SYSTEMATIC REVIEW

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Treatment strategy for acquired pure red cell aplasia: a systematic review and meta-analysis

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The treatment of autoimmune acquired pure red cell aplasia (aPRCA) is challenging. Guidelines are based on expert recommendations in the absence of controlled trials. We assessed the efficacy of the main treatment strategy through a systematic review and meta-analysis using MEDLINE, EMBASE, and the Cochrane Library up to September 2022. The overall response rate (ORR) was pooled using random-effects models. In total, 24 observational studies (19 retrospective, median follow-up of 48 months) encompassing 753 patients (49% male) were included. Primary aPRCA represented 57% of the cases. The risk of bias was moderate to high using the ROBINS-I tool. Substantial heterogeneity (I^2 > 50%) was retrieved. Corticosteroids as monotherapy as first-line treatment (186 patients, 13 studies) provided an ORR of 47% (95% confidence interval [CI], 34-60). Cyclosporine A was the most frequently used immunosuppressant agent (384 patients, 18 studies), providing an ORR of 74% (95% CI, 66-82) with a similar ORR in first- (73%) and second-line (76%) treatment and when cyclosporin was used as monotherapy (83%) or with corticosteroids (77%). A total of 112 patients (10 studies) received cyclophosphamide, with an ORR of 49% (95% CI, 35-64), which was higher when cyclophosphamide was combined with corticosteroids (48%) and used in second-line treatment (58%) than in monotherapy (31%), and in first-line treatment (44%). Sirolimus use was reported only after cyclosporine A failure and provided an ORR of 87% (95% CI, 68-100; 64 patients, 3 studies). Substantial uncertainty remains regarding the best treatment strategy in the absence of high-quality evidence. This study was registered on the PROPERO database as #CRD42022360452.

Introduction

Acquired pure red cell aplasia (aPRCA) is a very rare anemia due do the failure of erythropoiesis, causing profound reticulocytopenia, with an estimated annual incidence of 1.06 per million.[1] Erythropoiesis failure is assessed by bone marrow examination showing a drastic reduction of erythroid precursors without abnormalities in other cell lineages.[2] aPRCA are separated in primary and secondary

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Data are available on reasonable request from the corresponding author, Hervé Lobbes (hlobbes@chu-clermontferrand.fr).

The full-text version of this article contains a data supplement.

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subtypes depending on the existence of an underlying condition: solid tumors (notably thymoma), hematologic malignancies (including large granular lymphocyte leukemia [LGLL]), autoimmune diseases (AID; such as systemic lupus erythematosus or rheumatoid arthritis), infections (mainly parvovirus B19), pregnancy, and ABO-incompatible stem cell transplantation. Most of the mechanisms underlying aPRCA show an autoimmune disorder mediated either by autoantibodies or T-lymphocyte dysregulation.[3-5]

The treatment of aPRCA is challenging. A clear strategy has been identified for parvovirus B19–related pure red cell aplasia in patients who are immunocompromised: the administration of intravenous immunoglobulins is an effective and swift specific treatment.[6] In primary or other secondary forms of aPRCA, immunosuppression is recommended: corticosteroids are the first-step, occasionally associated from the start with cyclosporine A. Other immunosuppressants reported as effective options include cyclophosphamide, methotrexate, rituximab, and alemtuzumab.[7] In thymic tumor–related PRCA, the efficacy of thymectomy remains controversial.[8] Recently, several studies have highlighted the potential interest of sirolimus, a mammalian target of rapamycin (mTOR) inhibitor in patients who are refractory or cyclosporine A intolerant.[9] These data are derived from cohort studies, providing medium-quality evidence.

Therefore, we carried out a systematic review and meta-analysis to obtain a precise estimate of the efficacy of the most common treatment strategies in aPRCA and conducted a subgroup analysis to identify the best strategy per the existence of an underlying disease (LGLL, thymoma, and AID) and in primary aPRCA.

Methods

This meta-analysis was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (PRISMA)[10] and has been registered on the International Prospective Register of systematic reviews (PROSPERO CRD42022360452), in which the complete search strategy is available.

Search strategy and study selection

We proceeded with a MEDLINE, EMBASE, and Cochrane Library search from 1 January 1967 through 30 September 2022. We aimed to collect all published studies reporting the disease course of patients with aPRCA. Because of marked differences in the course of certain specific aPRCA etiologies (particularly because of marked differences in treatment strategy management), studies reporting parvovirus B19–related aPRCA, pregnancy-related aPRCA, ABO-incompatible stem cell transplantation–related aPRCA, and erythropoietin-induced aPRCA were excluded. The automation tool identified and excluded studies from the list obtained with the initial search strategy if the title included 1 of the following term: "mouse study," "animal study," "murine model," "ABO-mismatch," "parvovirus B19," "Diamond Blackfan," and/or "congenital." Preprint studies as well as non-English articles were not retained through the use of the specific language filter on the databases. No restriction in study design or article type was applied.

Two of the authors (H.L. and S.M.), who were blinded to author and journal names, independently reviewed titles and abstracts identified from the database search to select studies meeting the following inclusion criteria: (1) diagnosis of aPRCA, (2) study describing the aPRCA course of at least 5 patients, and (3) treatment strategy (immunosuppressive drug or thymectomy), with available detailed overall response rate (ORR, percentage of patients presenting complete or partial response [PR] to treatment), PR rate (percentage of patients presenting PR to treatment), or complete response rate (percentage of patients presenting complete response [CR] to treatment), as defined by the authors.

If pertinent, each reviewer retrieved and explored the complete articles to make a final decision about their inclusion in the meta-analysis. In the case of disagreement, a third reviewer (J.-C.L.) was consulted to reach a consensus. In the case of cohorts reported in multiple papers, the analysis was limited to the largest cohort, unless the necessary data had appeared only in another study. In the case of doubt or apparent inconsistency, H.L. was contacted to remove any ambiguity.

Data extraction and quality assessment

Data from the included studies were independently extracted by the 2 authors (H.L. and S.M.). The third reviewer was consulted to resolve any disagreement. The supplemental Materials were systematically checked to collect data of interest.

The following data were collected:

- Study characteristics: author, year, journal of publication, country, and study design.
- Patient characteristics: age, sex, hematologic parameters at aPRCA diagnosis (including hemoglobin, reticulocyte, and erythroblast count), type of aPRCA (primary form; and secondary form associated with thymoma, LGLL, AID, solid cancer, or indeterminate if details about the underlying disease were insufficient).
- Treatment and response rates, and follow-up duration. Response rates were collected for each treatment described in the study, therefore a patient who received multiple lines of treatment in a single study could be counted multiple times and the individual response for each drug was assessed. When available, we collected data on the line of treatment (either first-line or second-or-later line) and the possible combination of each immunosuppressive drug with corticosteroids.
- Because thymectomy is routinely performed for thymic tumor regardless of the existence of any associated disease, surgical procedures for thymoma-associated PRCA were analyzed separately.

Study outcomes

The treatment response was assessed using the response rates as defined by the authors. The congruity of the definitions of response to treatment to the standardized criteria was assessed for each study. The CR and PR in standardized definitions is transfusion independency with hemoglobin level normalization (hemoglobin of >120 g.L^{-1}) and transfusion independency with the persistence of anemia, respectively.[7] We excluded studies from the quantitative analyses when the response criteria were absent, unclear, or markedly more liberal than the conventional definitions.

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Statistical analysis

Descriptive data were reported as mean ± standard deviation or median (interquartile range). The pooled response rate with corresponding 95% confidence intervals (95% CI) were calculated at the study-treatment level (1 row for each drug in each study) in a random-effects model, irrespective of heterogeneity, using untransformed proportion and a continuity correction of 0.5 in studies with 0 cell frequencies. Heterogeneity between study-specific estimates was assessed using the inconsistency index I^2, with $I^2 > 50\%$ defining substantial heterogeneity.[11] We also explored pooled response rates for thymectomy and in each underlying disease using the same methodology.

The risk of publication bias was visually assessed using funnel plots.[12] The summary of the risk of bias was assessed using the ROBINS-I tool and the Newcastle-Ottawa scale for nonrandomized studies.[13,14] A P value $< .05$ was considered statistically significant. All analyses were performed using R version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria) with the metafor package (version 3.4-0).

Results

Characteristics of included studies and population

A total of 2540 records from databases were identified (Figure 1). Automation tools allowed excluding 933 records. We screened 1227 records and retained 137 reports. After full-text assessment, 28 studies[3,4,7-9,15-37] were included in the systematic review and 24 studies were included in the meta-analysis (Table 1), encompassing 753 patients (48.8% men; mean age, 55.6 ± 9.9 years; and a mean hemoglobin level of 62 ± 13 g/L at PRCA diagnosis).

All the studies were observational, mostly monocentric (63%, n = 15); 19 (79%) studies were retrospective. The largest cohort included 100 patients in a multicentric retrospective study.[16] There was a slight predominance of primary aPRCA (428 patients, 57%). Among secondary forms, thymoma was the most frequently reported disease (162 patients, 49%) followed by LGLL (147 patients, 45%). Only 24 cases of aPRCA were associated with AIDs (3% of the included population).

The median follow-up duration was 48 months (range, 27.5-62.5; 20 studies). The most frequently used immunosuppressant agent was cyclosporine A (384 patients, 18 studies[3,4,7-9,15-18,20,23,24,27,29,30,33-35]), followed by corticosteroids (186 patients, 13 studies[4,16,20,23,24,27-30,33-35,37]), and cyclophosphamide (112 patients, 10 studies[4,7,15,17,23,27,29,30,33,34]). Other regimens reported in multiple studies were sirolimus (64 patients, 3 studies[4,9,19]), methotrexate (18 patients, 5 studies[7,17,27,33,34]), azathioprine (12 patients, 3 studies[4,33,34]), rituximab (25 patients, 3 studies[4,7,19]), and alemtuzumab (31 patients, 2 studies.[7,23] Some treatment strategies were reported in isolated reports, such as stem cell transplantation[26] or daclizumab.[25] The effect of thymectomy on PRCA was assessed in only 5 studies[8,18,31,35,36] among the 17 studies that included patients with thymoma-associated PRCA.

Fourteen studies (50%)[3,4,7,15,16,23-25,27-30,33,37] used standardized criteria to define the response to treatment; 10 studies[8,9,17-20,26,31,34,35] (35.7%) used criteria with mild differences from the standardized definitions (notably using a hemoglobin threshold of >11 g/dL to define CR[8,9,19,20,31,34,35]). In 4 studies,[21,22,32,36] the criteria were not described or markedly different compared with the standardized definitions with less stringent thresholds for hemoglobin increase, leading us to exclude these studies from the quantitative analysis. The definitions used are described in supplemental Table 1.

The visual inspection of the funnel plot suggested the absence of publication bias and small-study effect regardless of the treatment strategy, as shown in supplemental Figure 1. The risk of bias assessed with the ROBINS-I tool is shown in Figure 2. In summary, the overall risk of bias was assessed as moderate (75%, 18 of 24) to high (25%, 6 of 24). Risk due to missing data was the most frequent domain with a high-level risk of bias (5 studies), followed by the risk of bias in outcome measurements (5 studies). The quality of included studies assessed with the Newcastle-Ottawa scale is available in supplemental Table 2.

Treatment efficacy in the overall population

Excluding thymectomy and irrespective of the disease or treatment, the pooled ORR for all the strategies was 59.2% (95% CI, 52.4-66; I^2, 86%) and is shown in Figure 3. The response rates per the line of treatment and per the association of immunosuppressive drugs with corticosteroids are shown in supplemental Figures 2 and 3, respectively.

Corticosteroids. In total, 186 patients (25% of the population) received corticosteroids as monotherapy, providing an ORR of 46.9% (95% CI, 33.6-60.2; I^2, 78%). No studies reported the use of corticosteroids as second-or-later line.

Cyclosporine A. Cyclosporine A was the most frequently used immunosuppressant agent (384 patients, 51%), providing an ORR of 74.1% (95% CI, 66.1-82.1; I^2, 59%) irrespective of the line of treatment or combination with corticosteroids. The use of cyclosporine A as monotherapy was reported in 137 patients and provided an ORR of 83.2% (95% CI, 72.3-94.1, I^2, 58%), whereas 124 patients were reported to receive cyclosporine combined with corticosteroids, providing an ORR of 77.3% (95% CI, 69.9-84.7, I^2, 0%). Similar response rates were found in first-line (73.3%, 216 patients) and in second-or-later line of treatment (75.6%, 43 patients).

Cyclophosphamide. Cyclophosphamide was used in 112 patients (15%), providing an ORR of 49.4% (95% CI, 35.1-63.7; I^2, 55%). The ORR of cyclophosphamide was higher when it was combined with corticosteroids (48.1%, 52 patients) and in second-line treatment (58.2%, 21 patients) than it was as monotherapy (30.6%, 15 patients), and in first-line treatment (44.3%, 17 patients).

Sirolimus. Sirolimus use was reported in 3 studies, encompassing 64 patients (8.5%), only as second-or-later line treatment after cyclosporine A failure or side effects. The ORR was 86.6% (95% CI, 67.9-100; I^2, 67%). In the 2 largest cohorts, encompassing 61 of 64 patients, sirolimus use was reported as monotherapy without corticosteroids, providing a similar ORR of 88.7%.

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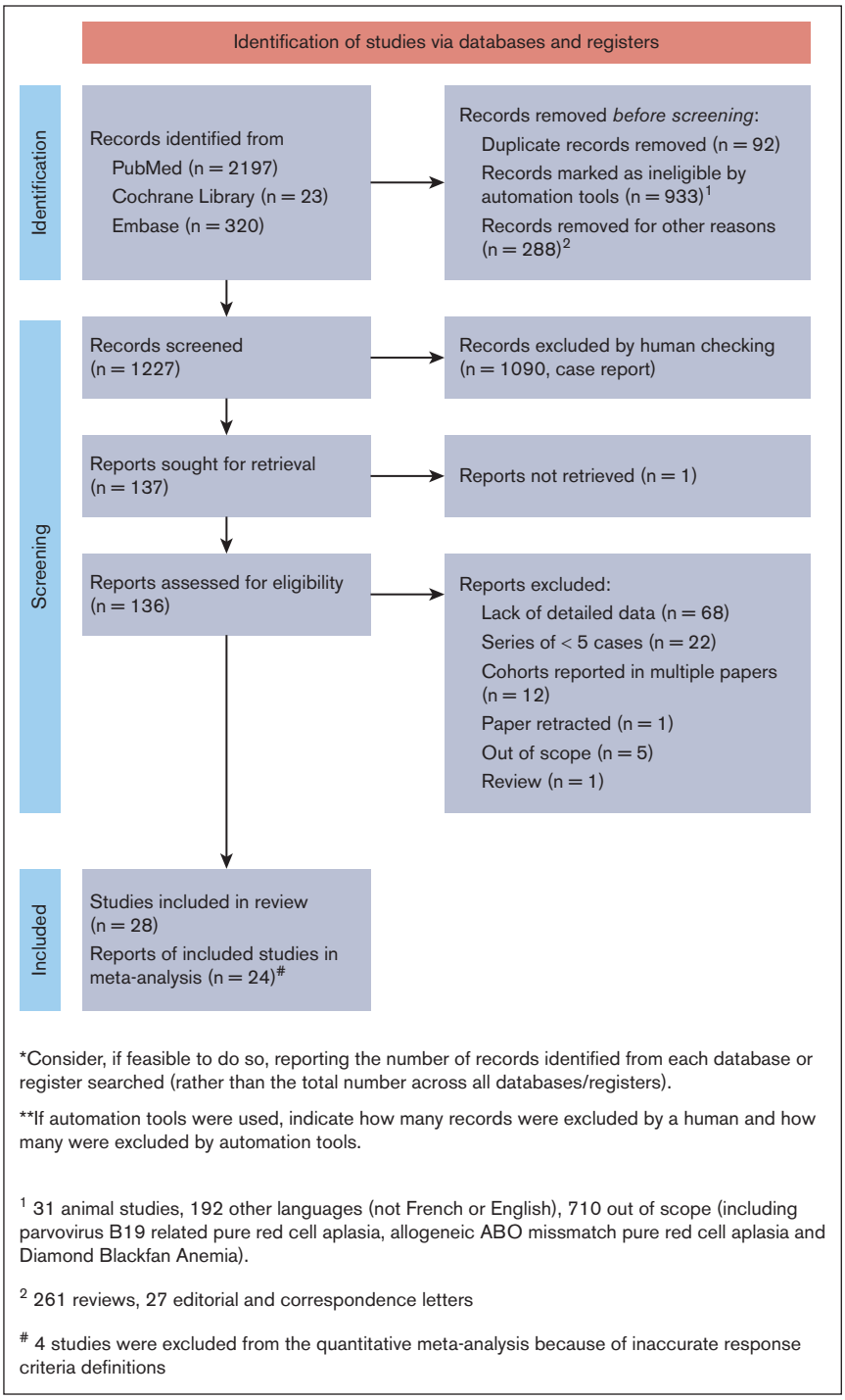

Figure 1. PRISMA flow diagram.

Other conventional immunosuppressive drugs. Methotrexate was used in 18 patients (2%, 5 studies) providing an ORR of 66.7% (95% CI, 34.9-98.5; I^2, 58%), which was lower in use as a first-line treatment (29.1%, 7 patients) than as second-or-later line treatment (69.4%, 10 patients). Rituximab was used in 3 studies, encompassing 25 patients (3%), providing an ORR of 52.0% (95% CI, 32.8-71.1; I^2, 0%) and 51.8% in second-line treatment (21 patients, 2 studies).

Rare strategies. Alemtuzumab use on a compassionate basis as second-or-later line treatment in 31 patients (4%) provided an ORR of 55.9% (95% CI, 0-100; I^2, 83%). No detail of the concomitant use of corticosteroids was available.

Autologous stem cell transplantation provided an ORR of 50% (4 patients), whereas a single report of allogeneic stem cell transplantation described a successful treatment. A single study

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Table 1. Characteristics of studies included in the systematic review and meta-analysis

			Population									Treatment	
Study (year)	Country	Design	N	Age, y	Male sex (%)	FU	Primary	Secondary	Thymoma	LGLL	AID	Drug	Line
Wu et al[16] (2022)	China	R, M	100	57	47	NA	60	40	6	28	2	CsA, CS	First
Kawakami et al[15] (2022)	Japan	R, M	90	65	NA	NA	26	NA	15	36	NA	CsA, CS	Combined
Huang et al[9] (2022)	China	P, m	64	63	56	12	40	20	5	6	5	CsA, sirolimus	Second-or-later
Salama et al[17] (2022)	United States	R, m	13	72	85	80	0	0	0	13	0	CsA, CYC, MTX	First
Yen et al[18] (2021)	Taiwan	R, m	7	NA	43	56	0	7	7	1	0	Thymectomy, CsA	First
Lobbes et al[4] (2021)	France	R, M	24	39	17	76	0	24	1	3	24	AZA, CS, CsA, CYC, MMF, RTX, sirolimus	Combined
Moriyama et al[8] (2018)	Japan	R, m	8	59	63	54.5	0	8	8	0	0	Thymectomy, CsA	First
Long et al[19] (2018)	China	P, m	21	59	48	17	21	0	0	0	0	Sirolimus	Second-or-later
Fu et al[20] (2018)	China	R, m	53	60	45	31	30	23	7	1	3	CS, CsA	First
Balasubramanian et al[7] (2018)	United States	R, m	62	62	55	40	32	23	9	14	0	ATZ, CsA, CYC, MTX, RTX	Combined
Chalayer et al[21] (2017)*	France	R, M	8	36	0	27	0	8	0	0	8	CS	First
Peng et al[22] (2016)*	China	R, m	10	54	90	30	0	10	0	10	0	CYC + CsA	Second-or-later
Rivoisy et al[23] (2016)	France	R, M	11	57	36	23	0	11	11	0	0	ATZ, CS, CsA, CYC, RTX	Combined
Kawano et al[24] (2013)	Japan	R, m	5	46	20	80	2	3	3	0	0	CS, CsA	Combined
Sloand et al[25] (2010)	United States	P, m	27	45	48	58	27	0	0	0	0	Daclizumab	NA
Passweg et al[26] (2008)	Europe	P, M	5	NA	NA	42	NA	NA				HSCT	Second-or-later
Fujishima et al[27] (2008)	Japan	R, M	14	60	57	90	0	14	0	14	0	CS, CsA, CYC, MTX	Combined
Malhotra et al[28] (2008)	India	R, m	7	40	57	NA	5	2	2	0	0	CS	First
Hirokawa et al[29] (2008)	Japan	R, M	41	66	43	18	0	41	41	0	0	CS, CsA, CYC	First
Sawada et al[30] (2007)	Japan	R, M	62	55	37	54	62	0	0	0	0	CS, CsA, CYC	First
Thompson et al[31] (2006)	United States	R, m	13	65	54	26	0	13	13	0	0	Thymectomy	First
Marsch et al[32] (2001)*	United Kingdom	P, m	5	48	40	10	NA	NA				ATZ	Second-or-later
Charles et al[33] (1996)	United States	R, m	24	59	58	30	12	12	3	3	4	AZA, CS, CsA, CYC, MTX	Second-or-later
Lacy et al[34] (1996)	United States	R, m	47	NA	60	54	25		4	9		AZA, CS, CsA, MTX	Combined
Kwong et al[35] (1996)	China	R, m	15	58	50	28	9	5	3	2	0	CS, CsA, thymectomy	First and second-or-later
Means[3] (1991)	United States	P, m	9	34	57	NA	NA	NA				CsA	Second-or-later
Masaoka et al[36] (1989)*	Japan	R, m	17	61	47	NA	0	17	17	0	0	Thymectomy	First-line
Clark et al[37] (1984)	United States	R, M	31	47	48	103	27	4	2	0	0	CS	NA

ATZ, alemtuzumab; AZA, azathioprine; CS, corticosteroid; CsA, cyclosporin A; CYC, cyclophosphamide; FU, follow-up; HSCT, hematopoietic stem cell transplantation; M, multicentric study; m, monocentric study; MMF, mycophenolate mofetil; MTX, methotrexate; N, number of patients; NA, not available; P, prospective design; R, retrospective design; RTX, rituximab.

*Studies excluded from the meta-analysis because of imprecise or inaccurate response criteria definitions.

Figure 2. Risk of bias across domains per the ROBINS-I tool.

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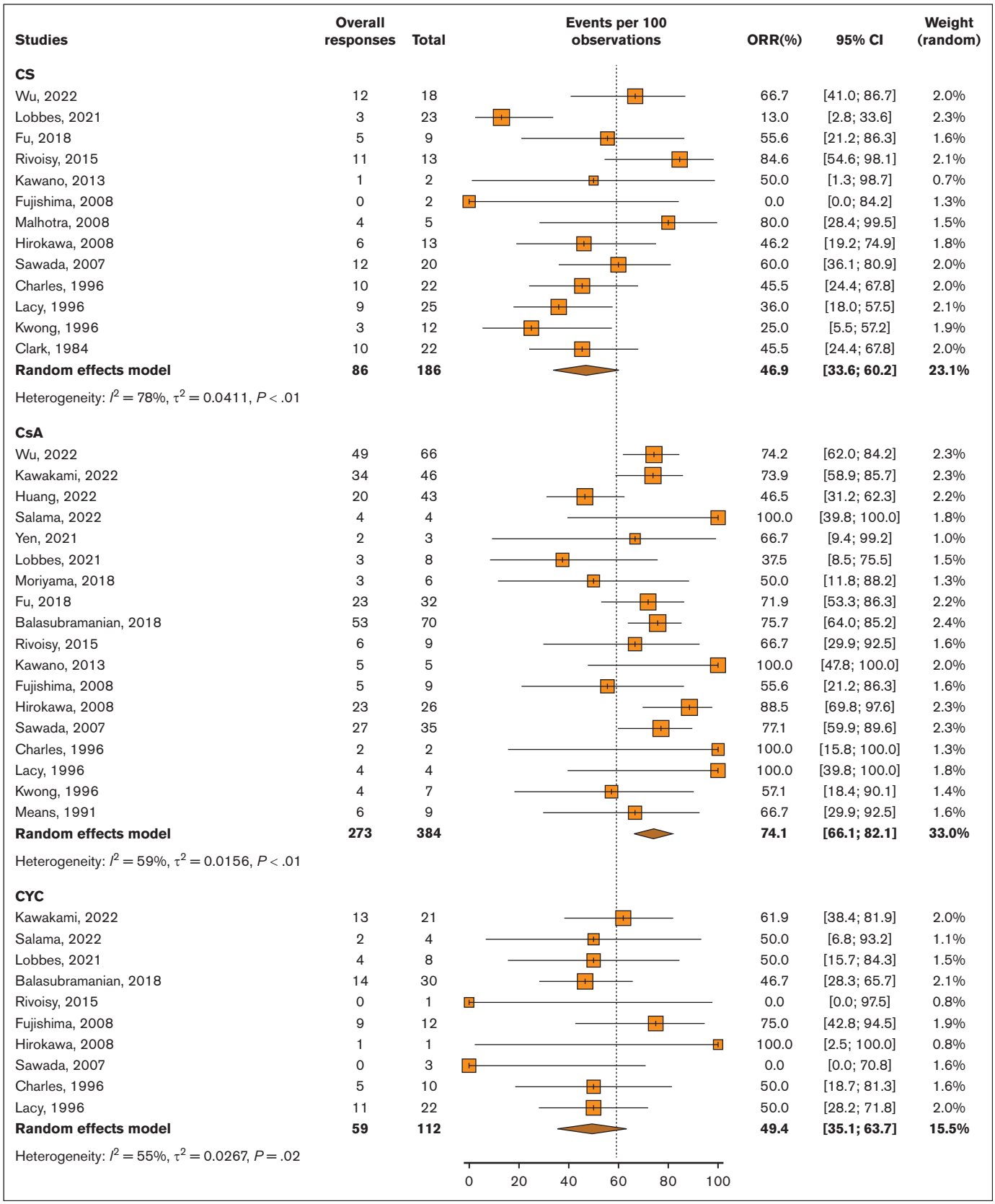

Figure 3. ORR per immunosuppressive strategies in the overall population (excluding thymectomy).

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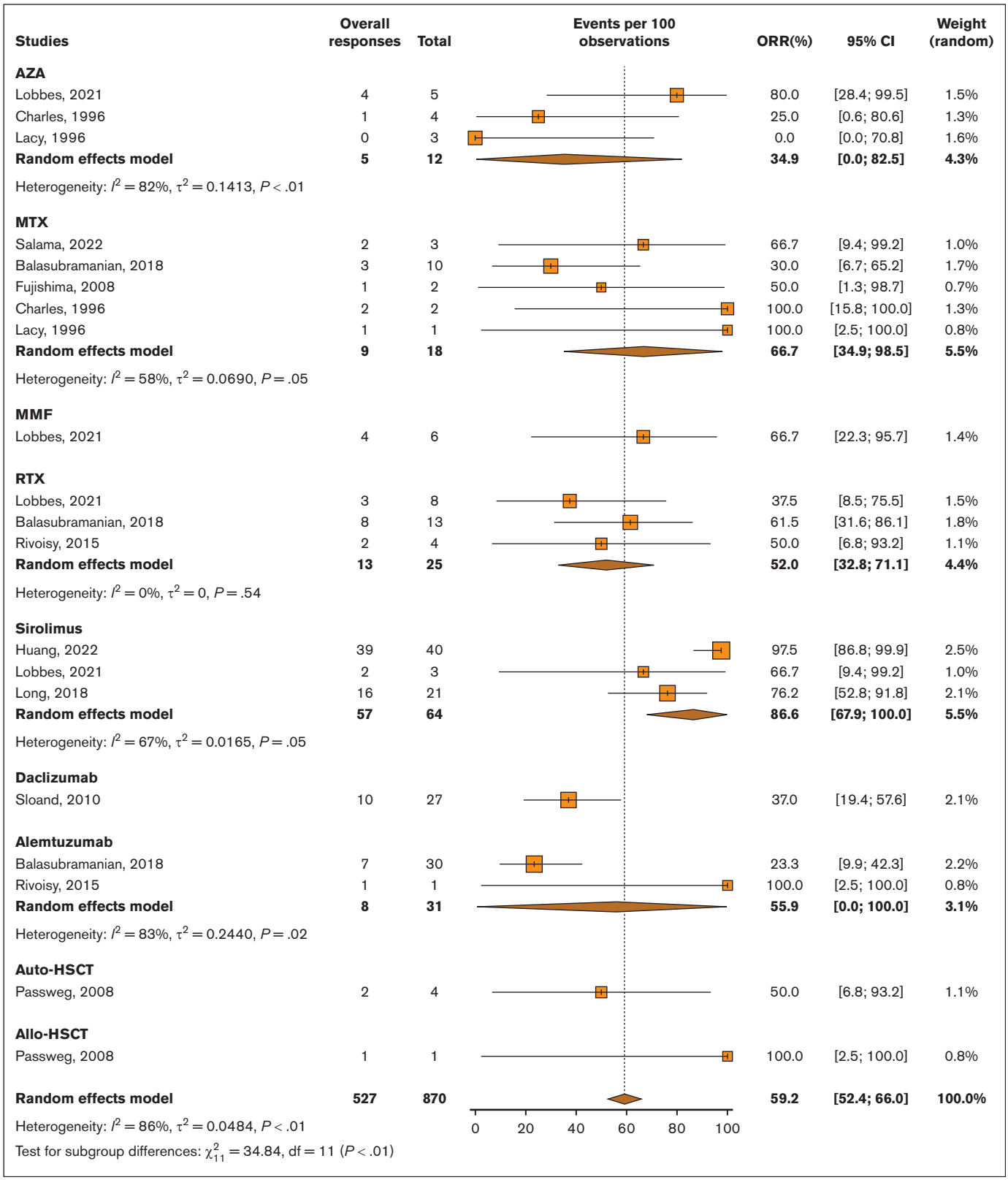

Figure 3 (continued)

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reported a response rate of 37% for 27 patients treated by daclizumab.

Treatment efficacy per the subtype of PRCA

Primary PRCA. Corticosteroids as monotherapy (82 patients, 7 studies) provided an ORR of 50.2% (95% CI, 36.8-63.6; I^2, 43%). Cyclosporine A (94 patients, 6 studies) provided an ORR of 82.9% (95% CI, 75.3-90.6; I^2, 0%). Sirolimus was the second most frequent immunosuppressive drug, used in 47 patients (2 studies) as second-line therapy after cyclosporine A failure, providing an ORR of 88% (95% CI, 68.7-100; I^2, 75%). Details of the other regimens are available in Figure 4A and supplemental Figure 4.

LGLL-associated PRCA. Only 7 patients received corticosteroids in monotherapy as first-line treatment, with no response. Cyclosporine A (81 patients, 8 studies) provided an ORR of 63.5% (95% CI, 42-85.1; I^2, 72%). Cyclophosphamide (48 patients, 5 studies) provided an ORR of 61.3% (95% CI, 48-74.7; I^2, 0%). Methotrexate (16 patients, 4 studies) provided an ORR of 55.4% (95% CI, 23-87.8; I^2, 39%). The response rates were higher for cyclosporine A and methotrexate in second-line treatment than in first-line treatment (57.3% vs 68.8% and 29.1% vs 62.7%, respectively) whereas the higher response rates for cyclophosphamide was in first-line treatment (68.2% vs 57.4%). Detailed responses are shown in Figure 4B and in supplemental Figure 5.

AID-associated PRCA. Corticosteroids in monotherapy (27 patients, 2 studies) provided an ORR of 23.7% (95% CI, 0-56.6; I^2, 51%). Sirolimus (2 studies, 6 patients) provided an ORR of 90.3% (95% CI, 60.7-100; I^2, 9%) and cyclophosphamide (2 studies, 11 patients) an ORR of 75.4% (95% CI, 26.4-100; I^2, 77%). Other regimens were reported in single studies, as shown in Figure 4C and in supplemental Figure 6.

Thymoma-associated PRCA. Corticosteroids (31 patients, 6 studies) in monotherapy provided an ORR of 76.1% (95% CI, 54.2-98.1; I^2, 36%). Cyclosporine A was the most frequently used immunosuppressive drug (61 patients, 8 studies) providing an ORR of 89.7% (95% CI, 80.1-99.3; I^2, 29%), mainly used as first-line treatment (36 patients; ORR, 93.3%) and without corticosteroids (39 patients; ORR, 90.1%). Other drugs were used in <5 patients. Thymectomy without any additional immunosuppressive regimen provided a low response rate (ORR, 2.4; 95% CI, 0-10.7; I^2, 33%; supplemental Figure 7). The detailed responses are shown in Figure 4D and supplemental Figure 8.

Discussion

In this meta-analysis encompassing 753 patients with aPRCA from 28 observational studies, the ORR of immunosuppressive therapy was 59.5%, with significant heterogeneity between studies.

Our meta-analysis reported 46% corticosteroid efficacy in monotherapy as first-line treatment irrespective of the subtype of PRCA. The common initial dosage of corticosteroids in monotherapy ranged from 0.3 to 1 mg/kg[16,20,27,29,30,33,34] per day for 6 weeks to 3 months followed by a taper in case of hemoglobin improvement, but no standardized scheme of tapering was described. Noticeably, some studies reported higher initial dosages of up to 2 mg/kg with a maintenance dosage at 0.1 mg/kg per day.[24] When corticosteroids were associated with an immunosuppressive drug (most commonly cyclosporine A), the initial dosage was lower (30 mg per day)[3] and was tapered gradually whereas the immunosuppressive drug was maintained for 1 to 2 years.

Numerous immunosuppressive drugs were reported, both as first-line and as second-line treatment. Cyclosporine A was the most frequently used immunosuppressant drug, providing an ORR of 74% in the overall population, with similar response rates as first and second-line treatment. The most commonly reported dosage was 3 to 5 mg/kg per day[3,20,30] to maintain a trough concentration ranging from 150 to 250 ng/mL. In patients expected to tolerate corticosteroids poorly, the association of corticosteroids and cyclosporine A could be proposed. However, high uncertainty remains because our analysis neither support a higher response rate with the combination of corticosteroids and cyclosporine A than with cyclosporine A alone, nor identify a shorter time-to-response or a longer duration of response.

Sirolimus was used without the concomitant use of corticosteroid in the majority of cases. The initial dosage of 2 mg per day was adjusted to obtain a trough concentration of 4 to 15 ng/mL. Efficacy appeared high (86% ORR) but uncertainty remains over the possible cumulative effect of previous lines of therapy to explain the high efficacy of sirolimus because sirolimus use was systematically reported as second-line treatment after cyclosporine A therapy (at least 6 months) in the case of failure or side effects.

Alemtuzumab was used in refractory or relapsing cases on a compassionate basis, providing a response rate of 46%. The dosage was reduced to limit toxicity: 10 mg per day for 10 days for a single course in the study of Marsh et al,[32] whereas Balasubramanian et al[7] reported their experience with a weekly infusion of 10 mg for 4 to 6 weeks after an initial infusion of 3 mg at the first week. In patients who experienced good response, alemtuzumab infusions were repeated at a dosage of 10 mg every 4 to 8 weeks. The use of azathioprine, mycophenolate mofetil, stem cell transplantation, and daclizumab was reported in a small number of studies with various efficacies and should be considered in an appropriate context such as autoimmune-associated disease requiring immunosuppressive drugs (eg, systemic lupus erythematosus) or in rescue therapy.

Primary aPRCA was the most frequent disease subgroup in our meta-analysis. Cyclosporine A and sirolimus were the most frequently reported immunosuppressive drugs. Sirolimus could therefore be used as a second-line treatment, but high uncertainty remains because most patients had already been treated with cyclosporine A, raising the question of an additional immunosuppressive effect. Despite the long screening period of our systematic review, AID-associated PRCA represents a small percentage of the total population with highly disparate treatment regimens (8 therapeutic strategies resulting in significantly high heterogeneity). The efficiency of corticosteroids appeared low but conflicting results were reported by Chalayer et al[21] albeit with unspecified response criteria. Noticeably, cyclosporine A use was very rarely reported in this population (3 patients, 1 study[4]) and may reflect physicians' practices, with cyclosporine A being an uncommon drug in systemic lupus erythematosus, which was the main AID included in the reports. Thymoma-associated PRCA was the second largest cohort: corticosteroids and cyclosporine A appeared highly effective, but Hirokawa et al[29] emphasized that the great

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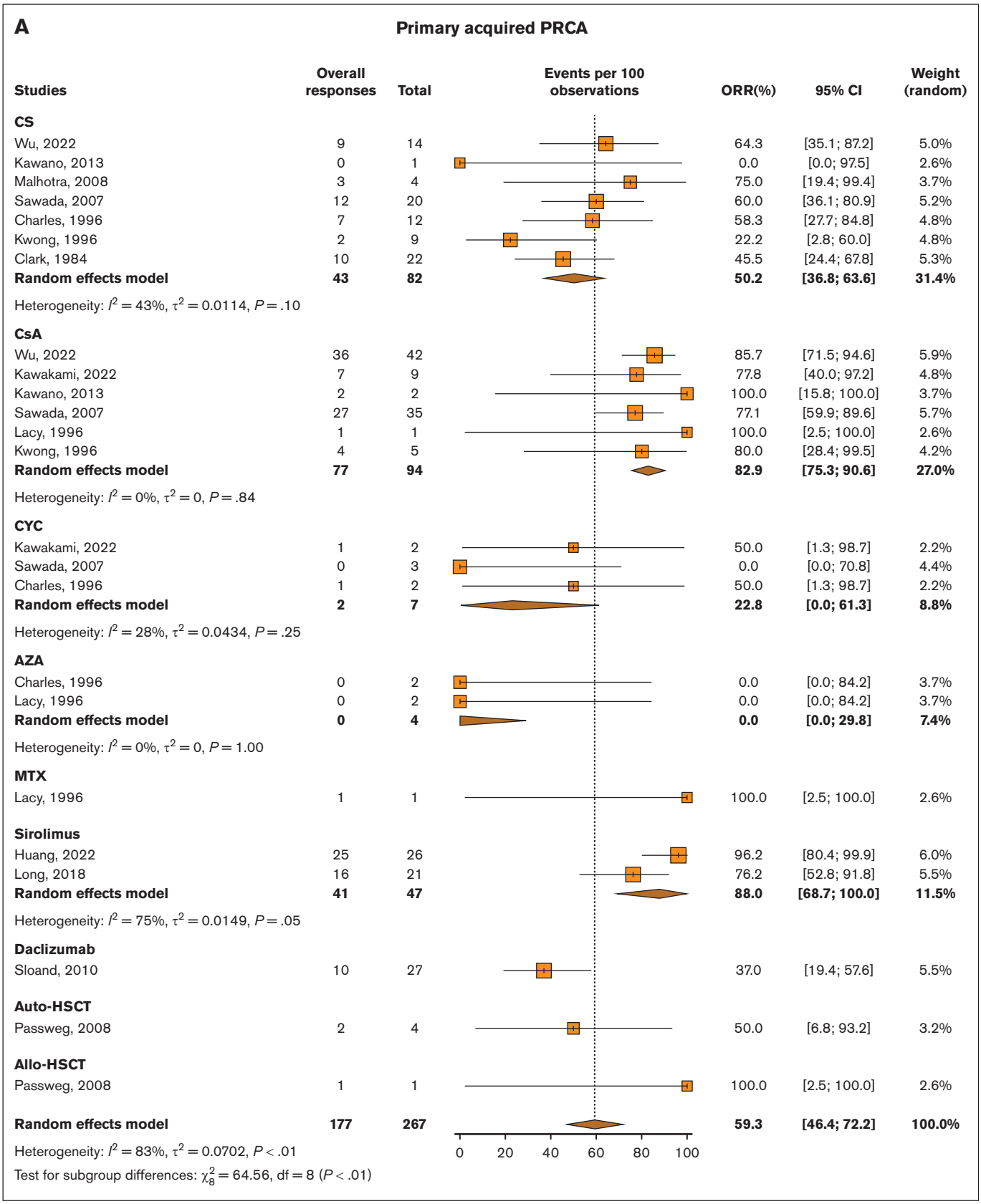

Figure 4. Overall response rate of the most commonly used immunosuppressive drugs in disease subgroup analysis. (A) Primary aPRCA, (B) LGLL-associated aPRCA, (C) AID-associated aPRCA, and (D) thymoma-associated aPRCA.

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B

Large granular lymphocyte leukemia associated PRCA

Studies	Overall responses	Total	ORR(%)	95% CI	Weight (random)
CS					
Fujishima, 2008	0	2	0.0	[0.0: 84.2]	3.9%
Charles, 1996	0	3	0.0	[0.0; 70.8]	4.6%
Kwong, 1996	0	2	0.0	[0.0; 84.2]	3.9%
Random effects model	**0**	**7**	**0.0**	**[0.0; 21.9]**	**12.4%**
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $P = 1.00$					
CsA					
Wu, 2022	8	19	42.1	[20.3; 66.5]	5.4%
Kawakami, 2022	16	24	66.7	[44.7; 84.4]	5.6%
Salama, 2022	4	4	100.0	[39.8; 100.0]	5.1%
Balasubramanian, 2018	11	20	55.0	[31.5; 76.9]	5.4%
Fujishima, 2008	5	9	55.6	[21.2; 86.3]	4.6%
Charles, 1996	2	2	100.0	[15.8; 100.0]	3.9%
Lacy, 1996	1	1	100.0	[2.5; 100.0]	2.8%
Kwong, 1996	0	2	0.0	[0.0; 84.2]	3.9%
Random effects model	**47**	**81**	**63.5**	**[42.0; 85.1]**	**36.6%**
Heterogeneity: $I^2 = 72\%$, $\tau^2 = 0.0688$, $P < .01$					
CYC					
Kawakami, 2022	10	16	62.5	[35.4; 84.8]	5.3%
Salama, 2022	2	4	50.0	[6.8: 93.2]	3.4%
Balasubramanian, 2018	7	13	53.8	[25.1; 80.8]	5.0%
Fujishima, 2008	9	12	75.0	[42.8; 94.5]	5.2%
Charles, 1996	1	3	33.3	[0.8; 90.6]	3.2%
Random effects model	**29**	**48**	**61.3**	**[48.0; 74.7]**	**22.1%**
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $P = .60$					
MTX					
Salama, 2022	2	3	66.7	[9.4; 99.2]	3.2%
Balasubramanian, 2018	3	10	30.0	[6.7; 65.2]	4.9%
Fujishima, 2008	1	2	50.0	[1.3; 98.7]	2.4%
Charles, 1996	1	1	100.0	[2.5: 100.0]	2.8%
Random effects model	**7**	**16**	**55.4**	**[23.0; 87.8]**	**13.2%**
Heterogeneity: $I^2 = 39\%$, $\tau^2 = 0.0451$, $P = .18$					
RTX					
Balasubramanian, 2018	1	2	50.0	[1.3; 98.7]	2.4%
AZA					
Lacy, 1996	0	1	0.0	[0.0; 97.5]	2.8%
Sirolimus					
Huang, 2022	4	4	100.0	[39.8; 100.0]	5.1%
Alemtuzumab					
Balasubramanian, 2018	6	20	30.0	[11.9; 54.3]	5.5%
Random effects model	**94**	**179**	**51.4**	**[37.9; 64.8]**	**100.0%**
Heterogeneity: $I^2 = 71\%$, $\tau^2 = 0.0749$, $P < .01$					
Test for subgroup differences: $\chi^2_7 = 44.68$, df = 7 ($P < .01$)					

Events per 100 observations

0 20 40 60 80 100

Figure 4 (continued)

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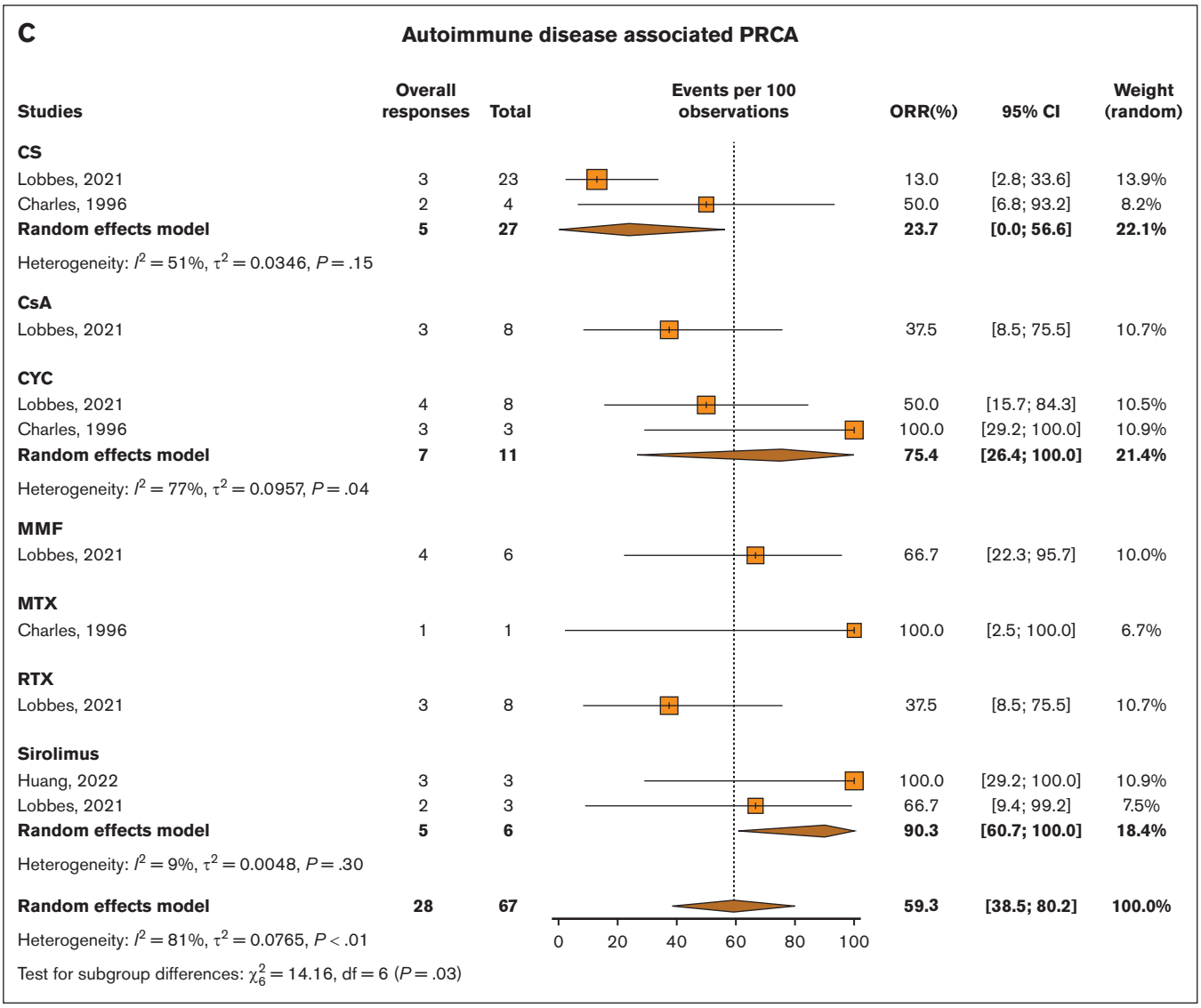

Figure 4 (continued)

majority of patients were maintained on immunosuppressive therapy. Noticeably, regarding thymectomy without immunosuppressive therapy for thymoma-associated PRCA, Masaoka et al[36] reported a response in 6 of 15 patients, which seems higher than our meta-analysis findings but the response definitions differed substantially from the standard criteria. Finally, LGLL-associated aPRCA was the disease subgroup with the lowest response rates. Our meta-analysis found similar response rates of cyclosporine A (63%) and cyclophosphamide (61%) that may support a similar positioning of the therapeutic strategy, because methotrexate is the third-line immunosuppressant commonly recommended in this condition (ORR, 55%). Cyclophosphamide was administered orally at a dosage ranging from 50 to 100 mg per day[27,30] for up to 1 year. A combination of cyclosporine A and intravenous cyclophosphamide was used by Peng et al[22] in relapsing or refractory LGLL-associated PRCA with an ORR of 60%, but half of the responders continued cyclosporine A treatment and the definition of the response differed from standardized criteria. No other studies reported a dual immunosuppressive therapy (apart from the association of corticosteroids and immunosuppressive drug) to manage aPRCA.

Scarce data were available concerning adverse effects occurring during follow-up; the assessment of side effects including iron overload was rarely reported in the studies, which could be explained by their retrospective design. In the most recent cohorts,[4,9,19] 28% to 75% of patients experienced infectious events. The main limitation of cyclosporine A is acute and long-term nephrotoxicity.[38] Thus, alterations of renal function or severe hypertension might be a reason to promptly switch from cyclosporine A to sirolimus or other second-line immunosuppressive agents.

Other reported side effects included cytopenia (neutropenia, anemia, and thrombocytopenia) with cyclosporine A, methotrexate,

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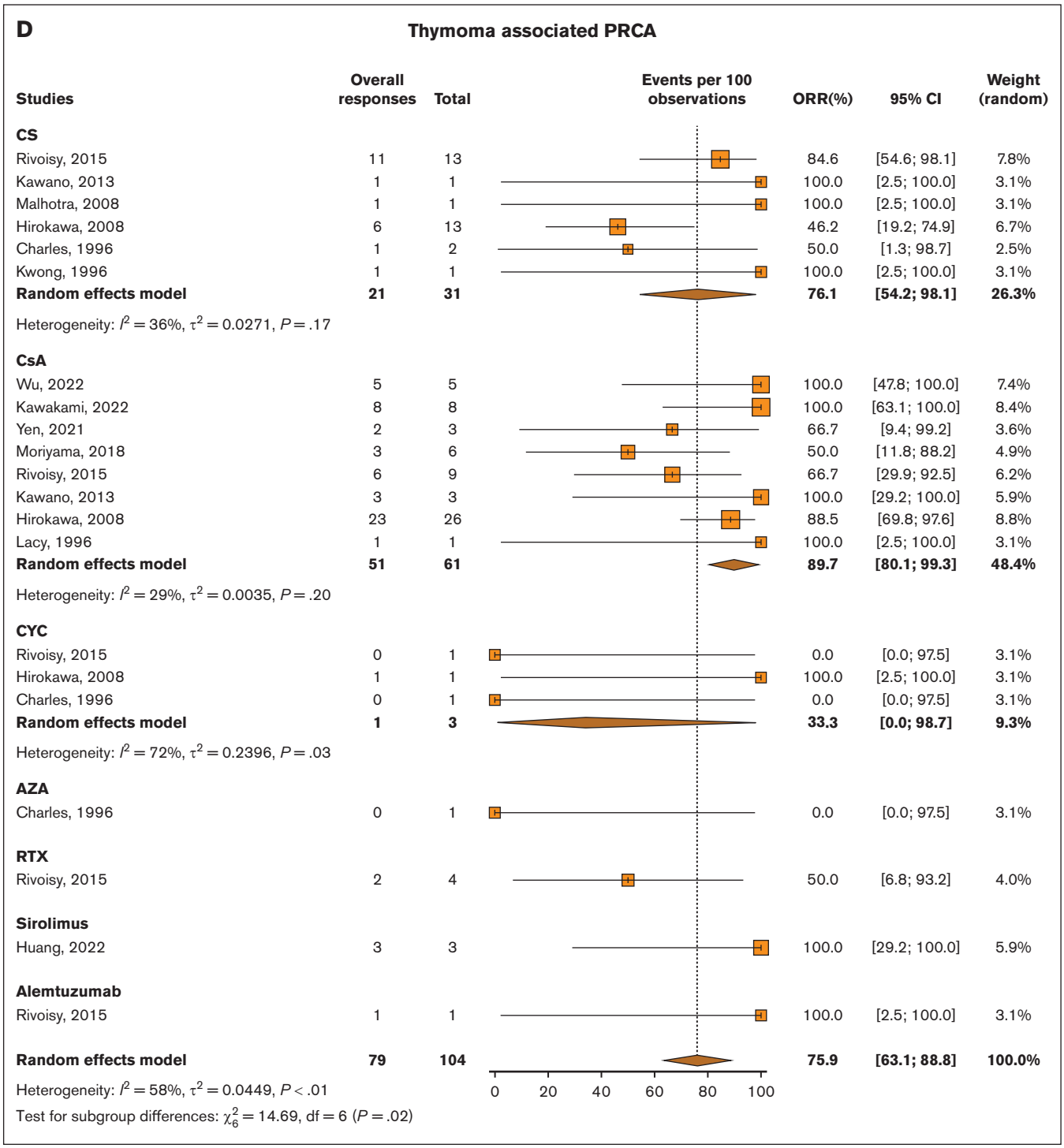

Figure 4 (continued)

alemtuzumab, and cyclophosphamide. The safety data of mTOR inhibitors have mainly been derived from its use in tuberous sclerosis complex or solid organ transplantation: side effects mainly included stomatitis, recurrent infections, and alterations of lipid metabolism,[39,40] which is also a common side effect of cyclosporine. In a recent report with a median follow-up of 36 months, the use of mTOR inhibitors in autoimmune cytopenia was associated with a high frequency of side effects (46%), mainly diarrhea and aphthous-like lesions.[41] However, long-term follow-up safety data are still required to consolidate the positioning of this drug in the therapeutic strategy of autoimmune cytopenia, but high uncertainty remains because of the lack of controlled studies.

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Time to therapeutic response as well as the length of response are of considerable interest to guide the choice of treatment. However, as individual data relating to each immunosuppressive drug were not available, it was not possible to assess the effect of the follow-up duration on the efficacy of individual drugs. The follow-up duration was not described in 5 of 28 studies, and in 26% (6/23) of studies the median follow-up was <24 months. Most studies reported a median delay of 2 to 4 months, which is in line with the standardized definition of treatment response, but conflicting data were found with some authors reporting shorter time-to-response (4 weeks) and others reporting delayed responses for up to 1 year. Another key criterion for the choice of treatment is the goal to achieve free immunosuppressive status without relapse. The course of PRCA after immunosuppressant discontinuation was rarely described: in the most recent reports a high relapse rate was described whereas in older studies freedom from immunosuppressant appeared to be associated with marked prolonged response.[33,34] However, the lack of individual data limited the identification of the population susceptible to obtain this type of response. The lack of standardization in data collection maintains a high degree of uncertainty regarding the generalizability of these results.

In summary, our meta-analysis provided precise estimates of immunosuppressive drug efficacy in aPRCA. Cyclosporine A, cyclophosphamide, and sirolimus were the most frequently reported agents, with response rates ranging from 60% to 90%, but high heterogeneity in treatment schemes and follow-up duration could have led to overestimating treatment efficacy in certain cases and do not allow the drawing of firm conclusions on the differential efficacy of these specific therapies. Apart from these limitations, This study provided useful estimates for designing prospective controlled studies, which are needed to precisely determine the efficacy of these drugs in the management of this severe condition. A rigorous assessment of treatment safety and the management of transfusion-related iron overload is required in prospective studies to improve the management of this rare condition.

Authorship

Contribution: H.L. proposed the work; H.L., J.-C.L., and S.M. were responsible for the conception and design of the study; H.L. and S.M. acquired the data; S.M. performed the statistical analyses; H.L. drafted the original manuscript; and all authors interpreted the data, made critical revisions to the manuscript for important intellectual content, and provided final approval of the manuscript.

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