der Population/Studien:

- adults (aged ≥ 18 years) with moderate-to-severe UC.
- patients with unspecified disease severity or those who had undergone intestinal surgery were excluded.

Qualität der Studien:

- Risk of bias in the included studies was principally considered to be low or was unclear (i.e. due to a lack of necessary information in the study reports).



Studienergebnisse:

- in ulcerative colitis cohorts, infliximab yielded better efficacy than vedolizumab for all analysed outcomes (CDAI-70, CDAI-100 responses, and clinical remission for Crohn's disease and clinical response and clinical remission for ulcerative colitis) during the induction phase, with non-overlapping 95% confidence intervals.
- in the maintenance phase, similar proportions of infliximab- or vedolizumab-treated patients achieved clinical response, clinical remission, or mucosal healing in ulcerative colitis.
- for the safety outcomes, rates of adverse events, serious adverse events, and discontinuations due to adverse events were similar in infliximab- and vedolizumab-treated patients in both diseases.
- infection rate was higher in infliximab for Crohn's disease and higher in vedolizumab when treating patients with ulcerative colitis. There was no difference between the treatments in the proportions of patients who reported serious infections in both indications.

Anmerkung/Fazit der Autoren

Indirect comparison of infliximab and vedolizumab trials in adult patients with moderate-to severe Crohn's disease or ulcerative colitis demonstrated that infliximab has better efficacy in the induction phase and comparable efficacy during the maintenance phase and overall safety profile compared to vedolizumab.

Kommentare zum Review

- Es wurden ausschließlich die Ergebnisse für die Indikation mittelschwere bis schwere Colitis ulcerosa dargestellt

Lasa JS et al., 2020 [10].

Efficacy and safety of biologics and small molecule drugs for patients with moderate-to-severe ulcerative colitis: a systematic review and network meta-analysis.

Fragestellung

Our aim was to compare the relative efficacy and safety of biologics and small-molecule drugs (SMDs) in patients with moderate-to-severe UC.

Methodik

Population:

- patients with moderate-to-severe UC

Intervention / Komparator:

- active comparator or placebo
  - biologic (infliximab, adalimumab, golimumab, vedolizumab, ustekinumab, etrolizumab) or a SMD (tofacitinib, filgotinib, ozanimod, upadacitinib) or placebo

Endpunkte:

- clinical remission (defined as a Mayo score of ≤ 2 with no individual subscore >1)
- endoscopic improvement (Mayo endoscopic subscore of 0 or 1)

Recherche/Suchzeitraum:

- MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) from January 1, 1990 until July 1, 2021

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias tool v2

Ergebnisse

Anzahl eingeschlossener Studien:

- 29 studies (4 were head-to-head RCTs)

Charakteristika der Population:

- induction and maintenance treatment of patients with moderate-to-severe UC

Qualität der Studien:

- Nicht dargestellt

Studienergebnisse:

Indirect comparisons of active treatments on network meta-analysis

- Indirect comparisons showed that upadacitinib was superior to all other interventions for induction of clinical remission [infliximab (OR, 2.53; 95% CI, 1.33-4.79), adalimumab (OR, 4.64; 95% CI, 2.47-8.71), golimumab (OR, 3; 95% CI, 1.32-6.82), vedolizumab (OR, 3.56; 95% CI, 1.84-6.91), ustekinumab (OR, 2.92; 95% CI, 1.31-6.51), etrolizumab (OR, 4.91; 95% CI, 2.59-9.31), tofacitinib (OR, 2.84; 95% CI, 1.28-6.31), filgotinib (OR, 4.49; 95% CI, 2.18-9.24), ozanimod (OR, 2.70; 95% CI, 1.18-6.20)].
- Upadacitinib ranked highest for induction of clinical remission (SUCRA 0.99). No significant differences between active interventions were observed when assessing adverse events (AEs) and serious adverse events (SAEs).

- Vedolizumab ranked lowest for both AEs and SAEs (SUCRA 0.18 and 0.13, respectively), whereas upadacitinib ranked highest for AEs (SUCRA 0.84) and ozanimod for SAEs (SUCRA 0.83).

Fazit der Autoren

In this systematic review and network meta-analysis of RCTs evaluating biologics and SMDs, upadacitinib was the best performing agent for efficacy outcomes in the overall population of patients with moderate to severe UC. However, upadacitinib was the worst performing agent in terms of AEs, and ozanimod in terms of SAEs. Vedolizumab was the best performing agent for safety outcomes. With paucity of direct comparisons, these results may help drug positioning.

Singh S et al., 2020 [16].

First- and Second-line Pharmacotherapies for Patients with Moderate to Severely Active Ulcerative Colitis: An Updated Network Meta-Analysis.

Fragestellung

[…] compared the efficacy and safety of different first-line (biologic-naïve) and second-line (prior exposure to tumor necrosis factor [TNF] antagonists) agents for treatment of moderate to severely active ulcerative colitis in a systematic review and network meta-analysis.

Methodik

Population:

- adults with moderate to severe ulcerative colitis who were either treatment-naïve (first-line) or previously exposed to TNFα antagonists (second-line)

Intervention:

- TNF antagonists, vedolizumab, tofacitinib, or ustekinumab, as first-line or second-line agents

Komparator:

- placebo or another active agent

Endpunkte:

- induction and maintenance of remission and endoscopic improvement; safety outcomes were serious adverse events and infections

Recherche/Suchzeitraum:

- searched publication databases through September 30, 2019

Qualitätsbewertung der Studien:

- Cochrane/GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

- 15 RCTs of first-line agents (in biologic-naïve patients), and 7 RCTs of second-line agents (in patients with prior exposure to TNFα antagonists), in patients with moderate-severe ulcerative colitis.

Charakteristika der Population:

- Median 40% (interquartile range, 30-50) patients were treated with concomitant immunomodulators and 51% (interquartile range, 45-57) were on corticosteroids at baseline.

Qualität der Studien:

- Overall, the studies were deemed to be at low risk of bias, and all included studies were industry-sponsored.

Studienergebnisse:

- Second-line Pharmacotherapy for Moderate-Severe Ulcerative Colitis
  Direct meta-analysis:
  - tofacitinib and ustekinumab, but not adalimumab or vedolizumab, were superior to placebo for induction of clinical remission.
  - tofacitinib and ustekinumab, but not vedolizumab or adalimumab, were superior to placebo for induction of endoscopic improvement

  Network Meta-Analysis:
  - In patients with prior exposure to TNF antagonists, ustekinumab (SUCRA,0.87) and tofacitinib (SUCRA,0.87) were ranked highest for induction of clinical remission and were superior to vedolizumab (OR vs ustekinumab, 5.99; 95% CI, 1.13–31.76 and OR vs tofacitinib, 6.18; 95% CI, 1.003–8.00; moderate confidence in estimates) and adalimumab (OR vs ustekinumab, 10.71; 95% CI, 2.01–57.20 and OR vs tofacitinib, 11.05; 95% CI, 1.79– 68.41; moderate confidence in estimates). Vedolizumab had lowest risk of infections (SUCRA, 0.81), followed by ustekinumab (SUCRA, 0.63) in maintenance trials.

Fazit der Autoren

In a systematic review and network meta-analysis, we found infliximab to be ranked highest in biologic-naïve patients, and ustekinumab and tofacitinib were ranked highest in patients with prior exposure to TNF antagonists, for induction of remission and endoscopic improvement in patients with moderate to severe ulcerative colitis. More trials of direct comparisons are needed to inform clinical decision-making with greater confidence.

3.3 Leitlinien

Raine T et al., 2022 [15].

European Crohn's and Colitis Organisation (ECCO)

ECCO Guidelines on Therapeutics in Ulcerative Colitis: Medical Treatment

Zielsetzung/Fragestellung

These guidelines set out the evidence for the use of different medical therapies in the treatment of UC.

Methodik

Grundlage der Leitlinie Repräsentatives Gremium;

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

Recherche/Suchzeitraum:

- The team of librarians performed a comprehensive literature search on PubMed/Medline, Embase, and the Cochrane Central databases using specific search strings for each PICO question (until January 2020)

LoE

- To determine the quality of the evidence for each outcome across all studies, we started with rating the evidence from RCTs as 'high' quality, and then assessed the following five factors that could lead to downrating the quality of evidence: risk of bias, inconsistency, indirectness, imprecision, and publication bias. Risk of bias was assessed using the Cochrane tool.
- GRADE

GoR

- The strength of each recommendation was graded either as 'strong' [meaning that the desirable effects of an intervention clearly outweigh the undesirable effects, or vice versa] or as 'weak' [meaning that the balance is less certain] while also considering the quality of evidence, values and preferences of patients, balance between desirable and undesirable effects, and cost effectiveness
- GRADE

Recommendations: Medical management of moderately-to-severely active ulcerative colitis

5.1: Induction of remission in moderately-to-severely active ulcerative colitis

- Recommendation 11: We recommend oral prednisolone for induction of remission in non-hospitalised patients with moderately-to-severely active UC [strong recommendation; very low quality of evidence].
- Recommendation 12: We recommend treatment with anti-TNF agents [infliximab, adalimumab, and golimumab] to induce remission in patients with moderate-to-severe UC who have inadequate response or intolerance to conventional therapy [strong recommendation, moderate-quality evidence].
- Recommendation 13: We recommend treatment with vedolizumab for the induction of remission in patients with moderately-to-severely active UC who have inadequate

response or intolerance to conventional therapy [strong recommendation, low quality of evidence].

- Recommendation 14: We recommend treatment with tofacitinib to induce remission in patients with moderate-to-severe UC who have inadequate response or intolerance to conventional therapy [strong recommendation, moderate quality of evidence].
- Recommendation 15: We recommend treatment with ustekinumab for the induction of remission in patients with moderately-to-severely active UC with inadequate response or intolerance to conventional therapy. [strong recommendation, moderate quality of evidence].

5.2: Maintenance of remission of moderately-to-severely active ulcerative colitis

- Recommendation 16: We recommend anti-TNF agents [infliximab, adalimumab, or golimumab] for the maintenance of remission in patients with UC who responded to induction therapy with the same drug [strong recommendation, high quality evidence].
- Recommendation 17: In UC patients who have lost response to an anti-TNF agent, there is currently insufficient evidence to recommend for or against the use of therapeutic drug monitoring to improve clinical outcomes.
- Recommendation 18: We recommend vedolizumab for maintenance of remission in patients with UC who responded to induction therapy with vedolizumab [strong recommendation, moderate-quality evidence].
- Recommendation 19: We suggest the use of vedolizumab rather than adalimumab for the induction and maintenance of remission in patients with moderately-to-severely active ulcerative colitis [weak recommendation, low level of evidence].
- Recommendation 20: We recommend tofacitinib for maintaining remission in patients with UC who responded to induction therapy with tofacitinib [strong recommendation, moderate quality of evidence].
- Recommendation 21: We recommend ustekinumab for the maintenance of remission in patients with UC who responded to induction therapy with ustekinumab [strong recommendation, moderate quality of evidence].

Spinelli A et al., 2022 [17].

European Crohn's and Colitis Organisation (ECCO)

ECCO Guidelines on Therapeutics in Ulcerative Colitis: Surgical Treatment

Zielsetzung/Fragestellung

The European Crohn's and Colitis Organisation [ECCO] aims to develop a practical guide for the medical and surgical management of adult patients with UC based on an interdisciplinary, evidence-based approach. The present article is focused on the first-line treatment of adult ASUC patients and on the surgical management of refractory adult UC patients, including preoperative assessment and technical aspects. The following statements are complementary to the guidelines on medical treatment of adult UC patients, which are presented in a separate article.

Methodik

Grundlage der Leitlinie

Update: The current guidelines, together with those on UC medical management, are intended to update the previous ECCO recommendations, published in 2017

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

Recherche/Suchzeitraum:

- PubMed/MEDLINE, EMBASE (Excerpta Medica Database), and Cochrane central databases

LoE/GoR

- Oxford 2011 Levels of Evidence (levels 1-5)
- High levels of evidence may not exist for answering clinical questions in the surgical research area, because of the nature of medical problems and research and ethical limitations. The steering committee felt that using the GRADE methodology for the surgical PICOs might often result in a statement of "insufficient evidence to make a recommendation", although the question itself might be of high clinical importance. For this reason, the steering committee decided that the formulation of the surgical PICOs, the professional literature search, and the process of selection of articles would be similar for the medical and surgical PICOs, and then each surgical PICO would generate a statement based on the "Oxford 2011 Levels of Evidence"[1]. This is an evidence-ranking system that can be used by clinicians and researchers to find the likely best evidence and answer clinical questions. This decision was approved by the ECCO GuiCom.

[1] OCEBM Levels of Evidence Working Group. The Oxford Levels of Evidence 2. https://www.cebm.ox.ac.uk/resources/levels-of-evidence/ocebm-levels-of-evidence (Oxford Centre for Evidence-Based Medicine, 2011).

1 Medical management of ASCU

Empfehlung 1 (Empfehlungsgrad)

1.1 Statement 1.1

Intravenous corticosteroids as the initial standard treatment for adult patients with ASUC is recommended, as this treatment induces clinical remission and reduces mortality [EL3]

1.2 Statement 1.2

Either infliximab or cyclosporine should be used in adult patients with steroid-refractory ASUC. When choosing between these strategies, centre experience and a plan for maintenance therapy after cyclosporine should be considered [EL3]

1.3 Statement 1.3

There is currently insufficient evidence to determine the optimal regimen of infliximab rescue therapy in patients with ASUC refractory to corticosteroid therapy [EL4]

1.4 Statement 1.4

Third-line sequential rescue therapies with calcineurin inhibitors [cyclosporine or tacrolimus] in ASUC refractory to corticosteroid therapy may delay the need for colectomy but are associated with high rates of adverse events and should only be administered in specialized centres [EL2a]

2 Medical versus surgical management of refractory moderate-to-severe UC

2.1 Statement 2.1

Reconstructive surgery may be offered to refractory and corticosteroid-dependent patients and improves quality of life despite the risk of early and late complications [EL2b]. Proctocolectomy with end ileostomy is an alternative for some patients and has lower morbidity and comparable quality of life [EL3a]

4 Surgical strategy of refractory moderate-to-severe UC

4.1 Statement 4.1

After total proctocolectomy for medically refractory UC, IPAA is the procedure of choice, but permanent end-ileostomy is also a reasonable option for some patients. A shared decision-making approach should be used to tailor procedure selection to the patient's preference [EL3]

4.2 Statement 4.2

In patients with medically refractory UC, a modified 2-stage IPAA is associated with fewer septic and non-septic complications and with shorter hospital length of stay than 3-stage or 2-stage IPAA [EL3]

Holubar SD et al., 2021 [9].

The American Society of Colon and Rectal Surgeons (ASCRS)

The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the Surgical Management of Ulcerative Colitis

Zielsetzung/Fragestellung

update to the ASCRS Practice Parameters for the Surgical Treatment of Ulcerative Colitis published in 2014.11 Although bowel preparation, enhanced recovery pathways, ostomy care, and prevention of thromboembolic disease are relevant to the surgical management of patients with UC, these topics are addressed in other ASCRS clinical practice guidelines and are beyond the scope of this guideline.

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:

- An organized search of MEDLINE, PubMed, EMBASE, Scopus, and the Cochrane Database of Collected Reviews limited to the English language was performed between January 1, 1995 and December 18, 2020.1

LoE/GoR:

TABLE 1. The GRADE System: grading recommendations

	Description	*Benefit versus risk and burdens*	*Methodologic quality of supporting evidence*	*Implications*
1A	Strong recommendation, High-quality evidence	Benefits clearly outweigh risk and burdens or vice versa	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1B	Strong recommendation, Moderate-quality evidence	Benefits clearly outweigh risk and burdens or vice versa	RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1C	Strong recommendation, Low- or very-low-quality evidence	Benefits clearly outweigh risk and burdens or vice versa	Observational studies or case series	Strong recommendation but may change when higher-quality evidence becomes available
2A	Weak recommendation, High-quality evidence	Benefits closely balanced with risks and burdens	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2B	Weak recommendations, Moderate-quality evidence	Benefits closely balanced with risks and burdens	RCTs with important limitations (inconsistent results, methodologic flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2C	Weak recommendation, Low- or very-low-quality evidence	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced	Observational studies or case series	Very weak recommendations; other alternatives may be equally reasonable

GRADE = Grades of Recommendation, Assessment, Development, and Evaluation; RCT = randomized controlled trial.
Adapted from Guyatt G, Gutermen D, Baumann MH, et al. Grading strength of recommendations and quality of evidence in clinical guidelines: report from an American College of Chest Physicians Task Force. *Chest*. 2006;129:174–181.[18] Used with permission.

Sonstige methodische Hinweise

/

Empfehlungen

MEDICALLY REFRACTORY ULCERATIVE COLITIS

Empfehlung 1 (Empfehlungsgrad: Strong recommendation based on low-quality evidence, 1C)

- A multidisciplinary approach including early surgical consultation should be used to guide optimal care in hospitalized patients with moderate-to-severe UC undergoing escalation of medical therapy. Grade of recommendation: Strong recommendation based on low-quality evidence, 1C.

Empfehlung 2 (Empfehlungsgrad: Strong recommendation based on low-quality evidence, 1C.)

- Patients with severe medically refractory UC, fulminant colitis, toxic megacolon, or colonic perforation should typically undergo total abdominal colectomy with end ileostomy. Grade of recommendation: Strong recommendation based on low-quality evidence, 1C.

Empfehlung 3 (Empfehlungsgrad: Strong recommendation based on low-quality evidence, 1C.)

- A staged approach for an IPAA should typically be considered in patients being treated with high-dose corticosteroids or monoclonal antibodies. Grade of recommendation: Strong recommendation based on low-quality evidence, 1C.

Referenzen aus Leitlinien
Referenzen
Referenzen

Feuerstein JD et al., 2020 [7] & Singh S et al., 2020 [4].

American Gastroenterological Association (AGA)

AGA Clinical Practice Guidelines on the Management of Moderate to Severe Ulcerative Colitis.

Fragestellung

(…) focuses on drugs and treatment strategies for the management of adult (18 years and older) outpatients with moderate to severe UC.

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:

- focuses on drugs and treatment strategies for the management of adult (18 years and older) outpatients with moderate to severe UC on May 2018.

LoE/GoR

- GRADE approach

Table 2. GRADE Definitions of Quality and 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

Table 3. GRADE Definitions on Strength of Recommendation and Guide to Interpretation

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

Recommendations

Recommendations	Strength of recommendation	Quality of evidence
1. In adult outpatients with moderate to severe UC, the AGA recommends using infliximab, adalimumab, golimumab, vedolizumab, tofacitinib, or ustekinumab over no treatment. (Medications are ordered based on year of approval by the US FDA.)	Strong	Moderate
2a. In adult outpatients with moderate to severe UC who are naïve to biologic agents, the AGA suggests using infliximab or vedolizumab rather than adalimumab, for induction of remission. Comment: Patients, particularly those with less severe disease, who place higher value on the convenience of self-administered subcutaneous injection, and a lower value on the relative efficacy of medications, may reasonably chose adalimumab as an alternative.	Conditional	Moderate
2b. In adult outpatients with moderate to severe UC who are naïve to biologic agents, the AGA recommends that tofacitinib only be used in the setting of a clinical or registry study. (No recommendation, knowledge gap) Comment: Updated FDA recommendations (July 26, 2019) on indications for use of tofacitinib in UC recommends its use only after failure of or intolerance to TNF-α antagonists.	No recommendation	Knowledge gap
2c. In adult outpatients with moderate to severe UC who have previously been exposed to infliximab, particularly those with primary nonresponse, the AGA suggests using ustekinumab or tofacitinib rather than vedolizumab or adalimumab for induction of remission.	Conditional	Low
3a. In adult outpatients with active moderate to severe UC, the AGA suggests against using thiopurine monotherapy for induction of remission.	Conditional	Very low
3b. In adult outpatients with moderate to severe UC in remission, the AGA suggests using thiopurine monotherapy rather than no treatment for maintenance of remission.	Conditional	Low
3c. In adult outpatients with moderate to severe UC, the AGA suggests against using methotrexate monotherapy for induction or maintenance of remission.	Conditional	Low
4a. In adult outpatients with active moderate to severe UC, the AGA suggests using biologic monotherapy (TNF-α antagonists, vedolizumab, or ustekinumab) or tofacitinib rather than thiopurine monotherapy for induction of remission.	Conditional	Low
4b. In adult outpatients with moderate to severe UC in remission, the AGA makes no recommendation in favor of or against using biologic monotherapy or tofacitinib rather than thiopurine monotherapy for maintenance of remission.	No recommendation	Knowledge gap
5a. In adult outpatients with moderate to severe UC, the AGA suggests combining TNF-α antagonists, vedolizumab or ustekinumab with thiopurines or methotrexate rather than biologic monotherapy. Comment: Patients, particularly those with less severe disease, who place higher value on the safety of biologic monotherapy and lower value on the efficacy of combination therapy may reasonably chose biologic monotherapy.	Conditional	Low
5b. In adult outpatients with moderate to severe UC, the AGA suggests combining TNF-α antagonists, vedolizumab, or ustekinumab with thiopurines or methotrexate rather than thiopurine monotherapy.	Conditional	Low
6. In adult outpatients with moderate to severe UC, the AGA suggests early use of biologic agents with or without immunomodulator therapy rather than gradual step up after failure of 5-ASA. Comment: Patients, particularly those with less severe disease, who place higher value on the safety of 5-ASA therapy and lower value on the efficacy of biologic agents or tofacitinib may reasonably chose gradual step therapy with 5-ASA therapy.	Conditional	Very low
7. In adult outpatients with moderate to severe UC who have achieved remission with biologic agents and/or immunomodulators or tofacitinib, the AGA suggests against continuing 5-ASA for induction and maintenance of remission.	Conditional	Very low
8. In hospitalized adult patients with ASUC, the AGA suggests using intravenous methylprednisolone dose equivalent of 40–60 mg/d rather than higher doses of intravenous corticosteroids.	Conditional	Very low
9. In hospitalized adult patients with acute severe UC without infection, the AGA suggests against	Conditional	Very low

10. In hospitalized adult patients with ASUC refractory to intravenous corticosteroids, the AGA suggests using infliximab or cyclosporine.	Conditional	Low
11. In hospitalized adult patients with acute severe UC being treated with infliximab, the AGA makes no recommendation on routine use of intensive vs standard infliximab dosing.	No recommendation	Knowledge gap

NICE, 2019 [12].

National Institute for Health and Care Excellence (NICE)

Ulcerative colitis: management

Evidence reviews for induction of remission in mild-to-moderate ulcerative colitis

Fragestellung

covers the management of ulcerative colitis in children, young people and adults. It aims to help professionals to provide consistent high-quality care and it highlights the importance of advice and support for people with ulcerative colitis.

Methodik

Grundlage der Leitlinie

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

Recherche/Suchzeitraum:

- May 2019: This guideline is an update of NICE guideline CG166 (published June 2013) and replaces it.
  - We have reviewed the evidence on inducing remission for people with mild-to-moderate ulcerative colitis. These recommendations are marked [2019].
  - Recommendations marked [2008] or [2013] last had an evidence review in 2008 or 2013. In some cases minor changes have been made to the wording to bring the language and style up to date, without changing the meaning.

LoE/GoR

- the wording of recommendation reflects the strength of recommendation (for example the word “offer” was used for strong recommendations and “consider” for weak recommendations)

Recommendations

Treating mild-to-moderate ulcerative colitis

Extensive disease

- To induce remission in people with a mild-to-moderate first presentation or inflammatory exacerbation of extensive ulcerative colitis, offer a topical aminosalicylate and a high-dose oral aminosalicylate as first-line treatment. [2019]
- If remission is not achieved within 4 weeks, stop the topical aminosalicylate and offer a high-dose oral aminosalicylate with a time-limited course of an oral corticosteroid. [2019]
- For people who cannot tolerate aminosalicylates, consider a time-limited course of an oral corticosteroid. [2019]

Biologics and Janus kinase inhibitors for moderately to severely active ulcerative colitis: all extents of disease

For guidance on biologics and Janus kinase inhibitors for treating moderately to severely active ulcerative colitis, see the NICE technology appraisal guidance on:

- infliximab, adalimumab and golimumab for moderately to severely active ulcerative colitis
  - Infliximab, adalimumab and golimumab are recommended, within their marketing authorisations, as options for treating moderately to severely active ulcerative colitis in adults whose disease has responded inadequately to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or who cannot tolerate, or have medical contraindications for, such therapies.
  - The choice of treatment between infliximab, adalimumab or golimumab should be made on an individual basis after discussion between the responsible clinician and the patient about the advantages and disadvantages of the treatments available. This should take into consideration therapeutic need and whether or not the patient is likely to adhere to treatment. If more than 1 treatment is suitable, the least expensive should be chosen (taking into account administration costs, dosage and price per dose).
  - Infliximab is recommended, within its marketing authorisation, as an option for treating severely active ulcerative colitis in children and young people aged 6–17 years whose disease has responded inadequately to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or who cannot tolerate, or have medical contraindications for, such therapies.
  - Infliximab, adalimumab or golimumab should be given as a planned course of treatment until treatment fails (including the need for surgery) or until 12 months after starting treatment, whichever is shorter. Specialists should then discuss the risks and benefits of continued treatment with the patient, and their parent or carer if appropriate:
  - They should continue treatment only if there is clear evidence of response as determined by clinical symptoms, biological markers and investigation, including endoscopy if necessary. People who continue treatment should be reassessed at least every 12 months to determine whether ongoing treatment is still clinically appropriate.
  - They should consider a trial withdrawal from treatment for all patients who are in stable clinical remission. People whose disease relapses after treatment is stopped should have the option to start treatment again.
- vedolizumab for treating moderately to severely active ulcerative colitis
  - Vedolizumab is recommended, within its marketing authorisation, as an option for treating moderately to severely active ulcerative colitis in adults only if the company provides vedolizumab with the discount agreed in the patient access scheme.
  - Vedolizumab should be given until it stops working or surgery is needed. At 12 months after the start of treatment, people should be reassessed to see whether treatment should continue. Treatment should only continue if there is clear evidence of ongoing clinical benefit. For people in complete remission at 12 months, consider stopping vedolizumab, resuming treatment if there is a relapse. People who continue vedolizumab should be reassessed at least every 12 months to see whether continued treatment is justified.
- tofacitinib for moderately to severely active ulcerative colitis

- Tofacitinib is recommended, within its marketing authorisation, as an option for treating moderately to severely active ulcerative colitis in adults when conventional therapy or a biological agent cannot be tolerated or the disease has responded inadequately or lost response to treatment. It is recommended only if the company provides tofacitinib with the discount agreed in the commercial arrangement.

Treating acute severe ulcerative colitis: all extents of disease

The multidisciplinary team

- For people admitted to hospital with acute severe ulcerative colitis:
  - ensure that a gastroenterologist and a colorectal surgeon collaborate to provide treatment and management
  - ensure that the composition of the multidisciplinary team is appropriate for the age of the person
  - seek advice from a paediatrician with expertise in gastroenterology when treating a child or young person
  - ensure that the obstetric and gynaecology team is included when treating a pregnant woman. [2013]

Step 1 therapy

- For people admitted to hospital with acute severe ulcerative colitis (either a first presentation or an inflammatory exacerbation):
  - offer intravenous corticosteroids to induce remission and
  - assess the likelihood that the person will need surgery. [2013]
- Consider intravenous ciclosporin or surgery for people:
  - who cannot tolerate or who decline intravenous corticosteroids or
  - for whom treatment with intravenous corticosteroids is contraindicated.

  Take into account the person's preferences when choosing treatment. [2013]

Step 2 therapy

- Consider adding intravenous ciclosporin to intravenous corticosteroids or consider surgery for people:
  - who have little or no improvement within 72 hours of starting intravenous corticosteroids or
  - whose symptoms worsen at any time despite corticosteroid treatment.

  Take into account the person's preferences when choosing treatment. [2013]
- Infliximab is recommended as an option for the treatment of acute exacerbations of severely active ulcerative colitis only in patients in whom ciclosporin is contraindicated or clinically inappropriate, based on a careful assessment of the risks and benefits of treatment in the individual patient. [2008]
- In people who do not meet the criterion above, infliximab should only be used for the treatment of acute exacerbations of severely active ulcerative colitis in clinical trials. [2008]

Maintaining remission in people with ulcerative colitis

All extents of disease

- Consider oral azathioprine or oral mercaptopurine to maintain remission:

  - after 2 or more inflammatory exacerbations in 12 months that require treatment with systemic corticosteroids or
  - if remission is not maintained by aminosalicylates. [2013]
- To maintain remission after a single episode of acute severe ulcerative colitis:
  - consider oral azathioprine or oral mercaptopurine
  - consider oral aminosalicylates if azathioprine and/or mercaptopurine are contraindicated or the person cannot tolerate them. [2013]

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 12 of 12, December 2023) am 04.12.2023

#	Suchfrage
1	[mh "Colitis, Ulcerative"]
2	[mh "Inflammatory Bowel Diseases"]
3	colitis:ti,ab,kw NEAR/3 (ulcerosa OR ulcerative):ti,ab,kw
4	(inflammatory NEXT bowel NEXT disease*):ti,ab,kw
5	#1 OR #2 OR #3 OR #4
6	#5 with Cochrane Library publication date from Dec 2018 to present, in Cochrane Reviews

Systematic Reviews in Medline (PubMed) am 04.12.2024

verwendete Suchfilter:
Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 14.02.2023.

#	Suchfrage
1	colitis, ulcerative/therapy[mh]
2	(ulcerative colitis[tiab]) OR (colitis ulcerosa[tiab])
3	(#2) 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]))
4	#1 OR #3
5	(#4) AND (systematic review[ptyp] OR meta-analysis[ptyp] OR network meta-analysis[mh] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab])) OR metareview*[tiab] OR umbrella review*[tiab] OR "overview of reviews"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR ((evidence-based medicine[mh] OR evidence synthes*[tiab]) AND review[pt]) OR ((("evidence based" [tiab:~3]) OR evidence base[tiab]) AND (review*[tiab] OR overview*[tiab])) OR (review[ti] AND (comprehensive[ti] OR studies[ti] OR trials[ti])) OR ((critical appraisal*[tiab] OR critically appraise*[tiab] OR study selection[tiab] OR ((predetermined[tiab] OR inclusion[tiab] OR selection[tiab] OR eligibility[tiab]) AND criteri*[tiab]) OR exclusion criteri*[tiab] OR screening criteri*[tiab] OR systematic*[tiab] OR data extraction*[tiab] OR data synthes*[tiab] OR prisma*[tiab] OR moose[tiab] OR entreq[tiab] OR mecir[tiab] OR stard[tiab] OR strobe[tiab] OR "risk of bias"[tiab]) AND (survey*[tiab] OR overview*[tiab] OR review*[tiab] OR search*[tiab] OR analysis[ti] OR apprais*[tiab] OR research*[tiab] OR synthes*[tiab]) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR bibliographies[tiab] OR published[tiab] OR

#	Suchfrage
	citations[tiab] OR database*[tiab] OR references[tiab] OR reference-list*[tiab] OR papers[tiab] OR trials[tiab] OR studies[tiab] OR medline[tiab] OR embase[tiab] OR cochrane[tiab] OR pubmed[tiab] OR "web of science" [tiab] OR cinahl[tiab] OR cinhal[tiab] OR scisearch[tiab] OR ovid[tiab] OR ebsco[tiab] OR scopus[tiab] OR epistemonikos[tiab] OR prospero[tiab] OR proquest[tiab] OR lilacs[tiab] OR biosis[tiab])) OR technical report[ptyp] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
6	(#5) AND ("2018/12/01"[PDAT] : "3000"[PDAT])
7	(#6) NOT "The Cochrane database of systematic reviews"[Journal]
8	(#7) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Leitlinien in Medline (PubMed) am 04.12.2024

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

#	Suchfrage
1	colitis, ulcerative[mh]
2	inflammatory bowel disease[majr:noexp]
3	(ulcerative colitis[ti]) OR (colitis ulcerosa[ti])
4	(inflammatory bowel[ti]) OR (IBD[ti])
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 ("2018/12/01"[PDAT] : "3000"[PDAT])
8	(#7) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Iterative Handsuche nach grauer Literatur, abgeschlossen am 05.12.2024

- 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)

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

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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