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Type I interferons for induction of remission in ulcerative colitis (Review)

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[Intervention Review]

Type I interferons for induction of remission in ulcerative colitis

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ABSTRACT

Background

Interferons (IFNs) are cytokines which possess immunoregulatory properties and have been used to successfully treat a number of chronic inflammatory disorders. It has been postulated that Type I IFNs may be able to re-establish the Th1/Th2 balance in Th2 predominant diseases like ulcerative colitis.

Objectives

To systematically evaluate the efficacy and safety of type I IFN therapy for induction of remission in ulcerative colitis.

Search methods

We searched MEDLINE, EMBASE, CENTRAL, the Cochrane IBD/FBD group specialised register, and ClinicalTrials.gov from inception to August 8, 2014. Reference lists of trials and review articles, as well as recent proceedings from major gastroenterology meetings were manually searched.

Selection criteria

Randomised controlled trials of type I IFNs for induction of remission in UC were included. The study population included patients of any age with active ulcerative colitis. There were no exclusions based on type, dose or duration of IFN treatment.

Data collection and analysis

Two independent authors reviewed studies for eligibility, extracted the data and assessed study quality using the Cochrane risk of bias tool. The overall quality of the evidence supporting the outcomes was evaluated using the GRADE criteria. The primary outcome was induction of remission of ulcerative colitis. Secondary outcomes included: time to remission, mean change in disease activity index score, clinical, histological or endoscopic improvement, improvement in quality of life, and adverse events. We calculated the risk ratio (RR) and corresponding 95% confidence interval (CI) for dichotomous outcomes. We calculated the mean difference and corresponding 95% confidence interval for continuous outcomes. Meta-analysis was performed using RevMan 5.3.5 software.

Main results

Six studies were eligible for inclusion (517 patients). Five studies compared type I IFNs to placebo injections (485 patients) and a single study compared IFNs to prednisolone enemas in patients with left-sided colitis (32 patients). The active comparator study was rated as high risk of bias due to an open-label design. Three studies were rated as unclear risk of bias for random sequence generation and allocation concealment. Two studies described as double blind were rated as unclear risk of bias for blinding. There was no significant benefit of type I IFNs over placebo for inducing clinical remission or improvement in patients with active ulcerative colitis. Thirty-six per cent (87/242) of patients in the type I IFNs group achieved clinical remission by 8 to 12 weeks compared to 30% (36/120) of placebo patients (RR 1.16, 95% CI 0.84 to 1.58; 4 studies, 362 patients). A GRADE analysis indicated that the overall quality of the evidence supporting the outcome clinical remission was moderate due to sparse data (123 events). Fifty-six per cent (149/264) of patients in the type I IFNs group improved clinically by 8 to 12 weeks compared to 48% (77/161) of placebo patients (RR 1.16, 95% CI 0.96 to 1.40; 4 studies, 425 patients). A GRADE analysis indicated that the overall quality of the evidence supporting the outcome clinical improvement was moderate due to sparse data (226 events). Patients who received type I IFNs were significantly more likely to withdraw from the studies due to adverse events than those who received placebo. Seven per cent (18/42) of type I IFNs patients withdrew due to adverse events compared to 2% (3/152) of placebo patients (RR 3.16, 95% CI 1.06 to 9.40). A GRADE analysis indicated that the overall quality of the evidence supporting the outcome withdrawal due to adverse events was low due to very sparse data (21 events). The study comparing type I IFNs to prednisolone enemas found no difference between the treatment groups in quality of life or disease activity scores. Common adverse events included headaches, arthralgias, myalgias, fatigue, back pain, nausea, application site reactions, rigors, and fevers. There were no statistically significant differences in the other secondary outcomes.

Authors' conclusions

Moderate quality evidence suggests that type I IFNs are not effective for the induction of remission in UC. In addition, there are concerns regarding the tolerability of this class of treatment.

PLAIN LANGUAGE SUMMARY

Type I interferons for treatment of active ulcerative colitis

What is ulcerative colitis?

Ulcerative colitis (UC) is a long-term (chronic) inflammatory bowel disease characterized by abdominal pain, bloody diarrhea, and a need to hurry to the toilet to pass feces (fecal urgency).

What are type I interferons?

Interferons (IFNs) are drugs that regulate the immune system and have been used to successfully treat a number of chronic inflammatory disorders. People with UC who are experiencing disease symptoms have ‘active’ disease, periods when the symptoms stop are called ‘remission’.

What did the researchers investigate?

The researchers investigated whether type I IFNs results in remission in people with active ulcerative colitis, and whether it causes any harms (side effects). The researchers searched the medical literature extensively up to August 8, 2014.

What did the researchers find?

The researchers identified six studies that included a total of 517 participants. Five studies (total 485 participants) compared type I IFNs to placebo (fake medicine) injections. One small (32 participants) low quality study compared types I IFNs to prednisolone (a steroid drug) enemas. This study did not measure remission and found no difference between the treatment groups in quality of life or disease activity scores. There was no difference between type I interferons and placebo treatment groups for the number of people who achieved remission or improvement of their symptoms. These results suggest that type I IFNs do not produce remission from ulcerative colitis. Common side effects included headaches, arthralgias (joint pain), myalgias (muscle pain), fatigue, back pain, nausea, injection site reactions, rigors (cold and shivering), and fevers.

At present, the results from medical trials do not support the use of type I IFNs for the production of remission in active ulcerative colitis.

Summary of findings for the main comparison. Type I Interferons compared to placebo for induction of remission in ulcerative colitis

Type I Interferons compared to placebo for induction of remission in ulcerative colitis

Patient or population: patients with induction of remission in ulcerative colitis
Settings: Outpatient
Intervention: Type I Interferons
Comparison: Placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Type I Interferons				
Remission Follow-up: 8-12 weeks	**300 per 1000** [1]	**348 per 1000** (252 to 474)	**RR 1.16** (0.84 to 1.58)	362 (4 studies)	⊕⊕⊕⊝ **moderate** [2]	
Clinical improvement Follow-up: 8-12 weeks	**478 per 1000** [1]	**554 per 1000** (459 to 669)	**RR 1.16** (0.96 to 1.40)	425 (4 studies)	⊕⊕⊕⊝ **moderate** [3]	
Serious adverse events Follow-up: 8-12 weeks	**46 per 1000** [1]	**34 per 1000** (6 to 190)	**RR 0.74** (0.13 to 4.14)	468 (4 studies)	⊕⊕⊝⊝ **low** [4]	
Withdrawals due to adverse events Follow-up: 8-12 weeks	**20 per 1000** [1]	**62 per 1000** (21 to 186)	**RR 3.16** (1.06 to 9.4)	394 (4 studies)	⊕⊕⊝⊝ **low** [5]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Control group risk comes from control arm of study
[2] Downgraded one level due to sparse data (123 events)
[3] Dowgraded one level due to sparse data (226 events)
[4] Downgraded two levels due to very sparse data (20 events)

[5] Downgraded two levels due to very sparse data (21 events)

BACKGROUND

Ulcerative colitis

Ulcerative colitis (UC) is characterized by chronic or recurrent contiguous inflammation of the colonic mucosa resulting in symptoms such as bloody diarrhoea, abdominal discomfort, urgency and tenesmus. Inflammation typically arises in the distal colon and extends in a proximal direction. The disease can be subcategorised by anatomic extent. Left sided colitis is defined by inflammation that does not extend beyond the splenic flexure, and pancolitis where there is more proximal involvement. UC varies in severity and patients often experience cycles of relapses and remissions. While the exact cause of the disorder remains to be determined, environmental factors are thought to modify disease presentation in genetically predisposed individuals (Ek 2014; Hansen 2010; Ko 2014; Zhang 2014; Hanauer 2006). From an immunological perspective, the naive T cells (Th0) preferentially differentiate into Th2 (T-helper) lymphocytes, which express a predominant interleukin-4 (IL-4), IL-5, IL-13 cytokine profile (Geremia 2014; Bouma 2003). However, UC represents an 'atypical' Th2 disease as increased circulating levels of interferon-γ and TNF-α (tumour necrosis factor-α) have also been identified (Tsukada 2002; Heller 2005; Jovanovic 2014). It is hypothesized that this imbalance in circulating pro-inflammatory and anti-inflammatory cytokines underlies the chronic disease state (Geremia 2014; Baumgart 2007).

The mainstay of UC treatment comprises anti-inflammatory agents in the form of 5-aminosalicylic acid compounds (Travis 2006), glucocorticoids (Truelove 1955), immunosuppressives (Timmer 2012), and more recently monoclonal antibodies against tumour necrosis factor-alpha (TNF-α) (Rutgeerts 2005) and integrin α4ß7 (Feagan 2013). These standard medical therapeutic options vary in efficacy, and importantly, toxicity (Bernstein 2015). While surgery may be considered 'curative' by some, this is often not ideal, rendering some patients with permanent ostomies and others with ongoing symptomatology, including that associated with suboptimal ileoanal pouch function. Therefore, alternative treatments are continually being evaluated.

Interferons

Interferons (IFNs) are cytokines which may be released in response to viruses, bacteria, parasites and tumour cells. Interferons possess immunoregulatory, antiviral and anti-cancer properties (George 2012). IFNs have been used to successfully treat a number of chronic inflammatory disorders including multiple sclerosis (Kasper 2014; Anonymous 1998; Anonymous 2001), and chronic viral hepatitis (Koretz 2013; Hoofnagle 2006). There are two main classes of IFNs: type I IFNs (which include α, β, ε, Ω, κ isoforms) (Ivashkiv 2014; Ludigs 2012), and type II IFNs (γ isoform) (Ghosh 2006). More recently a new family of antiviral cytokines, the type III IFNs (λ isoform) has been identified (Durbin 2013).

This systematic review will focus on the use of type I IFNs for the induction of remission of UC, specifically IFN-α and IFN-β which are marketed in standard recombinant or pegylated forms. IFN-α has been shown to enhance human Th1 responses. This helps to re-establish the Th1/Th2 balance in Th2 predominant diseases by down-regulating Th2 cytokines such as IL-4, IL-5 and IL-13 (Shibuya 2005; Brassard 2002). IFN-β increases the expression of anti-inflammatory IL-10, inhibits IFN-γ, TNF-α, and enhances regulatory T lymphocyte and NK (natural killer) cell activity (Graber 2007). As IFN-α and IFN-β share a cellular surface receptor, they both induce IL-1Ra.

Initial interest in IFNs for UC arose from an incidental observation of a patient with known UC who experienced a dramatic improvement in his UC symptoms when he was treated with IFN-α2a for concurrent chronic hepatitis B (Sümer 1995). This led to a small prospective open-label study by the same investigators in which 28 inpatients who had failed to respond to 5-aminosalicylic acid compounds and oral or topical corticosteroids were treated with IFN-α2a therapy for 6 to 12 months. Eighty-two percent of patients responded to therapy within 15 days and were in complete clinical endoscopic remission after 6 months of therapy (Sümer 1995). Subsequently, Musch 2002 trialed IFN-β-1a in 25 steroid refractory UC patients in an open label study. The decision to use IFN-β rather than IFN-α occurred in response to its clinical utility in the chronic inflammatory disorder, multiple sclerosis. Furthermore, in vitro studies had suggested that IFN-β, in contrast to IFN-α or IFN-γ did not enhance the production of inflammatory metabolites of arachidonic acid or leukotriene B4. A total of 88% of patients entered remission with a mean time to response of 21 days (Musch 2002).

The adverse effect profile of IFNs includes flu-like symptoms including fever, headache, malaise, alopecia and arthralgias. Other potential adverse events include skin rashes, psychological disturbances, and perturbations in the haematological profile. IFNs may also induce autoimmune complications including thyroid disorders, diabetes mellitus and alopecia (Borg 2007; Okanoue 1996). Of concern, there have been isolated case reports documenting the association between IFNs and the induction of ischaemic colitis (Okanoue 1996; Sparano 1991; Tada 1996), and ulcerative colitis (Tursi 2007; Watanabe 2006; Sprenger 2005; Mavrogiannis 2001). In contrast, Bargiggia 2005 conducted a case control study of IFN-α therapy in patients with concomitant inflammatory bowel disease and chronic active hepatitis C and determined that no patients developed an IBD relapse during IFN treatment or in the following 12 month follow-up. Therefore, there is a need to critically evaluate if IFN therapy results in improvement or detriment to patients with UC.

Commercially available type I IFNs have different pharmacokinetic profiles, and consequently there is variation in the frequency and mode of administration. IFNs can be administered on alternate days, thrice weekly, or once a week by subcutaneous or intramuscular injection. Some of the IFNs are available in pegylated forms to reduce clearance. Pegylation is the process by which the biologically inert polyethylene glycol chains are cross linked to the active moiety, in this case the IFN protein, to optimise overall pharmacokinetics (Foster 2004). Currently available type I IFNs include IFN α-2a (Roferon A® - Roche), IFN α-2b (Intron A® - Schering), pegylated IFN α-2a (Pegasys® - Roche), pegylated IFN α-2b (Pegatron® - Schering), IFN β-1a (Rebif® - Pfizer, EMD Serono), IFN β-1a (Avonex® - Biogen Idec), IFN β-1a (CinnoVex® - CinnaGen, Fraunhofer Gessellschaff Institute), and IFN β-1b (Betaseron® - Bayer HealthCare).

Importance of this review

In an effort to improve the management of UC, alternative therapeutic options need to be evaluated. Laboratory studies suggest that IFN treatment may attenuate chronic colitis. However, there is limited clinical information on the use of IFN therapy for UC, and there are concerns regarding its adverse effect profile.

Furthermore, there is variation in the types of IFN (IFN-α, IFN-β), formulations (standard versus pegylated), doses and dosing schedules used in clinical practice. Therefore, a systematic review was planned to assess the role of type I IFN therapy for induction of remission in UC. This systematic review is an update of a previously published Cochrane systematic review (New Reference).

OBJECTIVES

The primary objective of this review was to systematically evaluate the efficacy of type I IFN therapy (including IFN-β-1a, IFN-β-1b, IFN-α-2a, IFN-α-2b and associated pegylated formulations) for induction of remission in ulcerative colitis. The secondary objectives were to determine improvement in disease activity (including quality of life) and to evaluate adverse events associated with IFN therapy.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised, double-blind trials reporting either the primary or secondary objective and published in any language, with the following study designs: parallel arm placebo-controlled trials and trials comparing two active agents, were considered for this review. Studies published in abstract form were only included if enough data were provided to assess the validity of the study and reported outcomes.

Types of participants

UC is usually diagnosed using a combination of clinical, radiologic, endoscopic and histologic criteria. Patients (both paediatric and adult) with active UC at the time of recruitment were included. It was anticipated that there would be heterogeneity in defining disease activity, therefore the definitions used by the authors of the primary studies were accepted. These included some of the following published disease activity indices: the Colitis Activity Index (CAI) (Rachmilewitz 1989), the Powell-Tuck Index (Powell-Tuck 1978), the Simple Clinical Colitis Activity Index (SCCAI) (Walmsley 1998), Beattie's Colitis Symptom Score (Beattie 1996), Lichtiger Symptom Score for Acute Ulcerative Colitis (Lichtiger 1990), the Mayo Index (Schroeder 1987), the Seo Index (Seo 1992), the Truelove and Witt's Index (Truelove 1955), Ulcerative Colitis Scoring System (UCSS) (Schroeder 1987) and the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) (Travis 2012).

Types of interventions

Trials assessing type I IFNs (IFN-α or IFN-β) compared to placebo, no treatment, different regimens of interferon or an active comparator were included. Co-interventions were permitted if the co-interventions were balanced across the study groups. There were no exclusions based on type, dose or duration of IFN treatment.

Types of outcome measures

Primary outcome

The primary outcome was induction of remission of UC. Remission was defined by the primary studies (see disease activity indices described under 'Types of participants') and was expressed as the percentage of patients randomised (intention-to-treat analysis).

Secondary outcomes

The secondary outcomes included:
1. Time to remission;
2. The mean change in the disease activity index score;
3. Clinical, histological or endoscopic improvement as defined by the authors;
4. Improvement in quality of life as defined by a validated quality of life tool; and
5. Adverse events associated with IFN therapy for the treatment of UC.

Four different outcome measures were used to evaluate the safety of type I IFNs:

- The percentage of patients experiencing adverse events (which may have included but were not limited to flu-like symptoms, skin rashes, psychological disturbances, perturbations in the haematological profile, and autoimmune complications such as thyroid disorders, diabetes mellitus and alopecia);
- The percentage of patient withdrawals due to adverse events;
- The percentage of patients undergoing colectomy; and
- Mortality expressed as a percentage.

Search methods for identification of studies

Search sources

A. Electronic searching (Please see Appendix 1 for a complete list of search strategies)
1. MEDLINE (1950 - August 2014)
2. EMBASE (1980 - August 2014)
3. Cochrane Central Register of Controlled Trials
4. Cochrane Inflammatory Bowel Disease and Functional Bowel Disorders (IBD/FBD) Group Specialised Trial Register
5. Ongoing trials identified from ClinicalTrials.gov registry

B. Hand searching using reference lists of trials and review articles identified by means of the computer-assisted search.

C. Proceedings from major gastroenterology meetings (American Gastroenterology Association, British Society of Gastroenterology, United European Gastroenterology Week) were manually searched from 2002 onwards.

D. Pharmaceutical and personal contacts
Relevant pharmaceutical companies that have or are involved in the development of the type I IFNs, and leaders in the field of inflammatory bowel disease were contacted to try and identify further unpublished studies.

Data collection and analysis

Study selection

All the article abstracts identified by the above search strategies were reviewed for eligibility. The full text articles of potentially relevant studies were independently reviewed by YW and JKM for inclusion in the review. Review articles were also retrieved and reference lists were manually searched. Disagreements were resolved by consensus. Trials published in abstract form were only included if full details of the protocol and results could be obtained from the authors.

Data collection

The eligible articles were reviewed in duplicate (YW, JKM) and the results of the trials were abstracted onto specially designed

data extraction forms which mandated the following information be recorded:

1. General article information: Study title, first author, and year of publication.
2. Study design: Randomisation process, allocation concealment, and blinding.
3. Patient cohort: Countries in which study was performed, years patients were entered into the study, total number of patients screened, total number of patients randomised, inclusion/exclusion criteria, baseline characteristics (demographics, disease extent, disease severity).
4. Intervention: Type of IFN (α versus β), formulation of IFN (standard versus pegylated), route of administration, dose, and dosing schedule.
5. Control: No treatment, placebo, or details of co-intervention.
6. Primary outcome: Proportion of patients achieving remission in the intervention and control groups. Where available, the median number of days to remission and the mean change in the disease activity index score will be recorded.
7. Secondary outcomes: Data on other clinical, histologic, endoscopic measures of disease activity; quality of life information; adverse events; withdrawal of participants from either the intervention or control group, where provided.

Assessment of methodological quality of included studies

The methodological quality of the included studies was evaluated using the Cochrane risk of bias tool (Higgins 2011). This tool involves rating trials as high, low or unclear risk of bias for each of the following criteria:

1. Random sequence generation;
2. Allocation concealment;
3. Blinding;
4. Missing data and attrition;
5. Outcome reporting; and
6. Other sources of bias.

The overall quality of the evidence supporting the primary and secondary outcomes was evaluated using the GRADE approach (Guyatt 2008; Schünemann 2011). Outcome data are rated as being of high, moderate, low or very low quality evidence. Data from randomised controlled trials begin as high quality but can be downgraded based on the following criteria:

1. Risk of bias in the included trials;
2. Indirect evidence;
3. Inconsistent findings (including unexplained heterogeneity);
4. Imprecision (i.e. sparse data or wide confidence interval or both); and
5. Reporting bias.

The different quality ratings are interpreted as the likelihood that future research would affect the estimate of effect. An estimate of effect based on high quality evidence is unlikely to change with further research. If the overall evidence is of moderate quality further research may have an impact on our confidence in the estimate and may change the estimate. Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate when the evidence is rated as low quality. Very low quality research indicates significant uncertainty with the findings (Guyatt 2008; Schünemann 2011).

Statistical analysis

Measures of treatment effect

Data were extracted from the original studies and converted into individual 2 x 2 tables (e.g. remission versus no remission x IFN versus control) for each study. The proportion of patients who entered remission was calculated and reported as a relative risk (RR) and 95% confidence interval (95% CI). Where appropriate, the number needed to treat (NNT) and risk difference (RD) was also calculated. This was determined using an intention-to-treat analysis, based on the total number of patients randomised to each of the two groups, and the number of patients in remission at the end of follow-up in each group. For continuous variables, the results were presented as the mean difference (MD) and 95% CI or the standardised mean difference (SMD) when different scales were used to measure the same underlying construct. Where available, individual 2 x 2 tables for strata within studies were also abstracted.

Meta-analysis

For pooled analyses we utilized a random-effects or fixed-effect model depending on clinical and statistical heterogeneity.

Assessment of heterogeneity

The studies were first independently assessed for clinical or methodological heterogeneity. Then, the I^2 measure was calculated to quantify inconsistency. The I^2 statistic describes the percentage of total variation across studies that was due to heterogeneity rather than chance. We interpreted I^2 as follows: 25% - low heterogeneity, 50% - moderate heterogeneity, 75% - high heterogeneity (Higgins 2003). The Chi^2 test was also calculated. Being a relatively insensitive test for the presence of heterogeneity, a P-value < 0.10 was considered to be statistically significant.

Subgroup analysis

A priori subgroup analyses were planned for the different isoforms of type I IFN (IFN-α versus IFN-β), different formulations of IFN (standard versus pegylated), different doses, different durations of treatment, paediatric versus adult, and left-sided colitis versus pancolitis.

Sensitivity analysis

We performed sensitivity analyses excluding poor quality studies and studies published in abstract form. There were insufficient eligible trials to construct a 'funnel plot' to assess publication bias (Egger 1997).

Analyses were performed using the Review Manager software (RevMan 5.3.5, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

RESULTS

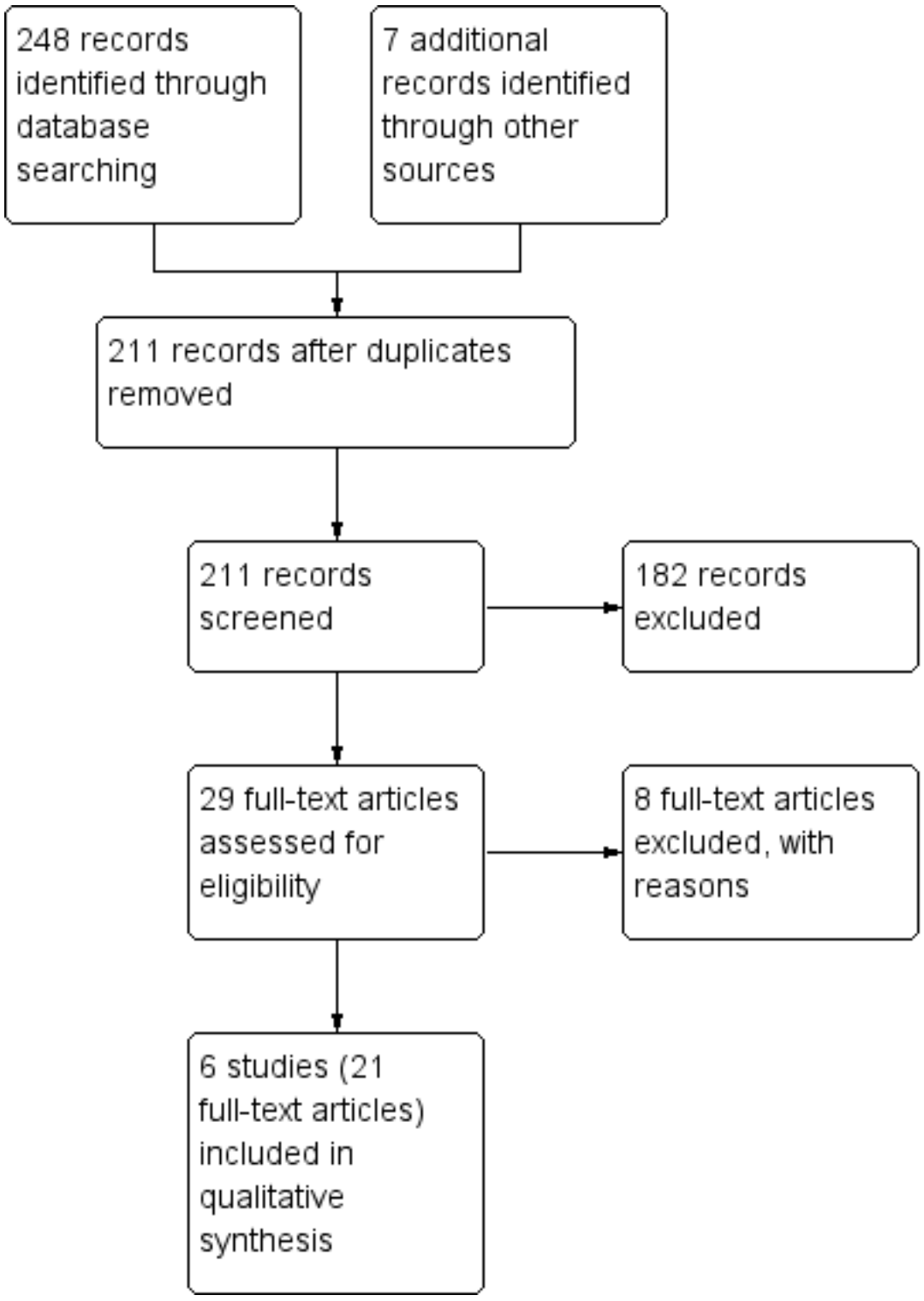
Description of studies

See Table of included studies (Characteristics of included studies), Table of excluded studies (Characteristics of excluded studies).

The initial search yielded 211 non-duplicated articles. Based on abstract review, all potential controlled trials and review articles were retrieved for full text review. A total of 29 full text manuscripts were obtained of which six randomised controlled trials (21 full-

text articles) were identified by the authors as being eligible for inclusion (See Figure 1). Eight studies were excluded. Agreement among authors regarding the eligibility of the included studies was 100%. Mannon 2010 was published as conference abstracts only. We contacted the lead author of the Mannon 2010 trial but were unable to obtain any additional information about the study.

Figure 1. Study flow diagram.



All six included studies (total of 517 patients) were conducted in adult patients aged 18 years and over. The studies can be differentiated by the comparison groups and formulation of interferon used. Five trials compared a type I IFN to placebo in

patients with active UC of any anatomic extent (Mannon 2010; Musch 2005; Nikolaus 2003; Pena-Rossi 2008; Tilg 2003). Of these, three studies compared IFN-β-1a injected subcutaneously three times a week to placebo (Musch 2005; Nikolaus 2003; Pena-Rossi 2008); and one study compared pegylated IFN-α injected subcutaneously once a week to placebo (Tilg 2003). The remaining trial compared IFN-α-2a to prednisolone enemas in patients with left sided UC (Madsen 2001).

Mannon 2010 was a multi-center phase II study in North America and Eastern Europe sponsored by Biogen Idec. This was a randomised, double blind, placebo-controlled trial of 123 adult patients who had active ulcerative colitis with a total Mayo score of 6 to 13 points including a Mayo endoscopic subscore of at least 2, indicating moderate to severe endoscopic activity, despite prior or concomitant treatment. Patients were randomly assigned to IFNβ 30 µg intramuscularly twice a week for 12 weeks (n = 62), or placebo injections (n = 61). The primary endpoint was clinical response at week 8, defined as a decrease from baseline in the total Mayo score by 30% and at least a 3 point decrement, accompanied by a decrease in the subscore for rectal bleeding of at least 1 point or an absolute endoscopic subscore of 0 or 1. The secondary endpoints were the safety and tolerability of IFNβ and the percentage of subjects with a decrease in the SCCAI score of ≥ 3 points at week eight.

Musch 2005 was conducted in Germany and the Czech Republic. This was a randomised, double-blind, placebo-controlled trial of 91 adult patients with steroid refractory, active UC defined by a CAI score of at least 8 points. Patients were randomly assigned to one of three groups. Patients in group one received three million international units (MIU) of IFN-β-1a by subcutaneous injection three times a week (n = 32). Patients in group two received one MIU of IFN-β-1a by subcutaneous injection three times a week (n = 30); and group three received placebo injections (n = 29). The total duration of treatment was eight weeks. The primary outcome was the response rate at the end of treatment. Response was defined as a reduction of six or more points on the CAI at week eight compared to baseline. Secondary endpoints included: the number of patients achieving a complete response (reduction of CAI to ≤4 points after 8 weeks of treatment); time until response; reduction of CAI after 4 and 8 weeks; reduction of the endoscopic index after 8 weeks; number of patients receiving colectomy; and reduction of steroid dose.

Nikolaus 2003 compared the effects of IFN-β-1a to placebo. The study was conducted in three countries; Belgium, Canada and Germany. This was a randomised, double blind, intra-individual, dose escalating trial of 17 adult patients with moderately active UC. This was defined by a UCSS score of 6 to 10, with a proctosigmoidoscopy score of 2. Patients were randomly assigned to IFN-β-1a by subcutaneous injection three times a week (n = 10) or placebo injections (n = 7). Patients in the IFN-β-1a group were started at 22 µg three times a week by subcutaneous injection. Dose escalation was dependent on 'improvement'. Improvement was defined as a decrease of one point in the combined score of UCSS symptoms and physician's global assessment (PGA). If no improvement was observed after six injections, the dose was increased to 44 µg three times a week. If no improvement was observed after six injections at the 44 µg dose, this was increased further to 88 µg three times a week. If improvement was observed after six injections at any dose, the patient entered a maintenance treatment phase of 6 to 12 injections at that dose. If no improvement was observed after six injections at 88 µg, or if remission occurred at any point, treatment was stopped. The maximum duration of treatment was eight weeks, and the minimum duration was four weeks. The primary end point was efficacy, which was defined by treatment response and remission. Treatment response was defined by a decrease of at least three points from baseline in the UCSS symptoms score and PGA (without the proctosigmoidoscopic score) during treatment. Remission was defined as complete resolution of clinical symptoms (all clinical UCSS subscores equal to zero), with a proctosigmoidoscopy score of zero or one at any time during treatment. Secondary end points included overall treatment and end point responses (defined as a decrease in UCSS symptoms score, PGA, and proctosigmoidoscopic scores of at least one point during or at the end of treatment), and clinical end point responses (a decrease of at least one point from baseline in UCSS symptoms scores and PGA, without the proctosigmoidoscopic score). Safety data were also collected.

Pena-Rossi 2008 was an European phase II clinical trial sponsored by EMD Serono. The study was randomised, multi-centred, double-blinded, and placebo-controlled. The trial involved 194 patients with moderately active ulcerative colitis, defined by a UCSS score between 6 and 10 with a UCSS PGA of less than three and a proctosigmoidoscopy score of two or three. Patients were randomised using stochastic minimization to one of three trial arms: IFN-β-1a 44 µg (n = 65), IFN-β-1a 66 µg (n = 65), or matching (same excipients but no IFN-β-1a) placebo (n = 64). All study drugs were given by subcutaneous injection three times a week for eight weeks and there was a four week follow-up period.The primary objective was to identify the best dose of IFN-β-1a for the induction of endoscopically confirmed remission and examine the safety profile of this dose. Safety, tolerability, quality of life and biological markers were also assessed as secondary outcomes.

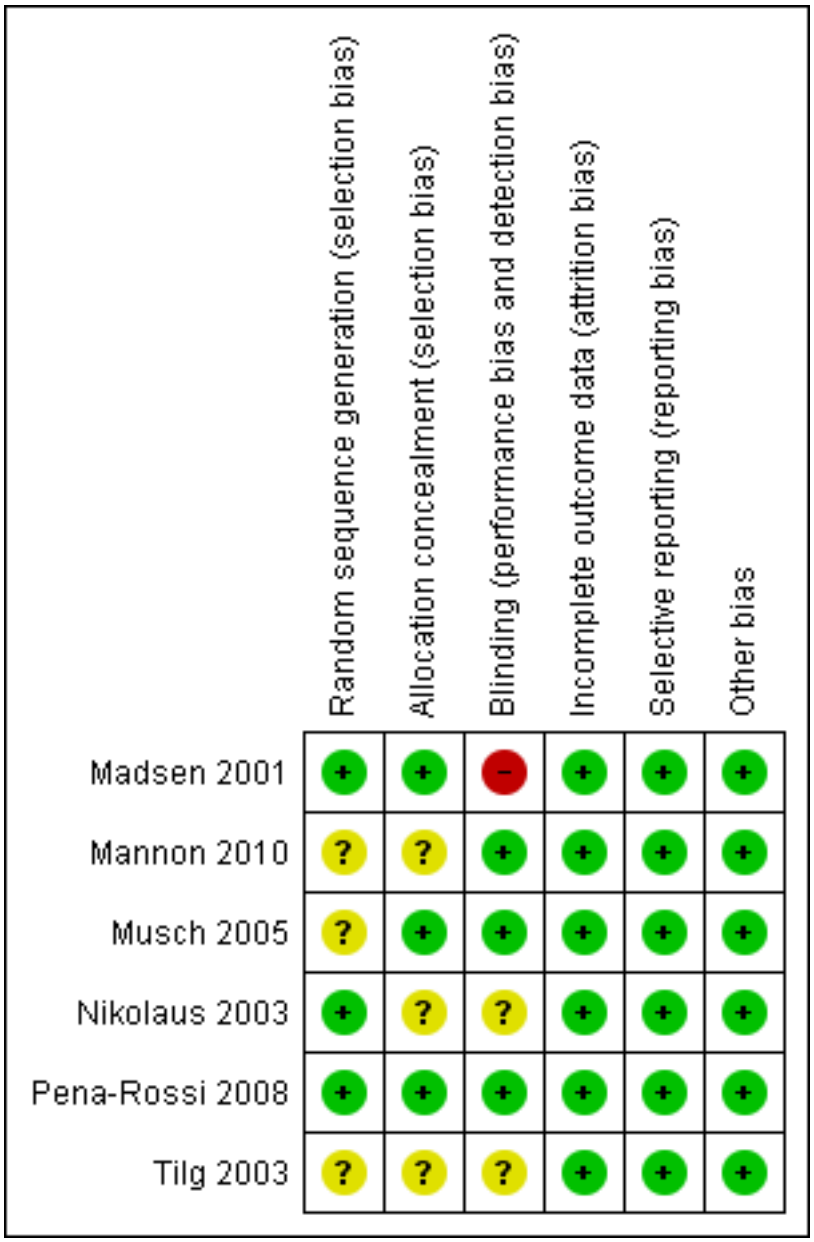
Tilg 2003 compared the effects of pegylated IFN-α (PegIFN) to placebo. The study was conducted in five university hospitals in four countries including Austria, Belgium, Germany and France. This was a multicentre double-blind randomised controlled trial of 60 adults with UC. Patients were randomly assigned to PegIFN 0.5 µg/kg (n = 19); PegIFN 1.0 µg/kg (n = 21); or placebo (n = 20). All therapies were administered by subcutaneous injection once a week, for a period of 12 weeks. Patients were eligible if they had evidence of clinical activity despite oral or topical 5-aminosalicylate maintenance therapy, stable doses of steroids or azathioprine. Active disease was defined by a CAI score of greater than six, and endoscopic activity was defined by a Rachmilewitz endoscopy score of greater than four. Clinical evaluation was performed before the start of treatment (day -8), then on days 0, +8, +15, +29, +43, +57, and at the end of treatment (day +85). Patients underwent sigmoidoscopy and/or colonoscopy on days -1, +29, and +85. The primary outcome was safety. All adverse events were recorded and classified as serious or non-serious, and likely or unlikely to be related to treatment. Other outcomes included disease remission (defined as a CAI score of less than or equal to four), endoscopic remission (defined as a score of less than four), and histological activity (graded on a scale from zero to three). These markers of remission were measured at week 12. Changes in serological inflammatory indices including haemoglobin, white cell count, platelet count, C reactive protein, α-1 acid glycoprotein, creatinine, liver function tests, and albumin were also recorded.

Madsen 2001 compared the effects of IFN-α-2a to prednisolone enemas. The study was conducted in Denmark. This was an open-label, randomised controlled trial of 32 adult patients. The patient cohort was restricted to those with active left-sided UC. Patients were randomly assigned to IFN-α-2a therapy by subcutaneous injection three times a week (n = 16) for 12 weeks; or prednisolone enemas 100 mL (25 mg) daily for 30 consecutive days (n = 16). The dose of IFN used was 9 MIU for the first week, 6 MIU for the second week, and 3 MIU from weeks 3 to 12 inclusive. All patients were treated with sulfasalazine or mesalazine compounds with a median daily dose of 2.4 g (range 1.2 to 3.6 g), and were not allowed dose adjustments for at least four weeks before entry. The patients receiving enemas were evaluated after one week, two weeks and on completion of the trial; while the IFN-α-2a group had appointments after one week, two weeks, four weeks, eight weeks, and after completion of the trial. Clinical and endoscopic disease activity was graded at each visit by semi-quantitative scales. Clinical activity assessment was based on the patient filling out a five point symptom scale daily; while a physician evaluated abdominal tenderness, enquired about limitations in the patient's daily activities, adverse events and extraintestinal manifestations at each clinic visit. Endoscopic evaluation involved proctoscopy or colonoscopy at each clinic visit, and histological assessment of disease activity (rectal biopsies) were obtained at entry and after treatment. The combined clinical and endoscopic Powell-Tuck Index was also calculated. Secondary outcomes included an assessment of quality of life, and tolerability of treatment. Remission was not defined by the authors, rather, the change in the activity indices were measured.

Risk of bias in included studies

The risk bias assessment results are summarized in Figure 2. A table detailing withdrawals or drop outs is provided (Table 1). While none of the studies were excluded on this basis, the studies have to be interpreted with caution given the substantial proportion of withdrawals or drop outs.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Mannon 2010 did not report on methods used for randomisation or allocation concealment. These items were rated as unclear. Patient drop-out data were not included in the abstract publications, but analyses were conducted on an intention-to-treat basis. Based on ClinicalTrial.gov (NCT00616434), 10% (6/62) of patients in the IFNβ-1a 30 µg treatment group and 13% (8/61) of patients in the placebo group did not complete the study. Musch 2005 was reported as randomised but the methods used to generate the random sequence were not described. There was an adequate description of the blinding process as well as allocation concealment. The drop-out rate was 12% (4/32) in the 3 MIU IFN-β-1a group, 17% (5/30) in the 1 MIU IFN-β-1a group, and 24% (7/29) in the placebo group. Nikolaus 2003 was a well designed but small study. However, there was a substantial drop out rate particularly in the intervention (IFN-β-1a) group where 60% (6/10) of patients withdrew. The withdrawal rate in the control group was 29% (2/7). There was a detailed description of the use of a centralised, computer generated list for randomisation. Study subjects were stratified by centre with a block size of three (a ratio of 2 to 1: IFN-β-1a to placebo). Allocation concealment was not described. The study design was described as double blind, but further details on how this was achieved were not reported. An intention-to-treat analysis was utilised. Pena-Rossi 2008 provided adequate descriptions regarding randomisation, allocation concealment, blinding and outcome data. Twenty per cent (13/65) of patients in 66 µg IFN-β-1a treatment group, 22% (14/65) of patients in 44 µg IFN-β-1a treatment group, and 17% (11/64) of patients in placebo group withdrew from the study. All efficacy endpoints were analysed using intention-to-treat (ITT) populations. Tilg 2003 was described as randomised, but there was no information provided on the generation of the randomisation sequence, nor on blinding or allocation concealment. Thirty-two per cent (6/19) of patients in

the PegIFN-α 0.5 µg/kg group withdrew from the study, compared to 48% (10/21) of patients in the PegIFN-α 1.0 µg/kg group, and 55% (11/20) of patients in the control group. The results were interpreted with caution given the high drop out rate. Madsen 2001 was an open-label study. There was an adequate description of the randomisation process (using a computer generated random number generator), as well as allocation concealment. All 16 patients in the prednisolone enema (control) group completed the trial compared to a withdrawal rate of 19% (3/16) in the IFN-α-2a group.

Effects of interventions

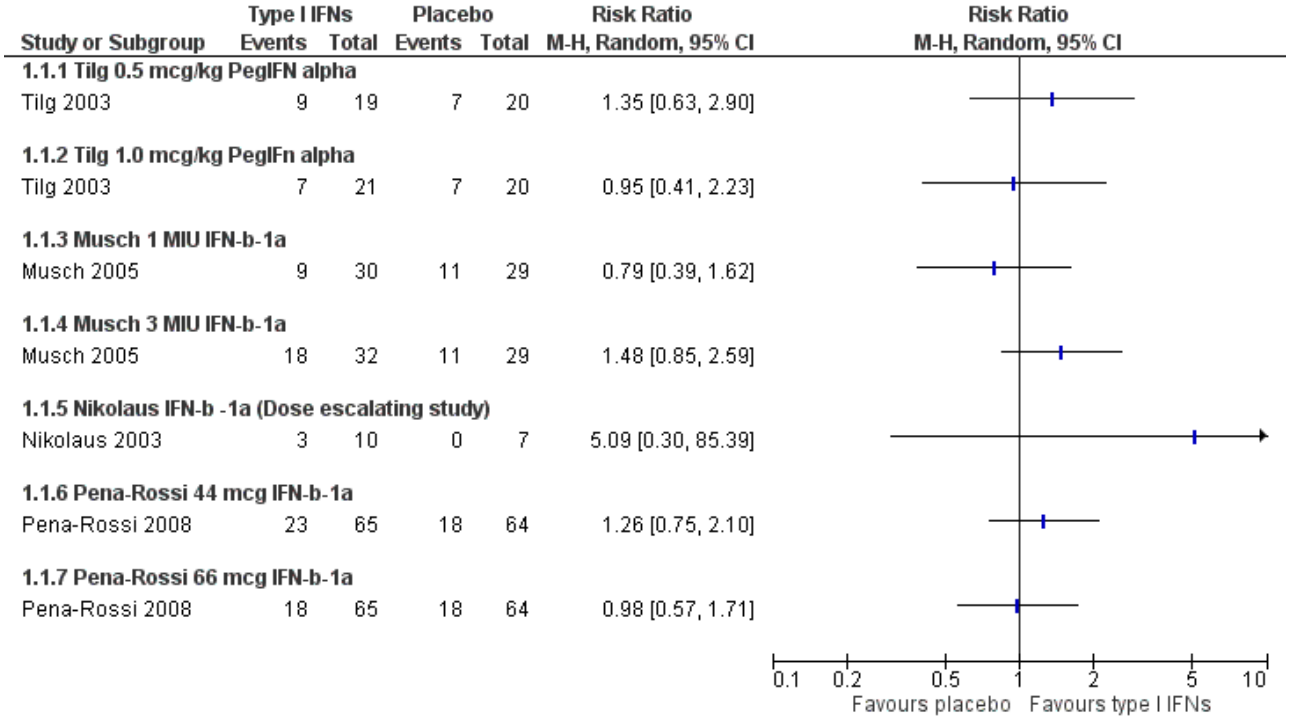
See: **Summary of findings for the main comparison** Type I Interferons compared to placebo for induction of remission in ulcerative colitis

Primary Outcome

The primary outcome was induction of remission of UC. Of the six studies satisfying the inclusion criteria, four studies reported on the proportion of patients achieving remission at the end of treatment (Musch 2005; Nikolaus 2003; Pena-Rossi 2008; Tilg 2003). There were three studies that compared IFN-β-1a versus placebo albeit using different formulations and doses (Musch 2005; Nikolaus 2003; Pena-Rossi 2008), and one study comparing PegIFN-α versus placebo (Tilg 2003).

After 8 weeks of treatment in the Musch 2005 study, 56% (18/32) of patients in the IFN-β-1a 3 MIU group achieved remission, compared to 30% (9/30) of the 1 MIU group and 38% (11/29) in the placebo group. The difference between the 3 MIU and the 1 MIU group was statistically significant with a P = 0.04, but not significant when compared with placebo. The authors concluded that IFN-β-1a was not more effective than placebo in steroid-refractory UC. The non-pooled dose-dependent data are presented in Figure 3.

Figure 3. Forest plot of comparison: 1 Type I Interferons versus placebo, outcome: 1.1 Remission (non pooled data).



In the IFN-β-1a dose escalating study by Nikolaus 2003, 30% (3/10) of the intervention group achieved remission compared to 0% in the placebo group. One patient received 44 µg IFN-β-1a injections whilst two were treated with 88 µg IFN-β-1a injections. The authors concluded that patients treated with escalating doses of IFN-β-1a tended to show a higher remission rate than those in the placebo group, however, the difference between the groups was not statistically significant.

In the Pena-Rossi 2008 study clinical remission was achieved by 35.4% (23/65) of patients treated in the 44µg IFN-β-1a group, 27.7% (18/65) of those in the 66µg IFN-β-1a group, and 28.1% (18/64) of patients in the placebo group. The differences between the groups were not statistically significant. Please note, only percentages were reported in the original publication, absolute numbers in brackets were calculated using the intention to treat population.

Tilg 2003 used a CAI of ≤ 4 to define remission. At week 12, 7/21 (33.3%) of the 1.0 µg/kg PegIFN-α group, 9/19 (47.4%) of the 0.5 µg/kg and 7/20 (35.0%) in the placebo group achieved remission. The authors concluded that there was no significant advantage of PegIFN over placebo.

Data from four studies were pooled in a meta-analysis. While three of the studies used IFN-β-1a (Musch 2005; Nikolaus 2003; Pena-Rossi 2008), and one study used PegIFN-α (Tilg 2003), the authors felt there was sufficient clinical homogeneity across both IFN preparations in immunological action, such that the data could be meta-analysed. There was no statistically significant difference in remission rates between IFNs and placebo. Thirty-six per cent

(87/242) of IFNs patients achieved remission compared to 30% (36/120) of placebo patients (RR 1.16, 95% CI 0.84 to 1.58; P = 0.37). A GRADE analysis indicated that the quality of evidence supporting the outcome clinical remission was moderate due to sparse data (See Summary of findings for the main comparison). However, these results should be interpreted with caution given variability in dosing, treatment duration, and the timing of outcome assessment. Table 2 documents the comparative doses of IFN-b-1a used in the Musch 2005, Nikolaus 2003 and Pena-Rossi 2008 trials. A 44 µg dose is approximately equivalent to 12 MIU (Antonetti 2002). Although the Musch 2005 trial suggested that remission may be dose dependent, the dosing was still lower than that used in the Nikolaus 2003 trial preventing comparisons of high versus low dose IFN across studies. The comparison was further confounded by differing durations of treatment; 8 weeks (56 days) in the Musch 2005 and Pena-Rossi 2008 trials compared to approximately 5 weeks (35.5 days) in the Nikolaus 2003 study.

A priori subgroup and sensitivity analyses were planned for the different IFN isoforms and according to study quality. The analysis was repeated excluding the Tilg 2003 study as patients were treated with the α−isoform preparation and this was the only study that was judged to be low quality. Analysis of the three IFN-β-1a, moderate quality studies (Musch 2005; Nikolaus 2003; Pena-Rossi 2008), did not change the results (RR 1.19, 95% CI 0.84 to 1.69).

Secondary outcomes

1. Time to remission (in days)
Two studies using IFN-β-1a reported on the mean number of days to remission (Musch 2005; Nikolaus 2003). In the Musch 2005 study, the time to complete response (remission) was 32.1 ± 17.9 days in the 3 MIU group; 34.3 ± 20.0 days in the 1 MIU group and 36.2 ± 16.4 days in the placebo group. The differences in mean time to remission were not statistically significant between the groups. Nikolaus 2003 reported the mean time to remission was 52 ± 7 days in the IFNs group. There were no patients in the placebo group who achieved remission within the study time frame. Pena-Rossi 2008 did not provide sufficient data for comparison. Mannon 2010, Tilg 2003 and Madsen 2001 did not report on this outcome.

2. Change in the disease activity index score
The change in disease activity index scores could not be pooled given the heterogeneity of indices and the differing time of outcome measurement used.

Musch 2005 reported the median change in CAI at four and eight weeks. All patients started with a CAI score of 10; at 4 weeks, there was a reduction of 5 points in the CAI in the 3 MIU group, 3 points in the 1 MIU group, and 4 points in the placebo group. The median change in CAI at eight weeks was six points in the 3 MIU group, three points in the 1 MIU group, and four points in the placebo group. There was no statistically significant difference between the three groups at either time point. Tilg 2003 measured the CAI at baseline and weeks 1, 2, 4, 6, 8 and 12. Results were reported as the mean score and standard deviation. Using the Follmann 1992 method, the mean change in the CAI and standard deviation were calculated. The mean reduction in CAI from baseline to week 12 was 4.0 ± 2.5 in the 1.0 µg/kg group, 4.9 ± 2.3 in the 0.5 µg/kg group and 6.3 ± 2.8 in the placebo group.

Both Musch 2005 and Tilg 2003 reported on end of treatment change in endoscopic index scores. Musch 2005 provided both the mean and median reduction of the endoscopic index score at eight weeks, while Tilg 2003 reported on endoscopic index values at baseline, week 4 (day 29), and at week 12 (day 85). Using the Follmann 1992 method, the mean change in endoscopic index score and standard deviation were calculated for the Tilg 2003 study. The mean reduction in scores in the Musch 2005 study was 4.4 ± 3.4 points in the 3 MIU group, 3.3 ± 4.1 in the 1 MIU group and 3.6 ± 3.4 points in the placebo group. The mean reduction in scores in the Tilg 2003 study was 3.6 ± 2.4 in the 1.0 µg/kg PegIFN-α group, 3.2 ± 3.6 in the 0.5 µg/kg group, and 4.0 ± 3.2 in the placebo group. The change in endoscopic index scores was not statistically significant in either study.

There were no statistically significant differences in any of the UCSS subscores between the IFN-β-1a and placebo groups four weeks after the end of treatment in the Nikolaus 2003 study. The change in UCSS symptom scores are as reported as follows: UCSS subscore type, change in score for IFN-β-1a group, change in score for the placebo group. Stool frequency, -1.0 ± 1.2, -0.14 ± 0.89; rectal bleeding, -0.4 ± 1.1, -0.42 ± 0.79; physician global assessment -0.56 ± 1.2, -0.38 ± 0.92; proctosigmoidoscopy score -0.8 ± 1.1, 0.14 ± 0.69.

Madsen 2001 reported a statistically significant improvement from baseline in the Powell-Tuck Index in the IFN-α-2a group (P = 0.0002), and in the prednisolone enema group (P = 0.0009). The median score in the IFN-α-2a group at baseline was 9.0 (95% CI 7.2 to 10.4), and post treatment 1.5 (95% CI 1.2 to 4.5). For the prednisolone enema group, the baseline score was 8 (95% CI 6.5 to 9.0) and post treatment 3 (95% CI 1.9 to 5.6). There was no statistically significant difference in Powell-Tuck scores between the intervention groups.

Mannon 2010 and Pena-Rossi 2008 did not provide sufficient data for comparison.

3. Clinical, histological or endoscopic improvement
Mannon 2010 reported the percentage of participants with a clinical response, defined as a decrease from baseline in the total Mayo score of at least 3 points and at least 30%, accompanied by a decrease in the subscore for rectal bleeding of at least 1 point or an absolute subscore of 1 or less. 53% (33/62) in IFN-β-1a group and 44% (27/61) in placebo group achieved a clinical response. There was no statistically significant difference between the groups.

Musch 2005 reported the proportion of patients achieving a clinical response at the end of treatment, defined by a reduction of 6 or more CAI points after the 8 week treatment period. In the 3 MIU IFN-β-1a group, 18/32 (56%) achieved a clinical response, this was achieved by 11/30 (36%) in the 1 MIU group, and 10/29 (34%) in the placebo group. There was no statistically significant difference between the groups.

Nikolaus 2003 reported the percentage of patients who achieved a clinical response (distinct from remission), which was defined as a decrease of at least 3 points in the UCSS. This was achieved by 5/10 (50%) in the IFN-β-1a group compared to 1/7 (15%) in the placebo group (P = 0.14).

Pena-Rossi 2008 reported the percentage of patients who achieved a clinical response (≥3-point decrease in UCSS and PGA scores), which was achieved in 64.6% (42/65) of IFN-β-1a 44 µg group, 61.5% (40/65) of IFN-β-1a 66 µg group, and 60.9% (39/64) of placebo group.

Data from four studies were pooled in a meta-analysis. There was no statistically significant difference in clinical improvement remission rates between IFNs and placebo. Fifty-six per cent (149/264) of IFN treated patients improved clinically compared to 48% (77/161) of placebo patients (RR 1.16, 95% CI 0.96 to 1.40; P = 0.13). A GRADE analysis indicated that the quality of evidence supporting this outcome was moderate due to sparse data (See Summary of findings for the main comparison).

Tilg 2003 reported the proportion of patients achieving endoscopic remission (defined by an endoscopic activity score of < 4 at 12 weeks). In the 1.0 µg/kg PegIFN-α group, 20% achieved this secondary endpoint, compared to 18% in the 0.5 µg/kg group and 26% in the placebo group. The authors reported that there was no difference in endoscopic activity between the three treatment groups at any time point. Rectal histological activity was assessed in a subgroup of patients, however at the end of treatment at week 12 (day 85), the data were too limited to allow comparison.

Madsen 2001 utilised clinical and endoscopic activity scores to document disease but these scoring systems were semi-quantitative and not validated.

4. Improvement in quality of life

Madsen 2001 used the Inflammatory Bowel Disease Questionnaire (IBDQ) to assess quality of life (Guyatt 1989). The following results represent an ITT analysis in patients with disease extension exceeding the rectum. The IBDQ has not been validated in patients with proctitis alone. Of the 12 patients randomised to IFN-α-2a, the baseline median IBDQ (total) score was 166 (95% CI 145.3 to 181.4), and post treatment was 193.5 (95% CI 181.0 to 204.6). The difference in scores from baseline for the IFNs group was statistically significant (P = 0.002). In the prednisolone enema group, there was no statistically significant difference before and after treatment (P = 0.055). The baseline median IBDQ score in the prednisolone enema group was 181 (95% CI 165.3 to 197.2) and the post treatment score was 207 (95% CI 178.5 to 215.3). There was no statistically significant difference in IBDQ scores between the treatment groups.

Pena-Rossi 2008 reported IBDQ scores as a secondary endpoint. The IBDQ improved meaningfully (≥15-point improvement) in 41% (26/64) of patients in the placebo group compared to 48% (31/65) of the IFN-β-1a 44 µg group, and 44.6% (29/65) of the IFN-β-1a 66 µg group.

5. Adverse events

a. Adverse eventsThe most common adverse events experienced by patients were consistent with the known side effect profile of IFNs and included headaches, arthralgias, myalgias, fatigue, back pain, nausea, application site reactions, rigors, and fevers. The adverse event profile of the different isoforms of IFN appeared similar. It was not possible to meta-analyse these adverse events due to variability in reporting. For example, a large number of patients experienced adverse events in the Nikolaus 2003 study, 100% of patients experienced at least one adverse event and 97% of these events were graded as mild or moderate in severity. In the Musch 2005 trial, 68.1% of patients experienced adverse events. However adverse events were not reported according to treatment allocation. Tilg 2003 tabulated all adverse events but did not report them per patient. There were 13 adverse effects in the placebo group, 47 in the PegIFN 0.5 mg/kg group, and 45 in the PegIFN 1.0 mg/kg group. Madsen 2001 reported that adverse events only occurred in the IFNs group. A table of adverse events was provided on a time line, using a semi-quantitative scale. However, this does not allow one to determine the total number of patients suffering an adverse event and the tolerability of treatment was assessed by the patient rather than the physician. The largest number of adverse events was reported during week one, where 35 events were reported by an undisclosed number of patients in the IFN-a-2a group. The authors commented that the adverse events were generally mild to moderate with the most common being flu-like symptoms. Mannon 2010 reported that 84% (52/62) of the IFN-β-1a group experienced at least one adverse event compared to 57% (35/61) of placebo patients. A more detailed breakdown of the adverse events is reported on ClinicalTrials.gov. Pena-Rossi 2008 listed common (>10% of patients) and less common (<10% of patients) adverse events and tabulated data for some mild to moderate adverse effects (e.g. headache, fever, influenza-like symptoms, and application-site disorders) and serious adverse effects.

Serious adverse events were more clearly documented. Musch 2005 reported 7 serious adverse events in 5 patients; 1/32 (3.1%) in the 3 MIU IFN-β-1a group experienced chest pain while 4/29 (13.8%) in the placebo group experienced a variety of adverse events including worsening UC symptoms, infection, and a respiratory disorder. There were no serious adverse events documented in the 1 MIU IFN group. Tilg 2003 reported that 3/21 (14.3%) in the 1.0 µg/kg group and 3/19 (15.8%) in the 0.5 µg/kg group experienced serious adverse events. The three adverse events in the higher dose (1.0 µg/kg IFN) group included a disease flare, thrombosis of the brachiocephalic vein, and a grand mal seizure. All serious adverse events in the 0.5 µg/kg group were related to lack of efficacy, resulting in hospitalisation and intensification of treatment in the three patients. There were no serious adverse events in the placebo group. Mannon 2010 found 4 serious adverse events, one (1/62, 1.61%) with worsening of ulcerative colitis in the IFN-β-1a group, and three in the placebo group (3/61, 4.92%), of which, two patients experienced worsening of UC and one patients had a tibial fracture. Pena-Rossi 2008 reported five serious adverse events (one event in the placebo group and two in each of the IFN-β-1a groups), A pooled analysis of four studies showed no statistically significant difference in the proportion of patients who experienced a serious adverse event. Four per cent (12/294) of IFN patients had a serious adverse event compared to 5% (8/174) placebo patients (RR 0.74, 95% CI 0.13 to 4.14). A GRADE analysis indicated that the quality of evidence supporting this outcome was low due to very sparse data (See Summary of findings for the main comparison). A sensitivity analysis excluding an abstract publication did not change the results (RR 1.03, 95% 0.10 to 10.87).

b. Withdrawals (including those due to adverse events)

Eighteen per cent (16/91) of patients withdrew from the Musch 2005 study. Withdrawal was most common in the placebo group at 24% followed by 17% in the low dose IFNs group and 12% in the high dose IFNs group. Reasons for discontinuation included two withdrawals due to worsening health and one withdrawal due to intolerable adverse events. However, the authors did not report which study medication these patients received. Nikolaus 2003 reported a 29% (2/7) withdrawal rate amongst placebo treated patients, and a substantial 60% (6/10) non-completion rate amongst IFNs treated individuals. Both of the placebo patients who withdrew and four of six IFNs patients withdrew due to

progressive disease. One IFNs patient withdrew due to an adverse event (influenza like symptoms). There were no withdrawals due to adverse events in the placebo group. A high withdrawal rate was documented in the Tilg 2003 study. More than half (11/20 = 55.0%) of the placebo patients dropped out, compared to 48% (10/21) of the high dose IFNs group, and 32% (6/19) in the low dose IFNs group. Of these, one individual (1/20 = 5%) in the placebo group and 2 patients (2/21 = 10%) in the high dose IFNs group withdrew due to adverse events (fever in the placebo treated patients, and unspecified 'serious' adverse events in the IFNs patients), while the remaining individuals withdrew due to disease progression. In the Madsen 2001 study, there were 3/16 (19%) withdrawals in the IFNs group, two of these patients were noted to have abnormal liver biochemistry and one experienced progressive disease. No patients withdrew from the prednisolone enema group. Mannon 2010 reported that 8% (5/62) of IFNs patients withdrew due to adverse events, compared to 3% (2/61) of placebo patients. Details of the adverse events were not reported. In Pena-Rossi 2008 study, ten patients withdrew from the study because of adverse events - four in the IFN-β-1a 44 µg group, six in the IFN-β-1a 66 µg group, and none in the placebo group. In the IFN-β-1a 44 µg group, two patients withdrew because of constitutional symptoms and one withdrew due to severe thrombocytopenia, anemia and macrohematuria concurrent with an exacerbation of ulcerative colitis. In the IFN-β-1a 66 µg group, three patients withdrew because of constitutional symptoms and one patient discontinued because of worsening of UC.

The data were meta-analysed in two ways: firstly, comparing the overall withdrawal rate amongst type I IFNs against placebo; then comparing the withdrawal rate due to adverse events for the same groups. A fixed-effect model was used for the overall withdrawal rate as there was minimal heterogeneity (P = 0.40, I^2=2.0%). All five placebo-controlled studies were used for the analysis, with a total of 485 patients (Mannon 2010; Musch 2005; Nikolaus 2003; Pena-Rossi 2008; Tilg 2003). There was no statistically significant difference in withdrawal rates. Twenty-one per cent (64/304) of patients in the IFNs group withdrew before the end of the study compared to 22% (39/181) of placebo patients (RR 0.91, 95% CI 0.65 to 1.29; P = 0.90). A sensitivity analysis excluding an abstract publication did not change the results (RR 0.95, 95% CI 0.66 to 1.36). A fixed-effect model was used for withdrawal due to adverse events as there was no evidence of statistical heterogeneity (P = 0.62, I^2 = 0%). Four trials with a total of 394 patients were included in this comparison (Mannon 2010; Nikolaus 2003; Pena-Rossi 2008; Tilg 2003). There was a statistically significant difference in withdrawals due to adverse events. Seven per cent (18/242) of patients in the IFNs group withdrew due to adverse events compared to 2% (3/152) of placebo patients (RR 3.16, 95% CI 1.06 to 9.40; P = 0.03). A GRADE analysis indicated that the quality of evidence supporting this outcome was low due to very sparse data (See Summary of findings for the main comparison).

c. Colectomy

In the Musch 2005 study, two patients underwent colectomy, 1/32 (3.1%) in the 1 MIU IFN-β-1a group at 8 weeks, and 1/29 (3.4%) in the placebo group 3 weeks into the trial. Madsen 2001 reported 1/16 (6.2%) patients in the IFN-α-2a group required a colectomy. There were no colectomies in the prednisolone enema control group (Madsen 2001). Mannon 2010, Nikolaus 2003, Pena-Rossi 2008 and Tilg 2003 did not report this outcome.

d. Mortality

There were no deaths reported in any of the six included studies.

DISCUSSION

Moderate quality evidence suggests that type I IFNs are not effective for the treatment of patients with active UC (Madsen 2001; Mannon 2010; Musch 2005; Nikolaus 2003; Pena-Rossi 2008; Tilg 2003). Meta-analysis of placebo-controlled studies showed no difference in clinical remission or response rates. There was no difference in the time to remission nor a difference in endoscopic activity index scores following treatment with IFN compared to placebo. The only study to show a statistically significant improvement in a clinical activity index and quality of life compared treatment with IFN-α-2a to prednisolone enemas in patients with left-sided colitis (Madsen 2001). The response to therapy may reflect the limited extent of the disease in these patients. The results of this study should be interpreted with caution due to risk of bias (i.e. open-label design) and the small number of patients enrolled.

The most common adverse events related to IFN therapy included headaches, arthralgias, myalgias, fatigue, back pain, nausea, application site reactions, rigors, and fever. There did not appear to be a difference in the adverse event profile of the different isoforms of IFN. There were no differences in the proportion of patients experiencing 'serious' adverse events which were defined as those that required specific treatment, including but not limited to escalation of therapy for UC, hospitalisation, or any symptoms which led to withdrawal from the trial. Based on the pooled data from four trials, there was an increased rate of withdrawals due to adverse events in IFN treated patients.

The above data could not fully address concerns raised by a handful of case reports that suggest that IFN therapy may exacerbate UC (Tursi 2007; Watanabe 2006; Sprenger 2005; Mavrogiannis 2001). This would need to be studied by reviewing controlled clinical trials of type I IFNs in patients who are in remission.

The results of this review should be interpreted with caution due to methodological concerns with the included studies. Even with data from the new included studies Pena-Rossi 2008 and Mannon 2010, there were only 362 patients in the pooled analysis for clinical remission and only 425 patients in the pooled analysis for clinical response. These sample sizes likely have suboptimal power to detect a difference in treatment effect should one exist. A sample size calculation was performed based on the magnitude of the observed treatment effect in the pooled analysis. Using the pooled proportion of patients achieving remission in the IFN group of 36.0% (87/242) and 30.0% (36/120) in the placebo group, α=0.05, β=0.8, a case sample size of 1954 individuals would be required assuming a 1:1 case:control ratio for two independent populations of UC patients and no cross-overs. Furthermore, this estimate is conservative and does not take into account the potential yet substantial withdrawal rates demonstrated in the existing trials.

There was clinical heterogeneity with variability in the isoform of IFN used (α versus β) and even in the studies using the same preparation of IFN-β-1a, there were marked differences in the dose used and the overall duration of treatment. It is possible that there may be isoform dependent and dose dependent effects.

The use of different clinical indices for measuring UC activity limited comparison of treatment efficacy data. The use of standardised validated clinical activity indices should be emphasised. The use

of the same endoscopic activity index permitted comparisons. However, the length of treatment and follow-up may have been insufficient to allow for maximal endoscopic response.

Based on the existing literature, the current evidence does not support the use of type I IFNs for induction of remission in patients with UC. Furthermore, there are concerns regarding the tolerability of this class of treatment.

AUTHORS' CONCLUSIONS

Implications for practice

Moderate quality evidence suggests that type I IFNs are not effective for induction of remission in UC. Furthermore, there are concerns regarding the tolerability of this class of treatment.

Implications for research

Several well-designed studies that were included in this review, did not demonstrate any benefit for type I IFNs therapy in patients with ulcerative colitis. Further research is unlikely to yield any drastically different results.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Madsen 2001

Methods	Open-label, randomised controlled trial
Participants	32 adult patients with active left-sided UC Group 1: n=16, M:F = 8:8, median age = 47 yrs (19-73), median disease duration 9.5 yrs (1-25), median Powell-Tuck Index score = 9 (5-16) Group 2: n=16, M:F = 11:5, median age = 49 yrs (29-68), median disease duration 3.5 yrs (0-34), median Powell-Tuck Index score = 8 (4-12)
Interventions	Group 1: IFN-a-2a therapy by SC injection t.i.w. for a total duration of 12 weeks. 9 MIU t.i.w. for week 1, 6 MIU t.i.w. for week 2, and 3 MIU t.i.w. from weeks 3-12 inclusive Group 2: Prednisolone enemas 100mL (25mg) daily for 30 days
Outcomes	Clinical, endoscopic and histological assessment of disease activity Quality of life assessment Tolerability of treatment
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The allocation schedule using random numbers was generated using a computer program
Allocation concealment (selection bias)	Low risk	Each 'treatment' was consecutively numbered on concealed envelopes, which were only opened after the patient had given informed consent to participate.
Blinding (performance bias and detection bias) All outcomes	High risk	The study was an open-label trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were accounted for 3/16 (18.8%) patients withdrew from IFN -a-2A group and 0/16 (0%) withdrew from the prednisolone enema group
Selective reporting (reporting bias)	Low risk	All outcomes were reported
Other bias	Low risk	No other issues were found

Mannon 2010

Methods	Double-blind, multicenter, randomised, placebo-controlled trial (Biogen Trial)
Participants	123 patients (18-65 year old) with moderate to severe UC (modified Mayo Score 6-13) Group 1: n=62, M:F = 43:19, median age = 41.1 yrs (21-64); Group 2: n=61, M:F = 35:26, median age = 41.0 yrs (20-65)
Interventions	Group 1: IFNβ-1a 30 µg IM twice a week for 12 weeks Group 2: placebo IM twice per week for 12 weeks
Outcomes	Primary endpoint: clinical response at week 8, defined as a decrease from baseline in the total Mayo score of at least 3 points and at least 30%, accompanied by a decrease in the subscore for rectal bleeding of at least 1 point or absolute subscore of 0 or 1 Secondary endpoints: safety and tolerability of IFNb and the percentage of subjects with a decrease in the Short Clinical Activity Index (SCCAI) score of ≥3 points at week 8
Notes	It is a conference abstract publication, efforts to locate the full journal article in the literature and to contact the trial lead author were unsuccessful

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not described in the publication
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind (subject, caregiver) - based on information published on clinicaltrials.gov; trial ID: NCT00616434
Incomplete outcome data (attrition bias) All outcomes	Low risk	All 123 enrolled patients were included in the intention to treat (ITT) population, 61 in placebo and 62 in IFNβ. 6/62 (9.68%) patients in the IFNβ-1a 30 µg treatment group and 8/61 (13.1%) patients in the placebo group did not complete the study
Selective reporting (reporting bias)	Low risk	Pre-defined outcomes were reported
Other bias	Low risk	No other issues were identified

Musch 2005

Methods	Randomised, double-blind, placebo-controlled, multicenter trial
Participants	91 adult patients with active UC defined by a Rachmilewitz CAI score of at least 8 points Group 1: n=32, M:F = 21:11, median age = 38.0 yrs, median disease duration 7.5 yrs, median Rachmilewitz CAI score = 10, mean endoscopic index score = 10 Group 2: n=30, M:F = 18:12, median age = 34.5 yrs, median disease duration 6.7 yrs, median Rachmilewitz CAI score = 10, mean endoscopic index score = 9

Musch 2005 *(Continued)*

	Group 3: n=29, M:F = 15:14, median age = 38.0 yrs, median disease duration 3.2 yrs, median Rachmilewitz CAI score = 10, median endoscopic index score = 9
Interventions	Group 1: 3 MIU IFN-β-1a by SC injection t.i.w Group 2: 1 MIU by SC injection IFN-β-1a t.i.w Group 3: placebo injections Duration of treatment 8 weeks
Outcomes	Primary outcome was response rate at the end of treatment. Response was defined as reduction of 6 or more CAI points at week 8 compared with baseline Secondary endpoints: 1. Number of patients with complete response - reduction of CAI to 4 points of less after 8 weeks of treatment; 2. Time until response; 3. Reduction of CAI after 4 and 8 weeks; 4. Reduction of the endoscopic index after 8 weeks; 5. Number of patients receiving colectomy; 6. Reduction of steroid dose
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Patients were assigned by a centralised randomisation schedule
Blinding (performance bias and detection bias) All outcomes	Low risk	The study was double-blind in design Supervision of the clinical trial was performed by a steering committee of investigators who were blinded from the results throughout the trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	4/32 patients in 3 MIU group, 5/30 patients in 1 MIU group, 7/29 patients in placebo group dropped out during treatment
Selective reporting (reporting bias)	Low risk	All pre-defined outcomes were reported
Other bias	Low risk	No other issues were identified

Nikolaus 2003

Methods	Randomised, double blind, intra-individual, dose escalating study
Participants	17 adult patients with moderately active UC defined by a UCSS score of 6-10, with a proctosigmoidoscopy score of 2 Group 1: n=10, M:F = 4:6, median age = 42.2 yrs (32-68), median disease duration 9.8 yrs (2.6-14.2), median UCSS score = 9 (7-10), left sided colitis n=5 Group 2: n=7, M:F = 2:5, median age = 35 yrs (30-63), median disease duration 9.0 yrs (2.6-40.3), median UCSS score = 9 (7-12), left sided colitis n=5
Interventions	Group 1: IFN-β-1a by SC injection t.i.w. at variable dose for a variable duration of treatment. Started at 22mcg (t.i.w.)

Nikolaus 2003 *(Continued)*

	Improvement was defined as a decrease of 1 point in the combined score of UCSS symptoms and PGA. If no improvement was observed after six injections, dose increased to 44 mcg t.i.w., and increased further to 88 mcg t.i.w., if no improvement was observed after six injections at 44 mcg dose If improvement was observed after six injections at any dose, the patient entered a maintenance treatment phase of 6-12 injections at that dose If no improvement was observed after six injections at 88 mcg, or if remission occurred at any point, treatment was stopped Group 2: placebo The maximum duration of treatment was eight weeks, and the minimum duration was four weeks
Outcomes	Efficacy end points were treatment response and remission Treatment response was defined as a decrease of at least 3 points from baseline in the UCSS symptoms score and PGA (without the proctosigmoidoscopic score) during treatment Remission was defined as complete resolution of clinical symptoms (all clinical UCSS subscores equal to 0), with a proctosigmoidoscopy score of 0 or 1 at any time during treatment Secondary end points included overall treatment and end point responses, and clinical end point responses Safety data were also collected
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Eligible patients were randomised by means of a computer generated list Randomisation was stratified by centre with block size of three (2:1 IFN-β-1a: placebo)
Allocation concealment (selection bias)	Unclear risk	Details were not provided in the published report
Blinding (performance bias and detection bias) All outcomes	Unclear risk	The trial is double blind in design but the methods used for blinding were not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	All enrolled patients (n=18) were accounted for. One patients was excluded a priori (before the code was broken) from the analysis, because of misallocation of study drug. 6/10 (60%) of IFN-β-1a group and 2/7 (28.6%) of control group stopped the treatment early
Selective reporting (reporting bias)	Low risk	All outcomes were reported
Other bias	Low risk	No other issues were identified

Pena-Rossi 2008

Methods	Multicentre, double-blind, randomised placebo-controlled trial (Serono Trial)
Participants	194 adult patients with diagnosed moderately active UC

Pena-Rossi 2008 *(Continued)*

	Group 1: n = 65, M:F = 37:28, mean age = 39.9 yrs (SD=14.0), mean disease duration 7.2 yrs (SD=6.5), mean UCSS score = 7.7 (SD=1.2), length of colonic involvement = 53.5 (SD=28.0); Group 2: n = 65, M:F = 30:35, mean age = 40.7 yrs (SD=13.3), mean disease duration 4.9 yrs (SD=5.1), median UCSS score = 7.8 (SD=1.2), length of colonic involvement = 50.2 (SD=27.5); Group 3: n = 64, M:F = 31:33, mean age = 41.1 yrs (SD=12.6), mean disease duration 5.6 yrs (SD=5.5), median UCSS score = 7.9 (SD=1.1), length of colonic involvement = 52.4 (SD=24.2)
Interventions	Group 1: 44 µg IFN-β-1a Group 2: 66 µg IFN-β-1a Group 3: matching placebo All study drugs were given sc t.i.w. for 8 weeks with 4-week follow-up period
Outcomes	Primary outcome: identify the best dose of IFN-β-1a for the induction of ECR and examine the safety profile of this dose Secondary outcomes: 1. investigate the safety and tolerability of IFN-β-1a; 2. establish the dose needed to enable clinical response and a change in disease severity; 3. estimate disease-related quality of life on IBDQ; 4. assess changes in biological markers of inflammation. Safety and antibodies to IFN-β were also evaluated
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomised centrally using stochastic minimization, which considered the overall balance, centre, region and current use of maintenance therapy as minimization factors
Allocation concealment (selection bias)	Low risk	Following central randomisation, each patient was assigned a treatment kit number corresponding to a blinded treatment kit containing sufficient medication for the 8 weeks of treatment
Blinding (performance bias and detection bias) All outcomes	Low risk	The solutions of study drug were physically indistinguishable from one another, prepared and administered using the same technique for all patients and the labelling and packaging were designed so as to preserve the blinded nature of the study
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised patients were accounted for. 13/65 (20.0%) patients in 66 µg IFN-β-1a treatment group, 14/65 (21.5%) patient in 44 µg IFN-β-1a treatment group, and 11/64 (17.2%) patients in control group withdrew from the study
Selective reporting (reporting bias)	Low risk	Clinically relevant outcomes were reported
Other bias	Low risk	No other issues were identified

Tilg 2003

Methods	Multicentre, double-blind, randomised, placebo controlled trial

Tilg 2003 *(Continued)*

Participants	60 adults with UC Group 1: n=19, M:F = 9:10, mean age = 36.90 yrs (13.19), mean disease duration 107.30 mths (64.11), mean Rachmilewitz CAI score = 8.0 (2.1), mean endoscopic index score = 8.3 (2.1) Group 2: n=21, M:F = 11:10, mean age = 40.90 yrs (10.84), mean disease duration 106.88 mths (71.83), mean Rachmilewitz CAI score = 7.9 (2.1), mean endoscopic index score = 8.3 (2.0), left sided colitis n=12 Group 3: n=20, M:F = 10:10, mean age = 46.95 yrs (14.43), mean disease duration 142.90 mths (132.01), mean Rachmilewitz CAI score = 8.7 (2.5), mean endoscopic index score = 8.2 (2.3), left sided colitis n=14
Interventions	Group 1: PegIFN 0.5 µg/kg Group 2: PegIFN 1.0 µg/kg Group 3: placebo All therapies were administered by subcutaneous injection once a week, for a period of 12 weeks
Outcomes	The primary outcome was safety Secondary outcomes were disease remission, (which was defined as a Rachmilewitz CAI score of <=4), endoscopic remission (which was defined as a score of <4), and histological activity (graded on a scale from 0 to 3) Outcomes were measured at week 12 Changes in serological inflammatory indices were also recorded
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	At entry, all patients were randomised to receive placebo, PegIFN 0.5 µg/kg, or PegIFN 1.0 µg/kg body weight
Allocation concealment (selection bias)	Unclear risk	Details were not provided in the published report
Blinding (performance bias and detection bias) All outcomes	Unclear risk	The study was double blind in design
Incomplete outcome data (attrition bias) All outcomes	Low risk	All enrolled patients were accounted for. 6/19 (31.6%) in the PegIFN-α 0.5 µg/kg group, 10/21 (47.6%) in the PegIFN-α 1.0 µg/kg group, and 11/20 (55.0%) in the control group withdrew from the study
Selective reporting (reporting bias)	Low risk	All outcomes were reported
Other bias	Low risk	No other issues were identified

CAI: Clinical Activity Index
Mean (standard deviation in brackets)
Median (range in brackets)
MIU: million international units
mths: months
PGA: Physician's global assessment
SC: subcutaneous
t.i.w.: three times a week
UCSS: Ulcerative colitis scoring system
yrs: years

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bargiggia 2005	Single centre case control study of 513 IBD patients with mildly active disease or disease in remission 21 IBD patients (11 with UC) had detectable hepatitis C antibodies, and were subsequently treated with IFN-alpha 6 MIU t.i.w. for 12 months Primary endpoint was related to treatment of hepatitis C (biochemical and virological response)
Hadziselimovic 1995	Single centre prospective cohort study of 8 children and adolescents with IBD treated with IFN-alpha-2a t.i.w. for variable treatment periods No comparison group is provided Only 2 of the 8 patients had UC
Maev 2002	Randomised controlled trial of 113 patients with UC The interventions were orally administered IFN inducers (amixin or cycloferon) rather than IFN itself
Mannon 2011	Open label pilot study enrolled 18 UC patients (SCCAI of 6) to receive interferon-β-1a 30 µg IM per week for 12 weeks. with 24-week follow-up Main outcomes included clinical response (SCCAI score drop ≥3 point for at least two consecutive visits), and effects on cytokine production No control group (NIAID trial)
Musch 2002	Open-label pilot study of IFN-beta in 25 adult patients Patients were administered 0.5 MIU human natural IFN-beta i.v. (n = 18) or 1 MIU recombinant IFN-beta-1a s.c. (n = 7) daily with the goal of induction of remission Subsequent maintenance treatment was provided at the same dose, t.i.w. for 52.0 +/- 78.8 weeks (range 4-336 weeks). No control group
Musch 2007	Non-randomised open-label study of IFN-beta in 46 adult patients Patients were administered 0.5 MIU human natural IFN-beta i.v. (n = 18) or 1 MIU recombinant IFN-beta-1a s.c. (n = 28) daily for 8 weeks Patients who achieved complete remission (CAI ≤ 4) during induction period received maintenance therapy at the same dose three times a week Remission, maintenance of remissions and safety were evaluated No control group
Sümer 1995	Open-label study of IFN-alpha-2a in 28 adult patients Patients received 6 to 12 months of IFN therapy by subcutaneous injection three times a week No control group

IBD: Inflammatory bowel disease
MIU: Million international units
t.i.w.: Three times a week
i.v.: Intravenous
s.c.: Subcutaneous

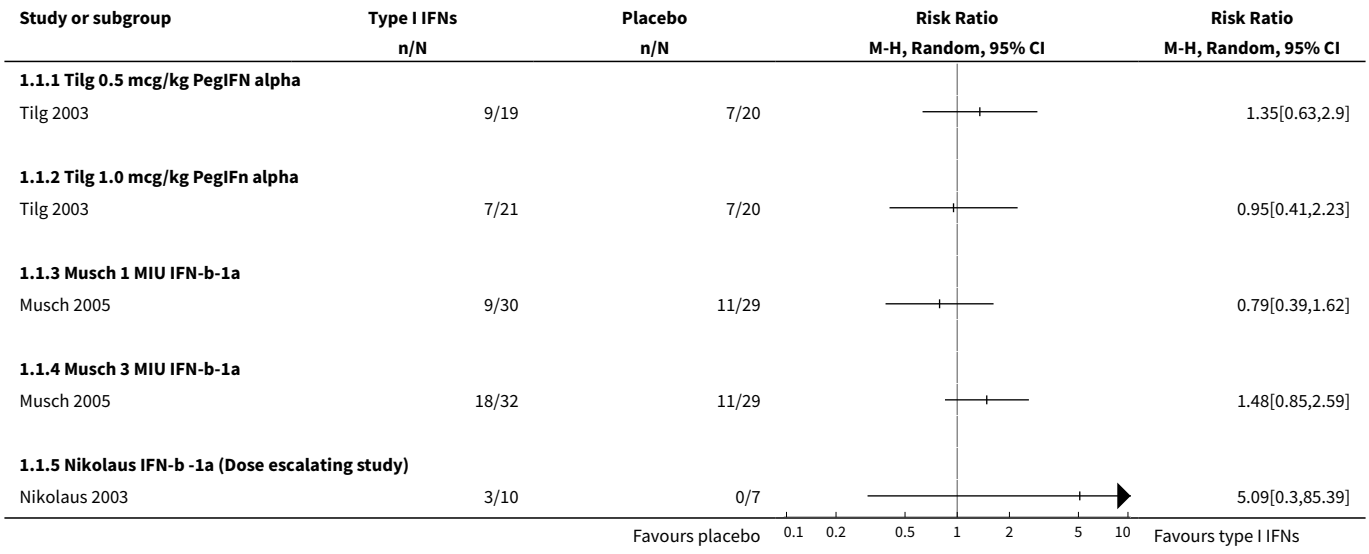
DATA AND ANALYSES

Comparison 1. Type I Interferons versus placebo

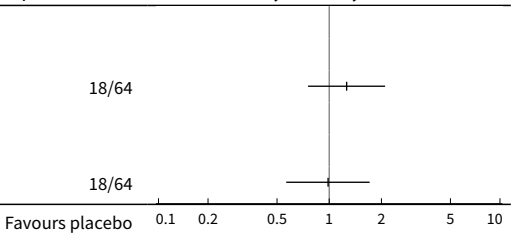
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Remission (non pooled data)	4		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Tilg 0.5 mcg/kg PegIFN alpha	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Tilg 1.0 mcg/kg PegIFn alpha	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 Musch 1 MIU IFN-b-1a	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.4 Musch 3 MIU IFN-b-1a	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.5 Nikolaus IFN-b -1a (Dose escalating study)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.6 Pena-Rossi 44 mcg IFN-b-1a	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.7 Pena-Rossi 66 mcg IFN-b-1a	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Remission (pooled data)	4	362	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.84, 1.58]
3 Remission - sensitivity analysis (IFN beta-isoform)	3	302	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.84, 1.69]
4 Remission - sensitivity analysis (IFN alpha-isoform)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 Time to remission	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 1 MIU IFN b-1-a	1	59	Mean Difference (IV, Fixed, 95% CI)	-1.90 [-11.22, 7.42]
5.2 3 MIU IFN b-1-a	1	61	Mean Difference (IV, Fixed, 95% CI)	-4.10 [-12.71, 4.51]
6 Clinical improvement	4	425	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.96, 1.40]
7 Clinical improvement - sensitivity analysis published manuscripts only (fixed-effect model)	3	302	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.91, 1.43]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 Endoscopic activity index score	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
8.1 1 MIU IFN b-1-a	1	59	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-2.22, 1.62]
8.2 3 MIU IFN b-1-a	1	61	Mean Difference (IV, Fixed, 95% CI)	0.80 [-0.91, 2.51]
8.3 0.5 mcg/kg IFN b-1-a	1	39	Mean Difference (IV, Fixed, 95% CI)	-0.80 [-2.94, 1.34]
8.4 1.0 mcg/kg IFN b-1-a	1	41	Mean Difference (IV, Fixed, 95% CI)	-0.40 [-2.14, 1.34]
9 Serious adverse events	4	468	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.13, 4.14]
10 Serious adverse events - sensitivity analysis published manuscripts only (random-effects model)	3	345	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.10, 10.87]
11 Overall withdrawals	5	485	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.65, 1.29]
12 Overall withdrawals - sensitivity analysis published manuscripts only (fixed-effect model)	4	362	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.66, 1.36]
13 Withdrawals due to adverse events	4	394	Risk Ratio (M-H, Fixed, 95% CI)	3.16 [1.06, 9.40]

Analysis 1.1. Comparison 1 Type I Interferons versus placebo, Outcome 1 Remission (non pooled data).

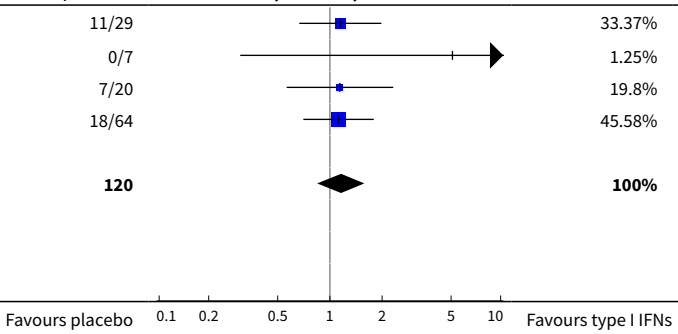


Study or subgroup	Type I IFNs n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
1.1.6 Pena-Rossi 44 mcg IFN-b-1a				
Pena-Rossi 2008	23/65	18/64		1.26[0.75,2.1]
1.1.7 Pena-Rossi 66 mcg IFN-b-1a				
Pena-Rossi 2008	18/65	18/64		0.98[0.57,1.71]



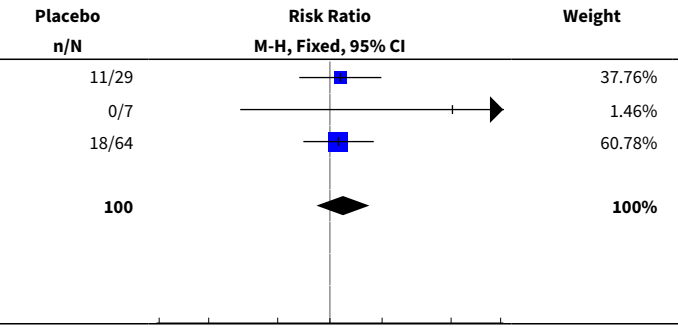
Analysis 1.2. Comparison 1 Type I Interferons versus placebo, Outcome 2 Remission (pooled data).

Study or subgroup	Type I IFNs n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Musch 2005	27/62	11/29		33.37%	1.15[0.67,1.98]
Nikolaus 2003	3/10	0/7		1.25%	5.09[0.3,85.39]
Tilg 2003	16/40	7/20		19.8%	1.14[0.56,2.32]
Pena-Rossi 2008	41/130	18/64		45.58%	1.12[0.7,1.79]
Total (95% CI)	**242**	**120**		**100%**	**1.16[0.84,1.58]**
Total events: 87 (Type I IFNs), 36 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.1, df=3(P=0.78); I^2=0%					
Test for overall effect: Z=0.9(P=0.37)					



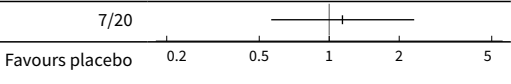
Analysis 1.3. Comparison 1 Type I Interferons versus placebo, Outcome 3 Remission - sensitivity analysis (IFN beta-isoform).

Study or subgroup	Type I IFNs n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Musch 2005	27/62	11/29		37.76%	1.15[0.67,1.98]
Nikolaus 2003	3/10	0/7		1.46%	5.09[0.3,85.39]
Pena-Rossi 2008	41/130	18/64		60.78%	1.12[0.7,1.79]
Total (95% CI)	**202**	**100**		**100%**	**1.19[0.84,1.69]**
Total events: 71 (Type I IFNs), 29 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.1, df=2(P=0.58); I^2=0%					
Test for overall effect: Z=0.97(P=0.33)					



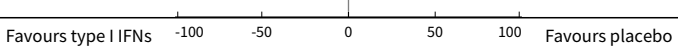
Analysis 1.4. Comparison 1 Type I Interferons versus placebo, Outcome 4 Remission - sensitivity analysis (IFN alpha-isoform).

Study or subgroup	Type I IFNs n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Tilg 2003	16/40	7/20		1.14[0.56,2.32]



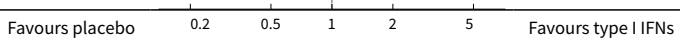
Analysis 1.5. Comparison 1 Type I Interferons versus placebo, Outcome 5 Time to remission.

Study or subgroup	Type I IFNs N	Type I IFNs Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.5.1 1 MIU IFN b-1-a							
Musch 2005	30	34.3 (20)	29	36.2 (16.4)		100%	-1.9[-11.22,7.42]
Subtotal ***	**30**		**29**			**100%**	**-1.9[-11.22,7.42]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.4(P=0.69)							
1.5.2 3 MIU IFN b-1-a							
Musch 2005	32	32.1 (17.9)	29	36.2 (16.4)		100%	-4.1[-12.71,4.51]
Subtotal ***	**32**		**29**			**100%**	**-4.1[-12.71,4.51]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.93(P=0.35)							
Test for subgroup differences: Chi^2=0.12, df=1 (P=0.73), I^2=0%							



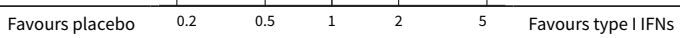
Analysis 1.6. Comparison 1 Type I Interferons versus placebo, Outcome 6 Clinical improvement.

Study or subgroup	Type I IFNs n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Mannon 2010	33/62	27/61		28.87%	1.2[0.83,1.73]
Musch 2005	29/62	10/29		14.45%	1.36[0.77,2.39]
Nikolaus 2003	5/10	1/7		1.25%	3.5[0.51,23.81]
Pena-Rossi 2008	82/130	39/64		55.43%	1.04[0.82,1.31]
Total (95% CI)	**264**	**161**		**100%**	**1.16[0.96,1.4]**
Total events: 149 (Type I IFNs), 77 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=2.5, df=3(P=0.48); I^2=0%					
Test for overall effect: Z=1.53(P=0.13)					

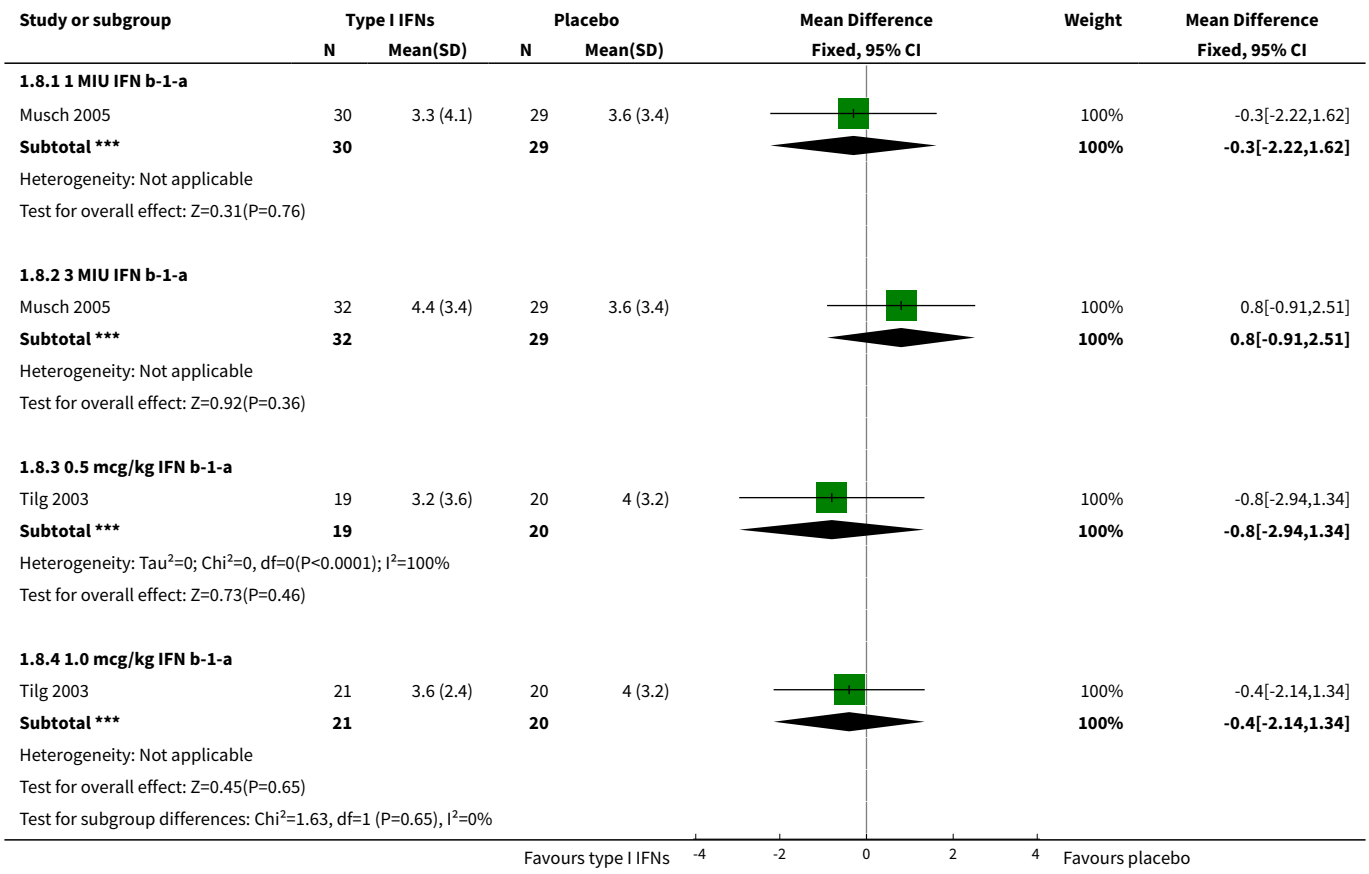


Analysis 1.7. Comparison 1 Type I Interferons versus placebo, Outcome 7 Clinical improvement - sensitivity analysis published manuscripts only (fixed-effect model).

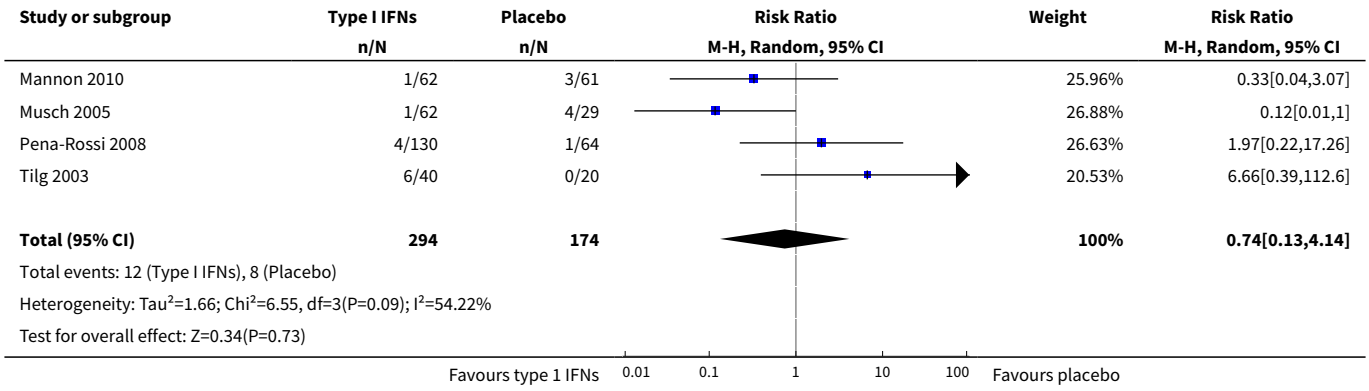
Study or subgroup	Type I IFNs n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Musch 2005	29/62	10/29		20.32%	1.36[0.77,2.39]
Nikolaus 2003	5/10	1/7		1.75%	3.5[0.51,23.81]
Pena-Rossi 2008	82/130	39/64		77.93%	1.04[0.82,1.31]
Total (95% CI)	**202**	**100**		**100%**	**1.14[0.91,1.43]**
Total events: 116 (Type I IFNs), 50 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=2.34, df=2(P=0.31); I^2=14.5%					
Test for overall effect: Z=1.18(P=0.24)					



Analysis 1.8. Comparison 1 Type I Interferons versus placebo, Outcome 8 Endoscopic activity index score.



Analysis 1.9. Comparison 1 Type I Interferons versus placebo, Outcome 9 Serious adverse events.



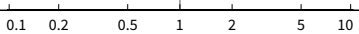
Analysis 1.10. Comparison 1 Type I Interferons versus placebo, Outcome 10 Serious adverse events - sensitivity analysis published manuscripts only (random-effects model).

Study or subgroup	Type I INFs n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Musch 2005	1/62	4/29		35.52%	0.12[0.01,1]
Pena-Rossi 2008	4/130	1/64		35.29%	1.97[0.22,17.26]
Tilg 2003	6/40	0/20		29.19%	6.66[0.39,112.6]
Total (95% CI)	**232**	**113**		**100%**	**1.03[0.1,10.87]**
Total events: 11 (Type I INFs), 5 (Placebo)					
Heterogeneity: Tau^2=2.87; Chi^2=5.96, df=2(P=0.05); I^2=66.46%					
Test for overall effect: Z=0.03(P=0.98)					

Favours type I IFNs — Favours placebo

Analysis 1.11. Comparison 1 Type I Interferons versus placebo, Outcome 11 Overall withdrawals.

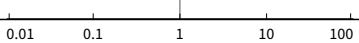
Study or subgroup	Type I INFs n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Mannon 2010	6/62	8/61		16.34%	0.74[0.27,2]
Musch 2005	9/62	7/29		19.32%	0.6[0.25,1.46]
Nikolaus 2003	6/10	2/7		4.77%	2.1[0.59,7.52]
Pena-Rossi 2008	27/130	11/64		29.86%	1.21[0.64,2.28]
Tilg 2003	16/40	11/20		29.71%	0.73[0.42,1.26]
Total (95% CI)	**304**	**181**		**100%**	**0.91[0.65,1.29]**
Total events: 64 (Type I INFs), 39 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=4.08, df=4(P=0.4); I^2=2.01%					
Test for overall effect: Z=0.51(P=0.61)					



Favours type I INFs — Favours placebo

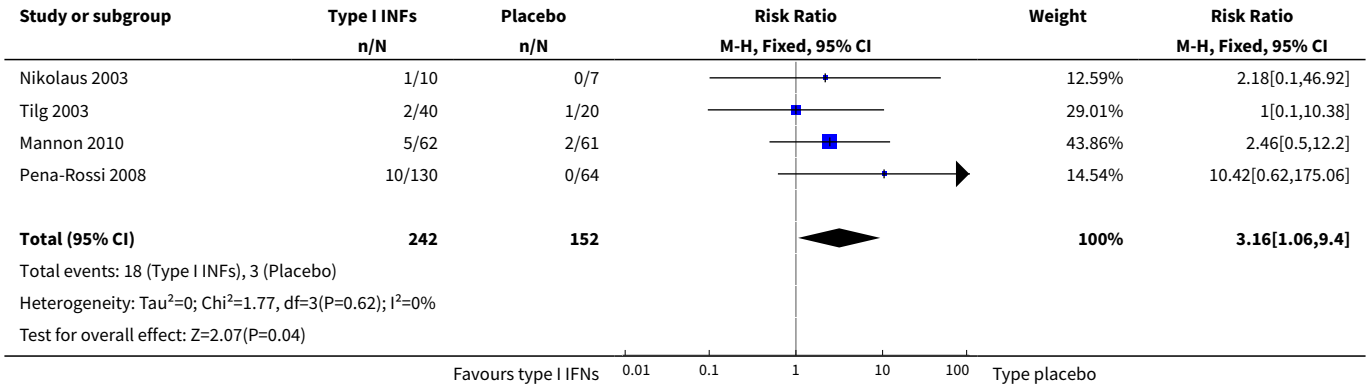
Analysis 1.12. Comparison 1 Type I Interferons versus placebo, Outcome 12 Overall withdrawals - sensitivity analysis published manuscripts only (fixed-effect model).

Study or subgroup	Type I INFs n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Musch 2005	9/62	7/29		23.1%	0.6[0.25,1.46]
Nikolaus 2003	6/10	2/7		5.7%	2.1[0.59,7.52]
Pena-Rossi 2008	27/130	11/64		35.7%	1.21[0.64,2.28]
Tilg 2003	16/40	11/20		35.51%	0.73[0.42,1.26]
Total (95% CI)	**242**	**120**		**100%**	**0.95[0.66,1.36]**
Total events: 58 (Type I INFs), 31 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=3.97, df=3(P=0.26); I^2=24.44%					
Test for overall effect: Z=0.29(P=0.77)					



Favours type I IFNs — Favours placebo

Analysis 1.13. Comparison 1 Type I Interferons versus placebo, Outcome 13 Withdrawals due to adverse events.



ADDITIONAL TABLES

Table 1. Overall withdrawals (%); Placebo versus Type I IFNs

Study	Placebo	IFN Total	High dose IFN	Low dose IFN
Mannon 2010	13.1	9.68		
Musch 2005	24.1	14.5	12.5	16.7
Nikolaus 2003	28.6	60.0		
Pena-Rossi 2008	17.2	20.8	20.0	21.5
Tilg 2003	55.0	40.0	47.6	31.6

Table 2. Comparative IFN-b-1a Doses used in the Nikolaus, Musch and Pena-Rossi Trials

Dose of IFN-b-1a	Remission (n)	Total (N)	%
Nikolaus 2003: Median treatment duration 35.5 days			
88mcg t.i.w	2	4	50
44mcg t.i.w.	1	2	50
22mcg t.i.w.	0	4	0
TOTAL (Nikolaus)	3	10	30
Musch 2005: Treatment duration: 56 days			
3MIU t.i.w. = 11mcg t.i.w.	18	32	56
1MIU t.i.w. = 3.7mcg t.i.w.	9	30	30
TOTAL (Musch)	27	62	43.5

Table 2. Comparative IFN-b-1a Doses used in the Nikolaus, Musch and Pena-Rossi Trials *(Continued)*

[12MIU = 44mcg] Reference: Antonetti 2002

Pena-Rossi 2008: Treatment duration: 56 days			
66mcg t.i.w.	18	65	27.7
44mcg t.i.w.	23	65	35.4
TOTAL (Pena-Rossi)	41	130	31.5

APPENDICES

Appendix 1. Search strategies

MEDLINE search strategy

1. random$.tw.
2. factorial$.tw.
3. (crossover$ or cross over$ or cross-over$).tw.
4. placebo$.tw.
5. single blind.mp.
6. double blind.mp.
7. triple blind.mp.
8. (singl$ adj blind$).tw.
9. (double$ adj blind$).tw.
10. (tripl$ adj blind$).tw.
11. assign$.tw.
12. allocat$.tw.
13. crossover procedure/
14. double blind procedure/
15. single blind procedure/
16. triple blind procedure/
17. randomized controlled trial/
18. or/1-17
19. (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)
20. 18 not 19
21. Colitis, Ulcerative/ or Inflammatory Bowel Diseases/
22. exp Interferons or interferons (nm) or interferon: .mp.
23. 21 and 22

24. 20 and 23

EMBASE search strategy

1. random$.tw.

2. factorial$.tw.

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

4. placebo$.tw.

5. single blind.mp.

6. double blind.mp.

7. triple blind.mp.

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

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

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

11. assign$.tw.

12. allocat$.tw.

13. crossover procedure/

14. double blind procedure/

15. single blind procedure/

16. triple blind procedure/

17. randomized controlled trial/

18. or/1-17

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

20. 18 not 19

21. Ulcerative Colitis/ or (inflammatory adj5 bowel).ti,ab.

22. exp INTERFERON/ or interferon:.mp. or 76543-88-9.rn.

23. 21 and 22

24. 20 and 23

Cochrane Central Library search strategy

1. Ulcerative Colitis OR Inflammatory Bowel Disease

2. "Interferon" or "76543-88-9" or "type 1 IFN" or "IFN" or "Interleukin 28A" or "Interleukin 29" or "Interleukin 6"

3. #1 and #2

SR-IBD search strategy

Interferon AND ulcerative colitis

WHAT'S NEW

Date	Event	Description
8 August 2014	New search has been performed	New literature search was performed on August 8, 2014.
8 August 2014	New citation required but conclusions have not changed	Substantively updated review with new authors

HISTORY

Protocol first published: Issue 4, 2007
Review first published: Issue 3, 2008

Date	Event	Description
7 July 2009	Amended	Contact details updated
28 April 2008	Amended	Converted to new review format.
25 March 2008	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

The following authors participated in the updated review:

YW was responsible for the updating the literature search, selecting and reviewing the studies, performing the analyses and updating the manuscript.
JKM was responsible for the updating the literature search, selecting and reviewing the studies, performing the analyses and updating the manuscript.
EIB provided IBD expert opinion and reviewed the manuscript.
AMG provided IBD expert opinion and reviewed the manuscript.
AHS provided IBD expert opinion and reviewed the manuscript.
RP provided IBD expert opinion and reviewed the manuscript.
CHS was responsible for updating the literature search, performing the analyses, and updating the manuscript.

The following authors were involved in the original review:

CHS was responsible for the literature search, selecting and reviewing the studies, performing the analyses and writing the manuscript.
EIB acted as co-reviewer of the studies, was involved in the analyses and reviewed the manuscript.
AHS provided methodological expertise, IBD expert opinion and reviewed the manuscript.
AMG provided IBD expert opinion and reviewed the manuscript.

DECLARATIONS OF INTEREST

YW: None known.

JKM: None known.

EIB: None known.

AMG: Anne Marie Griffiths has received fee(s) from Johnson and Johnson for Board membership; fee(s) from Janssen, Abbvie and Ferring for consultancy; grants or grants pending from Johnson and Johnson and Abbive; lecture fee(s) from: Abbvie and Merck and payment for development of educational presentations from Ferring. All of these activities are outside the submitted work.

AHS: Hillary Steinhart has received fee(s) from Janssen, Abbvie, Shire, Pendopharm, Pfizer, and Takeda for consultancy; and lecture fee(s) from: Janssen, Abbvie, Shire, Warner Chilcott, Aptalis, and Takeda. His institution has received grants or grants pending from Janssen, Abbvie, Pfizer, Amgen, Takeda and Actavis. All of these activities are outside the submitted work. AHS was a collaborator on the paper

"Interferon β-1a in ulcerative colitis: a placebo controlled, randomised, dose escalating study." (Gut 2003;52:1286-1290) and Mount Sinai Hospital, Toronto, Ontario, CANADA was one of the participating study centres in the clinical trial.

RP: Remo Panaccione has received fee(s) from Abbott, Abbvie, Allergan, Actavis, Biogen Idec, Celgene, Eisai, Elan, Ferring, Genentech, Janssen, Merck, Nestle, Osiris, Prometheus, Qu Biologics, Roche, Salix, Takeda, Teva, Vertex, Warner Chilcott for consultancy; grants or grants pending from Abbvie, Janssen; lecture fee(s) from: Abbott, Abbvie, Ferring, Janssen, Shire, Takeda; and payment for development of educational presentations from Abbvie, Janssen, Takeda, Shire. All of these activities are outside the submitted work. RP was a collaborator on the paper "Interferon-ß-1a in active moderate to severe ulcerative colitis: Efficacy and safety from a phase IIa multicenter study." (American Journal of Gastroenterology 2010;105:S446).

CHS: Cynthia Seow has served as a consultant and on advisory boards for Janssen Pharmaceuticals, Abbvie, Takeda, Shire and Actavis. She previously held a grant through Janssen Pharmaceuticals. Dr. Seow has also provided lectures for Janssen Pharmaceuticals and Warner Chilcott. All of these activities are outside the submitted work.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Inflammatory Agents [therapeutic use]; Colitis, Ulcerative [*drug therapy]; Enema [methods]; Induction Chemotherapy; Interferon Type I [*therapeutic use]; Interferon-alpha [therapeutic use]; Interferon-beta [therapeutic use]; Prednisolone [therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Humans