Reporting quality of Randomized Clinical Trials for anti-TNF agents for Crohn's disease published from 2005 to date using the CONSORT statement.

Διπλωματική εργασία

Από τον

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Summary

Purpose: The aim of this study was to examine the reporting quality of randomized controlled trials (RCTs) published during the last ten years concerning the use of Anti Tumor Necrosis (Anti-TN) Factors for Crohn's Disease.

Methods: A thorough computerized search in the scientific network databases of Pubmed was conducted for Crohn's Diseases and all the available Anti-TN Factors. The reporting quality was assessed using Consolidated Standards of Reporting Trails (CONSORT) statement checklist. Reporting was assessed in one pre-revision of CONSORT (2005-2010) and one post–revision (2010-2015) period. The effect of CONSORT statement in high- and low-ranked journals, according to their impact factor, has also been evaluated.

Results: 51 RCTs were indentified using eligible criteria from the title and the abstract. Only 15 of the 25 items of CONSORT statement were addressed in 75% or more of the studies. Methodological issues such as sample size, randomization, allocation, blinding and precision of estimated effect size were presented inadequately. Significant post-revision improvements were noted for the prior methodological items, while RCTs published in high-ranked journals failed to show improvement in the quality of reporting.

Conclusion: Overall, the reporting quality of RCTs in anti-TNF treatment of Crohn's disease requires improvement. The revision of the CONSORT statement provides significant details and information for robust and complete reporting of RCTs. This is of major importance since the optimal reporting of RCTs is an important prerequisite for the clinical decision –making.

Keywords: Anti-TNF, Crohn's Disease, Randomized clinical trial, CONSORT statement, Adalimubad, Infiximab, Certolizumab pegol, Vedolizumab, Ustekinumab

Abbreviations: Anti-TNF=Anti-Tumor Necrosis Factor, CD=Crohn's Disease, CONSORT= Consolidated Standards of Reporting Trails, ITT=Intention to Treat, CI=Confidence Interval, IF=Impact Factor.

Introduction

Reliable evidence and robust conclusions are likely to be derived from strict design and accurate methodology (Juni et al 2001 and Moher et al 2010). Amongst the various study designs, the randomized controlled trial (RCT) is considered as the 'gold standard' for assessing the effectiveness and safety of medical interventions. On the contrary, RCTs are prone to inadequacies and bias and therefore, several studies indicate that the quality of many RCTs is substandard (Schulz et al 1994 and Moher et al 1995).

The urgency for accurateness and transparency led to the development of the Consolidated Standards of Reporting Trials (CONSORT) guidelines by the CONSORT group. The main CONSORT document consists of 25 items and sets standard on how and what should be included in a RCT report in order to improve the quality standards along with the validity of the results (Moher et al 2010).

The CONSORT Statement is endorsed by over 580 prominent general medical journals, several specialty medical journals, leading editorial organizations and by over 50% of the core medical journals listed in the Abridged Index Medicus on PubMed. CONSORT is part of a broader effort, to improve the reporting of different types of health research and therefore to improve the quality of research used in decision-making in healthcare (CONSORT website assessed 2015). In gastroenterology, reporting quality of RCTs has been assessed in a number of general and specialized journals (Xu et al 2015, Qi et al 2014, Wang et al 2011, Rupinski et al 2011 and Areia et al 2010) indicating the prospective for further improvement. Additional, Zhu et al (2015) assessed the quality of RCTs using the CONSORT statement regarding aspects of nutrition in patients with Crohn's disease. However, there is a lack of studies comparatively evaluating recently published RCTs in efficacy and safety of Crohn's disease treatment and remission (Ophélie et al 2014).

Therefore, the primary objective of this study was to evaluate the reporting integrity of RCTs of Anti-Tumor Necrosis Factor (Anti-TNF) for Crohn's disease efficacy, safety, treatment and remission.

Materials and methods

Data Sources, Search Strategies and Studies Selection

A comprehensive computerized search of English language publications listed in the electronic databases of MEDLINE (source PUBMED) was conducted. The term "Crohn's disease" was combined respectively with the terms "Adalimubad, Certolizumab pegol Infiximab, Vedolizumab and Ustekinumab" which are the common Anti-TN factors. A filter of "Randomized Controlled trial" was selected and a "10 years Publication date" was applied. Initially, the abstract was read and any trials that were clearly RCTs were included. Other articles that used terminology in the title or abstract such as 'prospective', 'comparative', 'efficacy' or an indication was given that a comparison of treatment groups was assessed prospectively, were further investigated to examine whether randomization was implemented. Studies that did not involve humans as well as studies, in which it was concluded that no true randomization was implemented, were excluded. Screening and selection of the studies were conducted by the author.

Data Extraction and Reporting Assessment Tool

The information extracted from each of the article included the journal and the year of publication, the region of publication (Europe, Americas or other region), the ethical approval, the statistical significance of the main finding, the number of authors and whether the study was single centre or multicentre. The CONSORT checklist was used to evaluate the reporting completeness of RCTs. This checklist has 30 questions related to the CONSORT statements. The given score per statement ranged from 0 to 1, with 0 = no description and 1 = adequate description. Alternatives responses (apart from yes or no) in addition with unclear responses to each question were coded as negative response (0). The scores of the 25 statements were added, and a percentage score was calculated for each trial, whereas non-applicable items were not scored. A trial with adequate descriptions (score 1) for all items would receive a score of 25. All scores were converted to a percentage scale, and therefore, a score of 25 was equivalent to 100% in the percentage scale.

A revision of CONSORT checklist was conducted in 2010, which resulted in some evolutionary, but not revolutionary changes to the checklist. New additional items were added to improve the Consorts' urge for completeness, clarity and transparency of reporting (Shluz et al 2010).

Statistical analysis

Descriptive statistics were calculated for CONSORT scores and presented by trial characteristics. The numbers and proportions of the methodological items were reported by the publication years. The years were grouped into 2 periods: (1) trial reports published from 2005 until the CONSORT 2010 revision and (2) after the 2010 revision until July of 2015. The two time periods were compared to detect any improvement of reporting of CONSORT items, as well as to obtain an indication in improvement of validity and quality of RCTs.

The included studies were ranked according to the ISI (Institute for Scientific Information) impact factor (IF) list for 2015 and were divided into two groups in order to compare the adherence to the CONSORT statement of the articles in major IF medical journals (IF >10) with the remaining eligible papers (IF<10).The selection of IF<10 as the cut-off point was arbitrary.

In this comparison, all CONSORT items were not concluded, but only those that were considered subjectively to be strongly related to trial validity. Although all items in the CONSORT checklist were considered important for the improvement of the quality of the RCTs' reports, some were more subjective than others to assess potential biases. Emphasis

was placed on the reporting of the methodological items such as sample size, method of randomization and allocation concealment, performed statistical methods, description of baseline data, precision of estimated effect size, and reporting of Intention-to-treat (ITT) analysis.

Comparisons among periods as well as IF groups were made by using a chi-square test for trend. A P-value of 0.05 was considered statistically significant with a 95% confidence interval. Analyses were performed by the IBM SPSS statistical package version 21.

Results

Eligible studies

A total of 118 reports were screened after the Pubmed research and 7 were found to be duplicates (Figure 1). After eligibility screening, 14 citations that could not be accessed plus another 3 citations that failed to provide a full text were excluded. Furthermore, 43 citations that did not fulfill the inclusion criteria either by title or by abstract were excluded (i.e., RCTS for anti-TNF treatment of different diseases, RCTs in other subjects not relevant to Crohn's disease, non randomized trials, narrative reviews or systematic reviews or meta-analyses in Anti-TNF and Crohn's disease and other studies in several types of inflammatory bowel disease). Consequently, a total of 51 reports remained for analysis, requiring complete full-text evaluation. A full list of the 51 reports that were retrieved as full-text and included in the final analysis is presented in table 4. The included RCTs referred to a wide selection of topics ranging from efficacy, remission, postoperative treatment, cost and recurrence.

General trial characteristics

In Table 1 all the demographic and baseline characteristics of the 51 RCTs are presented. The journals contributing with the most RCTs were Gastroenterology (29.4%), followed by The America Journal of Gastroenterology (13.7%) and Clinical Gastroenterology and Hepatology (11.8%). The majority of RCTs were conducted under a global cooperation (45.1%) or under Europe and America contribution (19.6%). However, one RCT failed to provide information about ethical confirmation.

Most (90.2%) of the trials clearly demonstrated the application of a parallel-group design whilst one of them(2%) was clearly described as a cross over and the remaining (7.8 %) were presented with confused information. Overall, 43.1 % of the trials investigated anti-TNF as the primary intervention of interest regarding parameters as the efficacy and safety.

Fewer trials (33.3 %) investigate inferior aspects of Crohn's disease such as hospitalization, quality of life and treatment cost and even fewer trials (21.6%) were focused on remission and maintenance of Crohn's disease. One study was clearly focused only in recurrence of the disease (2.0 %).

The 84.3% of all reports clearly stated that trial's data collected from several centers and 15.7% stated that the trial took place at a single center. Most of the trails (74.5%) utilized double blind methods for medicine administration and analysis, 5.9 % applied single blind design and 19.6% were open labels trials. 70.6 % of all trials consisted of 2 study groups, while 29.4 % consisted of 3 or more groups. Twenty trials (39.2%) had sample size over 300, eighteen trials (35.3%) had sample size between 100 and 300 and thirteen trials (25.5%) had less than 100 patients as sample size.

According to the trails results and conclusions 80.4% of the trials reported statistically significant findings and moreover 56.9% of the trials were presented by Journals with Impact Factor greater to 10. Thirty-five trials (68.6%) were conducted by 7 to 11 authors, fourteen trials (27.5%) were presented by over 12 authors and only two (3.9%) were signed by less than 6 authors.

Main results

Table 2 shows information on the CONSORT compliances of the methodological items according to the publication periods of (1) 2005 to 2010 and (2) 2011 to July of 2015. Furthermore, of the 51 screened study reports, the 31 were published between 2005 -2010 (pre-revision) and the 20 between 2011-2015 (post-revision).

Only 15 items were reported by 75% or more of the studies in all of the time periods (see table 2). These include the following items:

- Item No2: reporting of the objective/hypothesis of the study.
- Item No3: description of the design and criteria.
- Item No 4: reporting allocation and data collection.
- Item No 5: reporting of interventions.
- Item No 6: reporting of identification and definition of measures.
- Item No 12: descriptions of statistical methods.
- Item No 13: flow chart of protocol presentation.
- Item No 14: reporting of end point and follow up.
- Item No 15: reporting of baseline data in each group.
- Item No 16: reporting of intention-to-treat principles.
- Item No 18: reporting ancillary analysis.

- Item No 19: description of side/adverse effects.
- Items No 20, 21, 22: descriptions of outcomes and reporting of summary results (interpretation, generalizability and overall evidence

In contrast, 10 items identified by data extraction were reported by only a small percentage of the trials in the two periods. These include the following item:

- Item No 1: Justification of the trial, only in 47% of the studies the term "randomized was clearly demonstrated in the title". On the other hand all studies used the term randomized in the abstract.
- Item No 7: Sample calculation was only described by the 63 % of the studies.
- Items No 8, 9, 10, 11: Only 47 - 63% of the reports provided the descriptions and the details of the randomization process, the allocation concealment, the personnel involved and the blinding procedure.
- Item No 17: Complete reporting of the results with precision of estimated effect size (95% confidence intervals) was only demonstrated by 63% of the studies.
- Items No 23, 24, 25: Other information such as registration number and funding was demonstrated adequately by 67-71% of the studies.

Period Effect

CONSORT revision improved 23 of the 25 items. One item, justification of the trial, presented degeneration which was not statistical significant (*P-value* 0.61) (see table 2).

Significant improvements ($p<0.05$) over time were seen only for 5 out of 25 CONSORT items, including:

- Item No7: The description of the pre-study sample size calculation (*P-value*=0.02, CI: 1.2 -15.6)
- Item No8: The reporting of the randomization method (*P-value*=0.02, CI: 1.2 -15.6)
- Item No9: The description of the allocation concealment (*P-value*=0.04, CI: 1.01-12.6)
- Item No10: The details of personnel in sequence allocation (*P-value*=0.02, CI: 1.2-13.1)
- Item No17: The reporting of results with precision to estimate effect size (*P-value*=0.03, CI: 1.15- 15.6)

Impact of CONSORT in High-Ranked Journals

Of the 51 study reports that were analyzed, 29 were published in high-ranked medical journals (IF>10.1) and 22 in lower ranked medical journals (IF<10). Table 3 shows the proportion of reporting of seven important CONSORT items for each of these two IF

groups and for the total analyzed papers. As previously noticed, these items provide critical information for the evaluation of the RCTs methodological quality. According to the results all journals have adhered adequate to the CONSORT statement. Frequencies of reporting of all observed data items, have improved but not with statistical significance ($p>0.05$) in this group of studies.

Discussion

In this study, the reporting quality of RCTs in the fields of Anti-TNF agents and Crohn's Disease was assessed using CONSORT statement. The mean CONSORT scores ranged from 47% to 98% among the journals included in the study, a finding similar to the scores reported in medical journals (Turner et al 2012, Klouklos et al 2015). Although all quality score scales, have inherent limitations and caution that should be used when evaluating reporting quality, the overall score indicates that there is room for improvement. Despite that surveys and studies similar to this one have been conducted previously; this study is the first which investigated the reporting of RCTs for Anti-TNF and Crohn's Disease with particular reference to CONSORT, covering a period of the last 10 years.

Justification of the trial as a randomized trial was poor (47%) according to the titles of the studies; this finding was possible due to the limitations of the journals regarding the size of the title. On the contrary the abstracts of all studies provided all the necessary information about the justification of the trials.

Pre-study sample size calculation is an important part of designing a trial, as well as guards against underpowered trials that may result in research waste (Al-Shahi Salman et al 2014). In the present study, 62% of the RCTs did not report sample size calculation at all or it was reported inadequately. Ziogas and Zintzaras (2009) reported that 37% of the 261 medical trials published in PubMed from 1998 to 2008 did not report sample size calculation. It seems that problematic reporting of pre-study sample size calculations in RCTs is a common finding in literature (Lu et al 2015, Kloukos et al 2015). As pointed out by other studies, trials with inadequate power could result in a high false-negative error rate and are likely associated with publication bias (Schulz and Grimes 2015, Chan and Altman 2005). Post-CONSORT revision studies appear to assimilate the necessity of the sample size calculation, increasing the percentages of the studies with adequate sample size calculation to 84%.

Reporting the methods of randomization sequence generation and allocation concealment has shown that it is strongly associated with effect estimates (Savovic et al 2012, Pildal et al 2007). For every RCT, the method of randomization is a key component to minimize any measured and unmeasured differences between the comparison groups.

Terms such as ‘patients were randomly assigned’ or ‘two groups were formed at random’ are considered inadequate. The current study showed that the generation of the unpredictable allocation sequence, allocation concealment and implementation was reported inadequately in 63%, 59% and 47%, of the cases respectively. However, the revision of CONSORT statement provided more details for the randomization and allocation improvement and therefore after the revision in the present study a statistical significant increase was reported in randomization and allocation procedures. A properly designed allocation concealment mechanism prevents selection bias and can always be successfully implemented (Savovic et al 2012).

Blinding is another important buffer against bias in RCTs and in some cases may not be feasible. Blinding is important to the validity of a trial, as it prevents performance and detection bias, and protects the sequence after allocation. Blinding is especially important for subjective outcomes (e.g. quality of life, discomfort, pain), as these are more prone to bias (Scluz and Grimes 2002,). Wood et al (2008) demonstrate that RCTs with unclear allocation concealment and non blinding procedures presented larger estimates of effects for subjective outcomes. The data of the present study suggest that there has been a significant improvement after the revision of CONSORT in reporting the quality parameters of allocation concealment. On the other hand, it should be clearly demonstrated as a topic of speculation that the current quality of reporting RCTs for parameters such as allocation enrolments and blinding participation are still below an acceptable level. Clark et al (2013) demonstrate similar results and speculations for the quality of key randomization and allocation concealment details.

Furthermore, the interpretation of the results demands unambiguous outcomes with statistical significance. Reporting of estimates and confidence intervals facilitates interpretation in relation to clinical importance. In the present study the CONSORT revision increase the thorough description of estimates and confidence interval but there is still vital space for improvement. Previous studies found inadequate results reporting in leading medical journals. Rios et al. (2008) found that Endocrinology trials also suffered from problematic reporting in this area of interest, with lack of description in 21% of the studied trials for the complete reporting of confidence interval.

Several limitations are ruling the present study. One limitation might be that the scoring of trials is always susceptible to some degree of subjectivity. Furthermore, the present study was only conducted using the most common medical database (PubMed) and therefore a main limitation is the lack of searching extension to Cochrane Collaboration database for more thorough and comparative exploration.

It should be also underlined that incomplete reporting of trials does not necessarily infer to low quality of conducting or false methodology. Researchers might have designed and conducted a study ideally, but they might have omitted reporting accurately all stages and aspects of their trial due to several reasons such as space limitations (Soares et al 2004). This is also problematic because a biased but well-reported trial will receive full credit. Yet another potential limitation is the significant number of publication with no access to full text or the lack of a full text (14.4%) which is a significant proportion of studies whose inclusions might have changed the overall results.

Conclusion

The effort of the current study was to assess the quality of RCTs focusing on the treatment of Crohn's Disease with the use of Anti-TNFs. The results highlight the improvement of reporting of RCTs after the revision of the CONSORT checklist in 2010. Critical items for the quality of RCTs showed statistically significant improvement after revision, but some important methodological descriptions such as allocation concealment, blinding and estimates effect size, are still in the necessity of further enrichment. As far as the battle for treatment and remission of Crohn's disease, the improvement of RCTs regarding refined medication such as Anti –TNF, will provide necessary and vital information for treatment decisions, risk, harms and future research. Especially nowadays in a period of new pharmaceutical and genetic discoveries and innovations, robust and crystal reports will facilitate to RCT interpretation, reduction of controversy conclusions and mainly to simplify decision-making about treatment.

Figure 1. Flow diagram of citations through the retrieval and the screening process.

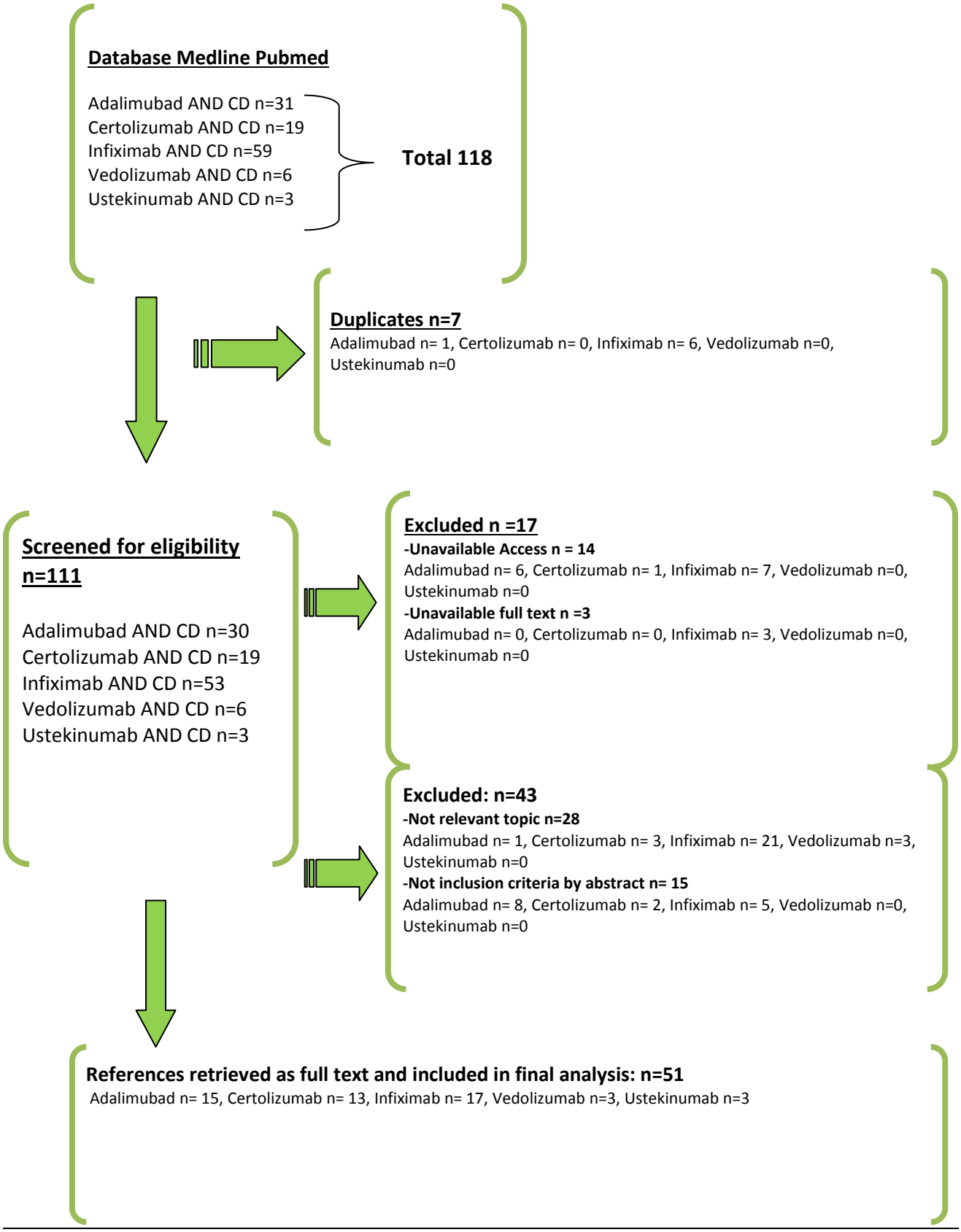

Table 1 Demographic and baseline characteristics of 51 RCTs.

	Category	N	%
Journal			
	Alimentary Pharmacology and Therapeutics	5	9.8
	America Journal of Gastroenterology	7	13.7
	Annals of internal Medicine	1	2.0
	Clinical Gastroenterology and Hepatology	6	11.8
	Digestive Disease and Science	1	2
	Gastroenterology	15	29.4
	Gut	5	9.8
	International Journal of Colorectal Disease	1	2
	Journal Of Crohn's and Colitis	2	3.9
	Lancet	1	2
	The New England Journal of Medicine	5	9.8
Trial location			
	Europe	9	17.6
	Global	23	45.1
	America/Europe	10	19.6
	America	9	17.6
Ethics committee approval			
	Yes	50	98.0
	No	1	2.0
Trial design			
	Parallel	46	90.2
	Crossover	1	2.0
	Other	4	7.8
Intervention			
	Maintenance/Remission	11	21.6
	Efficacy/Safety	22	43.1
	Recurrence	1	2.0
	Other	17	33.3
Number of center			
	Multi center	43	84.3
	Single center	8	15.7
Trial design (blind/open)			
	Blind (double)	38	74.5
	Blind (single)	3	5.9
	Open label	10	19.6
No of study groups			
	2	36	70.6
	>3	15	29.4
Sample size			
	<100	13	25.5
	101-300	18	35.3
	>301	20	39.2
Statistical significance of main findings			
	Yes	41	80.4
	No	10	19.6
Journal's impact factor			
	1-10.0	22	43.1
	>10.1	29	56.9
Number of authors			
	<6	2	3.9
	7-11	35	68.6
	>12	14	27.5

TABLE 2. Proportion of reporting of 25 data items in a total of 51 randomized controlled trials in Crohn's disease and Anti-TNFs by publication period (pre- and post-revision of CONSORT and combined)

TITLE/ABSTRACT	Combined 2005 to 2015 (n=50)*	Pre-CONSORT revision 2005-2010 (n=31)	Post-CONSORT revision 2010 –2015 (n=19)	P[a] Value 95%CI
1. Justification for the trial	0.47	0.52	0.40	0.61 0.24-2.3
INTRODUCTION				
2. Clear statement of hypothesis or objectives	0.92	0.90	0.95	0.49 0.21-23.0
METHODS				
3. Description design, allocation ratio and modifications	0.94	0.94	0.95	0.77 0.12-16.9
4. Detailed description of setting/location of recruitment and data collection	0.98	0.97	1.00	0.40 0.91-1.0
5. Details of intervention studied	0.94	0.94	0.95	0.77 0.12-16.9
6. Identification and definition of outcome measures	0.86	0.84	0.90	0.46 0.33-10.9
7. Description of pre-study sample size calculation	0.63	0.48	0.85	0.02 1.2-15.6
8. Description of the generation of unpredictable allocation sequence and details of any restriction used in randomization	0.63	0.48	0.85	0.02 1.1-15.6
9. Description of allocation concealment	0.59	0.45	0.80	0.04 1.01-12.6
10. Details of personnel involved in sequence allocation, enrollment, and assignment	0.47	0.32	0.70	0.02 1.2-13.1
11. Details of blinding of participants, providers, assessors and analyst	0.43	0.42	0.45	0.97 0.32-3.0
12. Description of statistical methods	0.98	0.97	1.00	0.40 0.91-1.0
RESULTS				
13. Flow chart describing patient numbers at different stages and clear description of protocol deviations	0.75	0.74	0.75	0.67 0.21-2.7
14. Description of dates of recruitment and follow up	0.90	0.90	0.90	0.95 0.16-6.9
15. Description of baseline characteristics	0.94	0.94	0.95	0.77 0.12-16.9
16. Reporting of intention-to-treat principle	0.75	0.74	0.75	0.82 0.32-4.2
17. Complete reporting of results with precision of estimated effect size	0.63	0.52	0.80	0.03 1.15-15.6
18. Ancillary analysis	0.82	0.77	0.90	0.20 0.54-15.6
19. Description of side/adverse effects	0.86	0.81	0.95	0.12 0.55-45.1
DISCUSSSION				
20. Interpretation of the results	0.80	0.77	0.85	0.93 0.26-4.4
21. Generalizability	0.94	0.94	0.95	0.77 0.12-16.9
22. Overall evidence	0.88	0.87	0.90	0.69 0.24-8.82
OTHER INFORMATION				
23. Registration number and name of trial	0.67	0.65	0.70	0.55 0.44-4.8
24. Trail protocol availability	0.69	0.65	0.75	0.33 0.53-6.5
25. Sources of funding	0.71	0.61	0.85	0.05 0.96-16.6

* Percentage of articles reporting the CONSORT item.

[a] P Values were obtained from chi-square tests for trend of associations between proportions for reporting an item and publication period across the two periods

TABLE 3. Proportion* of reporting of seven emphasized CONSORT data items in a total of 261 randomized controlled trials in myeloid malignancies by impact factor group

Emphasized CONSORT item	Total papers included (n=51)*	Low IF papers IF<10 (n=22)	High IF papers IF >10.1 (n=29)	P-value [a] 95% CI
1.Sample size	0.63	0.55	0.69	0.29 0.59-5.85
2.Method of randomization	0.63	0.55	0.69	0.29 0.59-5.85
3.Allocation concealment	0.59	0.45	0.69	0.09 0.84-8.42
4.Statistical method	0.94	0.91	0.97	0.38 0.97-1.11
5.Description of baseline data	0.88	0.86	0.90	0.12 0.98-1.26
6.Intent-to-treat analysis	0.75	0.68	0.79	0.36 0.50-6.37
7.Precision of estimated effect size	0.63	0.59	0.66	0.63 0.42-4.13

IF = impact factor.
*Percentage of articles reporting the CONSORT item.
[a] Values were obtained from chi-square tests for trend of associations between proportions for reporting an item across the two groups of papers.

Table 4. List of scored papers

No	Year	Journal	Issue (volume)	First Author	CONSORT %
1	2005	Gastroenterology	128	Lichtenstein	60
2	2005	Gastroenterology	129	Schreiber	88
3	2006	Gastroenterology	130	Hanauer	72
4	2006	Gastroenterology	130	Lemann	68
5	2006	Gastrointestinal Endoscopy	63 (3)	Rutgeerts	60
6	2006	Alimentary Pharmacology and Therapy	23	Sands	52
7	2007	Gastroenterology	132	Colombel	88
8	2007	Gastroenterology	132	Hyams	80
9	2007	The New England Journal of Medicine	357	Sandborn	80
10	2007	Annals of Internal Medicine	146	Sandborn	100
11	2007	Gut	56	Sandborn	76
12	2007	The New England Journal of Medicine	357	Schreiber	96
13	2008	Gastroenterology	134	Van Assche	68
14	2008	The Lancet	371	D'Haens	92
15	2008	Clinical Gastroenterology and Hepatology	6	Feagan	68
16	2008	Gastroenterology	135	Feagan	80
17	2008	American Journal of Gastroenterology	103	Loftus	68
18	2008	International Journal of Colorectal Disease	23	Rutgeerts	56
19	2008	Gastroenterology	135	Sandborn	88
20	2008	American Journal of Gastroenterology	103	Spradlin	48
21	2009	Gut	58	Colombel	72
22	2009	American Journal of Gastroenterology	104	Colombel	72
23	2009	American Journal of Gastroenterology	104	Feagan	64
24	2009	Gastroenterology	136	Regueiro	64
25	2009	American Journal of Gastroenterology	104	Toedter	52
26	2010	The New England Journal of Medicine	362	Colombel	76
27	2010	Alimentary Pharmacology and Therapy	31	Feagan	68
28	2010	Clinical Gastroenterology and Hepatology	8	Lichtenstein	64
29	2010	Clinical Gastroenterology and Hepatology	8	Sandborn	76
30	2010	Clinical Gastroenterology and Hepatology	8	Sandborn	80

31	2010	American Journal of Gastroenterology	105	Schreiber	72
32	2011	Gut	61	Van Assche	64
33	2011	Alimentary Pharmacology and Therapy	33	Feagan	76
34	2011	Alimentary Pharmacology and Therapy	34	Kamn	96
35	2011	Digestive Diseases and Science	56	Regueiro	68
36	2011	Clinical Gastroenterology and Hepatology	9	Sandborn	84
37	2011	Alimentary Pharmacology and Therapy	33	Schreiber	80
38	2012	Gastroenterology	143	Hyams	96
39	2012	Gastroenterology	142	Rutgeerts	76
40	2012	The New England Journal of Medicine	367	Sandborn	84
41	2012	Journal of Crohn's and Colitis	6	Watanabe	68
42	2013	Gut	63	Dewint	100
43	2013	The New England Journal of Medicine	369	Sandborn	84
44	2013	American Journal of Gastroenterology	108	Savarino	84
45	2014	Clinical Gastroenterology and Hepatology	12	Colombel	88
46	2014	Gastroenterology	146	Feagan	96
47	2014	Gastroenterology	147	Sands	88
48	2014	Gut	63	Steenholdt	100
49	2014	Techniques in Coloproctology	18	Tursi	56
50	2014	Journal of Crohn's and Colitis	8	Watanabe	84
51	2015	Gastroenterology	148	Casteele	92

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