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Clinical trial: colectomy after rescue therapy in ulcerative colitis; 3-year follow-up of the Swedish-Danish controlled infliximab study

Short Title: Rescue therapy with infliximab in UC

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Key-words:
Ulcerative colitis; infliximab; colectomy; rescue-therapy.

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SUMMARY

Background The long-term efficacy of infliximab as rescue therapy in steroid-refractory ulcerative colitis is not well described.

Aim We report a 3-year follow-up of a previous placebo-controlled trial of infliximab in acute steroid-refractory ulcerative colitis.

Method In the original study, 45 patients were randomised to a single infusion of infliximab 5 mg/kg or placebo, and at three months 7/24 patients given infliximab were operated versus 14/21 patients given placebo. Three years or later patients were asked to participate in a clinical follow-up.

Results Another 7 patients underwent colectomy during follow-up; 5 in the infliximab group and 2 in the placebo group. After 3 years, a total of 12/24 (50 %) patients given infliximab and 16/21 (76 %) given placebo (p=0.012) had had a colectomy. None of 8 patients in endoscopic remission at 3 months later had a colectomy compared with 7/14 (50%) patients not being in remission (p=0.02). There was no mortality.

Conclusion The benefit of rescue therapy with infliximab in steroid-refractory acute ulcerative colitis remained after 3 years. The main advantage of infliximab treatment occurred during the first 3 months, whereas subsequent colectomy rates were similar in the two groups. Mucosal healing at 3 months influenced later colectomy risk.

Introduction

A severe attack is seen in approximately 15% of patients with ulcerative colitis (UC).[1] Corticosteroids remain a mainstay in the management. However, about 30% of the patients are unresponsive and will require colectomy short-term,[2, 3] and long-term studies report even higher colectomy frequencies.[4] Therefore new therapeutic alternatives are searched for. Cyclosporine was the first successful rescue therapy.[5, 6] The short-term success rate was high with remission rates of 74-88% but the long-term efficacy has been disappointing. In retrospective analyses from Oxford and Leuven, colectomy rates after 7-8 years have reached 58-88%.[7, 8] Severe side effects including mortality have also limited its use. Infliximab treatment was subsequently introduced in unresponsive acute UC with conflicting results at first.[9, 10] In a controlled Swedish-Danish trial using infliximab as rescue therapy, colectomy rates after three months were lower in infliximab treated patients (29%) compared with placebo treated patients (67%).[11] However, the long-term prognosis after rescue therapy with infliximab is largely unknown.[12]

We present a 3-year follow-up study of patients that participated in the Swedish-Danish infliximab/placebo trial conducted between July 2001 and January 2004. The primary objective was to determine the number of patients escaping a colectomy at follow-up. Secondary objectives were to determine the number of patients in clinical and endoscopic remission and to assess health-related quality of life.

Methods

Patients

In the original trial,[11] 45 patients hospitalised due to a moderate to severe attack of UC were first treated with betamethason 8 mg/day i.v. Patients with corticosteroid refractory disease

were randomized, on day 4 according to the fulminant colitis index >8 on day 3 (n=28) or on day 5-7 according to the Seo index >150 (n=17), to a single infusion of infliximab (5 mg/kg) or placebo.[13, 14] Decision on colectomy was made on clinical grounds. Maintenance therapy with mesalamine and/or azathioprine was given according to the individual investigator's decision. At 3 months, 7/24 (29%) of infliximab treated patients and 14/21 (67%) in the placebo group (p=0.017) had had a colectomy. Patient demographics and disease characteristics are presented in detail in the original publication.[11]

Follow-up data

The patients were regularly followed by their local physician, who was aware of the original treatment first after June 2004. Three years or later after the randomization patients were asked to participate in a follow-up study. Clinical data and routine blood samples were collected, and a flexible rectosigmoidoscopy was performed in patients not having had a colectomy. All patients were asked to complete health-related quality of life questionnaires (SF-36 and Short Health Scale).[15-17] Mayo index was calculated in patients not having had a colectomy.[18]

Clinical remission was defined as total Mayo score ≤ 1, and endoscopic remission as Mayo endoscopic subscore = 0.[18] Relapse was defined as recurrence of clinical symptoms and need for intensified medical treatment. Maintenance treatment with immunomodulators refers to treatment with thiopurines for ≥ 6 months. General side effects and postoperative events during the first 3 months after randomization were described in the original study. Adverse events requiring hospitalization after 3 months were retrospectively assessed at follow-up.

Statistics

Data are reported as median (range). Time to colectomy was illustrated with Kaplan-Meier plot and differences between treatment groups were tested with log-rank test. Due to probable non-proportional hazard, we used logistic regression analysis to adjust for potential confounders and to calculate odds ratio (OR) with 95% confidence intervals (95% CI). Mann-Whitney U test was used to analyse time to first relapse. Differences between groups were tested with Fisher's exact test.

Ethics

The study was approved by the Regional Ethics Review Board in Uppsala.

Results

Patients

Clinical data, including colectomy, was available in all patients for a period of 3 years or more after randomisation with a median (range) follow-up time of 55 (36-79) months. Out of 45 patients, 41 completed the quality of life questionnaires, and 15 out of 17 patients not having had a colectomy consented to flexible rectosigmoidoscopy.

Colectomy

In addition to the 21 patients operated at 3 months' follow-up,[11] another seven patients had undergone colectomy at 3 years; five had been randomized to infliximab and two to placebo in the original study. Thus, in total 12/24 (50%) infliximab treated patients and 16/21 (76%) placebo treated patients had had a colectomy at 3-year follow-up (p=0.012) (Figure 1). The difference remained after multivariate logistic regression analysis adjusting for age, sex, extent of disease and earlier known or first attack of UC. The presence of mucosal healing

influenced the subsequent colectomy frequency. None out of eight patients in endoscopic remission at 3 months after rescue therapy later had a colectomy compared with 7/14 (50%) patients not being in endoscopic remission at 3 months (p=0.02) (endoscopic data missing in 2 patients, both escaped surgery). The indications for colectomy in the original infliximab treated group were; new severe attack of UC (n=3), or steroid dependant disease (n=2), and in the placebo treated group; steroid dependant disease (n=2). No further colectomies have been performed in patients followed for more than 3 years.

Maintenance therapy during follow-up from 3 months to 3 years

Data on maintenance therapy in patients who were not operated during the first 3 months after randomization is shown in table 1. Therapy with immunomodulators was prescribed to 16 patients (IFX=12, placebo=4), and to additionally two patients (infliximab; n=1, placebo; n=1) who discontinued treatment early due to side effects. Three patients randomized to infliximab also received a series of leucocytapheresis during follow-up, two of which had a colectomy.

Subsequent anti-TNF therapy during follow-up from 3 months to 3 years

In the original study a single infusion of infliximab was given. However, seven patients received additional anti-TNF therapy after 19 (6-30) months for clinical relapse of UC. Two patients, originally randomized to infliximab and on maintenance therapy with 5-ASA or azathioprine respectively, were given further rescue therapy with a single infusion of infliximab 5mg/kg without response and underwent colectomy. Three other patients, all given maintenance azathioprine, were successfully treated with scheduled maintenance infliximab 5

mg/kg. Two patients, originally randomized to placebo and given maintenance 5-ASA, were successfully treated with a single infusion of infliximab 5mg/kg as rescue therapy.

Clinical and endoscopic evaluation of patients not operated at follow-up

At follow-up, 11 out of 15 patients were in clinical remission and off steroids (4 patients in infliximab treated group were not in clinical remission), and 12/15 patients were in endoscopic remission. The median (range) time to first relapse after remission was similar; 7 (1-60) months in the infliximab treated group and 8 (5-48) months in the placebo treated group (p=0.741). Levels of ESR, CRP, haemoglobin and albumin at follow-up did not differ between the two patient groups (data not shown).

Adverse events during follow-up from 3 months to 3 years

There were no opportunistic infections, tuberculosis, malignancy or deaths. In the infliximab treated group, two operated patients were hospitalised at four occasions due to small intestinal obstruction (n=2), high ileostomy output (n=1), or anemia (n=1). In the placebo treated group six patients were hospitalised at seven occasions; postoperative small intestinal obstruction (n=3), high ileostomy output (n=2), non-specific dyspnoea (n=1), and viral meningitis (n=1).

Health-related quality of life

There were no differences between the two groups regarding outcome of SF-36 or SHS (data not shown).

Discussion

The aim with rescue therapy in UC is to induce clinical and endoscopic remission and to reduce colectomy frequency without increasing morbidity and mortality. This study

emphasizes the value of infliximab as rescue therapy in acute severe steroid-refractory UC, since the short-term response remained in a long-term perspective. In our original trial colectomy frequency after three months was significantly reduced in patients treated with infliximab compared with placebo.[11] Our short-term results are supported by uncontrolled studies, reporting colectomy frequencies between 15% and 33% during the first few months.[19-21] However, higher figures of up to 75-80% have been reported elsewhere.[22, 23]

The present study, which has the longest follow-up period, shows that a difference remains after three years in favour of infliximab, with a colectomy frequency of 50% compared with 76% in the placebo group. Most colectomies were performed during the first three months and only few during the subsequent follow-up period. Retrospective long-term follow-up data from other centres support our long-term results. In the largest series, Kohn et al reported colectomy free survival in 58/83 (70%) patients treated with infliximab for steroid-refractory severe UC during a median follow-up period of 23 months.[20] In a Scottish study, 13/39 patients underwent early colectomy after infliximab rescue therapy, and another two patients were operated later during a median follow-up of 203 days reaching a total colectomy frequency of 38%.[21] Jacobovits et al reported that out of a subgroup of 14 patients, treated as in-patients with infliximab owing to severe, steroid-refractory UC, eight (57%) patients had a colectomy during a follow-up for 274 days.[19] Others reported that 8 (38%) out of 21 infliximab treated patients were operated during a median follow-up of 155 days,[24] and in another small series 2 (18%) out of 11 patients had a colectomy.[25]

The comparison of these studies is impeded by differences regarding inclusion criteria, definition of steroid failure, treatment regime including number and time of infliximab infusions, subsequent maintenance therapy, duration of follow-up period, and the

retrospective uncontrolled study design. In our original trial, only hospitalised patients with an acute, steroid-refractory, moderate to severe attack of UC were included. We used one single infusion of infliximab 5 mg/kg as our original study was designed prior to the results of Active Ulcerative Colitis Trial (ACT)-1 and ACT-2 trials.[26] In these studies, patients with chronic steroid-dependant UC were included, whereas patients who had received intravenous corticosteroids within two weeks or were judged likely to require colectomy within 12 weeks were excluded.[27] Patients were randomised to receive infliximab infusions, 5 or 10 mg/kg, at weeks 0, 2, and 6 and then every 8 weeks or placebo. The cumulative colectomy frequencies through 54 weeks were low and reached 10% for patients given infliximab and 17% for those given placebo.[27] The low colectomy frequency in the placebo group illustrates that patients included in these trials had less severe UC compared with patients in our study and a comparison of outcome is therefore not justified.

In other studies,[24, 25] rescue therapy with a standard schedule of three infusions on week 0, 2 and 6 was given whereas others gave a various number of infusions.[19, 20] Kohn et al concluded that two or more infusions seemed more effective than one single infusion.[20] There is thus a need for prospective randomized trials to define the optimal dosing regime of infliximab as rescue therapy in UC.

The benefit of rescue therapy with infliximab obviously was achieved during the first 3 months (Figure 1), and during the subsequent follow-up period the proportion of colectomies was similar in the two groups; infliximab group 5/17 (29%) and placebo group 2/7 (29%). Mucosal healing is an important therapeutic goal in UC and has been shown to be a predictor of future disease course and long-term prognosis. It is associated with improved quality of life and with a lower risk of relapse, colectomy and colorectal cancer.[28] In this study, presence of

mucosal healing at 3 months predicted the future risk of colectomy. None of 8 patients achieving endoscopic remission (Mayo endoscopic subscore = 0) underwent surgery during the three-year follow-up compared with 7/14 patients without endoscopic remission. Likewise, in a population-based Norwegian cohort, a lower colectomy frequency was seen in UC patients with mucosal healing compared with those with inflammatory activity.[29]

The importance of optimal maintenance therapy after successful rescue therapy is emphasized by studies showing lower colectomy frequencies in patients who received thiopurines after cyclosporine rescue therapy compared with those not given immunomodulators.[8, 30, 31] It is reasonable to assume that the three-year colectomy rate is more dependent on the maintenance therapy than on a single infusion of infliximab as rescue therapy. However, there are currently no evidence that thiopurine therapy reduces the colectomy risk after rescue therapy with infliximab in a severe attack of UC.[19-21] Our original study design did not define treatment beyond 3 months, and the distribution of subsequent maintenance therapy thus differed between the two groups. In the infliximab treated group 12/16 patients received azathioprine compared with 4/7 in the placebo group. Colectomy frequencies did not differ in patients receiving azathioprine after infliximab compared with those not given thiopurines (3/12 *vs* 2/4, p=0.55) (table 1). Furthermore, some patients received additional therapy with anti-TNF or leucocytapheresis probably reflecting a more aggressive disease course. The use of maintenance therapy differed also in other studies using 5-ASA only, azathioprine or 6-mercaptopurine alone or in combination with 5-ASA or with scheduled infliximab.[19, 21, 24, 25] Accordingly, the best maintenance treatment after successful rescue therapy with infliximab needs further study. Azathioprine is superior to 5-ASA in corticosteroid dependant UC [32] and may be recommended as maintenance therapy in azathioprine naïve patients responding to infliximab induction. Scheduled infliximab infusions are an alternative in a patient, who

during immunosuppressive therapy develops a severe attack and responds to infliximab induction.[33] The evidence, however, for such a recommendation in a patient successfully treated with rescue therapy in severe UC is limited at present.

Adverse events were benign in the present series and did not differ between the two treatment groups. They occurred, as expected, during the first 3 months after the infliximab infusion.[11] During this follow-up period, adverse events, such as small intestinal obstruction or high ileostomy output were related to previous colectomy and not to infliximab therapy.

In conclusion, this study supports the use of infliximab in acute severe steroid refractory UC and the favourable short-term response remains in a long-term perspective. Mucosal healing at three months after rescue therapy influenced subsequent colectomy frequency. The optimal dosing of infliximab and best possible maintenance therapy after successful rescue therapy need to be defined. Infliximab treatment was safe but serious complications may occur.[20, 21] All these aspects must be taken into account and carefully discussed with the patient in the choice between rescue therapy or colectomy in a severe attack of UC.

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Declaration of personal interests

Drs. Blomquist, Halfvarson, Hertervig, Karlén, Tysk, Verbaan report having received lecture fees from Schering Plough. Dr Järnerot reports having received consulting fee from Centocor. The remaining authors disclose no conflicts of interest.

Declaration of funding interests

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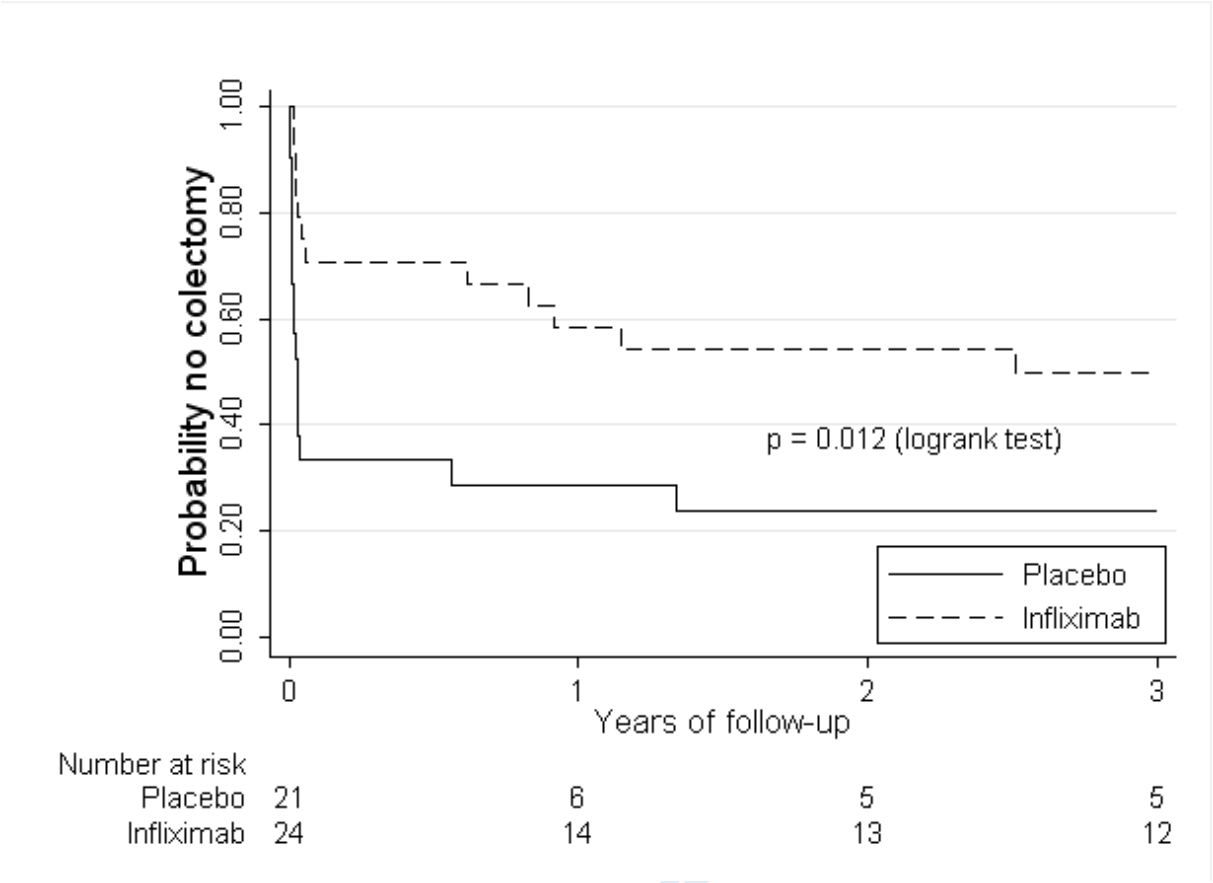
Table 1. Distribution of maintenance therapy with 5-ASA or immunomodulators during follow-up in patients randomised to infliximab or placebo, and subsequent treatment with infliximab or leucocytapheresis. Figures in parenthesis refer to number of patients referred to colectomy.

	5-ASA	**Immuno-modulators**	**Infliximab** Single infusion	**Infliximab** Scheduled	**Leucocytapheresis**
IFX n=16*	4 (2)	12 (3)	2 (2)	3 (0)	3 (2)
Placebo n=7	3 (1)	4 (1)	2 (0)		

IFX, randomized to infliximab in the original study
Placebo, randomized to placebo in the original study
5-ASA, aminosalicylates as maintenance therapy
Immunomodulators, immunosuppressive therapy as maintenance therapy for > 6months
*=missing data in one patient

Figure 1. Kaplan-Meier plot showing probability of colectomy-free survival in relation to time after randomisation.



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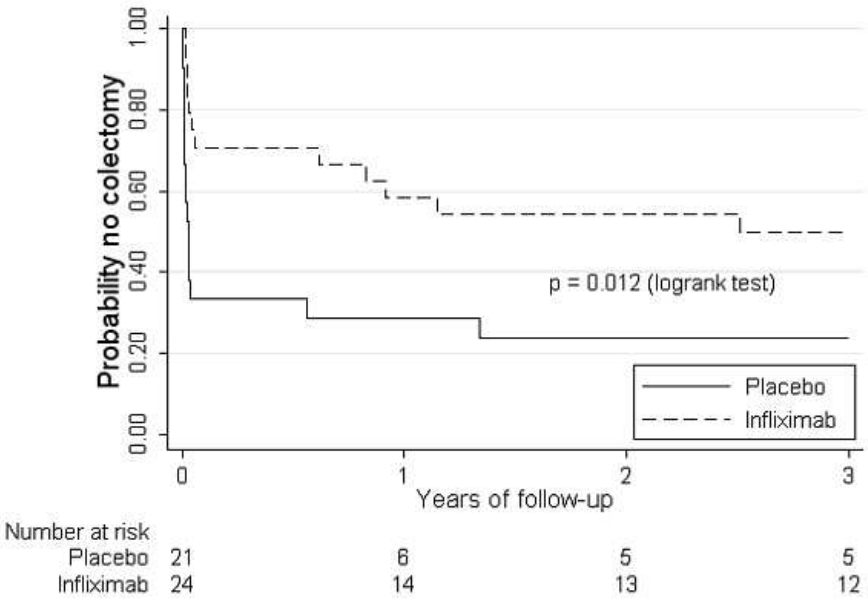

Kaplan-Meier plot of probability of not-colectomy in relation to time after randomisation
172x120mm (96 x 96 DPI)

CONSORT Statement 2001 Checklist

Items to include when reporting a randomized trial

* refers to pages 1805-1811 in original publication
** refers to pages in submitted manuscript

PAPER SECTION And topic	Item	Descriptor	Reported on Page #
TITLE & ABSTRACT	1	How participants were allocated to interventions (*e.g.*, "random allocation", "randomized", or "randomly assigned").	1806*
INTRODUCTION Background	2	Scientific background and explanation of rationale.	1805-1806 p 4**
METHODS Participants	3	Eligibility criteria for participants and the settings and locations where the data were collected.	1806
Interventions	4	Precise details of the interventions intended for each group and how and when they were actually administered.	1806, 1807
Objectives	5	Specific objectives and hypotheses.	1807 p 5
Outcomes	6	Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (*e.g.*, multiple observations, training of assessors).	1807
Sample size	7	How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules.	1807
Randomization -- Sequence generation	8	Method used to generate the random allocation sequence, including details of any restrictions (*e.g.*, blocking, stratification)	1806
Randomization -- Allocation concealment	9	Method used to implement the random allocation sequence (*e.g.*, numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned.	1806
Randomization -- Implementation	10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.	1806
Blinding (masking)	11	Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. If done, how the success of blinding was evaluated.	1806
Statistical methods	12	Statistical methods used to compare groups for primary outcome(s); Methods for additional analyses, such as subgroup analyses and adjusted analyses.	1807, 1808 p 6
RESULTS Participant flow	13	Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome. Describe protocol deviations from study as planned, together with reasons.	1808, 1809 p 6-7
Recruitment	14	Dates defining the periods of recruitment and follow-up.	1808 p 4
Baseline data	15	Baseline demographic and clinical characteristics of each group.	1807
Numbers analyzed	16	Number of participants (denominator) in each group included in each analysis and whether the analysis was by "intention-to-treat". State the results in absolute numbers when feasible (*e.g.*, 10/20, not 50%).	1808 p 7-8
Outcomes and estimation	17	For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision (*e.g.*, 95% confidence interval).	1808, 1809 p 6,7
Ancillary analyses	18	Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those pre-specified and those exploratory.	
Adverse events	19	All important adverse events or side effects in each intervention group.	1809 p 8
DISCUSSION Interpretation	20	Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision and the dangers associated with multiplicity of analyses and outcomes.	1810 p 9-12
Generalizability	21	Generalizability (external validity) of the trial findings.	1810 p 9-12
Overall evidence	22	General interpretation of the results in the context of current evidence.	1810 p 9-12

From Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. Lancet 2001; 357(9263):1191-1194.

The CONSORT Statement 2001 checklist is intended to be accompanied with the explanatory document that facilitates its use. For more information, visit www.consort-statement.org.