Anti-Drug Antibody Formation Against Biologic Agents in Inflammatory Bowel Disease: A Systematic Review and Meta-analysis.
Short Title: Anti-Drug Antibody Formation in IBD

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Biodrugs 2021

Supplementary Appendix 1: Search strategies

MEDLINE (OVID; 1946-present)

1. random$.tw.

2. factorial$.tw.

3. (crossover$ or cross over$ or cross-over$).tw.

4. placebo$.tw.

5. single blind.mp.

6. double blind.mp.

7. triple blind.mp.

8. (singl$ adj blind$).tw.

9. (double$ adj blind$).tw.

10. (tripl$ adj blind$).tw.

11. assign$.tw.

12. allocat$.tw.

13. crossover procedure/

14. double blind procedure/

15. single blind procedure/

16. triple blind procedure/

17. randomized controlled trial/

18. or/1-17

19. (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)

20. 18 not 19

21. exp Crohn disease/ or crohn*.mp.

22. (colitis and ulcerat*).mp.

23. ulcerative colitis.mp. or exp ulcerative colitis/

24. inflammatory bowel disease*.mp.

25. IBD.mp.

26. 21 or 22 or 23 or 24 or 25

27. 20 and 26

28. exp monoclonal antibody/

29. anti-tum*.mp. or exp anti tumor necrosis factor/

30. exp tumor necrosis factor antibody/ or exp tumor necrosis factor alpha antibody/ or anti-TNF.mp. or anti TNF.mp.

31. anti-alpha.mp.

32. infliximab.mp. or exp infliximab/ or cA2.mp.

33. ustekinumab.mp. or CNTO 1275.mp. or exp ustekinumab/

34. exp certolizumab pegol/ or certolizumab*.mp. or CDP870.mp.

35. natalizumab.mp. or exp natalizumab/ or alpha-4.mp. or alpha4.mp.

36. vedolizumab.mp. or exp vedolizumab/ or alpha4beta7.mp or alpha-4beta-7.mp or MLN02.mp or MLN-02.mp.

37. adalimumab.mp. or exp adalimumab/

38. exp golimumab/ or golimumab.mp. or CNTO*148.mp.

39. exp mucosal addressin cell adhesion molecule 1/ or anti-madcam.mp.

40.etrolizumab.mp.or rhuMAb Beta7.mp. or exp etrolizumab/

41. 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40

42. 27 and 41

EMBASE (Ovid; 1947-present)

1. random$.tw.

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26. 21 or 22 or 23 or 24 or 25

27. 20 and 26

28. exp monoclonal antibody/

29. anti-tum*.mp. or exp anti tumor necrosis factor/

30. exp tumor necrosis factor antibody/ or exp tumor necrosis factor alpha antibody/ or anti-TNF.mp. or anti TNF.mp.

31. anti-alpha.mp.

32. infliximab.mp. or exp infliximab/ or cA2.mp.

33. ustekinumab.mp. or CNTO 1275.mp. or exp ustekinumab/

34. exp certolizumab pegol/ or certolizumab*.mp. or CDP870.mp.

35. natalizumab.mp. or exp natalizumab/ or alpha-4.mp. or alpha4.mp.

36. vedolizumab.mp. or exp vedolizumab/ or alpha4beta7.mp or alpha-4beta-7.mp or MLN02.mp or MLN-02.mp.

37. adalimumab.mp. or exp adalimumab/

38. exp golimumab/ or golimumab.mp. or CNTO*148.mp.

39. exp mucosal addressin cell adhesion molecule 1/ or anti-madcam.mp.

40.etrolizumab.mp.or rhuMAb Beta7.mp. or exp etrolizumab/

41. 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40

42. 27 and 41

COCHRANE LIBRARY

1. Crohn

2. Colitis

3. Inflammatory bowel disease

4. IBD

5. monoclonal antibody

6. anti-tum* or anti tumor necrosis factor or tumor necrosis factor antibody or tumor necrosis factor alpha antibody or anti-TNF or anti TNF or anti-alpha

7. infliximab or cA2

8. ustekinumab or CNTO 1275

9. certolizumab or CDP870

10. natalizumab or alpha-4or alpha4

11. vedolizumab or alpha4beta7 or alpha-4beta-7 or MLN02 or MLN-02.

12. Adalimumab

13. Golimumab or CNTO148

14. mucosal addressin cell adhesion molecule 1 or anti-madcam

15. etrolizumab

16. #1 or #2 or #3 or #4

17. #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15

18. #16 and #17

Cochrane IBD/FBD Group Register

anti-tum* or anti tumor necrosis factor or tumor necrosis factor antibody or tumor necrosis factor alpha antibody or anti-TNF or anti TNF or anti-alpha or infliximab or cA2 or ustekinumab or CNTO 1275 natalizumab or alpha-4or alpha4 or vedolizumab or alpha4beta7 or alpha-4beta-7 or MLN02 or MLN-02 or adalimumab or golimumab or CNTO148 or mucosal addressin cell adhesion molecule 1 or anti-madcam or etrolizumab

Supplementary Table 1: Characteristics of included studies

INFLIXIMAB									
	Study & records	**N**	**Sample size**	**Population**	**Study type**	**Data type**	**Intervention/ Population**	**Control**	**Outcomes of interest**
1	Baert 2003[1]	125	125	CD	Observational	Observational	Infliximab + IM	Infliximab	-ADA formation -ADA concentration -Adverse events
2	Colombel 2010[2] *(SONIC)* *Records:* *-Colombel 2017[3]*	508	219	CD	RCT	Randomized	Infliximab + azathioprine	Azathioprine + placebo Infliximab + placebo	-ADA formation -Clinical outcomes
							ADA positive	ADA negative or inconclusive	
3	D'Haens 2018[4]	122	122	CD	RCT	Observational	Dose intensification algorithm	Dose intensification based on symptoms	-ADA formation
4	Farrell 2003[5]	53	53	CD	Observational	Observational	Infliximab ADA positive	Infliximab ADA negative	-ADA formation -Clinical outcomes
5	Farrel 2003[5]	80	68		RCT	Randomized	Infliximab + hydrocortisone premedication	Infliximab	-ADA formation -ADA concentration -Adverse events
6	Feagan 2014[6]	126	126	CD	RCT	Randomized	Infliximab + methotrexate	Infliximab + placebo	-ADA formation -Clinical outcomes
7	Fernandes 2020[7]	205			Observational	Observational	Treatment escalation based on TDM	Retrospective cohort without TDM	-ADA formation
							Infliximab + IM	Infliximab	-ADAformation
8	Hanauer 2002[8] *(ACCENT-1‡)* *Records:* *-Rutgeerts 2004[9]* *-Hanauer 2004[10]*	573	442	CD	RCT	Observational	Infliximab + IM	Infliximab	-ADA formation -Adverse events
							ADA positive	ADA negative or inconclusive	
9	Jiang 2015[11]	123	78	UC	RCT	Observational	ADA positive	ADA negative or inconclusive	-Clinical outcomes

10	Oh 2017[12]	138	138	CD	Observational	Observational	IFX ADA positive	IFX ADA negative	-Drug concentration
							IFX + IM	IM	-ADA formation
							Clinical response	No response	-ADA concentration
11	Panaccione 2014[13]	239	68	UC	RCT	Randomized	Infliximab + azathioprine	Infliximab + placebo Azathioprine + placebo	-ADA formation
12	Present 1999[14]	94	92	CD	RCT	Observational	Infliximab	placebo	-ADA formation
13	Regueiro 2016[15]	297	147	CD*	RCT	Observational	Infliximab + IM	Infliximab	-ADA formation
							ADA positive	ADA negative or inconclusive	-Endoscopic outcomes
14	Roblin 2017[16]	81	81	IBD	Open label trial	Observational	Infliximab + continued azathioprine Infliximab + lowered azathioprine	Infliximab + placebo	-ADA formation
15	Rutgeerts 1999[17]	73	47	CD	RCT	Observational	Infliximab	Placebo	-ADA formation
16.1	Rutgeerts 2005a[18] *(ACT-1)* *Records:* *-Reinisch 2012[19]* *-Adedokun 2014[20]* *-Vande Casteele 2019[21]*	364	229	UC	RCT	Observational	ADA positive	ADA negative or inconclusive	-Clinical outcomes -Drug concentration -Adverse events
16.2	Rutgeerts 2005b[18] *(ACT-2)* *Records:* *-Reinisch 2012[19]* *-Adedokun 2014[20]* *-Vande Casteele 2019[21]*	364	188	UC	RCT	Observational	ADA positive	ADA negative or inconclusive	-Clinical outcomes -Drug concentration -Adverse events
17	Sands 2004[22]	306	258	CD	RCT	Observational	Infliximab + IM Infliximab + CS	Infliximab	-ADA formation -Adverse events

							Infliximab + IM + CS		
							ADA positive	ADA negative or inconclusive	
18	Seow 2010[23]	115	108	UC	Observational	Observational	ADA positive	ADA negative	-Clinical outcomes -Drug concentration
19	Steenholdt 2014[24] *Records:* *-Steenholdt 2015[25]* *-Edlund 2017[26]*	69	69	CD	RCT	Observational	Infliximab intensification based on ADAs	Infliximab intensification based on algorithm	-ADA formation
20	Targan 1997[27]	108	101	CD	RCT	Observational	Infliximab	Placebo	-ADA formation
21	Van Assche 2008[28]	80	80	CD	RCT	Randomized	Infliximab + azathioprine	Infliximab + placebo (withdrawal of azathioprine)	-ADA formation
22	Vande Casteele 2015[29] *TAXIT* *Records:* *-van Stappen 2017[30]* *-van Stappen 2018[31]*	263	275 76	IBD	RCT	Observational	Infliximab intensification based on ADAs	Infliximab intensification based on symptoms	-ADA formation
							ADA positive	ADA negative or inconclusive	-Drug concentration
							Drug sensitive assay	Drug tolerant assay	-ADA formation -Clinical relevance
23	Vermeire 2007[32]	174	174	CD	Observational	Observational	Infliximab + methotrexate Infliximab + azathioprine	Infliximab + placebo	-ADA formation -ADA concentration
							ADA positive	ADA negative or inconclusive	-Drug concentration
24	Ye 2019[33]	220		CD	RCT	Observational	Biosimilar IFX	Originator IFX	-ADA formation
25	Yokoyama 2017[34]	21	21	UC	Observational	Observational	LOR	No LOR	-ADA formation
ADALIMUMAB									
26	**Study**	**N**	**Sample size**	**Population**	**Study type**	**Data type**	**Intervention/ Population**	**Control**	**Outcomes of interest**
27	Bodini 2014[35] *Records:* *-Savarino 2013[36]*	6	6	CD*	RCT	Observational†	Adalimumab	Azathioprine Mesalamine	-ADA formation

28	Hanauer 2006[37] *(CLASSIC-I)*	299	225	CD	RCT	Observational	Adalimumab	Placebo	-ADA formation
29	Matusumoto 2016[38] *Records: -Motoya 2017[39] -Nakase 2017[40]*	176	151	CD	RCT	Randomized	Adalimumab + azathioprine	Adalimumab + placebo	-ADA formation
30	Sandborn 2007a[41] *(CLASSIC II)*	276	269	CD	RCT	Observational	Adalimumab + IM	Adalimumab	-ADA formation
31	Sandborn 2007b[42] *(CLASSIC I)*	325	158	CD	RCT	Observational	Adalimumab + IM	Adalimumab	-ADA formation
32	Sandborn 2012a[43] ULTRA II *Records: -Awni 2013 [44] -Sandborn 2013[45]*	518	245	UC	RCT	Observational	Adalimumab	Placebo	-ADA formation
33	Suzuki 2014[46] *Records: -Suzuki 2017[47]*	274	240	UC	RCT	Observational	Adalimumab	Placebo	-ADA formation
34	Watanabe 2012[48] *Records: -Watanabe 2014[49]*	90	67	CD	RCT	Observational	Adalimumab + IM	Adalimumab	-ADA formation
35	Wright 2018[50]	52	52	CD	RCT subanalysis	Observational	Adalimumab + IM	Adalimumab	-ADA formation
							ADA positive	ADA negative	-Adalimumab concentration
36	Wu 2016[51]	30	30	CD	RCT	Observational	Adalimumab	Placebo	-ADA formation
INFLIXIMAB and ADALIMUMAB									
	Study	**N**	**Sample size**	**Population**	**Study type**	**Data type**	**Intervention/ Population**	**Control**	**Outcomes of interest**
37	Roblin 2020[52]	90	90	IBD	RCT	Observational	Anti-TNF + IM	Anti-TNF	-ADA formation -ADA disappearance
GOLIMUMAB									
38	Hibi 2017[53] *(PURSUIT-J)*	123	123	UC	RCT	Observational	Golimumab	Placebo	-ADA formation
39	Rutgeerts 2015[54] *(PURSUIT-IV)*	291	206	UC	RCT	Observational	Golimumab i.v.	Placebo	-ADA formation

40	Sandborn 2014[55, 56] *Records:* *-Adedokun 2013 (2x)*[57, 58] *-Adedokun 2017*[59] *-Sandborn 2017*[60] *-Reinisch 2018*[61] -Adedokun 2019[62]	1528	1103	UC	RCT	Observational	Golimumab + IM	Golimumab	-ADA formation
CERTOLIZUMAB PEGOL									
	Study	**N**	**Sample size**	**Population**	**Study type**	**Data type**	**Intervention/ Population**	**Control**	**Outcomes of interest**
41	Sandborn 2007c[63] PRECISE-1 *Records:* *-Sandborn 2015*[64]	662	331	CD	RCT	Observational	Certolizumab pegol + IM	Certolizumab pegol	-ADA formation
							ADA positive	ADA negative or inconclusive	-Drug concentration
42	Sandborn 2010b[65] *(PRECiSE 4)* *Records:* *-Sandborn 2015*[64] *-Sandborn 2016*[66]	124	124	CD	RCT	Observational	Certolizumab pegol	Placebo	-ADA formation
							ADA positive	ADA negative or inconclusive	-Drug concentration
43	Sandborn 2011[67]	438	223	CD	RCT	Observational	Certolizumab pegol	Placebo	-ADA formation
44	Sandborn 2017[68] *(PRECiSE-3)* *Records:* *-Lichtenstein 2010*[69] *-Sandborn 2015*[64]	595	595	CD	RCT	Observational	Certolizumab pegol + IM	Certolizumab pegol	-ADA formation
							ADA positive	ADA negative or inconclusive	-Biochemical outcomes -Drug concentration
45	Schreiber 2005[70]	292	73	CD	RCT	Observational	Certolizumab pegol	Placebo	-ADA formation
46	Schreiber 2007[71] PRECISE-2 *Records:* *-Sandborn 2015*[64]	668	668	CD	RCT	Observational	Certolizumab pegol + IM	Certolizumab pegol	-ADA formation -Drug concentration
							ADA positive	ADA negative or inconclusive	-Clinical outcomes
VEDOLIZUMAB									
	Study	**N**	**Sample size**	**Population**	**Study type**	**Data type**	**Intervention/ Population**	**Control**	**Outcomes of interest**
47	Feagan 2005[72]	181	30	UC	RCT	Observational	MLN02 (0.5 mg) MLN02 (2.0 mg)	Placebo	-ADA formation

48	Feagan 2008[73]	185	128	CD	RCT	Observational	MLN02 (0.5 mg) MLN02 (2.0 mg)	Placebo	-ADA formation
							ADA positive	ADA negative or inconclusive	-Adverse events -Clinical outcomes
49	Feagan 2013[74] (GEMINI 1) *Records:* *-Rosario 2015[75]* *-Feagan 2015[76]* *-Feagan 2017[77]* *-Loftus 2017[78]* *-Wyant 2019[79]*	895	620	UC	RCT	Observational	Vedolizumab	Placebo	-ADA formation
							ADA positive	ADA negative or inconclusive	-Adverse events
50	Motoya 2019[80]	292	167	UC	RCT	Observational	Vedolizumab	Placebo	-ADA formation
51	Parikh 2012[81] *Records:* *-Parikh 2013 (extension)[82]*	46 72	37 72	UC	RCT	Observational	Vedolizumab	Placebo	-ADA formation
							ADA positive	ADA negative or inconclusive	-Adverse events
52	Sandborn 2013[83] *Records:* *-Feagan 2015[76]* *-Vermeire 2017[84]* *-Wyant 2019[79]*	1115	814	CD	RCT	Observational	Vedolizumab	Placebo	-ADA formation
53	Sandborn 2020[85] (VISIBLE) *Records:* *-Sandborn 2019[86]*	383	106 s.c. 54 i.v.	UC	RCT	Observational	Vedolizumab i.v. + s.c. maintenance	Placebo	-ADA formation
54	Sands 2014[87]	416	209	CD	RCT	Observational	Vedolizumab	Placebo	-ADA formation
55	Watanabe 2020[88]	157	63	CD	RCT	Observational	Vedolizumab	Placebo	-ADA formation
NATALIZUMAB									
	Study	**N**	**Sample size**	**Population**	**Study type**	**Data type**	**Intervention/ Population**	**Control**	**Outcomes of interest**
56	Ghosh 2003[89]	248	185	CD	RCT	Observational	Natalizumab	Placebo	-ADA formation
57	Gordon 2001[90]	30	18	CD	RCT	Observational	Natalizumab	Placebo	-ADA formation
58	Gordon 2002[91]	10	10	UC	Open-label	Observational	Natalizumab	N/A	-ADA formation
59	Sandborn 2005a[92] *(ENACT-1)*	905	723	CD	RCT	Observational	Natalizumab + IM	Natalizumab	-ADA formation
60	Sandborn 2005b[92] *(ENACT-2)*	339	214	CD	RCT	Observational	Natalizumab + IM	Natalizumab	-ADA formation

61	Targan 2007[93]	509	241	CD	RCT	Observational	Natalizumab + IM	Natalizumab	-ADA formation
62	Sands 2007[94]	79	52	CD	RCT	Observational	Natalizumab	Placebo	-ADA formation
USTEKINUMAB									
	Study	**N**	**Sample size**	**Population**	**Study type**	**Data type**	**Intervention/ Population**	**Control**	**Outcomes of interest**
63	Sands 2019[95] (UNIFI) *Records:* -Adedokun 2019 (2x)[96, 97]	960	680	UC	Post-Hoc RCT	Observational	Ustekinumab	Placebo	-ADA formation
64	Feagan 2016[98] *(UNITI-1,* *UNITI-2,* *IM-UNITI)* *Records:* *-Hibi 2017[99]* *-Sandborn 2016[100]* *-Sandborn 2018[101]* *-Sandborn 2019 (IM-UNITI)[102]* *-Ghosh 2019 (IM-UNITI LTE)[103]* *-Hanauer 2020 (IM-UNITI LTE)[104]*	741 628 397 718	1154 237	CD	RCT	Observational	Ustekinumab	Placebo	-ADA formation
65	Sandborn 2008[105] (UCDS)	104	99	CD	RCT	Observational	Ustekinumab	Placebo	-ADA formation
66	Sandborn 2012b[106] (CERTIFI)	395	427	CD	RCT	Observational	Ustekinumab	Placebo	-ADA formation
ETROLIZUMAB									
	Study	**N**	**Sample size**	**Population**	**Study type**	**Data type**	**Intervention/ Population**	**Control**	**Outcomes of interest**
67	Rutgeerts 2013[107]	48	38	UC	RCT	Observational	Etrolizumab	Placebo	-ADA formation
68	Vermeire 2014[108]	124	81	UC	RCT	Observational	Etrolizumab	Placebo	-ADA formation

CD, Crohn's disease; IM, immunosuppressive; ADA, anti-drug antibody; RCT, randomized controlled trial; TDM, therapeutic drug monitoring; UC, ulcerative colitis

Supplementary Table 2: ADA formation rates and measurement time-points

Infliximab						
	Study	**Nr. Positive**	**Sample-size**	**Proportion**	**Measurement time-points**	**Time follow-up**
	Baert 2003[1]	76	125	60.8%	Unknown (variable)	36 months (median)
	Colombel 2010[2] *SONIC*	16	219	7.3%	weeks 0, 30, 46	30 weeks
	D'Haens 2018[4]	21	122	17.2%	Weeks 0,2 ,4 ,6 , 12, 14, every 4 weeks	54 weeks
	Farrell 2003[5]	19	53	35.8%	weeks 0, 24	20 weeks (median)
	Farrell 2003[5]	27	68	39.7%	weeks 0, 8, 16 weeks	16 weeks
	Feagan 2014[6]	16	126	12.7%	weeks 1, 3, 7, 14, 22, 30, 38, 46, 50	50 weeks
	Fernandes 2020[7]	13	205	6.3%	Week 14 and every 2 infusions	104 weeks
	Hanauer 2002[8] *ACCENT-1*‡	64	442	14.5%	Weeks 0, 14, 22, 54	54 weeks
	Jiang 2015[11]	4	78	5.1%	Weeks 0, 30	30 weeks
	Oh 2017[12]	47	138	34.1%	Every infusion	47 months (median)
	Panaccione 2014[13]	8	68	11.8%	Weeks 0, 16	16 weeks
	Present 1999[14]	3	92	3.3%	Weeks 0, 2, 6	12 weeks
	Regueiro 2016[15]	24	147	16.3%	Weeks 0, 72	104 weeks
	Roblin 2017[16]	6	81	7.4%	Every infusion	56 weeks
	Rutgeerts 1999	7	47	14.9%	Unknown	48 weeks
	Rutgeerts 2005a[18] *ACT-1*	14	229	6.1%	Weeks 0, 30, 54	54 weeks
	Rutgeerts 2005b[18] *ACT-2*	12	188	6.4%	Weeks 0, 30	30 weeks
	Sands 2004[22]	44	258	17.1%	Weeks 0, 14, 30, 54	54 weeks
	Seow 2010[23]	44	108	40.7%	10.7 months (median) 23 patients at week 1, 2, 4, 6, 14, 25 25 patients randomly for second measurement median 20 weeks after first measurement.	54 weeks
	Steenholdt 2015[25]	13	42	31.0%	At time of IFX failure	12 weeks
	Targan 1997[27]	6	101*	5.9%	Week 12	12 weeks
	Van Assche 2008[28]	7	80	8.8%	Every 16 weeks	104 weeks
	Vande Casteele 2015[29] *TAXIT*	18	275	2.9%	Screening measurement	Screening
	Vande Casteele 2015[29] *TAXIT*	3	226	1.3%	Every infusion	52 weeks
	Vermeire 2007[32]	96	174	55.1%	Before and 4 weeks after each infusion (unscheduled)	42 weeks (median)
	Ye 2019[33]	40	220	18.2%	Weeks 0, 14, 30, 54	54 weeks

	Yokoyama 2017[34]	1	21	4.8%	Unknown	54 weeks
Adalimumab						
	Bodini 2014[35]	1	6	16.7%	Every 8 weeks	104 weeks
	Hanauer 2006[37] *CLASSIC-1*	1	225	0.4%	Weeks 0, 1, 2, 4	4 weeks
	Matusumoto 2016[38]	13	151	8.6%	Week 26	52 weeks
	Sandborn 2007a[41] *CLASSIC II*	7	269*	2.6%	Week 0, 2, 4, 8, 12, 20, 24, 32, 40, 48, 56	56 weeks
	Sandborn 2007b[42] *CLASSIC I*	0	159	0%	Week 0, 1, 2, 4	4 weeks
	Sandborn 2012a[43]	7	245	2.9%	Week 0, 8, 32, 52, early termination	52 weeks
	Suzuki 2014[46]	12	240	5.0%	Week 2, 4, 8, 32, 52	52 weeks
	Watanabe 2012[48]	5	67	7.5%	Week 0, 4, 8, 12, 16, 20, 24, 36, 52	52 weeks
	Wright 2018[50]	15	52	28.8%	Month 6, 12 and 18	18 months
	Wu 2016[51]	0	30	0%	Week 0, 4 and 8	10 weeks
Infliximab and adalimumab						
	Roblin 2020[52]	90	unknown	unknown	Month 6, 12, 18, 24	24 months
Vedolizumab						
	Feagan 2005[72]	13	30	43.3%	Weeks 4, 8	8 weeks
	Feagan 2008[73]	29	128	22.7%	Days 1, 43, 155, 267, 379, 491	8 weeks
	Feagan 2013[74]	23	620	3.7%	Every 12 weeks	52 weeks
	Parikh 2012[81] Parikh 2013 (extension)	4 3	37 72	10.8% 4.2%	Days 1, 43, 155, 267, 379, 491	78 weeks
	Sandborn 2013[83]	33	814	4.2%	Unknown	52 weeks
	Sands 2014[87]	3	209	1.4%	Week 0, 6, 10	22 weeks
	Motoya 2019[80]	5	167	3.0%	Week 0, 10, 30, 60	60 weeks
	Sandborn 2020[85]	6	106	5.7%	Week 0, 6, 8, 14, 22, 30, 38, 46, 52	52 weeks
	Watanabe 2020[88]	1	60	1.7%	Week 0, 10, 30, 60, 76	60 weeks
Natalizumab						
	Ghosh 2003[89]	13	185	7.0%	Week 6	6 weeks
	Gordon 2001[90]	2	18	11.1%	Week 1, 2, 4, 8, 12	12 weeks
	Gordon 2002[91]	1	10	10.0%	Week 2	2 weeks
	Sandborn 2005a[92] *ENACT-1*	53	723	7.3%	Week 10	10 weeks
	Sandborn 2005b[92] *ENACT-2*	36	214	16.8%	Week 36	36 weeks
	Targan 2007[93]	23	241	9.5%	Week 8	12 weeks
	Sands 2007[94]	2	52	3.8%	Week 10	10 weeks
Ustekinumab						

	Feagan 2016[98] *UNITI-1* *UNITI-2* *IM-UNITI*	44	1154	3.8%	Week 0, 6, 12, 24, 36, 44	52 weeks
	Sands 2019[95] (UNIFI)	23	505	4.6%	Week 0, 4, 8, 12, 16, 24, 36, 44	52 weeks
	Sandborn 2008[105] (UCDS)	0	99	0%	Week 0, 16, 28, 54	28 weeks
	Sandborn 2012b[106] (CERTIFI)	3	427	0.7%	Week 0, 22, 36	36 weeks
Certolizumab Pegol						
	Sandborn 2007c[63] PRECISE-1	26	331	7.9%	Week 0, 2, 4, 6, 8, 12, 16, 20, 24, 26	26 weeks
	Sandborn 2010b[65] *PRECiSE 4*	30	124	24.2%	Week 0, 2, 4, 6, 8, 12, 12, 16, 18, 20, 22, ,24, 26	26 weeks
	Sandborn 2011[67]	7	223	3.1%	Week 2, 4, 6	6 weeks
	Sandborn 2017[68] *PRECISE-3*	134	595	22.5%	Week 0, every 4 weeks to week 106, week 130, 158, 182, 234, 258, 318	80 weeks
	Schreiber 2005[70]	9	73	12.3%	Unknown	12 weeks
	Schreiber 2007[71] PRECISE-2	58	668	8.7%	Week 0, 2, 4, 6, 8, 12, 16, 20, 24, 26	26 weeks
Golimumab						
	Hibi 2017[53] *PURSUIT-J*	5	123	4.1%	Week 0, 6, 28, 30, 52, 54, 68	54 weeks
	Rutgeerts 2015[54] *PURSUIT-IV*	0	206	0%	Week 0, 6, 30, 54 week	54 weeks
	Sandborn 2014[55, 56]	32	1103	2.9%	Week 0, 6, 30, 54	54 weeks
Etrolizumab						
	Rutgeerts 2013[107]	2	38	5.3%	Day 1, 15, 29, 57, 99, 127 in single ascending dose stage Day 1, 29, 57, 64, 85, 113, 141, 169, 197 in maintenance dose stage	197 days
	Vermeire 2014[108]	4	81	4.9%	Day 1, 5, 15, 29, 43, 57, 61, 71, 85, 113, 141	10 weeks

*Sample-size including placebo

Supplementary Table 3: Quality assessment of the randomized controlled studies

	Study	Random sequence allocation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective Reporting	Other sources of bias
Infliximab								
	Colombel 2010[2] *SONIC*	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk
	D'Haens 2018[4]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
	Farrell 2003[5] (study 2)	Low risk	Unclear risk	Low risk	Low risk	Unclear risk	Low risk	Low risk
	Feagan 2014[6]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
	Hanauer 2002[8] *ACCENT-1*	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
	Jiang 2015[11]	Low risk	Unclear risk	Low risk	Unclear risk	High risk	Low risk	Low risk
	Panaccione 2014[13]	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
	Present 1999[14]	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
	Regueiro 2016[15]	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk
	Roblin 2017[16]	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
	Rutgeerts 1999[17]	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
	Rutgeerts 2005a[18] *ACT-1*	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
	Rutgeerts 2005b[18] *ACT-2*	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
	Sands 2004[22]	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
	Steenholdt 2014[25]	Low risk	Low risk	Low risk	Unclear risk	Unclear risk	Low risk	Low risk
	Targan 1997[27]	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
	Van Assche 2008[28]	Unclear risk	Low risk	High risk	Unclear risk	Low risk	Low risk	Low risk
	Vande Casteele 2015[29]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
	Ye 2019[33]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Adalimumab								
	Bodini 2014[35]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
	Hanauer 2006[37]	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
	Matsumoto 2016[38]	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Low risk
	Sandborn 2007a[41]	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
	Sandborn 2007b[42]	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
	Suzuki 2014[46]	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
	Sandborn 2012a[43]	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
	Watanabe 2012[48]	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
	Wright 2018[50]	Low risk	Unclear risk	High risk	Low risk	Low risk	Low risk	Low risk
	Wu 2016[51]	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	Low risk

Infliximab and adalimumab								
	Roblin 2020[52]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Golimumab								
	Hibi 2017[53]	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
	Rutgeerts 2015[54]	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
	Sandborn 2014[55, 56]	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
Certolizumab Pegol								
	Sandborn 2007c[63]	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
	Sandborn 2010a[109]	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
	Sandborn 2010b[65]	Low risk	Low risk	High risk	Unclear risk	Low risk	Low risk	Low risk
	Sandborn 2011[67]	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
	Sandborn 2017[68]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
	Schreiber 2005[70]	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
	Schreiber 2007[71]	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk
Vedolizumab								
	Feagan 2005[72]	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
	Feagan 2008[73]	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
	Feagan 2013[74]	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk
	Motoya 2019[80]	Low risk	Low risk	High risk	Unclear risk	Low risk	Low risk	Low risk
	Parikh 2012[81]	Low risk	Unclear risk	High risk	High risk	Unclear risk	Low risk	Low risk
	Sandborn 2013[83]	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
	Sands 2014[87]	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
	Sandborn 2020[85]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
	Watanabe 2020[88]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Natalizumab								
	Ghosh 2003[89]	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
	Gordon 2001[90]	Unclear risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
	Sandborn 2005a[92]	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
	Sandborn 2005b[92]	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
	Targan 2007[93]	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
	Sands 2007[94]	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
Ustekinumab								
	Feagan 2016[98] UNITI-1	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
	UNITI-2	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
	IM-UNITI	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
	Sandborn 2008[105]	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
	Sandborn 2012b[106]	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
	Sands 2019[95]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Etrolizumab								
	Rutgeerts 2013[107]	Low risk	Unclear risk	Low risk	Low risk	Unclear risk	Low risk	Low risk
	Vermeire 2014[108]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

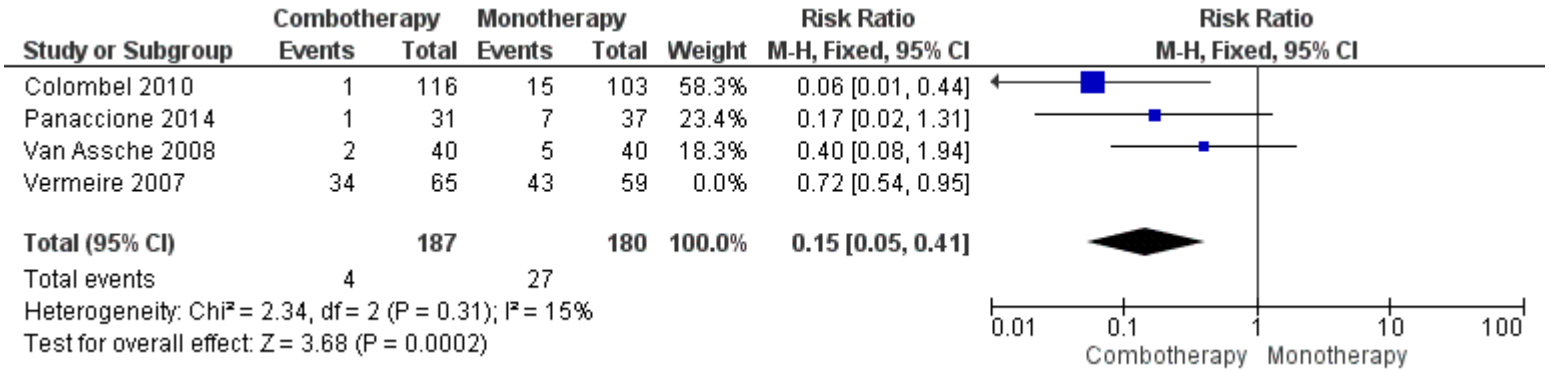
Supplementary Table 4: Quality assessment of the observational studies*

	Study	Selection (Max 4)	Comparability (Max 2)	Outcome (Max 3)	Total (Max 9)
Infliximab					
	Baert 2003[1]	****	**	***	9
	Farrell 2003[5] (study 1)	****	**	***	9
	Fernandes 2020[7]				
	Oh 2017[12]	****	**	**[1]	8
	Seow 2010[23]	****	**	***	9
	Vermeire 2007[32]	****	**	***	9
	Yokoyama 2017[34]	****	-	**[1]	6
Adalimumab					
	Regueiro 2016[15]	***[3]	**	**[1]	8
	Roblin 2017[16]	****	**	**[1]	8
	Rutgeerts 2005a[18]	****	**	**[1]	8
	Rutgeerts 2005b[18]	****	**	**[1]	8
	Sands 2004[22]	***[2]	**	**[1]	7
Certolizumab pegol					
	Gordon 2002[91]	****	**	**[1]	8
	Sandborn 2016[110]	****	**	**[1]	8

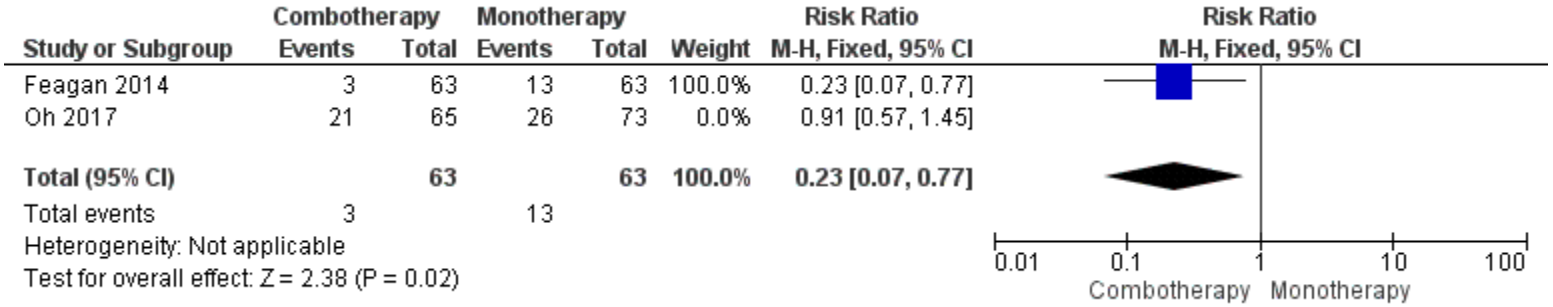
*The Newcastle-Ottawa Quality Assessment Scale for case-control studies was used for observational data. Comparisons of monotherapy versus combination therapy were considered observational if the patients were not randomized to monotherapy or combination therapy and the study reported event(s) of interest in these two groups.

[1]Unclear whether the assessment was independent and blinded
[2]Only included patients with fistulizing Crohn's disease
[3]Only included patients with CD who had undergone ileocolonic resection with ileocolonic anastomosis
[4]Single-country study

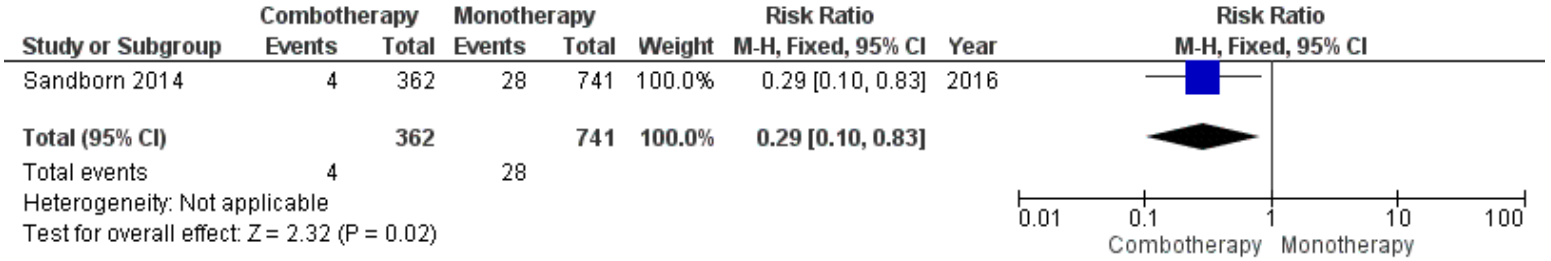
Supplementary Figure 1: ADA formation in infliximab combotherapy with thiopurine versus monotherapy (sensitivity analysis)



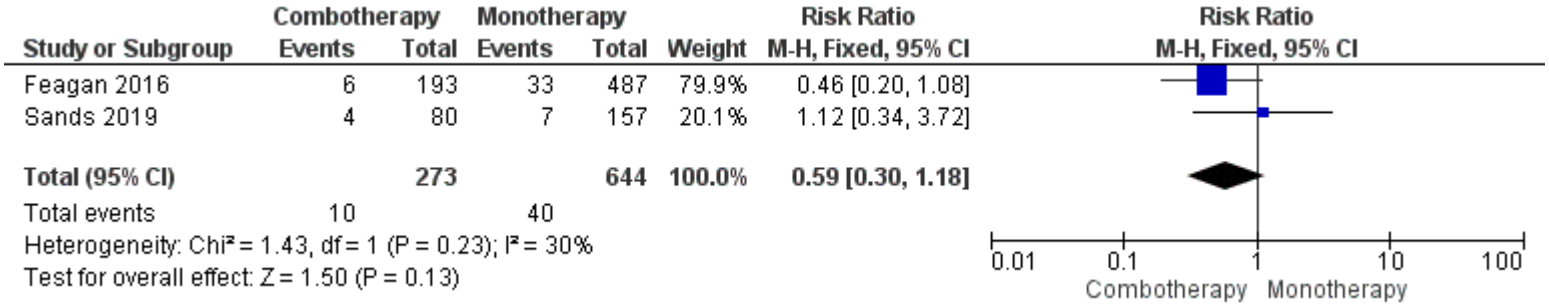
Supplementary Figure 2: ADA formation in infliximab combotherapy versus monotherapy in drug tolerant assays (sensitivity analysis)



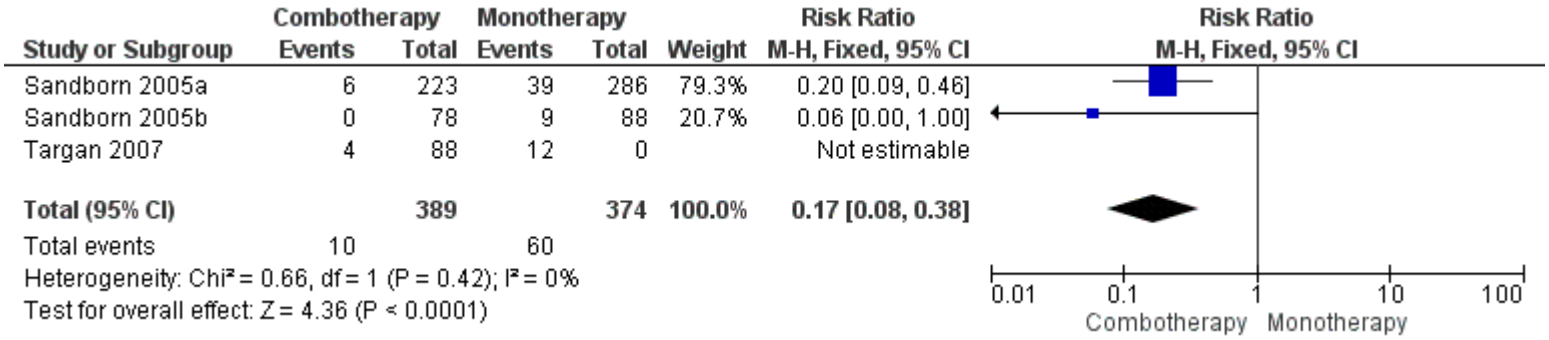
Supplementary figure 3: ADA formation in golimumab combo- versus monotherapy



Supplementary figure 4: ADA formation in ustekinumab combotherapy versus monotherapy



Supplementary Figure 5: ADA formation in natalizumab combotherapy versus monotherapy.



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