Surgery and medical therapy in Crohn's disease

Improving treatment strategies

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Treatment of perianal fistulas in Crohn's disease: a systematic review and meta-analysis comparing seton drainage and anti-TNF treatment

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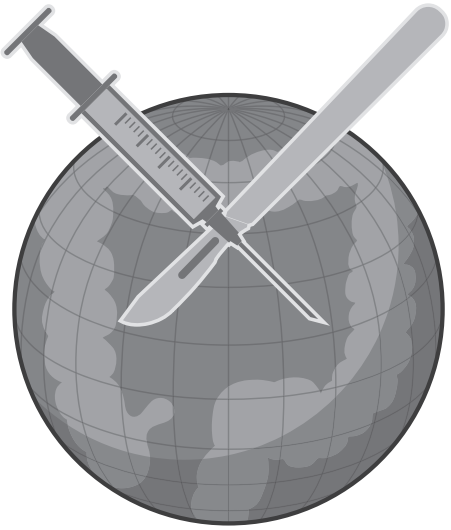

Abstract

Aim

The introduction of anti-tumour necrosis factor (anti-TNF; infliximab and adalimumab) has changed the management of Crohn's perianal fistula from almost exclusively surgical treatment to one with a much larger emphasis on medical therapy. The aim of this systematic review was to provide an overview of the success rates of setons and anti-TNF for Crohn's perianal fistula.

Method

Studies evaluating the effect of setons and anti-TNF on Crohn's perianal fistula were included. Studies assessing perianal fistula in children, rectovaginal and rectourinary fistulae were excluded. The primary end-point was the fistula closure rate. Partial closure and recurrence rates were secondary endpoints.

Results

Ten studies on seton drainage were included (n = 305). Complete closure varied from 13.6% to 100% and recurrence from 0% to 83.3%. In 34 anti-TNF studies (n = 1449), complete closure varied from 16.7% and 93% (partial closure 8.0–91.2%) and recurrence from 8.0% to 40.9%. Four randomized controlled trials (n = 1028) comparing anti-TNF with placebo showed no significant difference in complete or partial closure in meta-analysis (risk difference 0.12, 95% CI −0.06 to 0.30 and 0.09, 95% CI −0.23 to 0.41, respectively). Subgroup analysis (n = 241) showed a significant advantage for complete fistula closure with anti-TNF in two trials with follow-up > 4 weeks (46% vs 13%, P = 0.003 and 30% vs 13%, P = 0.03). Of four included cohort studies, two revealed a significant difference in response in favour of combined treatment (P = 0.001 and P = 0.014).

Conclusion

Closure and recurrence rates after seton drainage as well as anti-TNF vary widely. Despite a large number of studies, no conclusions can be drawn regarding the preferred strategy. However, combination therapy with (temporary) seton drainage, immunomodulators and anti-TNF may be beneficial in achieving perianal fistula closure.

Introduction

Crohn's disease (CD) is a common chronic disease with an incidence rate of 6.9 per 100 000 inhabitants per year in The Netherlands.[1] Perianal fistulation is common in patients with Crohn's disease, the estimated lifetime risk of perianal fistula being between 14% and 38% in population-based estimates.[2] Perianal fistulizing disease is associated with local pain, discharge and considerable morbidity (including destruction of the sphincter and perineal tissue), resulting in a negative impact on quality of life.[3] Unfortunately spontaneous fistula closure rates are low, with estimates ranging from 6% to 13%.[4, 5]
The management of Crohn's perianal fistulation has historically been surgical, with seton placement being the most frequently used technique. However, since the introduction of anti-tumour necrosis factor (anti-TNF) agents (infliximab and adalimumab), the treatment of Crohn's fistula has changed, with a larger emphasis on medical therapy.[6-9]
The purpose of this systematic review was to examine the reported success rate of both seton drainage and anti-TNF agents in patients with perianal Crohn's fistula.

Methods

A systematic review of the literature on seton drainage and anti-TNF (infliximab or adalimumab) for the treatment of perianal fistula in Crohn's disease was performed by two independent researchers (EJG and SS). The present review was conducted according to the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines.[10] The final search was performed on 15 April 2015.

Databases

MEDLINE, Embase and BIOSIS were searched. No restrictions on publication type were applied and no methodological filter was used.

Search terms

The MeSH terms and free text used in various forms and combinations were assembled with a medical librarian. Two independent searches where performed, one for seton drainage and one for anti-TNF treatment. The terms used in both searches were 'Crohn's disease' or 'Crohn' and 'rectal fistula' or 'fistula'. For the search on seton drainage the term 'seton' was added. For the search on anti-TNF the following terms were added:

'infliximab' or 'remicade' or 'Tumour Necrosis Factor-alpha' or 'Tumour Necrosis Factors' or 'tumour necrosis factor-α' or 'anti-TNF' or 'Cachectin-Tumour Necrosis Factor' or 'cachetin' or 'monoclonal antibody cA2' or 'MAb cA2' or 'adalimumab' or 'humira'. Details are provided in Appendix S1 in the Supporting Information.

Selection

The reviewers separately screened the title and abstract of the retrieved articles. Afterwards they assessed the articles by joint discussion. In the event of disagreement, a third reviewer (CJB) was involved. Studies addressing seton drainage and anti-TNF for treatment of perianal fistula in Crohn's disease were included. In addition, the included articles were hand searched for relevant references. Studies on perianal fistula in children, rectovaginal and rectourinary fistulae and review articles were excluded.

Primary and secondary outcomes

Each study was examined for the primary outcome of interest, complete fistula closure. Secondary outcome parameters were partial closure and recurrence.

Data extraction and statistical analysis

The two reviewers independently extracted data from the studies, and afterwards assessed the results in joint discussion. Statistical analysis was done using Review Manager, version 5.2 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). Two meta-analyses of randomised controlled trials (RCTs) comparing closure rates with anti-TNF therapy vs placebo were performed. Pooled effects were presented as risk differences with 95% CIs. Because heterogeneity was expected, the meta-analyses were done a priori with the use of a random effects model. Heterogeneity between studies was determined with the I^2 statistic.

Assessment of methodological quality

The methodological quality of the included studies was assessed by the two reviewers separately, using the Cochrane criteria for assessing risk of bias in RCTs. For cohort studies and case series, elements of the STROBE checklist were used (Table S1).[11] To assess the risk of bias, the following key elements were assessed: selection bias/confounding (consecutive or random inclusion, avoidance of inappropriate inclusion and exclusion, adequate description of the source of the patients, adequate description of baseline characteristics, description of confounders, whether potential confounders accounted

for in the analyses), performance bias (impact of a concurrent intervention, fidelity to the intervention protocol), attrition bias (handling of missing data), detection bias (follow-up, blinding, proper description of the procedure, clear definition of outcome parameters) and reporting bias (prespecification of potential outcomes, reporting of all prespecified outcomes). Risk of bias was scored as high, low or uncertain, and a total risk was calculated. If there was a high risk score for one or more key elements within a study, the overall risk was scored as high.

Table 1 Key-elements used for assessing risk of bias of cohort studies and case series.[11]

Type of bias	Risk of bias assessment	Study type
Selection/ Confounding	Were participants analysed within the groups they were originally assigned to?	Cohort
	Did the study apply inclusion/exclusion criteria uniformly to all comparison groups?	Cohort
	Did the strategy for recruiting participants into the study differ across study groups?	Cohort
	Does the design or analysis control account for important confounding and modifying variables through matching, stratification, multivariable analysis, or other approaches?	Cohort/Case series
Performance bias	Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results?	Cohort/Case series
	Did the study maintain fidelity to the intervention protocol?	Cohort/Case series
Attrition bias	If attrition (overall or differential nonresponse, dropout, loss to follow-up, or exclusion of participants) was a concern, were missing data handled appropriately (e.g., intention-to-treat analysis and imputation)?	Cohort/Case series
Detection bias	In prospective studies, was the length of follow-up different between the groups, or in case-control studies, was the time period between the intervention/exposure and outcome the same for cases and controls?	Cohort
	Were the outcome assessors blinded to the intervention or exposure status of participants?	Cohort/Case series
	Were interventions/exposures assessed/defined using valid and reliable measures, implemented consistently across all study participants?	Cohort/Case series
	Were outcomes assessed/defined using valid and reliable measures, implemented consistently across all study participants?	Cohort/Case series
	Were confounding variables assessed using valid and reliable measures, implemented consistently across all study participants?	Cohort/Case series
Reporting bias	Were the potential outcomes prespecified by the researchers? Are all prespecified outcomes reported?	Cohort/Case series

In addition, generalisability was assessed and graded based on the methodological design (multicentre or single-centre studies, patient population, sample size and follow-up) of the studies and overall scored as high, low or uncertain.

Results

Study selection process for seton drainage

The initial literature search for seton drainage identified 313 studies after removal of duplicates. Subsequently, titles and abstracts were screened, after which 74 potentially eligible publications remained. After full-text review of these publications, 10 studies, mainly case series, met the inclusion criteria and presented the primary or one secondary outcome parameter.[12-21] These studies were included in the analysis for treatment with seton drainage (Fig. 1).

Study selection process for anti-TNF

There were 1888 hits after duplicates were removed. After subsequent screening of titles and abstracts, 249 potentially eligible articles remained. Eventually, after full-text review, 42 studies remained (Fig. 2). Four RCTs comparing anti-TNF therapy regimens with placebo were included in a meta-analysis and reported separately.[4, 22-24] Also, four studies directly comparing (combined) anti-TNF and seton drainage on closure and recurrence rates were analysed separately.[25-28] Finally, 34 cohort studies and case-series on anti-TNF treatment were analysed.[6, 8, 9, 29-59]

Patient population and outcome analysis for seton drainage

Overall, 305 patients with Crohn's disease were treated with seton drainage for their perianal fistulae (Table S2).

Complete closure was reported in five studies; the rates varied between 13.6% and 100%. Among the included studies the single cohort study (retrospective) by Chung et al., mentioned a complete closure rate of 31.3%.[12] Partial closure was not reported in any of these studies. Recurrence rates were reported by 8 studies, and varied from 0% to 83.3%. The only included prospective cohort study by Shinozaki et al. reported a recurrence rate of 33.3%.[18] Timing of seton removal differed among the studies (from 3 weeks to 40 months). Because of the considerable heterogeneity among the studies no meta-analysis was performed.

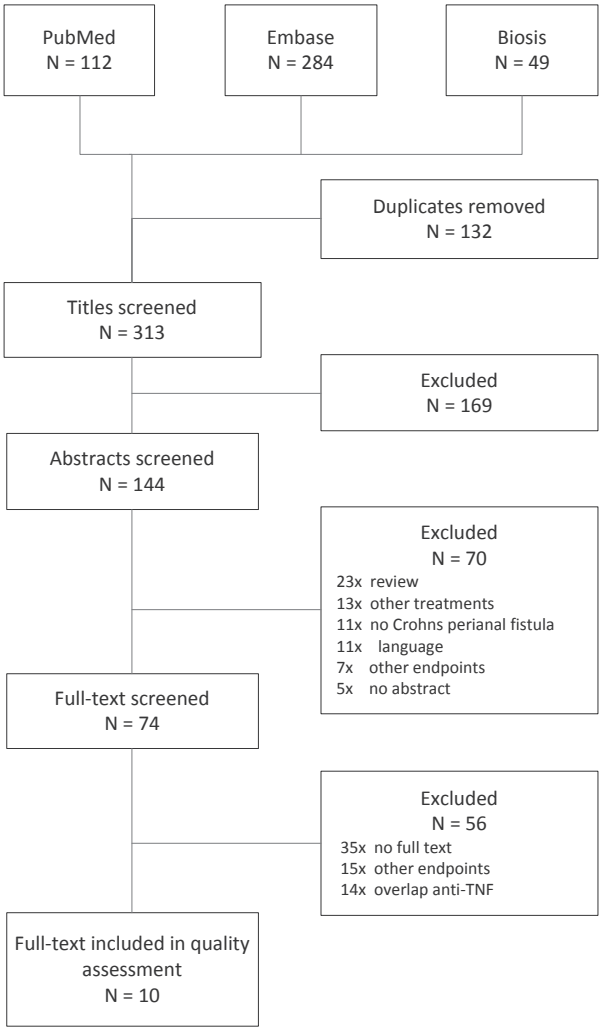

Figure 1 Flowchart seton drainage search.

Patient population and outcome analysis for anti-TNF

A total of 1449 patients with perianal fistula were treated with anti-TNF medication (Table S3). There were 22 studies assessing infliximab treatment, 8 studies on adalimumab and 4 on both infliximab and adalimumab without comparison with placebo. There were articles on induction as well as on maintenance therapy. Follow-up differed widely between the studies, where some assessed the endpoint at only 8 weeks, others had a mean follow-up of almost 5 years.

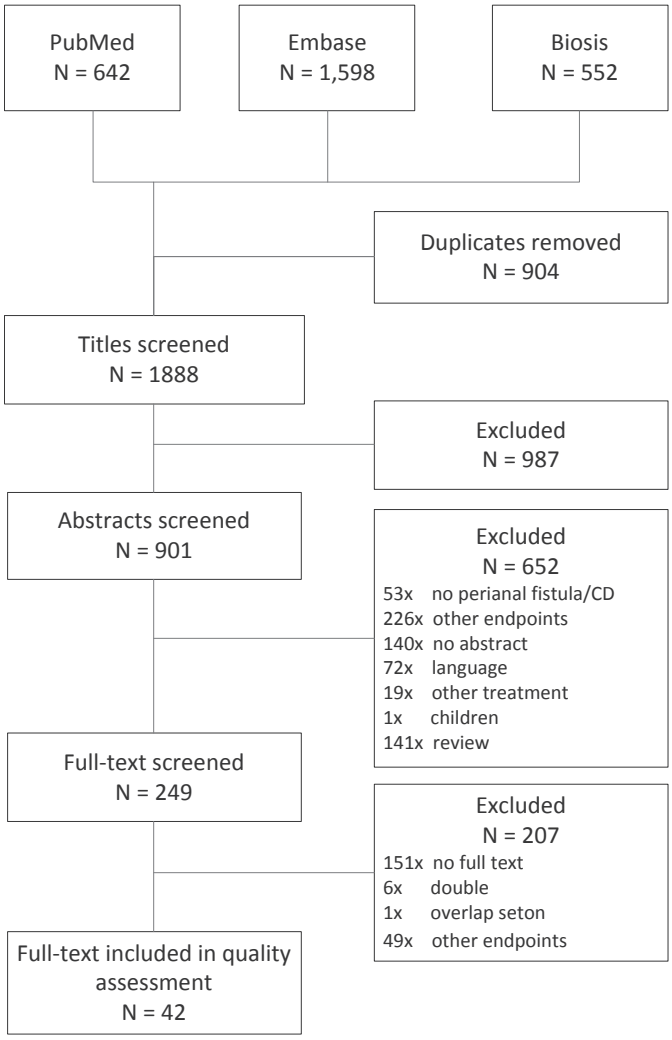

Figure 2 Flowchart anti-TNF search.

Complete closure rates were reported by all 34 studies and varied between 16.7% and 93%. Partial closure was described by 21 studies (8.0–91.2%) (Table S3). Among these studies one RCT by Dewint et al. was included.[31] In this study complete and partial closure rates were 43% and 54%, respectively, after 24 weeks of follow-up. Recurrence rates were only mentioned by 11 studies (8.0–40.9%) (Table S3).

Patient population and outcome analysis for studies directly comparing (combined) anti-TNF and seton drainage

4 Cohort studies directly compared combined therapy with anti-TNF (infliximab) treatment and/or seton drainage alone for patients with Crohn's perianal fistula (Table S4).[25-28] These studies mainly had a retrospective design, except for the study of Sciaudone et al.[27] Anti-TNF treatment has been administered to 132 patients in total, of whom 98 were simultaneously treated with seton drainage. Overall, 109 patients were treated with seton drainage without anti-TNF. Follow-up ranged from 15 weeks to a mean of 30 months. Complete closure rates for combined therapy varied widely (0–100%). In the study reporting zero complete fistula closures it was unclear whether the setons were removed.[26] Partial closure rates were only described by two studies for this treatment strategy (14.3–88.5%).[26, 27] Gaertner et al. reported a significant difference in response rates between combined treatment vs seton drainage without anti-TNF of 45% vs 17%, respectively (P = 0.001), whereas Regueiro and Mardini showed a significant difference between combined treatment vs anti-TNF therapy without seton drainage of 100% vs 82.6%, respectively (P = 0.014).[25, 28] Recurrence was described by two studies, of which one showed a significant difference in favour of combined treatment when compared with anti-TNF therapy without seton drainage (44.4% vs 78.9% respectively; P = 0.001).[25]

Table 2 Characteristics of included studies on seton drainage. (Pts = patients, N = number of patients, M/F = male/female, FU = follow-up, * = mean, IQR = inter quartile range).

Author	Year	Country	Centres	Study design	Comparison groups	Pts (N)	Pts CD (N)
Chung W. *et al.*[12]	2010	Canada	Single	Retrospective cohort	Fibrin glue/ advancement/ seton/plug	51	32
Galis-Rozen E. *et al.*[13]	2010	Israel	Multi	Case series	CD vs non CD	77	17
Higashi D. *et al.*[14]	2009	Japan	Single	Case series	X	93	93
Thornton M. *et al.*[15]	2005	Australia	Single	Case series	X	67	67
Buchanan GN. *et al.*[16]	2004	UK	Single	Case series	X	20	6
Takesue Y. *et al.*[17]	2002	Japan	Single	Case series	X	62	62
Shinozaki M. *et al.*[18]	2002	Japan	Single	Prospective cohort	Simultaneous bowel surgery vs not	39	39
Makowiec F. *et al.*[19]	1997	Germany	Single	Case series	X	126	126
Williams JG. *et al.*[20]	1991	USA	Single	Case series	X	55	55
Morrison JG. *et al.*[21]	1989	USA	Single	Case series	X	35	35

M/F	Age	Pts seton (N)	Seton removal (N)	Time seton drainage	FU	Complete closure N (%)	Recurrence N (%)
40/11	39 (21-66)	32	NR	3 weeks	12 weeks	10 (31.3%)	NR
54/23	41 (18-70)	17	NR	6-8 weeks	24 (6-48) months	10 (58.8%)	NR
NR	NR	86	22	NR	68.8 (12-184) months	22 (100%)	12 (14.0%)
8/20	36 (18-72)	28	NR	NR	13 (2-81) months	NR	6 (21.4%)
17/3	41 (24-70)	6	NR for CD	NR for CD	142 (125-153) months	NR	5 (83.3%)
20/12	25 (16-43)	32	9	11 (6-18) months	61 (19-122) months	NR	3 (33.3%)
26/13	27* (16-51)	39	21	> 3 months	21.4* months	NR	7 (33.3%)
39/30	32.1* (±8.3)	37	33	94 days (22-1217)	32* (±17) months	NR	9 (29.3%)
32/24	34 (14-72)	22	22	NR	4.5 (6-120) months	3 (13,6%)	0
19/16	30.8* (16-69)	6	NR	NR	3.5-10 years	6 (100%)	1 (16.7%)

Table 3 Characteristics of included studies on anti-TNF treatment (Pts = patients, N = number of patients, M/F = male/female, PF = perianal fistulas, In/Ma = induction/maintenance, FU = follow-up, * = mean, IQR = inter quartile range, # partial closure rates included complete closed fistulas as well).

Author	Year	Country	Centres	Study design	Comparison group	CD Pts (N)	M/F
Castaño-Milla C. *et al*[57].	2015	Spain	Multi	Case series	x	46	22/24
,,	,,	,,	,,	,,	,,	,,	,,
Yang B. *et al*[58].	2015	China	Single	Case series	x	28	23/5
Kotze PG. *et al*[59].	2014	Brazil	Multi	Case series	x	78	34/44
Bouguen G. *et al.*[30]	2013	France	Multi	Retrospective cohort	Closure versus recurrence	156	61/95
Dewint P. *et al.*[31]	2013	Netherlands	Multi	RCT	ciprofloxacin versus placebo	70	37/33
,,	,,	,,	,,	,,	,,	,,	,,
Antakia R. *et al.*[32]	2012	UK	Single	Case series	x	48	17/31
Duff S. *et al.*[33]	2012	UK	Single	Case series	x	52	25/27
El-Gazzaz G. *et al.*[34]	2012	USA	Single	Retrospective cohort	surgery versus surgery + anti-TNF	218	82/136
Fortea-Ormaechea JI. *et al.*[35]	2011	Spain	Multi	Retrospective cohort	response versus no response	174	87/87
,,	,,	,,	,,	,,	,,	,,	,,

Age	Pts fistulas (N)	Pts PF (N)	Pts (PF) anti-TNF (N)	Anti-TNF	Concomitant therapy	In/Ma	FU	Complete closure N (%)	Partial closure N (%)	Recurrence N (%)
36.5* (19-63)	46	46	46	ADA	Surgical (seton) & medical	Ma	6 months	25 (54%)	8 (18%)	NR
,,	,,	,,	,,	,,	,,	,,	12 months	16 (41%)	3 (8%)	NR
25.9* (±6.9)	28	28	28	IFX	Surgical (seton or fistulotomy) & medical	Ma	26.4 (14-41) months	25 (89.3%)	NR	2 (8.0%)
33 (2-80)	78	78	78	IFX/ ADA	Surgical (seton) & medical	Ma	48* (2-288) months	41 (52.6%)	8 (10.3%)	4 (9.8%)
30 (13-84)	156	156	156	IFX	Surgical (seton) & medical	In (151)/ Ma (42)	250 (IQR 124-381) weeks	108 (69%)	NR	36 (33.3%)
36.1*	70	70	70	ADA	Medical	Ma	12 weeks	34 (49%)	41 (59%)#	NR
,,	,,	,,	,,	,,	,,	,,	24 weeks	30 (43%)	38 (54%)#	NR
41 (20-82)	48	48	48	IFX	Medical	In (34)/ Ma (14)	20 months	14 (29%)	20 (42%)	12 (25%)
24 (15-72)	52	52	52	IFX	Surgical (seton) & medical	In (7)/ Ma (45)	36.5 (4-126) months	22 (42.3%)	23 (44.2%)	9 (40.9%)
38.8* (±12.2)	218	218	101	IFX/ ADA	Surgical & medical	In/Ma	2.51* (±2.24) years	37 (36.6%)	35 (34.7%)	NR
28* (±12)	52	52	52	ADA	Medical	Ma	1 month	25 (49%)	22 (42.9%)	NR
,,	,,	,,	,,	,,	,,	,,	6 months	26 (50%)	21 (39.6%)	NR

Table 3 Characteristics of included studies on anti-TNF treatment (Pts = patients, N = number of patients, M/F = male/female, PF = perianal fistulas, In/Ma = induction/maintenance, FU = follow-up, * = mean, IQR = inter quartile range, # partial closure rates included complete closed fistulas as well). (continued)

Author	Year	Country	Centres	Study design	Comparison group	CD Pts (N)	M/F
,,	,,	,,	,,	,,	,,	,,	,,
Karmiris K. *et al.*[35]	2011	Belgium	Single	Case series	x	59	22/37
Savoye-Collet C. *et al.*[37]	2011	France	Single	Prospective cohort	Nonresponder versus responder on MRI	20	6/14
Echarri A. *et al.*[38]	2010	Spain	Multi	Case series	x	16	10/6
,,	,,	,,	,,	,,	,,	,,	,,
,,	,,	,,	,,	,,	,,	,,	,,
Gligorijevic V. *et al.*[39]	2010	Servia	Single	Case series	x	24	18/6
Miheller P. *et al.*[40]	2009	Hungary	Multi	Case series	x	363	180/183
Ng SC. *et al.*[41]	2009	Australia	Single	Case series	x	26	10/16
Oussalah A. *et al.*[42]	2009	Algeria	Single	Case series	x	53	17/36
Tougeron D. *et al.*[43]	2009	France	Single	Case series	x	26	7/19
Trinder MW. *et al.*[44]	2009	Australia	Single	Prospective cohort	CD versus UC/ IBDU	38	15/23
Guidi L. et al.[29]	2008	Italy	Single	Case series	x	9	8/1

Age	Pts fistulas (N)	Pts PF (N)	Pts (PF) anti-TNF (N)	Anti-TNF	Concomitant therapy	In/Ma	FU	Complete closure N (%)	Partial closure N (%)	Recurrence N (%)
,,	,,	,,	,,	,,	,,	,,	36 (IQR 21-76) weeks	22 (41.5%)	19 (35.8%)	NR
23.1 (IQR 17.5-32.8)	59	59	59	IFX	Surgical (seton) & medical	Ma	9.8 (IQR 1.4-46.1) months	24 (41%)	21 (36%)	NR
33.7* (±12)	20	20	20	IFX (74)/ADA(27)	Surgical (seton) & medical	Ma	12 months	7 (35%)	8 (40%)	NR
33.9* (26-41)	16	16	16	ADA	Surgical (seton) & medical	Ma	4 weeks	8 (50%)	NR	NR
,,	,,	,,	,,	,,	,,	,,	24 weeks	7 (43.8%)	NR	1 (12.5%)
,,	,,	,,	,,	,,	,,	,,	48 weeks	7 (43.8%)	NR	1 (12.5%)
33.5* (±9.9)	24	24	24	IFX	Surgical (seton) & medical	In	14 weeks	11 (45.8%)	10 (41.7%)	3 (12.5%)
33.5* (±11.2)	195	148	148	IFX	Medical	In/Ma	12 weeks	72 (48.6%)	135 (91.2%)#	NR
36 (21-61)	26	26	26	IFX (19)/ADA(7)	Surgical (seton) & medical	Ma	12 months	12 (46.2%)	13 (50%)	NR
35.47* (±12.18)	22	10	10	ADA	Medical	Ma	43.55* (±33.19) weeks	6 (60%)	NR	NR
36.9* (±12.6)	26	26	26	IFX	Surgical (seton) & medical	In/Ma	4.9* (±9.6) years	13 (50%)	NR	2 (15.4%)
23.1* (±9.5) (SEM?)	9	6	6	ADA	Surgical (seton) & medical	Ma	12 weeks	3 (50%)	5 (83.3%)#	NR
35.4* (25-57)	9	8	8	IFX	Surgical (seton) & medical	Ma	29.1* (±11.8) months	8 (88.9%)	1 (11.1%)	2 (25%)

Table 3 Characteristics of included studies on anti-TNF treatment (Pts = patients, N = number of patients, M/F = male/female, PF = perianal fistulas, In/Ma = induction/maintenance, FU = follow-up, * = mean, IQR = inter quartile range, # partial closure rates included complete closed fistulas as well). (continued)

Author	Year	Country	Centres	Study design	Comparison group	CD Pts (N)	M/F
Lopez PN. *et al.*[45]	2008	Spain	Single	Case series	x	22	8/14
,,	,,	,,	,,	,,	,,	,,	,,
Spradlin NM. *et al*[46].	2008	USA	Single	RCT (pilot)	EUS control versus no EUS control	10	2/8
Hinojosa J. *et al.*[47]	2007	Spain	Multi	Case series	x	50	32/18
Hyder SA. *et al.*[48]	2006	UK	Single	Case series	x	22	6/16
Orlando A. *et al.*[9]	2005	Italy	Multi	Prospective cohort	non responder versus responder	573	308/265
Ardizzone S. *et al.*[49]	2004	Italy	Single	Case series	x	30	17/13
,,	,,	,,	,,	,,	,,	,,	,,
Luna-Chadid M. *et al.*[50]	2004	Spain	Multi	Prospective cohort	non responder versus responder	105	56/49
Rasul I. *et al.*[51]	2004	Canada	Single	Case series	x	35	16/19
Schroder O. *et al.*[52]	2004	Germany	Single	Case series	x	12	4/8
Bell SJ. *et al*[53].	2003	UK	Single	Case series	x	12	7/5

Age	Pts fistulas (N)	Pts PF (N)	Pts (PF) anti-TNF (N)	Anti-TNF	Concomitant therapy	In/Ma	FU	Complete closure N (%)	Partial closure N (%)	Recurrence N (%)
23.7 (IQR 15.2-30.5)	NR	6	6	ADA	Medical	In (6)/ Ma (5)	4 weeks	1 (16.7%)	4 (66.7%)	NR
,,	,,	,,	,,	,,	,,	,,	15.2 (IQR 11.7-19.4) months	1 (20%)	4 (80%)	NR
29.5 (20-69)	10	8	8	IFX	Surgical (seton) & medical	In	54 weeks	4 (50%)	NR	NR
37.4* (±10.4)	22	22	22	ADA	Medical	In	52 weeks	5 (22.7%)	9 (40.9%)	NR
35 (16-60)	22	22	22	IFX	Surgical (seton) & medical	In (22)/ Ma (4)	21 (4–31) months	4 (18%)	NR	NR
30.1	261	188	188	IFX	Surgical (seton) & medical	In	12 weeks	82 (44%)	143 (76%)#	NR
38.9* (±12.6)	30	22	22	IFX	Surgical (seton) & medical	In (22)/ Ma (7)	10 weeks	13 (59%)	NR	NR
,,	,,	,,	21	,,	,,	,,	15.5 (2-31) months	8 (38.1%)	NR	NR
38*	105	59	59	IFX	Medical	Ma	10 weeks	35 (60%)	21 (35%)	NR
34* (±1.7)	40	32	32	IFX	Medical	In/Ma	8 weeks	28 (86%)	NR	NR
29.5* (21-50)	12	7	7	IFX	Medical (MTX)	In	6 months	3 (42.9%)	NR	NR
37.7* (26-51)	12	5	5	IFX	Surgical (seton) & medical	In	14 weeks	3 (60%)	1 (20%)	NR

Table 3 Characteristics of included studies on anti-TNF treatment (Pts = patients, N = number of patients, M/F = male/female, PF = perianal fistulas, In/Ma = induction/maintenance, FU = follow-up, * = mean, IQR = inter quartile range, # partial closure rates included complete closed fistulas as well). (continued)

Author	Year	Country	Centres	Study design	Comparison group	CD Pts (N)	M/F
Topstad DR. *et al.*[54]	2003	Canada	Single	Case series	x	29	12/17
Ochsenkuhn T. *et al.*[55]	2002	Germany	Single	Case series	x	16	9/7
Poritz LS. *et al.*[8]	2002	USA	Single	Case series		26	14/12
Arnott ID. *et al.*[6]	2001	UK	Multi	Retrospective cohort	non responder versus responder	50	22/28
Farrell RJ. *et al.*[56]	2000	USA	Multi	Case series		100	47/53

Age	Pts fistulas (N)	Pts PF (N)	Pts (PF) anti-TNF (N)	Anti-TNF	Concomitant therapy	In/Ma	FU	Complete closure N (%)	Partial closure N (%)	Recurrence N (%)
31* (13-50)	29	21	21	IFX	Surgical (seton) & medical	In/Ma	8.6 months*	14 (67%)	4 (19%)	4 (28.6%)
37*	16	14	14	IFX	Medical	In	10* (6-11) months	13 (93%)	NR	NR
38* (±3.2)	26	9	9	IFX	Medical	In/Ma	6.5* (±2.5) months	4 (44.4%)	NR	NR
34 (16-70)	6	6	6	IFX	Medical	In	12 weeks	1 (16.7%)	3 (50%)	2 (33.3%)
41.4* (±13.9, 15-84)	33	33	33	IFX	Medical	In	18 weeks	23 (69%)	NR	NR

Table 4 Characteristics of included cohort studies directly comparing (combined) anti-TNF and seton drainage on closure and recurrence rates of perianal fistulas. (Pts = patients, N = number of patients, M/F = male/female, FU = follow-up, * = mean, In/Ma = induction/maintenance,).

Author	Year	Country	Study design	Comparison group	Pts perianal fistulas (N)	M/F	Age
Uchino M. *et al.*[26]	2011	Japan	Retrospective cohort		62	43/19	27.0 (12-58)
,,	,,	,,	,,	anti-TNF + seton	26	16/10	27.5 (16-55)
,,	,,	,,	,,	Seton	36	27/9	27.5 (16-41)
Sciaudone G. *et al.*[27]	2010	Italy	Prospective cohort		35	13/22	36.3 (19-63)
,,	,,	,,	,,	anti-TNF	11	4/7	36.3 (19-63)
,,	,,	,,	,,	Seton	10	3/7	33.1 (16-58)
,,	,,	,,	,,	anti-TNF + seton	14	6/8	35.3 (18-65)
Gaertner WB. *et al.*[28]	2007	USA	Retrospective cohort		226	105/121	39* (16-83)
,,	,,	,,	,,	anti-TNF + seton	49	NR	NR
,,	,,	,,	,,	Seton	63	NR	NR
Regueiro M. *et al.*[25]	2003	USA	Retrospective cohort		32	16/16	34.7* (12-58)
,,	,,	,,	,,	anti-TNF + seton	9	4/5	NR
,,	,,	,,	,,	anti-TNF	23	12/11	NR

Anti-TNF	Concomitant therapy	In/Ma	FU	Complete closure N (%)	Partial closure N(%)	*p* value response	Recurrence N (%)	*p* value recurrence
IFX	No	Ma	15 weeks			0.25		
,,	,,	,,	,,	0	22 (88.5%)		NR	
x	,,	x	,,	0	26 (72.2%)		,,	
IFX	Yes, medical	Ma	18.8 (8-38) months			0.74		0.2
,,	,,	,,	,,	7 (63.6%)	3 (27.3%)		3 (42.9%)	
x	,,	x	,,	7 (70%)	2 (20%)		3 (42.9%)	
IFX	,,	,,	,,	11 (79%)	2 (14.3%)		2 (18.2%)	
IFX	Yes, medical	Ma	30* (6-216) months			0.001		
,,	,,	,,	,,	22 (45%)	NR		NR	
x	,,	x	,,	11 (17%)	,,		,,	
IFX	Yes, medical	In	18 weeks		NR	0.014		0.001
,,	,,	,,	,,	9 (100%)	,,		4 (44.4%)	
,,	,,	,,	,,	19 (82.6%)	,,		15 (78.9%)	

Meta-analyses for anti-TNF

Four RCTs comparing anti-TNF regimens with placebo were included in the meta-analysis: one study on infliximab and three studies analysing adalimumab (CLASSIC, CHARM and GAIN trials) (Table S5).[4, 22-24] Patients with all kinds of fistulising disease were included in these trials (perianal, enterocutaneous and enteroenteral fistulae). Patients treated with either 5 mg/kg infliximab or 40–80 mg adalimumab were included in the meta-analysis since this is the recommended dose in several guidelines.[60] Seton insertion for perianal fistula was not mentioned in any of the RCTs. In total, 179 patients were treated with anti-TNF medication whereas 109 patients received placebo. All studies assessed complete closure rates and three studies reported partial closure rates. Recurrence rates were not reported. The mean follow-up time was 13 weeks (range 4–26).

Table 5 Characteristics of included randomised controlled trials in meta-analysis on anti-TNF treatment. (N = number, FU = follow-up,

Study	Therapy	Patients study (N)	Patients fistula (N)	FU weeks	Partial (>50%) fistula closure N (%)	Complete closure N (%)	*p*-value complete closure
Present *et al.* 1999	Infliximab	31	63	18	39 (62%)	29 (46%)	0.003
(ACCENT)[4]	Placebo	31	31		8 (26%)	4 (13%)	
Hanauer *et al*. 2006	Adalimumab	225	26	4	6 (23%)	3 (12%)	NS (0.73)
(CLASSIC)[22]	Placebo	74	6		2 (33%)	1 (17%)	
Colombel *et al.* 2007	Adalimumab	172	70	26	NR	21 (30%)	0.03
(CHARM)[23]	Placebo	170	47		NR	6 (13%)	
Sandborn *et al.* 2007	Adalimumab	159	20	4	3 (15%)	1 (5%)	NS (0.69)
(GAIN)[24]	Placebo	166	25		5 (20%)	2 (10%)	

In the anti-TNF group, 54 of 179 (30%) patients responded to treatment with complete fistula closure, whereas complete closure was seen in 13 of 109 (12%) patients in the placebo group. Partial fistula closure was seen in 48 of 109 (44%) patients in the anti-TNF group and in 15 of 62 (24%) patients in the placebo group. There was no significant difference in complete or partial closure rates between the groups [risk difference (RD) 0.12, 95% CI −0.06 to 0.30, I2 = 74%; and RD 0.09, 95% CI −0.23 to 0.41, I2 = 78%, respectively) (Figs 3 and 4). As heterogeneity among the studies was high, a random-effects model was used

to estimate the pooled total effect. Due a lack of Kaplan–Meier curves for fistula closure in the included studies, only dichotomous data were used and risk differences were reported. A subgroup analysis for complete fistula closure was performed based on studies with a follow-up longer than 4 weeks. This showed a significant advantage for complete fistula closure with anti-TNF in the two trials with follow-up longer than 4 weeks (Present et al., 46% vs 13%, P = 0.003; CHARM, 30% vs 13%, P = 0.043).[14, 23]

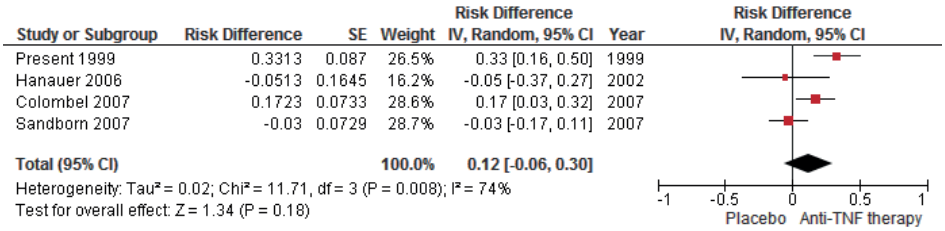

Figure 3 Meta-analysis of 4 randomised controlled trials comparing anti-TNF therapy with placebo for complete fistula closure.

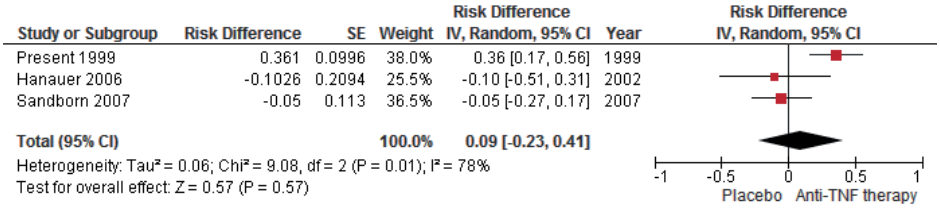

Figure 4 Meta-analysis of 3 randomised controlled trials comparing anti-TNF therapy with placebo for partial fistula closure.

Study quality and shortcomings

Studies on seton drainage were solely (prospective and retrospective) cohort studies and case series, mainly of questionable quality (Table S6). Among the studies on anti-TNF there were six RCTs (of which 4 were included in the meta-analysis), 8 cohort studies and 21 case series.

The methodological quality of the RCTs was high overall, whereas the quality of the cohort studies and case series was questionable (Tables S7–S9). The RCTs included in the meta-analysis were all funded by pharmaceutical companies.

Generalisability was less high for the RCTs, since stricter inclusion criteria were applied. Cohort studies and case series mainly focused on a more general population. Details on the patient population, procedure description and endpoint definitions for each study are provided in Tables S10–S13.

Discussion

Based on the results of this systematic literature review it can be concluded that closure and recurrence rates after treatment with seton drainage as well as with anti-TNF vary widely.

The studies that reported on seton drainage alone had several limitations. First of all, the included cohort studies and case series were mainly of questionable quality. One of the cohort studies on seton drainage with the highest fistula closure rate is over 20 years old, with a very small sample size (n = 6).[21] In addition, the most recent study (with 31.3% closure) assessed this outcome parameter after only 3 months, which is too short a time for a meaningful follow-up.[12] Secondly, in all studies, seton removal was at the discretion of the treating physician, which could introduce information bias. Since complete closure of the internal opening can only be achieved after seton removal, the fact that in some studies seton removal was not reported could introduce detection bias. The duration of seton drainage differed in the reported studies, and it remains unclear what the optimal timing for seton removal should be.

In the studies included, the definition of complete healing differed among studies or was not further defined. This was mainly the case in studies reporting on seton drainage (Tables S10–S13). In the majority of studies, closure was assessed by physical examination by the treating physician, which may have introduced a measurement bias. Only a few studies used MRI to assess closure of the fistula tracts.

When addressing the limitations of the studies of anti-TNF it must be emphasized that although overall a large group of patients were treated with anti-TNF, some studies only had a small sample of patients with Crohn's perianal fistula within the study group. In addition, the follow-up time varied widely between the studies. Whereas some studies were focusing on induction therapy, others were aiming for maintenance therapy. In several studies the endpoints were assessed after only 8–12 weeks (induction), which is too soon. This was also supported by the meta-analysis of the 4 RCTs included, which did not show a significant advantage for (complete or partial) fistula closure with anti-TNF as compared with placebo. However, subgroup analysis did show an advantage on complete fistula closure rates for anti-TNF treatment in the two trials with a follow-up longer than 4 weeks. Although closure rates with anti-TNF are disappointing, it is currently the most effective medical therapy for patients with inflammatory bowel disease refractory to standard medication. During the past decade more knowledge has been gained with respect to adequate dosing of anti-TNF by monitoring treatment effect and

measuring trough levels.[61] Concomitant immunomodulating therapy can decrease the formation of antibodies to anti-TNF and may improve long-term outcome.[62] Since fistulising Crohn's disease is a chronic condition, long-term results are of crucial importance. The long-term results of the CHARM trial demonstrated that all patients with complete fistula closure at week 26 continued to have complete fistula closure at week 56 when medication was not stopped. Long-term results of the ACCENT II trial have showed complete fistula closure in 34% of patients responding to infliximab therapy after 46 weeks vs 19% closure in the placebo group.[63] Since patients in this study were randomised after 14 weeks of infliximab treatment, it was not included in the meta-analysis. In addition, patients with rectovaginal fistula were included in the study by Sands et al., which is an exclusion criterion for the present review.[63] However, Lichtenstein et al. showed that the median length of time during which fistulae remained closed after cessation of medication was 3 months, with over 50% reopening of the fistula.[64] It remains unclear how long anti-TNF should be continued for sustained fistula closure.

The additional use of seton drainage prior to anti-TNF treatment varied among the studies. In cases of perianal sepsis, adequate seton drainage of a fistula is of key importance prior to starting anti-TNF medication. The available cohort series suggest that combining seton drainage with anti-TNF therapy is superior to either therapy alone. The results of this systematic review are in keeping with a systematic review by Yassin et al., who also found that a combination of surgical treatments (including seton drainage as well as other surgical treatments) with medical therapy (anti-TNF and immunomodulators) may have additional benefit on healing of perianal fistula in patients with Crohn's disease compared with surgery or medical therapy alone.[65] To date, there are no published RCTs comparing seton drainage and anti-TNF for Crohn's perianal fistulae directly. Furthermore, many patients were simultaneously treated with immunomodulators or other immunosuppressive medication. The use of concomitant medical therapy was reported in most studies, although it was not considered as a potential confounder in these series.

In this review it was intended to limit the analysis to closure rates and recurrences in perianal fistulae only in order to avoid selection bias. Therefore, data on rectovaginal or rectourinary fistulae were excluded where possible. However, the RCTs included in the meta-analysis comparing anti-TNF with placebo did not distinguish between perianal, enterocutaneous and enteroenteral fistulae. It was not possible to extract specific data on perianal fistulae alone, which was recognized as a severe limitation. However, it is likely that the majority of fistulae were of perianal origin, since these are much more

common than enterocutaneous fistulae in Crohn's disease. In the study by Present et al., the percentage of patients with perianal fistulae was 90% compared with 10% with enterocutaneous fistulae.[4]

Currently, with the development of new biologicals (e.g. vedolizumab) there are more medical treatment options nowadays. In a recent randomised controlled trial assessing the efficacy of vedolizumab, perianal fistulas closed in 17 patients (23%) treated with vedolizumab every 8 weeks and 22 patients (41%) with vedolizumab every 4 weeks compared to 18 patients (11%) in the placebo group (P = 0.32 and P = 0.03).[66]

In view of the limitations of the included studies and the drawbacks encountered in this systematic review, a well-designed clinical trial directly comparing seton drainage and anti-TNF therapy is warranted. Clear endpoint definitions and procedural descriptions are essential. It is also imperative that follow-up should be long enough to comment on recurrence rates after primary closure of the perianal fistula. The currently recruiting PISA trial may answer some of these questions. PISA is an 18-centre multinational (NTR4137) randomised parallel group trial comparing chronic seton drainage alone with 1-year anti-TNF with seton drainage or seton drainage followed by 4 months' anti-TNF treatment together with advancement plasty.[67] The primary endpoint in that study is the proportion of patients with re-interventions.

In summary, closure and recurrence rates after treatment with seton drainage as well as with anti-TNF vary widely. Despite a large number of studies analysing the results of both treatment options, no conclusion can be drawn regarding the preferred strategy. However, combination therapy with (temporary) seton drainage, an immunomodulatory and anti-TNF may be beneficial in achieving closure of perianal fistulae.

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Table 6 Overview of risk of bias and quality assessment of cohort studies and case series on seton drainage.

				Selection bias/ Confounding	Performance bias	Attrition bias	Detection bias	Reporting bias		
Author	**Journal**	**Year**	**Study design**			**Risk of bias key elements**			**Total risk**	**General-izability**
Chung W. *et al.*	Am J Surg	2010	Retrospective cohort	Low	Uncertain	Low	Uncertain	Low	Uncertain	High
Galis-Rozen E. *et al.*	Colorectal Dis	2010	Case series	High	Uncertain	Low	High	Low	High	High
Higashi D. *et al.*	Anticancer Res	2009	Case series	High	Uncertain	Low	High	High	High	High
Thornton M. *et al.*	Dis Colon Rectum	2005	Case series	Low	Uncertain	Uncertain	Uncertain	High	High	High
Buchanan GN. *et al.*	Br J Surg	2004	Case series	High	Uncertain	Low	High	High	High	Low
Takesue Y. *et al.*	J Gastroenterol	2002	Case series	High	Uncertain	Low	High	High	High	High
Shinozaki M. *et al.*	J Gastroenterol	2002	Prospective cohort	Low	Uncertain	Low	Low	Low	Uncertain	High
Makowiec F. *et al.*	Dis Colon Rectum	1997	Case series	Low	Uncertain	Low	High	High	High	High
Williams JG. *et al.*	Dis Colon Rectum	1991	Case series	High	Uncertain	Low	High	Uncertain	High	High
Morrison JG. *et al.*	Dis Colon Rectum	1989	Case series	High	Uncertain	Low	High	High	High	High

Table 7 Overview of risk of bias and quality assessment of randomised controlled trials comparing anti-TNF and placebo.

				Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)		Other bias
Author	**Journal**	**Year**	**Study design**	**Risk of bias**						**Total risk methodology**	**(Funding pharmacological industry)**
Present *et al.*	N Engl J Med	1999	RCT	Low	Low	Low	Uncertain	Low	Low	Uncertain	Uncertain
Hanauer *et al.*	Gastroenterol	2006	RCT	Low	Low	Low	Low	Low	Low	Low	High
Colombel *et al.*	Gastroenterol	2007	RCT	Low	Low	Low	Low	Low	Low	Low	High
Sandborn *et al.*	Ann Intern Med	2007	RCT	Low	Low	Low	Low	Low	Low	Low	High

Table 8 Overview of risk of bias and quality assessment of cohort studies directly comparing (combined) anti-TNF and seton drainage.

				Selection bias/ Confounding	Performance bias	Attrition bias	Detection bias	Reporting bias		
Author	**Journal**	**Year**	**Study design**	**Risk of bias**					**Total risk**	**Generalizability**
Uchino M. *et al.*	World J of Gastroenterol	2011	Retrospective cohort	Low	Uncertain	Low	Low	Low	Uncertain	High
Sciaudone G. *et al.*	Can J Surg	2010	Prospective cohort	Low	Uncertain	Low	Low	Low	Uncertain	High
Gaertner WB. *et al.*	Dis Colon Rectum	2007	Retrospective cohort	Low	Uncertain	Low	Uncertain	Low	Uncertain	High
Regueiro M. *et al.*	Inflamm Bowel Dis	2003	Retrospective cohort	Low	Uncertain	Low	High	Low	High	High

Table 9 Overview of risk of bias and quality assessment of cohort studies and case series on anti-TNF.

				Selection bias/ Confounding	Performance bias	Attrition bias	Detection bias	Reporting bias		
Author	**Journal**	**Year**	**Study design**			**Risk of bias**			**Total risk**	**Generalizability**
Castaño-Milla C. *et al.*	J Clin Gastroenterol	2015	Case series	Low	Low	Low	Low	High	High	High
Yang B. *et al.*	World J of Gastroenterol	2015	Case series	High	Uncertain	Low	Uncertain	High	High	Uncertain
Kotze PG. *et al.*	Arq Gastroenterol	2014	Case series	High	Uncertain	Low	Uncertain	Low	High	High
Bouguen G. *et al.*	Clin Gastroenterol Hepatol	2013	Case series	Uncertain	Uncertain	High	Low	Low	High	High
Dewint P. *et al.*	Gut	2013	RCT	Low	Low	Low	Low	Low	Low	High
Antakia R. *et al.*	Colorectal Dis	2012	Case series	High	High	Low	Uncertain	High	High	High
Duff S. *et al.*	Colorectal Dis	2012	Case series	High	High	Low	Uncertain	High	High	High
El-Gazzaz G. *et al.*	Colorectal Dis	2012	Retrospective cohort	Low	Uncertain	Low	Low	Low	Uncertain	High
Fortea-Ormaechea JI. *et al.*	Gastroenterol Hepatol	2011	Retrospective cohort	Low	Uncertain	Low	Low	Low	Uncertain	High
Karmiris K. *et al.*	Clin Gastroenterol Hepatol	2011	Case series	Low	Uncertain	Low	Low	Low	Uncertain	Uncertain
Savoye-Collet C. *et al.*	Inflamm Bowel Dis	2011	Prospective cohort	Low	Uncertain	Low	Low	Low	Uncertain	High
Echarri A. *et al.*	J Crohns Colitis	2010	Case series	Low	Uncertain	Low	Low	Low	Uncertain	High
Gligorijevic V. *et al.*	Acta Chir Iugosl	2010	Case series	High	Uncertain	Low	High	High	High	High
Miheller P. *et al.*	BMC Gastroenterol	2009	Case series	Low	Uncertain	Low	Low	Low	Uncertain	High
Ng SC. *et al.*	Aliment Pharmacol Ther	2009	Case series	High	High	Low	Uncertain	Low	High	High

Table 9 Overview of risk of bias and quality assessment of cohort studies and case series on anti-TNF. (continued)

				Selection bias/ Confounding	Performance bias	Attrition bias	Detection bias	Reporting bias		
Oussalah A. *et al.*	Aliment Pharmacol Ther	2009	Case series	High	Uncertain	Low	High	Low	High	Low
Tougeron D. *et al.*	Dig Dis Sci	2009	Case series	Low	Uncertain	Low	Low	Low	Uncertain	High
Trinder MW. *et al.*	J Gastroenterol Hepatol	2009	Prospective cohort	Low	Uncertain	Low	Low	Low	Uncertain	Low
Guidi L. et al.	Tech Coloproctol	2008	Case series	High	Uncertain	Low	Uncertain	Low	High	Low
Lopez PN. *et al.*	Rev Esp Enferm Dig	2008	Case series	High	Uncertain	Low	Uncertain	Low	High	Low
Spradlin NM. *et al.*	Am J Gastroenterol	2008	RCT (pilot)	Low	Uncertain	Low	Low	Low	Uncertain	Low
Hinojosa J. *et al.*	Aliment Pharmacol Ther	2007	Case series	High	Uncertain	Low	Uncertain	High	High	High
Hyder SA. *et al.*	Dis Colon Rectum	2006	Case series	High	Uncertain	Low	High	Low	High	High
Orlando A. *et al.*	Dig Liver Dis	2005	Retrospective cohort	Low	Uncertain	Low	Low	Low	Uncertain	High
Ardizzone S. *et al.*	Inflamm Bowel Dis	2004	Case series	High	Uncertain	Low	Uncertain	Low	High	Low
Luna-Chadid M. *et al.*	Rev Esp Enferm Dig	2004	Prospective cohort	Low	Uncertain	Low	Low	Low	Uncertain	High
Rasul I. *et al.*	Am J Gastroenterol	2004	Case series	Uncertain	Uncertain	Low	Low	Low	Uncertain	Low
Schroder O. *et al.*	Aliment Pharmacol Ther	2004	Case series	High	Uncertain	Low	Uncertain	Low	High	Low
Bell SJ. *et al.*	Aliment Pharmacol Ther	2003	Case series	High	Uncertain	Low	Uncertain	Low	High	Low
Topstad DR. *et al.*	Dis Colon Rectum	2003	Case series	High	Uncertain	Low	Uncertain	High	High	High
Ochsenkuhn T. *et al.*	Am J Gastroenterol	2002	Case series	High	Uncertain	Low	Uncertain	Low	High	Low
Poritz LS. *et al.*	Dis Colon Rectum	2002	Case series	High	Uncertain	Low	Uncertain	Low	High	Low
Arnott ID. *et al.*	Aliment Pharmacol Ther	2001	Retrospective cohort	Low	Uncertain	Low	Low	High	High	High
Farrell RJ. *et al.*	Am J Gastroenterol	2000	Case series	Low	Uncertain	Low	High	Low	High	High

Table 10 Details risk of bias and quality assessment of cohort studies and case series on seton drainage.

Quality assessment included studies on seton drainage		
Chung W. *et al.* (Am J Surg 2010)	Author's judgment	Support judgment
Patient population	clear	*All IBD patients treated for anal fistulas were identified. Inclusion criteria for this study were age older than 18 years and high transsphincteric fistulas secondary to IBD.'*
Outcome definition	clear	*Healing for the seton drain group was defined as a persistent fistula opening at the seton site but absence of drainage or infection.'*
Procedure description	clear	*The fistula tracts were probed and were opened external to the anal sphincter. Transsphincteric Ethibond sutures tied loosely were used'*
Galis-Rozen E. *et al.* (Colorectal Dis 2010)	Author's judgment	Support judgment
Patient population	clear	*...patients with complex perianal fistula who were treated by loose seton. The patients were divided into two groups based on whether or not they had CD.'*
Outcome definition	unclear	*...in the non-CD patients was healing rate and in CD patients it was clinical improvement.'*
Procedure description	clear	*...a loose seton was placed in the fistulous track where it remained for 6–8 weeks. During the second operation, a fistulotomy of the remaining fistula was performed'*
Higashi D. *et al.* (Anticancer Res 2009)	Author's judgment	Support judgment
Patient population	clear	*...seton placement was performed in 93 patients with anal fistulas due to CD. Of these, 86 patients had courses extending over one year.*
Outcome definition	unclear	*'69 percent of these had good courses…' 'Remission' or 'no worsening' not further defined'*
Procedure	unclear	*...seton placement was performed….'*
Thornton M. *et al.* (Dis Colon Rectum 2005)	Author's judgment	Support judgment
Patient population	clear	*...all patients with perianal Crohn's fistulas treated by the senior author with a long-term indwelling seton or mushroom catheter. Patients were referred after exhaustion of the medical options by gastroenterologists with a particular interest in Crohn's disease.'*
Outcome definition	clear	*Symptom control was defined as minimal perianal discharge and the absence of perianal pain.'*

Table 10 Details risk of bias and quality assessment of cohort studies and case series on seton drainage.

Quality assessment included studies on seton drainage (continued)		
Procedure	clear	*A probe was passed along the fistula tract usually from the external to the internal opening. A silk or nylon suture was passed along the gutter of the fistulotomy probes through the fistula tract. An Ethibond seton was then tied to the suture and pulled through the tract. This was secured loosly'*
Buchanan GN. *et al.* (Br J Surg 2004)	Author's judgment	Support judgment
Patient population	clear	*A consecutive series of 24 patients with fistula in ano was studied. Although 14 of these patients had cryptoglandular fistula in ano, six had Crohn's disease either at the time of their original surgery or subsequently diagnosed during follow-up.'*
Outcome definition	unclear	*success of the loose-seton technique was defined as complete eradication of sepsis following seton removal.'*
Procedure	clear	*...loose-seton technique included an initial examination under anaesthesia at which secondary extentions were identified and laid open. The intersphincteric space was laid open and by division of the internal anal sphincter and overlying epithelium, from the level of the primary track to the anal verge, eradicating the affected anal gland. A loosely tied no.1 nylon seton was then placed..'*
Takesue Y. *et al.* (J Gastroenterol 2002)	Author's judgment	Support judgment
Patient population	clear	*...62 patients with Crohn's disease underwent surgery for anal fistulae at Hiroshima University School of Medicine Hospital, and 32 patients (51.6%) underwent long-term seton drainage for complex anal fistulae.'*
Outcome definition	unclear	*Success rate or healing was not further defined*
Procedure	clear	*To identify the primary openings, we injected hydrogen peroxide through the secondary openings and then looked for air bubbles. Any secondary superficial tracts were opened and deep primary tracts alone were drained using the seton. Surgical silk, silicone tube, Vesseloops was loosely tied'*
Shinozaki M. *et al.* J Gastroenterol 2002)	Author's judgment	Support judgment
Patient population	clear	*From August 1993 to September 1998, 39 of 239 Crohn's disease patients underwent long-term seton drainage. The patients were divided into two groups: patients who received simultaneous bowel and anus operation (simultaneous group; n=11) and a control group (n=28).'*
Outcome definition	clear	*Healed anal fistula was defined as no discharge noted for more than 1 month after removal of all seton drains . Recurrence was defined as the presence of fistula discharge after closure of all the fistulas.'*

Table 10 Details risk of bias and quality assessment of cohort studies and case series on seton drainage.

Quality assessment included studies on seton drainage (continued)		
Procedure	clear	*after curettage of the fistula tract, preserving the anal sphincter, loosely tied Penrose drain(s) or rubber string(s) were introduced through the tract.'*
Makowiec F. *et al.* (Dis Colon Rectum 1997)	Author's judgment	Support judgment
Patient population	clear	*During a six-year period, from May 1989 to May 1995, 126 consecutive patients with perianal disease (fistulas and/or abscesses) were treated and followed-up prospectively in the Crohn's disease clinic of the Department of Surgery at the University of Tübingen.'*
Outcome definition	unclear	No clear definition of healing
Procedure	clear	*Superficial abscesses were treated by incision and subsequent insertion of a latex drain'*
Williams JG. *et al.* (Dis Colon Rectum 1991)	Author's judgment	Support judgment
	clear	*The clinical records of patients with Crohn's disease who underwent surgical treatment of anal fistulas between 1980 and 1989 were reviewed. The diagnosis of Crohn's disease was based on clinical, radiologic, and, where possible, pathologic criteria.*
Outcome definition	unclear	Healing not further defined/described
Procedure	clear	*seton insertion for high fistulas involving more of the sphincteric muscles. All external tracts were laid open, debrided, and marsupialized, but the deep fistula tract through the sphincters was identified and a seton placed loosely through the tract to maintain drainage. Fine Silastic tubing was the material usually employed'*
Morrison JG. *et al.* (Dis Colon Rectum 1989)	Author's judgment	Support judgment
Patient population	clear	*A retrospective review of 631 patients with Crohn's disease treated at the Ochsner Medical Institutions from 1973 to 1986 was undertaken to identify those patients who had undergone definitive operations for anorectal fistulas.'*
Outcome definition	unclear	Complete healing not further defined
Procedure	unclear	*Low fistulas were treated by fistulotomy alone in 17 patients and by partial fistulotomy and seton insertion in 6.'*

Table 11 Details risk of bias and quality assessment of randomised controlled trials comparing anti-TNF and placebo.

Quality assessment included studies in meta-analysis comparing anti-TNF and placebo		
Present *et al.* (N Engl J Med 1999)	Author's judgment	Support judgment
Methods		*Randomised Controlled Trial (double-blind, multicentre, placebo controlled).'*
Participants		*Patients who were 18 to 65 years of age and who had single or multiple draining abdominal or perianal fistulas of at least three months' duration as a complication of Crohn's disease That had been confirmed by radiography, endoscopy, or pathological examination.'*
Interventions		*Infliximab (2 regimens) or placebo.'*
Outcomes		*A reduction of 50 percent or more from base line in the number of draining fistulas observed at two or more consecutive study visits. Secondary: number of patients with a complete response (defined as the absence of any draining fistulas at two consecutive visits), the length of time to the beginning of a response, and the duration of the response. Changes in scores on the Crohn's Disease Activity Index and the Perianal Disease Activity Index were also evaluated.'*
Notes		*ACCENT-trial*
Bias		
Random sequence generation (selection bias)	low risk	*...eligible patients were randomly assigned to receive one of three treatments...'*
Allocation concealment (selection bias)	low risk	*Randomisation was performed by an independent organization (PPD Pharmaco, Austin, Tex.), using a stratified treatment assignment 20 with the investigational site and the number of fistulas (one or more than one) as the stratification variables.'*
Blinding of participants and personnel (performance bias)	low risk	*The placebo was identical in appearance to the infliximab solution.'*
Blinding of outcome assessment (detection bias)	uncertain risk	*not mentioned*
Incomplete outcome data (attrition bias)	low risk	*...Six patients discontinued treatment (four in the placebo group and two treated with infliximab)...'*
Selective reporting (reporting bias)	low risk	*X*
Other bias	uncertain risk	*Centocor involvement?*
Hanauer *et al.* (Gastroenterology 2006)	Author's judgment	Support judgment

Table 11 Details risk of bias and quality assessment of randomised controlled trials comparing anti-TNF and placebo. (continued)

Quality assessment included studies in meta-analysis comparing anti-TNF and placebo		
Methods		*Randomised Controlled Trial (double-blind, multicentre, placebo controlled)'*
Participants		*Patients included men and women (18–75 years of age) with Crohn's disease for at least 4 months who had moderate to severe disease as defined by a Crohn's Disease Activity Index (CDAI)24 score of 220–450 points.'*
Interventions		*The primary endpoint was demonstration of a significant difference in the rates of remission at week 4 (defined as a Crohn's Disease Activity Index score <150 points) among the 80 mg/40 mg, 160 mg/80 mg, and placebo groups.'*
Notes		*CLASSIC-1 trial*
Bias		
Random sequence generation (selection bias)	low risk	*Patients were screened for eligibility 2 weeks before enrolment into the trial. At week 0, all eligible patients were randomly assigned in a 1:1:1:1 ratio to receive one of the following subcutaneous induction regimens.' and 'An interactive voice response system generated and implemented the randomisation sequence using a block size of 8 per centre'*
Allocation concealment (selection bias)	low risk	*The patients, study coordinators, and study investigators were all blinded to treatment assignment.'*
Blinding of participants and personnel (performance bias)	low risk	*The interactive voice response system (IVRS) assigned patients to their groups, and all participants remained blinded to group assignments. A pharmacist blinded to the identity of the study drug prepared each injection of adalimumab or an identical-appearing placebo.'*
Blinding of outcome assessment (detection bias)	low risk	*The patients, study coordinators, and study investigators were all blinded to treatment assignment.'*
Incomplete outcome data (attrition bias)	low risk	*Overall, premature withdrawal from the study occurred in 6 patients (8%) in the placebo group versus 2 patients (3%) in the adalimumab 40 mg/20 mg group, 5 patients (7%) in the adalimumab 80 mg/40 mg group, and 2 patients (3%) in the adalimumab 160 mg/80 mg group.'*
Selective reporting (reporting bias)	low risk	*x*
Other bias	high risk	Grant Support: By Abbott Laboratories.
Colombel *et al.* (Gastroenterology 2007)	Author's judgment	Support judgment
Methods		*Randomised Controlled Trial (double-blind, multicentre, placebo controlled).'*

Table 11 Details risk of bias and quality assessment of randomised controlled trials comparing anti-TNF and placebo. (continued)

Quality assessment included studies in meta-analysis comparing anti-TNF and placebo		
Participants		*men and women 18–75 years of age with known CD of at least 4 months' duration (radiologic/endoscopic confirmation required) that at the screening visits was moderately to severely active, as defined by a baseline Crohn's Disease Activity Index (CDAI) score of 220–450 points.'*
Interventions		*Adalimumab (2 regimens after week 4) or placebo.'*
Outcomes		*Percentages of randomised responders who achieved clinical remission (Crohn's Disease Activity Index score <150) at weeks 26 and 56.'*
Notes		*CHARM-trial*
Bias		
Random sequence generation (selection bias)	low risk	*Patients, study coordinators, and study investigators were blinded to treatment assignment throughout the blinded portion of the study.'*
Blinding of participants and personnel (performance bias)	low risk	*The interactive voice response system (IVRS) assigned patients to their groups, and all participants remained blinded to group assignments. A pharmacist blinded to the identity of the study drug prepared each injection of adalimumab or an identical-appearing placebo.'*
Blinding of outcome assessment (detection bias)	low risk	*The patients, study coordinators and study investigators were all blinded to treatment assignment.'*
Incomplete outcome data (attrition bias)	low risk	*...76 withdrew before randomisation at week 4. The most common reasons for study discontinuation were adverse events and lack of efficacy.' and 'A total of 505 enrolled patients (59%) completed the 56-week study.'*
Selective reporting (reporting bias)	low risk	*X*
Other bias	high risk	*Grant Support: By Abbott Laboratories.*
Sandborn *et al.* (Ann Intern Med 2007)	Author's judgment	*Support judgment*
Methods		*Randomised Controlled Trial (double-blind, multicentre, placebo controlled)'*
Participants		*Patients included men and women 18 to 75 years of age with Crohn disease for at least 4 months that was moderately to severely active at baseline, defined by a Crohn's Disease Activity Index (CDAI) (12) score of 220 to 450 points (range, 0 to 600 points; greater scores indicate more severe disease activity).'*
Interventions		*Adalimumab or placebo.'*

Table 11 Details risk of bias and quality assessment of randomised controlled trials comparing anti-TNF and placebo. (continued)

Quality assessment included studies in meta-analysis comparing anti-TNF and placebo		
Outcomes		*Primary: efficacy end point was the proportion of patients with remission at week 4. Remission was defined as a CDAI score less than 150 points (12). Response was defined as a decrease from baseline in CDAI score of 70 points or more (70-point response) or of 100 points or more (100-point response) at week 4.'*
Notes		*GAIN-trial*
Bias		
Random sequence generation (selection bias)	low risk	*We randomly assigned eligible patients to receive subcutaneous injections of adalimumab...'*
Allocation concealment (selection bias)	low risk	*Randomisation was completed through a central computer-generated scheme stratified by site, with block sizes of 4. Patient numbers were centrally assigned by an interactive voice-response system in consecutive order.'*
Blinding of participants and personnel (performance bias)	low risk	*Patients, investigators, study site personnel, and Abbott Laboratories were unaware of treatment assignments.'*
Blinding of outcome assessment (detection bias)	low risk	*Patients, investigators, study site personnel, and Abbott Laboratories were unaware of treatment assignments.'*
Incomplete outcome data (attrition bias)	low risk	*A total of 325 patients were randomly assigned, and 301 patients completed the study. Fifteen patients did not enrol in the ongoing, open-label extension study, including 14 patients who discontinued treatment prematurely (10 in the placebo group and 4 in the adalimumab group) and 1 patient who completed the study.'*
Selective reporting (reporting bias)	low risk	*X*
Other bias	high risk	*Grant Support: By Abbott Laboratories*

Table 12 Details risk of bias and quality assessment of cohort studies directly comparing (combined) anti-TNF and seton drainage.

Quality assessment included studies directly comparing anti-TNF and seton drainage		
Uchino M. *et al.* (World J of Gastroenterol 2011)	Author's judgment	Support judgment
Patient population	clear	*...patients with a perianal CD lesion who required surgical treatment between September 1995 and April 2010 were reviewed retrospectively.'*
Outcome definition	clear	*...primary endpoint was a clinical response at 12-15 wk affter surgery. The effective response was defined as at least a one point or greater reduction in every major Element from baseline at week 12 as a short-term eEfficacy (a decreas of more than 4 points on the mPDAI score). Secondary endpoints were recurrence a reflected in the mPDAI score, defined as increased points in every major element (an increase of more than 4 points. The clinical responses were classified as completely healed (mPDAI=0), partially improved (mPDAI score decreased more than 4 points), and failure (mPDAI score increased or decreased less than 3 points).'*
Procedure description	clear	*...fistula tracts were thoroughly curetted, the abscess cavities were sufficiently drained and rubbed with a surgical spoon. Soft silastic or Teflon-coated vessel tape was inserted along the fistula tracts and tied loosely. Setons were removed in the outpatient clinic if the infection resolved on MRI findings and left in place if there were continuing signs of infection. Initial IFX infusions (5 mg/kg) were administered within 2 wk from seton drainage (0 wk), and consecutive infusions were administered 2 wk and 6 wk later. This was continued as maintenance therapy every 8 wk.'*
Sciaudone G. *et al.* (Can J Surg 2010)	Author's judgment	Support judgment
Patient population	clear	*...35 consecutive patients, all of European descent, with perianal complex fistulas because of Crohn disease were referred from gastroenterologists to our institution. Their disease had not responded to conventional medical treatments, including antibiotics (metronidazole 750–1500 mg/d or ciprofloxacin 1000 mg/d for 3 mo)12 and immunosuppressant therapy azathioprine 2–2.5 mg/kg/d or methotrexate 25 mg/wk for at least 2 mo).'*

Table 12 Details risk of bias and quality assessment of cohort studies directly comparing (combined) anti-TNF and seton drainage. (continued)

Quality assessment included studies directly comparing anti-TNF and seton drainage		
Outcome definition	clear	*We defined clinical response as complete if there was closure of all external openings and cessation of fistula drainage for more than 3 months. A reduction in the size, number, drainage or discomfort associated with a fistula was defined as a partial response. Patients with a persistent fistula at follow-up were considered to be nonresponders. We defined recurrence as the reopening of external fistula tracks with active drainage or the development of a perianal abscess at the site of the original fistula.'*
Procedure description	clear	*Infliximab was infused using a standard protocol (groups A and C; 5 mg/kg intravenously after intravenous infusion of 100 mg of steroids at 0, 2 and 6 wk). Patients with a partial response were given additional infliximab (5 mg/kg intravenously every 8 wk); infliximab was not continued in nonresponders Patients in groups B and C underwent examination under anaesthesia in the lithotomy position. Fistula tracks were treated by curettage,irrigation with saline and apposition of loose seton (soft silastic drain) to facilitate drainage.'*
Gaertner WB. *et al.* (Dis Colon Rectum 2007)	Author's judgment	Support judgment
Patient population	clear	*...patients with CD who underwent operative treatment of anal fistulas, with or without infliximab infusion, from March 1991 through December 2005 were reviewed. The diagnosis of CD was based on clinical, radiologic ,endoscopic, and,where possible, pathologic criteria.'*
Outcome definition	clear	*Patients were classified as completely healed (no clinical evidence of a fistula tract), minimally symptomatic (seton placement with minimal drainage and/or infliximab dependence), and failure (persistent or recurrent symptomatic fistula, diverting procedure or proctectomy). Patients who required infliximab infusions at six-week to eight-week intervals to maintain their response were intervals to maintain their response were classified as infliximab-dependent.'*
Procedure description	clear	*All abscesses were drained and when necessary noncutting setons were placed to control anorectal infection. Setons were removed in the office if anorectal infection resolved and left in place if there were continuing signs of infection. Sometimes, the seton was left in place prophylactically to prevent renewed infection Infliximab therapy was given after perianal infection resolved and included an induction regimen of 5 mg/kg at zero,two and six weeks. If equired, additional infusions were scheduled at four-rweek to six-week intervals.'*

Table 12 Details risk of bias and quality assessment of cohort studies directly comparing (combined) anti-TNF and seton drainage. (continued)

Quality assessment included studies directly comparing anti-TNF and seton drainage		
Regueiro M. *et al.* (Inflamm Bowel Dis 2003)	Author's judgment	Support judgment
Patient population	clear	*Between October 1999 and October 2001 there were 109 patients with Crohn's disease treated with infliximab at the University of Pittsburgh Medical Center Inflammatory Bowel Disease Clinic for actively draining perianal fistulas.'*
Outcome definition	clear	*Perianal fistula response was defined as complete closure and cessation of drainage from the fistula based on history and physical examination. Initial response was defined as fistula closure within 3 months of the third induction dose of infliximab. Recurrence was defined as reopening of the external fistula track with active drainage noted on history and examination.'*
Procedure description	unclear	*...who completed at least 3 infusions of infliximab (5 mg/kg at weeks 0, 2, and 6) for an actively draining perianal fistula and had at least 3 months of follow-up after the third infusion.'*

Table 13 Details risk of bias and quality assessment of cohort studies and case series on anti-TNF.

Quality assessment included studies on anti-TNF		
Castaño-Milla *et al*. (Clin Gastroenterol 2015)	Author's judgment	Support judgment
Patient population	clear	*...CD patients over 18 years of age with draining perianal fistulas for at least 3 months.'*
Outcome definition	clear	*Clinical fistula response was defined by the Fistula Drainage Assessment Index as the reduction of 50% or more from baseline in the number of draining fistulas upon gentle compression) for at least 2 consecutive visits at least 4 wk apart) Loss of response was defined clinically as a reappearance or recrudescence of a draining fistula in a patient who had initially responded to ADA'*
Procedure description	clear	*...patients received ADA 160mg at week 0 and 80 mg at week 2, or ADA 80 mg at week 0 and 40 mg at week 2 as induction doses followed by 40mg every other week. In case of loss of response or incomplete response, a dose escalation to 40 mg weekly could be administrated. Concurrent therapies for CD, including antibiotics and immunomodulators were permitted. Seton placement was allowed before ADA therapy.'*
Yang *et al*. (World J of Gatroenterol 2015)	Author's judgment	Support judgment
Patient population	clear	*...patients with perianal fistulising CD who received surgery combined with IFX therapy'*
Outcome definition	clear	*...closure of the external opening of the anal fistula and disappearance of secretions for three months or more was considered indicative of a clinical cure; a reduction in the number of fistula tracts, fistula size, secretions, and discomfort was considered as remission; persistent anal fistula was considered as ineffective treatment; and recurrence of active inflammation perianal abscesses was classified as recurrence.'*

Table 13 Details risk of bias and quality assessment of cohort studies and case series on anti-TNF. (continued)

Quality assessment included studies on anti-TNF		
Procedure description	clear	*A radial incision was made along the primary tract of the anal fistula from the internal opening towards the external side. The internal opening was excised, and the original infection foci were cleaned by scraping. The fistula tract on the external side of the anal sphincter and the lateral branches were radially incised in several places. Necrotic tissue within the fistula was removed by scraping, and rubber bands were used to loosely connect the incision of the main tract and various other drainage incisions, resulting in reliably sustained drainage...All patients received induction therapy by the intravenous infusion of IFX (at weeks 0, 2, and 6; 5mg/kg), and the first infusion (week 0) was started within the first week after surgery, which was followed by three administrations of maintenance therapy, performed at eight-week intervals. At the fourth IFX infusion, a concomitant immunosuppressive agent azathioprine was routinely co-administrated.'*
Kotze *et al*. (Arq Gastroenterol 2014)	Author's judgment	Support judgment
Patient population	clear	*' ...patients with CD at any age, diagnosed by clinical symptoms and imaging tests, associated with endoscopic examinations with biopsies. Patients with PFCD (with simple or complex fistulas)...All patients included did not use previously any anti-TNF agent (they were naïve to biological therapy).'*
Outcome definition	clear	*...complete perianal remission, which was defined as complete absence of perianal drainage from fistula tracks with gentle finger pressure, associated with seton withdrawal (complete closure of all fistula tracks, without setons). Patients that had absence of drainage that wanted to keep their setons in place were allowed to maintain them, but were considered as having not achieved this outcome. These were considered to have remission with setons (partial response). The others that had still persistence of drainage with setons, were considered to have active PFCD Recurrence was defined as reactivation of previous healed tracks, (recurrent drainage after complete perianal remission), the need for subsequent seton placement performed in EUA, due to new fistulas or the occurrence of perianal abscesses after healing during the follow-up period.'*

Table 13 Details risk of bias and quality assessment of cohort studies and case series on anti-TNF. (continued)

Quality assessment included studies on anti-TNF		
Procedure description	clear	*All patients from the four referral IBD units were treated with combined therapy After EUA and seton placement, The type of agent (IFX or ADA) was chosen in accordance to a patient and physician consensus, and anti-TNF therapy was initiated.IFX was initiated with the regular induction regimen of intravenous 5 mg/kg in weeks 0, 2 and 6, followed by maintenance infusions with the same dose every 8 weeks. ADA induction was performed with subcutaneous injections of 160 mg at week 0, 80 mg at week 2 and 40 mg every other week after week 4. During anti-TNF therapy, the patients could be treated with concomitant immunomodulators such as azathioprine or 6-mercaptopurine, or with biological monotherapy. All patients used antibiotics for at least 2 weeks the EUA and anti-TNF initiation seton removal could be performed any time during the follow-up visits.'*
Bouguen G. *et al.* (Clin Gastroenterol Hepatol 2013)	Author's judgment	Support judgment
Patient population	clear	*All adult patients with documented PCD at first IFX infusion and an established diagnosis of CD that was based on clinical, biological, radiological, endoscopic, and/or histologic evidence were included.'*
Outcome definition	clear	*Fistula closure was defined as the absence of any draining by fistula openings at 1 visit, recurrence of perianal Crohn's disease was defined by the presence of fistulas openings among patients who experienced fistula closure.'*
Procedure description	clear	*IFX was administered initially at a dose of 5 mg/kg as a 2-hour intravenous infusion in all patients patients received 1-3 doses of IFX at weeks 0, 2 and 6 as induction.'*
Dewint *et al.* (Gut 2013)	Author's judgment	Support judgment
Patient population	clear	*Men and women diagnosed with CD and between 18 and 70 years of age with active fistulising perianal disease at screening and baseline were included. Previous treatment with infliximab was permitted if infliximab had been discontinued at least 12weeks before the screening visit and the patient had initially experienced response to the agent (as judged by the investigating physician).'*
Outcome definition	clear	*The primary outcome of the ADAFI was at least 50% reduction of the number of draining fistulas from baseline to week 12. The proportion of patients with closure of all draining fistulas from baseline, defined as remission, at week 12 and week 24 was a secondary outcome.'*

Table 13 Details risk of bias and quality assessment of cohort studies and case series on anti-TNF. (continued)

Quality assessment included studies on anti-TNF		
Procedure description	clear	*All patients received an induction regimen with 160 mg adalimumab at day 0 and 80 mg at week 2. At week 4, patients received 40 mg adalimumab every other week until the end of follow-up at week 24'*
Antakia R. *et al.* (Colorectal Dis 2013)	Author's judgment	Support judgment
Patient population	clear	*Patients with complex perianal Crohn's disease. Perianal fistulae were defined as complex if they had multiple external openings or had tracts extending proximally beyond the lower-half of the anal sphincter mechanism.'*
Outcome definition	clear	*Complete response signified complete fistula closure with no further discharge expressed on digital pressure on two consecutive clinic visits at least 4 weeks apart. Partial response was defined as reduction in the size or the number of fistulae, reduction in the amount of discharge or improvement in perianal pain.'*
Procedure description	clear	*IFX was administered as 5mg/kg infusions given at 0, 2 and 6 weeks. Setons were empirically removed following the second dose of IFX.'*
Duff S. *et al.* (Colorectal Dis 2012)	Author's judgment	Support judgment
Patient population	clear	*Patients who started the treatment for complex perianal fistulae were identified from the database while those patients who were commenced on treatment for symptoms of luminal disease or alternative Crohn's fistulae including enterocutaneous, rectovaginal, peristomal and Intra-abdominal fistulae were excluded from this study. Complex fistulae were defined as those with multiple openings or those with a track or those with a track lying above more than half the anal sphincter mechanism.'*
Outcome definition	clear	*A complete response was defined as complete closure of the fistula with no further drainage on gentle finger pressure. A partial response was defined as either reduction in the size of fistulae, reduction in the number of fistulae,reduction in the drainage of the fistulae as reported by the patient, or improvement in the associated perianal pain.'*
Procedure description	clear	*All patients were treated with prophylactic preoperative antibiotics (metronidazole or ciprofloxacin) and then with draining seton sutures with eradication of sepsis as appropriate. The patients then received initial infusions of infliximab (5 mg/kg) at 0, 2 and 6 weeks, with removal of their seton sutures planned after their second infusion'*
El-Gazzaz G. *et al.* (Colorectal Dis 2012)	Author's judgment	Support judgment

Table 13 Details risk of bias and quality assessment of cohort studies and case series on anti-TNF. (continued)

Quality assessment included studies on anti-TNF		
Patient population	clear	*Patients with perineal Crohn's fistulas were identified from the CD database. Patients were stratified according to use of anti-TNF agents infliximab of adalimumab.'*
Outcome definition	clear	*Endpoints were defined as either complete healing (no symptoms or drainage for a minimum of 2 weeks), improvement (minimal symptoms and drainage) or unhealed, as noted at subsequent outpatient follow-up.'*
Procedure description	clear	*Prior to surgery perianal sepsis was eradicated with drains or setons. Definitive treatment of fistulas included fistulotomy if the track was subcutaneous and there was no evidence of perianal involvement with CD, cutting seton if the track was low transsphincteric and posterior, and rectal advancement flap repair at a second stage for more complex and higher fistulas. Infliximab or adalimumab were given after the perianal infection had resolved. The regimen for administering infliximab was 5 mg/kg at 0, 2 and 6 weeks. If clinically indicated additional infusions were given at 8–10 week intervals as maintenance therapy. Adalimumab was given subcutaneously, 160 mg at week 0, 180 mg at week 2then 40 mg every other week.'*
Fortea-Ormaechea JI. *et al.* (Gastroenterol Hepatol 2011)	Author's judgment	Support judgment
Patient population	clear	*Multicentre retrospective survey of all CD patients treated with adalimumab in 9 hospitals of the Madrid area.'*
Outcome definition	clear	*In perianal fistulising disease, complete response was defined as the closure of all fistulas. On the other hand, partial response was defined as the closure of at least 50% of all fistulas.'*
Procedure description	clear	*The great majority of patients (93.7%) received the ADA induction regimen with 160 and 80 mg at weeks 0 an2, respectively. Maintenance treatment consisted of the administration of 40 mg every two weeks or weekly, depending on the need for dose escalation due to a loss of response during follow-up.'*
Karmiris K. *et al.* (Clin Gastroenterol Hepatol 2011)	Author's judgment	Support judgment

Table 13 Details risk of bias and quality assessment of cohort studies and case series on anti-TNF. (continued)

Quality assessment included studies on anti-TNF		
Patient population	clear	*Medical records of all patients with pfCD who had been treated with IFX were reviewed. Eligible patients were men and women who (1) had a pfCD diagnosis of ≥3 months from baseline, on the basis of endoscopic, histopathologic, radiologic, and clinical criteria with an indication for IFX treatment; (2) demonstrated at least intermittent drainage from 1 or more perianal fistula orifices before inclusion; (3) had undergone a baseline MRI within 2 weeks before IFX therapy initiation; and (4) went through an examination under anaesthesia by an experienced proctologist, during which any clinically relevant collections were drained.'*
Outcome definition	clear	*Clinical improvement in pfCD was defined as a ≥ 50% decrease in the number of draining perianal fistulas from baseline during at least 2 consecutive treatment visits and remission as complete closure of all draining fistulas according to the treating physician's assessment.'*
Procedure description	clear	*After a thorough baseline clinical assessment, all patients received 5 mg/kg of IFX at weeks 0, 2, and 6 and every 8 weeks thereafter.*
Savoye-Collet C. et al. (Inflamm Bowel Dis 2011)	Author's judgment	Support judgment
Patient population	clear	*...patients diagnosed with CD on either endoscopy and/or histology with one or more draining perianal fistulas'*
Outcome definition	clear	*Clinical remission was defined as the absence of any draining fistulas at clinical examination according to present criteria within 2 months of the MRI evaluation and the absence of self-reported drainage episode by the patient within the same period of time.'*
Procedure description	clear	*All patients then received an anti-TNF-a induction regimen either with infliximab 5 mg/kg at weeks 0, 2, 6 or with adalimumab 160/80/40 mg every other week followed by maintenance therapy based on infliximab 5 mg/kg at week 14, 22, 30, 38, 46 or adalimumab 40 mg every other week. Seton removal was performed after the anti-TNF-a induction course based on clinician judgment.'*
Echarri A. *et al.* (J Crohns Colitis 2010)	Author's judgment	Support judgment
Patient population	clear	*Patients with active, draining perianal Crohn's fistulas who had experienced a decrease in the efficacy of infliximab, or had developed intolerance'*

Table 13 Details risk of bias and quality assessment of cohort studies and case series on anti-TNF. (continued)

Quality assessment included studies on anti-TNF		
Outcome definition	clear	*A complete response was defined as the absence of discharge between two consecutive visits and a partial response was defined as either closure of >50% in number number of externally draining fistulas, or a marked reduction in drainage of all fistulas together, sustained for at least two consecutive visits. Recurrence was defined as a reopened external fistula track with active drainage.'*
Procedure description	clear	*Draining of abscesses, cleaning of fistula tracks, and placement of loose setons were done when necessary. Patients with simple fistulas and proctitis received adalimumab treatment directly. After the initial evaluation, induction treatment with adalimumab was started at a dose of 160 mg/s, followed 2 weeks later by 80 mg/s. Maintenance therapy was 40 mg/s every other week. In case of the loss of response, a weekly dose was performed.'*
Gligorijevic V. *et al.* (Acta Chir Iugosl 2010)	Author's judgment	Support judgment
Patient population	clear	*...CD patients diagnosed in University Clinical Hospital was performed. The diagnosis of CD was based on standard clinical, radiological, endoscopic, and histological criteria. All patients had perianal disease with one or more active fistula and/or perianal abscess. The maintenance therapy was based on immunosuppressant and antibiotics.'*
Outcome definition	unclear	*Partial response is defined as a cessation of secretion and induration in at least 50% of fistulas presented at baseline.'*
Procedure description	clear	*Seton was placed to all patients regardless to type of fistula.Seton was left a long enough, depending on the clinical response to combination therapy, but no longer than 6months after the third induction dose of infliximab. Seton was removed when the drainage was completely reduced and fistula tracts width became approximately equal to the Seton diameter. All patients were treated with immunosuppressive therapy (azathioprine) from 6 months to 7 years. Antibiotics (metronidazole and ciprofloxacin) were prescribed periodically, especially during the episode of inflammation. All patients received at least, the induction of infliximab (5mg/kg at 0, 2 and 6 weeks).*
Miheller P. *et al.* (BMC Gastroenterol 2009)	Author's judgment	Support judgment
Patient population	clear	*Patients with Crohn's Disease eligible for this observational study had 1) single or multiple discharging and/or and/ or perianal fistulas of at least 3-6 months duration despiteconventional immunosuppressant and antibiotic therapy; 2)therapy refractory/steroid dependent luminal disease.'*

Table 13 Details risk of bias and quality assessment of cohort studies and case series on anti-TNF. (continued)

Quality assessment included studies on anti-TNF		
Outcome definition	clear	*In fistulizing disease response was defined as a decrease of 50% or more in the number of discharging fistulas compared to baseline and remission was defined as absence of any discharging fistulas measured at week 12.'*
Procedure description	clear	*As induction therapy five mg/kg body weight of infliximab was administered in a 2 hour infusion at weeks 0, 2 and 6.' Infliximab 5 mg/kg body weight was given as maintenance therapy after week 6. Maintenance was given every 8 weeks.'*
Ng SC. *et al.* (Aliment Pharmacol Ther 2009)	Author's judgment	Support judgment
Patient population	clear	*Patients with CD with draining perianal and / or rectovaginal fistulas for at least 3 months were consecutively recruited between 2006 and 2008. CD was confirmed by endoscopy, radiology and histopathology.'*
Outcome definition	clear	*Clinical fistula remission was defined as absence of perianal drainage to gentle finger compression of external opening and surrounding tissues and absence of spontaneous drainage between two consecutive visits. Clinical fistula response was defined as either closure of ≥ 50% in number of externally draining fistulas or a marked reduction in drainage of all fistulas together with less pain and induration as reported by patient, sustained for at least two consecutive visits. Lack of response was defined as closure of ≤50% of draining fistulas, recurrence of draining fistulas, need for a surgical procedure for fistulas or study medication discontinuation for reasons of lack of efficacy.'*
Procedure description	clear	*All patients were treated according to a pre- algorithm. algorithm.Infliximab was first line therapy; patients who failed infliximab received adalimumab. All patients received induction doses of anti-TNF followed 'y maintenance therapy. For infliximab,patients received 5 mg/kg intravenous infusion at weeks 0, 2and 6, followed by eight weekly infliximab infusion. For adalimumab, patients received 160 mg subcutaneously at week 0,80 mg subcutaneously at week 2, followed by 40 mg subcutaneously every other week.'*
Oussalah A. *et al.* (Aliment Pharmacol Ther 2009)	Author's judgment	Support judgment
Patient population	clear	*...patients who were treated with adalimumab therapy for CD with intolerance or lost response to infliximab at our centre (University Hospital of Nancy)'*
Outcome definition	clear	*complete fistula closure (evaluated by clinical examination and defined as closure of all fistulas that were draining at baseline) at last known follow-up'*

Table 13 Details risk of bias and quality assessment of cohort studies and case series on anti-TNF. (continued)

Quality assessment included studies on anti-TNF		
Procedure description	clear	*The patients received at week 0 a loading dose of 160 or 80mg adalimumab subcutaneously followed by a 80- or 40-mg dose at week 2 and thereafter 40 mg every other week. The interval between injections was decreased to 40mg weekly in patients who did not achieve clinical response, as judged by their treating physician.'*
Tougeron D. *et al.* (Dig Dis Sci 2009)	Author's judgment	Support judgment
Patient population	clear	*Crohn's disease patients requiring infliximab for an active perianal fistulising disease managed in our tertiary care academic center from January 1999 to December 2005.'*
Outcome definition	clear	*The criteria of response used in this study was remission defined as a complete response according to Present's criteria. A patient was considered as responder in the absence of drainage from all fistulas with or without cicatrisation of the external fistula orifice...clinical relapse (discharge from a previously closed or non- fistula).' fistula).'*
Procedure description	clear	*...scheduled combined therapy consisted of abscess drainage (when appropriate) and seton placement accompanied by a short, 2-week course of antibiotics (metronidazole and/or ciprofloxacin) followed by infliximab induction treatment (three i.v.; administrations at 5 mg/kg at Week 0, Week 2,and Week 6). Seton removal was scheduled between the second and the third or the third and the fourth infliximab injections.'*
Trinder MW. et al. (J Gastroenterol Heptol 2009)	Author's judgment	Support judgment
Patient population	clear	*Crohn's disease or UC/IBD unclassified (UC/IBDU) patients received adalimumab after failure of disease control with conventional therapies or loss of control by infliximab.'*
Outcome definition	clear	*fistula response was defined as any decrease in fistulae drainage and/or pain, and fistula remission was sustained cessation of drainage and resolution of the fistula with removal of setons.'*
Procedure description	clear	*Patients treated with adalimumab received a 160 mg loading dose at week 0 followed by a second 80 mg loading dose at week 2. Patients then received 40 mg subcutaneous injections fortnightly. Depending on the patient response by week 8,the adalimumab dosing was changed to weekly 40 mg subcutaneous injections.'*
Guidi L. *et al.* (Tech Coloproctol 2008)	Author's judgment	Support judgment

Table 13 Details risk of bias and quality assessment of cohort studies and case series on anti-TNF. (continued)

Quality assessment included studies on anti-TNF		
Patient population	clear	*Nine consecutive patients with CD with complex perianal fistulas were enrolled. Fistulas were defined as complex if there was deep involvement of the anal sphincters or extension of the fistula above the dentate line, according to the results of preinclusion AE which was performed in all patients, possibly supplemented by CT or MRI in those with suspected wide pelvic involvement.'*
Outcome definition	clear	*complete clinical response was defined as no further discharge from the fistula on firm finger pressure. A partial response was defined as the presence of one of the following conditions: reduction in the number of fistulas, in the amount of drainage, in the size of the fistulas, or in the PDAI score...Secondary end points were the time to complete response (to define by AE of the optimal time for seton removal)and the incidence of recurrence or complications during follow-up.'*
Procedure	clear	*Perianal abscesses were drained when present and setons were placed' Infliximab was administered at a dose of 5mg/kg in weeks 0, 2 and 6 and then about every 8 weeks..' AZA at a dose of 2.5mg/kg was also administered'*
Lopez PN. *et al.* (Rev Esp Enferm Dig 2008)	Author's judgment	Support judgment
Patient population	clear	*...patients with CD diagnosed by clinical, endoscopic, and histological criteria and who were treated with adalimumab at Hospital Clínico San Carlos, Madrid, between March 2004and December 2007 were consecutively included.'*
Outcome definition	clear	*Remission was defined as the total closure of all fistulas with cessation of fistula drainage, and partial response as a decrease in the number, form, drainage, or discomfort associated with fistulas.'*
Procedure description	clear	*All patients received induction therapy with 160 mg adalimumab s.c. at week 0 followed by 80 mg s.c. at week 2.Responders received maintenance therapy with 40 mg s.c. every 14 days. In the event of loss of response the dosing interval was decreased to 40 mg s.c. every week.'*
Spradlin NM. *et al.* (Am J Gastroenterol 2008)	Author's judgment	Support judgment
Patient population	clear	*...patients with fistulising perianal Crohn's disease participated in this prospective randomised pilot study.'*

Table 13 Details risk of bias and quality assessment of cohort studies and case series on anti-TNF. (continued)

Quality assessment included studies on anti-TNF		
Outcome definition	clear	*The primary end point of this pilot study was the difference in the cessation of fistula drainage at week 54 For the purpose of the study, "cessation of drainage" was defined according to the criteria established by the Drainage Drainage Assessment measure. Using this measure, a fistula is considered open if an investigator can express purulent material from the fistula with the application of gentle pressure to the tract. In addition, the patients were considered treatment failures if they required repeat surgical interventions for recurrent perianal disease, including interventions after 54 wk if prompted by the week 54 EUS'*
Procedure description	clear	*The patients were randomised to either the EUS cohort or the control group. All patients underwent a rectal EUS to delineate underwent a rectal EUS to delineate fistula anatomy followed by an examination under anaesthesia by colorectal surgeon with seton placement and/or incision and drainage, as indicated. Medical treatment was maximized with 6-mercaptopurine (1.0–1.5 mg/kg) or azathioprine (2.0–2.5 mg/kg), ciprofloxacin (1,000 mg a day) or metronidazole (1,500 mg a day), and infliximab (5 mg/kg at 0, 2, and 6 wk and then every 8 wk).'*
Hinojosa J. *et al.* (Aliment Pharmacol Ther 2007)	Author's judgment	Support judgment
Patient population	clear	*...patients with luminal or fistulising CD who lost response to or were intolerant of infliximab treatment.'*
Outcome definition	clear	*In patients with fistulising disease, response was defined as ≥50% decrease in the number of perianal fistulas that were draining at baseline during at least two consecutive treatment visits. Fistula remission was defined as the complete closure of all perianal fistulas that were draining at baseline during at least two consecutive treatment visits.'*
Procedure description	clear	*All patients received an initial dose of adalimumab 160 mg at the baseline visit followed by 80 mg at week 2.'*
Hyder SA. *et al.* (Dis Colon Rectum 2006)	Author's judgment	Support judgment
Patient population	clear	*All patients with fistulating anal Crohn's disease who received infliximab between 2000 and 2004 were identified from a prospective colorectal database.'*
Outcome definition	clear	*...complete fistula healing (defined as no discharge for 6 months).'*

Table 13 Details risk of bias and quality assessment of cohort studies and case series on anti-TNF. (continued)

Quality assessment included studies on anti-TNF		
Procedure description	clear	*Fistula tracks were thoroughly curetted, cleaned using "cytology"-type brushes, and irrigated with saline. Seton drains (soft silastic) were inserted along fistula tracks and tied loosely to facilitate drainage where appropriate. 'Infliximab infusions (5 mg/kg) were administered within 24 hours of surgery (Time 0), hours of surgery (Time 0), 2 weeks, and 6 weeks later. Infliximab was not continued as maintenance therapy however,episodic reinfusion was given if clinically indicated. Infliximab was contraindicated in patients with evidence of active sepsis or a past history of tuberculosis. Seton drains were removed in the outpatient clinic after the second dose of infliximab'*
Orlando A. *et al.* (Dig Liver Dis 2005)	Author's judgment	Support judgment
Patient population	clear	*From April 1999 to December 2003, 573 patients with luminal refractory moderate to severe CD or with fistulising disease or both of them (71 patients) in 12 Italian referral centres.'*
Outcome definition	clear	*Clinical response to infliximab was determined 12 weeks after the first infusion for all patients. Primary were: (b) were: (b)reduction of at least 50% of the number of fistulas or complete closure of fistulas in patients with fistulising disease.'*
Procedure description	clear	*...treated with a dose of 5 mg/kg of body weight... of of infliximab treatment was either single/three infusion for luminal disease or three infusions (at 0, 2 and 6 weeks) for fistulising disease...As far as perianal disease is concerned, before starting infliximab a complete drainage of abscesses (with or without seton) was performed.'*
Ardizzone S. *et al.* (Inflamm Bowel Dis 2004)	Author's judgment	Support judgment
Patient population	clear	*The study population comprised 30 consecutive CD patients presenting with single or multiple draining perianal and/or rectovaginal fistulae of at least 3 months' duration between June 1999 and February 2002.'*
Outcome definition	clear	*...treatment response was classified into two categories: complete response or nonresponse. Complete response was defined as closure of any draining fistulae. A fistula was defined as closed when it no longer drained despite gentle finger pressure.'*
Procedure description	clear	*All patients received an infusion of infliximab at a dose of 5 mg/kg over 2 hours, with 2 hours postinfusion observation, at weeks 0, 2, and 6,according to a titration rate schedule adopted in the Present's trial.'*

Table 13 Details risk of bias and quality assessment of cohort studies and case series on anti-TNF. (continued)

Quality assessment included studies on anti-TNF		
Luna-Chadid M. *et al.* (Rev Esp Enferm Dig 2004)	Author's judgment	Support judgment
Patient population	clear	*All the consecutive CD patients who were treated with intravenous infusions of infliximab 5 mg/kg at seven University Hospitals in Madrid, from October 1999 to March 2001, were evaluated in a prospective cohort study...CD patients with one or more open fistulas; patients receiving medications for fistulising CD'*
Outcome definition	clear	*Complete response was defined as the complete cessation of drainage from all fistulas despite gentle finger compression. Partial response was defined as at least 50% reduction from baseline in the number of fistulas or drainage for at least 4consecutive weeks after the discontinuation of drug infusions.'*
Procedure description	clear	*...patients who were treated with intravenous infusions of infliximab 5 mg/kg...three infliximab infusions completed at 0, 2, and 6 weeks.'*
Rasul I. *et al.* (Am J Gastroenterol 2004)	Author's judgment	Support judgment
Patient population	Clear	*All patients were selected from a single tertiary outpatient clinic between February 2000 and January 2002 with single or multiple draining fistulas and/or rectovaginal fistulas of at least 3 months duration, as a complication of Crohn's disease that had been confirmed by radiology, endoscopy or pathological examination.'*
Outcome definition	Clear	*…fistula remission was defined as the absence of perianal drainage to finger compression and no interval spontaneous drainage between consecutive follow-up visits. Fistula improvement was defined as a closure of ≥50% of fistulas that were draining at the baseline evaluation. Lack of response was defined as closure of <50% of fistulas that were draining at the baseline evaluation.'*
Procedure description	Clear	*The dose of infliximab used was 5 mg/kg in all patients given intravenously at weeks 0, 2 and 8 and thereafter at 8-wk intervals up to 48 wk.'*
Schroder O. *et al.* (Aliment Pharmacol Ther 2004)	Author's judgment	Support judgment
Patient population	Clear	*Twelve consecutive patients (eight women and four men) with single or multiple draining fistulas persistent for at least 3months, as a complication of Crohn's disease, were enrolled.The diagnosis of fistulas was confirmed by endoscopy, radiography or pathological examination.'*

Table 13 Details risk of bias and quality assessment of cohort studies and case series on anti-TNF. (continued)

Quality assessment included studies on anti-TNF		
Outcome definition	clear	*...primary endpoint of this study was defined as sustained closure of all draining fistulas for at least 6 months after initial closure. A fistula was considered to be completely closed when it no longer drained despite gentle finger compression.'*
Procedure description	clear	*Patients received 5 mg of infliximab per kilogram body weight,which was administered intravenously in 250 mL of saline solution over 2 h. This treatment was repeated after 2 and 6weeks. In addition, patients received six infusions of 20 mg methotrexate at weeks 0-5, followed by weekly oral methotrexate at a dosage of 20 mg for ≥52 weeks.'*
Bell SJ. *et al.* (Aliment Pharmacol Ther 2003)	Author's judgment	Support judgment
Patient population	clear	*Patients with fistulas related to Crohn's disease were referred for consideration of inclusion in a study of infliximab treatment.'*
Outcome definition	clear	*'...a fistula was defined as closed if drainage had ceased on history and no drainage could be demonstrated on gentle compression of the fistula site. Clinical response was defined as closure of at least 50% of draining fistulas at two consecutive time points 4 weeks apart, whilst remission was defined as closure of all draining fistulas also at these time points.'*
Procedure description	clear	*All eligible patients received three doses of infliximab, 5 mg⁄kg,at weeks 0, 2 and 6 of the trial... Patients had their seton removed if the fistula appeared to be healing after infliximab treatment, two weeks after the first infliximab dose.'*
Topstad DR. *et al.* (Dis Colon Rectum 2003)	Author's judgment	Support judgment
Patient population	clear	*All patients with fistulising anorectal Crohn's disease who were treated with infliximab were identified using data from the Peter Lougheed Centre Inflammatory Disease Disease Clinic between March 1, 2000, and February 28, 2002.'*
Outcome definition	clear	*Clinical response was classified as complete, partial, or no response. A complete response was defined as complete cessation of fistula drainage with gentle finger compression on two or more consecutive visits. A partial response was definedas a reduction in size, number, drainage, or discomfort associated with the fistula. Patients who required infliximab infusions at six to eight week intervals to maintain their response were classified as infliximab dependent. All other outcomes were defined as no response.'*

Table 13 Details risk of bias and quality assessment of cohort studies and case series on anti-TNF. (continued)

Quality assessment included studies on anti-TNF		
Procedure description	clear	*All abscesses were drained, setons were placed to control anorectal infection, and ostomies were created necessary. necessary.Following this initial approach, patients received an induction regimen of infliximab 5 mg/kg at zero, two, and six weeks.'*
Ochsenkuhn T. *et al.* (Am J Gastroenterol 2002)	Author's judgment	Support judgment
Patient population	clear	*...patients who had draining fistulas persistent for at least 3 months as a complication of Crohn's disease.'*
Outcome definition	clear	*The primary endpoint of this study was defined as complete closure of all draining fistulas for at least 6 months. A fistula was considered to be completely closed when it no longer drained despite gentle finger compression.'*
Procedure description	clear	*Patients received 5 mg of infliximab/kg body weight, was was administered i.v. in 250 ml of saline solution over 2 h. This treatment was repeated after 2 and 6 w In 14 patients,azathioprine was started within 2 days before or after the initial infliximab infusion as a p.o. maintenance therapy at a dose of 2–2.5 mg/kg body weight, respectively.'*
Poritz LS. *et al.* (Dis Colon Rectum 2002)	Author's judgment	Support judgment
Patient population	clear	*...all adult patients treated with infliximab for FCD at The Milton S. Hershey Medical Center from September 1998 to October 2000.'*
Outcome definition	clear	*The healing of fistulas in response to infliximab treatment was defined as: complete response (C), partial response (P), or no response (N). Complete response: fistula closure, no surgical intervention required, and maintenance of fistula closure until October 2000 (end of this retrospective study). Partial response: decreased fistula drainage and/ or fistula size in response to infliximab, with or without subsequent surgical intervention. No response: No change in fistula characteristics.The response was determined by a combination of gastroenterologic and surgical assessment as documented in the patient's medical record.'*
Procedure description	clear	*Infliximab was given as an intravenous infusion during two hours at a dose of 5 mg/kg. Patients were expected to receive three infusions at zero, two, and six weeks; however, the number of infusions received per patient ranged from one to six.'*
Arnott ID. *et al.* (Aliment Pharmacol Ther 2001)	Author's judgment	Support judgment

Table 13 Details risk of bias and quality assessment of cohort studies and case series on anti-TNF. (continued)

Quality assessment included studies on anti-TNF		
Patient population	clear	*We prospectively audited the use of Infliximab at the Western General Hospital, Edinburgh and St John's Hospital at Howden, Livingston...All patients who were treated for refractory Crohn's disease were previously given at least one course of corticosteroids in an attempt to induce remission.'*
Outcome definition	clear	*A response of a fistula was defined as a 50% reduction in the number of draining fistulae as previously described. A fistula was defined as closed when it no longer drained despite gentle finger compression. A complete response was defined as the absence of any draining fistulae. It was also noted whether the fistulae had completely healed or not and whether there was cessation of drainage.'*
Procedure description	clear	*Patients with fistulating disease received three infusions at 0, 2 and 6 weeks.*
Farrell RJ. *et al.* (Am J Gastroenterol 2000)	Author's judgment	Support judgment
Patient population	clear	*Between October 1998 and June 1999, the first 100 consecutivepatients with Crohn's disease referred for infliximab infusion were enrolled in the study.'*
Outcome definition	unclear	*Clinical response was defined as ≥50% reduction of PDAI compared to baseline scores.'*
Procedure description	clear	*All patients received the same dosage of infliximab (5 mg/kg) per infusion as outpatients, administered over 2 h according to a titration rate schedule recommended by Centocor.'*

Search terms

Pubmed

Seton:

("Crohn Disease"[Mesh] OR crohn*[tiab]) AND (seton*[tiab]) AND ("Rectal Fistula"[Mesh] OR fistul*[tiab])

Anti-TNF:

("Crohn Disease"[Mesh] OR crohn*[tiab]) AND ("infliximab" [Supplementary Concept] OR infliximab[tiab] OR "Tumour Necrosis Factor-alpha"[MeSH] OR "Tumour Necrosis Factors"[Mesh] OR "Tumour Necrosis Factor-alpha"[nm] OR tumour necrosis factor-alpha[tiab] OR anti-tumour necrosis factor-alpha[tiab] OR tumour necrosis factor-α[tiab] OR anti-TNF[tiab] OR anti-TNF-α[tiab] OR anti-TNF-alpha[tiab] OR TNF-α[tiab] OR TNF-alpha[tiab] OR Tumour Necrosis Factor[tiab] OR TNFalpha[tiab] OR Cachectin-Tumour Necrosis Factor[tiab] OR Cachectin[tiab] OR "adalimumab" [Supplementary Concept] OR adalimumab[tiab] OR humira[tiab] OR remicade[tiab] OR monoclonal antibody cA2[tiab] OR MAb cA2[tiab]) AND ("Rectal Fistula"[Mesh] OR fistul*[tiab])

EMBASE

Seton:

1. crohn disease/
2. crohn*.ti,ab,kw.
3. 1 or 2
23. seton.ti,ab,kw.
24. rectum fistula/
25. anus fistula/
26. enterocutaneous fistula/
27. fistul*.ti,ab,kw.
29. 24 or 25 or 26 or 27
30. 3 and 23 and 29

Anti-TNF:

1. crohn disease/
2. crohn*.ti,ab,kw.
3. 1 or 2
4. infliximab/
5. infliximab.ti,ab,kw.
6. remicade.ti,ab,kw.
7. adalimumab/
8. adalimumab.ti,ab,kw.
9. Mab cA2.ti,ab,kw.
10. monoclonal antibody cA2.ti,ab,kw.
11. humira.ti,ab,kw.
12. tumour necrosis factor alpha/
13. TNF-alfa.ti,ab,kw.
14. TNF-alpha.ti,ab,kw.
15. anti-tumour necrosis factor-alpha.ti,ab,kw.
16. anti-TNF.ti,ab,kw.
17. anti-TNF-alpha.ti,ab,kw.
18. anti-TNF-alfa.ti,ab,kw.
19. tumour necrosis factor/
20. TNFalpha.ti,ab,kw.
21. Cachectin-Tumour Necrosis Factor.ti,ab,kw.
22. Cachectin.ti,ab,kw.
23. 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 or 18 or 19 or 20 or 21 or 22
24. rectum fistula/
25. anus fistula/
26. enterocutaneous fistula/
27. fistul*.ti,ab,kw.
28. 24 or 25 or 26 or 27
39. 3 and 23 and 28

BIOSIS

Seton:

1. crohn's disease.mp.
2. crohn*.ti,ab,kw.
3. 1 or 2
4. seton drainage.mp.
5. seton.mp.
6. rectal fistula.mp.
7. anal fistula.mp.
8. enterocutaneous fistula.mp.
9. fistul*.ti,ab,kw.
10. 4 or 5
11. 6 or 7 or 8 or 9
12. 3 and 10 and 11

Anti-TNF:

1. crohn's disease.mp.
2. crohn*.ti,ab,kw.
3. 1 or 2
4. infliximab.mp.
5. infliximab.ti,ab,kw.
6. remicade.mp.
7. adalimumab.mp.
8. monoclonal antibody cA2.mp.
9. Mab cA2.mp.
10. humira.mp.
11. tumour necrosis factor-alpha.mp.
12. tumour necrosis factor inhibitor.mp.
13. anti-tumour necrosis factor therapy.mp.
14. anti-TNF.mp.
15. TNF-alpha.mp.
16. Tumour necrosis factor.mp.
17. TNFalpha.mp.
18. Cachectin-Tumour Necrosis Factor.mp.
19. Cachectin.mp.

20. rectal fistula.mp.
21. anal fistula.mp.
22. enterocutaneous fistula.mp.
23. fistul*.ti,ab,kw.
24. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 16 or 17 or 18 or 19
25. 20 or 21 or 22 or 23
26. 3 and 24 and 26