Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2018-09-01-D-374Tofacitinib

Stand: Januar 2018

I. Zweckmäßige Vergleichstherapie: Kriterien der VerfO	
Tofacitinib **Behandlung erwachsener Patienten mit mittelschwerer bis schwerer aktiver Colitis ulcerosa**	
Kriterien gemäß 5. Kapitel § 6 Absatz 3 Satz 2 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
Als Vergleichstherapie sollen bevorzugt Arzneimittel-anwendungen oder nicht-medikamentöse Behandlungen herangezogen werden, deren patientenrelevanter Nutzen durch den Gemeinsamen Bundesausschuss bereits festgestellt ist.	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 Verfahren nach § 35a SGB V: - Vedolizumab (Beschluss vom 08.01.2015) Verfahren nach § 35 Abs.1 SGB V: Arzneimittel-Richtlinie/Anlage IX: Einleitung eines Stellungnahmeverfahrens – Festbetragsgruppenbildung Infliximab, Gruppe 1, in Stufe 1 (Beschluss vom 06.12.16) 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**
Zu prüfendes Arzneimittel:	
Tofacitinib Xelianz®	XELJANZ ist indiziert für die Induktions- und Erhaltungstherapie bei erwachsenen Patienten mit mittelschwerer bis schwerer aktiver Colitis ulcerosa, 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®	[…] 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. …Colitis ulcerosa bei Kindern und Jugendlichen 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.
Adalimumab L04AB04 Humira®	[…] Colitis ulcerosa Humira ist indiziert zur Behandlung der mittelschweren bis schweren aktiven Colitis ulcerosa bei erwachsenen Patienten, die auf die konventionelle Therapie, einschließlich Glukokortikoide und 6-Mercaptopurin (6-MP) oder Azathioprin (AZA), unzureichend angesprochen haben oder die eine Unverträglichkeit gegenüber einer solchen Therapie haben oder bei denen eine solche Therapie kontraindiziert ist.
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.
Integrininhibitor	
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.
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.
Sulfasalazin A07EC01 Colo-Pleon® Tabl.	Akutbehandlung und Rezidivprophylaxe der Colitis ulcerosa […]
Olsalazin A07EC03 Dipentum® Tabl.	Leichte und mittelschwere Schübe der akuten Colitis ulcerosa. Rezidivprophylaxe der Colitis ulcerosa. […]
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)
Kortikosteroide	
Budesonid A07EA06 Generisch	(topisch) Akutbehandlung der Colitis ulcerosa, die auf das Rektum und das Colon sigmoideum beschränkt ist.

z.B. Budenofalk® Rektalschaum	
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.
Hydrocortison-acetat Colifoam® H02AB09 Rektalschaum	(topisch) Entzündliche Erkrankungen im unteren Dickdarmbereich wie Colitis ulcerosa oder Morbus Crohn und Proktosigmoiditis.
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 generisch z.B. Prednisolon acis Tab.	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). […] <u>Gastroenterologie/Hepatologie:</u> • Colitis ulcerosa (DS: b – c)
Methylprednisolon H02AB04 generisch z.B.	Erkrankungen, die einer systemischen Therapie mit Glukokortikoiden bedürfen. Hierzu gehören je nach Erscheinungsform und Schweregrad zum Beispiel: […] Magen-Darm-Erkrankungen: – Colitis ulcerosa,

Methylprednisolon JENAPHARM®	
Betamethason A07EA04 generisch z.B. Betnesol Rektal-Instillation	(topisch) Linksseitige Colitis ulcerosa im unteren Darmbereich

Quellen: AMIS Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie (zVT):

Inhalt

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenz-basierten systematischen Leitlinien zur Indikation Colitis ulcerosa durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 13.03.2017 abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, Clinical Evidence, DAHTA, G-BA, GIN, IQWiG, NGC, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 919 Quellen, die anschließend in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 29 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Indikation:

„… for the induction and maintenance of treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent.“

Abkürzungen:

ADA	Adalimumab
AZA	Azathioprin
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CU	Colitis ulcerosa
DAHTA	Datenbank der Deutsche Agentur für Health Technology Assessment
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GOL	Golimumab
IBDQ	Inflammatory bowel disease questionnaire
IFX	Infliximab
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
NGC	National Guideline Clearinghouse
NHS CRD	National Health Services Center for Reviews and Dissemination
NICE	National Institute for Health and Care Excellence
SIGN	Scottish Intercollegiate Guidelines Network
TNF	Tumornekrosefaktor
TRIP	Turn Research into Practice Database
VEDO	Vedolizumab
WHO	World Health Organization

IQWiG-Berichte/G-BA-Beschlüsse

G-BA, 2015 [9]. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Vedolizumab vom 8. Januar 2015 Vgl. **IQWiG, 2014 [12].** Vedolizumab – Nutzenbewertung gemäß § 35a SGB V	**Zugelassenes Anwendungsgebiet:** Colitis ulcerosa Vedolizumab (Entyvio®) ist indiziert für die Behandlung von erwachsenen Patienten mit mittelschwerer bis schwerer aktiver Colitis ulcerosa, die entweder auf konventionelle Therapie oder einen der Tumornekrosefaktor-alpha (TNFα)-Antagonisten unzureichend angesprochen haben, nicht mehr darauf ansprechen oder eine Unverträglichkeit gegen eine entsprechende Behandlung aufweisen. **Fazit:** Patienten mit mittelschwerer bis schwerer aktiver Colitis ulcerosa, die auf konventionelle Therapie unzureichend angesprochen haben, nicht mehr darauf ansprechen oder eine Unverträglichkeit gegen eine entsprechende Behandlung aufweisen. *Zweckmäßige Vergleichstherapie:* Ein TNF-alpha-Antagonist (Adalimumab oder Infliximab) *Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Adalimumab:* Ein Zusatznutzen ist nicht belegt. Patienten mit mittelschwerer bis schwerer aktiver Colitis ulcerosa, die auf einen der Tumornekrosefaktor-alpha (TNFα)-Antagonisten unzureichend angesprochen haben, nicht mehr darauf ansprechen oder eine Unverträglichkeit gegen eine entsprechende Behandlung aufweisen. *Zweckmäßige Vergleichstherapie:* Ein TNF-alpha-Antagonist (Adalimumab oder Infliximab unter Berücksichtigung der Vortherapien) (Hinweis: Bei Versagen der Therapie mit einem TNF-alpha-Antagonisten (Adalimumab oder Infliximab) ist eine Dosisanpassung oder ein Wechsel auf jeweils den anderen TNF-alpha-Antagonisten möglich.) *Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Adalimumab:* Ein Zusatznutzen ist nicht belegt. Anmerkung: Nur das betreffende AWG zur Colitis ulcerosa dargestellt (Morbus Crohn nicht dargestellt

Cochrane Reviews

Timmer A et al., 2016 [26]. Azathioprine and 6-mercaptopurine for maintenance of remission in ulcerative colitis	1. Fragestellung To assess the effectiveness and safety of azathioprine and 6-mercaptopurine for maintaining remission of ulcerative colitis.
	2. Methodik Population: Patients in whom azathioprine or 6-mercaptopurine were used to treat ulcerative colitis in remission, with or without a preceding period of induction of remission were considered for inclusion Intervention: azathioprine or 6-mercaptopurine with Komparator: placebo or standard maintenance therapy (e.g. mesalazine) Endpunkte: The primary outcome: failure to maintain clinical or endoscopic remission at 12 months from randomization or later, (i.e. clinical or endoscopic relapse, or early withdrawal from the study as defined by the investigators) For studies where life table analysis was used the estimated probability of relapse over time was to be examined. Secondary outcomes included the occurrence of any adverse event (particularly opportunistic infection, pancreatitis, bone marrow suppression, cancer and death) and withdrawal due to adverse events Recherche: The MEDLINE, EMBASE and Cochrane Library databases were searched from inception to 30 July 2015. Anzahl eingeschlossene Studien/Patienten (Gesamt): Seven studies including 302 patients with ulcerative colitis were included in the review. Qualitätsbewertung der Studien: Cochrane risk of bias tool /GRADE
	3. Ergebnisdarstellung Qualität der Studien: The risk of bias was high in three of the studies due to lack of blinding (siehe zusätzliche Angaben bei den Ergebnissen) • Azathioprine was shown to be significantly superior to placebo for maintenance of remission. Fourty-four per cent (51/115) of azathioprine patients failed to maintain remission compared to 65% (76/117) of placebo patients (4 studies, 232 patients; RR 0.68, 95%CI 0.54 to 0.86). A GRADE analysis rated the overall quality of the evidence for this outcome as low due to risk of bias and imprecision (sparse data). • Two trials that compared 6-mercaptopurine tomesalazine, or azathioprine to sulfasalazine showed significant heterogeneity and thus were not pooled. (…) Fifty-eight per cent (7/12) of azathioprine patients failed to maintain remission compared to 38% (5/13) of sulfasalazine patients (1 study, 25 patients). • One very small study compared azathioprine with cyclosporin and found that there was no significant difference between patients failing remission on azathioprine (50%, 4/8) or cyclosporin (62.5%, 5/8) (1 study, 16 patients).

	• When placebo-controlled studies were pooled with aminosalicylate-comparator studies to assess adverse events, there was no statistically significant difference between azathioprine and control in the incidence of adverse events. • Nine per cent (11/127) of azathioprine patients experienced at least one adverse event compared to 2% (3/130) of placebo patients (5 studies, 257 patients). • Patients receiving azathioprine were at significantly increased risk of withdrawing due to adverse events. Eight per cent (8/101) of azathioprine patients withdrew due to adverse events compared to 0% (0/98) of control patients (5 studies, 199 patients; RR 5.43, 95% CI 1.02 to 28.75). Adverse events related to study medication included acute pancreatitis (3 cases, plus 1 case on cyclosporin) and significant bone marrow suppression (5 cases). Deaths, opportunistic infection or neoplasia were not reported.
	4. Fazit der Autoren: Azathioprine therapy appears to be more effective than placebo for maintenance of remission in ulcerative colitis. Azathioprine or 6-mercaptopurine may be effective as maintenance therapy for patients who have failed or cannot tolerate mesalazine or sulfasalazine and for patients who require repeated courses of steroids. More research is needed to evaluate superiority over standard maintenance therapy, especially in the light of a potential for adverse events from azathioprine. This review updates the existing review of azathioprine and 6-mercaptopurine for maintenance of remission in ulcerative colitis which was published in the Cochrane Library (September 2012). 5. Kommentare zum Review • Da 6-mercaptopurine in DE nicht zugelassen ist, wurden die Ergebnisse fokussiert für Azathioprine dargestellt.
Sherlock ME et al., 2015 [24]. Oral budesonide for induction of remission in ulcerative colitis.	1. Fragestellung The primary objective was to evaluate the efficacy and safety of oral budesonide for the induction of remission in ulcerative colitis.
	2. Methodik Population: Patients with active UC Intervention / Komparator: oral budesonide versus a control, which could be either a placebo or an active agent such as a traditional corticosteroid or 5-ASA product. Endpunkte: • Primary outcome: induction of remission of active ulcerative colitis. Clinical remission was defined by the primary studies and was expressed as the percentage of patients randomised (intention- to-treat analysis).

	• Secondary outcomes: 1. clinical, endoscopic and histologic improvement; 2. endoscopic mucosal healing; 3. change in disease activity index score; 4. quality of life; 5. hospital admissions; 6. the need for intravenous corticosteroids; 7. surgery; 8. adverse events; and 9. study withdrawal Recherche: MEDLINE, EMBASE, CENTRAL, and the Cochrane IBD Group Specialised Register from inception to April 2015. Also search of reference lists of articles, conference proceedings and ClinicalTrials.gov. Anzahl eingeschlossene Studien/Patienten (Gesamt): Six studies (1808 participants) were included. Qualitätsbewertung der Studien: Cochrane risk of bias tool / GRADE
	3. Ergebnisdarstellung Qualität der Studien: Four studies were rated as low risk of bias and two studies had an unclear risk of bias A pooled analysis of three studies (900 participants) showed that budesonide-MMX® 9 mg was significantly superior to placebo for inducing remission (combined clinical and endoscopic remission) at 8 weeks. Fifteen per cent (71/462) of budesonide-MMX® 9 mg patients achieved remission compared to 7% (30/438) of placebo patients (RR 2.25, 95% CI 1.50 to 3.39). A GRADE analysis indicated that the overall quality of the evidence supporting this outcome was moderate due to sparse data (101 events). A subgroup analysis by concurrent mesalamine use suggests higher efficacy in the 442 patients who were not considered to be mesalamine-refractory (RR 2.89, 95%CI 1.59 to 5.25). A subgroup analysis by disease location suggests budesonide is most effective in patients with left-sided disease (RR 2.98, 95% CI 1.56 to 5.67; 289 patients). A small pilot study reported no statistically significant difference in endoscopic remission between budesonide and prednisolone. GRADE indicated that the overall quality of the evidence supporting this outcome was very low due to unclear risk of bias and very sparse data (10 events). Standard oral budesonide was significantly less likely to induce clinical remission than oral mesalamine after 8 weeks of therapy (RR 0.72, 95% CI 0.57 to 0.91; 1 study, 343 patients). A GRADE analysis indicated that the overall quality of the evidence supporting this outcome was moderate due to sparse data (161 events). Another study found no difference in remission rates between budesonide-MMX® 9 mg and mesalamine (RR 1.48, 95% CI 0.81 to 2.71; 247 patients). GRADE indicated that the overall quality of the evidence supporting this outcome was low due to very sparse data (37 events). One study found no difference in remission rates between budesonide-MMX® 9mg and standard budesonide. A GRADE analysis indicated that the overall quality of the evidence supporting this outcome was low due to very sparse data (32 events).

	Suppression of plasma cortisol was more common in prednisolone-treated patients (RR 0.02, 95% CI 0.0 to 0.33). While budesonide does appear to suppress morning cortisol to some extent, mean morning cortisol values remained within the normal range in 2 large studies (n = 899) and there was no difference in glucocorticoid-related side-effects across different treatment groups. Further, study withdrawal due to adverse events was not more common in budesonide compared with placebo treated patients. Common adverse events included worsening ulcerative colitis, headache, pyrexia, insomnia, backpain, nausea, abdominal pain, diarrhoea, flatulence and nasopharyngitis.
	4. Fazit der Autoren: Moderate quality evidence to supports the use of oral budesonide-MMX® at a 9 mg daily dose for induction of remission in active ulcerative colitis, particularly in patients with left-sided colitis. Budesonide-MMX® 9 mg daily is effective for induction of remission in the presence or absence of concurrent 5-ASA therapy. Further, budesonide-MMX® appears to be safe, and does not lead to significant impairment of adrenocorticoid function compared to placebo. Moderate quality evidence from a single study suggests that mesalamine may be superior to standard budesonide for the treatment of active ulcerative colitis. Low quality evidence from one study found no difference in remission rates between budesonide MMX® and mesalamine. Very low quality evidence from one small study showed no difference in endoscopic remission rates between standard budesonide and prednisolone. Low quality evidence from one study showed no difference in remission rates between budesonide-MMX® and standard budesonide. Adequately powered studies are needed to allow conclusions regarding the comparative efficacy and safety of budesonide versus prednisolone, budesonide-MMX® versus standard budesonide and budesonide versus mesalamine.
LeBlanc K et al., 2015 [16]. The impact of biological interventions for ulcerative colitis on health-related quality of life	5. Fragestellung To assess the impact of biologic therapy on the HRQL of UC patients
	6. Methodik **Population:** Adult patients with UC (active or quiescent) defined by a combination of clinical, radiographic, endoscopic and histological criteria were considered for inclusion. **Intervention:** biologics including but are not limited to infliximab, adalimumab, certolizumab pegol, golimumab, vedolizumab, natalizumab, interferon alpha and rituximab. **Komparator:** k.A. **Endpunkte:** proportion of patients achieving improvement in HRQL as defined by the studies (e.g. validated HRQL instruments such as the IBDQ, SF-36 or EQ-5D) expressed as a percentage of patients randomized or absolute counts; Changes in mean difference in quality of life scores

	Recherche: in Medline, Embase, CENTRAL, DDW abstracts of randomized controlled and controlled clinical trials up tp 09/2015 **Anzahl eingeschlossene Studien**/Patienten (Gesamt): 9 (n=dddd) **Qualitätsbewertung der Studien**: Cochrane Risk of Bias Tool; GRADE for assessing the overall quality of evidence for primary and secondary outcomes
	7. Ergebnisdarstellung *Included studies* • interferon-ß-1a: 1 trial (Pena-Rossi 2008), • rituximab: 1 trial (Leiper 2011), • infliximab: 2 studies (Probert 2003; Rutgeerts 2005), • adalimumab: 3 trials (Reinisch 2011; Sandborn 2012; Suzuki 2014), • golimumab: 1 trial (Sandborn 2014), • vedolizumab: 1 study (Feagan 2013). *Risk of bias* • 8 studies with low risk of bias • 1 study with high risk of bias (Leiper 2011) *Effects of interventions* **Interferon-ß-1a versus placebo** → nicht relevant **Rituximab versus placebo** → nicht relevant **Infliximab versus placebo** → superiority of IFX • statistically significant improvement in the mean IBDQ score among infliximab patients compared to placebo at week 6 or 8 o 5 mg/kg: MD18.58, 95% CI 13.19 to 23.97; high quality of evidence) o 10mg/kg: MD 15.00, 95% CI 9.46 to 20.54, high quality of evidence • Improved IBDQ (≥ 16 points or ≥ 32 points from baseline) at week 8 o ≥ 16 points. RR1.39, 95%CI 1.21 to 1.60, high quality of evidence o ≥ 32 points: RR 1.67, 95% CI 1.37 to 2.03, moderate quality of evidence • Improved SF-36 physical component summary score (PCS) (≥ 3 or ≥ 5 points from baseline) o ≥ 3 points: RR 1.46, 95% CI 1.23 to 1.72, moderate quality o ≥ 5 points: RR 1.51, 95% CI 1.23 to 1.85, moderate quality • Improved SF-36 mental component summary score (MCS) (> 3 or > 5 points from baseline)

	o ≥ 3 points: RR 1.47, 95% CI 1.21, moderate quality o ≥ 5 points RR 1.44, 95% CI 1.16 to 1.79, moderate quality **Adalimumab versus placebo** → superiority of ADA • Improvement in IBDQ at week 8 or 52 o Week 8: Statistically significant difference (MD 9.00, 95% CI 2.65 to 15.35). quality of evidence: moderate quality o Week 52: Statistically significant difference (MD 8.00, 95% CI 0.68 to 15.32). quality of evidence: moderate quality • Improved IBDQ (≥ 16 points from baseline) at week 8 or 52: o Week 8: RR 1.23, 95% CI 1.06 to 1.43), moderate quality o Week 52: RR 1.73, 95% CI 1.28 to 2.34, moderate quality of evidence **Golimumab versus placebo** → superiority of GOL • Improvement in IBDQ at week 6 o 200mg/100mg: statistically significant difference (MD 12.20, 95% CI 6.52, 17.88;504 patients), high quality of evidence o 400 mg/200 mg (MD 12.10, 95% CI 6.40 to 17.80; 508 patients), high quality of evidence **Vedolizumab versus placebo** → superiority of VEDO • Improved IBDQ (≥ 16 points from baseline) at week 6 or 52 o Week 6: RR 1.62, 95% CI 1.15 to 2.27, moderate qualtiy o Week 52: RR 1.67, 95% CI 1.31 to 2.12, moderate quality • SF-36 PCS at week 6 or 52 o Week 6: MD 2.60, 95% CI 1.22 to 3.98, moderate qualtiy o Week 52: vedolizumab every 4w: MD 2.60, 95% CI 1.22 to 3.98; Vedolizumab every 8w: (MD 3.40, 95% CI 1.56 to 5.24; moderate quality • Improved SF-36 MCS at week six and 52. o Week 6: MD 4.60, 95% CI 2.69 to 6.51, moderate quality o Week 52: MD4.80, 95%CI 2.33 to 7.27, moderate quality **TNF-alpha antagonists versus placebo** → superiority of TNF-alpha antagonists o The pooled analysis revealed a statistically significant improvement in the mean IBDQ scores favouring TNF-alpha antagonist treatment (MD 13.71, 95% CI 10.40 to 17.01), moderate quality of evidence o There was a statistically significant difference in the proportion of patients who had improved IBDQ scores (RR 1.32, 95% CI 1.19 to 1.46), high quality of evidence
	8. Anmerkungen/Fazit der Autoren These results suggest that biologics have the potential to improveHRQL in UC patients. High quality evidence suggests that infliximab provides a clinically

	meaningful improvement in HRQL inUC patients receiving induction therapy. Moderate quality evidence suggests that vedolizumab provides a clinically meaningful improvement in HRQL inUC patients receiving maintenance therapy. These findings are important since there is a paucity of effective drugs for the treatment of UC that have the potential to both decrease disease activity and improve HRQL. More research is needed to assess the long-term effect of biologic therapy on HRQL in patients with UC. More research is needed to assess the impact of golimumab and adalimumab on HRQL in UC patients. Trials involving direct head to head comparisons of biologics would help determine which biologics provide optimum benefit for HRQL. 9. *Kommentare zum Review* Alle eingeschlossenen Studien zu TNF-alpha-Antagonisten oder Vedolizumab untersuchten Patienten mit aktiver moderater-schwerer CU und inadäquter Response oder Intoleranz ggü. Kortikosteroiden, Immunmodulatoren oder TNF-a-Antagonisten (letzteres gilt nur für VEDO)
Bickston SJ et al., 2014 [2]. Vedolizumab for induction and maintenance of remission in ulcerative colitis Weitere SR zu Vedolizumab vs Placebo (non-Cochrane Reviews): **Wang MC et al., 2014 [28].** **Kawalec P et al., 2014 [14].** **Jin Y et al., 2015 [13].** **Lin L et al., 2015 [17].**	1. Fragestellung The primary objectives were to determine the efficacy and safety of vedolizumab used for induction and maintenance of remission in ulcerative colitis.
	2. Methodik **Population:** Adult patients (>18 y) with active or quiescent ulcerative colitis as defined by conventional clinical, histological or endoscopic criteria **Intervention**: Vedolizumab **Komparator:** Placebo or a control medication **Endpunkte**: clinical remission and relapse, clinical response, endoscopic remission, endoscopic response, quality of life, adverse events, serious adverse events, withdrawal due to adverse events **Recherche**: in Medline, Embase, CENTRAL bis 06/2014 **Anzahl eingeschlossene Studien** / Patienten: 4 / n=606 **Qualitätsbewertung der Studien**: Cochrane risk of bias tool. GRADE for assessing overall quality of evidence for outcomes
	3. Ergebnisdarstellung 4 included studies with low risk of bias *Vedolizumab versus placebo in ulcerative colitis* Efficacy • statistically significant difference in failure of clinical remission favouring vedolizumab over placebo (RR 0.86, 95% CI 0.80 to 0.91), high quality of evidence • statistically significant difference in failure of clinical response favouring vedolizumab over placebo (RR 0.68, 95% CI 0.59 to 0.78), moderate quality • statistically significant difference in failure of endoscopic remission

	favouring vedolizumab over placebo (RR 0.82, 95% CI 0.75 to 0.91), high quality of evidence • no statistically significant difference in failure to achieve endoscopic response was found between vedolizumab and placebo patients (RR 1.00; 95% CI 0.62 to 1.61) • statistically significant difference in clinical relapse rates at week 52 favouring vedolizumab over placebo (RR 0.67, 95% CI 0.59 to 0.77), moderate quality of evidence • statistically significant difference in endoscopic relapse rates at week 52 favouring vedolizumab over placebo (RR 0.58, 95% CI 0.49 to 0.68), moderate quality of evidence Safety • no statistically significant difference in the incidence of adverse events between vedolizumab and placebo patients (RR 0.99, 95% CI 0.93 to 1.07), high quality of evidence • statistically significant difference in withdrawal due to adverse events favouring vedolizumab over placebo RR 0.55, 95% CI 0.35 to 0.87) • no statistically significant difference in the incidence of serious adverse events between vedolizumab and placebo patients (RR 1.02, 95% CI 0.73 to 1.42), moderate qualtiy of evidence
	4. Anmerkungen/Fazit der Autoren Moderate to high quality data from four studies shows that vedolizumab is superior to placebo for induction of clinical remission and response and endoscopic remission in patients with moderate to severely active ulcerative colitis and prevention of relapse in patients with quiescent ulcerative colitis. Moderate quality data from one study suggests that vedolizumab is superior to placebo for prevention of relapse in patients with quiescent ulcerative colitis. Adverse events appear to be similar to placebo. Future trials are needed to define the optimal dose, frequency of administration and long-term efficacy and safety of vedolizumab used for induction and maintenance therapy of ulcerative colitis. Vedolizumab should be compared to other currently approved therapies for ulcerative colitis in these trials. 5. *Kommentare zum Review* Heterogene Patientenpopulation: milde bis schwere CU, unterschiedlicher Vorbehandlungsstatus bzw. keine Angaben zur Vortherapie Weitere systematische Reviews (Kawalec, 2014 [14]; Lin, 2015 [17]; Jin, 2015 [13]; Wang, 2014 [28]) erzielen gleiche Schlussfolgerung zu Vedolizumab vs Placebo.

Systematische Reviews

Archer R et al., 2016 [1]. Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy (including a review of TA140 and TA262): clinical effectiveness systematic review and economic model Vgl. weitere NMA zum anti-TNFa-Vergleich: **Kawalec P et al., 2016 [15].** **Stidham RW et al., 2014 [25].** **Galvan-Banqueri M et al., 2015 [8].** **Mao EJ et al., 2017 [20].** Weitere Meta-Analysen zu anti-TNF-alpha: <u>Anti-TNF-alpha vs. Placebo:</u> **Lopez A et al., 2015 [18].** <u>Adalimumab vs Placebo:</u> **Zhang ZM et al., 2016 [29].** **Chen X et al.,**	1. Fragestellung To assess the clinical effectiveness and cost-effectiveness of infliximab (IFX), adalimumab (ADA) and golimumab (GOL) for the treatment of patients with moderately to severely active UC after the failure of conventional therapy. 2. Methodik - NMA **Population:** • Adults aged ≥ 18 years with moderately to severely active UC who have had an inadequate response to conventional therapy including corticosteroids and mercaptopurine or AZA, or who are intolerant to, or have medical contraindications against, such therapies. As referred to in the final NICE scope severity of disease in adults would be defined according to the modified Truelove and Witts' severity index. • Children and adolescents aged 6–17 years (inclusive) with severely active UC, who have had an inadequate response to conventional therapy including corticosteroids and mercaptopurine or AZA, or who are intolerant to, or have medical contraindications against, such therapies. As described in NICE Clinical Guideline 166,1 severity of UC in children and adolescents was to be assessed using the PUCAI **Intervention:** • in adults: ADA, IFX, GOL. • in children and adolescents: IFX. Biosimilar versions of IFX (Remsima and Inflectra) are also licensed for the same indications and are considered as part of the evidence base for IFX within this assessment report **Komparator:** • interventions are compared against each other. • Other relevant comparators include standard clinical management options, which could include a combination of aminosalicylates (sulfasalazine, mesalazine, balsalazide or olsalazine), corticosteroids (beclomethasone, budesonide, hydrocortisone or prednisolone), thiopurines (mercaptopurine or AZA), calcineurin inhibitors or elective surgical intervention. Emergency surgical intervention is not considered as a comparator in this assessmt. **Endpunkte** • mortality • measures of disease activity • rates of and duration of response, relapse and remission • rates of hospitalisation • rates of surgical intervention (both elective and emergency) • time to surgical intervention (both elective and emergency) • AEs of treatment (including leakage and infections following surgery) • HRQoL. Data relating to mucosal healing were not considered eligible for this assessment **Recherche:** • in MEDLINE, EMBASE, CINAHL, CDSR, CCRT, DARE, the HTA database and NHS Economic Evaluation Database; ISI Web of Science Citation Index, and the Conference Proceedings Citation

2016 [5]. Golimumab vs Placebo: **CADTH, 2014 [4].** **Kawalec P et al., 2014 [14].**	Index-Science and BIOSIS Previews. • FDA website and EMA website were also searched as were research registers, conference proceedings and key journals. • to December 2013 **Anzahl eingeschlossene Studien**:10 RCT **Qualitätsbewertung der Studien:** Cochrane risk-of-bias tool Protocol for this review is registered with PROSPERO (CRD42013006883). Funding was provided by the HTA programme of the National Institute for Health Research.
	3. Ergebnisdarstellung *Study characeristics* 9 trials related to adults, 1 trial related to paediatric population. Adults (9 trials) • 4 RCT on IFX o ACT1 (Rutgeerts et al. 2005, NCT00096655) o ACT2 (Rutgeerts et al. 2005, NCT00036439) o Probert et al. 2003 o UC-SUCCESS (Panacionne et al. 2014, NCT00537316) Plus ACT1-/ ACT2- extension studies (Reinisch et al. 2012) • 3 RCT on ADA o ULTRA1 (Reinisch et al. 2011, NCT00385736) o ULTRA2 (Sandborn et al. 2012, NCT00408629) o Suzuki et al. 2014 (NCT00853099) Plus ULTRA3 (Reinisch et al., 2013)= extension of ULTRA1+2 • 2 RCT on GOL o PURSUIT-SC (Sandborn et al. 2014a, NCT00487539) o PURSUIT-Maintenance (Sandborn et al. 2014b, NCT00488631), Comparator in the included trials was PBO, with the exception of UC-SUCCESS which assessed the use of IFX against active comparators of AZA and combination IFX/AZA. No head-to-head RCTs comparing interventions of interest against each other were identified for adults. Paediatric population • 1 RCT on IFX: Comparison of 2 different IFX-Maintenance regimens (Hyams et al. 2012; NCT00336492) *risks of bias assessment:* • Only 3 RCTs could be considered as being at overall low risk of bias (as

	allocation concealment, blinded outcome assessment and completeness of outcome data were all judged as low risk); • 6 trials were high risk of (attrition) bias • It should be noted that one of the maintenance trials (PURSUIT-Maintenance) rerandomised patients who had previously responded to GOL induction therapy in 2 previous trials; the extent of this potential bias on patient outcomes is unclear *Results* **Direct comparision: Adults** Clinical response/ remission • patients receiving IFX, ADA or GOL were more likely to achieve clinical response and remission at induction and maintenance time points than patients receiving PBO. Colectomy • ADA vs placebo: o colectomies to week 8 were lower in the 160 mg/80 mg of ADA group than PBO (1.4% vs. 3.6%; p-value not reported; elective or emergency not reported). o Colectomy rates were very slightly lower through week 52 in the ADA group (4%) vs. PBO (4.9%) (p-value not reported; elective or emergency not reported). • GOL vs placebo: Limited data available: only 2–3% of GOL induction responders rerandomised to 50 mg or 100 mg of GOL in PURSUIT-Maintenance48 received colectomy at the end of maintenance • IFX vs placebo: o Colectomy and ostomy rates through week 54 of ACT1 were both slightly lower in the 5 mg/kg of IFX group (5.8% and 2.5%, respectively) than in the PBO group (7.4% and 4.1% respectively) (p-values not reported). o One patient in each case from the PBO arm was reported as having the outcomes of colectomy and an ostomy (0.7% and 0.7%) through week 54 of ACT2, while no patients in the 5 mg/kg IFX group underwent colectomy or ostomy. o Limited details were available from the Probert et al trial to the effect that a single patient in the PBO arm received a colectomy during the intervention period. Hospitalisation • Adalimumab (ULTRA1 +ULTRA2): all-cause hospitalisation incidence rate was lower for ADA than PBO (p=0.047), as was the UC-related hospitalisation incidence rate (p=0.002), with a relative risk for UC-related hospitalisation of 0.48 for ADA versus PBO (p<0.001) • Infliximab (ACT1 and ACT2): hospitalisations through week 54 were reported to be lower for the 5 mg/kg of IFX group than PBO (ACT1,

p=0.061; ACT2, p=0.009).

Health-related quality of life

- ADA vs. Placebo
  - Induction: n.s.
  - Maintenance: week 52 IBDQ scores were higher in ADA group than PBO, indicating more favourable HRQoL in the ADA group (27 vs. 19; p<0.05). A greater proportion of patients experienced an increase in IBDQ of ≥ 16 points from baseline by week 52 in the ADA group than PBO (26.2% vs. 16.3%; p<0.05).
- GOL vs Placebo (Induction):
  - In both Phase II and Phase III of the PURSUIT-SC GOL trial, patients in the 200 mg/100 mg of GOL induction arms reported a greater change in IBDQ from baseline to week 6 than the patients of PBO groups [Phase II, mean 24.9 vs. 14.8 (p-value n.s.); Phase III mean 27.0 vs. 14.8; p<0.0001].
  - Greater proportions of patients in each GOL group achieved 'any improvement' to 'clinically meaningful improvement' in IBDQ (51.1% vs. 35.2%; p<0.001), physical component summary (41.0% vs. 31.6%; p=0.01) and mental component summary scores (42.7% vs. 28.5%; p<0.001) at w6.
- IFX (induction)
  - ACT1 trial: greater changes from baseline in SF-36 physical + mental component summary scores to week 8 for 5 mg/kg IFX than for PBO (both p<0.05).
  - ACT1 +ACT2 trials combined: Stat. sign. improvements in IBDQ and SF-36 components with 5 mg/kg IFX compared with PBO to week 8
  - Greater improvements in IBDQ and EQ-5D from baseline to week 6 in the IFX group than PBO in Probert et al.(p-value not reported).
  - greatest changes from baseline to week 16 in both IBDQ and SF-36 physical function were observed in the IFX/AZA combination treatment arm (p < 0.05 vs. AZA, p < 0.05 vs. IFX for both outcomes).

Safety

- The main safety issues highlighted in the RCT evidence appeared to be generally consistent with those previously discussed in the respective Summary of Product Characteristics (including serious infections, malignancies and administration site reactions).
- Deaths occurring during and after the study period were described in some trials evaluating GOL (PURSUIT-Maintenance) +IFX (ACT1+2) of which infection or malignancy were most commonly implicated.
- This underlines the importance of monitoring and treating serious infections and malignancies in patients receiving immunosuppressive

	treatment **Direct comparision: children and adolescents aged 6-17 years *(siehe Methodik*)** *Maintenance with 5 mg/kg of IFX every 8 weeks vs 5 mg/kg of IFX every 12 weeks (*Hyams et al. trial) Measures of disease activity • At week 8, the median reductions in partial Mayo scores were 4 points for both the 5 mg/kg of IFX every 8 weeks group and 5 mg/kg of IFX every 12 weeks group. • By week 30, the median reduction in partial Mayo score was approximately 3 points for the every 8 weeks group and 1 point for the every 12 weeks group. Mortality: No deaths were reported Rates of hospitalisation: No hospitalisation-related outcome data were reported Rates of surgical intervention (both elective and emergency) • 1 of 22 patients (4.5%) in the 5 mg/kg of IFX every 8 weeks group required colectomy through week 54 as compared with 2 out of 23 (8.7%) patients in the 5 mg/kg of IFX every 12 weeks treatment arm. • Colectomy rates during maintenance: The between-group at week 54 was not significant [RR = 0.52 (random effects), 95% CI 0.05 to 5.36; p = 0.59] Time to surgical intervention (both elective and emergency):No data reported Health-related quality of life: No data . Adverse events of treatment (including leakage and infections following surgery) • Discontinuations due to AE: Through week 54, discontinuations due to at least one AE were higher in the 5 mg/kg of IFX every 12 weeks group than the every 8 weeks frequency group (6/23, 26.1% vs. 3/22, 13.6%) • Number of patients experiencing one or more AE: All patients in both treatment arms reported at least one AE (22/22, 100% vs. 23/23, 100%) • Number of patients experiencing 1 or more serious AE: The numbers of patients reporting at least 1 SAE were similar between the 5 mg/kg of IFX every 12 weeks (5/23, 21.7%) and every 8 weeks (4/22, 18.2%) treatment arms. • Infections The occurrence of infections was comparable between 5 mg/kg of IFX every 8 weeks (13/22, 59.1%) and every 12 weeks (14/23, 60.9%) • Serious infections No cases of serious infection were • Reactivation of tuberculosis No cases were reported. • Reactivation of hepatitis B No cases were reported. • Administration reactions (injection site reactions/infusion reactions/serious allergic reactions) The number of patients experiencing infusion reactions were similar between treatment groups (4/22, 18.2% vs. 3/23, 13.0%).

Network meta-analysis (anti-TNF-alpha naive population)

Treatment effects were estimated using NMAs of clinical response and remission as defined by the complete Mayo score.

Base case: Clinical response in the induction phase

Probabilities of treatment rankings for this analysis: ...The model fitted the data reasonably well, with the total residual deviance, 18.16, being close to the total number of data points included in the analysis, 20. The between-study SD was estimated to be 0.12 [95% credible interval (CrI) 0.01 to 0.50], which implies mild to moderate heterogeneity between studies in treatment effects.

- All treatments were associated with beneficial treatment effects relative to PBO with the greatest effect being associated with IFX.
- All treatment effects were stat. significant at a conventional 5% level.
- IFX was associated with the greatest effect –0.92 (95% CrI –1.27 to –0.56) and was most likely to be the most effective treatment (probability of being the best = 0.93).

Table 13 presents the probabilities of achieving each of the following categories: no response, response and remission for the base-case induction phase.

- IFX was associated with the highest probability of moving from no response to response and no response to remission respectively.
- The effects of ADA and GOL on each transition probability were comparable

TABLE 13 Base case: probabilities of being in each category for the induction phase

	No response			Response			Remission		
Treatment	Mean	Median	95% CrI	Mean	Median	95% CrI	Mean	Median	95% CrI
PBO	0.640	0.641	0.568 to 0.706	0.260	0.260	0.214 to 0.308	0.099	0.097	0.062 to 0.147
ADA	0.485	0.485	0.330 to 0.642	0.324	0.327	0.247 to 0.385	0.190	0.185	0.092 to 0.322
GOL	0.448	0.447	0.262 to 0.645	0.333	0.337	0.244 to 0.393	0.219	0.212	0.094 to 0.390
IFX	0.292	0.289	0.170 to 0.438	0.351	0.353	0.280 to 0.412	0.356	0.352	0.209 to 0.523

Base case: Clinical response in maintenance phase 8-32 week

1. Patients starting in response

Probabilities of treatment rankings for this analysis:.. There was some suggestion that the model did not represent the data well with the total residual deviance, 11.73, being smaller than would be expected given the total number of data points included in the analysis, 18. The probability of observing a value < 11.73 was 0.139, which means that it could be a chance event. All four studies had smaller residual deviances than expected (ULTRA2: deviance 3.0 compared with 4 data points; ACT1: deviance 2.1 compared with 4 data points; ACT2: deviance 2.66 compared with 4 data points; and PURSUIT: deviance 4.0 compared with 6 data points). The between-study SD was estimated to be 0.17 (95% CrI 0.01 to 0.61), which implies mild to moderate heterogeneity between studies in treatment effects.

- All treatments were associated with beneficial treatment effects relative to PBO with the greatest effect being associated with 100 mg of GOL.
- none of the treatment effects were stat. signif. at a conventional 5% level.
- 100 mg of GOL was associated with the greatest effect –0.42 (95% CrI –0.78 to 0.29) and was most likely to be the most effective treatment (probability of being the best = 0.47).

Table 14 presents the probabilities of achieving each of the following categories: no response, response and remission for the base-case maintenance phase at 8–32 weeks for patients starting in response.

- 100 mg of GOL was associated with the highest probability of moving from response to remission and staying in the response state at 8–32 weeks.
- GOL was associated with the smallest probability of moving from response to no response.
- The probabilities of staying in response were comparable among all treatments at 8–32 w.

TABLE 14 Base case: probabilities of being in each category for the maintenance phase at 8–32 weeks for patients starting in response

	No response			Response			Remission		
Treatment	Mean	Median	95% CrI	Mean	Median	95% CrI	Mean	Median	95% CrI
PBO	0.524	0.525	0.426 to 0.622	0.270	0.270	0.198 to 0.341	0.206	0.202	0.117 to 0.311
ADA	0.512	0.512	0.230 to 0.782	0.261	0.267	0.140 to 0.354	0.227	0.211	0.055 to 0.493
50 mg of GOL	0.403	0.399	0.173 to 0.660	0.283	0.285	0.176 to 0.374	0.313	0.303	0.108 to 0.588
100 mg of GOL	0.368	0.360	0.149 to 0.619	0.285	0.288	0.176 to 0.377	0.347	0.338	0.129 to 0.623
IFX	0.432	0.430	0.220 to 0.659	0.282	0.283	0.189 to 0.371	0.286	0.276	0.109 to 0.518

2. Patients starting in remission

Probabilities of treatment rankings for this analysis:.The model fitted the data well, with the total residual deviance, 18.20, being close to the total number of data points included in the analysis, 18. The between-study SD was estimated to be 0.18 (95%CrI 0.01 to 0.64), which implies mild to moderate heterogeneity between studies in treatment effects.

- All treatments except ADA were associated with beneficial treatment effects relative to PBO with the greatest effects being associated with 50 mg of GOL (–0.63, 95% CrI –1.36 to 0.11) and 100 mg of GOL (–0.61, 95% CrI –1.32 to 0.11).
- none of the treatment effects was statistically significant at a conventional 5% level.
- 50 mg and 100 mg of GOL was most likely to be the most effective treatments (probability of being the best = 0.47 and 0.42 respectively).

Table 15 presents the probabilities of achieving each of the following categories: no response, response and remission for the base-case maintenance phase at 8–32 weeks for patients starting in remission.

- 50 mg and 100 mg of GOL were associated with the highest probability of staying in remission and the smallest probability of moving from remission to response or remission no response at 8–32 weeks.

TABLE 15 Base case: probabilities of being in each category for the maintenance phase at 8–32 weeks for patients starting in remission

	No response			Response			Remission		
Treatment	Mean	Median	95% CrI	Mean	Median	95% CrI	Mean	Median	95% CrI
PBO	0.353	0.347	0.168 to 0.572	0.180	0.174	0.070 to 0.316	0.467	0.466	0.225 to 0.708
ADA	0.428	0.420	0.099 to 0.803	0.166	0.164	0.053 to 0.297	0.406	0.392	0.083 to 0.804
50 mg of GOL	0.177	0.152	0.027 to 0.457	0.136	0.131	0.028 to 0.283	0.687	0.708	0.321 to 0.933
100 mg of GOL	0.182	0.158	0.029 to 0.469	0.138	0.134	0.030 to 0.285	0.680	0.700	0.322 to 0.929
IFX	0.325	0.309	0.084 to 0.648	0.169	0.165	0.057 to 0.304	0.506	0.509	0.178 to 0.829

Base case: maintenance phase 32–52 weeks

1. Patients starting in response

Probabilities of treatment rankings for this analysis:…The model fitted the data reasonably well, with the total residual deviance, 12.88, being close to the total number of data points included in the analysis, 14. The between-study SD was estimated to be 0.21 (95% CrI 0.01 to 0.71), which implies mild to moderate heterogeneity between studies in treatment effects.

- All treatments except 100 mg of ADA and GOL were associated with beneficial treatment effects relative to PBO with the greatest effect being associated with 50 mg of GOL;
- none of the treatment effects was stat. sign. at a conventional 5% level.
- IFX was associated with the greatest effect –0.36 (95% CrI –1.33 to 0.62) and was most likely to be the most effective treatment (probability of being the best = 0.56).

Table 16 presents the probabilities of achieving each of the following categories: no response, response and remission for the base-case maintenance phase at 32–52 weeks for patients starting in response.

- IFX was associated with the highest probability of moving from response to remission and the smallest probability of moving from response to no response at 32–52 weeks.
- probabilities of staying in the response state were comparable among treatments at 32–52 weeks.

TABLE 16 Base case: probabilities of being in each category for the maintenance phase at 32–52 weeks for patients starting in response

	No response			Response			Remission		
Treatment	Mean	Median	95% CrI	Mean	Median	95% CrI	Mean	Median	95% CrI
PBO	0.338	0.319	0.066 to 0.711	0.370	0.378	0.122 to 0.604	0.292	0.259	0.027 to 0.717
ADA	0.450	0.440	0.063 to 0.889	0.327	0.340	0.067 to 0.562	0.223	0.167	0.005 to 0.716
50 mg of GOL	0.295	0.258	0.025 to 0.750	0.353	0.363	0.081 to 0.616	0.352	0.319	0.021 to 0.842
100 mg of GOL	0.410	0.393	0.055 to 0.852	0.342	0.353	0.083 to 0.581	0.248	0.199	0.009 to 0.741
IFX	0.250	0.205	0.013 to 0.716	0.341	0.353	0.065 to 0.621	0.409	0.385	0.029 to 0.892

2. Patients starting in remission

Probabilities of treatment rankings for this analysis:… The model fitted the data well, with the total residual deviance, 18.46, being close to the total number of data points included in the analysis, 18. The between-study SD was estimated to be 0.21 (95% CrI 0.01 to 0.72), which implies mild to moderate heterogeneity between studies in treatment effects.

- All treatments except 50 mg of GOL were associated with beneficial treatment effects relative to PBO with the greatest effect being associated with ADA.

- only the treatment effects of ADA were statistically significant at a conventional 5% level.
- ADA was associated with the greatest effect –1.04 (95% CrI –1.93 to –0.12) and was most likely to be the most effective treatment (probability of being the best = 0.84).

Table 17 presents the probabilities of achieving each of the following categories: no response, response and remission for the base-case maintenance phase at 32–52 weeks for patients starting in remission.

- ADA was associated with the highest probability of staying in remission and the smallest probability of moving from remission to response or from remission to no response at 32–52 weeks.

TABLE 17 Base case: probabilities of being in each category for the maintenance phase at 32–52 weeks for patients starting in remission

	No response			Response			Remission		
Treatment	Mean	Median	95% CrI	Mean	Median	95% CrI	Mean	Median	95% CrI
PBO	0.301	0.296	0.174 to 0.449	0.164	0.147	0.029 to 0.449	0.536	0.548	0.237 to 0.734
ADA	0.081	0.059	0.005 to 0.288	0.084	0.061	0.005 to 0.337	0.834	0.874	0.447 to 0.985
50 mg of GOL	0.329	0.314	0.080 to 0.664	0.155	0.141	0.024 to 0.415	0.515	0.523	0.135 to 0.851
100 mg of GOL	0.266	0.245	0.052 to 0.604	0.147	0.132	0.020 to 0.417	0.587	0.604	0.169 to 0.894
IFX	0.247	0.220	0.033 to 0.613	0.140	0.126	0.017 to 0.413	0.613	0.634	0.174 to 0.928

4. Anmerkungen/Fazit der Autoren

Evidence was identified to demonstrate that patients receiving IFX, ADA or GOL were more likely to achieve clinical response and remission at induction and maintenance time points than patients receiving PBO. Patients in the UC-SUCCESS trial who received combination treatment with IFX and AZA experienced the most favourable rates of steroid-free remission when compared with IFX and AZA treatment groups. Seven RCTs performed on adult populations contributed data on clinical response and remission at induction or maintenance time points to NMAs.

Based on the NMA, in the induction phase all treatments were associated with statistically significant beneficial effects relative to PBO, with the greatest effect being associated with IFX.

For patients classified as responders at the end of the induction phase, treatment effects were not statistically significant, although the greatest effect at 8–32 weeks was associated with 100 mg of GOL. At 32–52 weeks, only IFX and 50 mg of GOL were associated with beneficial effects on clinical response.

For patients classified as being in remission at the end of the induction phase, all treatments except for ADA were associated with beneficial treatment effects relative to PBO, with the greatest effect being associated with 50 mg and 100 mg of GOL, although the effects were not statistically significant at 8–32 weeks. At 32–52 weeks, all treatments except 50 mg of GOL were associated with beneficial

	treatment effects relative to PBO, with the greatest effect being associated with ADA (the only treatment with statistically significant effect). ADA was associated with the highest probability of staying in remission and the smallest probability of moving from remission to response and from remission to no response. *5. Kommentare zum Review* • indirekte Vergleiche beruhen nur auf placebo-kontrollierten Studien, es liegen keine Studien mit aktiven Vergleichen vor • zentrale Annahme der Konsistenz der Ergebnisse aus direkten und indirekter Evidenz kann aufgrund fehlender direkter Vergleiche nicht beurteilt werden • Überprüfung der zentralen Annahme der Ähnlichkeit: Patientencharakteristika und Design der Studien detailliert beschrieben und diskutiert • Sensitivitätsanalysen durchgeführt, um den Impact der verschiedenen Studien und Populationen auf die Ergebnisse zu bewerten • Placebo (=Brückenkomparator) zwischen den Studien aufgrund der verschiedenen Applikationsschemata der aktiven Medikamente unterschiedlich (i.v. / SC / unterschiedliche Häufigkeit der Anwendung); Placebo-Response der Patienten varierte zwischen den Studien → Eingeschränkte Aussagesicherheit der NMA Weitere Netzwerkmetaanalysen mit gleicher Fragestellung erzielen ähnliche Schlussfolgerungen: • Kawalec et al. 2016 [15]: No significant differences in efficacy in the maintenance phase between infliximab and golimumab or adalimumab were revealed. Infliximab proved to be more effective than adalimumab but of similar efficacy to that of golimumab in the induction phase. • Stidham et al. 2014 [25]: Compared to placebo, infliximab, adalimumab and golimumab are all effective for the induction and maintenance of remission in ulcerative colitis. However, network meta-analysis demonstrates that no single agent is clinically superior to the others and therefore, other factors such as cost, safety, route of administration and patient preference should dictate our choice of anti-TNF agents. A randomised comparative efficacy trial between infliximab and adalimumab in UC is of practical size and should be performed. • Galvan-Banqueri et al.2015 [8]: In relation to the clinical remission, in the induction and maintenance period, there are no statistically significant differences between the three anti-TNF drugs. In relation to the clinical response and mucosal healing, in the induction period, there are statistically significant differences between infliximab and adalimumab. In conclusion, infliximab, adalimumab and golimumab appear to be similarly effective therapeutic alternatives. Therefore, other considerations such as safety, tolerance and cost-effectiveness should be taken into account in order to select the most appropriate treatment. • Mao et al. 2017 [20] (Focus on hospitalisation and surgery; inclusion of

	ULTRA1+ULTRA2 [ADA] and ACT1+ACT2 [IFX]): Based on NMA no differences between infliximab and adalimumab were observed in the rates of UC-related hospitalisation. The rates of colectomy were also comparable for adalimumab compared to infliximab Eingeschlossene Studien in weiteren systematischen Reviews abgebildet: • Anti-TNF-alpha vs. Placebo: Lopez et al. 2015 [18] • Adalimumab vs Placebo: Zhang et al. 2016 [29]; Chen et al. 2016 [5] • Golimumab vs Placebo: CADTH 2014 [4], Kawalec et al. 2014 [14] Ergebnisse zur Lebensqualität im Vergleich zu Placebo: siehe auch LeBlanc K et al., 2015 [16] im Abschnitt Cochrane Reviews
Vickers AD et al., 2016 [27]. Systematic Review with Network Meta-Analysis: Comparative Efficacy of Biologics in the Treatment of Moderately to Severely Active Ulcerative Colitis Vgl. weitere NMA: **Danese S et al., 2014 [6].**	1. Fragestellung To compare the efficacy of biologics in adults with moderately-to-severely active UC, stratified by prior exposure to anti-tumour necrosis factor (anti-TNF) therapy.
	2. Methodik - NMA **Population:** patients with moderately to severely active UC **Intervention**: adalimumab, infliximab, golimumab, vedolizumab **Komparator**. k.A. **Endpunkte**: • efficacy outcome: clinical response, durable clinical response, clinical remission, durable clinical remission, Inflammatory Bowel Disease Questionnaire (IBDQ) response, steroid-free (SF) remission, mucosal healing and durable mucosal healing. • safety outcomes: surgery required, hospitalisations, overall adverse events (AEs), serious AEs, discontinuations due to AEs, severe AEs and fatal AEs. • quality-of-life outcomes (IBDQ, SF-36 Health Survey), **Recherche**: in MEDLINE, Embase and the Cochrane library from initiation until 11 February 2014 **Anzahl eingeschlossene Studien** / Patienten:8 RCTs **Qualitätsbewertung der Studien:** risk of bias assessment based on National NICE "specification for manufacturers"
	3. Ergebnisse *Included RCT* None of the studies were head-to-head comparisons of biological agents, so all results are based on indirect comparisons. No prospective non-RCTs with more than one treatment arm were identified for inclusion in the review • ADA vs placebo: 3 trials (ULTRA1, ULTRA2, Suzuki, 2014) • IFX vs placebo: 2 trials (ACT1, ACT2) • GOL vs placebo: 2 trials (PURSUIT-SC, PURSUIT-Maintenance) • VEDO vs placebo: 1 trial (GEMINI 1) *Risk of bias*

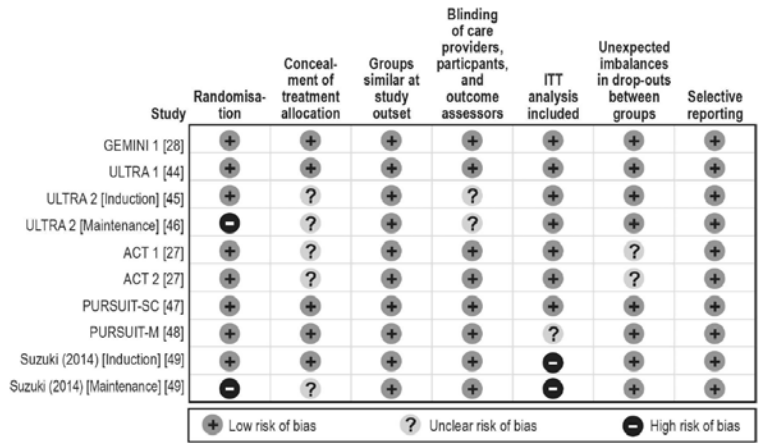

Fig 2. Risk of bias assessment of trials included in the mixed-treatment comparison. ITT, intent-to-treat.

5 studies with low or unclear risk of bias, 3 studies with high risk of bias

Effects of intervention in anti-TNF therapy-naïve subpopulation

Induction (7 trials)

- All biologics (vedolizumab, adalimumab, golimumab and infliximab) showed significantly better clinical response, clinical remission and mucosal healing than placebo during the induction phase (Fig.3)

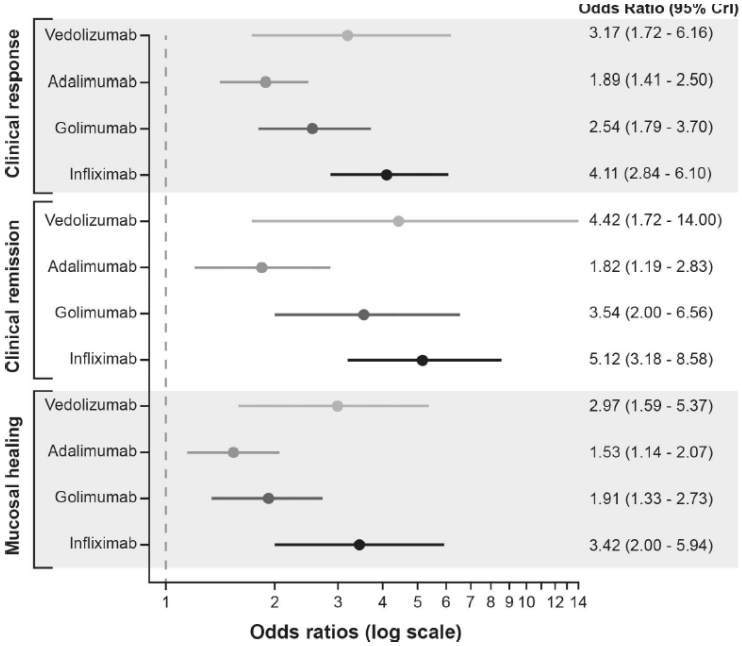

Fig 3. Forest plot of the odds ratios for biologics vs. placebo for anti-TNF therapy-naïve patients in induction studies. CrI, credible interval; TNF, tumour necrosis factor. Note: Adalimumab induction dose: 160 mg followed by 80 mg; vedolizumab induction dose: 300 mg; golimumab induction dose: 200 mg subcutaneous at week 0, followed by 100 mg at week 2 and then 100 mg every 4 weeks; infliximab induction dose: 5 mg/kg intravenously at week 0, followed by 5 mg/kg at 2 and 6 weeks.

- Infliximab demonstrated a significant improvement over adalimumab in
  - clinical response (OR [95% CrI], 2.19 [1.35–3.55]),
  - clinical remission (OR [95% CrI], 2.81 [1.49–5.49]), and
  - mucosal healing (OR [95% CrI], 2.23 [1.21–4.14])
- There was no evidence to suggest differences between infliximab and vedolizumab, between infliximab and golimumab, or between labelled

doses of the other licensed treatments (vedolizumab, adalimumab, and golimumab) for clinical response, clinical remission, or mucosal healing.

- Vedolizumab showed significantly better results for discontinuation due to AEs than adalimumab (0/130 patients vs. 11/220 patients, respectively, OR [95% CrI], 0.00 [0.00– 0.19]); however, the results were from a smaller network of evidence.

Maintenance (5 trials)

In 2 of the 5 maintenance studies (PURSUIT-M and GEMINI 1), only patients who achieved clinical response at induction were eligible and were rerandomised to placebo or active treatment for maintenance therapy. The maintenance analysis presented includes the ULTRA 2, ACT 1, and Suzuki et al, which did not rerandomise after induction.

- Vedolizumab and golimumab both showed significantly better durable clinical response than placebo during the maintenance phase (Fig 5).
- All biologics, except infliximab, showed significantly better clinical remission at maintenance than placebo. (Fig 5).
- Only vedolizumab showed significantly better mucosal healing at maintenance than placebo (OR [95% CrI], 4.79 [2.33– 9.93]). (Fig 5).

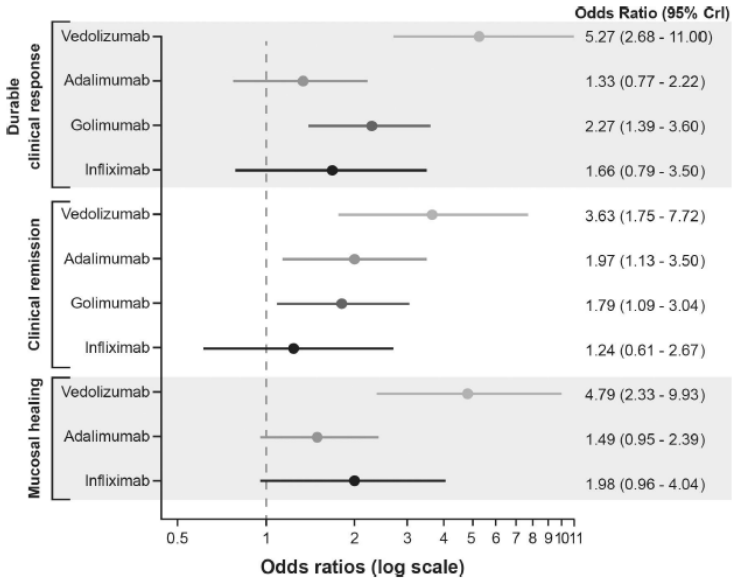

Fig 5. Forest plot of the odds ratios for biologics vs. placebo for anti-TNF therapy-naïve patients in maintenance studies. CrI, credible interval; TNF, tumour necrosis factor. Note: Adalimumab maintenance dose: 40 mg every other week; vedolizumab maintenance dose: 300 mg every 8 weeks; golimumab maintenance dose: 100 mg every 4 weeks; infliximab maintenance dose: 5 mg/kg intravenously every 8 weeks.

- vedolizumab showed significantly better durable clinical response than
  - adalimumab (OR [95% CrI], 3.96 [1.67–9.84]),
  - infliximab (OR [95% CrI], 3.18 [1.14–9.20]), and
  - golimumab (OR [95% CrI], 2.33 [1.04–5.41]) (Fig 6).
- Vedolizumab showed at maintenance:
  - a significant improvement in clinical remission over infliximab (OR [95% CrI], 2.93 [1.03–8.28]) and
  - significant improvement in mucosal healing over adalimumab (OR [95% CrI], 3.21 [1.33– 7.35]) at maintenance. (Fig 6).

- Vedolizumab (3/79 patients) showed significantly better results for discontinuation due to AEs than
    - adalimumab (22/177 patients, OR [95% CrI], 0.14 [0.02–0.67]),
    - golimumab (14/154 patients, OR [95% CrI], 0.21 [0.03–0.99]).

A) Durable Clinical Response

Vedolizumab			
OR, 3.18 (95% CrI, 1.14-9.20)	Infliximab		
OR, 2.33 (95% CrI, 1.04-5.41)	OR, 0.73 (95% CrI, 0.31-1.77)	Golimumab	
OR, 3.96 (95% CrI, 1.67-9.84)	OR, 1.24 (95% CrI, 0.51-3.15)	OR, 1.69 (95% CrI, 0.85-3.70)	Adalimumab

B) Clinical Remission

Vedolizumab			
OR, 2.93 (95% CrI, 1.03-8.28)	Infliximab		
OR, 2.03 (95% CrI, 0.84-5.05)	OR, 0.69 (95% CrI, 0.29-1.77)	Golimumab	
OR, 1.81 (95% CrI, 0.74-4.90)	OR, 0.63 (95% CrI, 0.24-1.63)	OR, 0.90 (95% CrI, 0.43-1.98)	Adalimumab

C) Mucosal Healing

Vedolizumab			
OR, 2.43 (95% CrI, 0.87-6.66)	Infliximab		
–	–	Golimumab	
OR, 3.21 (95% CrI, 1.33-7.35)	OR, 1.31 (95% CrI, 0.57-3.12)	–	Adalimumab

Fig 6. Comparative efficacy of biological agents as maintenance therapy for anti-TNF therapy-naïve subpopulation. CrI, credible interval; OR, odds ratio; TNF, tumour necrosis factor. Note: Treatment effect estimates come from Bayesian mixed-treatment comparison. ORs >1.0 favour the treatment in the left upper square. To obtain ORs for comparison in the opposite direction, reciprocals should be calculated.

Efficacy and safety of biological agents in the anti-TNF therapy experienced/ failure subpopulation

Analyses based on the anti-TNF therapy-failure population in the vedolizumab study (GEMINI 1) and the anti-TNF therapy-experienced population adalimuab study ULTRA 2

Induction (Table 3)

- Vedolizumab showed significant improvement in clinical response over placebo (OR [95% CrI], 2.5 [1.2–5.5]); in other comparisons with placebo, significant differences were not seen
- There was no evidence to suggest differences between adalimumab and vedolizumab for clinical response, clinical remission, or mucosal healing

Maintenance (Table 3)

- Both vedolizumab and adalimumab were significantly better than placebo for clinical remission at maintenance (ORs [95% CrI], 12.0 [3.14–78.0] and 3.6 [1.01–18.0], respectively).
- only vedolizumab demonstrated significantly better durable clinical response (OR [95% CrI], 4.89 [1.74–16.0]) and mucosal healing (OR [95% CrI], 9.09 [2.74– 40.0]) than placebo

- There was no evidence to suggest differences between adalimumab and vedolizumab for durable clinical response and clinical remission
- Vedolizumab showed significantly improved mucosal healing over adalimumab (OR [95% CrI], 6.72 [1.36–41.0]).

Table 3. Comparative efficacy of biological agents for induction and maintenance therapy for anti-TNF therapy-experienced subpopulation.

	Odds ratio (95% CrI)		
Time point (Endpoint)	Vedolizumab vs. adalimumab	Vedolizumab vs. placebo	Adalimumab vs. placebo
Induction			
Clinical response	1.74 (0.69–4.45)	2.51* (1.18–5.48)	1.43 (0.79–2.64)
Clinical remission	2.72 (0.43–23.79)	3.66 (0.87–27.98)	1.37 (0.47–4.03)
Mucosal healing	1.56 (0.57–4.22)	1.70 (0.80–3.81)	1.09 (0.60–2.10)
Maintenance			
Durable clinical response	2.04 (0.44–9.01)	4.89* (1.74–15.89)	2.47 (0.90–6.99)
Clinical remission	3.40 (0.40–32.52)	12.14* (3.14–78.38)	3.60* (1.01–18.23)
Mucosal healing	6.72* (1.36–41.17)	9.09* (2.74–40.06)	1.36 (0.50–3.91)

CrI, credible interval; OR, odds ratio; TNF, tumour necrosis factor.
* = significant.

4. Fazit der Autoren

In the anti-TNF–naïve population, infliximab demonstrated a significant improvement over adalimumab for these endpoints in the induction setting; however, there was no evidence to suggest differences between infliximab and vedolizumab, between infliximab and golimumab, or between labelled doses of the other biologics (vedolizumab, adalimumab, and golimumab).

In the maintenance setting, there is a suggestion that vedolizumab demonstrates benefits compared with comparators, irrespective of prior anti-TNF–therapy exposure for both durable clinical response and mucosal healing.

A head-to-head study is necessary to definitively demonstrate differences in efficacy between the biological therapies used to treat UC.

5. Kommentare zum Review

- indirekte Vergleiche beruhen nur auf placebo-kontrollierten Studien;
- zentrale Annahme der Konsistenz der Ergebnisse aus direkten und indirekter Evidenz kann aufgrund der fehlenden direkten Vergleiche nicht beurteilt werden
- zentrale Annahme der Ähnlichkeit: Patientencharakteristika und Studiendesign grob beschrieben und diskutiert
- Placebo (=Brückenkomparator) zwischen den Studien aufgrund der verschiedenen Applikationsschemata der aktiven Medikamente unterschiedlich (i.v. / SC / unterschiedliche Häufigkeit der Anwendung); Placebo-Response der Patienten varierte zwischen den Studien

→ geringe Aussagesicherheit der Ergebnisse

Weitere NMA zu dieser Fragestellung mit ähnlicher Schlussfolgerungen (gleiche Studien eingeschlossen)

- Danese et al. 2014 [6]: The results of network meta-analysis suggested that infliximab is more effective to induce clinical response and mucosal healing than adalimumab. No other indirect comparison reached statistical significance. For maintenance, 6 double-blind, placebo-controlled trials that were rated high risk of bias showed that all biological agents have greater clinical efficacy than placebo. The occurrence of

	adverse events was not different between biological agents and placebo.
Lv R et al., 2014 [19]. Tumor necrosis factor alpha blocking agents as treatment for ulcerative colitis intolerant or refractory to conventional medical therapy: a meta-analysis	1. Fragestellung To assess the efficacy and safety of anti-TNF-α agents for treatment of ulcerative colitis patients who were intolerant or refractory to conventional medical therapy.
	2. Methodik **Population:** adult patients with UC resistant to conventional therapy of corticosteroids and/or immunosuppressive agents or refractory to intravenous corticosteroids; **Intervention**: anti-TNF-alpha **Komparator** placebo or other intervention **Endpunkte**: frequency of clinical remission (Mayo score ≤ 2 with no individual subscore exceeding 1), frequency of long-term mucosal healing, steroid-free remission, colectomy and severe side effects **Recherche**: 1991 –07/2013 **Anzahl eingeschlossene Studien** / Patienten: 8/ n = 2122 Patienten **Qualitätsbewertung der Studien**: Risk of bias was assessed by Cochrane risk of bias tool; The quality of the RCTs was assessed by the Jadad scoring system by two independent investigators.
	3. Ergebnisdarstellung *Included Studies:* **Study** / **Participants(UC)** / **Intervention** / **Control** / **Follow-up** **Armuzzi 2004** / Steroid-dependent / Infliximab / Methylprednisolone / 9.8±1.1 months **Gavalas 2007** / Steroid-dependent / Infliximab / Methylprednisolone / 21months **Laharie 2012** / Not respond to intravenous steroid / Infliximab / Ciclosporin / 98 days **Ochsenkühn 2004** / Refractory to 5-aminosalicylates. / Infliximab / Prednisolone / 13 weeks **Rutgeerts 2005 ACT 1** / Not respond to conventional therapy / Infliximab / Placebo / 54 weeks **Rutgeerts 2005 ACT2** / Not respond to conventional therapy / Infliximab / Placebo / 30-week **Sandborn 2009** / Not respond to conventional therapy / Infliximab / Placebo / 54 weeks **Sandborn 2012** / Not respond to conventional therapy / Adalimumab / Placebo / 54 weeks Quality of the studies ranged from moderate to high (Jadad score >3). Two studies were rated at high risk of bias due to lack of proper blinding controls *Clinical remission (6 trials; n=1279 patients)* • IFX (2 trials) or ADA(1 trial) vs. placebo: TNF-α blocker was significantly superior to placebo for maintenance of clinical remission (RR = 2.29; 95% [1.73, 3.03], Z =5.78, p<0.00001) • IFX vs. methylprednisolone (2 trials) or prednisolone (1 trial): no significant difference in clinical remission rates between the anti-TNF-α agents and glucocorticoid treatment (RR = 1.01; 95% [0.73, 1.42], Z =0.09, p = 0.93) *Mucosal healing (5 trials; n=1345 patients)* • IFX (2 trials) or aADA (1 trial) vs. placebo: TNF-α blocker was significantly superior to placebo for healing of the mucosa (RR = 1.89; 95% [1.55, 2.31],

	p<0.00001) • IFX vs. prednisolone (1 trial): both are equally effective for sustaining mucosal healing in UC (RR = 0.88; 95% [0.31, 2.44], p =0.80) • IFX vs. cyclosporine (1 trial): both are equally effective for sustaining mucosal healing in UC (RR =1.04; 95% [0.70, 1.55], p =0.85) *Steroid-free remission (3 trials; n= 698 patients)* • IFX (2 trials) or ADA (1 trial) vs. placebo: superiority of TNF-a blockers (RR = 2.97; 95% [1.77, 4.96], p<0.0001). *Colectomy rate (3 trials; n= 863 patients)* • IFX vs. placebo (1 trial): superioriy of IFX (RR = 0.64; 95% [0.43, 0.97], p=0.03) • IFX vs prednisolone (1 trial): the colectomy rate was equivalent between those receiving infliximab and those receiving prednisolone (RR =3.00; 95% [0.14, 65.90], p =0.49) • IFX vs. cyclosporine (1 trial): infliximab is as effective as cyclosporine in preventing patient colectomy (RR = 1.22; 95% [0.57, 2.60], p = 0.60) *Serious side effects (5 trials; n= 2088 patients)* • IFX (3 trials) or ADA (1 trial) vs. placebo: the occurrence of serious side effects was equivalent between TNF-α and placebo (RR = 0.83; 95%[0.69, 1.00], Z =1.98, p =0.05) • IFX vs. cyclosporine (1 trial): no significant difference was found between the anti-TNF-α group and the cyclosporine in terms of serious side effects (RR = 0.63; 95% [0.30, 1.34], Z = 1.19, p = 0.23)
	4. Anmerkungen/Fazit der Autoren TNF-a blockers are effective and safe therapies for the induction and maintenance of long-term remission and prevention of treatment by colectomy for patients with refractory ulcerative colitis where conventional treatment was previously ineffective. Furthermore, infliximab and cyclosporine were found to be comparable for treating acute severe steroid-refractory ulcerative colitis. 5. *Kommentare zum Review* Placebo-kontrollierten Studien in weiteren Reviews eingeschlossen (siehe Archer et al. 2016)
Ford AC et al., 2013 [7]. Opportunistic Infections With Anti-Tumor Necrosis Factor- α Therapy in Inflammatory Bowel Disease: Meta-Analysis of Randomized	1. Fragestellung Several anti-tumor necrosis factor- α (TNF α) antibodies have demonstrated efficacy in Crohn's disease (CD) and ulcerative colitis (UC). These drugs carry the theoretical risk of opportunistic infection, but no systematic review and meta-analysis has examined this issue specifically.
	2. Methodik **Population:** Patienten mit mittelschwerer bis schwerer Colitis ulcerosa (> 90 % of participants over the age of 16 years) **Intervention:** anti-TNF α (adalimumab, certolizumab, golimumab, or infliximab) **Komparator:** plazebo **Endpunkte:** Opportunistic infections (*Mycobacterium tuberculosis* , oral or esophageal candidiasis, varicella-zoster virus infection, herpes zoster infection,

Controlled Trials	Epstein-Barr virus or cytomegalovirus infection, *Nocardia* infection, *Pneumocytsis jirovecii* infection, m*ycobacterium avium complex* infection, herpes simplex infection, or other unspecified opportunistic infections) **Suchzeitraum (**Aktualität der Recherche): 1946 bis 11/2011 **Anzahl eingeschlossene Studien**/Patienten (Gesamt): 22 studies (n=4,135 patients) **Qualitätsbewertung der Studien:** Risk of bias was assessed as described in the Cochrane handbook
	3. Ergebnisdarstellung • 7 der eingeschlossenen Studien relevant für Fragestellung, Anzahl der Patienten (n=2488) • Subgroup analyses of RR of opportunistic infection with anti-TNF therapies vs. placebo in UC: 1.78; 95% CI 0.72 – 4.42 Overall risk of opportunistic infections with anti-TNF a therapy vs. placebo: • The RR of developing an opportunistic infection was significantly higher with anti-TNF α therapy (2.05; 95 % CI 1.10 – 3.85, NNH = 500; 95 % CI 200 – 1,567). • The RR of tuberculosis infection was 2.52 (95 % CI 0.62 – 10.21).
	4. Anmerkungen/Fazit der Autoren Anti-TNF therapy doubles the risk of opportunistic infections in inflammatory bowel disease patients. This underlines the importance of adherence to guidelines for their prevention and management.
Gisbert JP et al., 2015 [10]. Systematic review with meta-analysis: the efficacy of a second anti-TNF in patients with inflammatory bowel disease whose previous anti-TNF treatment has failed	1. Fragestellung To investigate the efficacy and safety of a second anti-TNF agent after primary/secondary failure or intolerance to a first drug.
	2. Methodik **Population:** IBD patients after failure (primary or secondary) or intolerance to a first anti-TNF treatment. **Intervention:** anti-TNF treatment **Komparator:** k.A. **Endpunkte:** • <u>primary outcome</u>: percentage of remission and/or response obtained with the second anti-TNF, depending on the type of IBD. • <u>Secondary outcomes:</u> incidence of severe AEs or SAEs related to the second anti-TNF given, and its relation with the need of discontinuing the therapy. **Studientyp**: prospective and retrospective studies **Recherche:** in Medline + Embase in 10/2014 **Anzahl eingeschlossene Studien** / Patienten: 46 (37 focused on CD, 8 on UC, and 1 on pouchitis) **Qualitätsbewertung der Studien**: keine The publication/ reporting bias was assessed by funnel plots only in those analyses including more than 10 studies. None of the funnel plots showed evidence of publication bias.

	3. Ergebnisdarstellung (Fokus auf CU-Studien) *Primary failure* was defined as no response to the first anti-TNF, *secondary failure* as a loss of response (after a previous response), and intolerance as discontinuation of the first treatment owing to AEs. *Remission and response in UC (Eight studies)* • Treatment was switched to ADA after discontinuation of IFX in all studies • No sub-analyses could be performed, as follow-up times were not consistent and most authors did not subdivide results regarding the reason for switching (see Appendix: table S3) *Switching to an alternative anti-TNF drug in UC (six studies)* • All UC studies switched IFX -> ADA • Only four studies reported remission rates, with figures ranging from 0% to 50%. • No sub-analyses could be performed, as most studies did not coincide in follow-up times for measurement and most authors did not subdivide results regarding the reason for switching *Severe and serious adverse events related to the administration of a second anti-TNF in UC patients* • AE rates ranged from 20% to 39% • SAEs ranging from 0% to 7% • discontinuation of therapy related to AEs ranging from 0% to 48%
	4. Anmerkungen/Fazit der Autoren Therefore, more studies are necessary to further investigate the efficacy of a second anti-TNF drug in patients with UC whose first drug fails or who could not tolerate their first drug. *Kommentare zum Review:* • Keine Bewertung der Studienvalidität, Einschluss unkontrollierter prospektiver und retrospektiver Studien → sehr limitierte Aussagekraft • Charakteristika/Ergebnisse der eingeschlossenen Studien siehe Anhang

Leitlinien

Bressler B et al., 2015 [3]. Clinical Practice Guidelines for the Medical Management of Nonhospitalized Ulcerative Colitis: The Toronto Consensus	Leitlinie der Toronto Ulcerative Colitis Consensus Group „to develop specific recommendations for ambulatory patients with mild to severe active UC“
	Methodik – systematic literature search of MEDLINE (1946 on), EMBASE (1980 on), and CENTRAL up to February 2014 – quality of evidence was assessed according to GRADE approach – Consensus Process: • consensus group =23 voting participants, including academic and community gastroenterologists with expertise in various aspects of UC management, a pharmacist, and a nonvoting facilitator; declaration of conflict of interest • preparation of statement drafts by working groups, discussion and finalization of statements during consensus conference • A statement was accepted if >75% of participants voted 4 (agree) or 5 (strongly agree) on a scale of 1 to 5 (with 1, 2, and 3 indicating disagree strongly, disagree, and uncertain, respectively) – GoR: strength of each recommendation was assigned per GRADE system, as strong (“we recommend…”) or weak (“we suggest…”). – Funding: • consensus meeting was funded by unrestricted grants to the Canadian Association of Gastroenterology from AbbVie Canada, Actavis Specialty Pharmaceuticals, Janssen Inc, Shire Pharma Canada ULC, Takeda Canada, and the Canadian Institutes of Health Research. The Canadian Association of Gastroenterology administered all aspects of the meeting, and the funding sources had no role in drafting or approving these guidelines.
	Empfehlungen Statement 20. In patients with UC who fail to respond to thiopurines or corticosteroids, we recommend anti-TNF therapy to induce complete corticosteroid-free remission. *GRADE: Strong recommendation, high-quality evidence. Vote: strongly agree, 70%; agree, 30%.* The anti-TNF therapies, infliximab, adalimumab, and golimumab, have shown efficacy for the induction and maintenance of remission in patients with moderate to severe active UC. Infliximab: • Ford AC et al. Efficacy of biological therapies in inflammatory bowel disease: systematic review and meta-analysis. Am J Gastroenterol 2011;106:644–659; quiz 660. • Lawson MM et al. Tumour necrosis factor alpha blocking agents for induction of remission in ulcerative colitis. Cochrane Database Syst Rev 2006: CD005112. • Lv R et al. Tumor necrosis factor alpha blocking agents as treatment for ulcerative colitis intolerant or refractory to conventional medical therapy: a meta-analysis.

	PLoS One 2014;9:e86692. Adalimumab • Reinisch W et al. Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial. Gut 2011;60:780–787. • Sandborn WJ et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology 2012;142:257–265. e1–3. Golimumab: • Sandborn WJ et al. Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology 2014;146:85–95; quize14–e15. Statement 21. When starting anti-TNF therapy, we recommend it be combined with a thiopurine or methotrexate rather than used as monotherapy to induce complete remission. *GRADE: Strong recommendation, moderate-quality evidence for azathioprine and very low-quality evidence for methotrexate. Vote: strongly agree, 26%; agree, 65%; uncertain, 9%.* ….The data from RCTs regarding the use of anti-TNF therapies and azathioprine in combination are sparse, and no such data exist for combination therapy with methotrexate. The efficacy of anti-TNF therapy in combination with azathioprine is supported by the results of the UC SUCCESS trial and observational data…. Statement 25. In patients with UC who have a suboptimal response to anti-TNF induction therapy, we recommend dose intensification to achieve complete remission. *GRADE: Strong recommendation, very low-quality evidence. Vote: strongly agree, 39%; agree, 61%.* Statement 26. In patients with UC who lose response to anti-TNF maintenance therapy, we recommend optimizing dose to recapture complete remission. *GRADE: Strong recommendation, very low-quality evidence. Vote: strongly agree, 61%; agree, 39%.* Statement 28 In patients with primary failure to an anti-TNF therapy, we recommend switching to vedolizumab over switching to another anti-TNF therapy to induce complete corticosteroid-free remission. *GRADE: Strong recommendation, very low quality evidence. Vote: strongly agree, 48%; agree, 43%; uncertain, 9%.* Statement 29. In patients with secondary failure to an anti-TNF therapy, we recommend switching to another anti-TNF therapy or vedolizumab based on therapeutic drug monitoring results to induce complete corticosteroid-free remission. *GRADE: Strong recommendation, very low-quality evidence. Vote: strongly agree, 43%; agree, 57%.* Statement 30. In patients with moderate to severe active UC who fail to respond to corticosteroids, thiopurines, or anti-TNF therapies, we recommend vedolizumab to induce complete corticosteroid-free remission. *GRADE: Strong recommendation, moderate quality evidence. Vote: strongly agree, 70%; agree, 26%; disagree, 4%.* In patients with biologic failure despite dose intensification, no studies have directly compared switching to vedolizumab and switching to an alternate anti-TNF therapy. The available observational data suggest that switching to a different anti-TNF therapy may be more effective in patients who develop ADAs and less effective in primary failure.

	• Roblin X et al. Association between pharmacokinetics of adalimumab and mucosal healing in patients with inflammatory bowel diseases. Clin Gastroenterol Hepatol 2014;12:80–84.e2. • Afif W et al. Clinical utility of measuring infliximab and human anti-chimeric antibody concentrations in patients with inflammatory bowel disease. Am J Gastroenterol 2010;105:1133–1139. • Roblin X et al. Development of an algorithm incorporating pharmacokinetics of adalimumab in inflammatory bowel diseases. Am J Gastroenterol 2014;109:1250–1256. Because vedolizumab acts via a different mechanism than anti-TNF therapies, it is possible that switching to this class of agents may be effective in patients with either primary or secondary anti-TNF therapy failure.
NICE, 2013 [21]. Ulcerative colitis Management in adults, children and young people	NICE Guideline produced by National Clinical Guideline Centre (NCGC)
	Methodik Grundlage der Leitlinie – multidisciplinary Guideline Development Group (GDG) comprising professional group members and consumer representatives of the main stakeholders developed this guideline – systematic search in MEDLINE, Embase, Cinahl, Cochrane Library up to 11/2012 – relevant studies were critically appraised using the appropriate checklists as specified in The Guidelines Manual. – summaries of the evidence were generated by outcome: quality of evidence assessed by GRADE approach, GRADE profiles were reported – 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) – public consultation and feedback as part of the quality assurance and peer review
	Empfehlungen **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 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. **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. For guidance on infliximab for treating acute severe ulcerative colitis (all extents of disease) in people for whom ciclosporin is contraindicated or clinically inappropriate, refer to Infliximab for acute exacerbations of ulcerative colitis (NICE technology appraisal guidance 163).
Gomollon F et al., 2013 [11]. Therapeutic guidelines on ulcerative colitis: A GRADE methodology based effort of GETECCU	Guidelines of Spanish Group of Ulcerative Colitis and Crohn's disease (GETECCU)
	Methodik **Grundlage der Leitlinie**: AGREE methodology was followed – Interdisciplinary working team including gastroenterologists, surgeons, primary care physicians, nurses and patients – Systematic Literature Review: o Recherche: in PUBMED, EMBASE, TRIPDATABASE, COCHRANE COLLABORATION; keine explizite Angabe des Suchzeitraumes; Berücksichtigung von Studien bis Februar 2011 o assessment of overall quality of evidence by GRADE approach – For recommendations, consideration of o quality of the evidence, o weighing between the potential benefits and risks, o applicability in the population that will be treated and, o costs. **GoR** GRADE methodology The recommendations issued are classified into four degrees: • we recommend, which implies strongly advising the clinician: Do it; • we suggest which means to advise the clinical probably do it; • we do no suggest which implies the same as probably don't do it; and • we recommend avoiding or we do not recommend which strongly and clearly indicates don't do it.
	Empfehlungen We recommend the use of infliximab in induction of remission in patients with a severe UC flare, especially if they are refractory to steroids with an induction dose of 5 mg/kg, followed by another dose at 14 days, and a third dose at 42 days. (moderate quality of evidence) We suggest the use of infliximab as maintenance treatment in patients with severe UC who have obtained remission with infliximab. (low quality of evidence) We do suggest surgery as an option in severe flares of steroid-resistant UC, although in most cases, a rescue treatment with infliximab or cyclosporine must be tried previously. In some clinical scenarios, the indication is absolute, and so surgery is to be recommended: perforation, massive haemorrhage, and refractory toxic megacolon (low quality of evidence)

We suggest the use of adalimumab in the treatment of moderate flare of steroid-dependence or steroid-resistance ulcerative colitis (moderate quality of evidence)

Table 2 Summary of the quality of the evidence and grade of the recommendation for the 32 statements.

Action (and clinical scenary)	Quality of evidence	Recommendation	For the clinician
Maintenance treatment of UC in remission			
Oral salicylates (after remission with oral salicylates)	High	Strong for (recommended)	Do it
Rectal salicylates (after remission with rectal salicylates, left-colitis)	Moderate	Strong for (recommended)	Do it
Thiopurines for steroid-dependent	Moderate	Strong for (recommended)	Do it
Methotrexate for steroid-dependent	Low	Weak against (not suggested)	Probably do not do it
Infliximab for steroid failure	High	Strong for (recommended)	Do it
Thiopurine (after remission with infliximab)	Very low	No recommendation	
Infliximab (after remission with infliximab)	Low	Weak for (suggested)	Probably do it
Thiopurine (after remission with cyclosporine)	Low	Weak for (suggested)	Probably do it
Cyclosporine (after remission with cyclosporine)	Very low	Strong against (not recommended)	Do not do it
Tacrolimus (after remission with tacrolimus)	Very low	Strong against (not recommended)	Do not do it

Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

NICE, 2015 [22].
Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy (including a review of TA140 and TA262)
	• 1.1 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.
	• Golimumab is recommended only if the company provides the 100 mg dose of golimumab at the same cost as the 50 mg dose, as agreed in the patient access scheme.
	•
	• 1.2 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).
	•
	• 1.3 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.
	•
	• 1.4 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.
	•

NICE, 2015 [23]. Vedolizumab for treating moderately to severely active ulcerative colitis."	• 1.1 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. • • 1.2 Vedolizumab should be given until it stops working or surgery is

Technology appraisal guidance TA342.	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.

Detaillierte Darstellung der Recherchestrategie

Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database) am 06.03.2017

#	Suchfrage
1	MeSH descriptor: [Colitis, Ulcerative] explode all trees
2	MeSH descriptor: [Inflammatory Bowel Diseases] this term only
3	colitis:ti,ab,kw and (ulcerosa or ulcerative):ti,ab,kw (Word variations have been searched)
4	"inflammatory bowel disease":ti,ab,kw (Word variations have been searched)
5	#1 or #2 or #3 or #4
6	#5 Publication Year from 2012 to 2017, in Cochrane Reviews (Reviews only) and Technology Assessments

SR, HTAs in Medline (PubMed) am 07.03.2017

#	Suchfrage
1	Search colitis, ulcerative[MeSH Terms]
2	Search inflammatory bowel disease[mesh:noexp]
3	Search ulcerative colitis[Title/Abstract] OR colitis ulcerosa[Title/Abstract]
4	Search inflammatory bowel disease*[Title]
5	Search #1 OR #2 OR #3 OR #4
6	Search ((((((((((treatment*[Title/Abstract]) OR therapy[Title/Abstract]) OR therapies[Title/Abstract]) OR therapeutic[Title/Abstract]) OR monotherap*[Title/Abstract]) OR polytherap*[Title/Abstract]) OR pharmacotherap*[Title/Abstract]) OR effect*[Title/Abstract]) OR efficacy[Title/Abstract]) OR treating[Title/Abstract]) OR treated[Title/Abstract]) OR management[Title/Abstract]) OR drug*[Title/Abstract]
7	Search #5 AND #6
8	Search "colitis, ulcerative/therapy"[MeSH Terms]
9	Search inflammatory bowel disease/therapy[mesh:noexp]
10	Search #7 OR #8 OR #9
11	Search #10 AND ((Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp]) OR (((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))
12	Search #11 Filters: Publication date from 2012/03/01 to 2017/03/07

Leitlinien in Medline (PubMed) am 07.03.2017

#	Suchfrage

1	Search colitis, ulcerative[MeSH Terms]
2	Search inflammatory bowel disease[mesh:noexp]
3	Search ulcerative colitis[Title/Abstract] OR colitis ulcerosa[Title/Abstract]
4	Search inflammatory bowel disease*[Title]
5	Search #1 OR #2 OR #3 OR #4
6	Search (((((Guideline[Publication Type]) OR Practice Guideline[Publication Type]) OR Consensus Development Conference[Publication Type]) OR Consensus Development Conference, NIH[Publication Type]) OR guideline*[Title]) OR recommendation*[Title]
7	Search #5 AND #6
8	Search #5 AND #6 Filters: Publication date from 2012/01/01 to 2017/03/07

Appendix

Gisbert 2015: Systematic review with meta-analysis: the efficacy of a second anti-TNF in patients with inflammatory bowel disease whose previous anti-TNF treatment has failed

Table 3. Studies evaluating the remission and response obtained with a second anti-TNF after failure of a first one, in ulcerative colitis.

				2nd anti-TNF dosage (mg)		Patients			RESPONSE								REMISSION						
Author	Year	Design	1st/2nd anti-TNF	Induction	Maintenance	1st anti-TNF failure	n	%	Overall n/N	%	Week	Reason for 1st anti-TNF failure	n/N	%	Week		Overall n/N	%	Week	Reason for 1st anti-TNF failure	n/N	%	Week
Afif[18]	2009	Prosp.	IFX/ADA	160/80	40 EOW	PF: SF: I: **Tot.**	0 6 7 **13**	0 46 54	3/13	23	8	-					0/13	0	8	SF: I:	0/6 0/7	0 0	8 8
Armuzzi[59]	2013	Retrosp.	IFX/ADA	160/80 and 80/40	NR	PF: SF: I: **Tot.**	5 27 23 **69**	100	-			-					11/69 17/69 25/69 30/69	16 25 36 43	4 12 24 54	PF:	0/5 0/5 0/5 0/5	0 0 0 0	4 12 24 54
Baert[60]	2014	Retrosp.	IFX/ADA	160/80	40 EOW	PF: SF: I: **Tot.**	11 42 18 **73**	15 57.5 24.6	22/73 38/73	30 52	12 52	-					16/73	22	52	-			
Barreiro[19] (pouchitis)	2012	Retrosp.	IFX/ADA	160/80	40 EOW	PF: SF: I: **Tot.**	0 3 5 **8**	0 38 62	5/8 3/8	62 38	8 26	-					1/8 1/8 2/8	13 13 25	8 26 52	-			
Garcia-Bosch[26]	2013	Retrosp.	IFX/ADA	160/80 and 80/40	40 EOW	PF: SF: I: **Tot.**	6 33 0 **39**	15 85 0	23/39	69	12	PF: SF:	2/6 25/33	33 76	12 12		-			-			
Oussalah[39]	2008	Prosp.	IFX/ADA	160/80	40 EOW	PF: SF: I: **Tot.**	0 8 5 **13**	0 62 38	12/13 11/13 8/13 4/13	92 85 61 32	4 12 24 104	SF: I:	3/8 2/5	38 40	104 104		-			-			
Peyrin-Biroulet[44]	2007	Prosp.	IFX/ADA	160/80	-	PF: SF: I: **Tot.**	0 6 4 **10**	0 60 40	4/10	40	4	-					1/10	10	4	-			
Sandborn[49]	2012	Prosp.	IFX/ADA	160/80	40 EOW	PF: SF: I: **Tot.**	NR NR NR **98**	NR NR NR	36/98 20/98	37 20	8 52						9/98 10/98	9.2 10	8 52				
Taxonera[55]	2011	Retrosp.	IFX/ADA	160/80	40 EOW	PF: SF: I: **Tot.**	2 16 12 **30**	7 53 40	16/30 18/30	53 60	4 12	PF: SF: I:	0/2 10/16 8/12	0 62 67	12 12 12		3/30 8/30 15/30	10 27 50	4 12 52	-			

Literatur:

1. **Archer R, Tappenden P, Ren S, Martyn-St James M, Harvey R, Basarir H, et al.** Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy (including a review of TA140 and TA262): clinical effectiveness systematic review and economic model. Health Technology Assessment 2016;20(39):1-364.

2. **Bickston SJ, Behm BW, Tsoulis DJ, Cheng J, MacDonald JK, Khanna R, et al.** Vedolizumab for induction and maintenance of remission in ulcerative colitis. Cochrane Database of Systematic Reviews [online]. 2014(8):Cd007571. URL: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007571.pub2/abstract.

3. **Bressler B, Marshall JK, Bernstein CN, Bitton A, Jones J, Leontiadis GI, et al.** Clinical practice guidelines for the medical management of nonhospitalized ulcerative colitis: the Toronto consensus. Gastroenterology 2015;148(5):1035-1058 e1033.

4. **Canadian Agency for Drugs and Technologies in Health (CADTH).** Golimumab (Simponi) (Subcutaneous Injection): adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to, or have medical contraindications for, conventional therapies including corticosteroids, aminosalicylates, azathioprine or 6-mercaptopurine [online]. Ottawa (CAN): CADTH; 2014. [Zugriff: 13.03.2017]. (Common drug review: clinical review report). URL: https://www.cadth.ca/sites/default/files/cdr/clinical/SR0341_Simponi_CL_Report_e.pdf.

5. **Chen X, Hou J, Yuan Y, Huang C, Liu T, Mo C, et al.** Adalimumab for Moderately to Severely Active Ulcerative Colitis: A Systematic Review and Meta-Analysis. BioDrugs 2016;30(3):207-217.

6. **Danese S, Fiorino G, Peyrin-Biroulet L, Lucenteforte E, Virgili G, Moja L, et al.** Biological agents for moderately to severely active ulcerative colitis: a systematic review and network meta-analysis. Ann Intern Med 2014;160(10):704-711.

7. **Ford AC, Peyrin-Biroulet L.** Opportunistic infections with anti-tumor necrosis factor-alpha therapy in inflammatory bowel disease: meta-analysis of randomized controlled trials. Am J Gastroenterol 2013;108(8):1268-1276.

8. **Galvan-Banqueri M, Vega-Coca MD, Castillo-Munoz MA, Beltran Calvo C, Molina Lopez T.** Indirect comparison for Anti-TNF drugs in moderate to severe ulcerative colitis. Farm Hosp 2015;39(2):80-91.

9. **Gemeinsamer Bundesausschuss (G-BA).** Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Vedolizumab vom 8. Januar 2015 [online]. Berlin (GER): G-BA; 2015. [Zugriff: 13.03.2017]. URL: https://www.g-ba.de/downloads/39-261-2143/2015-01-08_AM-RL-XII_Vedolizumab_2014-07-15-D-122_BAnz.pdf.

10. **Gisbert JP, Marin AC, McNicholl AG, Chaparro M.** Systematic review with meta-analysis: the efficacy of a second anti-TNF in patients with inflammatory bowel disease whose previous anti-TNF treatment has failed. Aliment Pharmacol Ther 2015;41(7):613-623.

11. **Gomollon F, Garcia-Lopez S, Sicilia B, Gisbert JP, Hinojosa J.** Therapeutic guidelines on ulcerative colitis: a GRADE methodology based effort of GETECCU. Gastroenterol Hepatol 2013;36(2):104-114.

12. **Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWIG).** Vedolizumab – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A14-23 [online]. Köln (GER): IQWIG; 2014. [Zugriff: 07.03.2017]. (IQWiG-Berichte Band 247). URL: https://www.iqwig.de/download/A14-23_Vedolizumab_Nutzenbewertung-35a-SGB-V.pdf.

13. **Jin Y, Lin Y, Lin LJ, Zheng CQ.** Meta-analysis of the effectiveness and safety of vedolizumab for ulcerative colitis. World J Gastroenterol 2015;21(20):6352-6360.

14. **Kawalec P, Mikrut A, Lopuch S.** Systematic review of the effectiveness of biological therapy for active moderate to severe ulcerative colitis. J Gastroenterol Hepatol 2014;29(6):1159-1170.

15. **Kawalec P, Pilc A.** An indirect comparison of infliximab versus adalimumab or golimumab for active ulcerative colitis. Arch Med Sci 2016;12(5):1097-1109.

16. **LeBlanc K, Mosli MH, Parker CE, MacDonald JK.** The impact of biological interventions for ulcerative colitis on health-related quality of life. Cochrane Database of Systematic Reviews [online]. 2015(9):Cd008655. URL: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008655.pub3/abstract.

17. **Lin L, Liu X, Wang D, Zheng C.** Efficacy and safety of antiintegrin antibody for inflammatory bowel disease: a systematic review and meta-analysis. Medicine (Baltimore) 2015;94(10):e556.

18. **Lopez A, Ford AC, Colombel JF, Reinisch W, Sandborn WJ, Peyrin-Biroulet L.** Efficacy of tumour necrosis factor antagonists on remission, colectomy and hospitalisations in ulcerative colitis: Meta-analysis of placebo-controlled trials. Dig Liver Dis 2015;47(5):356-364.

19. **Lv R, Qiao W, Wu Z, Wang Y, Dai S, Liu Q, et al.** Tumor necrosis factor alpha blocking agents as treatment for ulcerative colitis intolerant or refractory to conventional medical therapy: a meta-analysis. PLoS One 2014;9(1):e86692.

20. **Mao EJ, Hazlewood GS, Kaplan GG, Peyrin-Biroulet L, Ananthakrishnan AN.** Systematic review with meta-analysis: comparative efficacy of immunosuppressants and biologics for reducing hospitalisation and surgery in Crohn's disease and ulcerative colitis. Aliment Pharmacol Ther 2017;45(1):3-13.

21. **National Clinical Guideline Centre (NCGC).** Ulcerative colitis: Management in adults, children and young people [online]. London (GBR): National Institute for Health and Care Excellence (NICE); 2013. [Zugriff: 07.03.2017]. (Clininal Guideline; Band 166). URL: https://www.nice.org.uk/guidance/cg166/evidence/full-guideline-190220365.

22. **National Institute for Health and Care Excellence (NICE).** Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy [online]. London (GBR): NICE; 2015. [Zugriff: 07.03.2017]. (NICE technology appraisal guidance; Band 329). URL: https://www.nice.org.uk/guidance/ta329/resources/infliximab-adalimumab-and-golimumab-for-treating-moderately-to-severely-active-ulcerative-colitis-after-the-failure-of-conventional-therapy-82602495307717.

23. **National Institute for Health and Care Excellence (NICE).** Vedolizumab for treating moderately to severely active ulcerative colitis [online]. London (GBR): NICE; 2015. [Zugriff: 07.03.2017]. (NICE technology appraisal guidance; Band 342). URL: https://www.nice.org.uk/guidance/ta342/resources/vedolizumab-for-treating-moderately-to-severely-active-ulcerative-colitis-82602604482757.

24. **Sherlock ME, MacDonald JK, Griffiths AM, Steinhart AH, Seow CH.** Oral budesonide for induction of remission in ulcerative colitis. Cochrane Database of Systematic Reviews [online]. 2015(10):Cd007698. URL: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007698.pub3/abstract.

25. **Stidham RW, Lee TC, Higgins PD, Deshpande AR, Sussman DA, Singal AG, et al.** Systematic review with network meta-analysis: the efficacy of anti-tumour necrosis factor-alpha agents for the treatment of ulcerative colitis. Aliment Pharmacol Ther 2014;39(7):660-671.

26. **Timmer A, Patton PH, Chande N, McDonald JW, MacDonald JK.** Azathioprine and 6-mercaptopurine for maintenance of remission in ulcerative colitis. Cochrane Database of Systematic Reviews [online]. 2016(5):Cd000478. URL: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000478.pub4/abstract.

27. **Vickers AD, Ainsworth C, Mody R, Bergman A, Ling CS, Medjedovic J, et al.** Systematic Review with Network Meta-Analysis: Comparative Efficacy of Biologics in the Treatment of Moderately to Severely Active Ulcerative Colitis. PLoS One 2016;11(10):e0165435.

28. **Wang MC, Zhang LY, Han W, Shao Y, Chen M, Ni R, et al.** PRISMA--efficacy and safety of vedolizumab for inflammatory bowel diseases: a systematic review and meta-analysis of randomized controlled trials. Medicine (Baltimore) 2014;93(28):e326.

29. **Zhang ZM, Li W, Jiang XL.** Efficacy and Safety of Adalimumab in Moderately to Severely Active Cases of Ulcerative Colitis: A Meta-Analysis of Published Placebo-Controlled Trials. Gut Liver 2016;10(2):262-274.

				2nd anti-TNF dosage (mg)		Patients			RESPONSE							REMISSION						
Author	Year	Design	1st/2nd anti-TNF	Induction	Maintenance	1st anti-TNF failure	n	%	Overall n/N	%	Week	Reason for 1st anti-TNF failure	n/N	%	Week	Overall n/N	%	Week	Reason for 1st anti-TNF failure	n/N	%	Week
Afif[18]	2009	Prosp.	IFX/ADA	160/80	40 EOW	PF: SF: I: **Tot.**	0 6 7 **13**	0 46 54	3/13	23	8	-				0/13	0	8	SF: I:	0/6 0/7	0 0	8 8
Armuzzi[59]	2013	Retrosp.	IFX/ADA	160/80 and 80/40	NR	PF: SF: I: **Tot.**	5 27 23 **69**	100	-			-				11/69 17/69 25/69 30/69	16 25 36 43	4 12 24 54	PF:	0/5 0/5 0/5 0/5	0 0 0 0	4 12 24 54
Baert[60]	2014	Retrosp.	IFX/ADA	160/80	40 EOW	PF: SF: I: **Tot.**	11 42 18 **73**	15 57.5 24.6	22/73 38/73	30 52	12 52	-				16/73	22	52	-			
Barreiro[19] (pouchitis)	2012	Retrosp.	IFX/ADA	160/80	40 EOW	PF: SF: I: **Tot.**	0 3 5 **8**	0 38 62	5/8 3/8	62 38	8 26	-				1/8 1/8 2/8	13 13 25	8 26 52	-			
Garcia-Bosch[26]	2013	Retrosp.	IFX/ADA	160/80 and 80/40	40 EOW	PF: SF: I: **Tot.**	6 33 0 **39**	15 85 0	23/39	69	12	PF: SF:	2/6 25/33	33 76	12 12	-			-			
Oussalah[39]	2008	Prosp.	IFX/ADA	160/80	40 EOW	PF: SF: I: **Tot.**	0 8 5 **13**	0 62 38	12/13 11/13 8/13 4/13	92 85 61 32	4 12 24 104	SF: I:	3/8 2/5	38 40	104 104	-			-			
Peyrin-Biroulet[44]	2007	Prosp.	IFX/ADA	160/80	-	PF: SF: I: **Tot.**	0 6 4 **10**	0 60 40	4/10	40	4	-				1/10	10	4	-			
Sandborn[49]	2012	Prosp.	IFX/ADA	160/80	40 EOW	PF: SF: I: **Tot.**	NR NR NR **98**	NR NR NR	36/98 20/98	37 20	8 52					9/98 10/98	9.2 10	8 52				
Taxonera[55]	2011	Retrosp.	IFX/ADA	160/80	40 EOW	PF: SF: I: **Tot.**	2 16 12 **30**	7 53 40	16/30 18/30	53 60	4 12	PF: SF: I:	0/2 10/16 8/12	0 62 67	12 12 12	3/30 8/30 15/30	10 27 50	4 12 52	-			