American Gastroenterological Association Technical Review on the Pharmacological Management of Moderate to Severe Ulcerative Colitis

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SUPPLEMENTARY APPENDIX

Search Strategy

Search date: March 18, 2018
Databases searched: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>; Elsevier Embase; Wiley Cochrane

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

#	Searches	Results
1	exp *Inflammatory Bowel Diseases/	60748
2	(inflammatory bowel disease* or IBD or Crohn* or (ulcerative adj2 colitis)).ti.	57541
3	1 or 2	68443
4	exp *Mercaptopurine/	7472
5	(6-Mercaptopurine or 6-MP or Purinethol or Purixan or azothioprine or Azathioprine or Azasan or Imuran).ti.	4985
6	exp *METHOTREXATE/	16094
7	(Methotrexate or Otrexup or Rasuvo or Rheumatrex or Trexall or MTX or Amethopterin).ti.	15528
8	exp *Antibodies, Monoclonal/	103894
9	(Infliximab or remicade or adalimumab or humira or golimumab or simponi or vedolizumab or entyvio or tofacitinib or Xeljanz or Jakvinus).ti.	7752
10	exp *Adrenal Cortex Hormones/	190542
11	(corticosteroid* or steroid* or prednisolone or hydrocortisone or methylprednisolone).ti.	108154
12	exp *Cyclosporine/	15762
13	exp *Tacrolimus/	9218
14	(cyclosporin* or Neoral or Gengraf or Sandimmune).ti.	20976
15	(tacrolimus or Prograf or Astagraf or Envarsus).ti.	6319
16	exp *Anti-Bacterial Agents/	411920
17	(antibiotic* or ciprofloxacin or metronidazole or rifaximin or clarithromycin).ti.	103467
18	or/4-17	829520
19	3 and 18	8113
20	animals/ not (humans/ and animals/)	4401096
21	19 not 20	8005
22	limit 21 to english language	7135
23	limit 22 to (case reports or comment or editorial or letter)	2166
24	22 not 23	4969

Elsevier Embase

#23 #21 NOT #22 AND [medline]/lim **5,685**
#22 #21 NOT #22 **6,931**
#21 #21 AND ('conference abstract'/it OR 'conference paper'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) **5,747**
#20 #3 AND #18 AND [english]/lim AND [humans]/lim **12,678**
#19 #3 AND #18 **16,831**
#18 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 **2,123,164**
#17 antibiotic*:ti OR ciprofloxacin:ti OR metronidazole:ti OR rifaximin:ti OR clarithromycin:ti **130,200**
#16 'antiinfective agent'/exp/mj **1,290,425**
#15 tacrolimus:ti OR prograf:ti OR astagraf:ti OR envarsus:ti **9,454**
#14 'tacrolimus'/exp/mj **15,210**
#13 cyclosporin*:ti OR neoral:ti OR gengraf:ti OR sandimmune:ti **25,473**
#12 'cyclosporine'/exp/mj **39,406**
#11 corticosteroid*:ti OR steroid*:ti OR prednisolone:ti OR hydrocortisone:ti OR methylprednisolone:ti **135,069**
#10 'steroid'/exp/mj **604,283**
#9 infliximab:ti OR remicade:ti OR adalimumab:ti OR humira:ti OR golimumab:ti OR simponi:ti OR vedolizumab:ti OR entyvio:ti OR tofacitinib:ti OR xeljanz:ti OR jakvinus:ti **14,671**
#8 'monoclonal antibody'/exp/mj **176,629**
#7 methotrexate:ti OR otrexup:ti OR rasuvo:ti OR rheumatrex:ti OR trexall:ti OR mtx:ti OR amethopterin:ti **21,573**
#6 'methotrexate'/exp/mj **47,846**
#5 '6 mercaptopurine':ti OR '6 mp':ti OR purinethol:ti OR purixan:ti OR azothioprine:ti OR azathioprine:ti OR azasan:ti OR imuran:ti **6,399**
#4 'mercaptopurine'/exp/mj **9,222**
#3 #1 OR #2 **98,937**
#2 inflammatory:ti AND bowel:ti AND disease*:ti OR ibd:ti OR crohn*:ti OR ((ulcerative NEAR/2 colitis):ti) **87,466**
#1 'inflammatory bowel disease'/exp/mj **80,278**

Wiley Cochrane

ID Search Hits
#1 MeSH descriptor: [Mercaptopurine] explode all trees 1300
#2 '6 mercaptopurine':ab or '6 mp':ab or purinethol:ab or purixan:ab or azothioprine:ab or azathioprine:ab or azasan:ab or imuran:ab 2414
#3 MeSH descriptor: [Methotrexate] explode all trees 3084
#4 methotrexate:ti or otrexup:ti or rasuvo:ti or rheumatrex:ti or trexall:ti or mtx:ti or amethopterin:ti 30
#5 MeSH descriptor: [Antibodies, Monoclonal] explode all trees 7736
#6 infliximab:ti or remicade:ti or adalimumab:ti or humira:ti or golimumab:ti or simponi:ti or vedolizumab:ti or entyvio:ti or tofacitinib:ti or xeljanz:ti or jakvinus:ti 2290
#7 MeSH descriptor: [Adrenal Cortex Hormones] explode all trees 13477
#8 corticosteroid*:ti or steroid*:ti or prednisolone:ti or hydrocortisone:ti or methylprednisolone:ti 13558
#9 MeSH descriptor: [Cyclosporine] explode all trees 2360
#10 cyclosporin*:ti or neoral:ti or gengraf:ti or sandimmune:ti 3339
#11 MeSH descriptor: [Tacrolimus] explode all trees 1383
#12 tacrolimus:ti or prograf:ti or astagraf:ti or envarsus:ti 1847
#13 MeSH descriptor: [Anti-Bacterial Agents] explode all trees 11141
#14 antibiotic*:ti or ciprofloxacin:ti or metronidazole:ti or rifaximin:ti or clarithromycin:ti 10281

#15	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14	60308
#16	MeSH descriptor: [Inflammatory Bowel Diseases] explode all trees	2416
#17	(inflammatory bowel disease* or IBD or Crohn* or (ulcerative near/2 colitis)):ti	4479
#18	#16 or #17	4758
#19	#15 and #18	1450

Additional side effects of pharmacotherapy for moderate-severe UC

While a thorough review of side effects of different medications was out of the scope of the review, key agent-specific risks are summarized below. t

Thiopurines: Dose-dependent side effects of thiopurines include bone marrow suppression and hepatotoxicity, and require monitoring of labs at frequent intervals. Dose-independent side effects including gastrointestinal intolerance; rarely, <1% patients may develop a hypersensitivity reaction to thiopurines including fever, or drug-induced pancreatitis. These reactions typically occur within the first 2-4 weeks of use.

Methotrexate: Common side effects with methotrexate including gastrointestinal intolerance, stomatitis, myelosuppression, headache, fatigue, malaise, or impaired ability to concentrate and mild elevation in liver enzymes. Similar to thiopurines, this also requires interval monitoring of liver enzymes and blood count. Prolonged exposure may increase risk of hepatic fibrosis. In addition, methotrexate has been associated with pulmonary toxicity. It is contraindicated in pregnant women, and strict contraception is recommended in methotrexate-treated patients.

TNF-α antagonists: Infliximab has been associated with acute infusion reactions which may or may not be IgE-mediated, as well as delayed infusion reactions characterized by diffuse arthralgias and myalgias, skin rash, etc. Injectable TNF-α antagonists have been associated with local injection site reactions. TNF-α antagonists have also been associated with demyelinating diseases, and is contraindicated in patients with multiple sclerosis. It is also contraindicated in patients with heart failure. A variety of skin reactions have also been observed with TNF-α antagonists, including psoriasiform lesions which rarely may be severe enough to warrant treatment discontinuation. Other rare side effects including drug-induced lupus, systemic vasculitis, leukopenia, etc.

Vedolizumab: Besides infusion reactions, no unique class-specific serious adverse events have been reported with vedolizumab.

Tofacitinib: Tofacitinib has been associated with increase in cholesterol, which requires monitoring. However, this has not translated into an increased risk of cardiovascular events in clinical trials. In trials of rheumatoid arthritis, rare reports of spontaneous gastrointestinal perforation has been reported, though the incidence of this in clinical trials of UC was 0.2 per 100 person-years.

Study, setting	Patients	Serious Infections	Opportunistic Infections
Kirchgesner, 2018; France; Nationwide cohort, 2009-14	190,694 patients with IBD (49.7% UC); 24.9%, 13.8% and 6.3% on IMM monotherapy, TNF-α monotherapy and combination therapy, respectively	**Incidence rate (per 1000 p-y):** • Unexposed: 8.4 • IMM mono: 10.5 • TNF-α mono: 18.9 • Combination: 22.4 **Adjusted analysis** • TNF-α mono vs. IMM: 1.71 (1.56-1.88) • Combination vs. IMM: 2.11 (1.80-2.48) • Combination vs. TNF-α mono: 1.23 (1.05-1.45)	**Incidence rate (per 1000 p-y):** • Unexposed: 0.4 • IMM mono: 1.7 • TNF-α mono: 2.1 • Combination: 4.1 **Adjusted analysis** • TNF-α mono vs. IMM: 1.08 (0.83-1.40) • Combination vs. IMM: 2.11 (1.45-3.08) • Combination vs. TNF-α mono: 1.96 (1.32-2.91)
Nyboe Andersen, 2017; Denmark; Nationwide register-based propensity score matched cohort study, 2002-12	52,392 patients with IBD, of whom 4300 received TNF-α antagonists; matched 1543 TNF-α antagonist users vs. 1543 TNF-α antagonist non-users	**90 day risk period after start of medication:** • TNF-α antagonist user vs. non-user: 1.63 (1.01-2.63) • TNF-α mono vs. IMM: 2.17 (0.85-5.52) **365 day risk period after start of medication:** • TNF-α antagonist user vs. non-user: 1.27 (0.92-2.27) • TNF-α mono vs. IMM: 2.05 (0.97-4.36)	Not reported
Grijlava, 2011; United States; multi-institutional collaboration, 1998-2007	45,188 patients with IBD; 9.4% and 6.8% treated with IMM and TNF-α antagonist, respectively; 2323 TNF-α antagonist users vs. 2323 propensity score matched TNF-α antagonist non-users	**Incidence rate (per 1000 p-y):** • IMM therapy: 96.0 • TNF-α antagonists: 109.1 **Adjusted analysis** • TNF-α user vs. IMM user: 1.10 (0.83-1.46)	**Herpes Zoster** **Incidence rate (per 1000 p-y):** • IMM therapy: 9.4 • TNF-α antagonists: 11.3 **Adjusted analysis** • TNF-α user vs. IMM user: 0.79 (0.41-1.53)
Schneweiss, 2009; British Columbia; population-based cohort study, 2001-06	10,622 patients with IBD; 27.0% and 4.9% treated with IMM and TNF-α antagonist, respectively	**Incidence rate (per 1000 p-y):** • IMM mono: 8.9 • TNF-α mono: 4.3 • Combination: 7.3 **Adjusted analysis** • TNF-α mono vs. IMM: 0.74 (0.10-5.53) • Combination vs. IMM: 1.05 (0.14-7.81)	Not reported
Lewis, 2018; United States; Medicare-Medicaid, 2001-13	3224 patients with UC treated with TNF-α antagonists vs. 459 patients treated with prolonged corticosteroids	**Incidence rate (per 1000 p-y):** • TNF-α antagonist user: 47.0 • Prolonged corticosteroid use: 54.9 **Adjusted analysis** • TNF-α antagonist user vs. prolonged corticosteroid use: 0.99 (0.78-1.26)	Not reported

eTable 1. Risk of serious and opportunistic infections with immunomodulators and/or TNF-α antagonists in key cohort studies

Study/Setting	Patients	Malignancy
Lemaitre, 2018; France; Nationwide cohort, 2009-15	189,289 patients with IBD, median follow-up 6.7y; 65%, 27%, 16% and 7.5% were unexposed, on IMM monotherapy, TNF-α monotherapy and combination therapy, respectively	**Incident lymphoma** **Incidence rate (per 1000 p-y):** • Unexposed: 0.26 • IMM mono: 0.54 • TNF-α mono: 0.41 • Combination: 0.95 **Adjusted analysis** • IMM vs. unexposed: 2.60 (1.96-3.44) • TNF-α mono vs. unexposed: 2.41 (1.60-3.64) • Combination vs. unexposed: 6.11 (3.46-10.8) • TNF-α mono vs. IMM: 0.93 (0.60-1.44) • Combination vs. IMM: 2.35 (1.31-4.22) • Combination vs. TNF-α mono: 2.53 (1.35-4.77)
Nyboe Andersen, 2014; Denmark; Nationwide register-based propensity score matched cohort study, 1999-2012	56,146 patients with IBD, median follow-up 9.3y; 8.1% exposed to TNF-α antagonists	**Overall malignancy** **Incidence rate (per 1000 p-y):** • TNF-α antagonist non-user: 7.4 • TNF-α antagonist user: 4.4 **Adjusted analysis (including adjusting for IMM use)** • TNF-α antagonist user vs. non-user: 1.07 (0.85-1.36) **Hematopoetic and lymphoid malignancy** **Incidence rate (per 1000 p-y):** • TNF-α antagonist non-user: 0.55 • TNF-α antagonist user: 0.43 **Adjusted analysis (including adjusting for IMM use)** • TNF-α antagonist user vs. non-user: 0.90 (0.42-1.91)
Beaugerie, 2009; France; Prospective nationwide observational cohort, 2004-07	19,486 patients with IBD, median follow-up, 3y; 30.1% and 5% treated with thiopurines and TNF-α antagonists, respectively	**Incident lymphoproliferative disorder** **Incidence rate (per 1000 p-y), standardized incidence ratio:** • Unexposed: 0.26; SIR: 1.45 (0.53-3.16) • IMM: 0.90; SIR: 6.86 (3.84-11.31) • TNF-α antagonist user: 0.48; SIR: 4.53 (0.55-16.4) • Combination: 1.03; SIR: 10.2 (1.24-36.9)
Haynes, 2013; United States; multi-institutional collaboration, 1998-2007	6357 patients with IBD (1508 p-y); 58.2% and 41.8% treated with IMM and TNF-α antagonist, respectively	**Incident lymphoma or leukemia** **Incidence rate (per 1000 p-y):** • IMM user: 0.5 • TNF-α antagonist user: 0.6 **Any solid organ cancer** **Incidence rate (per 1000 p-y):** • IMM user: 8.2 • TNF-α antagonist user: 4.1

		Adjusted analysis • TNF-α antagonist user vs. IMM user: 1.42 (0.47-4.26)
Herrinton, 2011; United States; Kaiser Permanente IBD Registry, 1996-2009	16,023 patients with IBD; median follow-up, 5.8y; 24% and 9% on IMM and TNF-α antagonist, respectively	**Incident lymphoma** **Incidence rate (per 1000 p-y), standardized incidence ratio:** • Unexposed: 0.49; SIR: 1.0 (0.95-1.1) • IMM mono: 0.46; SIR: 1.4 (1.2-1.7) • TNF-α antagonist mono: 1.49; SIR: 5.2 (3.5-6.8) • Combination: 1.91; SIR: 6.6 (4.4-8.8)

eTable 2. Risk of malignancy, in particular hematological malignancy, with immunomodulators and/or TNF-α antagonists in key cohort studies

	Trial and Intervention Characteristics	Definition and Timing of Outcome (CRem)	Mean age (y) (standard deviation); Sex (% male)	Mean Disease duration (y) (standard deviation); Disease extent (% extensive colitis)	Concomitant medications		Mean CRP (mg/L) (standard deviation)	Prior anti-TNF therapy (%)
					Immunomodulators (%)	Corticosteroids (%)		
INFLIXIMAB								
ACT 1[√] (Induction and Maintenance therapy)	62 sites, 2002-05; P: 121; I: IFX 5mg/kg, wk 0,2,6, then q8w – 121	MCS≤2; W8, W54	P: 41 (14); 60 I: 42 (14); 65	6.2 (5.9); 45 5.9 (5.4); 47	43.8 54.5	65.3 57.9	17 (27) 14 (19)	0 0
ACT 2[√] (Induction and Maintenance therapy)	55 sites, 2002-05; P: 123; I: IFX 5mg/kg, wk 0,2,6, then q8w – 121	MCS≤2; W8, W30	P: 39 (14); 58 I: 41 (13); 63	6.5 (6.7); 42 6.7 (5.3); 41	43.9 43.0	48.8 49.6	16 (29) 13 (23)	0 0
Jiang et al[√] (Induction and Maintenance therapy)	1 site (China), 2008-13; P: 41; I: IFX 5mg/kg, wk 0,2,6, then q8w – 41	MCS≤2; W8, W30	P: 35 (15); 61 I: 34 (14); 63	4.4 (2.6); 61 4.4 (2.8); 59	31.7 29.3	51.2 53.7	NR	0 0
NCT0155129[√] (Induction and Maintenance therapy)	12 sites (China), 2012-14; P: 49; I: IFX 5mg/kg, wk 0,2,6, then q8w – 50	MCS≤2; W8, W26	Entire group: 37; NR	3.7; NR	NR	80 60	NR	0 0
ADALIMUMAB								
ULTRA 1 (Induction therapy)	94 sites, 2007-10; P: 130; I: ADA 160/80/40, wk 0,2,4,6 – 130	MCS≤2; W8	P: 37 (18-72)[❖]; 64 I: 37 (18-75)[❖]; 64	5.4 (0.3-34.1)[❖]; 56 6.1 (0.2-34.4)[❖]; 46	39.9 39.2	67.6 54.6	3.2 (0.2-280)[❖] 3.3 (0.1-109)[❖]	0 0
ULTRA 2[√] (Induction and Maintenance therapy)	103 sites, 2006-10; P: 246; I: ADA 160/80/40, wk 0,2,4,6 – 248	MCS≤2; W8	P: 41 (13); 62 I: 40 (12); 57	8.5 (7.4); 49 8.1 (7.1); 48	50.8 57.7	75.2 80.7	13.1 (36.7) 14.5 (32.1)	41[§] 39[§]
Suzuki et al[√] (Induction and Maintenance therapy)	65 sites, 2009-11; P: 96; I: ADA 160/80/40, wk 0,2,4,6 – 90	MCS≤2; W8	P: 41 (14); 73 I: 43 (15); 68	7.8 (7.1); 62 7.8 (6.6); 70	54.2 45.6	60.4 63.3	3.4 (0.5-87.2)[❖] 2.2 (0.5-62.8)[❖]	0 0
GOLIMUMAB								
PURSUIT Phase 2 and 3 (Induction therapy)	217 sites, 2007-10; P: 331; I: GLM 200/100, wk 0,2 - 331	MCS≤2; W6	P: 39 (13); 53 I: 40 (14); 54	6.0 (6.7); 43 6.4 (6.2); 42	32.0 31.7	42.9 44.7	10.7 (16.8) 11.3 (15.3)	0 0
PURSUIT-M[¶]	251 sites, 2007-11;	MCS≤2;	P: 40 (14); 48	6.9 (7.0); NR	33.3	53.2	9.6 (15.5)	0

(Maintenance therapy)	P: 156; I: GLM 100mg q4w - 154	W54	I: 39 (13); 58	7.2 (7.0); NR	31.2	51.2	8.9 (14.7)	0
PURSUIT-J[¶] (Maintenance therapy)	49 sites (Japan), 2013-16; P: 31 I: GLM 100mg q4w – 32	MCS≤2; W54	P: 43 (14); 61 I: 39 (12); 69	5.7 (5.3); 39 5.4 (6.1); 38	41.9 50.0	29.0 28.1	4.1 (7.7) 5.3 (14.8)	0 0
VEDOLIZUMAB								
GEMINI I[¶] (Induction and Maintenance therapy)	211 sites, 2008-12; P(i): 149; I(i): VDZ 300mg, wk 0,2 – 746 P(m): I(m):	MCS≤2; W6(i); W52(M)	P: 41 (13); 62 I: 40 (13); 58 P(m): 40 (14); 55 I(m): 41 (13); 57	7.1 (7.2); 46 6.8 (6.2); 50 7.8 (7.0); 50 6.2 (5.0); 43	29.5 35.4 40 36	56.3 53.2 57 57	NR NR	49[*] 48[*] 37[**] 42[**]
Motoya et al (Induction and Maintenance therapy)	100 sites, 2014-18; P(i): 82; I(i): VDZ 300mg, wk 0,2,6 – 164 P(m): 42 I(m): VDZ 300mg q8w; 41	MCS≤2; W10(i); W60(m)	P(i): 44 (16); 67 I(i): 42 (14); 60 P(m): 43 (14); 55 I(m): 43 (14); 51	8.6 (8.0); 62 7.2 (6.2); 62 8.7 (7.0); 55 8.6 (7.8); 68	52.5 48.8 50.0 53.8	30.5 31.7 35.7 31.8	>3mg/L: 39 >3mg/L: 54 NR	50[∞] 51[∞] 33[∞∞] 42[∞∞]
VARSITY[√] (Induction and Maintenance therapy)	245 sites, 2015-19; ADA 160/80/40, wk 0,2,4 then q2w; 386 VDZ 300mg, wk 0,2,6, then q8w - 385	MCS≤2; W12	ADA: 41 (13); 56 VDZ: 41 (14); 61	6.4 (6.0); NR 7.3 (7.2); NR	25.9 26.2 Proportion of patients receiving both IM and CS not reported	36.3 36.1	NR	21[∂] 21[∂]
TOFACITINIB								
OCTAVE 1 (Induction therapy)	178 sites, 2012-15; P: 122 I: Tofacitinib 10mg po b.d. - 476	MCS≤2, with rectal bleeding score 0; W8	P: 42 (15); 63 I: 41 (14); 58	6.0 (0.5-36.2)[❖]; 54 6.5 (0.3-42.5)[❖]; 53	NA	47.5 45.0	4.7 (0.1-82.5)[❖] 4.4 (0.1-208.4)[❖]	53 53
OCTAVE 2 (Induction therapy)	182 sites, 2012-15; P: 112 I: Tofacitinib 10mg po b.d. - 429	MCS≤2, with rectal bleeding score 0; W8	P: 40 (13); 49 I: 41 (14); 60	6.2 (0.4-27.9)[❖]; 51 6.0 (0.4-39.4)[❖]; 49	NA	49.1 46.2	5.0 (0.2-205.1)[❖] 4.6 (0.2-156.0)[❖]	58 58
OCTAVE-Sustain[¶] (Maintenance therapy)	178 sites, 2012-15; P: 198 I: Tofacitinib 5mg po b.d. - 198	MCS≤2, with rectal bleeding score 0; W8	P: 43 (14); 59 I: 42 (14); 52	7.2 (0.6-42.7)[❖]; 55 6.5 (0.6-40.3)[❖]; 52	0 0	50.5 51.0	1.0 (0.1-45.0)[❖] 0.7 (0.1-33.7)[❖]	46.5 45.5
USTEKINUMAB								
UNIFI (Induction and Maintenance therapy)	244 sites, 2015-18; P(i): 319 I(i): UST 6mg/kg, wk 0 – 322 P(m): 175 I(m): UST 90mg	MCS≤2; W8(i); W44(m)	P(i): 41 (14); 62 I(i): 42 (14); 61 P(m): 42(14); 61 I(m): 40 (13); 53	8.0 (7.2); 47 8.2 (7.8); 47 7.5 (6.8); 49 8.1 (6.7); 46	27.9 27.6 28.0 25.6	49.2 52.2 54.3 54.0	4.7 (1.4-10.) 4.8 (1.8-13.7) 3.4 (1.4-9.7) 4.0 (1.4-12.7)	51[Δ] 52[Δ] 50[Δ] 52[Δ]

	q8w - 176							

[§]Reasons for discontinuation of prior anti-TNF therapy: Primary non-response, 0%; Secondary loss of response or intolerance, 100%;
[*]Reasons for discontinuation of prior anti-TNF therapy: Primary non-response, 48%; Secondary loss of response, 38%; Intolerance, 14%
[**]Reasons for discontinuation of prior anti-TNF therapy: Primary non-response, 36%; Secondary loss of response, 30%; Intolerance, 18%
[∞]Reasons for discontinuation of prior anti-TNF therapy: Primary non-response, 58%; Secondary loss of response, 40%; Intolerance, 2%
[∞∞∞]Reasons for discontinuation of prior anti-TNF therapy: Primary non-response, 43%; Secondary loss of response, 50%; Intolerance,7%
[∂]Reasons for discontinuation of prior anti-TNF therapy: Primary non-response, 50%; Secondary loss of response, 35%; Intolerance, 7%
[Δ]Includes patients with prior exposure to TNF antagonist with or without vedolizumab (13-18% had prior exposure to vedolizumab)
[√]Maintenance therapy with treat straight-through design
[¶]Only including patients with initial response to induction therapy who were re-randomized to placebo or active intervention
❖Median (range)
[Abbreviations: ADA-Adalimumab, CRP-C-reactive protein, GLM-Golimumab, IFX-Infliximab, i-induction, LOR-Loss of response; MCS-Mayo Clinic Score; m-maintenance; NR-Not reported; P-Placebo; PNR-Primary non-response, TNF-tumor necrosis factor; VDZ-Vedolizumab, W-Week]

eTable 3. Trial and patient characteristics in included trials of induction and maintenance therapy for moderate to severe ulcerative colitis. Endoscopic remission was defined as MCS 0 or 1 for all trials, except Probert et al (defined as Baron score 0) and Sandborn et al (Mayo score 0)

	Any Adverse Event (%)	Any Adverse Event leading to drug discontinuation (%)	Serious Adverse Events (%)	Any Infections (%)	Serious Infections (%)	Infusion/Injection-site Reaction (%)
INFLIXIMAB						
ACT 1[√]	P: 85.1 I: 87.6	9.1 8.3	25.6 21.5	38.8 43.8	4.1 2.5	10.7 9.9
ACT 2[√]	P: 73.2 I: 81.8	9.8 1.7	19.5 10.7	23.6 27.3	0.8 1.7	8.1 11.6
Jiang et al[√]	P: 39.0 I: 41.5	4.9 2.4	9.8 7.3	12.2 14.6	0 2.4	4.9 7.3
NCT01551290[√]	P: 63.3 I: 66.0	4.1 8.0	8.2 14.0	16.3 28.0	0 0	NR
ADALIMUMAB						
ULTRA 2[√]	P: 83.8 I: 82.9	13.1 8.9	12.3 12.1	39.6 45.1	1.9 1.6	3.8 12.1
Suzuki et al[*√]	P: 35.4[*] I: 44.4[*]	6.3 12.4	14.6 18.6	72.9 75.7	2.1 4.5	4.2 11.3
GOLIMUMAB						
PURSUIT-M	P: 66.0 I: 73.4	6.4 9.1	7.7 14.3	28.2 39.0	1.9 3.2	1.9 7.1
PURSUIT-J	P: 71.0 I: 96.9	NR	12.9 3.1	35.5 65.6	NR	0 18.8
VEDOLIZUMAB						
GEMINI I	P: 84.1 I: 82.0	NR	15.9 8.2	70.6 71.3	3.2 2.5	1.6 2.5
Motoya et al	P: 78.6 I: 87.8	14.3 4.9	7.1 9.8	NR	2.4 2.4	0 0
VARSITY[√]	ADA: 69.2 VDZ: 62.7	6.5 4.4	11.0 13.7	32.1 26.8	2.1 1.8	NR
TOFACITINIB						
OCTAVE-Sustain	P: 75.3 I: 72.2	18.7 9.1	6.6 5.1	24.2 35.9	1.0 1.0	N/A
USTEKINUMAB						
UNIFI	P: 78.9 I: 77.3	11.4 2.8	9.7 8.5	46.3 48.9	2.3 1.7	2.3 2.8

[*] Reports only “probably drug-related” adverse events.
[√] Maintenance therapy with treat straight-through design

eTable 4. Rate of adverse events in included trials of maintenance therapy for moderate-severe ulcerative colitis. Only data on randomized patients are included.

Study	Overall outcomes	Intensive infliximab regimen	Factors predictive of colectomy
Choy, 2018; Australia (7 centers); 2014-15; median 4-5 days of intravenous corticosteroids	3m colectomy = 15% (8/52, including 2 in-hospital) 12m colectomy = 27% (14/52)	14/51, 3 induction doses within median 25 days; at physician's discretion based on (i) a lack of adequate response to the first dose of infliximab; or (ii) an initial response followed by deterioration in symptoms such as stool frequency or rectal bleeding; or (iii) rise in inflammatory markers.	• Mayo score 3 • CRP/albumin ratio >0.37 at discharge
Gibson, 2015; Ireland; 2005-13 (accelerated in 2011); median 7 days of intravenous corticosteroids	Colectomy during induction = 28% (14/50) 2y colectomy = 44% (22/50)	15/50, 3 induction doses within median 24 days; at physician's discretion - any rebound in inflammation during the induction period after initial improvement in symptoms or CRP	• Low serum albumin (continuous) • Standard IFX dosing
Govani, 2016 (Abstract); Michigan, USA; 2000-15 (accelerated in 2013)	3m colectomy = 13/57 (23%)	17/57; starting in 2013 offered 2nd dose of IFX within 4 days if CRP had not declined <7mg/L	NR
Shah, 2018; New York, USA; 2011-16; median 3-4 days of intravenous corticosteroids	1m colectomy = 17% (25/146) 3m colectomy = 23% (33/146) 12m colectomy = 28% (41/146)	High-dose induction 10mg/kg vs. standard-dose induction 5mg/kg – only first dose (note: 22/120 patients with standard induction dose received 2nd induction dose within 7 days)	• Hemoglobin nadir <8 • Accelerated IFX dosing • Worsening hypoalbuminemia
Nalagatla, 2018; 3 sites, USA; 2005-17	In-hospital colectomy = 18/213 (8.5%); 3m colectomy = 34/213 (16%) 12m colectomy = 59/212 (28%)	81/213 (60 with upfront 10mg/kg vs. 21 with 5mg/kg chaser doses); At 2 centers, patients perceived to have more severe disease clinically or based on endoscopic severity often received upfront 10mg/kg, while those with partial response to the initial 5mg/kg dose received either another infusion at the same dose or 10mg/kg in 3-5 days. At 3rd center, patients with a CRP/albumin ratio > 1 received up front 10mg/kg infliximab; responders received a subsequent infusion at 10mg/kg in 2 weeks while partial or non-responders received a second dose at 10mg/kg in 3-5 days	• Low albumin

[Abbreviations: CRP=C-reactive protein, IFX=Infliximab, NR=Not reported]

eTable 5. Characteristics of studies comparing intensive infliximab dosing regimens vs. standard infliximab dosing regimens in hospitalized patients with acute severe ulcerative colitis, refractory to intravenous corticosteroids, being treated with infliximab.

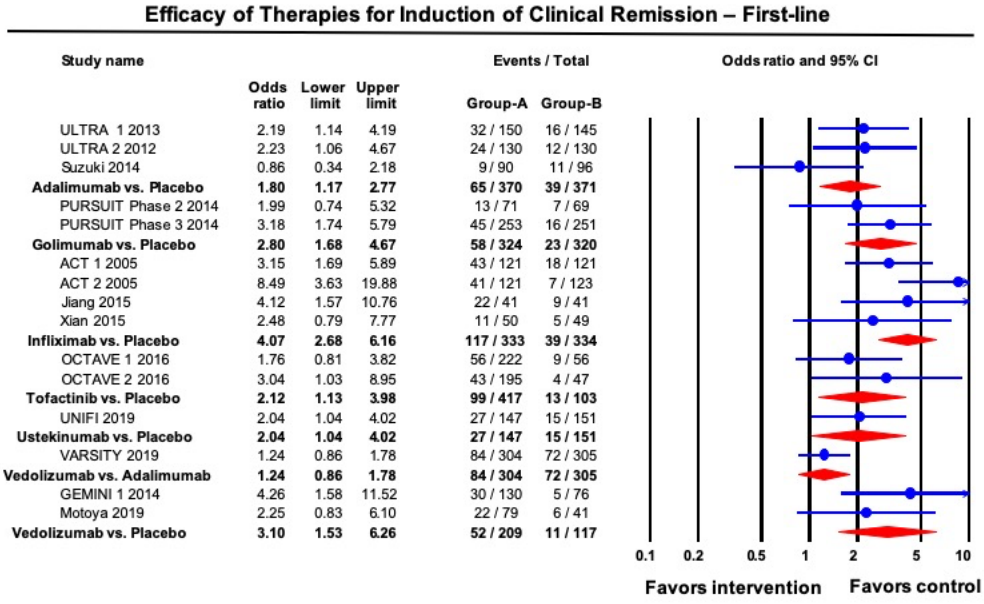
Study	(No. of patients), Age, % males	CRP at induction (mg/L)	Albumin at induction	CRP/albumin ratio	% severe endoscopy	1m colectomy	3m colectomy	12m colectomy
Choy	II (14): 37y, 64 SI (37): 33y, 62	35 (10-79) 17 (5-42)	23 (18-31) 26 (22-31)	2.0 (0.6-5.2) 0.6 (0.2-1.7)	85 57	NR	3/14 3/35	5/14 7/35
Gibson	II (15): 38y; 53 SI (35): 34y; 43	67 (24-83) 32 (7-71)	22 (22-25) 23 (20-30)	NR	53 66	1/15 13/35	NR	2y: 4/15 18/35
Govani	II (17): NR SI (40): NR	58±39 37±30	NR	NR	NR	NR	8/17 5/40	
Shah*	II (26): 22y, 62 SI (120): 35y, 49	CRP>5: 72 87	Alb <3: 58 69	NR	74 70	4/26 21/120	6/26 27/120	7/26 34/120
Nalagatla	II (81): 31y, 68 SI (132): 33y, 55	36 (55) 30 (52)	31 (7) 32 (7)	NR	84 73	In-hospital: 7/81 11/132	16/81 18/132	23/81 36/132

*If we combine high-dose induction + accelerated standard dose (as other studies have been done), then 26+22 (48) patients received accelerated induction vs. 98 standard IFX induction – 1m colectomy rate = 13/48 vs. 12/98
[Abbreviation: CRP=C-reactive protein, II=Intensive infliximab dosing regimen, m=month, SI=Standard infliximab dosing regimen]

eTable 6. Characteristics and outcomes of patients in studies comparing intensive infliximab dosing regimens vs. standard infliximab dosing regimens in hospitalized patients with acute severe ulcerative colitis, refractory to intravenous corticosteroids, being treated with infliximab.

FIGURES – Forest Plots

A.



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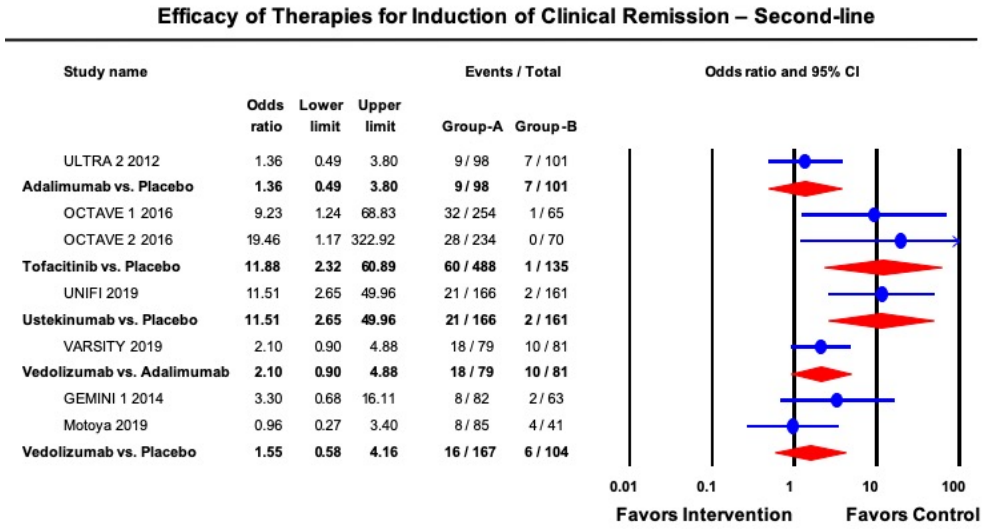
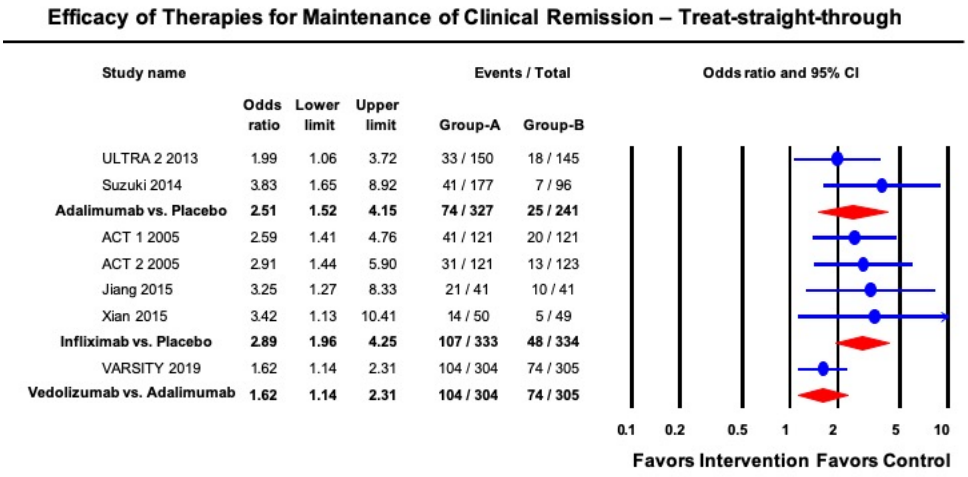


eFigure 1. Pair-wise meta-analysis: Efficacy of pharmacological agents in **(A)** biologic-naïve patients, or **(B)** in patients with prior exposure to TNFα antagonists, with moderate-severe ulcerative colitis for induction of clinical remission.

A.



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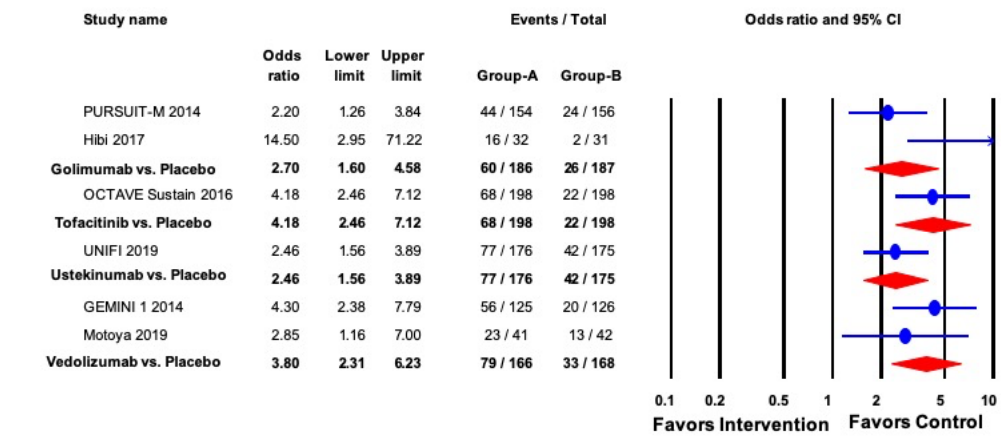
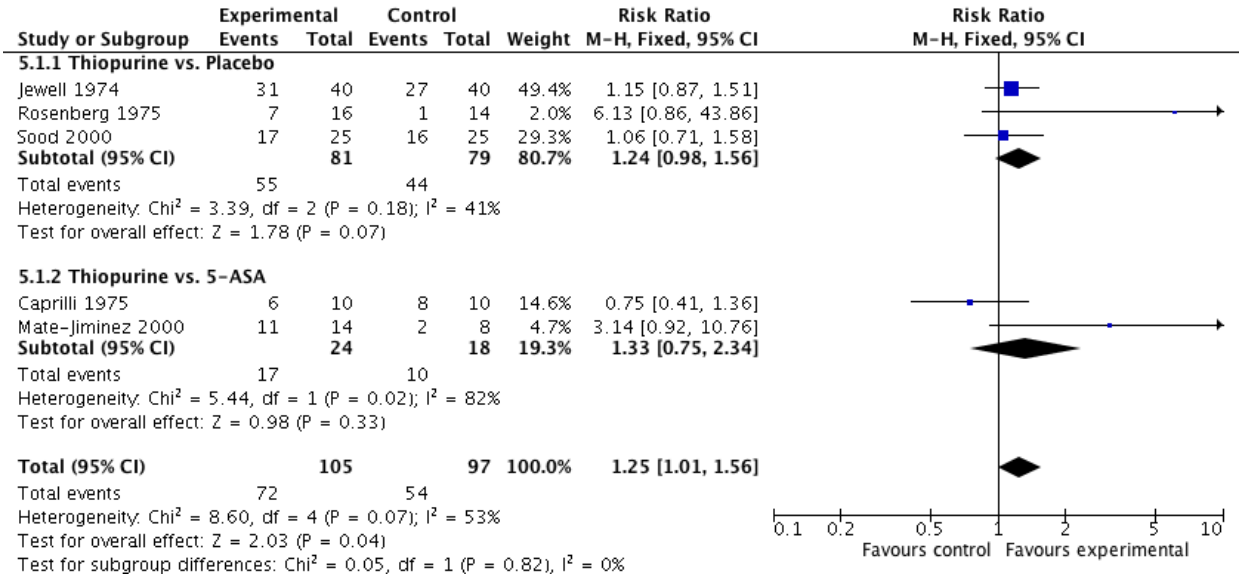
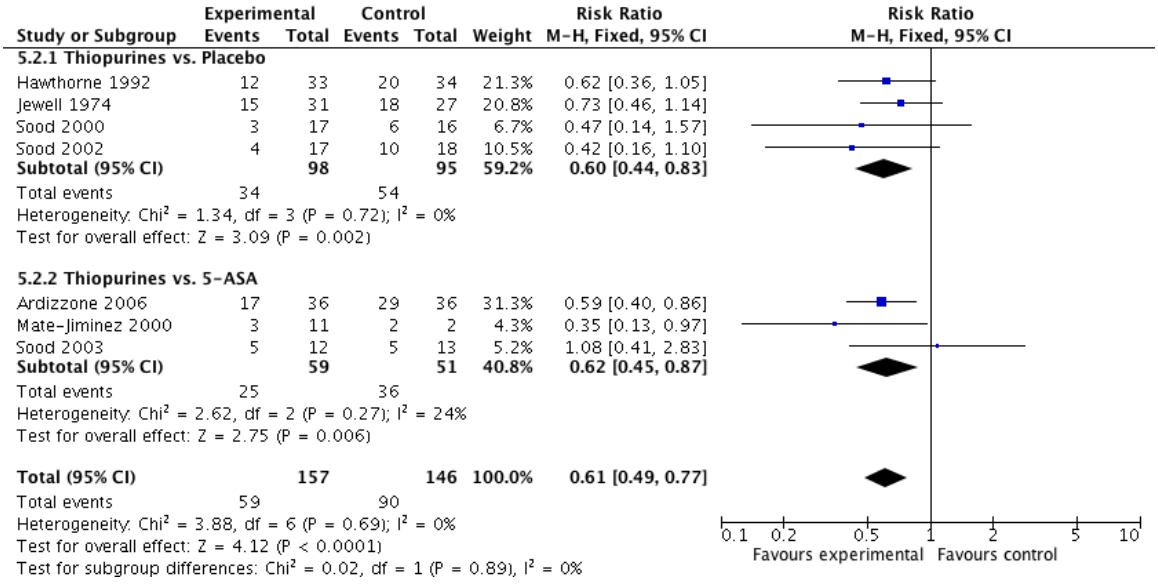


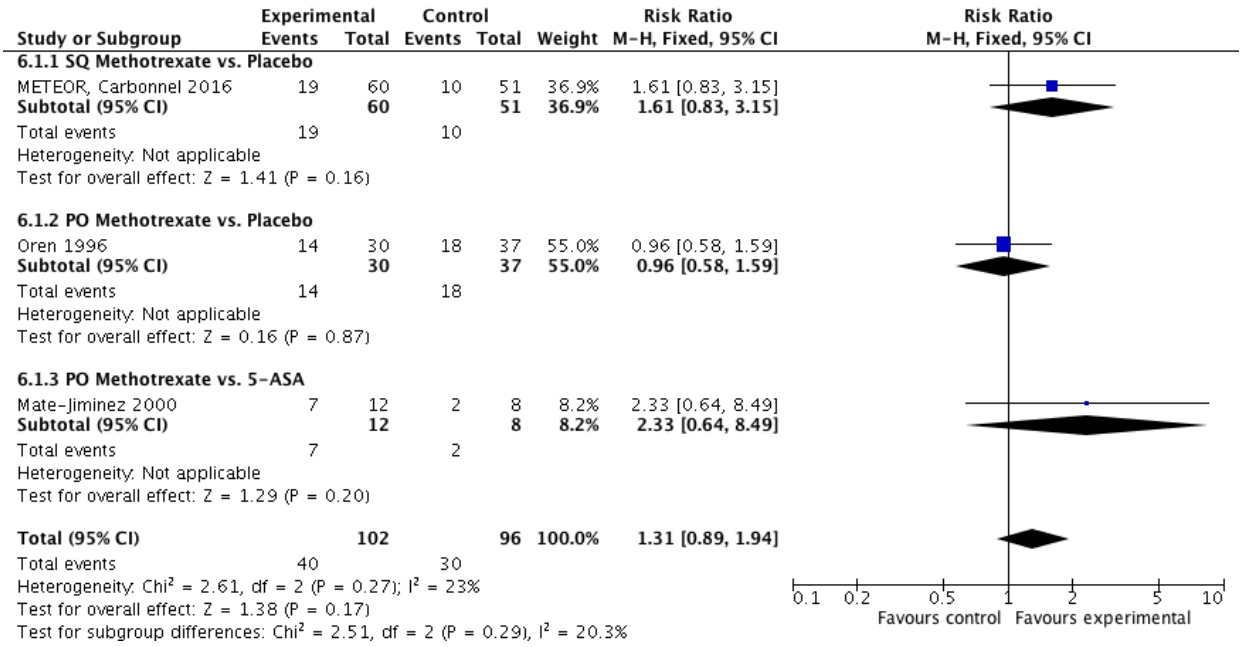
eFigure 2. Pair-wise meta-analysis: Efficacy of pharmacological agents for moderate-severe ulcerative colitis for maintenance of clinical remission in (A) treat straight-through trial design, and (B) in trials with re-randomization of responders.



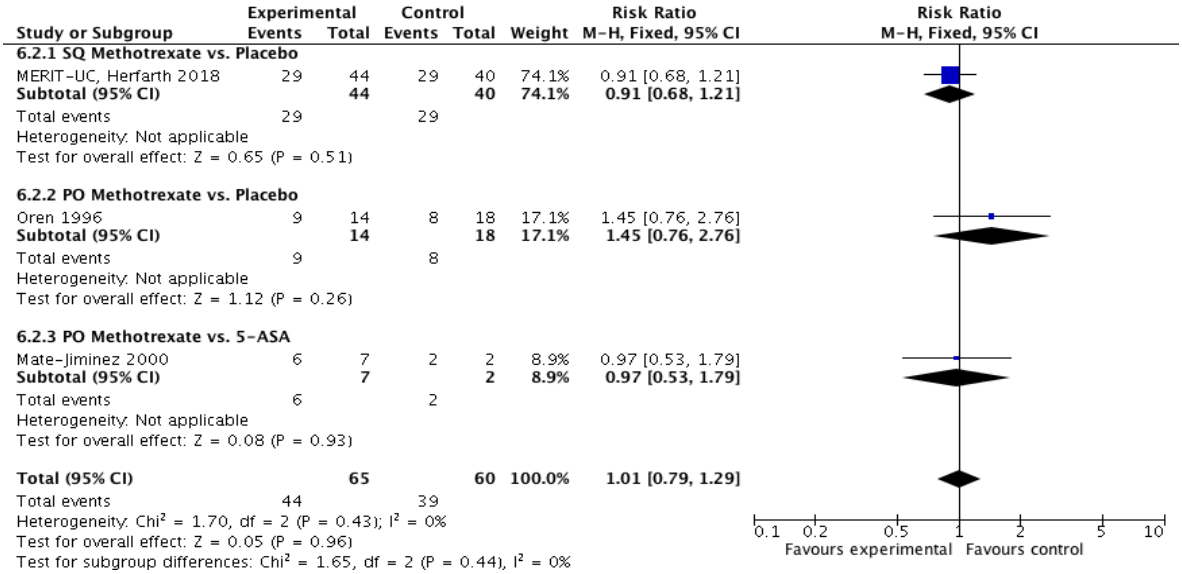
eFigure 3. Forest plot – Thiopurine monotherapy vs. No thiopurines – Achieving Clinical Remission



eFigure 4. Forest plot – Thiopurine monotherapy vs. No thiopurines – Preventing Relapse after Clinical Remission

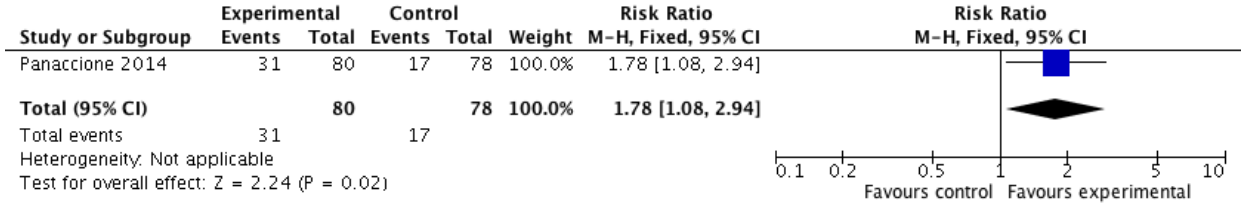


eFigure 5. Forest plot – Methotrexate monotherapy vs. No methotrexate – Achieving Clinical Remission



eFigure 6. Forest plot – Methotrexate monotherapy vs. No methotrexate – Preventing Relapse after Clinical Remission

A.



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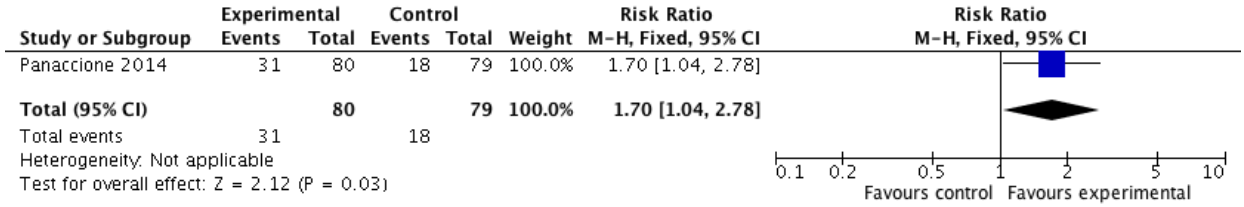
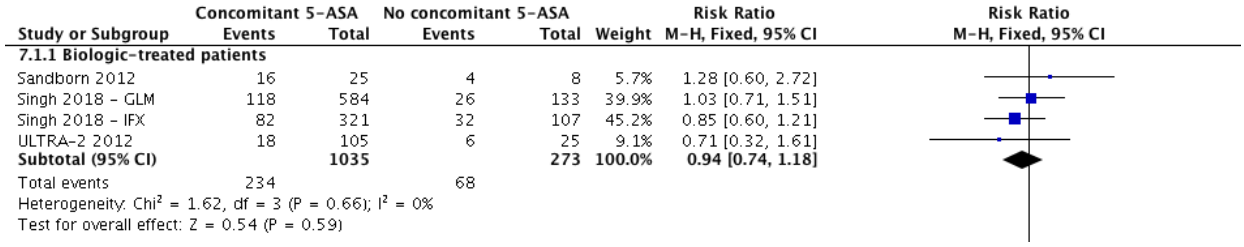


eFigure 7. Forest plot - (A) Infliximab+azathioprine vs. Infliximab monotherapy and (B) Infliximab+azathioprine vs. azathioprine monotherapy – Achieving Clinical Remission

A.



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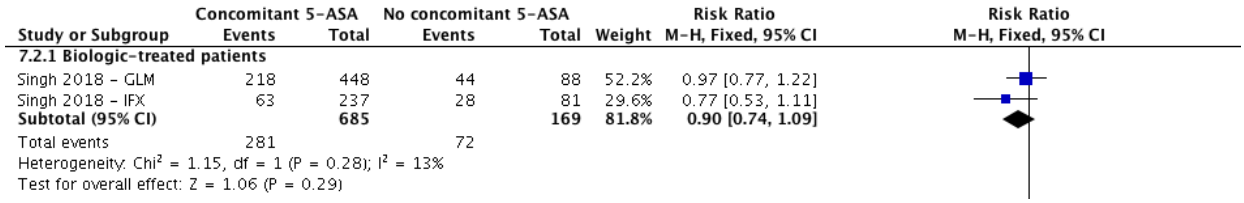
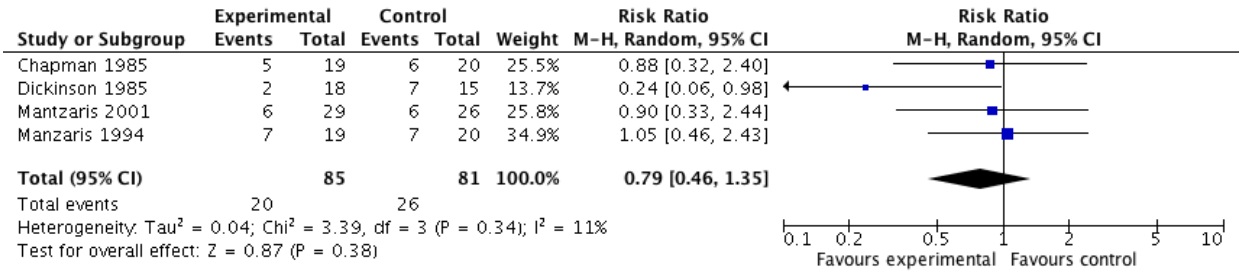
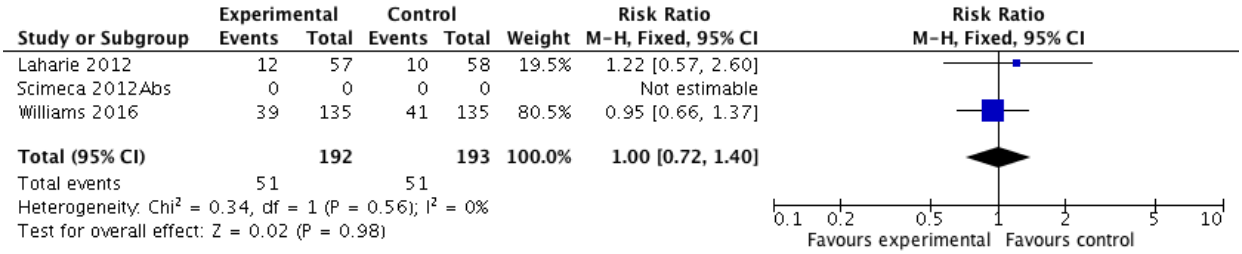


eFigure 8. Forest plot – Concomitant 5-ASA vs. no 5-ASA for (A) induction and (B) maintenance of remission in biologic-treated patients with moderate to severe ulcerative colitis



eFigure 9. Forest plot – Adjuvant antibiotics vs. no antibiotics in patients hospitalized with acute severe ulcerative colitis



eFigure 10. Forest plot – Infliximab vs. cyclosporine in patients hospitalized with corticosteroid-refractory acute severe ulcerative colitis