Meta-Analysis

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Efficacy and safety of rituximab for minors with immune thrombocytopenia: a systematic review and meta-analysis

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Abstract

Objective: We reviewed relevant research on rituximab (RTX) treatment for pediatric immune thrombocytopenia (ITP) to elucidate the efficacy and safety of RTX.

Methods: Prospective clinical trials of RTX for the treatment of pediatric ITP were collected by searching the PubMed, Cochrane Library, Web of Science, and OVID: EMBASE databases and ClinicalTrials.gov. We examined rates of overall response (OR), complete response (CR), partial response (PR), sustained response (SR), relapse (R), and adverse drug reaction (ADR). The Methodological Index for Nonrandomized Studies scale was used, and sensitivity analyses were performed.

Results: For five studies, including 100 patients, the pooled OR, CR, PR, SR, R, and ADR rates were 52% (95% CI: 0.36–0.77, $I^2 = 78\%$), 52% (95% CI: 0.41–0.67, $I^2 = 45\%$), 18% (95% CI: 0.10–0.33, $I^2 = 33\%$), 43% (95% CI: 0.29–0.63, $I^2 = 0\%$), 25% (95% CI: 0.06–0.96, $I^2 = 52\%$), and 30% (95% CI: 0.15–0.58, $I^2 = 64\%$), respectively.

Conclusion: There is evidence, albeit low quality, that RTX may be a better second-line therapy than splenectomy for children with ITP; however, its efficacy and safety need to be validated by further high-quality clinical trials, such as randomized controlled trials.

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Introduction

Childhood immune thrombocytopenia (ITP) is a pediatric autoimmune disease characterized by low platelet counts ($<100 \times 10^9$/L) arising from platelet-associated autoantibodies.[1,2] Children with mild virus usually develop acute purpura and mucosal bleeding, and most recover spontaneously within 6 to 12 months.[2–4] Young children tend to have spontaneous remission, but the incidence of spontaneous remission decreases with age.[5] Epidemiological investigations of childhood ITP data suggest that the incidence of ITP in children is 4.2 per 100,000 persons annually. In the majority of ITP patients, thrombocytopenia due to other primary causes has been excluded; diagnostic measures include a complete patient history, physical examination, blood count, and peripheral blood smear. In particular, pediatric patients with persistent or chronic ITP should undergo quantitative immunoglobulin (Ig) testing for basic measures. ITP is rarely fatal, but it results in a lower quality of life due to bleeding events and anxiety of potential hemorrhage. Currently, in accordance with the American Society of Hematology (ASH) guidelines, first-line treatment includes observation, corticosteroids, intravenous immunoglobulin (IVIG), and anti-D immunoglobulin.[4,6]

Clinical manifestations related to bleeding have occurred as a result of platelet destruction and production disorders. Regarding the mechanisms involved in platelet lysis, B cells that produce antiplatelet antibodies cannot be overlooked. Widely distributed B cells lead to antibody presence in the spleen, blood, and bone marrow. CD20 often resides in B cells, except in pro-B cells and plasma cells. Therefore, treating ITP with B-cell depletion management may be beneficial.[2,7] Rituximab (RTX), which is a chimeric anti-CD20 antibody, is an off-label agent used as a second-line therapy in children with ITP, and it plays an important role in the management of relapsed or refractory ITP. Its mechanisms of action include antibody-dependent cellular cytotoxicity, complement-mediated cellular lysis, and induction of apoptosis. Because of its B-cell-depleting effect, RTX has been used to treat several autoimmune conditions such as ITP. Many reports have demonstrated the efficacy and safety of RTX treatment for patients with relapsed or refractory ITP, and guidelines have recommended RTX rather than splenectomy in children after failure of first-line therapy.[6] One systematic review showed that after RTX treatment, the complete response (CR) rate (platelet count $\geq 100 \times 10^9$/L) of primary pediatric ITP was 39%, and the response rate (platelet count $>=30\times10^9$/L) was 68%.[8] However, a single-arm trial of RTX application in chronic pediatric patients revealed that the CR rate was lower than the previously reported 39%.[9] Because the efficacy and safety of RTX are ambiguous, we aimed to clarify these two points by systematically reviewing all available evidence.

Material and methods

Ethics statement

Ethical approval for this meta-analysis was deemed unnecessary because all data had been previously published.

Search strategy

We searched four common medical databases, including PubMed, Cochrane Library, Web of Science, and OVID: EMBASE (OVID: 1946 to October 5, 2019; EMBASE: 1996 to November 12, 2019). Articles were retrieved from the first three databases from their inception to November 12, 2019. The PubMed database search was executed by combining (1) the medical subject headings (MeSH) terms "Adolescent" or "adolescent" or "Child" or "child" or "Child, Preschool" or "child preschool" or "Infant" or "infant" or "age before 18"; (2) MeSH terms ITP or "immune thrombocytopenia" or "thrombocytopenia" or "Thrombocytopenia", and (3) MeSH terms "Rituximab" or "rituximab." Similar strategies were adapted for the Cochrane Library, OVID: EMBASE, and Web of Science searches. We also searched ClinicalTrials.gov and found 13 related studies.

Eligibility criteria

We filtered all prospective clinical trials. The standard dose of RTX (375 mg/m^2 weekly for four doses) was applied in all pediatric ITP patients. The age of patients was limited to a range from 1 month to 18 years (before their 19th birthday). We conducted pooled analyses on the overall response (OR) rate. The secondary outcomes were CR rate; partial response (PR) rate; sustained response (SR) rate, meaning that at 6 or 12 months or after the end of treatment in clinical trials, the curative effect of treatment remained unchanged without recurrence; R rate; and adverse drug reaction (ADR) rate. The studies were limited to the English language. The exclusion criteria were as follows: studies in which the number of participants was <10; studies for which there was no full text or valid outcome data; and duplicate studies and reviews. Based on the titles and abstracts, studies were preliminarily selected by one author. Then, two authors screened potentially eligible full-text articles. If a dispute occurred, both authors discussed the study and a third (senior) author arbitrated. The study selection process is shown in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart (Figure 1).

Data collection and quality assessment

Data extraction was independently carried out by two authors. For this systematic review and meta-analysis, the following data were collected: (1) patient information (age, sex, ITP stage); (2) study information (first author, study region, study design, number of patients, publication date); (3) outcomes (OR, CR, PR, SR, R, and ADR rates and their definitions); and (4) other relevant information (dosage of RTX, follow-up time, baseline platelet counts). Any discrepancies in the data exaction process were discussed with the senior author until agreement was reached.

Because the included studies were single-arm trials, we used the Methodological Index for Nonrandomized Studies (MINORS) scale as a quality assessment tool to assess methodologic quality. For noncomparative studies, the MINORS scale includes eight items: a clearly stated aim, inclusion of consecutive patients, prospective collection of data, endpoints appropriate to the aim of the study, unbiased assessment of the study endpoint, follow-up period appropriate to the aim of the study, loss to follow-up less than 5%,

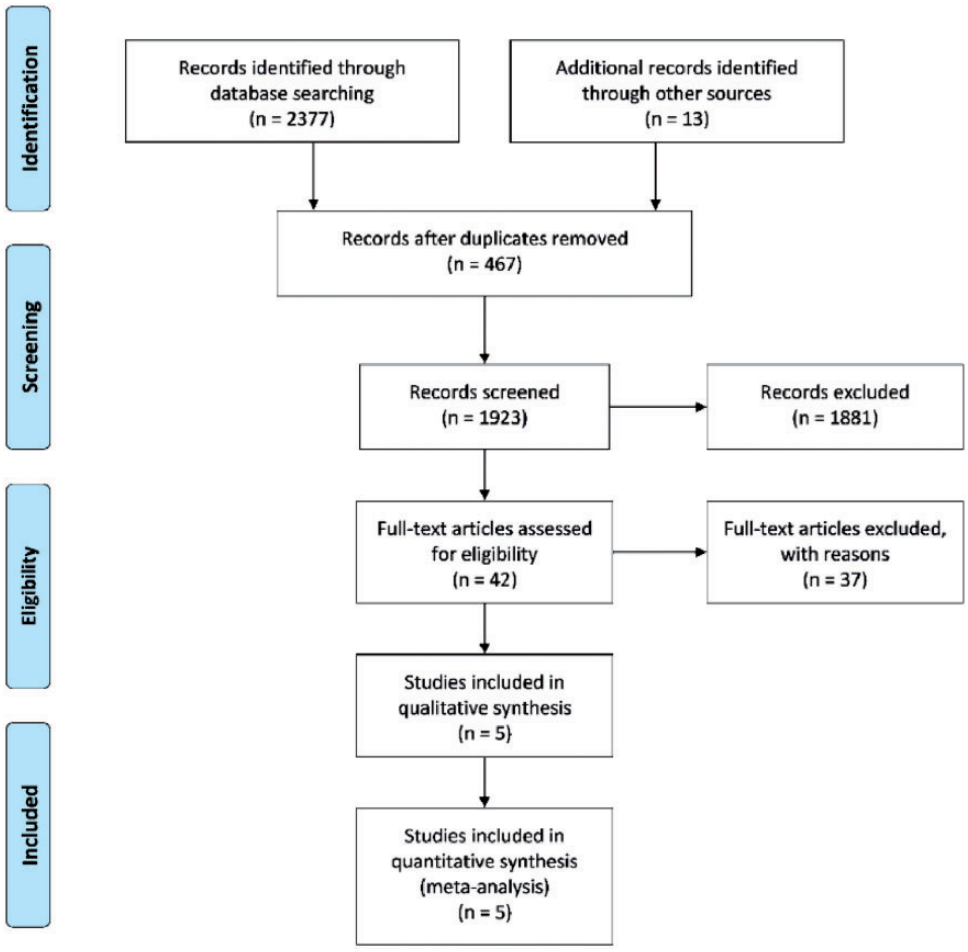

Figure 1. PRISMA flowchart showing the study selection process for the systematic review. PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses.

and prospective calculation of the study size. The items are scored as 0 (not reported), 1 (reported but inadequate), or 2 (reported and adequate). The optimal total score is 16.[10] Considering the small number of studies, assessing publication bias was deemed inappropriate.[11]

Outcomes

In accordance with 2009 outcome criteria for ITP from an international working group, the CR rate was defined as any platelet count $\geq 100 \times 10^9$/L and the absence of bleeding. Some studies reported a healthy platelet count to be between 100×10^9/L and 150×10^9/L, which was acceptable for that time.[12] However, before 2009, the CR rate often referred to any platelet count $\geq 150 \times 10^9$/L. Therefore, we collected data on the outcome criteria as defined in each included study. The definition of the R rate was a platelet count $\leq 30 \times 10^9$/L after CR or PR.

Furthermore, a platelet count $\geq 50 \times 10^9$/L was considered for PR. Different studies had different definitions of SR, R, OR, and ADR rates.

Data analysis

All statistical analyses were conducted using R 3.6.1 software (https://www.R-project.org/). We used I^2 statistics and forest plots to test heterogeneity. When the test results showed $I^2 < 50\%$, a fixed effect model was adopted to analyze the collected data, whereas when $I^2 > 50\%$, a random effects model was used. To assess the stability of the outcomes, we performed a sensitivity analysis. In five studies, the number of participants ranged from 10 to 36. They were small studies; therefore, the statistical data are subject to risk of reporting and selection bias.

Results

Study selection and quality assessment

A total of 2390 citations were identified by the search strategy. After excluding 467 duplicates, the remaining 1923 citations were subjected to screening of the titles and abstracts, after which 1881 were excluded. The full texts of the final 42 articles were screened to identify eligible articles (Figure 1). Because only one randomized control trial (RCT) was included, we ruled it out by discussion. In the end, five prospective, single-arm trials were enrolled in this meta-analysis. The fundamental characteristics of the studies are provided in Tables 1 and 2. All studies underwent quality assessment (Table 3).

Efficacy and safety outcomes

Five studies,[9,13–16] including 100 pediatric patients, reported efficacy and safety outcomes associated with RTX; all studies reported the OR rate. Both CR and PR rates were reported in four studies.[9,13,15,16] The ADR rate was reported in three studies.[13–15] SR and R were reported in only two studies.[13,16] In the single-arm synthesis, with low heterogeneity, the CR, PR, and SR rates were 52% (95% CI: 0.41–0.67, $P = 0.14$, $I^2 = 45\%$), 18% (95% CI: 0.10–0.33, $P = 0.21$, $I^2 = 33\%$), and 43% (95% CI: 0.29–0.63, $P = 0.46$, $I^2 = 0\%$), respectively, under the fixed-effects model. Because of high heterogeneity, other outcomes included the OR (52%, 95% CI: 0.36–0.77, $P < 0.01$, $I^2 = 78\%$), R (25%, 95% CI: 0.06–0.96, $P = 0.15$, $I^2 = 52\%$), and ADR (30%, 95% CI: 0.15–0.58, $P = 0.06$, $I^2 = 64\%$) under the random effects model. The associated forest plots are shown in Figure 2. In the included trials, the most common adverse reactions reported were serum conditions such as decreased IgM or depletion of peripheral B cells. One trial showed that itching and scratching occurred in patients during RTX infusion. Fortunately, the adverse reactions were mild and reversible in most cases. Therefore, RTX is beneficial for some pediatric patients with severe, chronic ITP. Further clinical trials in children are needed to confirm these results.

Sensitivity analyses

To assess heterogeneity, we deleted each clinical trial individually to determine whether the results differed significantly from the original results. If significant differences were found, the eliminated clinical trial could be considered a source of heterogeneity. All results are presented in Figure 3. As an example, in Figure 2a, the overall response was 0.52 (95% CI: 0.36–0.77); when the study by Wang et al. (2005)[13] was deleted, the resulting overall response was 0.46 (95% CI: 0.25–0.82), resulting in no significant difference. Thus, the sensitivity analysis results of the

Table 1. Fundamental characteristics of the studies on pediatric immune thrombocytopenia (ITP).

Study	Study location	Classification	Age	Sex (M/F)	Dosage regimen	Follow-up	Outcomes	Diagnostic criteria
Wang et al., 2005[13]	China	Chronic ITP	2–19 years	10/14	Standard dose	>30 months	OR, CR, PR, SR, ADR	CR $\geq 150 \times 10^9$/L; PR: 50–150 $\times 10^9$/L; OR = CR + PR
Bennett et al., 2006[14]	United States	Chronic and refractory ITP	11.2 (2.6–18.3) years	21/15	Standard dose	16 months	OR, R, ADR	OR $\geq 50 \times 10^9$/L
Dogan et al., 2009[15]	Turkey	Chronic ITP	83.4 ± 44.58 months	4/6	Standard dose	25.10 ± 13.03 months	OR, CR, PR, ADR	CR $\geq 150 \times 10^9$/L; PR: 50–150 $\times 10^9$/L; OR = CR + PR
Citak and Citak, 2011[16]	Turkey	Refractory ITP	6 (4–14) years	8/4	Standard dose	>12 months	OR, CR, PR, SR, R	CR $\geq 100 \times 10^9$/L; PR/response rate: 30–100 $\times 10^9$/L; OR = CR + PR
Ansari et al., 2014[9]	Iran	Chronic and refractory ITP	4.28 ± 8.27 years	10/8	Standard dose	60 months	OR, CR, PR	CR $\geq 100 \times 10^9$/L; PR: 50–100 $\times 10^9$/L; OR = CR + PR

OR, overall response; CR, complete response; PR, partial response; SR, sustained response; R, relapse; ADR, adverse drug reaction; standard dose of rituximab (RTX): 375 mg/m^2 weekly for four doses.

Table 2. Outcomes assessed (number assessed/total number of patients) in each of the studies.

	Outcome					
Study	OR	CR	PR	SR	R	ADR
Wang et al., 2005[13]	17/24	15/24	2/24	9/24		11/24
Bennett et al., 2006[14]	11/36				1/11	6/36
Dogan et al., 2009[15]	3/10	2/10	1/10			3/10
Citak and Citak, 2011[16]	10/12	6/12	4/12	6/12	4/10	
Ansari et al., 2014[9]	8/18	6/18	2/18			

OR, overall response; CR, complete response; PR, partial response; SR, sustained response; R, relapse; ADR, adverse drug reaction.

Table 3. Methodological Index for Nonrandomized Studies (MINORS) scores for the included studies.

Item	Wang et al., 2005[13]	Bennett et al., 2006[14]	Dogan et al., 2009[15]	Citak and Citak, 2011[16]	Ansari et al., 2014[9]
Clear aims	2	2	1	1	2
Inclusion of consecutive patients	2	2	1	1	2
Prospective	2	2	2	2	2
Appropriate endpoints	2	2	2	2	2
Unbiased estimate of endpoint	0	0	0	0	0
Appropriate follow-up	2	2	2	2	2
Lost to follow-up <5%	2	2	2	2	2
Prospective sample size calculation	0	2	0	0	0
Final score	12	14	10	10	12
Maximum score	16	16	16	16	16

Scores = 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate). The total ideal score is 16. Although the article scores were low, they all had relevant outcomes.

included trials were consistent and the data were appropriate.

Discussion

This meta-analysis aimed to evaluate the efficacy and safety of a standard dose of RTX for children with ITP. Our results indicated that the CR rate was 52%, which is higher than the 39% reported in a previous study.[8] In our study, we developed strict inclusion and exclusion criteria and excluded trials with fewer than 10 participants. We used the R software for analysis, and the CR rate was 52%, the I^2 value was 45%, and $P = 0.14$. The homogeneity of our study was better than that of previous studies. Four additional studies confirmed CR rates from 39% to 63%,[17–20] so our rate of 52% was within this range. Some ADRs associated with RTX, such as fever, itching, scrapes, joint pain, and rash, were mild and reversible in the included studies, and only a few pediatric ITP patients who accepted RTX therapy experienced serum sickness. In the study by Parodi et al.[17], 49 children with ITP received RTX therapy, and nine

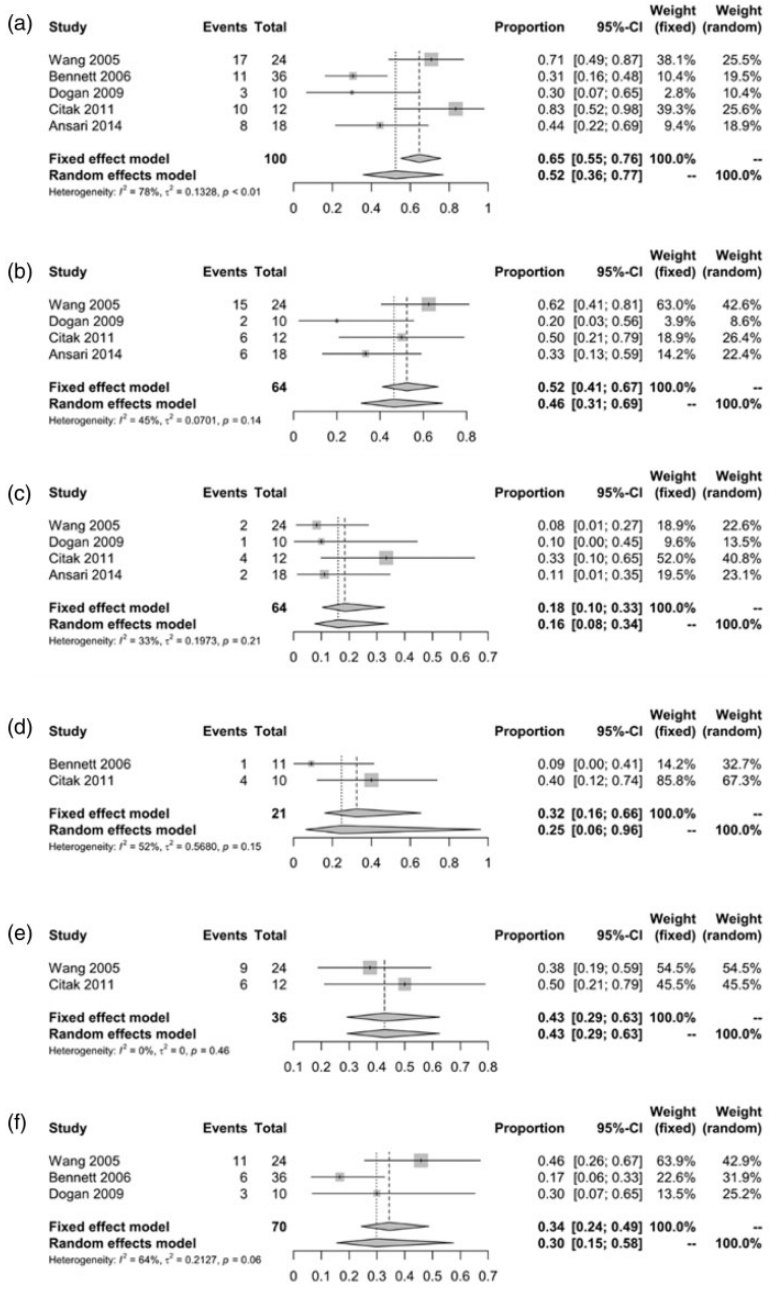

Figure 2. Meta-analysis results of (a) overall response, (b) complete response, (c) partial response, (d) relapse, (e) sustained response, and (f) adverse drug reactions in the five papers evaluated: Wang et al. (2005),[13] Bennett et al. (2006),[14] Dogan et al. (2009),[15] Citak and Citak (2011),[16] and Ansari et al. (2014)[9]
95% CI, 95% confidence interval.

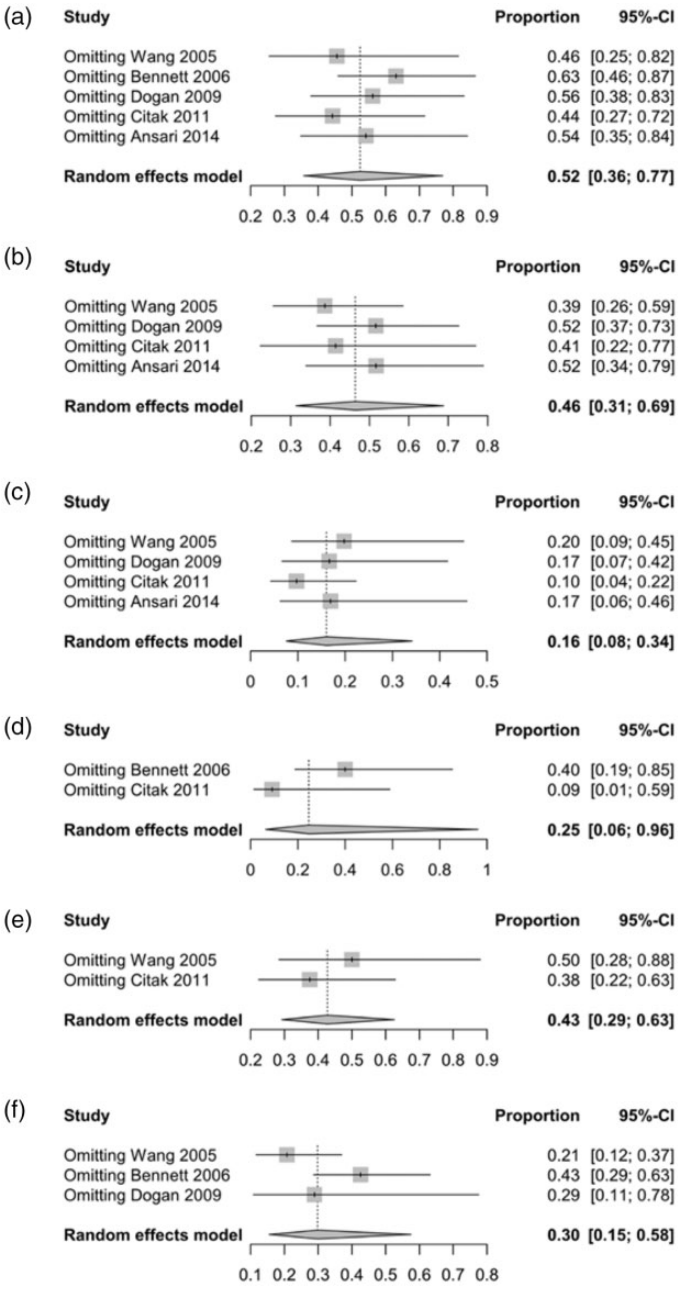

Figure 3. Sensitivity analysis results of (a) overall response, (b) complete response, (c) partial response, (d) relapse, (e) sustained response, and (f) adverse drug reactions in the five papers evaluated: Wang et al. (2005),[13] Bennett et al. (2006),[14] Dogan et al. (2009),[15] Citak and Citak (2011),[16] and Ansari et al. (2014)[9]
95% CI, 95% confidence interval.

experienced only mild transitory side effects, resulting in an ADR rate of 18.4%. To assess safety, we also calculated the incidence of adverse events in three studies,[13–15] which was 30%. Compared with Parodi et al.,[17] these studies reported increased incidence rates of adverse events. Different ADR rates indicate that RTX should be initiated cautiously for pediatric ITP. In addition to the standard dose, some studies also reported that a low dose (100 mg flat dose weekly for 4 weeks) or two fixed doses (1000 mg on days 1 and 15) of RTX was effective for ITP.

In the study by Zaja et al.,[21] 57 adult patients with ITP were split into two groups: 32 patients received a standard dose of RTX and 25 patients received low-dose RTX. The results showed that the OR rate in the standard dose RTX group was higher than that in low-dose RTX group (66% vs. 52%); the duration of response was longer in the standard-dose group than in the low-dose group. A standard dose of RTX may be suitable to treat ITP patients in the long term.[21] The OR rate was 43.5% (47/108) in Tran et al.[22] In that study, the efficacy of two fixed doses of RTX in ITP patients was similar to that in patients who received the standard dose of RTX. Our results showed that the OR, PR, SR, and R rates in pediatric ITP were 52%, 18%, 43%, and 25%, respectively. Published OR rates in pediatric ITP patients varied widely, ranging from 31% to 70%.[7,17–20,23,24] One study showed that OR may be positively associated with the proportion of secondary ITP, and the univariate analysis revealed that secondary ITP was a predictor of RTX response (odds ratio 6.8, $P < 0.01$).[23] There are many varieties of second-line therapeutic agents for childhood ITP. In an RCT by Dai et al.,[20] healthy children (n = 20) were used as the control group, and 50 children with refractory ITP were randomly divided into an RTX group (n = 26) and a vincristine group (n = 24). The results showed that the OR rate of the RTX group (69.2%) was greater than that of the vincristine group (37.2%), and recurrence in the RTX group was lower than that in the vincristine group. Thus, RTX is more suitable than vincristine to treat children with refractory ITP. PR rates varied from 6% to 27%,[17–20] and our PR rate was in line with previously reported rates. Because pediatric ITP has a good chance of resolving spontaneously, and splenectomy has a higher risk of infection than RTX treatment, the ASH guideline panel recommends using RTX rather than splenectomy as the second-line treatment in children with ITP following first-line therapy failure.[6]

According to this meta-analysis, although the quality of individual studies was not high, RTX as a second-line agent results in a good treatment response in children with ITP. Pediatric ITP has a low risk of bleeding, and the rate of severe bleeding in children was only 20.2%;[25,26] however, the small number of patients makes high-quality research difficult. Additional controlled prospective trials are urgently needed to verify the efficacy and safety of RTX.

Conclusions

Because of the small number of clinical trials available, most of which were single-arm studies, we obtained data from only five clinical trials showing that RTX has a therapeutic effect on pediatric ITP. However, some heterogeneity was found in our studies, and we hope that more clinical trials will be conducted to further explore the results.

Authors' contributions

ZPZ and MQ designed this research project; MQ, JZ, and SJY contributed to the application software, data analysis, and data interpretation; and MQ and ZPZ prepared the manuscript. All authors participated in writing of relevant

sections of the manuscript. All authors read and approved the manuscript and agree to be accountable for all aspects of the research in ensuring that the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Availability of data and materials

The datasets used during the present study are available from the corresponding author upon reasonable request.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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