Rituximab as maintenance therapy for patients with follicular lymphoma (Review)

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TABLE OF CONTENTS

HEADER . . . 1
ABSTRACT . . . 1
PLAIN LANGUAGE SUMMARY . . . 2
BACKGROUND . . . 2
OBJECTIVES . . . 3
METHODS . . . 3
RESULTS . . . 5
Figure 1. . . . 7
Figure 2. . . . 7
Figure 3. . . . 8
Figure 4. . . . 9
Figure 5. . . . 10
Figure 6. . . . 11
Figure 7. . . . 12
Figure 8. . . . 13
Figure 9. . . . 14
Figure 10. . . . 15
Figure 11. . . . 16
Figure 12. . . . 17
Figure 13. . . . 17
DISCUSSION . . . 17
AUTHORS' CONCLUSIONS . . . 17
ACKNOWLEDGEMENTS . . . 18
REFERENCES . . . 18
CHARACTERISTICS OF STUDIES . . . 21
DATA AND ANALYSES . . . 32
Analysis 1.1. Comparison 1 Overall survival, Outcome 1 Overall survival, rituximab maintenance vs. control. . . . 33
Analysis 2.1. Comparison 2 Secondary outcomes, rituximab maintenance versus observation, Outcome 1 Event free survival. . . . 34
Analysis 2.2. Comparison 2 Secondary outcomes, rituximab maintenance versus observation, Outcome 2 Progression free survival. . . . 34
Analysis 3.1. Comparison 3 Subgroup analysis (OS), Outcome 1 Rituximab in induction. . . . 35
Analysis 3.2. Comparison 3 Subgroup analysis (OS), Outcome 2 Type of rituximab maintenance schedule. . . . 35
Analysis 3.3. Comparison 3 Subgroup analysis (OS), Outcome 3 Number of induction therapy (maintenance after one vs. after more than one). . . . 36
Analysis 3.4. Comparison 3 Subgroup analysis (OS), Outcome 4 Type of control. . . . 37
Analysis 4.1. Comparison 4 Sensitivity analysis (OS), Outcome 1 Quality of allocation concealment. . . . 38
Analysis 4.2. Comparison 4 Sensitivity analysis (OS), Outcome 2 Type (place) of publication. . . . 39
Analysis 5.1. Comparison 5 Adverse events with rituximab maintenance therapy vs. observation, Outcome 1 Grade III/IV. . . . 40
Analysis 5.2. Comparison 5 Adverse events with rituximab maintenance therapy vs. observation, Outcome 2 Infectious. 40
Analysis 5.3. Comparison 5 Adverse events with rituximab maintenance therapy vs. observation, Outcome 3 Infectious, severe. . . . 41
APPENDICES . . . 41
HISTORY . . . 42
CONTRIBUTIONS OF AUTHORS . . . 42
DECLARATIONS OF INTEREST . . . 42

[Intervention Review]

Rituximab as maintenance therapy for patients with follicular lymphoma

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ABSTRACT

Background

Rituximab, a monoclonal anti-CD20 antibody, in combination with chemotherapy improves overall survival compared to chemotherapy alone when used for induction therapy for patients with newly diagnosed or relapsed indolent lymphoma. Randomised controlled trials have demonstrated that maintenance treatment with rituximab prolongs progression-free survival but evidence of effect on overall survival is lacking.

Objectives

To evaluate the effects of maintenance treatment with rituximab on overall survival in patients with follicular lymphoma.

Search strategy

We electronically searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2007, Issue 2), PubMed (June 2007), EMBASE (June 2007), LILACS (June 2007), databases of ongoing trials, and relevant conference proceedings. References of identified trials were searched and the first author of each included trial was contacted.

Selection criteria

Randomised controlled trials that compared rituximab maintenance therapy to observation, treatment at relapse (no maintenance therapy), or other maintenance treatment.

Data collection and analysis

Two authors independently appraised the quality of each trial and extracted data from included trials. Hazard ratios (HR) and relative risks with 95% confidence intervals (CI) were estimated and pooled using the fixed-effect model.

Main results

Five trials including 1056 adult patients were included in the review. Four trials (895 patients) were included in the analysis of overall survival. Patients treated with rituximab as maintenance therapy had a significantly better overall survival compared to observation alone (HR 0.53, 95% CI 0.38 to 0.73).

Authors' conclusions

Rituximab maintenance therapy should be added to standard therapy of patients with relapsed or refractory follicular lymphoma following a successful induction treatment. The drug should be given either as four weekly infusions every six months or as a single infusion every two to three months. Future randomised controlled trials should explore the effect of different protocols of rituximab maintenance therapy on overall survival.

PLAIN LANGUAGE SUMMARY

Rituximab as maintenance therapy for patients with follicular lymphoma

Follicular lymphoma is a B-cell lymphoma characterised by an initial response to treatment that is usually followed by relapse and progression. Most patients present with advanced disease that cannot be cured. Lymphoma B-cells express CD20. Rituximab, a monoclonal anti-CD20 antibody, is expected to be active against cells that express CD20. Compared to chemotherapy alone, rituximab in combination with chemotherapy improves overall survival when used for induction therapy (treatment designed as a first step toward reducing the number of cancer cells) for patients with newly diagnosed or relapsed indolent lymphoma. Clinical trials that have shown improved event-free survival were inconsistent regarding overall (all-cause) survival. We aimed to evaluate the effects of maintenance therapy with rituximab on overall survival in patients with follicular lymphoma.

Study design: systematic review and meta-analysis of five randomised controlled trials (1056 patients).

Contribution: patients with follicular lymphoma and high tumour burden treated with rituximab maintenance therapy had better overall survival and disease control but more infections than patients who were observed without rituximab.

Implications: rituximab maintenance therapy should be added to the standard therapy of patients with relapsed or refractory (to treatment) follicular lymphoma following a successful induction treatment.

Limitations: variability in treatment regimens among trials precluded determination of the optimal rituximab maintenance regimen. One trial compared rituximab maintenance to rituximab at disease progression for patients with lower tumour burden and found both options to be comparable.

Future research should focus on:

the effect of rituximab maintenance compared to rituximab at progression;

defining which patients benefit the most from rituximab, according to burden of disease, prognostic score, the type of chemotherapy regimens used for induction, and the inclusion of rituximab in induction; and

the optimal duration of maintenance treatment, as well as its schedule.

Both randomised controlled trials and observational trials should have longer follow up in order to assess the long-term toxicity of rituximab, and should evaluate quality of life outcomes.

BACKGROUND

Follicular lymphoma (FL) is a subgroup of B-cell non-Hodgkin lymphoma that accounts for 15% to 30% of newly diagnosed lymphomas. Follicular lymphoma is an indolent lymphoma characterised by slow growth, high initial response rate but relapsing and progressive disease. Most patients present with advanced disease, that is stage III/IV, that cannot be cured with currently available therapies. The initiating genetic event found in 70% to 90% of patients with FL is the t(14;18), causing over-expression of the anti-apoptotic Bcl-2 protein (Cleary 1985). Clinical trials have demonstrated an association between absence of the Bcl-2 rearrangement following therapy and reduced risk of reoccurrence (Corradini 2004; Lopez-Guillermo 2000; Rambaldi 2002).

New treatment modalities are therefore being sought. The

chimeric monoclonal antibody rituximab, targeted against CD20, is expected to be active in many B-cell lymphomas as these cells express CD20. Rituximab, administered intravenously, in combination with chemotherapy was demonstrated to improve overall survival (OS) compared to chemotherapy alone for patients with newly diagnosed or relapsed indolent lymphoma (Schulz 2005). The value of rituximab as maintenance therapy for patients who responded to induction therapy is yet to be determined. Non-comparative series suggest that rituximab may improve response rates (Hainsworth 2002; Gordan 2005). Although clinical trials have demonstrated that rituximab maintenance treatment may prolong complete remission and progression-free survival, clear evidence of improvement in OS is lacking (Ghielmini 2004). In practice rituximab maintenance therapy is not recommended in the current guidelines (http://www.nccn.org/professionals/physician_gls/f_guidelines.asp).

To date, there are limited data from randomised clinical trials available to guide the use of rituximab as maintenance therapy in this patient population, and few long-term results. We performed a systematic review and meta-analysis of the literature to evaluate the long-term effects and OS with rituximab maintenance treatment in patients with follicular lymphoma.

OBJECTIVES

To evaluate the efficacy of rituximab maintenance therapy for patients with follicular lymphoma.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised trials irrespective of language and publication status.

Types of participants

Patients histologically diagnosed with B-cell follicular lymphoma (FL). We included patient populations that received maintenance therapy after their first induction therapy or patients with relapsed or refractory FL (after receiving two or more induction therapies).

Types of interventions

Intervention: rituximab maintenance therapy
Comparison interventions: observation or another maintenance treatment
Maintenance therapy is any treatment given beyond induction therapy.

Types of outcome measures

Primary outcomes

- Overall survival (OS)

as defined in Cheson 2007

Secondary outcomes

- Event-free survival (EFS)
- Progression-free survival (PFS)
- Response duration
- Quality of life (as defined in each trial)
- Bcl-2 conversion rate
- Adverse events
    - grade III/IV according to common toxicity criteria (CTC)
    - requiring discontinuation of therapy
    - infectious

Search methods for identification of studies

Electronic searches

We searched the following databases:

- Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2007, Issue 2) (see Appendix 1),
- MEDLINE (1966 to June 2007) (through PubMed, see Appendix 2),
- EMBASE (1974 to June 2007) (see Appendix 3),
- LILACS (1982 to June 2007) (see Appendix 4),
- clinical trials in haematological malignancies (www.hematology-studies.org) (see Appendix 5).

The search terms were combined with the highly sensitive search strategy for identifying reports of randomised controlled trials (Higgins 2006).

Searching other resources

We searched the conference proceedings of the American Society of Hematology (1995 to 2006), conference proceedings of the American Society of Clinical Oncology Annual Meeting (1995 to 2006), and proceedings of the European Hematology Association for relevant abstracts.
We searched available databases of the European Agency for the Evaluation of Medicinal Products (EMEA) and the Food and Drug Administration (FDA).
We searched the following trial databases for ongoing and unpublished trials:

- http://www.controlled-trials.com/;
- http://www.centerwatch.com/;
- http://www.clinicaltrials.gov/ct;
- http://clinicaltrials.nci.nih.gov/;
- www.eortc.be/;
- www.ctc.usyd.edu.au/;
- http://www.trialscentral.org/.

We contacted the first or corresponding author of each included study and the researchers active in the field for information regarding unpublished trials or complementary information on their own trial.
We checked the citations of included trials and major reviews for additional studies.

Data collection and analysis

Selection of studies

One review author inspected the title and, when available, the abstract of each reference identified in the search and applied the inclusion criteria. Where relevant articles were identified, the full article was obtained and inspected independently by two review authors.

Data extraction and management

Two review authors independently extracted the data of included trials. In cases of disagreement between the two review authors, a third author independently extracted the data. The data extraction was discussed, decisions documented, and where necessary the authors of the studies were contacted for clarification. The justification for excluding studies from the review was documented. All data were collected on an intention-to-treat basis, where possible. The following data were extracted, checked, and recorded.

1. Characteristics of trials
    - Publication status: published; published as abstract; unpublished
    - Year (defined as recruitment initiation year) and country or countries of study
    - Trial sponsor
    - Intention-to-treat analysis: performed; possible to extract; efficacy analysis
    - Design (method of allocation generation and concealment; blinding)
    - Unit of allocation (patient, episodes, cluster)
    - Duration of study follow up
    - Response definition, event definitions
    - Case definitions used (inclusion and exclusion criteria)
2. Characteristics of patients
    - Type of induction therapy
    - Number of participants in each group
    - Number of complete and partial responders (candidates for maintenance therapy)
    - Disease status (newly diagnosed; relapsed or refractory)
    - Age (mean and standard deviation)
    - Number of patients above 60 years
    - Number of patients with performance status 0, 1, 2, > 2
    - Number of patients with grade 1, 2, 3 FL (International Working Formulation (IWF) classification)
    - Number of patients with stage III/IV disease (Ann Arbor)
    - Number of patients with follicular lymphoma international prognostic index (FLIPI score) 0 to 2, 3 to 5
    - Number of patients with bulky disease
    - Number of patients with elevated lactate dehydrogenase (LDH)
3. Characteristics of interventions
    - Dose, number administered doses, and total duration of therapy
    - Regimen (monotherapy; type of combination therapy)
4. Characteristics of outcome measures (extracted for each group)
    - Number of deaths at 12, 36, 48, 60 months
    - Number of patients available for follow up at the time of evaluation of survival risk
    - Hazard ratio (HR) of OS and its standard error (SE), confidence interval (CI) or P value
    - HR of EFS and its SE, CI or P value
    - HR of PFS and its SE, CI or P value
    - Number of patients who were Bcl-2 positive at randomisation; and at 12, 36, 48, 60 months post-randomisation
    - Adverse events (any, grade 3 to 4, requiring discontinuation of treatment, infectious)
    - Number of patients excluded from outcome assessment after randomisation, and the reasons for their exclusion

Assessment of risk of bias in included studies

We assessed the quality of the trials to be included in terms of allocation concealment, blinding (patients, caregivers, and assessors), allocation generation, and intention-to-treat analysis. Two review authors independently performed the quality assessment. Methodological quality classification was based on the evidence that there is a strong association between poor allocation concealment and an over-estimation of effect, and was defined by:

- A (low risk of bias; adequate allocation concealment),
- B (moderate risk of bias; some doubt about allocation concealment),
- C (high risk of bias; inadequate allocation concealment) (Schulz 1995).

Data synthesis

We pooled log HR for time-to-event outcomes using an inverse variance method. If not enough data were available, we estimated HRs indirectly using methods described by Parmar 1998. We estimated relative risks (RR) and their CI for dichotomous data using the Mantel-Haenszel method. We used a fixed-effect model. We repeated the primary analysis using a random-effects model (DerSimonian and Laird method, DerSimonian 1986) in a sensitivity analysis.

Subgroup analysis and investigation of heterogeneity

Heterogeneity (degree of difference between the results of different trials) in the results of the trials was graphically inspected and assessed by applying a test of heterogeneity (Chi^2 and I^2 statistic). We anticipated between-trial variations in the estimation of mortality for studies comparing monotherapy and combination therapy, and for studies comparing patients at different disease stages and status (stage I/II versus III/IV, newly diagnosed versus relapsed). We explored heterogeneity by stratifying defined patient subgroups, given below; allocation concealment; blinding; and size of studies.
We performed the following subgroup analyses.
Patient characteristics:

- advanced stage (III/IV), early stage (I/II);
- age (above 60 years, equal to or below 60 years);
- FLIPI score at baseline (0 to 2, 3 to 5), where FLIPI is a prognostic index that predicts survival of patients with FL (Solal-Celigny 2004);
- performance status (0, 1 to 2);
- grade I/II, III;
- newly diagnosed patients, patients with relapsed or refractory disease.

Treatment characteristics:

- induction therapy: chemotherapy, rituximab, chemotherapy + rituximab, rituximab or chemotherapy + rituximab;
- rituximab schedule:
  - one infusion every two months,
  - four weekly infusions every six months;
- Length of maintenance therapy:
  - up to two years;
  - more than two years.

We examined a funnel plot of the treatment effect against the precision of trials (plots of the log of the relative risk for efficacy against the standard error) in order to estimate potential asymmetry that may indicate selection bias (the selective publication of trials with positive findings) or methodological flaws in the small studies. We also estimated publication bias using the formal linear regression test (Egger 1997).

Sensitivity analysis

We performed sensitivity analyses using the method of allocation concealment (Schulz 1995); blinding (patients, caregivers, and assessors); allocation generation; the type of publication (full paper, abstract, unpublished); and the size of trials.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.
We screened 265 titles and abstracts. Twenty-seven of them were relevant and retrieved for full details. An additional 10 abstracts from conference proceedings and five potentially relevant ongoing trials were identified. Thirty-two studies were excluded. Reasons for exclusion were the following: non-randomised trials (Cheung 2007; Coiffier 2002; Ghielmini 2005; Ghielmini 2006; Kober 2006; Leppa 2006; No author 2002; No author 2004; No author 2004b; Rubio-Martinez 2006; Solal-Celigny 2006; Tomas 2006); no rituximab maintenance therapy (Baltasar 2003; Fisher 2005; Forstpointner 2004; Herold 2003; Herold 2007; Hiddemann 2003; Hiddemann 2006; Kaplan 2005; Marcus 2005; McLaughlin 2000; Ogura 2006; Sarris 2002; Schultz, ongoing); no reported outcomes (Witzens-Harig 2005); and seven were double publications. Four currently ongoing trials had no reported outcomes and were not included after communicating with the investigators (Ardeshna; Pettengell; Salles, PRIMA; Williams 2004).
Five trials fulfilled inclusion criteria (Forstpointner 2006; Ghielmini 2004; Hainsworth 2005; Hochster 2005; Hochster 2007; van Oers 2006). Hochster 2005 and Hochster 2007 were abstracts that reported the outcomes of different patients from one trial;
1056 adult patients were randomised in these trials between the years 1998 and 2004. The median follow up ranged from 26 to 41 months.

Type of patients

All five eligible trials included patients with indolent lymphoma. Three trials (Forstpointner 2006; Ghielmini 2004; van Oers 2006)

included patients with FL of any grade. One trial also included patients with mantle cell lymphoma (Forstpointner 2006). Two trials included patients with FL grades 1 and 2 or small lymphocytic lymphoma (Hainsworth 2005; Hochster 2005; Hochster 2007).
The minimal requirement for inclusion was either stable disease after induction in three trials (Ghielmini 2004; Hainsworth 2005; Hochster 2005; Hochster 2007) or partial remission in two trials.
Most patients had relapsed or refractory disease. One trial included both patients with relapsed disease (where patients received maintenance after more than one induction therapy) and patients with newly diagnosed disease (patients after first induction) (Ghielmini 2004). One trial included only patients after the first induction (Hochster 2005; Hochster 2007).
Common inclusion criteria were: good performance status ($\leq$ 2 by ECOG or WHO) with exclusion of patients with active infection, symptomatic central nervous system disease, or a history of significant medical conditions.
The percentage of patients with stage III/IV follicular lymphoma ranged from 85% to 100% in four trials and was not reported in one trial (Hainsworth 2005).

Study design

In three trials (Forstpointner 2006; Hochster 2005; Hochster 2007; van Oers 2006) two consecutive randomisation processes were performed (patients were randomised to type of induction therapy and then randomised again to maintenance therapy or observation). In the other two trials the randomisation was only for maintenance treatment.

Induction treatment

Prior rituximab treatment was not allowed in two trials (Ghielmini 2004; Hainsworth 2005).
Induction therapy included three options.

- Chemotherapy alone: consisting of cyclophosphamide, vincristine, prednisone (CVP); or fludarabine, cyclophosphamide (FC) in one trial (Hochster 2005; Hochster 2007).
- Chemotherapy with or without rituximab in two trials: chemotherapy consisted of fludarabine, cyclophosphamide, mitoxantrone (FCM) (Forstpointner 2006); and cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) (van Oers 2006).
- Rituximab alone in two trials (Ghielmini 2004; Hainsworth 2005).

Patients in the control group received rituximab upon progression of FL in one trial (Hainsworth 2005) and were observed during the trial period in the other four trials.

Interventions

Dose: in all the trials the dose of rituximab was 375 mg/m²/d; it was not adjusted according to the drug blood level.
Schedule: in three trials rituximab was administered weekly for four consecutive weeks (four doses) every six months (Forstpointner 2006; Hainsworth 2005; Hochster 2005; Hochster 2007); in two trials a single infusion of rituximab was administered every two to three months (Ghielmini 2004; van Oers 2006).
The duration of treatment varied as well: In three trials it was two years (van Oers 2006, Hainsworth 2005; Hochster 2005; Hochster 2007); in two trials it was eight or nine months (Ghielmini 2004; Forstpointner 2006).

Outcomes assessed

All trials assessed OS (either reported in the publication or obtained from authors) but not as the primary outcome. The outcomes and their definitions are specified in the table 'Characteristics of included studies'.

Risk of bias in included studies

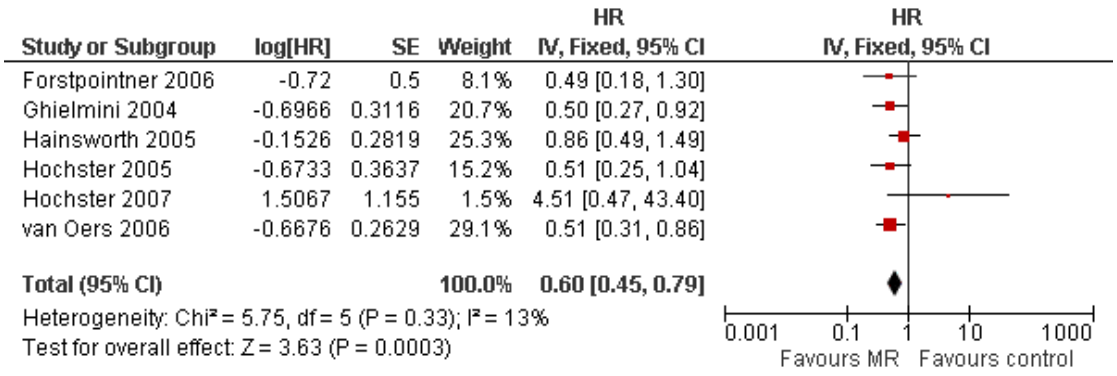
Generation of randomisation sequence was assessed as adequate for two trials (Forstpointner 2006; Hainsworth 2005). The other studies did not describe the methods used for generation of randomisation and hence were classified as B.
Allocation concealment was assessed as adequate in three trials (Forstpointner 2006; Hainsworth 2005; Ghielmini 2004) and not reported in the other trials.
None of the trials were blinded.
Intention-to-treat analysis (where all randomised patients were included for assessment of the primary outcome) was performed in two trials (Hainsworth 2005; van Oers 2006). The rate of dropouts was less than 10% in four trials (Forstpointner 2006; Ghielmini 2004; Hainsworth 2005; van Oers 2006).
Four trials were published in peer-reviewed papers and one was published as an abstract (Hochster 2005; Hochster 2007).
All trials but one (Hochster 2005; Hochster 2007) reported ethics committee approval and that informed consent was obtained from the patients. A statement of conflict of interest was published in one trial (Hainsworth 2005).
Four of the trials were funded by external resources: in three trials the funding was academic (Forstpointner 2006; Hainsworth 2005; van Oers 2006) and in three funding was received from the pharmaceutical industry (Ghielmini 2004; Hainsworth 2005; van Oers 2006). No information about resources was reported in Hochster 2005 and Hochster 2007.

Effects of interventions

Overall survival (OS)

Five trials (985 patients with FL) were eligible for inclusion in the analysis of OS. Patients treated with rituximab maintenance therapy had a significantly better OS compared to randomised to observation or to treatment with rituximab at progression (HR 0.60, 95% CI 0.45 to 0.79) (Figure 1).

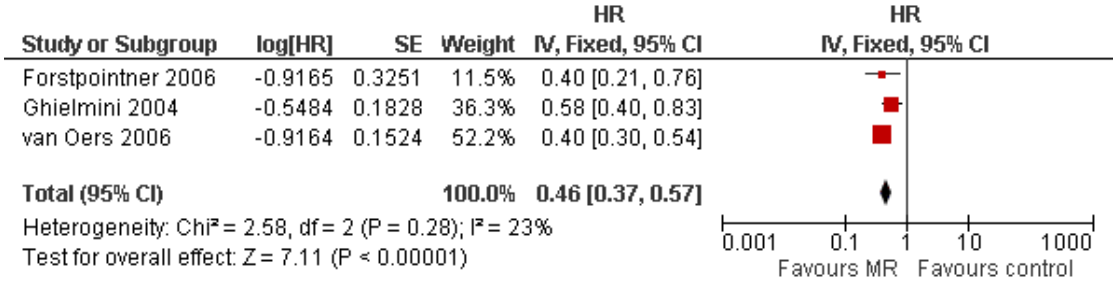
Figure 1. Forest plot of comparison: 1 Overall survival, outcome: 1.1 Overall survival, rituximab maintenance vs. control.



Event-free survival

From three trials (589 patients) the pooled HR was 0.46 (95% CI 0.37 to 0.57) (Figure 2).

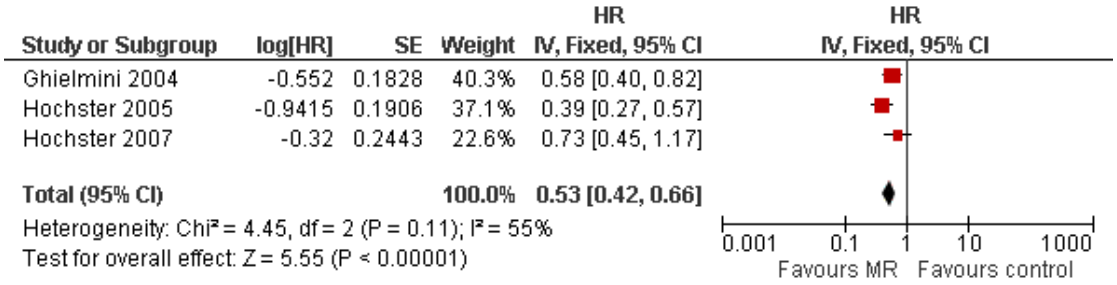
Figure 2. Forest plot of comparison: 2 Secondary outcomes, rituximab maintenance vs. observation, outcome: 2.3 Event free survival.



Progression-free survival

From three trials (454 patients) the pooled HR was 0.53 (95% CI 0.42 to 0.66) (Figure 3).

Figure 3. Forest plot of comparison: 2 Secondary outcomes, rituximab maintenance vs. observation, outcome: 2.4 Progression free survival.



Bcl-2 conversion rate

Not reported and possibly not evaluated in the included trials.

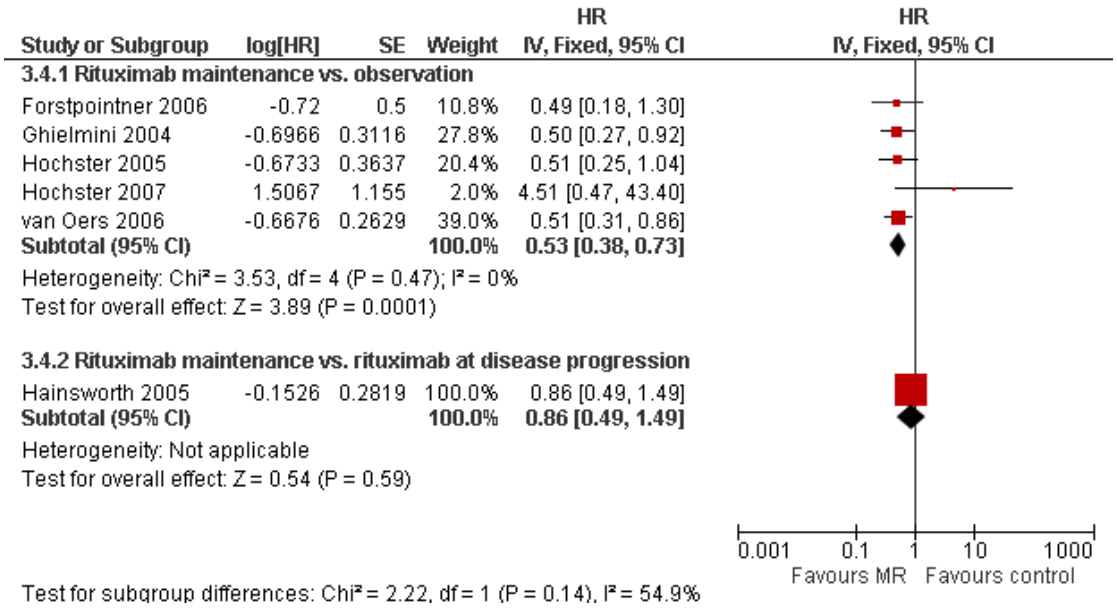
Quality of life

Not reported and possibly not evaluated in the included trials.

Subgroup analysis (on OS)

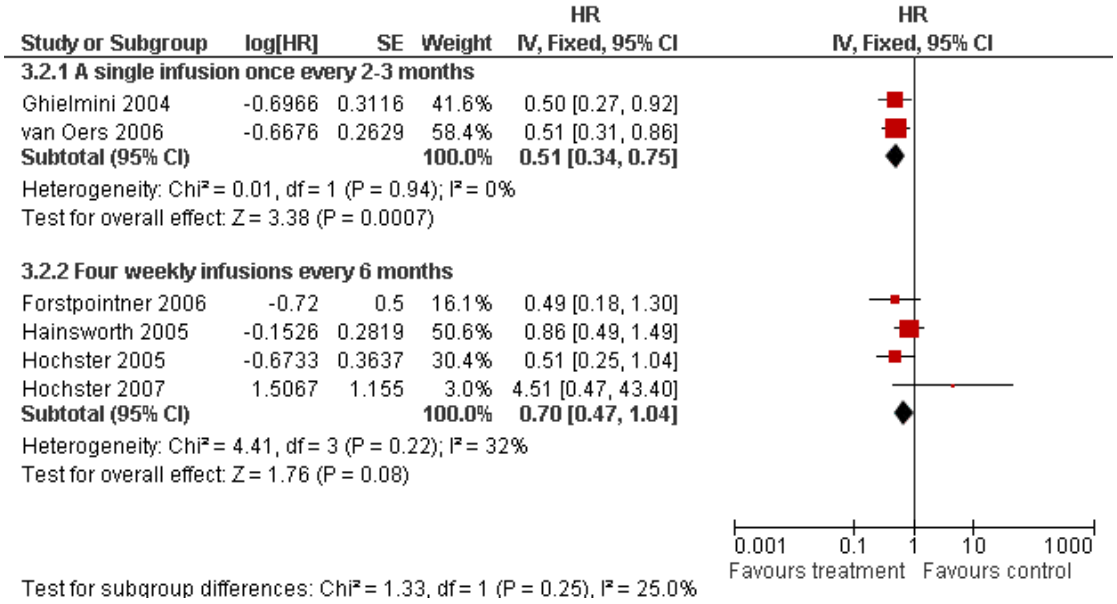
Treatment in control group: in one trial (Hainsworth 2005) patients were treated with rituximab upon relapse whereas the other trials used observation. We repeated the analysis without that trial with no effect on the outcomes (Figure 4).

Figure 4. Forest plot of comparison: 4 Subgroup analysis (OS), outcome: 4.4 Type of control.



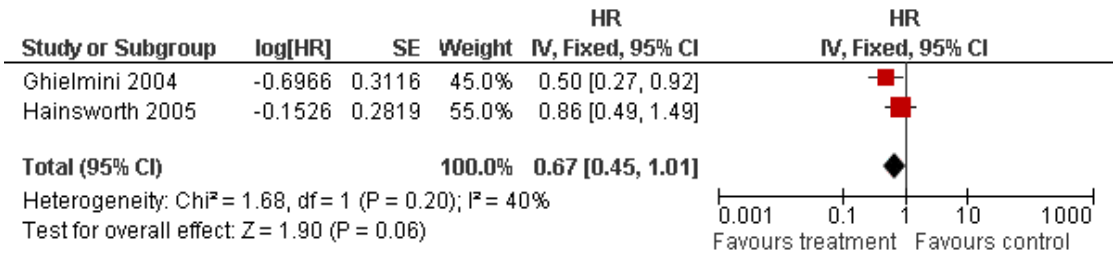
Maintenance schedule: there was no statistically significant effect of the rituximab schedule used on the outcomes (Figure 5).

Figure 5. Forest plot of comparison: 4 Sensitivity analysis (OS), rituximab maintenance therapy vs. observation, outcome: 4.5 Type of rituximab maintenance schedule.



Type of induction: inclusion of rituximab as part of the induction protocol did not significantly change the outcomes. Patients who received rituximab in induction therapy and later were treated with rituximab maintenance had an HR of 0.67 (95% CI 0.45 to 1.01; 2 trials, 240 patients) (Figure 6).

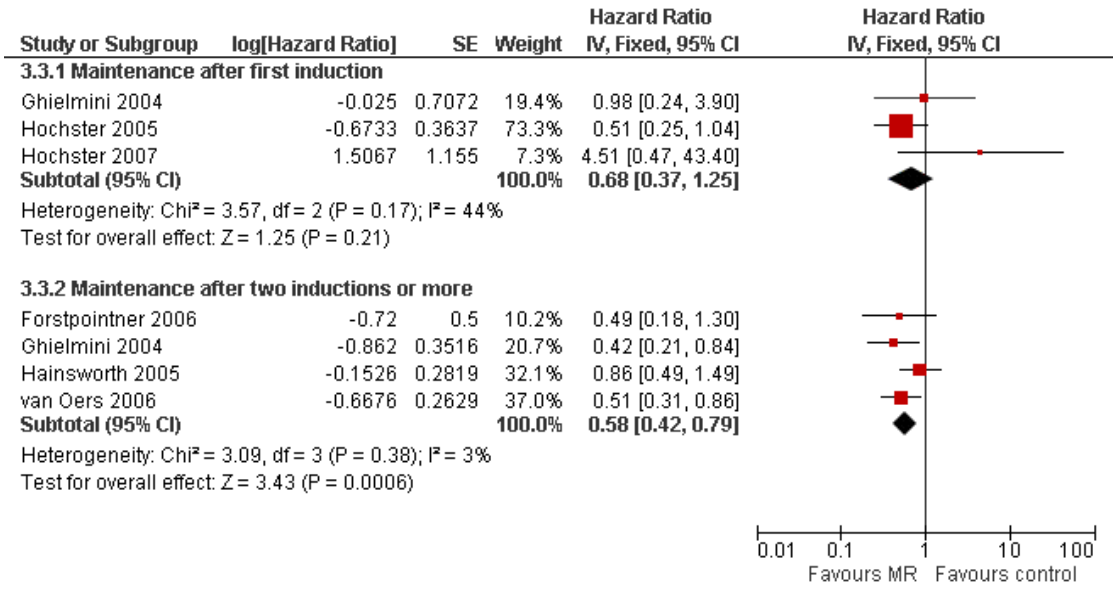
Figure 6. Forest plot of comparison: 4 Subgroup analysis (OS), outcome: 4.1 Rituximab in induction.



There were not enough data to analyse OS according to: age, FLIPI score at baseline, performance status of patients, and grade of lymphoma. Almost all patients had stage III/IV, relapsed or refractory disease.

Previous treatment: patients who had received induction therapy in the past and had a refractory or relapsed FL (received two or more inductions) had a clear survival benefit with maintenance rituximab therapy compared with observation (Forstpointner 2006; Ghielmini 2004; Hainsworth 2005; van Oers 2006); patients who had not been treated in the past (maintenance treatment after first induction therapy) (Ghielmini 2004, Hochster 2005, Hochster 2007) did not receive such benefit (HR 0.68, 95% CI 0.37 to 1.25) (Figure 7).

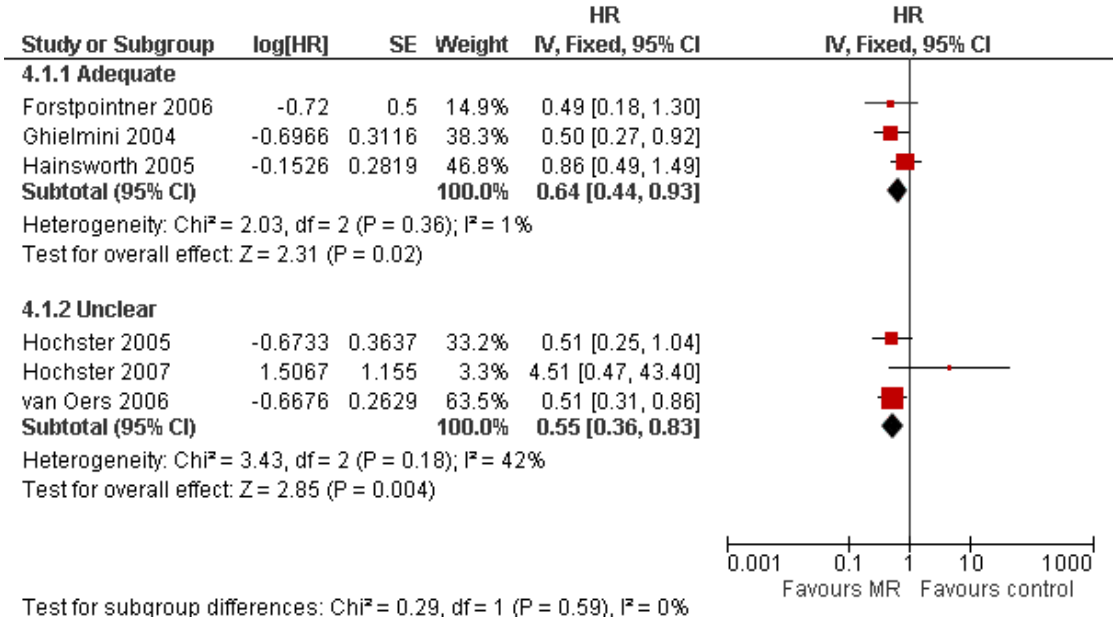
Figure 7. Forest plot of comparison: 4 Subgroup analysis (OS), outcome: 4.3 Number of induction therapy (maintenance after one vs. after more than one).



Sensitivity analysis

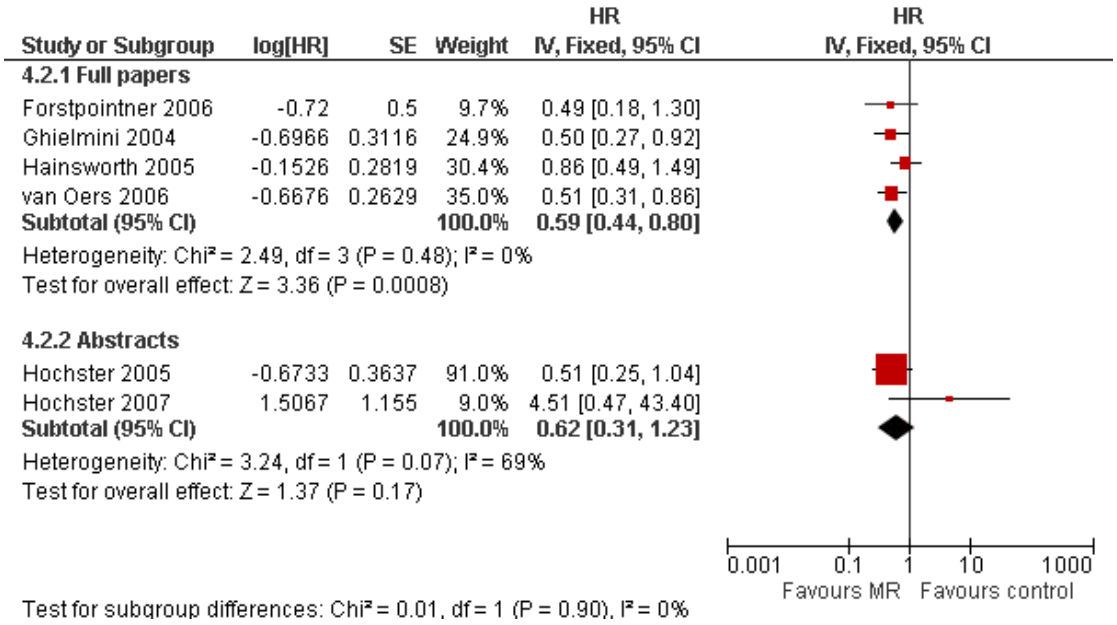
Allocation concealment: quality of allocation concealment (adequate or not reported) had no effect on the outcomes. The benefit of rituximab maintenance was shown in trials of adequate quality (HR 0.64, 95% CI 0.44 to 0.93) and in those with unclear allocation concealment (RR 0.55, 95 CI 0.36 to 0.83) (Figure 8).

Figure 8. Forest plot of comparison: 5 Sensitivity analysis (OS), outcome: 5.1 Quality of allocation concealment.



Type of publication (full papers, abstracts, unpublished): analysis of full papers only did not change the pooled OS (HR 0.59, 95% CI 0.44 to 0.80). When only abstracts were included in the analysis (one trial, Hochster 2005; Hochster 2007) no statistically significant benefit was shown (HR 0.62, 95% CI 0.31 to 1.23) (Figure 9).

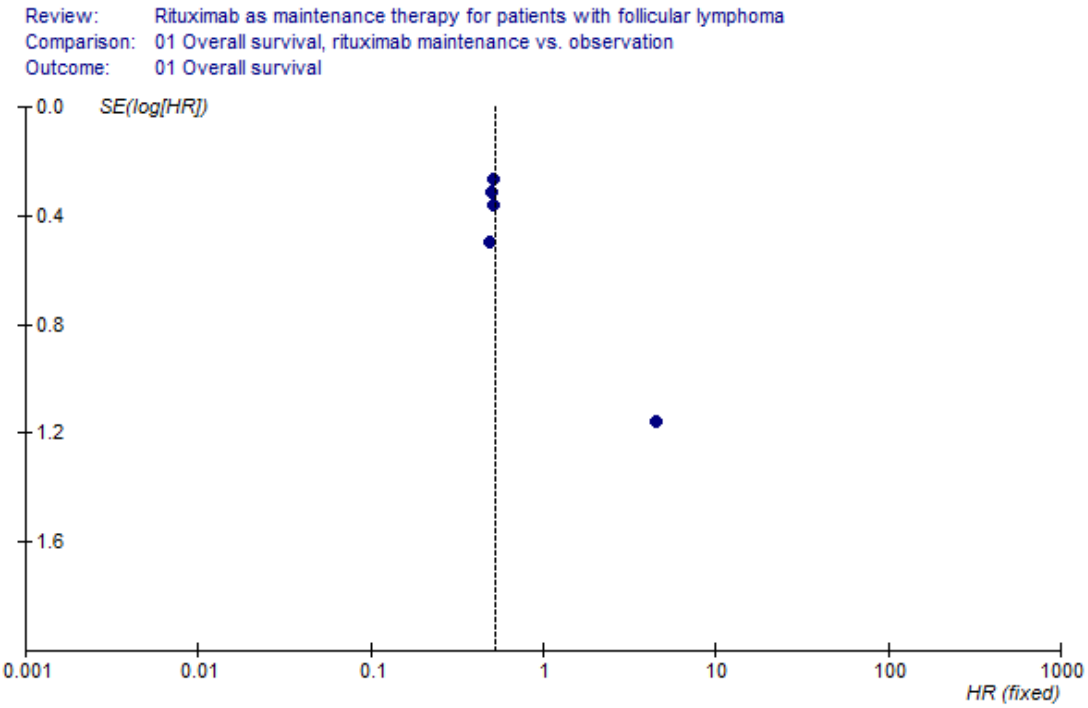
Figure 9. Forest plot of comparison: 5 Sensitivity analysis (OS), outcome: 5.2 Type (place) of publication.



Heterogeneity and funnel plot

No statistical heterogeneity was demonstrated (I^2 statistic, Chi^2 test). The funnel plot did not support publication bias (Figure 10).

Figure 10. Forest plot, overall survival



Adverse events

The rate of grade III/IV adverse events was reported in two trials and was higher with rituximab maintenance therapy compared to observation (RR 1.52, 95% CI 1.00 to 2.30) (Figure 11). Specifically, patients treated with rituximab maintenance had significantly more infection-related adverse effects compared to observation (RR 1.99, 95% CI 1.21 to 3.27) (Figure 12). When only severe infectious adverse events were included in the analysis this effect was even more pronounced (RR 2.90, 95% CI 1.24 to 6.76) (Figure 13). The infections were described in one trial (van Oers 2006) as mainly ear, nose and throat infections and hospitalisation was required for all the patients with grade III/IV adverse infectious events.

The rate of adverse events that required discontinuation of treatment was reported in one trial (van Oers 2006) and was higher in the group that received rituximab maintenance therapy.

Figure 11. Forest plot of comparison: 3 Adverse events with rituximab maintenance therapy vs. observation, outcome: 3.2 Life threatening or associated with permanent disability.

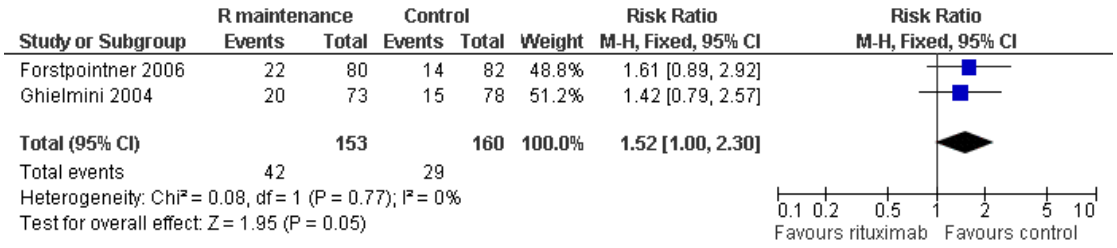


Figure 12. Forest plot of comparison: 3 Adverse events with rituximab maintenance therapy vs. observation, outcome: 3.4 Infectious.

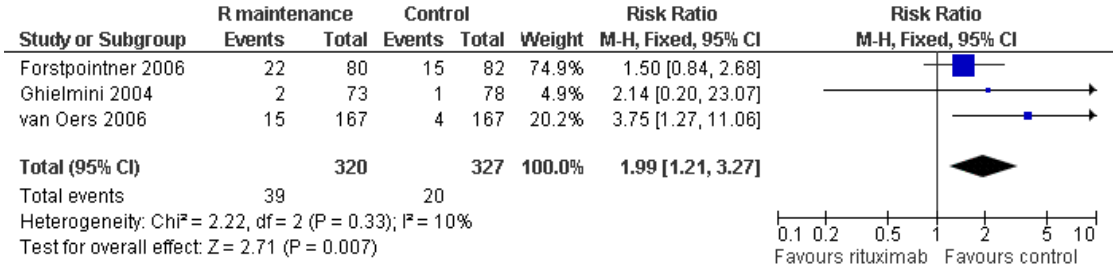
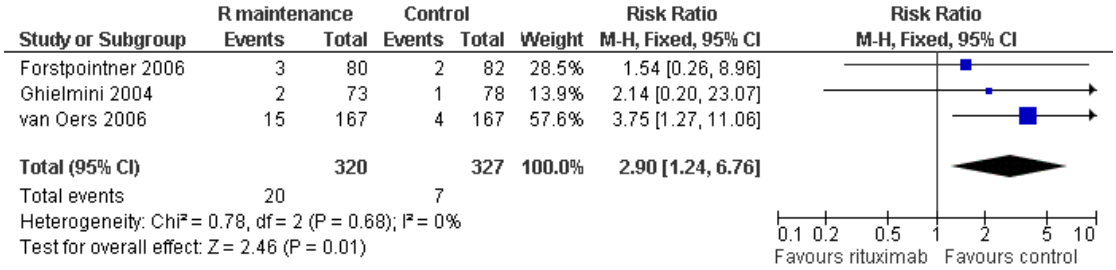


Figure 13. Forest plot of comparison: 3 Adverse events with rituximab maintenance therapy vs. observation, outcome: 3.5 Infectious, severe.



DISCUSSION

Our review demonstrates that rituximab maintenance therapy improves overall survival (OS) and disease control compared to observation in patients with refractory or relapsed follicular lymphoma (FL) who respond to induction therapy. The effect on OS is significant despite a higher rate of severe adverse events, mainly infection-related adverse events.

Our review has several limitations as the five included studies differ in their induction therapy. In one trial no chemotherapy was given, and the chemotherapy regimen used varied among the other trials. Rituximab maintenance therapy retained survival benefit irrespective of the different induction regimen. The trial by Hochster (Hochster 2007) had a subgroup of patients treated with cyclophosphamide and fludarabine who experienced a poorer outcome with maintenance therapy, though not statistically significant, which may suggest a possible interaction between the type of chemotherapy regimen and the effect of rituximab maintenance therapy. In addition, as these trials were conducted before rituximab was considered part of standard induction therapy for patients with FL, some of the patients did not receive rituximab in their induction regimen.

Further to its place in induction therapy, the optimal timing and schedule of rituximab treatment in FL is still unclear. Despite clear survival benefit when compared to observation, no benefit was demonstrated (Hainsworth 2005) when rituximab maintenance was compared to rituximab at progression. The included trials represent two major approaches to the rituximab maintenance schedule; weekly infusions for four consecutive weeks every six months or a single infusion of rituximab every two to three months. Again, it should be noted that the different rituximab schedules did not significantly affect the results.

Despite those differences the results of the trials tended toward the same effect and no heterogeneity was shown, which supports the robustness of our results.

Three trials were terminated earlier than initially planned, after meeting the criteria set for stopping the trials. Statistical theories and the results of a systematic review of randomised trials stopped early for apparent benefit suggest that stopping trials early systematically overestimates treatment effects. The scientific validity of trials that are stopped early is further compromised when trials yield inconclusive data about outcomes that did not influence trial truncation, in this case OS.

AUTHORS' CONCLUSIONS

Implications for practice

Rituximab maintenance therapy, either as four weekly infusions every six months or as a single infusion every two to three months, should be added to the standard therapy of patients with relapsed or refractory follicular lymphoma following a successful induction treatment.

Implications for research

The effect of rituximab maintenance therapy compared to rituximab at progression should be further explored. If rituximab maintenance therapy is found to give better outcomes, then the optimal protocol of maintenance treatment should be evaluated.

Future trials should focus on defining which patients benefit the most from rituximab, according to the type of chemotherapy regimens used for induction and the inclusion of rituximab in induction.

The optimal duration of maintenance treatment (that is, one year versus three years) as well as its schedule (that is, weekly for four weeks every six months versus a single infusion every two months) should be assessed in randomised controlled trials.

Both randomised controlled trials and observational trials should have longer follow up in order to assess the long-term toxicity of rituximab.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Forstpointner 2006

Methods	Allocation generation: adequate, stratified by histology, response to induction therapy and the number of previous therapies Allocation concealment: central Blinding: no ITT: no Dropouts: 19/195 Median follow up: 26 months
Participants	195 randomised, 176 evaluable, 162 described adult patients Type of lymphoma: follicular (105 patients) or mantle cell (57 patients) Stage: III/IV Relapsed or refractory after at least one preceding chemotherapy or recurrence after ASCT Prior rituximab: allowed
Interventions	Two courses of rituximab at 3 and 9 months after completion of salvage therapy. Each course consisted of four doses of 375 mg/m²/d given at four consecutive weeks versus observation Induction type: chemotherapy+or-rituximab (24 FCM or 81 RFCM)
Outcomes	Overall survival: survival from enrolment until death Time to progression: the interval between the start of treatment and documentation of progressive disease (event defined as PFS) Response duration was defined from the end of successful therapy to documentation of progression or death Adverse events
Notes	Funding: academic

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Ghielmini 2004

Methods	Allocation generation: unclear, stratified by centre, disease status (newly diagnosed versus relapsed/refractory), response to induction rituximab treatment Allocation concealment: central Blinding: no ITT: Number of dropouts: 1/151 Median follow up: 35 months
Participants	151 adults Type of lymphoma: follicular Stage: I/II 23 patients, III/IV 134 patients Grade: I-III Newly diagnosed (51/151 were chemotherapy naive) and relapsed or refractory Type of response prior to maintenance: stable disease/PR/CR Prior rituximab: not allowed Other: Eastern Cooperative Oncology Group performance status $\leq$2, a cardiac ejection fraction $\geq$50% Excluded: symptomatic central nervous system disease, a history of significant medical conditions, reduced renal function or liver function, patients with active opportunistic infections or with known HIV, hepatitis B or C infections
Interventions	A single infusion of rituximab 375 mg/m^2 at week 12, and again at months 5, 7 and 9 versus observation Induction type: rituximab
Outcomes	Overall survival: survival from date of second randomisation, about 8-12 weeks after induction rituximab treatment EFS - disease progression, relapse, 2nd tumour, or death from date of second randomisation PFS - disease progression, relapse, or death due to lymphoma from date of second randomisation RD - the same as progression free survival, but only for patients with CR or PR at randomisation Adverse events
Notes	Funding: industry

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Hainsworth 2005

Methods	Allocation generation: random card system Allocation concealment: central Blinding: no ITT: yes Number of dropouts: 0/90 Median follow up: 41 months
Participants	90 adults Type of lymphoma: grade 1 or 2 follicular (62 patients), or small lymphocytic lymphoma (28 patients) Stage: Relapsed or refractory Prior rituximab: not allowed Other: Eastern Cooperative Oncology Group performance status $\leq$2, life expectancy more than 12 weeks; WBC $\geq$3000/L, platelets $\geq$100,000/L,serum bilirubin $\leq$2.0 mg/dL, serum creatinine $\leq$2.0 mg/dL, without serious active infections or other serious uncontrolled medical illnesses, without CNS involvement Stable disease/CR/PR after 2 weeks of induction therapy
Interventions	Rituximab 375 mg/m^2 IV weekly for 4 consecutive weeks at 6-month intervals, until lymphoma progression or for a total of four rituximab courses versus rituximab (375 mg/m^2 IV weekly for 4 consecutive weeks) at progression Type of induction: rituximab
Outcomes	Duration of rituximab benefit PFS (Cheson criteria) Objective response rate Complete response rate
Notes	Funding: industry (Genentech) and academic

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Hochster 2005

Methods	Allocation generation: unclear Allocation concealment: unclear Blinding: no ITT: unclear Number of dropouts: not reported Median follow up: 3 years
Participants	304 adult patients, 237 with FL Type of lymphoma: stage III-IV follicular grade 1-2 and small lymphocytic lymphoma Untreated patients Prior rituximab: not mentioned Other: stable/PR/CR after induction
Interventions	Rituximab 375 mg/m^2 weekly for 4 weeks every 6 months x 4 versus observation Induction type: chemotherapy (CVP)
Outcomes	OS PFS no definitions
Notes	Early termination

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Hochster 2007

Methods	Allocation generation: unclear Allocation concealment: unclear Blinding: no ITT: unclear Number of dropouts: not reported Median follow up: 3 years
Participants	69 patients Type of lymphoma: stage III-IV follicular grade 1-2 and small lymphocytic lymphoma Untreated patients Prior rituximab: not mentioned Other: stable/PR/CR after induction

Hochster 2007 (*Continued*)

Interventions	Rituximab 375 mg/m^2 weekly for 4 weeks every 6 months x 4 versus observation Induction type: chemotherapy (CF)
Outcomes	OS PFS no definitions
Notes	Early termination

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

van Oers 2006

Methods	Allocation generation: unclear, stratified by the treatment allocated by the first randomisation, the quality of the response obtained after induction (CR/PR), and centre Allocation concealment: unclear Blinding: no ITT: yes Number of dropouts: 0/334 Median follow up: 33.3 months
Participants	340? eligible, 334 randomised adult patients Type of lymphoma: grade 1-3 follicular Stage: Ann Arbor stage III/IV Relapsed or refractory Prior rituximab: as part of induction Other: WHO performance status $\leq$2, CR/PR after induction, known HIV positivity, symptomatic CNS lymphoma, IgG levels <3 g/l, severe concomitant disease (in first randomisation), active infection
Interventions	Rituximab 375 mg/m^2 IV once every 3 months until relapse or for a maximum period of 2 years versus observation Type of induction: chemotherapy+or-rituximab (55% of patients CHOP, 59% RCHOP)
Outcomes	Overall survival: survival from second randomisation PFS: interval between the date of second randomisation and date of first relapse, progression, or death (if death of any cause, as EFS)
Notes	Funding: academic, the study drug was provided by F Hoffmann-La Roche Ltd Pharmaceuticals Division

van Oers 2006 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

CF - cyclophosphamide 1 g/m² day 1, fludarabine 20 mg/m² days 1-5 every 28 days
FCM - fludarabine 25 mg/m²/day over 30 minutes IV on days 1-3, cyclophosphamide 200 mg/m²/day as a 4-hour infusion on days 1-3 and mitoxantrone 8 mg/m²/day over 30 minutes IV on day 1
RFCM - rituximab at a dose of of 375 mg/m²/day on day 0, fludarabine 25 mg/m²/day over 30 minutes IV on days 1-3, cyclophosphamide 200 mg/m²/day as a 4-hour infusion on days 1-3 and mitoxantrone 8 mg/m²/d over 30 minutes IV on day 1
PR - partial response
CR - complete response
CVP - cyclophosphamide 1 g/m² on day 1, vincristine 1.4 mg/m² (max 2 mg) on day 1, prednisone 100 mg/m² days 1-5
FL - follicular lymphoma

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

Baltasar 2003	No maintenance therapy
Cheung 2007	A systematic review on rituximab in non-Hodgkin's lymphoma, and guidelines (with no meta-analysis)
Coiffier 2002	Not a randomised controlled trial
Fisher 2005	No maintenance rituximab therapy CHOP versus CHOP+rituximab versus CHOP+tositumomab (induction)
Forstpointner 2004	No reported maintenance rituximab therapy
Ghielmini 2005	Not a randomised controlled trial (review)
Ghielmini 2006	Not a randomised controlled trial (review)
Herold 2003	No maintenance rituximab therapy
Herold 2007	No maintenance rituximab therapy
Hiddemann 2003	No maintenance rituximab therapy
Hiddemann 2006	No maintenance rituximab therapy
Kaplan 2005	No maintenance rituximab therapy

(*Continued*)

Kober 2006	A review
Leppa 2006	Not a randomised controlled trial
Marcus 2005	No maintenance rituximab therapy
McLaughlin 2000	No maintenance rituximab therapy
No author 2002	Not a randomised controlled trial (a summary of Ghielmini 2004)
No author 2004	Not a randomised controlled trial
No author 2004b	Not a randomised controlled trial
Ogura 2006	No maintenance therapy
Rubio-Martinez 2006	Not a randomised controlled trial
Sarris 2002	No maintenance therapy; no clinical outcomes
Schultz, ongoing	No maintenance therapy; 8-weekly infusion of rituximab, patients randomised to 2 different doses of rituximab
Solal-Celigny 2006	Not a randomised controlled trial (review)
Tomas 2006	Not a randomised controlled trial
Witzens-Harig 2005	No outcomes reported

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

Ardeshna

Trial name or title	Rituximab in treating patients with newly diagnosed stage II, stage III, or stage IV follicular non-Hodgkin's lymphoma
Methods	Randomised controlled trial
Participants	Adult patients with newly diagnosed stage II, stage III, or stage IV follicular non-Hodgkin's lymphoma with no symptoms
Interventions	Arm I: patients undergo observation only until disease progression Arm II: patients receive induction rituximab IV on day 1. Treatment repeats weekly for up to 4 weeks Arm III: patients receive induction rituximab as in arm II. Patients then receive maintenance rituximab IV once on day 1 of weeks: 12, 20, 28, 36, 44, 52, 60, 68, 76, 84, 92, and 100
Outcomes	Time until initiation of therapy (chemotherapy or radiotherapy) Secondary outcome measures: frequency of clinical spontaneous remission, cause-specific survival, overall survival, disease-free survival, response rate
Starting date	First published: 5/23/2005
Contact information	Trial lead organization: University College of London Hospitals Kirit Ardeshna, Protocol chair Ph: 44-192-384-4413 Email: kirit.ardeshna@uclh.nhs.uk
Notes	http://www.cancer.gov/clinicaltrials/CRUK-2004-001621-16 ClinicalTrials.gov identifier NCT00112931

Pettengell

Trial name or title	Combination chemotherapy plus peripheral stem cell transplantation with or without rituximab in treating patients with relapsed non-Hodgkin's lymphoma
Methods	
Participants	Adult patients with relapsed follicular lymphoma
Interventions	Patients are randomised to receive either in vivo rituximab purging or no purging following restaging after completion of induction. For those patients receiving purging (arms I and II), rituximab is administered IV once weekly for 4 weeks Patients are further randomised to receive either rituximab maintenance or observation only. For those patients receiving maintenance (arms I and III), rituximab is administered IV once every 2 months for 4 doses beginning 30 days after PBSC re-infusion

Pettengell (*Continued*)

Outcomes	Time to disease progression Secondary outcome measures: response rate and survival, molecular remission rates, safety
Starting date	
Contact information	
Notes	No longer recruiting ClinicalTrials.gov Identifier: NCT00005589

Salles, PRIMA

Trial name or title	Advanced follicular lymphoma evaluating the benefit of maintenance therapy with rituximab (MabThera®) after induction of response with chemotherapy plus rituximab in comparison with no maintenance therapy
Methods	Randomised controlled trial
Participants	Adult patients with previously untreated grade 1, 2 or 3a follicular lymphoma, with at least one symptom requiring initiation of treatment
Interventions	After induction with rituximab combined with CVP, CHOP, FCM, or MCP patients were randomised to rituximab 375 mg/m^2 every 8 weeks for 24 months (12 injections) or control with no treatment
Outcomes	Progression-free survival (PFS) defined as the time from randomisation to progression, relapse, death from any cause, response rate, EFS, PFS, OS, and quality of life
Starting date	August 22, 2005
Contact information	Principal Investigator: Gilles A Salles, MD PhD, Groupe d'Etude des Lymphomes de l'Adulte
Notes	Completed Study ID Number: PRIMA ClinicalTrials.gov Identifier: NCT00140582

Williams 2004

Trial name or title	Rituximab in treating patients with low tumor burden indolent non-Hodgkin's lymphoma
Methods	
Participants	Adult patients with low tumor burden indolent stage III IV non-Hodgkin's lymphoma

Williams 2004 (*Continued*)

Interventions	After induction therapy of rituximab IV once a week for 4 weeks patients are randomised to: arm I (retreatment rituximab): patients receive rituximab IV once a week for 4 weeks upon disease progression provided time to progression is more than 6 months arm II (scheduled rituximab): patients receive a single dose of rituximab IV once every 12 weeks until disease progression and in the absence of unacceptable toxicity
Outcomes	Time to rituximab failure Secondary outcome measures: time to first cytotoxic therapy, toxic effects, quality of life
Starting date	November 2003
Contact information	Comprehensive Cancer Center Michael E Williams, MD, University of Virginia
Notes	Study ID Numbers: CDR0000346359; ECOG-E4402 ClinicalTrials.gov Identifier: NCT00075946

DATA AND ANALYSES

Comparison 1. Overall survival

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival, rituximab maintenance vs. control	6		HR (Fixed, 95% CI)	0.60 [0.45, 0.79]

Comparison 2. Secondary outcomes, rituximab maintenance versus observation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Event free survival	3		HR (Fixed, 95% CI)	0.46 [0.37, 0.57]
2 Progression free survival	3		HR (Fixed, 95% CI)	0.53 [0.42, 0.66]

Comparison 3. Subgroup analysis (OS)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Rituximab in induction	2		HR (Fixed, 95% CI)	0.67 [0.45, 1.01]
2 Type of rituximab maintenance schedule	6		HR (Fixed, 95% CI)	Subtotals only
2.1 A single infusion once every 2-3 months	2		HR (Fixed, 95% CI)	0.51 [0.34, 0.75]
2.2 Four weekly infusions every 6 months	4		HR (Fixed, 95% CI)	0.70 [0.47, 1.04]
3 Number of induction therapy (maintenance after one vs. after more than one)	6		Hazard Ratio (Fixed, 95% CI)	Subtotals only
3.1 Maintenance after first induction	3		Hazard Ratio (Fixed, 95% CI)	0.68 [0.37, 1.25]
3.2 Maintenance after two inductions or more	4		Hazard Ratio (Fixed, 95% CI)	0.58 [0.42, 0.79]
4 Type of control	6		HR (Fixed, 95% CI)	Subtotals only
4.1 Rituximab maintenance vs. observation	5		HR (Fixed, 95% CI)	0.53 [0.38, 0.73]
4.2 Rituximab maintenance vs. rituximab at disease progression	1		HR (Fixed, 95% CI)	0.86 [0.49, 1.49]

Comparison 4. Sensitivity analysis (OS)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Quality of allocation concealment	6		HR (Fixed, 95% CI)	Subtotals only
1.1 Adequate	3		HR (Fixed, 95% CI)	0.64 [0.44, 0.93]
1.2 Unclear	3		HR (Fixed, 95% CI)	0.55 [0.36, 0.83]
2 Type (place) of publication	6		HR (Fixed, 95% CI)	Subtotals only
2.1 Full papers	4		HR (Fixed, 95% CI)	0.59 [0.44, 0.80]
2.2 Abstracts	2		HR (Fixed, 95% CI)	0.62 [0.31, 1.23]

Comparison 5. Adverse events with rituximab maintenance therapy vs. observation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Grade III/IV	2	313	Risk Ratio (M-H, Fixed, 95% CI)	1.52 [1.00, 2.30]
2 Infectious	3	647	Risk Ratio (M-H, Fixed, 95% CI)	1.99 [1.21, 3.27]
3 Infectious, severe	3	647	Risk Ratio (M-H, Fixed, 95% CI)	2.90 [1.24, 6.76]

Analysis 1.1. Comparison 1 Overall survival, Outcome 1 Overall survival, rituximab maintenance vs. control.

Review: Rituximab as maintenance therapy for patients with follicular lymphoma

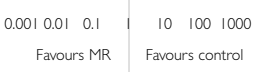
Comparison: 1 Overall survival

Outcome: 1 Overall survival, rituximab maintenance vs. control

Study or subgroup	log [HR] (SE)	HR IV,Fixed,95% CI	Weight	HR IV,Fixed,95% CI
Forstpointner 2006	-0.72 (0.5)		8.1 %	0.49 [0.18, 1.30]
Ghielmini 2004	-0.6966 (0.3116)		20.7 %	0.50 [0.27, 0.92]
Hainsworth 2005	-0.1526 (0.2819)		25.3 %	0.86 [0.49, 1.49]
Hochster 2005	-0.6733 (0.3637)		15.2 %	0.51 [0.25, 1.04]
Hochster 2007	1.5067 (1.155)		1.5 %	4.51 [0.47, 43.40]
van Oers 2006	-0.6676 (0.2629)		29.1 %	0.51 [0.31, 0.86]
Total (95% CI)			**100.0 %**	**0.60 [0.45, 0.79]**

Heterogeneity: Chi² = 5.75, df = 5 (P = 0.33); I² =13%

Test for overall effect: Z = 3.63 (P = 0.00028)



Analysis 2.1. Comparison 2 Secondary outcomes, rituximab maintenance versus observation, Outcome 1 Event free survival.

Review: Rituximab as maintenance therapy for patients with follicular lymphoma

Comparison: 2 Secondary outcomes, rituximab maintenance versus observation

Outcome: 1 Event free survival

Study or subgroup	log [HR] (SE)	HR IV,Fixed,95% CI	Weight	HR IV,Fixed,95% CI
Forstpointner 2006	-0.9165 (0.3251)		11.5 %	0.40 [0.21, 0.76]
Ghielmini 2004	-0.5484 (0.1828)		36.3 %	0.58 [0.40, 0.83]
van Oers 2006	-0.9164 (0.1524)		52.2 %	0.40 [0.30, 0.54]
Total (95% CI)			**100.0 %**	**0.46 [0.37, 0.57]**

Heterogeneity: Chi² = 2.58, df = 2 (P = 0.28); I² =23%

Test for overall effect: Z = 7.11 (P < 0.00001)

Analysis 2.2. Comparison 2 Secondary outcomes, rituximab maintenance versus observation, Outcome 2 Progression free survival.

Review: Rituximab as maintenance therapy for patients with follicular lymphoma

Comparison: 2 Secondary outcomes, rituximab maintenance versus observation

Outcome: 2 Progression free survival

Study or subgroup	log [HR] (SE)	HR IV,Fixed,95% CI	Weight	HR IV,Fixed,95% CI
Ghielmini 2004	-0.552 (0.1828)		40.3 %	0.58 [0.40, 0.82]
Hochster 2005	-0.9415 (0.1906)		37.1 %	0.39 [0.27, 0.57]
Hochster 2007	-0.32 (0.2443)		22.6 %	0.73 [0.45, 1.17]
Total (95% CI)			**100.0 %**	**0.53 [0.42, 0.66]**

Heterogeneity: Chi² = 4.45, df = 2 (P = 0.11); I² =55%

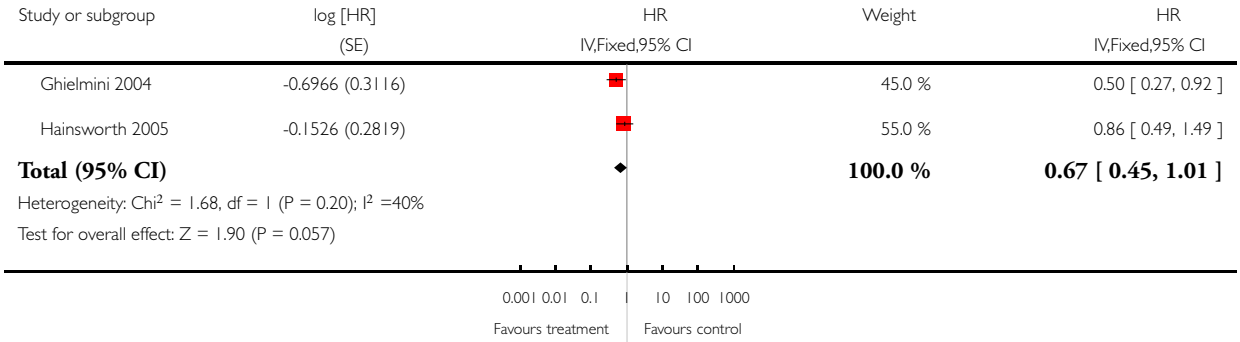
Test for overall effect: Z = 5.55 (P < 0.00001)

Analysis 3.1. Comparison 3 Subgroup analysis (OS), Outcome 1 Rituximab in induction.

Review: Rituximab as maintenance therapy for patients with follicular lymphoma

Comparison: 3 Subgroup analysis (OS)

Outcome: 1 Rituximab in induction

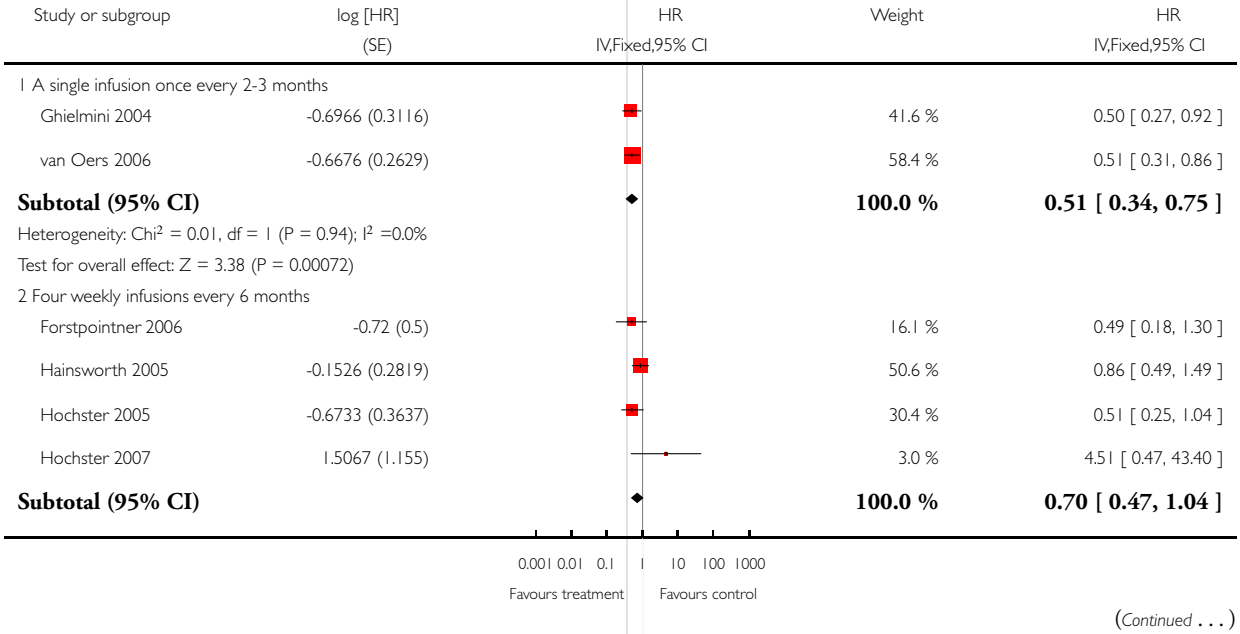


Analysis 3.2. Comparison 3 Subgroup analysis (OS), Outcome 2 Type of rituximab maintenance schedule.

Review: Rituximab as maintenance therapy for patients with follicular lymphoma

Comparison: 3 Subgroup analysis (OS)

Outcome: 2 Type of rituximab maintenance schedule



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Study or subgroup	log [HR] (SE)	HR IV,Fixed,95% CI	Weight	HR IV,Fixed,95% CI
Heterogeneity: Chi² = 4.41, df = 3 (P = 0.22); I² =32%				
Test for overall effect: Z = 1.76 (P = 0.079)				
Test for subgroup differences: Chi² = 1.33, df = 1 (P = 0.25), I² =25%				

Analysis 3.3. Comparison 3 Subgroup analysis (OS), Outcome 3 Number of induction therapy (maintenance after one vs. after more than one).

Review: Rituximab as maintenance therapy for patients with follicular lymphoma

Comparison: 3 Subgroup analysis (OS)

Outcome: 3 Number of induction therapy (maintenance after one vs. after more than one)

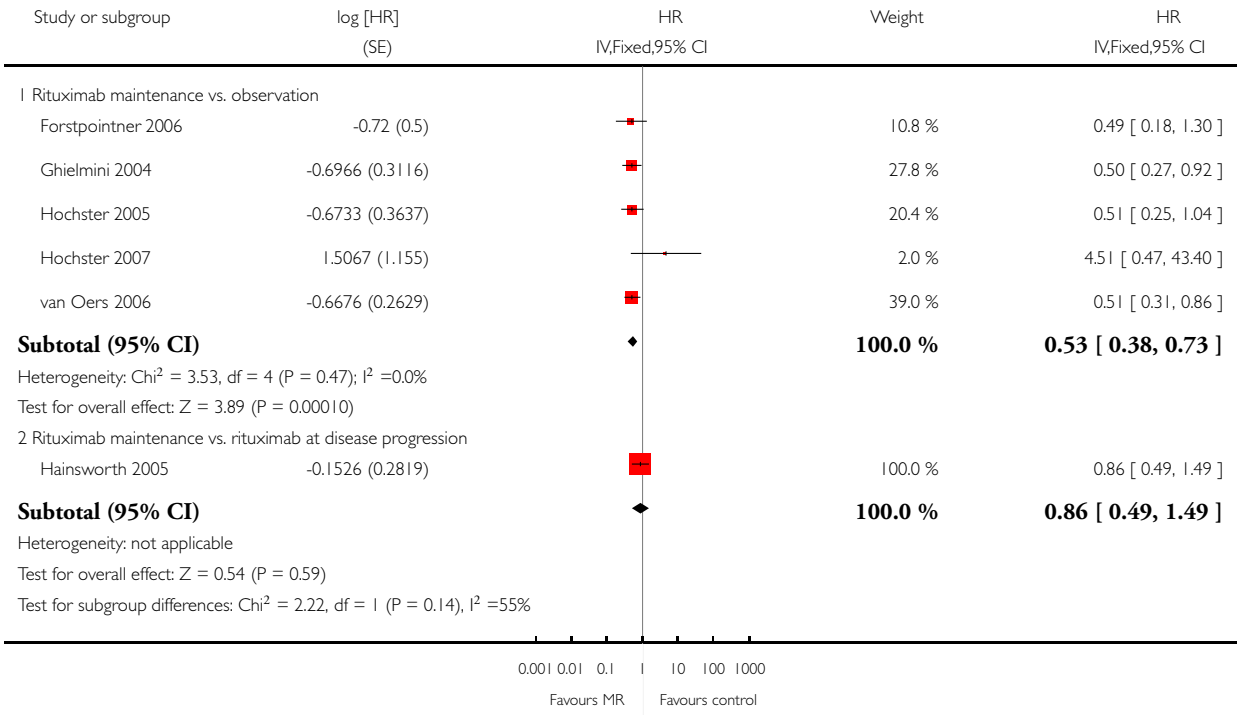
Study or subgroup	log [Hazard Ratio] (SE)	Hazard Ratio IV,Fixed,95% CI	Weight	Hazard Ratio IV,Fixed,95% CI
1 Maintenance after first induction				
Ghielmini 2004	-0.025 (0.7072)		19.4 %	0.98 [0.24, 3.90]
Hochster 2005	-0.6733 (0.3637)		73.3 %	0.51 [0.25, 1.04]
Hochster 2007	1.5067 (1.155)		7.3 %	4.51 [0.47, 43.40]
Subtotal (95% CI)			**100.0 %**	**0.68 [0.37, 1.25]**
Heterogeneity: Chi² = 3.57, df = 2 (P = 0.17); I² =44%				
Test for overall effect: Z = 1.25 (P = 0.21)				
2 Maintenance after two inductions or more				
Forstpointner 2006	-0.72 (0.5)		10.2 %	0.49 [0.18, 1.30]
Ghielmini 2004	-0.862 (0.3516)		20.7 %	0.42 [0.21, 0.84]
Hainsworth 2005	-0.1526 (0.2819)		32.1 %	0.86 [0.49, 1.49]
van Oers 2006	-0.6676 (0.2629)		37.0 %	0.51 [0.31, 0.86]
Subtotal (95% CI)			**100.0 %**	**0.58 [0.42, 0.79]**
Heterogeneity: Chi² = 3.09, df = 3 (P = 0.38); I² =3%				
Test for overall effect: Z = 3.43 (P = 0.00061)				
Test for subgroup differences: Chi² = 0.21, df = 1 (P = 0.65), I² =0.0%				

Analysis 3.4. Comparison 3 Subgroup analysis (OS), Outcome 4 Type of control.

Review: Rituximab as maintenance therapy for patients with follicular lymphoma

Comparison: 3 Subgroup analysis (OS)

Outcome: 4 Type of control

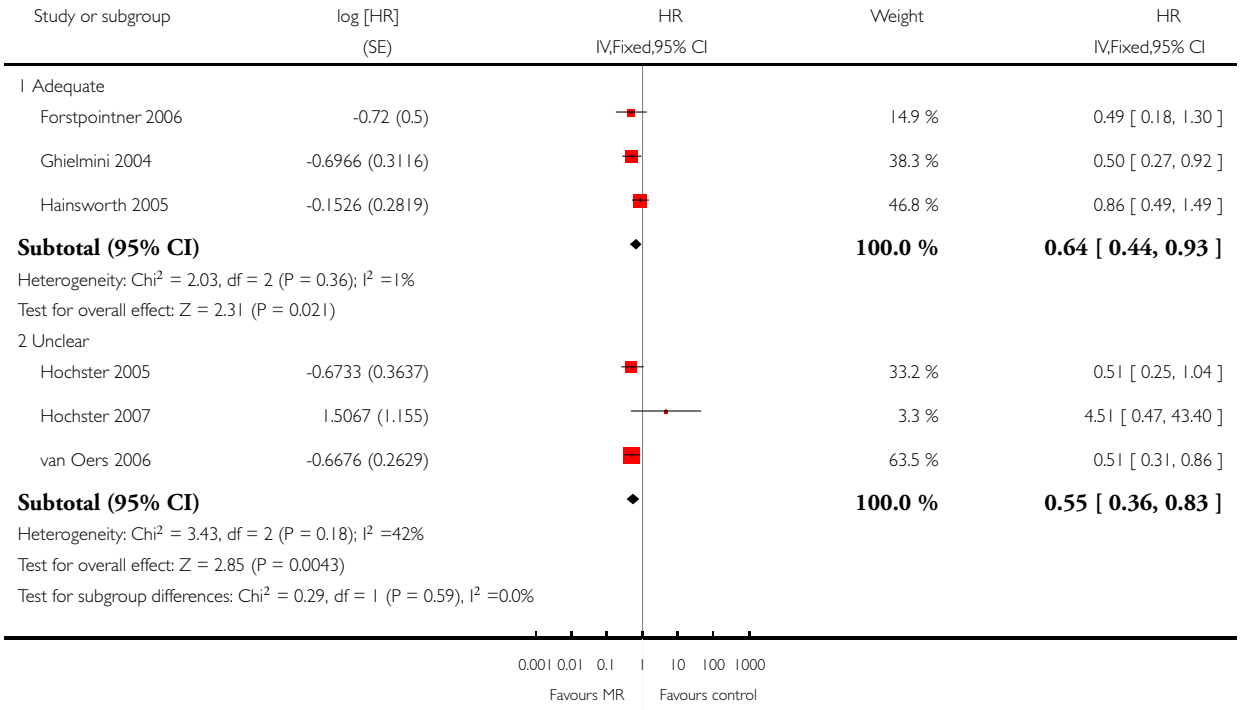


Analysis 4.1. Comparison 4 Sensitivity analysis (OS), Outcome 1 Quality of allocation concealment.

Review: Rituximab as maintenance therapy for patients with follicular lymphoma

Comparison: 4 Sensitivity analysis (OS)

Outcome: 1 Quality of allocation concealment

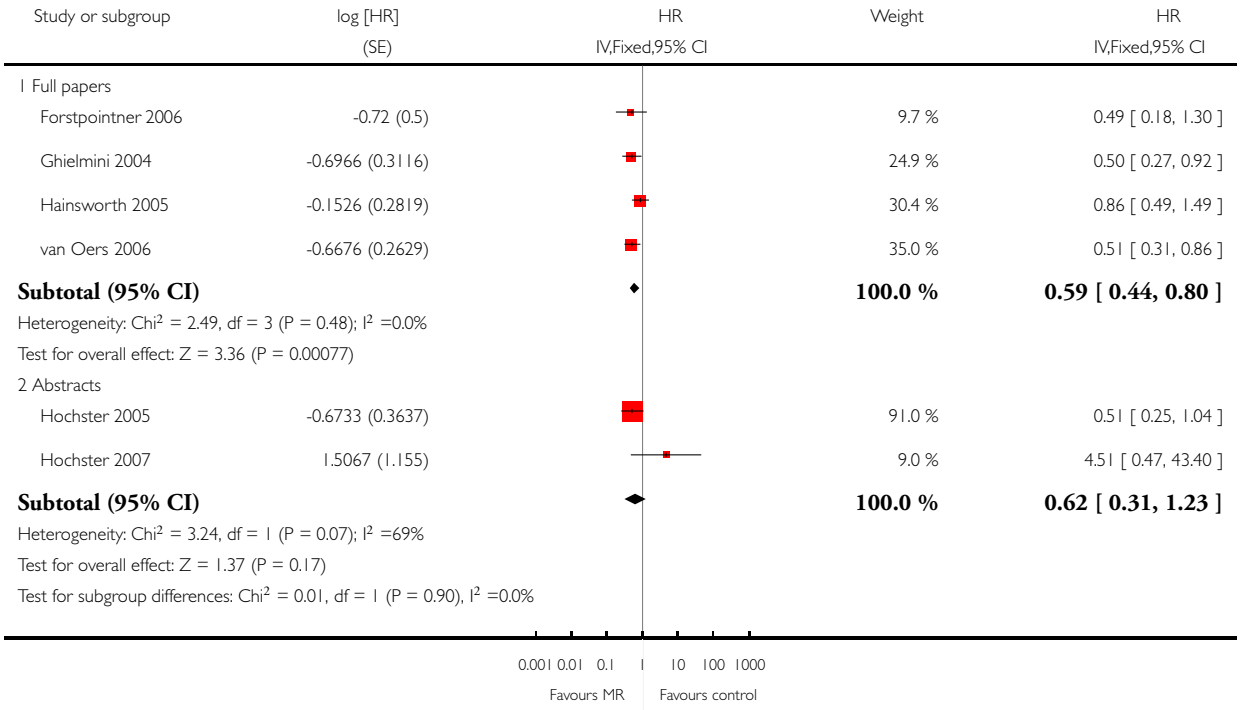


Analysis 4.2. Comparison 4 Sensitivity analysis (OS), Outcome 2 Type (place) of publication.

Review: Rituximab as maintenance therapy for patients with follicular lymphoma

Comparison: 4 Sensitivity analysis (OS)

Outcome: 2 Type (place) of publication



Analysis 5.1. Comparison 5 Adverse events with rituximab maintenance therapy vs. observation, Outcome 1 Grade III/IV.

Review: Rituximab as maintenance therapy for patients with follicular lymphoma

Comparison: 5 Adverse events with rituximab maintenance therapy vs. observation

Outcome: 1 Grade III/IV

Study or subgroup	R maintenance n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Forstpointner 2006	22/80	14/82		48.8 %	1.61 [0.89, 2.92]
Ghielmini 2004	20/73	15/78		51.2 %	1.42 [0.79, 2.57]
Total (95% CI)	**153**	**160**		**100.0 %**	**1.52 [1.00, 2.30]**

Total events: 42 (R maintenance), 29 (Control)

Heterogeneity: $Chi^2 = 0.08$, df = 1 (P = 0.77); $I^2 = 0.0\%$

Test for overall effect: Z = 1.95 (P = 0.051)

Analysis 5.2. Comparison 5 Adverse events with rituximab maintenance therapy vs. observation, Outcome 2 Infectious.

Review: Rituximab as maintenance therapy for patients with follicular lymphoma

Comparison: 5 Adverse events with rituximab maintenance therapy vs. observation

Outcome: 2 Infectious

Study or subgroup	R maintenance n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Forstpointner 2006	22/80	15/82		74.9 %	1.50 [0.84, 2.68]
Ghielmini 2004	2/73	1/78		4.9 %	2.14 [0.20, 23.07]
van Oers 2006	15/167	4/167		20.2 %	3.75 [1.27, 11.06]
Total (95% CI)	**320**	**327**		**100.0 %**	**1.99 [1.21, 3.27]**

Total events: 39 (R maintenance), 20 (Control)

Heterogeneity: $Chi^2 = 2.22$, df = 2 (P = 0.33); $I^2 = 10\%$

Test for overall effect: Z = 2.71 (P = 0.0067)

Analysis 5.3. Comparison 5 Adverse events with rituximab maintenance therapy vs. observation, Outcome 3 Infectious, severe.

Review: Rituximab as maintenance therapy for patients with follicular lymphoma

Comparison: 5 Adverse events with rituximab maintenance therapy vs. observation

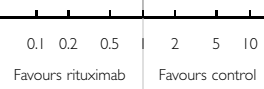
Outcome: 3 Infectious, severe

Study or subgroup	R maintenance n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Forstpointner 2006	3/80	2/82		28.5 %	1.54 [0.26, 8.96]
Ghielmini 2004	2/73	1/78		13.9 %	2.14 [0.20, 23.07]
van Oers 2006	15/167	4/167		57.6 %	3.75 [1.27, 11.06]
Total (95% CI)	**320**	**327**		**100.0 %**	**2.90 [1.24, 6.76]**

Total events: 20 (R maintenance), 7 (Control)

Heterogeneity: $Chi^2 = 0.78$, df = 2 (P = 0.68); $I^2 = 0.0\%$

Test for overall effect: Z = 2.46 (P = 0.014)



APPENDICES

Appendix 1. CENTRAL search strategy

((mabthera OR rituximab OR rituxan OR (monoclonal NEAR antibod*) OR (MeSH descriptor, Radioimmunotherapy this term only in MeSH products) OR (MeSH descriptor , Antibodies, Monoclonal, this term only in MeSH products)) AND ((MeSH descriptor, Lymphoma, Non-Hodgkin, this term only in MeSH products) OR lymphom*)

Appendix 2. MEDLINE search strategy

(follicular OR indolent OR "low grade" OR "Lymphoma, Follicular"[MeSH] OR "Lymphoma, Low-Grade"[MeSH]) AND ("Lymphoma, Non-Hodgkin"[MeSH] OR lymphoma OR NHL) AND (rituximab OR mabthera OR rituxan OR IDEC-102 OR IDEC-C2B8 OR Rituksimabi OR Rituximabum OR (monoclonal NEAR antibod*) OR anti-CD20 OR Antibodies, Monoclonal [MESH] OR immunotherapy OR "rituximab"[Substance Name] OR "131I-rituximab"[Substance Name] OR "rituximab-alliinase conjugate"[Substance Name])

Appendix 3. EMBASE search strategy

('nonhodgkin lymphoma' OR lymphoma OR NHL) AND ('follicular lymphoma' OR follicular OR indolent OR 'b cell lymphoma') AND ('monoclonal antibody' OR 'rituximab' OR rituximab OR rituxan OR mabthera)

Appendix 4. LILACS search strategy

(“LYMPHOMA” or “LYMPHOMA, FOLLICULAR”) and (((rituxan) or (rituximab) or “RITUXIMAB” or “RITUXIMABE”) or “MONOCLONAL ANTIBODIES”)

Appendix 5. Database of clinical trials in haematological malignancies search strategy

(Free Search = rituxan OR Free Search = rituximab OR Free Search = mabthera OR Free Search = monoclonal antibody* OR Free Search = MoAb OR Free Search = immunotherapy) AND (Free Search = lymphom*)

HISTORY

Protocol first published: Issue 2, 2007

Review first published: Issue 2, 2009

12 June 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

LV is the co-ordinator of the review, guided by LL.

LV is responsible for data collection, writing to authors for additional information, and organising retrieval of papers.

LV is responsible for constructing the search strategy.

AGG is responsible for undertaking searches.

AGG, LV, and OS are responsible for screening search results, abstracting data from papers, screening retrieved papers against inclusion criteria, and appraising quality of papers; the latter review author was in charge, in case of disagreement.

LV is responsible for entering data into RevMan.

All review authors participated in analysis and interpretation of data.

LV is responsible for writing the review.

DECLARATIONS OF INTEREST

None