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Response of patients with refractory myasthenia gravis to rituximab: a retrospective study

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***Abstract*:**
Introduction: Myasthenia gravis, an autoimmune disorder of neuromuscular transmission, is treated by an array of immunomodulating therapies. A variable response is observed with certain patients being medically refractory.
Methods: We report the results of 14 refractory generalized myasthenia gravis patients (6 AChR+; 8 MuSK+) treated with rituximab.
Results: Sustained clinical improvement was observed in all patients as well as a reduction of conventional immunotherapies. Prednisone dose decreased a mean of 65.1%, 85.7%, and 93.8% after cycle 1, 2, and 3 of rituximab therapy, respectively. A statistically significant reduction in plasma exchange sessions was seen after cycle 1 with all patients being off of plasma exchange after cycle 3. Acetylcholine receptor antibody titers decreased a mean of 52.1% ($p = 0.0046$) post-cycle 2.
Conclusion: Our results support the hypothesis that rituximab is beneficial and well tolerated in managing refractory myasthenia gravis and nearly doubles published cases. We propose that B-cell-directed therapies may become an attractive option and suggest pursuit of a prospective trial.

***Keywords*:** B-cell depletion, immunosuppression, myasthenia gravis, rituximab, treatment

Introduction

Myasthenia gravis (MG) is a prototypical antibody-mediated neurologic autoimmune disorder and is characterized by fatigable oculobulbar and limb weakness. The estimated annual incidence is about 1 to 2 per 100,000 with prevalence as high as 20 to 50 per 100,000 [Conti-Fine *et al.* 2006; Drachman, 1994]. Current treatment of MG consists of symptomatic therapy with acetylcholinesterase inhibitors and immunotherapy such as corticosteroids, mycophenolate mofetil (MM), azathioprine, cyclosporine, plasmapheresis and intravenous immunoglobulin (IVIg) [Gold and Schneider-Gold, 2008; Sathasivam, 2008; Conti-Fine *et al.* 2006]. Despite these therapies there are patients who continue to remain refractory to treatment with medication side effects being common. New therapeutics are thus desirable, particularly long-term steroid sparing agents with few adverse effects. Disease remission would be an ideal goal.

Autoreactive B cells play an important role in the immunopathogenesis of MG and as such would seem to be appropriate for targeted drug therapy investigation [Dalakas, 2008]. Recent examples from other autoimmune disorders such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and multiple sclerosis (MS), which also frequently have poor response to current conventional therapy and frequent relapses or refractory disease, have suggested benefit with B-cell-directed therapies [Dörner *et al.* 2009; Dörner and Lipsky, 2007; Edwards *et al.* 2004; Silverman and Weisman, 2003]. B-cell depletion may therefore be a beneficial therapeutic goal in certain autoimmune diseases based on this experience [Perosa *et al.* 2010].

Currently, rituximab is the only B-cell-directed biologic approved for use clinically. Rituximab is a chimeric monoclonal antibody that targets the CD20 antigen found on B lymphocytes and

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modulates B-cell activation. CD20 is a 33-kDa protein expressed by all mature B cells, but not on pre-B mature or differentiated plasma cells. Rituximab has been used as part of the standard therapy for non-Hodgkin's lymphoma (NHL) as well as a number of autoimmune diseases [Stasi, 2010; Dörner *et al.* 2009; Boye *et al.* 2003]. Interest in its use for MG began in 2004 after Gajra and coworkers reported a patient with both NHL and MG who responded favorably to rituximab [Gajra *et al.* 2004]. Since that time there have been several case reports and case series that demonstrate the benefits of rituximab in both acetylcholine receptor (AChR) and muscle specific kinase (MuSK) antibody-positive MG patients [Zebardast *et al.* 2010; Lebrun *et al.* 2009; Stieglbauer *et al.* 2009; Illa *et al.* 2008b; Baek *et al.* 2007; Thakre *et al.* 2007; Hain *et al.* 2006].

We report our experience with rituximab in 14 patients with refractory generalized MG: six with AChR antibody and eight with MuSK antibody types. To date this is the largest study from one center.

Methods

Patients

A retrospective study was performed of MG patients referred to the Yale Neuromuscular Clinic from 2003 to 2009. Fourteen patients were identified with refractory generalized disease (Table 1). Both MuSK and AChR antibody-positive groups were included; seronegative cases were excluded. Patients were defined as refractory when they could not lower their immunotherapy without clinical relapse, were not clinically controlled on their immunotherapy regimen, or had severe side effects from immunosuppressive therapy. All clinical exams were completed or supervised by one senior neurologist. Physical exams were evaluated before and after rituximab treatment. Owing to the retrospective nature of this study objective MG scales were unable to be applied and clinical response was assessed qualitatively by comparing symptoms and exam findings before and after rituximab treatment. There were no predefined criteria used to state clinical response *versus* no clinical response.

Rituximab

Rituximab was given at a standard dose of 375 mg/m^2. Each cycle is defined as one infusion per week for four consecutive weeks. Interval between cycles was set at 6 months. Infusions were completed per protocol in the hematology department at our institution.

Antibody titer

AChR antibody titers were collected in our lab and tested at Mayo Medical Laboratories (Rochester, Minnesota). Qualitative MuSK antibody testing was performed at Athena Diagnostics (Four Biotech Park, Worcester, Massachusetts). Pretreatment AChR antibody titers were normalized to 100% for each patient.

Conventional immunotherapy

Immunosuppressive treatment with prednisone was included as it is a first-line therapy for MG; 13 of the 14 patients were on prednisone just prior to rituximab treatment. Plasma exchange (PE) sessions were also included in our study as many patients required PE prior to rituximab due their refractory disease; 12 of the 14 patients had received PE before initiating rituximab. Five of the patients identified for our study were also being treated with either azathioprine or MM in addition to prednisone, PE or both.

Safety and adverse events

To assess preliminarily the safety and adverse effect profile, we reviewed the infusion center notes as well as complete blood count (CBC) and liver function test (LFT) profiles available in our electronic medical record.

Statistical analysis

We used *t*-test analysis to evaluate differences. Statistics were performed using SigmaPlot 8.0®; results were considered significant when $p < 0.05$.

Results

Effect on corticosteroids

Thirteen refractory MG patients were identified on oral corticosteroids. A dose of prednisone before and after each rituximab cycle was followed to assess rituximab effect (Figure 1A). Patients 4, 7, 10, 11, 12 and 13 received two rituximab cycles to date. Patients 1, 2, 3, 5, 6, 8, 9 and 14 received three or more rituximab cycles. All 13 patients showed a dose reduction of whom 8 were completely tapered off prednisone after cycle 3; five were prednisone-free after cycle 2. The prednisone dose decreased a mean of 65.1% ($p = 2.3 \times 10^{-8}$) after cycle 1, 85.7% ($p = 2.2 \times 10^{-13}$) after cycle 2, and 93.8%

Table 1. Patient characteristics and response to rituximab treatment.

Patient	Age/Sex	Disease onset	Antibodies		Past treatments	Status before rituximab*	Status after rituximab*	Most recent status	Number of rituximab cycles	Current medication
			MuSK	AChR						
1	60/F	04/03	+	NA	P, PPX, Az, Py	Lw, Di	Di	Di	3	None
2	58/F	7/03	+	−	Py, P, Az, Cs, PPX	Dya, Dyp, lw	None	None	5	None
3	34/F	4/94	+	−	T, Py, MM, P, PPX	Di, Pt, lw	None	Di	3	Py
4	31/F	6/03	+	NA	T, Py, P, PPX	None	None	^ Dyp, Pt, Di, lw	2	None
5	39/F	6/04	+	−	Py, P, PPX, IVIg	Di, lw	None	None	4	P
6	21/F	7/04	+	NA	T, P, PPX, Az, Py	None	None	None	3	None
7	21/F	01/09	+	NA	P, PPX	Pt, Dya, lw, Dyp, Di	None	None	2	None
8	54/F	7/04	NA	+	T, Py, P, Az, PPX	Di, Dya, Dyp, lw	None	None	3	P
9	56/F	4/03	−	+	T, Py, P, Az, PPX	Di, Pt, Dya, Dyp, lw	None	None	3	None
10	36/F	12/08	NA	+	T, P	Pt, Dya, lw	None	None	2	P
11	29/M	10/08	NA	+	T, P, Az, PPX	Di, lw	None	None	2	P, Az
12	38/F	11/08	NA	+	T, P, PPX, Az, Py	Pt, Dya, Dyp, lw	None	None	2	P, Az
13	63/M	02/06	NA	+	P, Py, Az	Di	Di	None	2	P
14	68/M	12/04	+	NA	P, PPX	Pt, Di, lw	lw	lw	3	None

NA, not available; Az, azathioprine; Cs, cyclosporine; MM, mycophenolate mofetil; P, prednisone; Py, pyridostigmine; PPX, plasma exchange; T, thymectomy; Di, diplopia; Pt, ptosis; Dya, dysarthria; Dyp, dysphagia; lw, limb weakness.
*Exam prior to first rituximab treatment and following last rituximab treatment.
^Awaiting exam post second treatment.

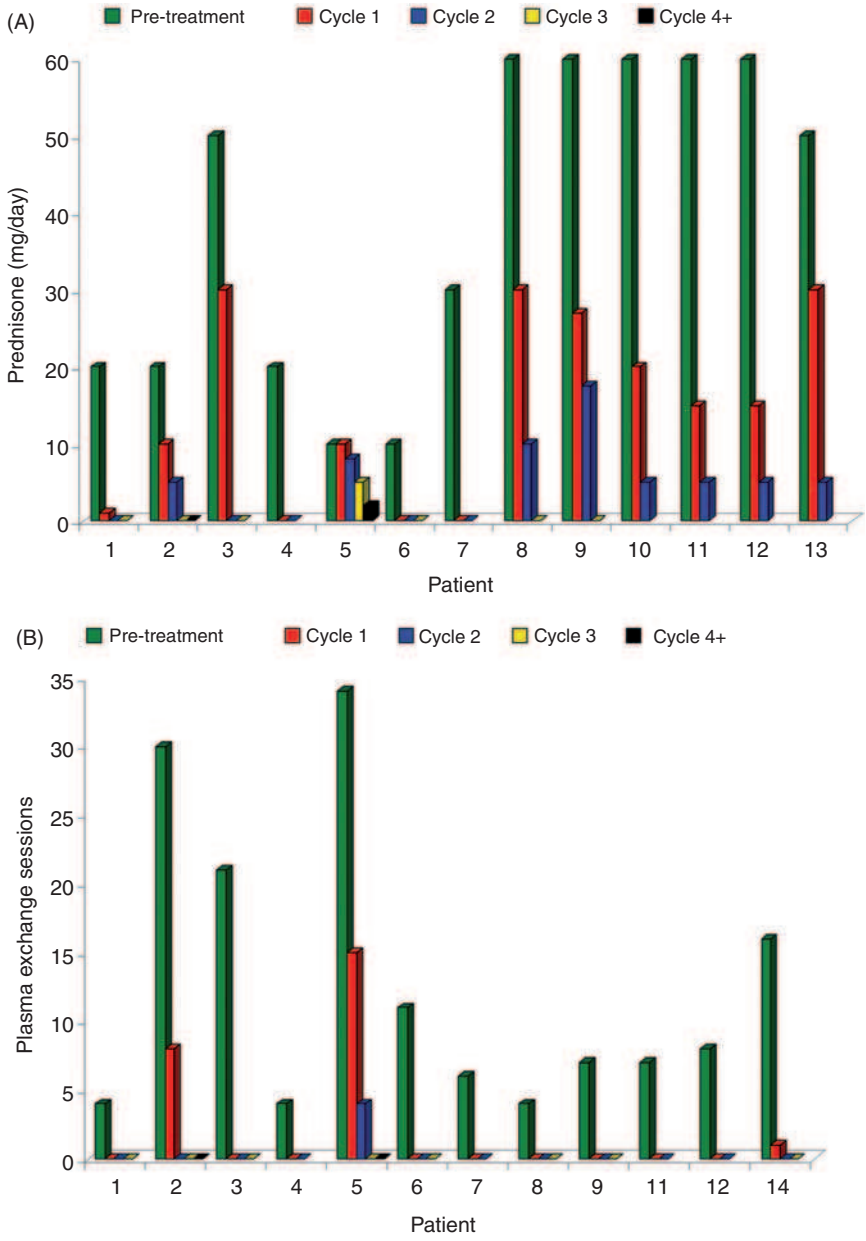

Figure 1. Effect of rituximab on conventional immunosuppression. (A) Prednisone dose of 13 refractory myasthenia gravis (MG) patients before and after cycle 1, 2, 3 and 4+ of rituximab treatment. (B) The number of plasma exchange treatment sessions in 12 refractory MG patients before and after rituximab treatment. Pretreatment bars represent the total number of plasma exchanges in a period prior to initiation of rituximab, whereas, cycle 1, 2, 3 and 4+ bars represent the total number of plasma exchanges in the periods following the each rituximab infusion cycle (note: the interval between each cycle is 6 months). Note that where no colored bars exist indicates data not yet available.

($p = 2.7 \times 10^{-14}$) after cycle 3 of rituximab therapy.

Plasma exchange reduction

The number of plasma exchange treatment sessions was analyzed in 12 refractory MG patients before and after rituximab treatment (Figure 1B). Pretreatment bars represent the total number of plasma exchanges in the 12-month period prior to initiation of rituximab (except for patient 8 which is a 24-month period as no PE in the 1 year before starting rituximab infusions), whereas, the cycle 1, 2, 3 and 4+ bars represent the total number of plasma

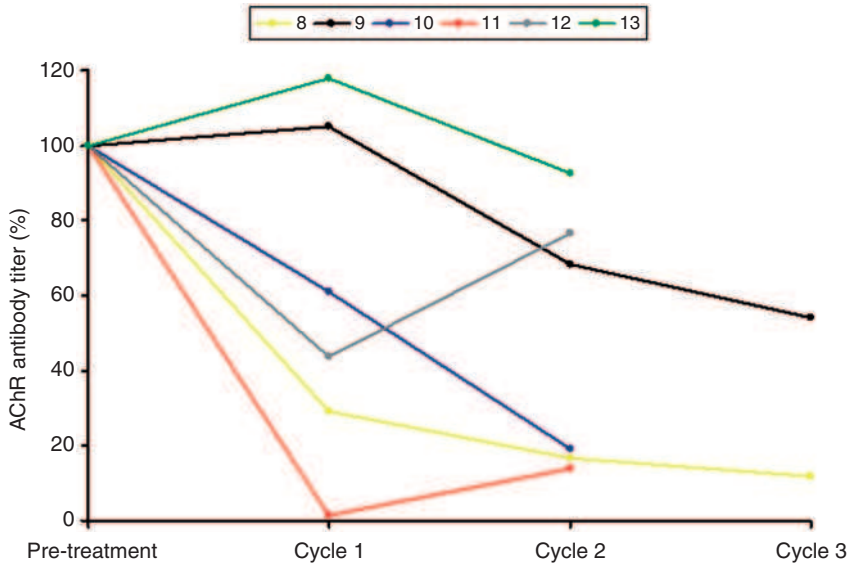

Figure 2. AChR antibody titers in six patients. A value of 100% was assigned to the titers before treatment with rituximab and data expressed as percent decrement or increment following each cycle (cycles 1–3) to date.

exchanges in the periods following the first rituximab infusion. Note that where no colored bars exist indicates data not yet available. There was a statistically significant reduction in plasma exchange sessions in the groups analyzed after cycle 1, 2, 3 and 4+ with p-values of 0.0038, 0.0005, 0.0018 and 0.0017, respectively. Nine of the 12 patients no longer required plasma exchange at 6 months (cycle 1) and 11 were PE-free at 12 months (cycle 2) following initiation of rituximab. The three patients (patients 2, 5 and 14) that continued to require PE after first rituximab cycle no longer needed it after cycle 3.

Reduction of other immunotherapy

One patient was on MM at time of initiation of rituximab. One month after the first rituximab cycle, patient 3 (MuSK antibody positive) was able to completely discontinue MM from a pretreatment maintenance dose of 1.5 g/day. Four patients, all of which were AChR antibody positive, were on azathioprine (150 mg/day) for immunosuppression at time of rituximab initiation. Patient 8 was able to discontinue azathioprine after cycle 1 and patient 13 after cycle 2. Patients 11 and 12 could not reduce their azathioprine dose despite both receiving two cycles of rituximab to date, however, were able to taper other immunotherapy.

Antibody titer

Six AChR antibody-positive patients refractory to conventional therapy were identified. AChR antibody titers were followed to assess rituximab effect (Figure 2). A value of 100% was assigned to the titers before treatment with rituximab and data expressed as percent decrement or increment following each cycle (cycles 1–3) to date. Of note, the titer for patient 13 was 4 months before treatment, whereas other titers were measured just prior to rituximab infusion.

Antibody titer decreased a mean of 40.2%, 52.1% and 67% post treatment cycle 1, 2 and 3, respectively (cycle 1: $p = 0.052$; cycle 2: $p = 0.0046$; cycle 3: data insufficient).

Clinical response

Clinical improvement was also observed in parallel to reduction of other conventional therapies as well as AChR antibody titers (AChR+ patients). There was a reduction of symptoms and abnormal exam findings as compared with before treatment with rituximab (Table 1). These observations were qualitative as no predefined criteria or objective MG scales were used in this retrospective study.

Safety and adverse events

A total of 132 infusion notes were available in our electronic medical record. Six of these had reactions documented during rituximab infusion. Three of the six occurred during the first infusion of cycle 1. The reactions reported were pruritis and flushing (patient 6), flushing and dyspnea (patient 10) and chills/rigors (patient 14).

The other three nonfirst infusion events involved patient 14 who had recurrence of chills/rigors during two subsequent infusions and patient 9 during an isolated infusion reported a 'hot sensation' throughout her body without any flushing. All of the infusion reactions resolved spontaneously with either transiently stopping the infusion and restarting at a slower rate or simply decreasing the rate of infusion. No further medical treatment was required.

LFT and CBC profiles available were reviewed and found to be unremarkable except in the case of patient 13 who had a relative leukopenia after initiating rituximab which later resolved. Notably leukopenia occurred in the setting of patient 13 also being on azathioprine.

Discussion

In this retrospective analysis of 14 patients with refractory generalized MG we show that rituximab led to a sustained clinical improvement in parallel to a reduction or discontinuation of corticosteroid therapy and plasma exchange treatments. This was accompanied by a statistically significant reduction in AChR antibody titers in all six AChR-positive patients studied. It is important to note that there are no published data that show a correlation between antibody titer and disease severity. The clinical significance of the titer reduction is as yet not entirely clear and warrants further investigation in a larger cohort of patients. At time of this analysis, all patients had been followed for a minimum of 1 year and up to 2 years or more following first rituximab infusion. Our results support the hypothesis that rituximab can be helpful in managing refractory MG and is in agreement with previous smaller reports of its efficacy [Zebardast *et al.* 2010; Lebrun *et al.* 2009; Stieglbauer *et al.* 2009; Illa *et al.* 2008b; Baek *et al.* 2007; Thakre *et al.* 2007; Hain *et al.* 2006]. To date there are less than 25 known reported cases of MG treated with rituximab in peer-reviewed literature with our current study now nearly doubling known treated cases.

The understanding of rituximab in the treatment of MG is still incomplete, as there is variability in the number of treatments required to obtain clinical response as well as lack of immunobiology and pharmacokinetic studies. That said, however, most patients showed response after the first cycle of treatment. Although it is difficult to draw absolute conclusions from a small retrospective study, patients seem to require two or three cycles of rituximab for marked reductions and cessation of other immunotherapies as well as achievement of a disease remission-like state. We looked at refractory patients with either MuSK or AChR antibody-positive MG in our clinic. While these two groups of patients likely have differences in their immunopathology, both are antibody-mediated diseases. Our observation of AChR antibody reduction is very interesting and exciting but the clinical significance has not yet been firmly established. At the time of this study there was no commercial assay available for measuring MuSK antibody titers. Therefore, it is unknown whether there is a similar decline in MuSK antibody titers as is seen with AChR-positive patients. Illa and coworkers in 2008, however, did report a decline in MuSK antibody titers in three of three patients treated with rituximab in an assay available in their lab which paralleled clinical improvement [Illa *et al.* 2008b]. It is still too early to say whether there are any marked differences between the MuSK-positive and AChR-positive patients from our study. Both groups, however, respond similarly to rituximab with reduction of immunotherapy and clinical improvement. There was no difference noted in efficacy between patients that had a thymectomy compared with those who had not undergone thymectomy.

As there is no established infusion protocol for rituximab use in MG, we used the most popular protocol adopted from NHL regimen of four weekly infusions at 375 mg/m^2 which represents one cycle. This was followed by repeat treatment every 6 months. Other pilot studies have also used similar dosing regimens [Zebardast *et al.* 2010; Lebrun *et al.* 2009; Stieglbauer *et al.* 2009; Illa *et al.* 2008b; Baek *et al.* 2007; Thakre *et al.* 2007; Hain *et al.* 2006]. An ideal dose or schedule has not yet been established, however; some have used peripheral B-cell count as a marker to guide retreatment with rituximab and to reduce potential side effects [Stieglbauer *et al.* 2009; Thakre *et al.* 2007]. Further studies are as such needed to identify the best objective clinical markers to follow as well as to establish pharmacokinetics in this patient population. B-cell counts, immunoglobulin levels and antibody titers would seem the most obvious at this time. Owing to the retrospective nature of our study we do not have B-cell counts or total immunoglobulin levels, but are interested in following these markers in the future.

The need for additional treatments for patients who do not respond to traditional therapy has led to a search for new options. Rituximab is an appealing treatment choice due to its mechanism of action targeting CD20-positive B cells which are involved with antibody production [Shiratori *et al.* 2008; Boye *et al.* 2003]. There is also precedence for using rituximab in the treatment of immune-mediated disease such as RA [Dalakas *et al.* 2009; Dörner *et al.* 2009; Edwards *et al.* 2004; Silverman and Weisman, 2003]. Reduction of antibody titers and the decreased need for other immunotherapy combined with parallel clinical improvement suggest that rituximab can be very effective in these patients. The mechanism of antibody reduction and whether or not the actual titer is clinically relevant needs to be further explored as the efficacy of rituximab may be due to other effects on the autoimmune milieu. B-cell-directed therapies and specifically B-cell depletion may become a beneficial as well as attractive therapeutic option particularly if it is shown to have sustained efficacy and a good safety profile in MG patients in larger studies powered to address these issues. As further knowledge emerges regarding the basic immunopathology, B-cell-directed therapies may become first- or second-line steroid sparing agents.

The patients in our study were monitored clinically for rituximab adverse effects while in the infusion center as well as with CBC and LFT at baseline and after each infusion. All patients studied appeared to tolerate rituximab with no severe hematologic derangements except for a transient leukopenia in a single patient who was also concurrently receiving azathioprine. It is as such difficult to conclude that this was due to rituximab alone and is more likely related to dual therapy. The most common side effect reported in general in the literature is an infusion reaction consisting mainly of fever, chills, rigors, nausea and hypotension. We found flushing and chills/rigors to be the most prevalent in our small group. Reactivation of hepatitis B and other viral infections have also been reported by others. Tumor lysis syndrome and renal toxicity are other known complications but are specific to patients being treated for hematologic malignancies [McDonald and Leandro, 2009]. Progressive multifocal leukoencephalopathy (PML) after rituximab therapy is also of concern as risk is increased, however, relative risk is thought to be low per a recent review [Carson *et al.* 2009]. It is important to minimize the combination of other immunosuppressants with rituximab as this may increase the risk of PML.

The small, retrospective and uncontrolled nature is a limitation of the current study. This underscores the need for a large prospective controlled trial to make more definitive conclusions regarding the efficacy of rituximab in the treatment of refractory MG.

The objective MG rating scales were unable to be used due to the retrospective nature of the study. This will be addressed in a prospective trial where these scales will be included as part of the efficacy measures. It is also important to point out that clinical response observed in our study was qualitative as no predefined criteria or objective measures were used.

In conclusion, the marked effect of rituximab in patients with refractory MG in our clinic as well as in similar studies is promising and suggests that further investigation of this agent in MG is warranted [Illa *et al.* 2008a; Tandan *et al.* 2008]. We propose that a prospective trial be undertaken, where the efficacy, safety and pharmacodynamics in this patient population can be more carefully assessed.

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Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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