Review

Efficacy and safety of rituximab for relapsing-remitting multiple sclerosis: A systematic review and meta-analysis

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ABSTRACT

Objective: To evaluate the efficacy and safety of rituximab for relapsing-remitting multiple sclerosis.
Results: Fifteen studies that collectively included 946 patients were selected for the meta-analysis. Rituximab therapy was associated with the mean annualized relapse rates decreasing by 0.80 (95% confidence interval, 0.45–1.15) and the mean Expanded Disability Status Scale score decreasing by 0.46 (95% confidence interval, 0.05–0.87). The likelihood of patients experiencing a relapse after starting rituximab therapy was only 15% (95% confidence interval, 7%–26%). Although mild-to-moderate adverse events occurred in 29.6% of the patients, there were no severe adverse events.
Conclusions and relevance: This systematic review and meta-analysis shows that rituximab is associated with reduced annualized relapse rates and disability levels in patients with relapsing-remitting multiple sclerosis. It is also well tolerated and is not associated with serious adverse events.

1. Introduction

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system. It has traditionally been regarded as T cell–mediated [1], but recent studies have also implicated B cells and antibodies in the pathogenesis of MS [2,3]. The evidence for the involvement of B cells and humoral immunity includes the presence of antibodies and complements within active MS lesions, the presence of ectopic lymphoid follicles and B cell–related chemokines in patients' central nervous systems, and the detection of intrathecally produced immunoglobulins in samples from patients [4,5]. Of the various MS phenotypes, the most common is relapsing-remitting MS (RRMS), which is characterized by a cycle of exacerbations of neurologic symptoms followed by complete or incomplete remission [6], and the involved molecular mechanisms are very complex [7]. > 80% of individuals with MS initially experience RRMS [8].

Greater disease severities, disease progression, and relapses lead to high disability [9] and are all associated with substantial treatment costs, quality-of-life impairments, and functional disabilities [10,11]. Treatments that reduce relapse frequencies and prevent progression could therefore reduce patients' medical expenses, improve their quality of life, and reduce the broader social burden of MS [12].

One method for treating RRMS is to develop drugs that target CD20, a B cell surface antigen that is involved in the cells' activation, differentiation, and growth [13], and one such drug is ocrelizumab, which has recently been approved by the US Food and Drug Administration as a treatment for RRMS [14]. However, the availability of this drug is limited, especially for patients in developing countries, partly because of its relatively high price and various countries' import controls [15].

An alternative anti-CD20 agent is rituximab, a mouse-human chimeric immunoglobulin G1 monoclonal antibody against CD20 that is approved for certain cancers and autoimmune diseases, including rheumatoid arthritis. Rituximab is also increasingly used off-label to treat MS [16]. A recent retrospective cohort study showed that patients treated with rituximab were less likely to experience relapses and adverse events than patients treated with injectable disease-modifying therapies were. A rituximab regimen consisting of biannually administered single doses of 500–1000 mg is cheaper than even platform therapies [17].

However, past studies examining the therapeutic efficacy of rituximab for RRMS have been so inconsistent in terms of doses, administration routes, follow-up periods, and evaluation methods that

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CONSORT

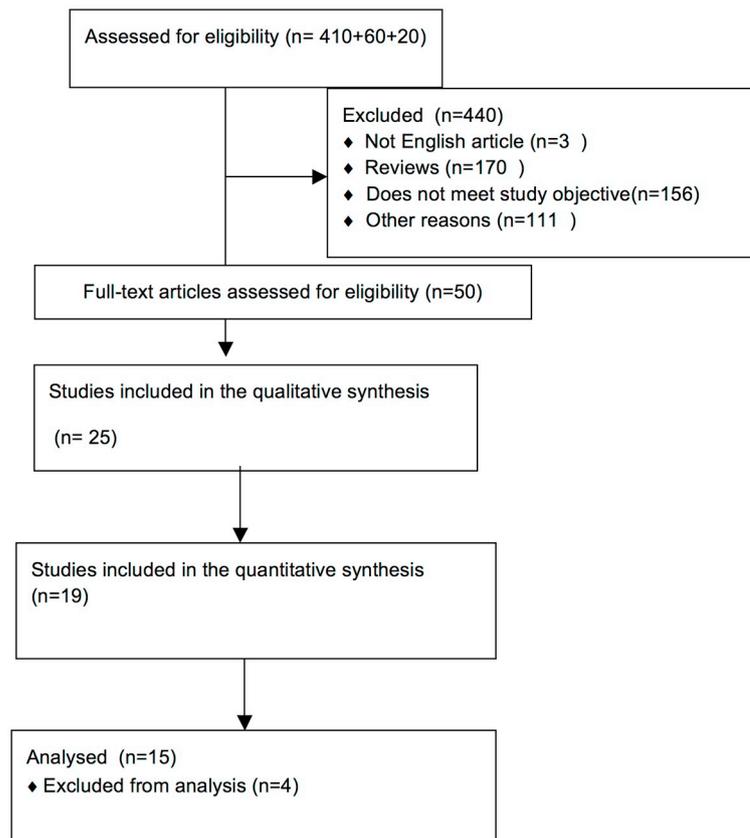TRANSPARENT REPORTING of TRIALS

CONSORT 2010 Flow Diagram

Fig. 1. PRISMA flow diagram of the preferred reporting items for systematic reviews and meta-analyses.

rituximab's overall therapeutic efficacy is difficult to determine. To clarify the current state of evidence and identify appropriate future research directions, we performed a meta-analysis of data from all relevant studies that examined the efficacy and safety of rituximab therapy for RRMS.

2. Methods

2.1. Study selection

Two study authors independently used the search terms multiple sclerosis and rituximab to query MEDLINE, the Central Register of Controlled Trials, and ClinicalTrials.gov for English-language studies that investigated the efficacy and safety of rituximab therapy for RRMS and that were published between January 1, 2000, and December 18, 2018. The same two study authors read the retrieved articles and abstracts, including secondary references, in their entirety to assess each study's appropriateness for inclusion in the meta-analysis. We followed the PRISMA Statement guidelines for conducting a systematic review and used the Newcastle–Ottawa scale to evaluate the quality of the studies that we found.

2.2. Inclusion and exclusion criteria

Randomized clinical trials were included in the meta-analysis, but very few of them were identified, so we also included uncontrolled observational studies. Case reports and studies concerning a single patient were excluded.

2.3. Data collection

For each study, we collected information about the study design, including the number of participants and the participant characteristics; the treatment regimens; the randomization and blinding procedures, if applicable; the outcome measures; and the follow-up durations. We also collected outcomes data including Expanded Disability Status Scale (EDSS) scores, relapse counts, and annualized relapse rates (ARR) recorded before and after the initiation of rituximab therapy and any adverse events noted after the initiation of rituximab therapy.

2.4. Efficacy and safety outcomes

We considered three primary efficacy outcomes: (1) changes in ARRs when comparing the periods before and after the rituximab

Table 1
Basic characteristics of 946 patients From 15 studies included in the systematic review and meta-analysis.

Study	Year	Region	Number of Cases	Female, No. (%)	Age at Start of RTX, mean (SD), y	Diaease Duration Before Drug, mean(SD), y	RTX Treatment Duration, mean(SD), m	RTX dose	First-line DMT (IFN/GA)	Second-line DMT (NTZ/FGM)	INS (MTZ, CTX, ASCT)	Others/No Detailed Data	No Previous Treatment	Follow Up, mean(SD), m
Alldredge	2018	USA,Ohio	23	18(78)	40.8(NA)	6.6(NA)	30(NA)	NA	0	0	0	20	3	36(NA)
Ellrichmann	2018	Germany	72	50(69)	36.56(9.49)	6.38(5.89)	NA	250 mg for 22.3%; 500 mg for 40.9%;1000 mg for23.0% and > 1000 mg for 13.8%	28	54	33	21	2	24.28 (19.52)
Alcalá	2018	Spain	31	23(74)	NA	9.5(6.3)	30.5(17.9)	At frst, a dose of 1000 mg intravenous RTX was administered twice, on day 1 and day 15.For maintenance, an isolated dose of 1000 mg was administered when the percentage of total CD19 + cells was 2% or more.	3	23	3	2	0	31.3(20.0)
Scotti	2018	Southern Switzerland	43	32 (74)	NA	NA	NA	NA	13	23	0	5	2	36(NA)
Durozard	2018	France	50	38(76)	37.5(11)	1.1(1.48)	exceed 6	The first infusion of rituximab was 375 mg/m² (administered four times at 1-week intervals) in four patients and was 1000 mg (administered twice at 15 day intervals) in 46 patients. The maintenance infusions were performed every 6 months: one administration of 1000 mg in 25 patients and two administrations of 1000 mg spaced by 15 days in 25 patients.	0	47	3	0	0	1.1 (0.4-6.4) y
Barra	2016	USA	54	18(32)	42.2 (13)	NA	32.9(25.0)	1000 mg at week 0 and a subsequent repeat 1000 mg for 90%.A single dose of rituximab 1000 mg for 9%, and a single dose of rituximab 100 mg for 1%.	NA					9 m after RTX
Salzer	2016	Sweden	557	387 (69)	39.6 (10.8)	8.9 (7.2)	7.2 (3.7)	Patients were usually treated with single infusions of 500 or 1000 mg rituximab IV every 6-12months	170	238	0	30	119	21.9 (15.4)m
Topping	2016	England	4	2(50)	43(5.23)	4(0.82)	NA	Intrathecal rituximab was administered to all patients at 3 timepoints at increasing doses: 5 mg on D0, 10 mg on D7 and 15 mg on D14.	4	0	0	0	0	NA
Berenguer-Ruiz	2016	Spain	12	9(75)	NA	NA	39.6(16.1)	(1) 4 weekly infusions of intravenous (IV) rituximab at a dose of 375 mg/m2 or (2) two 1000-mg IV infusions of rituximab separated by a 2-week interval	5	6	0	1	0	40(18–72) months
Beres	2014	USA	2	2(100)	15.1(0.57)	3.8(0.14)	NA	An infusion dose of 1168 and 750 mg/m² was administered twice, 2 weeks apart,respectively. Patients with 750 mg/m² started with higher dose of 1089 mg/m² afterwards.	2	2	1	2	0	exceed 6
Bar-Or	2008	Canada	26	21(81)	40.4(8.7)	7.2(NA)	72(0) (w)	Rituximab (1000 mg) was administered through a dedicated intravenous line on days 1 and 15, with the repeat course administered on weeks 24 and 26.	NA					72(0) (w)

Table 1 (continued)

Study	Year	Region	Number of Cases	Female, No. (%)	Age at Start of RTX, mean (SD), y	Disease Duration Before Drug, mean(SD), y	RTX Treatment Duration, mean(SD), m	RTX dose	Treatment before RTX					Follow Up, mean(SD), m
									First-line DMT (IFN/GA)	Second-line DMT (NTZ/FGM)	INS (MTZ, CTX, ASCT)	Others/No Detailed Data	No Previous Treatment	
D'Amico	2018	Italy	8	NA	NA	NA	NA	1000 mg RTX intravenously twice with 2 weeks apart, in a single course. 500 mg RTX intravenously twice with 2 weeks apart as pediatric dosage	NA					22.6(22.9)
Hagens	2017	The Netherlands	3	NA	NA	NA	NA	NA	NA					6(NA) (d)
Stüve	2009	Germany	2	0(0)	25(2.83)	NA	NA	A cumulative dose of 13,000 mg within 204 weeks for one and 9000 mg for the other.	NA					NA
Yamout	2018	Lebanon	59	NA	NA	7.9(6.2)	22.2(24.8)	1000 or 2000 mg rituximab IV every 6–12 months for a mean duration of 22.2 ± 24.8 months.	NA					exceed 3

Abbreviations: NA not available, IFN interferon beta, GA glatiramer acetate, NTZ natalizumab,FGM fingolimod, INS immunosuppressants, MTZ mitoxantrone, CTX cyclophosphamide, ASCT autologous stem cell transplantation.

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therapy, (2) changes in mean EDSS scores when comparing the periods before and after the rituximab therapy, and (3) the likelihood of participants experiencing relapses after rituximab therapy. The primary safety outcome was the occurrence of adverse events, including infusion-related adverse events, infections, and hematological disorders.

2.5. Statistical analyses

We used R software (version 3.3.3; R Foundation for Statistical Computing, Vienna, Austria) to conduct a meta-analysis. We defined statistical significance as $P < 0.05$. We converted the outcomes data into logit-transformed proportions and then pooled the proportions with a random-effects inverse variance method. We calculated effect sizes as mean differences between the periods before and after the initiation of rituximab therapy. We used a Der Simonian-Laird random meta-analysis model and Hedges calculations to comprehensively estimate effect sizes. We also calculated the likelihoods of participants experiencing a relapse after initiating rituximab therapy. We used the I^2 test and sensitivity analysis to assess between-study heterogeneity and funnel plots to detect publication bias.

3. Results

3.1. Study characteristics

The initial search identified 410 articles through MEDLINE, 60 articles through the Central Register of Controlled Trials, and 20 articles through ClinicalTrials.gov. After reviewing these studies, we identified 15 that were suitable for inclusion in our meta-analysis (Fig. 1, Table 1) [18–32].

These 15 studies collectively included 946 patients with RRMS who were treated with rituximab. The patients' baseline ages ranged from 15.1 year to 43 years. The disease durations at the initial rituximab infusions ranged from 1.1 years to 9.5 years, and the studies' mean follow-up durations ranged from 6 days to 40 months. Details of the rituximab regimens were given for 877 patients and varied between the studies, with 688 patients receiving single intravenous rituximab infusions, 10 patients receiving weekly 375-mg/m^2 infusions for 4 weeks, 165 patients receiving two fortnightly 1-g infusions, and 14 patients receiving different therapeutic regimens.

3.2. Efficacy outcomes: EDSS scores

EDSS score data were reported in six of the studies included in the meta-analysis, and five of these studies reported EDSS score reductions, which indicate reduced disability levels, following the initiation of rituximab therapy. Our meta-analysis showed that the initiation of rituximab treatment was associated with the mean EDSS score decreasing by 0.46 (95% confidence interval, 0.05–0.87) (Fig. 2). The between-study heterogeneity was higher than what would be expected from sampling error alone and thus cannot be ignored ($I^2 = 61\%$; $\tau^2 = 0.1354$). The sensitivity analysis revealed that the major between-study heterogeneity was from a multicenter study with a larger sample size than the other five studies, which showed stable EDSS scores before and after rituximab therapy (eFigure1).

3.3. Efficacy outcomes: ARRs

ARRs were reported in two of the studies included in the meta-analysis, and both of them reported ARR reductions following the rituximab therapy. Our meta-analysis showed that the rituximab treatment was associated with the mean ARR decreasing by 0.80 (95% confidence interval, 0.45–1.15) (Fig. 3). The between-study heterogeneity was high ($I^2 = 69\%$; $\tau^2 = 0.0447$) (eFigure2), but because only two studies were included in the meta-analysis, we could not conduct meta-regression analyses to explore the reasons for this heterogeneity.
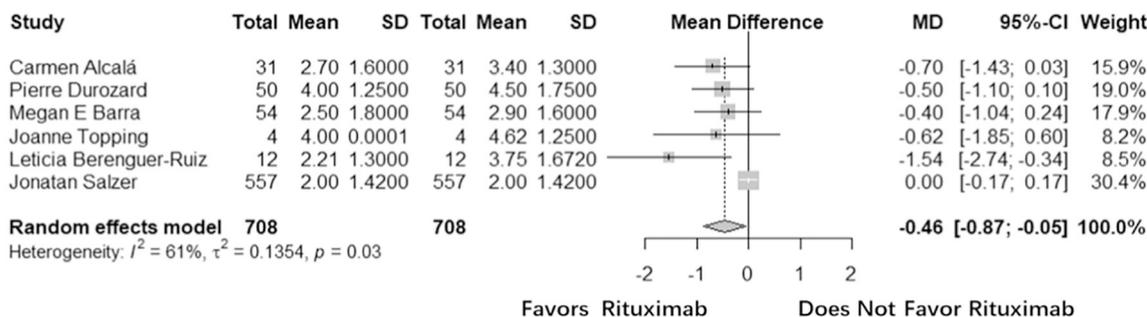
Fig. 2. Forest plot showing the mean effect size and 95% confidence interval for the reduction in Expanded Disability Status Scale scores associated with the rituximab therapy in patients with relapsing-remitting multiple sclerosis.
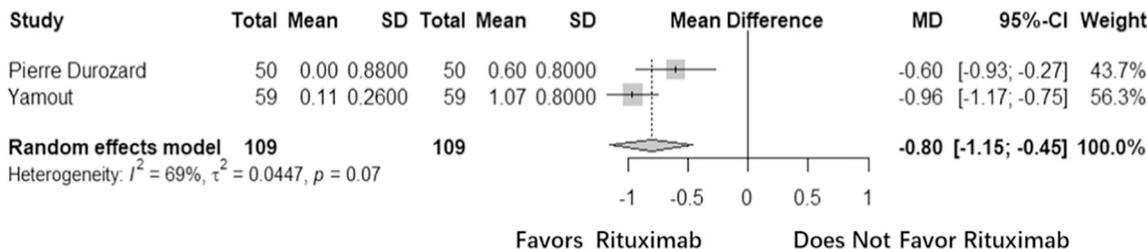

Fig. 3. Forest plot showing the mean effect size and 95% confidence interval for the reduction in annualized relapse rates associated with the rituximab therapy in patients with relapsing-remitting multiple sclerosis.

3.4. Efficacy outcomes: relapse likelihoods

Relapse likelihoods following the rituximab therapy were reported in 11 studies. Our meta-analysis showed that relapses following the rituximab therapy occurred in only 15% of patients (95% confidence interval, 7%–26%) (Fig. 4). The between-study heterogeneity was high ($I^2 = 87\%$; $\tau^2 = 0.0338$). The sensitivity showed a relatively stable result (eFigure3).

3.5. Safety outcomes

Adverse events were studied in 253 patients treated with rituximab and 75 (29.6%) were recorded, with 12 patients experiencing infusion-related adverse events, 60 developing infections, and 3 developing hematological disorders.

3.6. Publication bias

The funnel plots of the EDSS score and ARR data were asymmetrical (eFigure4 and 5), which suggested a prominent publication bias to the left of the estimate.

4. Discussion

Several reviews focusing on rituximab for MS have been published, but our study is the first meta-analysis to concentrate specifically on the efficacy and safety of rituximab as a treatment for RRMS. By conducting this meta-analysis of 15 studies that collectively included 946 patients with RRMS, we found that rituximab treatment is associated with reduced disability levels, as measured with EDSS scores, and reduced ARRs. Furthermore, the risk of relapse after starting rituximab treatment was very low. As for safety concerns, we found that adverse events occurred frequently but were not serious and usually occurred less frequently following subsequent infusions. We thus conclude that rituximab is effective and sufficiently safe for treating patients with RRMS.

Rituximab is a chimeric monoclonal antibody that can deplete CD20-expressing B cells by targeting plasma cell precursors [33]. B cell depletion affects antibody production, cytokine networks, and B cell–mediated antigen presentation and activation of T cells and macrophages, which persist in peripheral blood for 12 months after a rituximab infusion [34]. The relapse rate reductions achieved with monoclonal antibodies exceed those achieved with first-line disease-
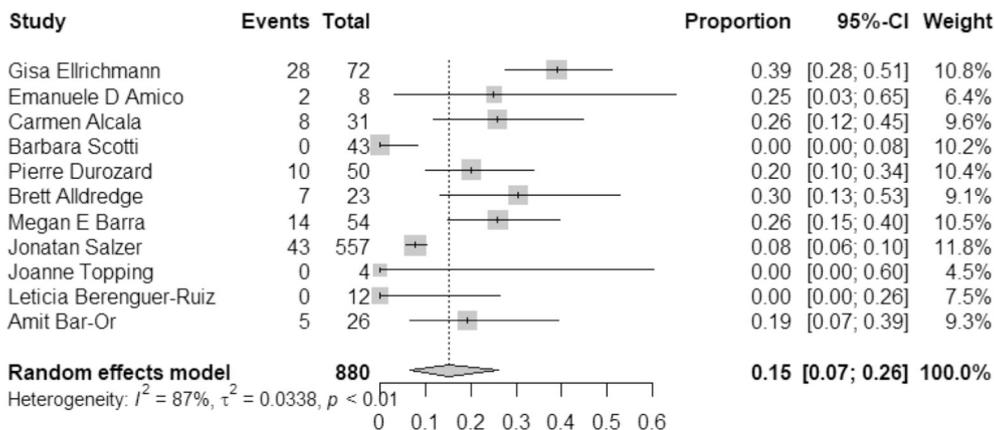

Fig. 4. Forest plot showing the relapse likelihood following the rituximab therapy in patients with relapsing-remitting multiple sclerosis.

modifying therapies [35,36]. However, because rituximab does not affect the levels of autoreactive and polyreactive B cells, it does not reset the defective early B cell tolerance checkpoints [37].

In our meta-analysis, we found that rituximab was associated with reduced EDSS scores. Of the six studies that provided EDSS score data, five showed EDSS score improvements, but one showed no effect. Furthermore, the study reporting no effect had a larger sample size than the other five did, and it hence had a greater weight in the meta-analysis. However, our meta-analysis showed a significant association between the rituximab and EDSS score reductions even when this study was included. Our meta-analysis also showed that rituximab was associated with reduced ARRs, but only two papers provided pre- and post treatment ARR data. In contrast, 11 studies reported the relapse likelihoods after the rituximab therapy, so our finding that rituximab is associated with a low relapse risk has stronger support.

Two published clinical trials have reported the therapeutic efficacy of rituximab in patients with RRMS. A phase 2, double-blind, 48-week trial involving 104 patients with RRMS showed that a single rituximab injection reduced the number of inflammatory brain lesions visible in enhanced magnetic resonance imaging scans and reduced the number of clinical relapses occurring within 48 weeks of treatment initiation [38]. A smaller open-label phase 2 study performed in patients with RRMS also observed a reduction in the number of relapse occurring within 52 weeks, but this study was not designed to detect relapse rate reductions.3 The relapse rate reductions observed in these two studies were similar to or greater than those observed in the pivotal trials of natalizumab [39,40].

All the studies in the meta-analysis reported that following their first infusions, the patient in the rituximab groups experienced greater adverse event rates than the patients in the placebo groups did. There were no severe infections or infusion-related adverse events, and the infusion-related adverse events occurred less frequently with subsequent infusions. These results indicate that the use of rituximab in patients with RRMS is associated with adverse events that are frequent but not serious and occur less frequently with subsequent infusions. Our meta-analysis included a 72-week clinical trial that evaluated the safety of a rituximab regimen involving two doses administered at baseline and 24 weeks later.[14] The study reported no serious adverse events, and those adverse events that did occur were mostly infusion-related events known to result from cytokine release during B cell lysis. The infection-related adverse events were of mild-to-moderate severities. Furthermore, the study found that B cell depletion was accompanied by a sustained reduction in relapse frequencies and lesion counts in magnetic resonance imaging scans throughout the 72-week duration. Based on these findings, we conclude that rituximab is sufficiently safe for patients with RRMS.

Our study has several limitations. Most of the studies included in our meta-analysis were uncontrolled observational trials with highly heterogeneous designs that precluded any direct comparisons of study outcomes. Furthermore, we could not perform meta-regression analyses because of the limited number of studies. The various studies used inconsistent definitions of relapse, and only two provided ARR data. As for the meta-analysis itself, its internal and external validities are obviously confounded by the non-negligible publication bias. Rituximab's apparent efficacy might have been amplified to some extent by the non-publication of studies that contained neutral or negative data. Our findings support continued off-label prescribing of rituximab for patients with RRMS and highlight the necessity of large randomized clinical trial to thoroughly characterize the efficacy and safety of rituximab as a treatment for RRMS.

5. Conclusions

Our systematic review and meta-analysis provides evidence that rituximab therapy is associated with reduced relapse rates and disability levels in patients with RRMS and that rituximab therapy is well tolerated and associated with no serious adverse events.

Author contributions

Dr. Tian had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Hu, Tang, Tian.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Hu, Tian.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Hu, Nie, Yu, Qin, Tian.
Obtained funding: Tian.
Administrative, technical, or material support: Hu, Nie, Wu.
Study supervision: Tang, Tian.

Conflict of interest disclosures

The authors have declared no conflict of interest.

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Declarations of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.autrev.2019.03.011.

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