

Rituximab Maintenance for the Treatment of Patients With Follicular Lymphoma: Systematic Review and Meta-analysis of Randomized Trials

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- Background** Follicular lymphoma is characterized by slow growth and an initially high rate of response to treatment, but patients typically relapse and experience progressive disease. Rituximab in combination with chemotherapy has been shown to improve overall survival in patients with follicular lymphoma compared with chemotherapy alone, but data from randomized clinical trials evaluating rituximab maintenance treatment in these patients are limited. We aimed to evaluate the effect of maintenance treatment with rituximab on the overall survival of patients with follicular lymphoma.
- Methods** We performed a systematic review and meta-analysis of randomized controlled trials that compared rituximab maintenance therapy with observation or treatment at relapse (no maintenance therapy). We searched *The Cochrane Library*, PubMed, EMBASE, LILACS, conference proceedings, databases of ongoing trials, and references of published trials. Two reviewers independently assessed the quality of the trials and extracted data. Hazard ratios for time-to-event data were estimated and pooled.
- Results** Five trials including 1143 adult patients were included in this meta-analysis. Data for 985 patients with follicular lymphoma were available for the meta-analysis of overall survival. Patients treated with maintenance rituximab had statistically significantly better overall survival than patients in the observation arm or patients treated at relapse (hazard ratio [HR] for death = 0.60, 95% confidence interval [CI] = 0.45 to 0.79). The rate of infection-related adverse events was higher with rituximab maintenance treatment (HR = 1.99, 95% CI = 1.21 to 3.27). Patients with refractory or relapsed (ie, previously treated) follicular lymphoma had a survival benefit with maintenance rituximab therapy (HR for death = 0.58, 95% CI = 0.42 to 0.79), whereas previously untreated patients did not (HR for death = 0.68, 95% CI = 0.37 to 1.25).
- Conclusions** These results suggest that maintenance therapy with rituximab, either as four weekly infusions every 6 months or as a single infusion every 2–3 months, should be added to standard therapy for patients with relapsed or refractory (ie, previously treated) follicular lymphoma after successful induction therapy. The higher rate of infections with rituximab therapy should be taken into consideration when making treatment decisions.

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Follicular lymphoma, which represents 15%–30% of newly diagnosed lymphomas, is an indolent lymphoma that is characterized by slow growth and a high initial response rate but relapsing and progressive disease (1,2). Most patients are diagnosed with advanced disease, that is, stage III or IV, and cannot be cured with currently available conventional therapies. New treatment modalities are therefore urgently needed.

The chimeric monoclonal antibody rituximab targeted against CD20, a protein that is expressed on the surface of all mature B cells, is active in many B-cell lymphomas that express this molecule. Rituximab administered intravenously in combination with chemotherapy improves overall survival in patients with newly diagnosed and relapsed indolent lymphoma compared with chemotherapy alone (3). The value of rituximab as maintenance therapy for patients who responded to induction therapy is yet to

be determined. Phase 2 studies suggest that rituximab may improve response rates (4,5). Although clinical trials have demonstrated that rituximab maintenance treatment may prolong complete

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remission and the progression-free interval, clear evidence of improvement in overall survival is lacking (6). Thus, rituximab maintenance therapy for follicular lymphoma is not recommended in current treatment guidelines (http://www.nccn.org/professionals/physician_gls/f_guidelines.asp).

To date, limited data from randomized clinical trials are available to guide the use of rituximab as maintenance therapy for patients with follicular lymphoma who respond to induction therapy, and few long-term data have been published. We performed a systematic review of the literature and a meta-analysis of all randomized trials to evaluate the effects of rituximab maintenance treatment on the overall survival of patients with follicular lymphoma.

Methods

Data Sources

We searched The Cochrane Central Register of Controlled Trials, published in *The Cochrane Library* (issue 2, 2007); PubMed (1966 to June 2007); EMBASE (1974 to June 2007); LILACS (1982 to June 2007); the database of clinical trials in hematologic malignancies (www.hematology-studies.org); conference proceedings of the American Society of Hematology (1995–2007), conference proceedings of the American Society of Clinical Oncology Annual Meeting (1995–2007), and proceedings of the European Hematology Association; and databases of ongoing and unpublished trials: <http://www.controlled-trials.com/>, <http://www.clinicaltrials.gov/ct>, <http://clinicaltrials.nci.nih.gov/>. The terms “follicular” or “indolent lymphoma” and similar terms and “rituximab” or “monoclonal antibodies” and similar terms were cross-searched. We scanned references of all included trials and reviews identified for additional studies.

Study Selection

We included all randomized controlled trials that compared rituximab maintenance therapy with observation or treatment at relapse (no maintenance therapy) in patients with histologically confirmed B-cell follicular lymphoma. We included trials regardless of publication status, date of publication, and language.

Data Extraction and Quality Assessment

Two reviewers (L. Vidal and A. Gafter-Gvili) independently extracted data regarding case definitions, characteristics of patients, and outcomes from included trials. In the event of disagreement between the two reviewers regarding any of the above, a third reviewer (O. Shpilberg) extracted the data. Data extraction was discussed, and decisions were documented.

We contacted the first or corresponding author of each included trial and the researchers who were active in the field to obtain information on unpublished trials or additional information on the published trials. Two reviewers (L. Vidal and A. Gafter-Gvili) independently assessed the trials for methodological quality. Allocation concealment, generation of the allocation sequence, and blinding were individually assessed and graded as adequate, unclear, or inadequate (7). We also collected data on exclusions after randomization and whether the primary analysis was per-

CONTEXT AND CAVEATS

Prior knowledge

Most follicular lymphoma patients respond to initial treatment, but they often experience disease relapse.

Study design

Meta-analysis of randomized controlled trials of patients with follicular lymphoma comparing rituximab maintenance therapy with observation or treatment at relapse.

Contributions

Maintenance rituximab therapy improved overall survival of follicular lymphoma patients compared with observation or treatment at relapse but led to higher rates of infection-related adverse events. Previously treated patients had improved survival with maintenance rituximab therapy, but previously untreated patients did not.

Implications

Maintenance therapy with rituximab improves survival in patients who have previously been treated for follicular lymphoma, but the high rate of infection should be considered when making treatment decisions.

Limitations

Three of the five trials included in the meta-analysis were terminated before the planned endpoint of the study, so longer follow-up was not possible and treatment effects may have been overestimated.

From the Editors

formed according to the intention-to-treat principle or per protocol.

Outcome Measures

The primary outcome was overall survival [as defined in (8,9)]. Secondary outcomes included event-free interval, progression-free interval, and adverse events.

Data Synthesis and Statistical Analysis

Hazard ratios (HRs) and variances for time-to-event outcomes were estimated as described by Parmar et al. (10,11) and pooled according to Peto's method (Review Manager [RevMan], version 4.2 for Windows; The Cochrane Collaboration, Oxford, UK). A hazard ratio less than 1.0 was in favor of rituximab maintenance therapy. Relative risks (RRs) and 95% confidence intervals (CIs) for dichotomous data were estimated using the Mantel-Haenszel method. We used a fixed effect model, and when possible, we performed a sensitivity analysis by repeating the above analysis using a random effects model (the DerSimonian and Laird method) (12).

We assessed heterogeneity of trial results by the chi test of heterogeneity and the *I*² statistic of inconsistency. Statistically significant heterogeneity was defined as *P* less than .1 or an *I*² statistic greater than 50% (13). Potential sources of heterogeneity were explored through stratifying by type of induction therapy (chemotherapy, rituximab, chemotherapy + rituximab), rituximab schedule (one infusion every 2 months; four weekly infusions every 6 months), allocation concealment, blinding, and size of studies. All statistical tests were two-sided.

Publication Bias and Small Studies' Effect

We examined the funnel plot for overall survival to estimate the effect of small study size (ie, publication bias).

Results

Description of Trials

The literature search identified 265 trials, of which 27 were considered potentially relevant. Additional trials were identified by searching conference proceedings and electronic resources of ongoing trials. Figure 1 illustrates the process of study selection. Reasons for exclusion are detailed in Supplementary Table 1 (available online). Five trials that were performed between 1998 and 2004 fulfilled the inclusion criteria (6,14–18). Two of the included abstracts (17,18) reported the outcomes of different subsets of patients from the same trial (Eastern Cooperative Oncology Group study E1496).

Patient Characteristics. All trials included patients with indolent lymphoma. Three trials included patients with follicular lymphoma of any grade (6,14,16). Two trials included patients with follicular lymphoma grade 1 or 2 or with small lymphocytic lymphoma (15,17,18). One trial (15) also included patients with mantle cell lymphoma (Table 1) (16). The minimal requirement for inclusion in the original trials was either stable disease (three trials) (6,15,17,18) or partial remission (two trials) (14,16) after induction therapy. Most patients (67%) had relapsed or refractory disease. One trial (6) included patients with relapsed disease and chemotherapy-naïve patients. One trial included untreated patients only (17,18). Other common exclusion criteria of the original trials were poor performance status, active infection, symptomatic central nervous system disease, and a history of serious medical conditions. The percentage of patients with stage III or IV follicular lymphoma ranged from 85% to 100% and was not reported in one trial (15). In that trial, 88% of patients had low or low-to-intermediate international prognostic index scores. The median follow-up ranged from 26 to 41 months.

Trial Design. In three trials (14,16–18), patients were randomly assigned to a type of induction therapy and subsequently underwent a second random assignment to maintenance therapy or observation.

In the other two trials (6,15), all patients were treated with the same induction therapy and were subsequently randomly assigned to maintenance therapy or observation.

Induction Therapy and Maintenance Protocol. Induction therapy included three options: chemotherapy alone (17,18), chemotherapy with or without rituximab (14,16), and rituximab alone (6,15). Prior rituximab treatment was not allowed in two trials (6,15). In one trial (15), patients in the control group received rituximab upon progression of follicular lymphoma; in the other four trials, patients in the control group were observed without rituximab treatment. In all trials, a dose of rituximab consisted of 375 mg/m²/d and was not adjusted according to blood concentration. The treatment schedule differed among the trials: In three trials (15–18), rituximab was administered weekly for 4 consecutive weeks (four doses) every 6 months, and in two trials (6,14), a single infusion of rituximab was administered every 2–3 months. The duration of treatment also varied, from 8–9 months (6,16) to 2 years (14,15,17,18).

Quality of Trials. Allocation concealment was reported as adequate in three trials (6,15,16) and was not reported in the other two trials. None of the trials were conducted in a blinded fashion. An intention-to-treat analysis (ie, all randomly assigned patients were included for assessment of the primary outcome) was performed in two trials (14,15). The rate of dropout was less than 10% in four trials (6,14–16). The quality of allocation concealment and of generation of randomization sequence and the funding sources of the trials are described in detail in Table 1.

Overall Survival

All five trials (985 patients) were eligible for the meta-analysis of overall survival. The numbers of randomly assigned and analyzed patients in each included trial are described in Table 1. Patients who were treated with rituximab maintenance therapy had statistically significantly better overall survival than patients in the control group (HR of death = 0.60, 95% CI = 0.45 to 0.79) (Figure 2). No statistically significant heterogeneity was observed for overall survival. The funnel plot of the primary outcome did not support a publication bias (Figure 2).

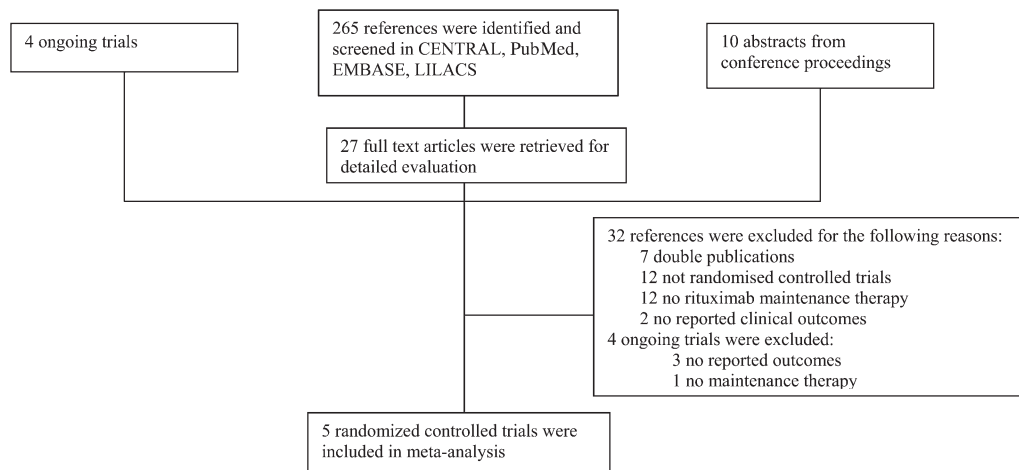


Figure 1. Flow diagram of publications identified for study and exclusions.

Table 1. Description of quality of included trials, characteristics of patients, and treatment*

Trial ID (reference)	No. of randomly assigned patients	No. of patients in meta-analysis	Quality of allocation concealment	Quality of sequence generation	No. (%) dropouts	Funding source(s)	Type of lymphoma	Induction therapy	Response to induction	Rituximab maintenance protocol	Median follow-up, mo
Hainsworth et al. (15)	90	90	Adequate	Adequate	0	Academic, industry	Previously treated FL, SLL	Rituximab	Stable disease/ PR/CR	Weekly for 4 wk every 6 mo for 2 y	41
Hochster et al. (17, 18)	CVP (17), 304; FC (18), 69	CVP (16), 237†; FC (17), 69	Unclear	Unclear	Not reported	Not reported	Untreated FL, SLL‡ (17); untreated FL, SLL (18)	CVP, FC	Stable disease/ PR/CR	Weekly for 4 wk every 6 mo for 2 y	36
Forstpointner et al. (16)	195	105§	Adequate	Adequate	19 (10)	Academic	Relapsed FL, MCL‡	FCM ± rituximab	PR/CR	Weekly for 4 wk, at 3 and 9 mo	26
Ghielmini et al. (6)	151	150	Adequate	Unclear	1 (0.7)	Academic, industry	Newly diagnosed and relapsed FL	Rituximab	Stable disease/ PR/CR	A single infusion every 2 mo for four doses	35
van Oers et al. (14)	334	334	Unclear	Unclear	0	Academic, industry	Relapsed FL	CHOP ± rituximab	PR/CR	A single infusion every 3 mo for 2 y	33.3

* CVP = cyclophosphamide, vincristine, prednisone; FC = fludarabine, cyclophosphamide; FL = follicular lymphoma; SLL = small lymphocytic lymphoma; MCL = mantle cell lymphoma; FCM = fludarabine, cyclophosphamide, mitoxantrone; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; PR = partial response; CR = complete response.

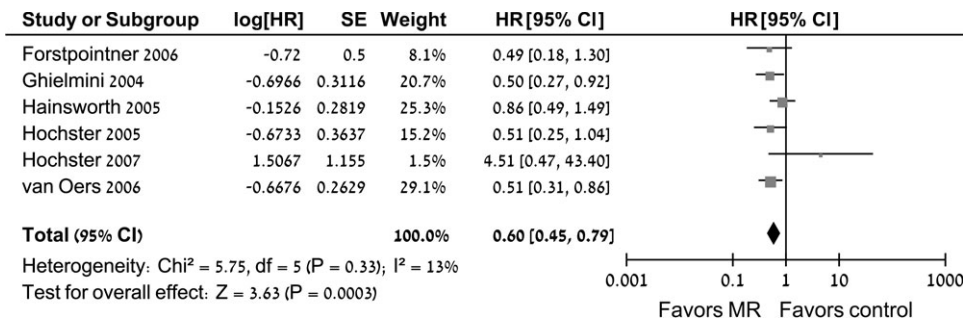
† Three hundred four randomly assigned patients, 237 of all included patients had FL.

‡ Separate analysis was possible for patients with FL.

§ One hundred ninety-five randomly assigned patients, of them 19 were lost to follow-up. Of the 176 analyzed patients, 105 had FL.

|| One hundred fifty-one randomly assigned patients, one lost to follow-up.

Figure 2. Pooled estimates of overall survival with rituximab maintenance therapy for patients with follicular lymphoma compared with observation and rituximab at disease progression. **Black squares** represent the point estimate, **their sizes** represent their weight in the pooled analysis, and the **horizontal bars** represent the 95% CI. The **black diamond** at the bottom represents the pooled point estimate. HR = hazard ratio for death; CI = confidence interval; MR = maintenance therapy with rituximab.



Sensitivity Analysis. One published abstract was excluded in the sensitivity analysis of overall survival, as recommended by its authors (17). Excluding these data did not change the pooled overall survival results.

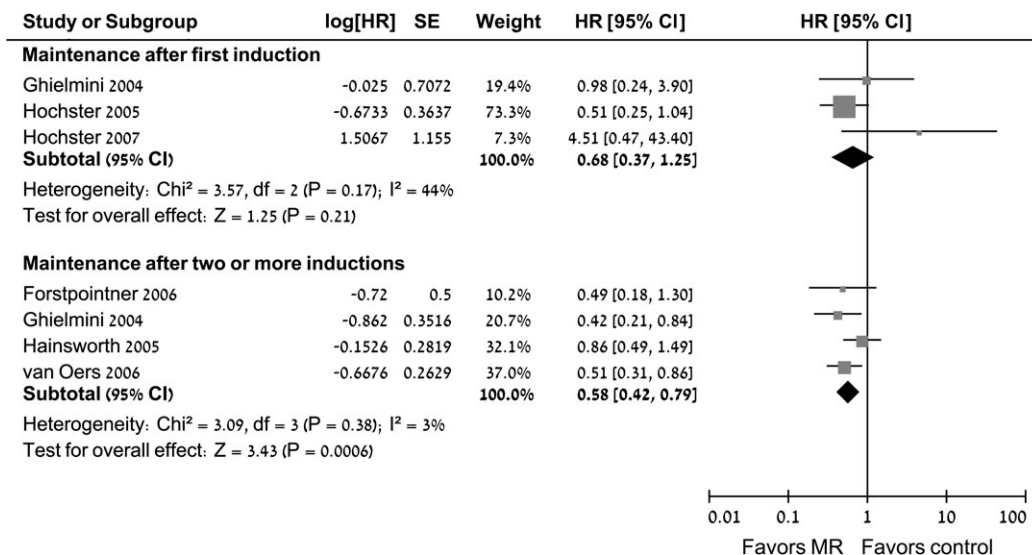
In addition, overall survival in the trials was analyzed separately according to the following variables: type of control arm (observation vs treatment at progression), maintenance schedule, previous treatment, and rituximab induction therapy.

Four trials compared rituximab maintenance therapy with observation (HR of death = 0.53, 95% CI = 0.38 to 0.73) (6,14, 16–18), and one trial compared rituximab maintenance therapy with rituximab treatment on progression of lymphoma (HR of death = 0.86, 95% CI = 0.49 to 1.49) (15). However, it is important to note that the latter trial lacked statistical power to show an effect of rituximab maintenance, if such an effect existed.

The type of rituximab maintenance schedule had no effect on overall survival. Treatment with a single infusion of rituximab every 2–3 months improved overall survival (HR of death = 0.51, 95% CI = 0.34 to 0.75), but weekly treatment with rituximab for 4 weeks every 6 months resulted in only borderline benefit (HR of death = 0.70, 95% CI = 0.47 to 1.04; three trials) (15–18) compared with observation or rituximab at progression.

Patients with refractory or relapsed follicular lymphoma had a clear survival benefit with maintenance rituximab therapy compared with patients who underwent observation (HR of death = 0.58, 95% CI = 0.42 to 0.79; four trials) (6,14–16) (Figure 3).

Figure 3. Pooled HRs of overall survival of patients with refractory or relapsed follicular lymphoma and of untreated patients with follicular lymphoma. **Black squares** represent the point estimate, **their sizes** represent their weight in the pooled analysis, and the **horizontal bars** represent the 95% CI. The **black diamond** at the bottom represents the pooled point estimate. HR = hazard ratio for death; CI = confidence interval; MR = maintenance therapy with rituximab.



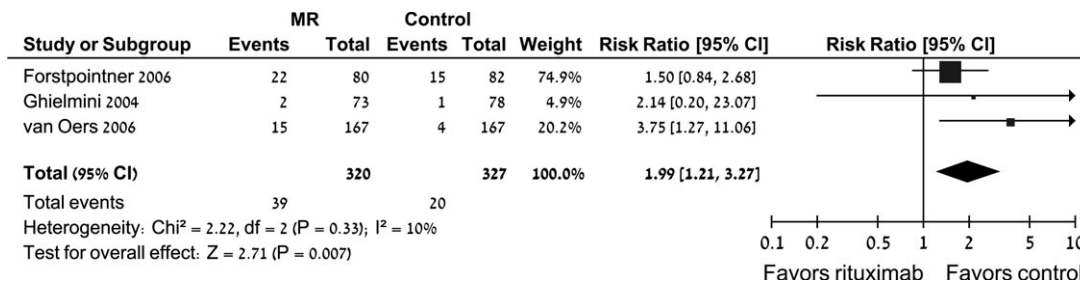


Figure 4. Infection-related adverse events in patients with follicular lymphoma treated with rituximab maintenance compared with observation. **Black squares** represent the point estimate, **their sizes** represent their weight in the pooled analysis, and the **horizontal bars** represent the 95% CI. The **black diamond** at the bottom represents the pooled point estimate. CI = confidence interval; MR = maintenance therapy with rituximab.

maintenance treatment on quality of life were not reported for the included trials.

Adverse Events

The rate of grade 3 or 4 adverse events was reported in three trials (6,14,16) and was higher in the rituximab maintenance therapy arm than in the observation arm (RR = 1.52, 95% CI = 1.00 to 2.30). Specifically, patients who underwent rituximab maintenance therapy had more infection-related adverse events than patients in the observation arm (RR = 1.99, 95% CI = 1.21 to 3.27) (Figure 4). When only grade 3 or 4 infection-related adverse events were included in the analysis, this effect was even more pronounced (RR = 2.90, 95% CI = 1.24 to 6.76). In one trial (14), mainly infections of the upper respiratory tract occurred, and hospitalization was required for all grade 3 or 4 infection-related adverse events. The rate of adverse events requiring discontinuation of therapy was reported in one trial (14) and was higher in the group that received rituximab maintenance therapy.

Discussion

This meta-analysis demonstrates for the first time, to our knowledge, that rituximab maintenance therapy improves overall survival and disease control compared with observation in patients with refractory or relapsed follicular lymphoma who responded to induction therapy. This effect on overall survival was statistically

significant, despite higher rates of severe adverse events, and especially treatment-related infections. Based on data from one trial, no difference in overall survival was observed when rituximab maintenance was compared with retreatment with rituximab at disease progression.

Despite different kinds of induction therapy and maintenance schedule, the point estimate for all pooled analyses favored rituximab maintenance therapy. This clinical heterogeneity in the absence of statistical heterogeneity supports the robustness of our results.

However, rituximab maintenance therapy has its drawbacks. The most common adverse events were infections, some life threatening. Rituximab may cause immunosuppression through several mechanisms, as delayed-onset cytopenia, particularly neutropenia (19), and hypogammaglobulinemia (20–23). Both cytopenia and hypogammaglobulinemia have been reported to various degrees among patients who were treated with rituximab for various reasons. These effects might be of even greater clinical significance when rituximab is administered for a longer period, as it is in maintenance therapy (24). In addition to the clinical effects of prolonged treatment, the financial costs of this rituximab maintenance therapy should be taken into consideration.

Several limitations of our analysis merit consideration. The included studies differed in their induction therapy: in two trials, rituximab monotherapy was given and the chemotherapy regimens varied among the other trials. In the trial by Hochster et al. (18), patients who

Table 2. Description of ongoing trials of rituximab maintenance therapy*

Investigator/protocol chair (reference), ClinicalTrials.gov web site	Patients	Induction	Intervention
Williams/Kahl (28), http://clinicaltrials.gov/ct2/show/NCT00075946	Patients with low tumor burden, stage III–IV indolent lymphoma	Rituximab	Arm I: rituximab upon disease progression Arm II: MR
Taverna (29), http://clinicaltrials.gov/ct2/show/NCT00227695	Patients with untreated or resistant or relapsed FL	Rituximab	Arm I: MR for 8 mo Arm II: MR up to 5 y
Pettengell and Linch (30), http://clinicaltrials.gov/ct2/show/NCT00005589	Patients with relapsed FL	Chemotherapy + HSCT + in vivo rituximab purging	Arm I: MR Arm II: observation
Ardeshna (31), http://clinicaltrials.gov/ct2/show/NCT00112931	Patients with newly diagnosed stage II–IV FL with no symptoms	See Intervention	Arm I: observation Arm II: induction rituximab Arm III: induction rituximab and MR
Salles (32), http://clinicaltrials.gov/show/NCT00140582	Patients with untreated FL requiring treatment	Rituximab with chemotherapy	Arm I: MR Arm II: no treatment

* FL = follicular lymphoma; HSCT = hematopoietic stem cell transplantation; MR = rituximab maintenance therapy.

were treated with fludarabine and cyclophosphamide had a worse outcome with maintenance therapy than those who received cyclophosphamide, vincristine, and prednisone during induction therapy, suggesting a possible interaction between the type of chemotherapy used in induction therapy and the effect of rituximab maintenance therapy. In addition, because these trials were conducted before rituximab was considered part of standard therapy in patients with follicular lymphoma, some of the patients did not receive rituximab during induction therapy. The maintenance schedule also varied—weekly infusions for 4 consecutive weeks every 6 months or a single infusion of rituximab every 2–3 months. Again, it should be noted that these differences in rituximab schedule did not change the results.

Three trials were terminated earlier than initially planned after the stopping criteria were met (14,16–18). Statistical theories and the results of a systematic review of randomized trials that were stopped early for apparent benefit suggest that the early stopping of trials leads to a systematic overestimation of the treatment effects (25,26). The scientific validity of trials that are stopped early is further compromised when trials yield inconclusive data about outcomes that did not influence trial termination, in this case overall survival.

A recently published systematic review on rituximab in non-Hodgkin lymphoma favors the use of maintenance rituximab for patients with follicular lymphoma who respond to treatment with combination chemotherapy and/or rituximab (27). However, these recommendations were not based on overall survival and did not include a statistical summary of pooled outcomes.

Our results suggest that rituximab maintenance therapy for up to 2 years, either as four weekly infusions every 6 months or as a single infusion every 2–3 months, should be added to standard therapy of patients with relapsed or refractory follicular lymphoma after successful induction treatment.

Open questions still exist regarding the effect of rituximab maintenance on the outcome of patients with follicular lymphoma, some of which are currently being evaluated in randomized clinical trials (Table 2). These questions include the effects of rituximab maintenance therapy compared with rituximab at disease progression, effects of rituximab maintenance therapy in previously untreated patients with advanced follicular lymphoma, effects of rituximab maintenance therapy in patients with follicular lymphoma following rituximab and chemotherapy induction, the optimal duration of rituximab maintenance therapy, and the optimal schedule of rituximab maintenance. Finally, both randomized controlled trials and observational studies should have longer follow-up to assess the long-term toxicity of rituximab.

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Roche had no role in the study design, the collection and analysis of the data, the interpretation of the results, the preparation of the manuscript, the decision to submit the manuscript for publication, or in the funding of the study.

The study was conducted as part of the Cochrane Collaboration, and its protocol is available in *The Cochrane Library*.

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