REVIEW

Efficacy of Rituximab in the Setting of Steroid-Refractory Chronic Graft-versus-Host Disease: A Systematic Review and Meta-Analysis

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Increased insight into the role of B lymphocytes in the pathophysiology of graft-versus-host disease has led to a number of studies assessing the efficacy of the anti-CD20 monoclonal antibody (mAb) rituximab in treating steroid-refractory chronic graft-versus-host disease (cGVHD). Findings vary greatly among these studies, however. We conducted a systematic review to summarize the totality of evidence on the efficacy of rituximab in steroid-refractory cGVHD. We performed a PubMed search and contacted experts in the field to identify relevant studies. Endpoints included overall response rate (including organ-specific) and ability of rituximab to allow dosage reduction of immunosuppressive therapies. Data were pooled under a random-effects model. Seven studies (3 prospective and 4 retrospective, with a total of 111 patients) met the inclusion criteria. The pooled proportion of overall response was 0.66 (95% confidence interval = 0.57 to 0.74). There was no heterogeneity among the pooled studies. Response rates were 13% to 100% for cGVHD of the skin, 0 to 83% for cGVHD of the oral mucosa, 0 to 66% for cGVHD of the liver, and 0 to 38% for cGVHD of the lung. Common adverse events were related to infusion reactions or infectious complications. The relatively small number of patients and the varying criteria for reporting organ response and dosage reduction of steroids, among other limitations, hinders our ability to reach definitive conclusions on the overall efficacy of rituximab for cGVHD involving other organs.

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INTRODUCTION

Chronic graft-versus-host disease (cGVHD) represents one of the most challenging sequelae of allogeneic hematopoietic cell transplantation (allo-HCT), resulting in significant long-term morbidity and mortality. The continuous growth in the number of allo-HCTs using alternate donors, particularly HLA-mismatched donors, is further increasing the incidence of cGVHD [1,2]. The increasing use of mobilized peripheral blood stem cells (PBSC) as the graft source also is contributing to the increasing prevalence of cGVHD [1-3].

A recently released National Institutes of Health (NIH) working group report on criteria for clinical trials in cGVHD provides standardized criteria for diagnosis of cGVHD and an improved scoring system that better describes the extent and severity of cGVHD for each organ, taking into account the importance of preserving function [4]. Similarly, expert consensus opinion has resulted in the establishment of more practical criteria aimed at assessing the therapeutic response in patients with cGVHD more objectively [5]. Unfortunately, however, treatment outcomes for cGVHD remain disappointing. Systemic corticosteroid therapy is the most commonly used first-line treatment for patients with established cGVHD, but long-term corticosteroid use is limited by the increased risk of infection, which remains the leading cause of death in cGVHD [6]. There is no consensus regarding the best treatment option for patients with cGVHD who

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do not respond to or progress after corticosteroid therapy. Encouraging responses have been reported using extracorporeal photopheresis [7,8], mycophenolate mofetil (MMF) [9,10], and low-dose methotrexate (MTX), among other modalities [11].

Advances in the understanding of cGVHD have implicated B lymphocytes in the pathophysiology of cGVHD. Miklos et al. [12] demonstrated a correlation between cGHVD and development of antibody responses to H-Y minor histocompatibility antigens in cases of sex-mismatched (male recipients with female donors) allo-HCT. These findings provided the scientific rationale for a number of studies exploring rituximab to treat patients with steroid-refractory cGVHD. These studies yielded varying findings regarding organ-specific responses, however. Consequently, we performed a systematic review to evaluate the totality of evidence regarding the efficacy of rituximab in treating steroid-refractory cGVHD.

METHODS

Literature Search

We searched the Medline (Pubmed) database using a broad search strategy to identify prospective or retrospective studies evaluating the efficacy of rituximab in patients with steroid-refractory cGVHD. The search was conducted using following terms: "Rituximab"[Substance Name] AND "Graft vs. Host Disease"[MeSH]. Relevant references in each obtained article were scanned to identify other relevant studies. In addition, experts in the field were approached for unpublished data or to identify additional studies in the subject area. No search limits were applied.

Inclusion Criteria

All prospective studies evaluating the efficacy of rituximab in cGVHD were included regardless of the number of patients enrolled. Retrospective studies were included if they evaluated the efficacy of rituximab in cGVHD in a minimum of 5 patients. Single case reports were excluded.

Study Selection, Quality Assessment, and Data Extraction

Two reviewers (A.M. and A.K.) appraised the list of references and selected the studies in consultation with other reviewers (M.K.D. and C.C.). Disagreements were resolved by consensus. Two reviewers (A.M. and A.K.) independently extracted the data from selected articles. Data were extracted on specific clinical outcomes (benefits and harms), as well as on the methodological quality of the studies.

Data Analysis and Statistical Methods

For the purpose of meta-analysis, the proportions were first transformed into a quantity according to the Freeman-Tukey variant of the arcsine square root transformed proportion [13]. The pooled proportion was calculated as the back-transform of the weighted mean of the transformed proportions, using a random-effects model [14].

A formal statistical test for heterogeneity using an I^2 test was performed [15]. The heterogeneity and robustness of the findings also were evaluated through additional sensitivity analyses. The possibility of publication bias was assessed using the Begg and Egger funnel plot method [16]; although this method has some limitations, it is widely used to assess publication bias [17]. The meta-analysis was performed using StatsDirect software (StatsDirect Ltd, Altrincham, Cheshire, UK). The work was performed ion accordance with the guidelines promulgated at the Quality of Reporting of Meta-Analyses conference [15].

RESULTS

Identification of Studies

Figure 1 summarizes the process used to identify and select the studies for the systematic review. The initial search yielded 37 articles, of which 31 were excluded for the reasons shown in Figure 1. Of the 6 studies that met the inclusion criteria, 3 were categorized as prospective studies and 3 were retrospective analyses. One retrospective case series was identified through expert contact [18]. We found no randomized controlled trials evaluating the efficacy of rituximab versus other therapeutic alternatives for treating steroid-refractory cGVHD.

Methodological Quality of Studies

We conducted a critical appraisal of the methodological quality of all studies.

Prospective Studies

Unclear reporting of sampling procedures makes it difficult to determine whether the study sample consisted of consecutive series of patients or a convenient sampling method was used, possibly introducing a selection or an ascertainment bias that could potentially plague observational studies.

Retrospective Studies

Whether an analysis addressed a priori hypothesis or was a result of some post hoc observation was unclear. In addition, the relatively small sample sizes (range, 8 to 38 patients) limited our ability to draw definitive conclusions from these studies.

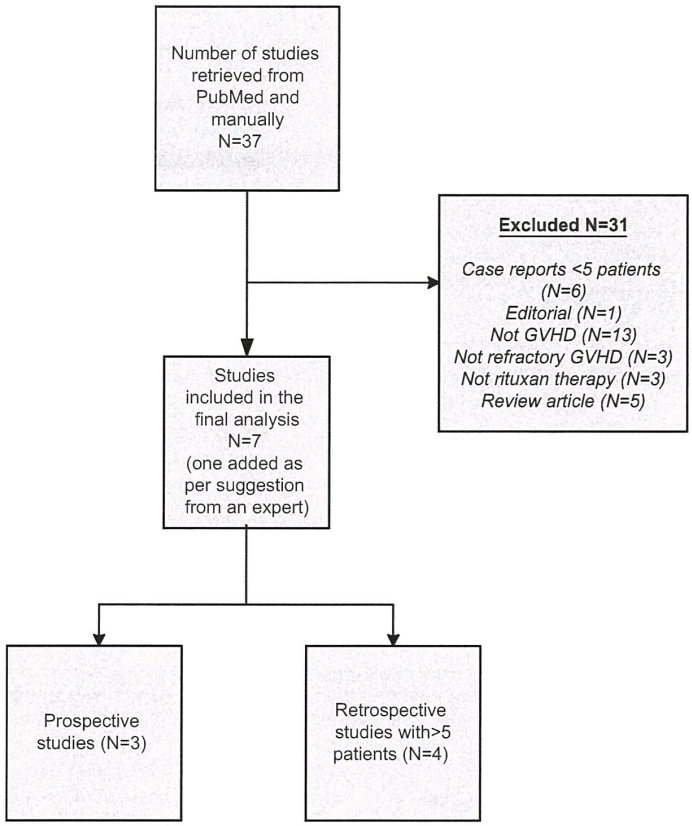

Figure 1. Identification and selection of studies.

Publication Bias

A Begg and Egger funnel plot showed a symmetric distribution, indicating the absence of a publication bias for all of the outcomes assessed here (results not shown).

Outcomes

Mortality

Mortality data were extractable from all 7 studies [18-24]. The pooled proportion of mortality from 7 studies involving 111 patients was 0.158 (95% confidence interval [CI] = 0.083 to 0.253) (Fig 2A). There was no statistically significant heterogeneity among the studies ($I^2 = 32.7\%$; $P = .178$). The pooled proportion of mortality was 0.122 (95% CI = 0.034 to 0.253) in 3 prospective studies involving 37 patients [19,20,22] and 0.158 (95% CI = 0.08 to 0.252) in 4 retrospective studies evaluating 74 patients [18,21,23,24].

Overall Response Rate

Overall response rate (ORR) data were extractable from 6 studies involving a total of 108 patients (Fig 2B) [18-21,23,24]. The pooled proportion of ORR was 0.66 (95% CI = 0.57 to 0.74), and there was no statistically significant heterogeneity among the studies ($I^2 = 0\%$; $P = .90$). The pooled proportion of ORR was 0.70 (95% CI = 0.54 to 0.83) in 2 prospective studies evaluating 34 patients [19,20] and 0.64 (95% CI = 0.53 to 0.74) in 4 retrospective studies involving 74 patients [18,21,23,24].

Organ-Specific Response

Skin cGVHD

Data on cutaneous cGVHD were extractable from 6 studies involving a total of 67 patients [18,19,21-24]. The pooled proportion ORR was 0.60 (95% CI = 0.41 to 0.78) (Fig 2C). There was a statistically significant heterogeneity among the pooled studies ($I^2 = 60\%$; $P = .03$). The pooled proportion ORR was 0.85 (95% CI = 0.59 to 0.98) in 2 prospective studies enrolling 9 patients [19,22] and 0.51 (95% CI = 0.308 to 0.717) in 4 retrospective studies involving 58 patients [18,21,23,24].

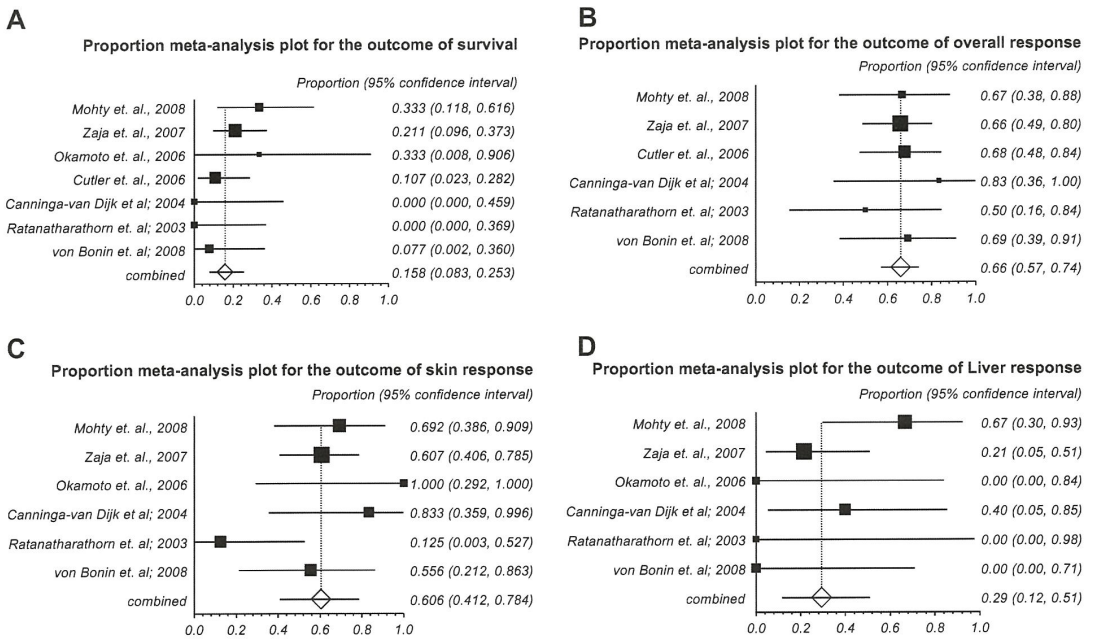

Figure 2. Forest plot for the outcomes of survival, overall response and organ specific response (skin and liver). The summary effect estimate (proportion) for individual studies are indicated by black rectangles (the size of the rectangle is proportional to the study weight), with the lines representing 95% confidence intervals (CIs). The overall summary effect estimate (proportion) and 95% CI are indicated by the diamond.

Mucosa (Oral) cGVHD

Data on cGVHD of the oral mucosa were extractable from 5 studies involving a total of 46 patients [18-20,22,24]. The pooled proportion of ORR was 0.36 (95% CI = 0.12 to 0.65). There was a statistically significant heterogeneity among the included studies for this outcome (I^2 = 73%; P = .0046). The pooled proportion of oral cGVHD response was 0.26 (95% CI = 0.007 to 0.84) in 3 prospective studies involving 15 patients [19,20,22] and 0.45 (95% CI = 0.29 to 0.62) in 2 retrospective studies involving 31 patients [18,24].

Liver cGVHD

ORR data for the outcome of liver cGVHD were extractable from 6 studies involving a total of 34 patients [18,19,21-24]. The pooled proportion of ORR was 0.29 (95% CI = 0.12 to 0.51) (Fig 2D). There was no statistically significant heterogeneity among the pooled studies for this outcome (I^2 = 41.8%; P = .126). The pooled proportion ORR was 0.28 (95% CI = 0.03 to 0.64) in 2 prospective studies enrolling 7 patients [19,22] and 0.29 (95% CI = 0.06 to 0.59) from 4 retrospective studies involving 27 patients [18,21,23,24].

Gastrointestinal cGVHD

Data on response rate for gastrointestinal (GI) cGVHD were reported in 4 studies (1 prospective and 3 retrospective) involving a total of 12 patients [18,21,22,24]. The pooled proportion ORR was 0.31 (95% CI = 0.07 to 0.62). There was no statistically significant heterogeneity among the pooled studies (I^2 = 35.7%; P = .19). One prospective study showed no response to rituximab treatment in 1 patient with steroid-refractory gastrointestinal cGVHD [22]. The pooled proportion ORR in 3 retrospective studies involving 11 patients was 0.346 (95% CI = 0.05 to 0.72) [18,21,24].

Lung cGVHD

Data on response rates in cases of steroid-refractory cGVHD involving the lung were extractable from 4 studies involving a total of 15 patients [18,22-24]. In 1 prospective study, rituximab produced no response [22]. The pooled proportion of lung cGVHD response in 3 retrospective studies involving 14 patients was 0.30 (95% CI = 0.11 to 0.53) [18,23,24]. There was no significant heterogeneity among the pooled studies (I^2 = 0%; P = .58).

Other Organs with cGVHD

Reponses to rituximab also were reported in patients with steroid-refractory ocular cGVHD, with rates ranging from 13% (1/8) to 38% (6/16) [23,24], and in patients with steroid-refractory cGVHD of the musculoskeletal system, with response rates of 100% (1/1) and 75% (3/4) [18,23].

Does Administration of Rituximab Allow Reduction (or Discontinuation) of Immunosuppressive Therapies, Including Corticosteroids?

Administration of rituximab facilitates dosage reduction of previous immunosuppressive therapies in patients with refractory cGVHD. Zaja et al. [24] reported a median dosage reduction of immunosuppressive therapy (including corticosteroids) of 82% (range, 0 to 100%), mostly in cases of steroid-refractory cGVHD involving the skin and oral mucosa.

Two studies specifically addressed the glucocorticoid-sparing effect of rituximab in patients with steroid-refractory cGVHD. Mohty et al. [21] reported a median glucocorticoid dosage reduction of 86% (range, 0 to 100%) in 11 of 15 patients (73%) treated with rituximab; this steroid sparing-effect also was more pronounced in skin and oral mucosal cGVHD, consistent with a previous report [24]. Similarly, Cutler et al. [20] reported a 75% median dosage reduction of prednisone (from 40 mg to 10 mg) in more than two-thirds of their patients. These and other studies are summarized in Table 1.

Treatment-Related Morbidity and Mortality (TRM)

Rituximab appears to be relatively well tolerated, with side effects related mainly to infusion reactions (5% to 11%) and infectious complications, including sepsis (3% to 33%), pneumonia (8% to 33%), viral conjunctivitis (5%), diarrhea (14%), and herpes zoster reactivation (33%; 1/3), among others [18-24]. Long-term toxicities related to treatment were not reported [18-24].

None of the studies, prospective or retrospective, reported mortality attributable to rituximab treatment.

Sensitivity Analyses

Because of the limited number of prospective studies available, as well as the relatively small number of patients for each cGVHD manifestation, we could not perform a sensitivity analysis to explore the reasons behind the heterogeneity in the outcomes of organ-specific responses related to cGVHD of the skin and mucosa. This heterogeneity can be attributed to several clinical factors, however. The patients enrolled in these studies had a wide range of diseases and previous interventions (eg, differing conditioning regimens, number of treatments for cGVHD before rituximab therapy, concomitant treatment with corticosteroids or other immunosuppressive treatments), as well as differing criteria for assessing response rates. All of these factors may possibly contribute to the heterogeneity for some of the outcomes.

DISCUSSION

The totality of the evidence on the efficacy of rituximab for treating steroid-refractory cGVHD demonstrates that the skin is the most responsive organ (Table 2) [19-22,24]. Responses were impressive in cases of sclerodermatous or lichenoid cutaneous cGVHD [20,22]. In the prospective study of Okamoto et al. [22], 3 patients (100%) with sclerodermatous cGVHD had responses occurring between 60 and 90 days from initiation of therapy. Similarly, Cutler et al. [20] reported a decrease in median body surface area (BSA) involved with sclerodermatous cGVHD from 35% to 25% after 2 cycles of therapy, followed by a further decrease to 20% at 1 year after the initiation of rituximab. Cases of lichenoid cutaneous cGVHD also responded to rituximab therapy, showing a decrease in median BSA involvement from 20% to 5% after 2 cycles and a further decrease to 3% after 1 year [20]. It is important to keep in mind that clinical responses may continue to improve several months after the start of rituximab. In summary, these findings suggest that rituximab is effective in treating cutaneous cGVHD.

Table 1. Dose Reduction of Immunosuppressive or Corticosteroid Therapy after Initiation of Rituximab

Author, Year	Median Dose Reduction(Range)	Proportion of Patients Discontinuing Immunosuppressive Therapy(n/N)
Von Bonin et al., 2008 [18]	NR	23% (3/13)*
Mohty et al., 2008 [21]	86% (33%-100%)	NR
Zaja et al., 2007 [24]	82% (0-100%)†	NE
Okamoto et al., 2006 [22]	NE‡	NA
Cutler et al., 2006 [20]	75% (NE)	11% (3/28)*
Canninga-Van Dijk et al., 2004 [19]	NE	67% (4/6)
Ratanatharathorn et al., 2003 [23]	NR (68.75%-87.5%)§	NR

NR indicates not reported; NE, not extractable; NA, not available.
*Updated data were provided by the authors (Cutler et al., CS).
†Zaja et al. reported organ-specific dose reduction; the numbers given here are for median % dose reduction of CS for 10 patients evaluable for skin response.
‡Okamoto et al. reported no change in the dose of immunosuppressive drugs during rituximab therapy.
§Ratanatharathorn et al. reported data for dose reduction of CS extractable for 2 of the 4 patients who showed a response to rituximab; the values for % CS dose reduction are 68.75% for one patient and 87.5% for the other patient.

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