



Meta-Analysis of Interleukin-2 Receptor Antagonists as the Treatment for Steroid-Refractory Acute Graft-*Versus*-Host Disease

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Shen M-Z, Li J-X, Zhang X-H, Xu L-P, Wang Y, Liu K-Y, Huang X-J, Hong S-D and Mo X-D (2021) Meta-Analysis of Interleukin-2 Receptor Antagonists as the Treatment for Steroid-Refractory Acute Graft-Versus-Host Disease. Front. Immunol. 12:749266. doi: 10.3389/fimmu.2021.749266 Acute graft-versus-host disease (aGVHD) is a major complication after allogeneic hematopoietic stem cell transplantation (HSCT). Corticosteroid is the first-line treatment for aGVHD, but its response rate is only approximately 50%. At present, no uniformly accepted treatment for steroid-refractory aGVHD (SR-aGVHD) is available. Blocking interleukin-2 receptors (IL-2Rs) on donor T cells using pharmaceutical antagonists alleviates SR-aGVHD. This meta-analysis aimed to compare the efficacy and safety of four commercially available IL-2R antagonists (IL-2RAs) in SR-aGVHD treatment. A total of 31 studies met the following inclusion criteria (1): patients of any race, any sex, and all ages (2); those diagnosed with SR-aGVHD after HSCT; and (3) those using IL-2RA-based therapy as the treatment for SR-aGVHD. The overall response rate (ORR) at any time after treatment with basiliximab and daclizumab was 0.81 [95% confidence interval (CI): 0.74-0.87)] and 0.71 (95% CI: 0.56-0.82), respectively, which was better than that of inolimomab 0.54 (95% CI: 0.39-0.68) and denileukin diffitox 0.56 (95% CI: 0.35-0.76). The complete response rate (CRR) at any time after treatment with basiliximab and daclizumab was 0.55 (95% CI: 0.42-0.68) and 0.42 (95% CI: 0.29-0.56), respectively, which was better than that of inolimomab 0.30 (95% CI: 0.16–0.51) and denileukin diffitox 0.37 (95% CI: 0.24–0.52). The ORR and CRR were better after 1-month treatment with basiliximab and daclizumab than after treatment with inolimomab and denileukin diffitox. The incidence of the infection was higher after inolimomab treatment than after treatment with the other IL-2RAs. In conclusion, the efficacy and safety of different IL-2RAs varied. The response rate of basiliximab was the highest, followed by that of daclizumab. Prospective, randomized controlled trials are needed to compare the efficacy and safety of different IL-2RAs.

Keywords: acute graft-versus-host disease, interleukin-2 receptor antagonist, second-line treatment, steroid-refractory, meta-analysis

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INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is a curative measure for hematopoietic malignancies (1). However, its outcome has been compromised by acute graft-versus-host disease (aGVHD), which is a major complication that occurs early post-HSCT. Although many efforts have been made to prevent aGVHD, it is still responsible for early mortality post-transplantation (2). Corticosteroid is the first-line treatment of aGVHD. However, its response rate is only approximately 50% (3). Thus far, no universally accepted treatment for steroid-refractory aGVHD (SR-aGVHD) is available, and survival is poor (4).

One of the critical pathophysiological mechanisms of aGVHD is mediated by T-lymphocyte activation, which exclusively expresses the interleukin-2 receptor (IL-2R) alpha chain (5). Blocking IL-2R on donor T cells using pharmaceutical antagonists alleviates aGVHD, especially SR-aGVHD (6). Some commercially available IL-2R antagonists (IL-2RAs) are basiliximab, daclizumab, inolimomab, and denileukin diftitox. The first three are monoclonal antibodies, which can directly interrupt subsequent T-cell activation by binding to CD25 with high affinity. Inolimomab is a murine anti-human monoclonal antibody with a half-life of 44.5 h (7). Basiliximab is a murine chimeric monoclonal antibody with a half-life of 7 days (8). Daclizumab is a humanized monoclonal antibody with a half-life of 21-25 days (9). In addition, denileukin difititox is a recombinant fusion protein made of diphtheria toxin and human IL-2 sequence, which binds to IL-2R and poisons activated T lymphocytes afterward (10). The half-life of denileukin difititox is 70-80 min (11). Since the 1990s, emerging studies have identified the efficacy and safety of these IL-2RAs in SR-aGVHD treatment (8, 10, 12-41); however, the results varied dramatically because of the great heterogeneity in the study design. So far, no study has been designed to compare the efficacy of different IL-2RAs. Thus, this meta-analysis was conducted to compare the efficacy and safety of these four IL-2RAs in SR-aGVHD treatment.

METHODS

Inclusion Criteria

The inclusion criteria were as follows (1): patients of any race, any sex, and all ages (2); those diagnosed with SR-aGVHD after HSCT; and (3) those using IL-2RA-based therapy as the treatment for SR-aGVHD. Reviews, case reports, duplicates, and conference abstracts were excluded. Multiple studies reporting the same data were considered as one.

Search Strategy

A literature search was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement (42). The PubMed and Embase databases were searched, published from January 2000 through December 2020, with the search strategy following the Population (patients with steroid refractory acute graft versus host disease), Intervention (interleukin-2 receptor antagonists), Comparison(between four different interleukin-2 receptor antagonists), Outcomes (overall response rate [ORR], complete response rate [CRR], chronic GVHD [cGVHD], overall survival [OS] rate, and infectious complications), and Study framework (retrospective, prospective non-randomized and randomized trials) (43): (interleukin-2 OR IL-2 OR CD25 OR Daclizumab OR Basiliximab OR Inolimomab OR Denileukin) AND (steroid refractory OR steroid-refractory OR steroid resistant OR steroidresistant OR corticosteroid refractory OR corticosteroidrefractory) AND (acute graft versus host disease OR aGVHD) AND 2000/01/01[dp]:2020/12/31[dp].

Data Extraction and Outcomes

The ORR, CRR, cGVHD, overall survival rate, and infectious complications at any time after treatment with IL-2RAs were chosen as the primary end points. In addition, the response rate at 1 month after IL-2RA treatment was assessed. As different studies had different time points, the time frame for the evaluation of response rate at 1 month after IL-2RA treatment was prolonged. That is, the earliest studies evaluating at 3 weeks while the latest studies evaluating at 6 weeks after treatment with IL-2RAs were enrolled in this analysis. Missing data were documented as "not available (NA)".

Statistical Analysis

The "meta" package version 4.18-0 (44) (R Project for Statistical Computing, version 4.0.5) was used to perform the metaanalysis. Statistical heterogeneity among studies was assessed using the I^2 statistics and Cochran Q-test. The random-effects model was adopted, with the heterogeneity test showing $I^2 > 50\%$ and P < 0.10. Also, the "stats" package version 4.0.5 (45) was used to perform the *t* test for comparison between the means of two subgroups, including the organ response rates, infection rates, cGVHD rates and OS rates. The null hypothesis was set to no difference. A *P* value <0.05 was considered statistically significant to reject the null hypothesis.

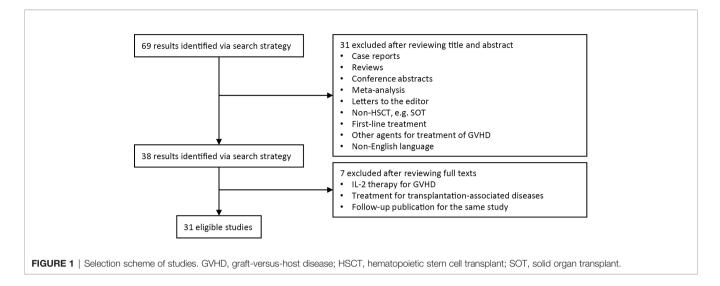
RESULTS

Included Studies

A total of 31 studies reporting on basiliximab (8, 13–20), daclizumab [(22–32); one study using the domestic generic drug (21)], inolimomab (33–40), and denileukin diftitox (10, 41) were included in this meta-analysis (**Figure 1**). A total of 1360 patients were enrolled, including 533, 337, 438, and 52 patients treated with basiliximab, daclizumab, inolimomab, and denileukin diftitox, respectively (**Tables 1**, **2**, and **Supplementary Table 1**). Three (15–17), four (22, 23, 29, 30), and two (34, 36) studies used combined therapies of basiliximab, daclizumab, and inolimomab, respectively.

ORR After Treatment With IL-2RAs

The results showed that ORR of basiliximab and daclizumab was 0.81 [95% confidence interval (CI): 0.74–0.87] and 0.71 (95% CI:



0.56–0.82), respectively, which seemed to be better than that of inolimomab 0.54 (95% CI: 0.39–0.68) and denileukin diffutox 0.56 (95% CI: 0.35-0.76) (**Figure 2A**).

In retrospective studies, ORR of basiliximab, daclizumab and inolimomab was 0.78 (95% CI: 0.68–0.85), 0.70 (95% CI: 0.48–0.85) and 0.55 (95% CI: 0.37–0.71), respectively. In prospective unrandomized studies, ORR of basiliximab, daclizumab, inolimomab, and denileukin diftitox was 0.87 (95% CI: 0.80–0.92), 0.73 (95% CI: 0.53–0.86), 0.48 (95% CI: 0.28–0.68), and 0.56 (95% CI: 0.35–0.76), respectively (**Supplementary Figure S1**). Only 1 randomized controlled trial (RCT) identifying the efficacy of inolimomab about SR-aGVHD did not provide the data about ORR (33).

In the analysis of ORR at 1 month after treatment, 4 (8, 18–20), 5 (22, 23, 27, 29, 30), and 2 (38, 40) studies on basiliximab, daclizumab, and inolimomab were excluded due to insufficient data. The ORR at 1 month after treatment with IL-2RA of basiliximab and daclizumab was 0.80 (95% CI: 0.68–0.88) and 0.69 (95% CI: 0.47–0.85), respectively, which seemed to be better than that of inolimomab 0.55 (95% CI: 0.35–0.73) and denileukin diftitox 0.56 (95% CI: 0.35–0.76) (**Figure 2B**).

In retrospective studies, the ORR at 1 month after treatment with IL-2RA of basiliximab, daclizumab, and inolimomab was 0.76 (95% CI: 0.63–0.85), 0.66 (95% CI: 0.31–0.89), and 0.57 (95% CI: 0.33–0.79), respectively. In prospective unrandomized studies, the ORR at 1 month after treatment with IL-2RA of basiliximab, daclizumab, inolimomab, and denileukin diftitox was 0.88(95% CI: 0.79-0.94), 0.73 (95% CI: 0.47–0.89), 0.48 (95% CI: 0.28–0.68), and 0.56 (95% CI: 0.35–0.76), respectively (**Supplementary Figure S2**). The RCT about inolimomab did not provide the data about ORR at 1 month after treatment (33).

CRR After Treatment With IL-2RAs

The CRR at any time after treatment with basiliximab and daclizumab was found to be 0.55 (95% CI: 0.42–0.68) and 0.42 (95%CI: 0.29–0.56), respectively, which was better than that of inolimomab 0.30 (95% CI: 0.16–0.51) and denileukin diffutox 0.37 (95% CI: 0.24–0.52) (**Figure 3A**).

In retrospective studies, the CRR of basiliximab, daclizumab and inolimomab was 0.64 (95% CI: 0.55–0.72), 0.44 (95% CI: 0.29–0.60), 0.31 (95% CI: 0.14–0.56), respectively. In prospective unrandomized studies, CRR of basiliximab, daclizumab, inolimomab and denileukin diftitox was 0.44 (95% CI: 0.21–0.70), 0.39 (95% CI: 0.19–0.64), 0.29 (95% CI: 0.13–0.51), and 0.37 (95% CI: 0.24–0.52), respectively (**Supplementary Figure S3**). The RCT about inolimomab did not provide the data about CRR (33).

In the analysis of CRR at 1 month after treatment, 4 (8, 18–20), 5 (22, 23, 27, 29, 30), and 1 (40) studies on basiliximab, daclizumab, and inolimomab, respectively, were excluded due to insufficient data. The CRR at 1 month after treatment with IL-2RAs of basiliximab and daclizumab was found to be 0.62 (95% CI: 0.47–0.74) and 0.37 (95% CI: 0.19–0.60), respectively, which was better than that of inolimomab 0.31 (95% CI: 0.13–0.57) and denileukin diffitox 0.37 (95% CI: 0.24–0.52) (**Figure 3B**).

In retrospective studies, the CRR at 1 month after treatment with IL-2RAs of basiliximab, daclizumab and inolimomab was 0.63 (95% CI: 0.50–0.74), 0.37 (95% CI: 0.15–0.67) and 0.32 (95% CI: 0.10–0.66), respectively. In prospective unrandomized studies, the CRR at 1 month after treatment with IL-2RAs of basiliximab, daclizumab, inolimomab and denileukin diftitox was 0.58 (95% CI: 0.25–0.85), 0.38 (95% CI: 0.13–0.71), 0.29 (95% CI: 0.13–0.51) and 0.37 (95% CI: 0.24–0.52), respectively (**Supplementary Figure S4**). The RCT about inolimomab did not provide the data about CRR at 1 month after treatment (33).

Response According to the Involved Organs After Treatment With IL-2RAs

The ORRs and CRRs of different organs involved for these four drugs were compared. Five (13–15, 19, 20), five (21, 24–26, 31), two (38, 40), and one (41) studies on basiliximab, daclizumab, inolimomab, and denileukin diftitox, respectively, were included in the analysis of the ORRs. The ORRs of skin, gut, and liver at any time after treatment were all comparable among these four IL-2RAs (**Supplementary Figure S5A**).

Two (15, 20), five (21, 24, 25, 31, 32), and two (10, 41) studies on basiliximab, daclizumab, and denileukin diffitox, respectively,

TABLE 1 | Main characteristics of 31 included studies.

Studies	Study design	Ν	Response/event (n)				cGVHD	Overall	median
			ORR	ORR at 1 month	CR	CR at 1 month	incidence (%)	survival rate	follow-up (months)
Basiliximab-based tre	atment								
Liu, (13)	retrospective	230	151	151	140	140	44.80	0.617	41.8
Tang, (14)	retrospective	100	85	85	74	74	43.75	0.762	25.3
Tan, (15)	prospective, unrandomized	65	59	59	49	49	50.00	0.547	18.5
Chakupurakal, (8)	prospective, unrandomized	14	13	NA	7	NA	NA	NA	NA
Nadeau, (16)	retrospective	21	16	16	9	9	71.43	0.24	34.5
Jaiswal, (17)	prospective, unrandomized	10	7	7	3	3	16.67	NA	4.2
Wang, (18)	retrospective	53	46	NA	37	NA	69.39	0.514	0.2
Schmidt-Hieber, (19)	prospective, unrandomized	23	19	NA	4	NA	62.50	NA	6.1
Massenkeil, (20)	retrospective	17	12	NA	9	NA	61.54	NA	4.1
Daclizumab-based tre	1				0		0.10.		
Tao, (21)	retrospective	64	53	53	37	37	34.38	0.729	0.1
Rager, (22)	retrospective	17	8	NA	4	NA	NA	NA	1.5
Rao, (23)	retrospective	22	19	NA	12	NA	50.00	NA	16.2
Miano, (24)	retrospective	13	12	12	6	6	66.67	NA	14.0
Hui, (25)	retrospective	12	2	2	1	1	NA	NA	4.0
Perales, (26)	retrospective	57	31	31	NA	NA	NA	NA	98.0
eachey, (27)	retrospective	11	7	NA	5	NA	NA	NA	NA
Bordigoni, (28)	prospective, unrandomized	62	56	56	43	43	67.80	NA	1.5
Nolff, (29)	prospective, unrandomized	21*	14	NA	8	NA	66.67	NA	19.5
Srinivansan, (30)	retrospective	3	3	NA	3	NA	100.00	NA	4.0
Villenbacher, (31)	prospective, unrandomized	12	8	8	1	1	NA	NA	15.3
Preziprka, (32)	prospective, unrandomized	43	22	22	16	16	NA	0.4	2.6
nolimomab-based tre	atment								
Girerd, (34)	prospective, randomized	49	NA	NA	NA	NA	NA	0.469	58.4
Garcia-Cadenas, (35)	retrospective	98	38	38	NA	NA	NA	0.454	19.4
van Groningen, (36)	prospective, unrandomized	21	10	10	6	6	NA	0.1	1.8
Girerd, (37)	retrospective	33	30	30	24	24	63.33	0.79	NA
Garcia-Cadenas, (35)	retrospective	92	39	39	13	13	NA	0.22	60.0
(haard, (38)	retrospective	20	7	NA	NA	NA	NA	0.3	74.0
Pinana, (39)	retrospective	40	20	20	8	8	78.26	0.3	1.9
Bay, (40)	retrospective	85	54	NA	25	NA	NA	0.26	20.0
Denileukin diftitox trea									
Shaughnessy, (10)	prospective, unrandomized	22	9	9	9	9	60.00	NA	4.0
Ho, (41)	prospective, unrandomized	30	17	17	8	8	NA	NA	7.2

NA, not available; ORR, overall response rate; CR, complete response rate; cGVHD, chronic graft-versus-host disease.

*Only 20 patients were eligible for evaluation because 1 patient died 5 days after treatment due to rapid progression of pre-existing invasive aspergillosis.

were included in the analysis of CRRs. In the gut and liver aGVHD, basiliximab showed a higher CRR at any time compared with daclizumab [gut: 0.76 (95% CI: 0.34–1.19) *vs* 0.34 (95% CI: 0.05–0.62), P = 0.012; liver: 0.74 (95% CI: 0.67–0.82) *vs* 0.14 (95% CI: 0.08–0.20), P < 0.001; **Supplementary Figure S5B**].

Infections After Treatment With IL-2RAs

Seven (13–15, 17–20), nine (21–26, 28, 29, 31), five (33–35, 37, 39), and two (10, 41) studies on basiliximab, daclizumab, inolimomab,

and denileukin diftitox, respectively, were enrolled to analyze the incidence of infection after IL-2RA treatment. Two of them did not have information on viral infection and were excluded from the analysis of viral infections [daclizumab (25) and denileukin diftitox (41)]. The incidence of infection after inolimomab treatment [1.65 cases per person (95% CI: 0.78–2.53 cases per person)] was the highest compared with other IL-2RAs. The infection rates were comparable between the basiliximab group [1.19 cases per person (95% CI: 0.51–1.86 cases per person)] and

TABLE 2 | Other characteristics of 31 included studies.

Studies	Median age/year (range)	HLA matching (n)				aGVHD grade (n)			Median time from	
		MRD	mMRD	MUD	mMUD	I	II	ш	IV	SR-aGVHD diagnosis to the application of IL-2RAs/day (range)
Basiliximab-based tre	eatment									
Liu, (13)	NA	17	208		5	0	191	25	14	5 (3–20)
Tang, (14)	10 (1–17)	NA	NA	NA	NA	0	57	27	16	NA
Tan, (15)	13 (9–55)	13	40	12	0	0	0	21	44	8 (3–49)
Chakupurakal, (8)	41 (20–69)	0	1	6	7	1	1	5	7	NA
Nadeau, (16)	57 (20–71)	7	1	10	3	0	0	13	8	5(NA)
Jaiswal, (17)	7 (2–20)	0	10	0	0	0	0	1(С	NA
Wang, (18)	25 (8–52)	NA	NA	NA	NA	0	10	27	16	NA
Schmidt-Hieber, (19)	51 (31–63)	7	1	12	3	0	11	12	0	NA
Massenkeil, (20)	39 (23–50)	6	0	11	0	0	3	12	2	7 (3–25)
Daclizumab-based tro	eatment									
Tao, (21)	35 (13–57)		45		19	0	3	28	33	NA
Rager, (22)	47 (35–63)	5	0	9	2	0	3	10	4	7 (2–26)
Rao, (23)	NA	4	0	12	6	0	0	7	15	NA
Miano, (24)	NA		3		10	0	4	4	5	48 (12–201)
Hui, (25)	38.5 (25–55)	9	0	2	1	0	0	12	0	8.5 (3–28)
Perales, (26)	28.9 (0.7–57.7)	21	12	13	11	5	23	14	15	ŇA
Teachey, (27)	NA	NA	NA	NA	NA	0	6	3	2	NA
Bordigoni, (28)	25.4 (1.5–53)	32	1	11	18	0	41	2		NA
Wolff, (29)	44 (15–61)	6	0	14	1	0	1	17	3	17 (3–66)
Srinivansan, (30)	33 (33–46)	NA	NA	NA	NA	0	0	1	2	NA
Willenbacher, (31)	46 (28–56)	3	1	5	3	0	0	1	11	5 (3–13)
Preziprka, (32)	31 (1–53)	14	15	14	0	1	22	12	8	NA
Inolimomab-based tr	· · · · · · · · · · · · · · · · · · ·				0				0	
Girerd, (34)	NA	15	0	31	3	0	0	100	0	6 (3–9)
Garcia-Cadenas, (36)	50 (17–70)	54	-	44	-	0	6	51	41	15 (4–91)
van Groningen, (36)	54 (24–66)	11	0	7	3	0	0	17	4	NA
Girerd, (34)	44 (17–65)	6	9	11	7	0	7	19	7	15 (3–36)
Garcia-Cadenas, (35)	50 (17–68)	52	-	40	-	0	66	48	38	17 (2–204)
Xhaard, (38)	42 (5–64)	4	0	11	5	0	13	7	0	12 (NA)
Pinana, (39)	47 (17–63)	27	1	5	7	0	2	22	16	21 (4–91)
Bay, (40)	29.5 (0.2–61)	41	8	27	9	0	26	26	33	13 (8–23)
Denileukin diftitox tre			0	<i>L</i> 1	0	0	20	20	00	10 (0 20)
Shaughnessy, (10)	44 (9–59)	12	0	8	2	0	7	7	8	NA
Ho, (41)	43 (20–63)	2	26	1	1	0	, 11	13	6	NA

NA, not available; HLA, human leukocyte antigen; MRD, matched related donor; MUD, matched unrelated donor; mMRD, mismatched related donor; mMUD, mismatched unrelated donor; aGVHD, acute graft-versus-host disease; IL-2RAs, interleukin-2 receptor antagonists.

the daclizumab group [0.95 cases per person (95% CI: 0.58–1.32 cases per person)], which both seemed to be higher than those in the denileukin diftitox group [0.24 cases per person (95% CI: 0–1.76 cases per person)]. The frequencies of viral infection were comparable among the four IL-2RAs (**Supplementary Figure S6**).

cGVHD

Eight (13–20), six (21, 23, 24, 28–30), two (34, 39) and one (10) studies on basiliximab, daclizumab, inolimomab and denileukin diftitox, respectively, could be enrolled in the analysis of cGVHD. The incidence of cGVHD after basiliximab, daclizumab, inolimomab and denileukin diftitox treatment was 52.5% (95% CI: 37.5%–67.5%), 64.3% (95% CI: 41.3%–87.2%), 70.8% (95% CI: 24.0%–100.0%) and 60.0%, respectively. In retrospective studies, the incidence of basiliximab, daclizumab and inolimomab was 58.2% (95% CI: 41.8%–74.6%), 62.8% (95% CI: 18.0%–100.0%) and 70.8% (95% CI: 24.0%–100.0%), respectively. In prospective unrandomized studies, the incidence of basiliximab, daclizumab and denileukin diftitox.

was 43.1% (95% CI: 15.8%–100.0%), 67.2% (95% CI: 60.1%–74.4%) and 60.0%, respectively. The RCT about inolimomab did not provide the data about cGVHD (33).

OS

Five (13–16, 18), two (21, 32), and eight (33–40) studies on basiliximab, daclizumab, and inolimomab, respectively, were included in the survival analysis. Two studies on denileukin diftitox were excluded because they did not provide the information on OS. The OS rate for basiliximab and daclizumab was 53.6% (95% CI: 29.9%–77.31%) and 56.5% (only two studies were enrolled, ranging from 40% to 72.9%), respectively, which seemed to be higher than that in the inolimomab group [36.2% (95% CI: 18.6%–53.8%)] (Figure 4).

In retrospective studies, only one study for daclizumab could be observed and its OS rate was 72.9%. The OS rate of basiliximab and inolimomab was 53.3% (95% CI: 18.3%– 88.4%) and 38.7% (95% CI: 16.4%–61.0%), respectively. One study each for basiliximab, daclizumab, and inolimomab could

Proportion 95%-Cl

Α					
Study	Events	Total		Proportion	95%-CI
group = Basiliximab-ba					
.iu, 2020 Tang, 2020	151 85	230 100		0.66	[0.59; 0.72] [0.76; 0.91]
Fan, 2017	59	65	-		[0.81; 0.97]
Chakupurakal, 2015	13	14			[0.66; 1.00]
vadeau, 2016	16	21		0.76	[0.53; 0.92]
laiswal, 2016	7	10		0.70	[0.35; 0.93]
Vang, 2011	46	53		0.87	[0.75; 0.95] [0.61; 0.95]
Schmidt-Hieber, 2005	19 12	23 17		0.83	[0.61; 0.95] [0.44; 0.90]
Massenkeil, 2002 Fixed effect model	12	533		0.71	[0.44; 0.90]
Random effects model		000	\$		[0.74; 0.87]
Heterogeneity: $I^2 = 73\%$, τ^2	² = 0.2375	, p < 0.01			
group = Daclizumab-ba	ased				
Tao, 2015	53	64		0.83	[0.71; 0.91]
Rager, 2011	8	17		0.47	[0.23; 0.72]
Rao, 2009	19	22			[0.65; 0.97]
Viano, 2009	12	13			[0.64; 1.00]
Hui, 2008 Perales, 2007	2 31	12 — 57			[0.02; 0.48]
eachey, 2006	7	11			[0.31; 0.89]
ordigoni, 2006	56	62			[0.80; 0.96]
Volff, 2005	14	20		0.70	[0.46; 0.88]
Srinivansan, 2004	3	3		 1.00 	[0.29: 1.00]
Villenbacher, 2001	8	12		0.67	[0.35; 0.90
Preziprka, 2000 Tixed effect model	22	43 336			[0.35; 0.67 [0.65; 0.75]
Random effects model		550			[0.65; 0.75]
leterogeneity: $I^2 = 76\%$, τ^2	² = 0.9212	, p < 0.01		9.71	F21661 0107
roup = Inolimomab-b	ased				
Garcia-Cadenas, 2017	38	98		0.39	[0.29; 0.49]
Groningen, 2016	10	21		0.48	[0.26; 0.70]
Girerd, 2013	30	33		0.91	[0.76; 0.98]
Barcia-Cadenas, 2013	39	92			[0.32; 0.53]
Khaard, 2011 Pinana, 2006	7 20	20 40			[0.15; 0.59] [0.34; 0.66]
Bay, 2005	20 54	40 85	-	0.64	[0.52; 0.74]
ixed effect model		389		0.51	[0.46; 0.56]
andom effects model	2			0.54	[0.39; 0.68]
eterogeneity: $I^2 = 79\%$, τ^2	^c = 0.5502	, p < 0.01			
roup = Denileukin dift					
haughnessy, 2005	9	22		0.41	[0.21; 0.64
lo, 2004	17	24		0.71	[0.49; 0.87]
ixed effect model		46			[0.42; 0.70]
tandom effects model leterogeneity: $I^2 = 75\%$, τ^2	² = 0.2151	. p = 0.04	1	0.56	[0.35; 0.76]
ixed effect model Random effects model		1304			[0.64; 0.69] [0.61; 0.77]
eterogeneity: / ² = 83%, τ	² = 0.8473	, p < 0.01	0.2 0.4 0.6 0.8	ן 1	
5					
	Events	Total		Proportion	95%-C
roup = Basiliximab-ba	ased	230		0.66	[0,59: 0.72
Study group = Basiliximab-ba .iu, 2020 īang, 2020	ased 151 85	230 100		0.85	[0.76; 0.91]
roup = Basiliximab-ba iu, 2020 īang, 2020 īan, 2017	ased 151 85 59	100 65	-	0.85 0.91	[0.76; 0.91] [0.81; 0.97]
roup = Basiliximab-ba iu, 2020 īang, 2020 īan, 2017 Jadeau, 2016	ased 151 85 59 16	100 65 21		0.85 0.91 0.76	[0.76; 0.91 [0.81; 0.97 [0.53; 0.92]
roup = Basiliximab-ba iu, 2020 ang, 2020 an, 2017 iadeau, 2016 aiswal, 2016	ased 151 85 59	100 65 21 10	*** 	0.85 0.91 0.76 0.70	[0.76; 0.91 [0.81; 0.97 [0.53; 0.92 [0.35; 0.93
roup = Basiliximab-ba u, 2020 ing, 2020 in, 2017 adeau, 2016 iswal, 2016 xed effect model andom effects model	ased 151 85 59 16 7	100 65 21 10 426	**	0.85 0.91 0.76 0.70 0.75	[0.76; 0.91 [0.81; 0.97 [0.53; 0.92 [0.35; 0.93 [0.70; 0.79]
roup = Basiliximab-ba u, 2020 ang, 2020 an, 2017 adeau, 2016 aiswal, 2016 ixed effect model andom effects model	ased 151 85 59 16 7	100 65 21 10 426	**	0.85 0.91 0.76 0.70 0.75	[0.76; 0.91 [0.81; 0.97 [0.53; 0.92 [0.35; 0.93 [0.70; 0.79]
roup = Basiliximab-ba iu, 2020 ang, 2020 an, 2017 addau, 2016 aiswal, 2016 ixed effect model andom effects model eterogeneity: /² = 82%, t² roup = Daclizumab-ba	ased 151 85 59 16 7 ² = 0.2972 ased	100 65 21 10 426 , <i>p</i> < 0.01		0.85 0.91 0.76 0.70 0.75 0.80	[0.76; 0.91] [0.81; 0.97] [0.53; 0.92] [0.35; 0.93] [0.70; 0.79] [0.68; 0.88]
roup = Basiliximab-bu lu, 2020 ang, 2020 an, 2017 adeau, 2016 aiswal, 2016 ixed effect model andom effects model eterogeneity: l ² = 82%, t ² roup = Daclizumab-bi ao, 2015	ased 151 85 59 16 7 ² = 0.2972 ased 53	100 65 21 10 426 , p < 0.01 64	***	0.85 0.91 0.76 0.70 0.75 0.80	[0.76; 0.91] [0.81; 0.97] [0.53; 0.92] [0.35; 0.93] [0.70; 0.79] [0.68; 0.88]
roup = Basiliximab-bi iu, 2020 ang, 2020 ang, 2010 aiswal, 2016 aiswal, 2016 ixed effect model andom effects model eterogeneity: I ² = 82%, τ ² roup = Daclizumab-bi ao, 2015 liano, 2009	ased 151 85 59 16 7 ² = 0.2972 ased 53 12	100 65 21 10 426 , p < 0.01 64 13	**	0.85 0.91 0.76 0.70 0.75 0.80 - 0.83	[0.76; 0.91] [0.81; 0.97] [0.53; 0.92] [0.35; 0.93] [0.70; 0.79] [0.68; 0.88]
roup = Basiliximab-bi iu, 2020 an, 2017 adeau, 2016 alswal, 2016 alswal, 2016 alswal, 2016 alswal, 2016 alswal, 2016 alswal, 2016 alswal, 2016 alswal, 2016 alswal, 2015 liano, 2009 ui, 2008	ased 151 85 59 16 7 ² = 0.2972 ased 53 12 2	100 65 21 10 426 , p < 0.01 64 13 12 —	*	0.85 0.91 0.76 0.70 0.75 0.80 - 0.83 - 0.92 0.17	[0.76; 0.91] [0.81; 0.97] [0.53; 0.92] [0.35; 0.93] [0.70; 0.79] [0.68; 0.88] [0.71; 0.91] [0.64; 1.00] [0.02; 0.48]
vu 2020 u, 2020 ang, 2020 ang, 2020 ang, 2016 aiswal, 2016 aiswal, 2016 aiswal, 2016 andom effects model andom effects model andom effects model eterogeneity: I ² = 82%, c ² roup = Daclizumab-ba ao, 2015 liano, 2009 ui, 2008 erales, 2007	ased 151 85 59 16 7 ² = 0.2972 ased 53 12 2 31	100 65 21 10 426 , p < 0.01 64 13 12		0.85 0.91 0.76 0.75 0.80 - 0.92 0.17 0.54	[0.76; 0.91] [0.81; 0.97] [0.53; 0.92] [0.35; 0.93] [0.70; 0.79] [0.68; 0.88] [0.71; 0.91] [0.64; 1.00] [0.22; 0.48] [0.41; 0.68]
oup = Basiliximab-bi u, 2020 ang, 2010 ang, 2017 adeau, 2016 aiswal, 2016 aiswal	ased 151 85 59 16 7 ² = 0.2972 ased 53 12 2 31 56 8	100 65 21 10 426 , p < 0.01 64 13 12 — 57 62 12		0.85 0.91 0.76 0.70 0.75 0.80 - 0.83 - 0.92 0.17 0.54 0.90 0.67	[0.76; 0.91] [0.81; 0.97] [0.53; 0.93] [0.35; 0.93] [0.70; 0.79] [0.68; 0.88] [0.64; 1.00] [0.64; 1.00] [0.41; 0.68] [0.41; 0.68] [0.80; 0.96] [0.35; 0.90]
oup = Basiliximab-bi , 2020 m, 2017 adeau, 2016 adeau, 2016 adeau	ased 151 85 59 16 7 ² = 0.2972 ased 53 12 2 31 56	100 65 21 10 426 , p < 0.01 64 13 12 57 62 12 43		0.85 0.91 0.76 0.70 0.75 0.80 0.83 0.92 0.17 0.54 0.90 0.67 0.51	[0.76; 0.91] [0.81; 0.97] [0.53; 0.92] [0.35; 0.93] [0.70; 0.79] [0.68; 0.88] [0.64; 1.00] [0.64; 1.00] [0.64; 1.00] [0.64; 1.00] [0.41; 0.68] [0.41; 0.68] [0.35; 0.90] [0.35; 0.67]
yup = Basiliximab-bi , 2020 ig, 2020 , 2017 , 2017 , 2017 deau, 2016 swal, 2016 deat field model andom effects model terogeneity: / ² = 82%, c ² swal, 2016 ano, 2009 i, 2006 rales, 2007 rales, 2007 rales, 2007 digoni, 2006 lienbacher, 2001 sziprka, 2000 de offect model	ased 151 85 59 16 7 ² = 0.2972 ased 53 12 2 31 56 8	100 65 21 10 426 , p < 0.01 64 13 12 — 57 62 12		- 0.83 0.81 0.76 0.70 0.75 0.80 - 0.92 0.17 0.54 0.90 0.67 0.51 0.70	[0.76; 0.91] [0.81; 0.97] [0.53; 0.92] [0.35; 0.93] [0.70; 0.79] [0.68; 0.88] [0.71; 0.91] [0.64; 1.00] [0.64; 1.00] [0.64; 1.068] [0.41; 0.68] [0.35; 0.90] [0.35; 0.67] [0.64; 0.75]
oup = Basiliximab-bi J, 2020 m, 2017 debau, 2016 debau, 2016 deba	ased 151 85 59 16 7 ² = 0.2972 ased 53 12 2 31 56 8 22	100 65 21 10 426 , p < 0.01 64 13 12 57 62 12 43 263		- 0.83 0.81 0.76 0.70 0.75 0.80 - 0.92 0.17 0.54 0.90 0.67 0.51 0.70	[0.76; 0.91] [0.81; 0.97] [0.53; 0.92] [0.35; 0.93] [0.70; 0.79] [0.68; 0.88] [0.71; 0.91] [0.64; 1.00] [0.64; 1.00] [0.64; 1.068] [0.41; 0.68] [0.35; 0.90] [0.35; 0.67] [0.64; 0.75]
uup = Basiliximab-bi, 1, 2020 up = Basiliximab-bi, 1, 2017 deau, 2016 deau, 2016 deau, 2016 deau, 2016 deau, 2016 site and the analysis of the analysis ano, 2016 ano, 2009 1, 2008 lienbacker, 2007 railes, 2007 railes, 2007 railes, 2007 calgoni, 2008 lienbacker, 2001 deau, 2009 lienbacker, 2001 deau, 2008 deau, 2007 railes, 20	ased 151 85 59 16 7 2 2 0.2972 ased 53 12 2 31 56 8 22 2 31 2 2 31 2 2 31 2 2 31 56 8 2 2 2 31 56 8 2 2 2 3 12 2 2 3 12 2 2 3 12 2 2 3 12 2 2 3 12 2 2 3 12 2 2 3 12 2 2 3 12 2 2 3 12 2 2 3 12 2 2 3 1 56 8 2 2 2 3 1 56 8 2 2 2 2 3 1 56 8 2 2 2 2 3 1 56 8 2 2 2 2 3 1 56 8 2 2 2 2 3 1 56 8 2 2 2 3 1 56 8 2 2 2 3 1 56 8 2 2 2 3 1 56 8 2 2 2 3 1 56 8 2 2 2 3 1 56 8 2 2 2 3 1 56 8 2 2 2 3 1 56 8 2 2 2 3 1 56 8 2 2 2 2 3 1 56 8 2 2 2 2 3 1 56 8 2 2 2 2 3 1 56 8 2 2 2 2 2 3 1 56 8 2 2 2 2 2 3 1 56 8 2 2 2 2 2 3 1 3 1 5 6 8 2 2 2 1 3 1 3 1 5 6 8 1 3 1 1 1 1 1 1 1 1 1 1 1 1 1	100 65 21 10 426 , p < 0.01 64 13 12 57 62 12 43 263		- 0.83 0.81 0.76 0.70 0.75 0.80 - 0.92 0.17 0.54 0.90 0.67 0.51 0.70	[0.76; 0.91 [0.81; 0.97 [0.53; 0.92 [0.35; 0.93 [0.70; 0.79 [0.68; 0.88] [0.71; 0.91 [0.64; 1.00 [0.02; 0.48 [0.41; 0.68 [0.35; 0.90 [0.35; 0.67 [0.64; 0.75]
oup = Basiliximab-bi , 2020 ng, 2020 ng, 2017 adeau, 2016 iswal, 2016 iswal, 2016 iswal, 2016 iswal, 2016 aterogeneity: /² = 82%, c' oup = Daclizumab-bi o, 2015 ano, 2009 ii, 2008 irales, 2007 vrdigoni, 2006 iilenbacher, 2001 eziprka, 2000 xed effect model andom effects model andom effects andom effect	ased 151 85 59 166 7 ² = 0.2972 ased 53 12 2 31 566 8 22 ² = 1.3150 ased	100 65 21 10 426 , p < 0.01 64 13 12 - 57 62 12 43 263 , p < 0.01		0.85 0.91 0.70 0.75 0.80 - 0.92 0.17 0.54 0.90 0.67 7 0.54 0.90 0.67 0.51 0.70 0.69	[0.76; 0.81 [0.81; 0.97 [0.53; 0.82 [0.35; 0.83 [0.70; 0.79 [0.68; 0.88 [0.71; 0.91 [0.64; 1.00 [0.22; 0.48 [0.41; 0.68 [0.80; 0.96 [0.35; 0.80 [0.35; 0.67 [0.64; 0.75 [0.47; 0.85]
oup = Basiliximab-bi u, 2020 ing, 2017 adeau, 2016 adeau, 2016 adeau, 2016 ateau, 2016 ateau, 2016 ateau, 2016 ateau, 2016 ateau, 2016 ateau, 2016 ateau, 2017 ateau, 2009 i, 2008 illenbacher, 2001 ateapather, 200	ased 151 85 59 16 7 ² = 0.2972 ased 53 12 2 31 56 8 22 ² = 1.3150 ased 38	$\begin{array}{c} 100\\ 65\\ 21\\ 10\\ 426\\ , p < 0.01\\ 64\\ 13\\ 12\\ -\\ 57\\ 62\\ 12\\ 43\\ 263\\ , p < 0.01\\ 98\\ \end{array}$		0.85 0.91 0.76 0.75 0.80 - 0.92 0.17 0.54 0.90 0.54 0.90 0.55 0.51 0.70 0.69 0.69 0.67	[0.76; 0.81 [0.81; 0.97 [0.53; 0.82 [0.70; 0.79 [0.68; 0.88 [0.70; 0.79 [0.68; 0.88 [0.71; 0.91 [0.64; 1.00 [0.22; 0.48 [0.41; 0.68 [0.35; 0.67 [0.54; 0.75 [0.47; 0.85
roup = Basiliximab-bi u, 2020 ing, 2020 an, 2017 adeau, 2016 isiwal, 2016 isiwal, 2016 isiwal, 2016 isiwal, 2016 adom effects model aterogeneity: $l^2 = 82\%$, c^2 roup = Daclizumab-bi ano, 2015 iano, 2009 ui, 2008 arales, 2007 ordigoni, 2006 fillenbacher, 2001 xed effect model andom effects model aterogeneity: $l^2 = 85\%$, c^2 roup = Inolimomab-bi arcia-Cadenas, 2017 oningen, 2016	ased 151 85 59 16 7 ² = 0.2972 ased 53 12 2 31 56 8 22 ² = 1.3150 ased	100 65 21 10 426 , p < 0.01 64 13 12 - 57 62 12 43 263 , p < 0.01		0.85 0.91 0.76 0.75 0.80 - 0.92 0.17 0.51 0.97 0.51 0.70 0.51 0.70 0.51	[0.76; 0.91 [0.81; 0.97; [0.53; 0.92 [0.53; 0.93 [0.70; 0.79] [0.68; 0.88] [0.71; 0.91 [0.68; 0.88] [0.41; 0.68 [0.80; 0.96 [0.41; 0.68 [0.80; 0.96 [0.35; 0.90] [0.35; 0.90] [0.35; 0.90] [0.35; 0.90] [0.47; 0.85
va post va	ased 151 85 59 16 7 ² = 0.2972 ased 53 12 2 31 56 8 22 ² = 1.3150 ased 38 10	100 65 21 10 426 , $p < 0.01$ 64 13 12 		0.85 0.91 0.76 0.75 0.80 - 0.82 0.17 0.54 0.92 0.54 0.54 0.55 0.55 0.55 0.55 0.55 0.55	[0.76; 0.91 [0.81; 0.97 [0.53; 0.92 [0.53; 0.92 [0.70; 0.79] [0.68; 0.88] [0.71; 0.91 [0.64; 1.00 [0.02; 0.48 [0.85; 0.90 [0.35; 0.67 [0.44; 0.75 [0.44; 0.75 [0.44; 0.75] [0.29; 0.49 [0.26; 0.70 [0.26; 0.70] [0.76; 0.98
oup = Basiliximab-bi u, 2020 ang, 2017 adeau, 2016 aiswal, 2016 adeau, 2016 adeau, 2016 adeau, 2016 aswal effect model andom effects model andon effects model andom effect model andom effects model andom ef	ased 151 85 59 16 7 ² = 0.2972 ased 53 12 2 31 56 8 22 31 56 8 22 31 56 8 22 31 56 8 22 31 56 3 3 3 3 3 3 3 3 3 3 3 3 3	$\begin{array}{c} 100\\ 65\\ 21\\ 10\\ 426\\ ,p < 0.01\\ 64\\ 13\\ 12\\ -\\ 57\\ 62\\ 12\\ 43\\ 263\\ ,p < 0.01\\ 98\\ 21\\ 33\\ 92\\ 40\\ \end{array}$		0.85 0.911 0.76 0.70 0.75 0.80 0.80 0.80 0.82 0.92 0.92 0.92 0.92 0.92 0.92 0.92 0.9	$ \begin{bmatrix} 0.76; 0.91\\ (0.81; 0.97\\ (0.53; 0.92\\ (0.35; 0.93\\ (0.76; 0.79\\ (0.68; 0.83\\ (0.71; 0.91\\ (0.64; 1.00\\ (0.22; 0.48\\ (0.41; 0.68\\ (0.41; 0.68\\ (0.35; 0.67\\ (0.64; 0.75\\ (0.47; 0.85\\ (0.35; 0.67\\ (0.64; 0.75\\ (0.47; 0.85\\ (0.22; 0.48\\ (0.22; 0.53\\ (0.22; 0.53\\ (0.34; 0.66\\ ($
roup = Basiliximab-bi iu, 2020 ang, 2020 ang, 2017 adeau, 2016 aiswal, 2016 aiswal, 2016 aiswal, 2016 aiswal, 2016 aiswal, 2016 aiswal, 2016 aiswal, 2016 aiswal, 2018 andom effects model andom effects model arcia-Cadenas, 2013 inana, 2006 ixed effect model	ased 151 85 59 16 7 ² = 0.2972 ased 53 12 2 31 56 8 22 ² = 1.3150 ased 38 10 39	100 65 21 10 426 , p < 0.01 64 13 12 - 57 62 12 43 263 , p < 0.01 98 21 33 92		0.85 0.91 0.76 0.77 0.75 0.80 0.92 0.92 0.92 0.92 0.92 0.92 0.92 0.9	[0.76; 0.91] [0.81; 0.97] [0.53; 0.92] [0.35; 0.93] [0.76; 0.79] [0.66; 0.88] [0.71; 0.91] [0.64; 1.00] [0.64; 1.00] [0.41; 0.68] [0.41; 0.68] [0.41; 0.68] [0.45; 0.90] [0.45; 0.90] [0
roup = Basiliximab-bi u, 2020 ang, 2017 adeau, 2016 aiswal, 2016 adeau, 2016 adeau, 2016 adeau, 2016 andom effects model andom effects model andom effects model andom effect model andom effects model andam effects model arciac-Cadenas, 2017 roningen, 2016 irerd, 2013 arcia-Cadenas, 2017 arcia-Cadenas, 2017 arcia-Cadenas, 2013 arcia-Cadenas, 2017 arcia-Cadenas, 2013 arcia-Cadenas, 2014 arcia-Cadenas, 2015 arcia-Cadenas, 201	ased 151 85 59 16 7 ² = 0.2972 ased 56 8 22 2 31 56 8 22 ² = 1.3150 ased 38 10 30 39 20	$\begin{array}{c} 100\\ 65\\ 21\\ 10\\ 426\\ , p < 0.01\\ \hline \\ 64\\ 13\\ 12\\ - \\ 57\\ 62\\ 12\\ 43\\ 263\\ , p < 0.01\\ \hline \\ 98\\ 21\\ 33\\ 92\\ 40\\ 284\\ \end{array}$		0.85 0.91 0.76 0.77 0.75 0.80 0.92 0.92 0.92 0.92 0.92 0.92 0.92 0.9	[0.76; 0.91] [0.81; 0.97] [0.53; 0.92] [0.35; 0.93] [0.76; 0.79] [0.66; 0.88] [0.71; 0.91] [0.64; 1.00] [0.64; 1.00] [0.41; 0.68] [0.41; 0.68] [0.41; 0.68] [0.45; 0.90] [0.45; 0.90] [0
roup = Basiliximab-bi u, 2020 an, 2017 adeau, 2016 aiswal, 2016 aiswal, 2016 aiswal, 2016 aiswal, 2016 aiswal, 2016 aiswal, 2016 aiswal, 2016 aiswal, 2016 aiswal, 2016 airan, 2009 ui, 2008 arales, 2007 ordigoni, 2009 ui, 2008 arales, 2007 ordigoni, 2006 airano, 2006 aradom effects model andom effects model aradom effects model aradom effects model aracia-Cadenas, 2017 oroingen, 2016 irerd, 2013 araia-Cadenas, 2013 araia-Cadenas, 2013 araia-Cadenas, 2013 araia-Cadenas, 2013 araia-Cadenas, 2013 araia-Cadenas, 2017 araia-Cadenas, 2013 araia-Cadenas, 2013 araia-Cadenas, 2013 araia-Cadenas, 2013 araia-Cadenas, 2013 araia-Cadenas, 2013 araia-Cadenas, 2013 araia-Cadenas, 2013 araia-Cadenas, 2013	ased 151 85 59 16 7 ² = 0.2972 ased 56 8 22 2 31 56 8 22 ² = 1.3150 ased 38 10 30 39 20	$\begin{array}{c} 100\\ 65\\ 21\\ 10\\ 426\\ , p < 0.01\\ \hline \\ 64\\ 13\\ 12\\ - \\ 57\\ 62\\ 12\\ 43\\ 263\\ , p < 0.01\\ \hline \\ 98\\ 21\\ 33\\ 92\\ 40\\ 284\\ \end{array}$		0.85 0.91 0.76 0.77 0.75 0.80 0.92 0.92 0.92 0.92 0.92 0.92 0.92 0.9	[0.76; 0.91] [0.81; 0.97] [0.53; 0.92] [0.35; 0.93] [0.76; 0.79] [0.66; 0.88] [0.71; 0.91] [0.64; 1.00] [0.64; 1.00] [0.41; 0.68] [0.41; 0.68] [0.41; 0.68] [0.45; 0.90] [0.45; 0.90] [0
roup = Basiliximab-bi iu, 2020 an, 2017 adeau, 2016 alawal, 2018 alawal, 2009 ui, 2008 erales, 2007 ordigoni, 2006 Villenbacher, 2001 ordigoni, 2006 Villenbacher, 2001 vized effect model andom effects model arcia-Cadenas, 2017 oroup = Inolimomab-bi arcia-Cadenas, 2013 inana, 2006 ixed effect model andom effects model andom effects model eterogeneity: l ² = 85%, c ² oroup = Inolimomab-bi arcia-Cadenas, 2017 inana, 2006 ixed effect model andom effects model andom effe	ased 151 85 59 16 7 7 2 = 0.2972 2 = 0.2972 2 = 1.3150 3 = 2 2 = 1.3150 3 = 2 2 = 0.2952 2 = 0.2955 2 = 0.2952 2 = 0.2952 2 = 0.2952 2 = 0.2952	$\begin{array}{c} 100\\ 65\\ 21\\ 10\\ 426\\ p < 0.01\\ 64\\ 13\\ 12\\ -p\\ 57\\ 62\\ 12\\ 43\\ 263\\ p \\ 21\\ 33\\ 92\\ 40\\ 284\\ 0, p < 0.01\\ \end{array}$		0.85 0.91 0.76 0.75 0.80 0.80 0.92 0.92 0.92 0.92 0.92 0.92 0.92 0.9	$ \begin{bmatrix} 0.76; 0.91\\ [0.81; 0.97]\\ [0.81; 0.97]\\ [0.55; 0.93\\ [0.76; 0.79]\\ [0.66; 0.86]\\ \\ \hline \end{bmatrix} \\ \begin{bmatrix} 0.71; 0.91\\ [0.64; 1.00\\ [0.25] 0.48\\ [0.41; 1.00\\ [0.25] 0.48\\ [0.41; 0.68\\ [0.35; 0.90\\ [0.35; 0.90\\ [0.26] 0.48\\ \\ \hline \end{bmatrix} \\ \begin{bmatrix} 0.29; 0.49\\ [0.26] 0.70\\ [0.76; 0.98\\ [0.35; 0.73\\]\\ [0.35; 0.73\\]\\ \\ \hline \end{bmatrix} $
roup = Basiliximab-b: na, 2020 an, 2017 adeau, 2016 aiswal, 2016 aiswal, 2016 aiswal, 2016 aiswal, 2016 aiswal, 2016 aiswal, 2016 andom effects model atomore and a strain and a construction and a andom effects model andom effects model atoria. 2016 izeral, 2013 inana, 2006 ixed effect model andom effects model andom effects andom effects a	ased 151 85 59 16 7 7 2 2 2 2 2 2 2 2 2 2 2 2 2	$\begin{array}{c} 100\\ 65\\ 21\\ 10\\ 426\\ 26\\ 77\\ 62\\ 12\\ 43\\ 263\\ p < 0.01\\ 98\\ 21\\ 33\\ 92\\ 40\\ 284\\ p < 0.01\\ 22\\ \end{array}$		0.85 0.911 0.76 0.75 0.80 - 0.92 0.17 0.54 0.92 0.92 0.92 0.75 0.51 0.70 0.69 0.65 0.70 0.51 0.70 0.55 0.23 0.48 0.55	[0.76; 0.81 [0.81; 0.87] [0.53; 0.93 [0.55; 0.93 [0.55; 0.93 [0.55; 0.93 [0.56; 0.83] [0.70; 0.79] [0.66; 0.83] [0.71; 0.84] [0.84; 1.00 [0.21; 0.64] [0.25; 0.90 [0.35; 0.80] [0.35; 0.80] [0.26; 0.77] [0.26; 0.77] [0.26; 0.73] [0.24; 0.64] [0.35; 0.83] [0.35; 0.83] [0.35; 0.83] [0.35; 0.83] [0.35; 0.73]
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yup = Basiliximab-bi, , 2020 19, 2020 19, 2020 19, 2021 19, 2017 19, 2017 19, 2017 19, 2017 19, 2017 19, 2017 19, 2017 19, 2015 19, 2015 19, 2015 19, 2008 19,	ased 151 85 59 16 7 7 2 2 2 2 2 2 2 2 2 2 2 2 2	$\begin{array}{c} 100\\ 65\\ 21\\ 10\\ 426\\ 26\\ 77\\ 62\\ 12\\ 43\\ 263\\ p < 0.01\\ 98\\ 21\\ 33\\ 92\\ 40\\ 284\\ p < 0.01\\ 22\\ \end{array}$		0.85 0.911 0.76 0.75 0.80 0.80 0.92 0.92 0.92 0.92 0.92 0.92 0.92 0.9	[0.76; 0.91] [0.81; 0.97] [0.83; 0.92] [0.35; 0.93] [0.76; 0.79] [0.68; 0.88] [0.76; 0.79] [0.68; 0.88] [0.76; 0.79] [0.41; 0.68] [0.80; 0.96] [0.41; 0.68] [0.41; 0.68] [0.41; 0.68] [0.42; 0.49] [0.26; 0.70] [0.26; 0.70] [0.26; 0.70] [0.24; 0.54] [0.34; 0.54] [0.34; 0.54] [0.34; 0.54] [0.34; 0.54] [0.34; 0.54] [0.34; 0.64] [0.34; 0.64] [0.34; 0.64] [0.34; 0.64]
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Study	Events 1	otai		Proportion 95
group = Basiliximab-I	based		11	
Liu, 2020	140	230		0.61 [0.54
Tang, 2020	74	100		0.74 [0.64
Tan, 2017	49	65		0.75 [0.63
Chakupurakal, 2015	7	14		0.50 [0.23
Nadeau, 2016	9	21		0.43 [0.22
Jaiswal, 2016	3	10 -		0.30 [0.07
		53		
Wang, 2011	37			0.70 [0.56
Schmidt-Hieber, 2005	4	23 -		0.17 [0.05
Massenkeil, 2002	9	17	<u> </u>	0.53 [0.28
Fixed effect model		533	•	0.62 [0.58
Random effects mode				0.55 [0.42]
Heterogeneity: $I^2 = 77\%$,	$\tau^2 = 0.5162,$	p < 0.01		
group = Daclizumab-I	based			
Tao, 2015	37	64	÷	0.58 [0.45
Rager, 2011	4	17 -		0.24 [0.07
Rao, 2009	12	22		0.55 [0.32
Miano, 2009	6	13		0.46 [0.19
Hui, 2008	1	12 -+		0.08 [0.00
Teachev, 2006	5	11		0.45 [0.17
Bordigoni, 2006	43	62		0.69 [0.56
Wolff, 2005	43	20		0.40 [0.19
Srinivansan, 2004	3	20		1.00 [0.29
Willenbacher, 2004	1	12		0.08 [0.00
Preziprka, 2000	16	43		0.37 [0.23
Fixed effect model		279	Q -	0.49 [0.43
Random effects mode				0.42 [0.29]
Heterogeneity: $I^2 = 66\%$,	$\tau^{\circ} = 0.6077,$	p < 0.01		
group = Inolimomab-I	based			
Groningen, 2016	6	21		0.29 [0.11
Girerd, 2013	24	33	· · · · · · · · · · · · · · · · · · ·	0.73 [0.54
Garcia-Cadenas, 2013		92 -		0.14 [0.08
Pinana, 2006	8	40 -		0.20 [0.09
Bay, 2005	25	85		0.29 [0.20
Fixed effect model	20	271	8	0.28 [0.23]
Random effects mode	a.	set 1		0.30 [0.16:
Heterogeneity: /2 = 88%,		0.001		0.30 [0.10]
meterogeneity: /* = 88%;	v = 0.8132,	p = 0.01		
group = Denileukin dit		00		
Shaughnessy, 2005	9	22		0.41 [0.21
Ho, 2004	8	24		0.33 [0.16
Fixed effect model		46	~~~	0.37 [0.24]
Random effects mode	1			0.37 [0.24]
Heterogeneity: $l^2 = 0\%$, τ	$p^2 = 0, p = 0.6$	30		
Fixed effect model	ł	129	-	0.50 [0.47]
Random effects mode			\diamond	0.43 [0.34]
Heterogeneity: /2 = 85%,		n < 0.01		
iotorogeneity. / = 00%,	0.7590,	p ~ 0.01	0.2 0.4 0.6 0.8 1	

Events Total

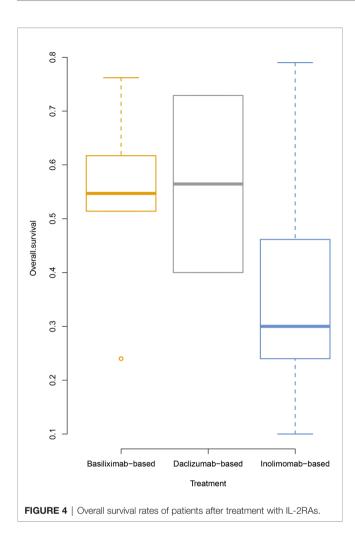
A Study

Study	Events Tota	d	Proportion	95%-C
group = Basiliximab-l Liu, 2020 Tang, 2020 Tan, 2017 Nadeau, 2016 Fixed effect model Random effects model Heterogeneity: I ² = 76%,	140 23 74 10 49 6 9 2 3 1 42		- 0.74 - 0.75 0.43 0.30 0.65	[0.54; 0.67 [0.64; 0.82 [0.63; 0.85 [0.22; 0.66 [0.07; 0.65] [0.60; 0.69] [0.47; 0.74]
group = Daclizumab-l Tao, 2015 Miano, 2009 Hui, 2008 Bordigoni, 2006 Willenbacher, 2001 Preziprka, 2000 Fixed effect model Random effects model Heterogenetity: / ² = 78%,	37 6 6 1 1 1 43 6 1 1 16 4 20		0.46 0.08 0.69 0.08 0.37 0.50	[0.45; 0.70] [0.19; 0.75] [0.00; 0.38] [0.56; 0.80] [0.00; 0.38] [0.23; 0.53] [0.44; 0.57] [0.19; 0.60]
group = Inolimomab- Groningen, 2016 Girerd, 2013 Garcia-Cadenas, 2013 Pinana, 2006 Fixed effect model Random effects model Heterogeneity: / ² = 01%,	6 2 24 3 13 9 8 4 18		- 0.73 0.14 0.20 0.27	[0.11; 0.52 [0.54; 0.87] [0.08; 0.23] [0.09; 0.36] [0.21; 0.34] [0.13; 0.57]
group = Denileukin di Shaughnessy, 2005 Ho, 2004 Fixed effect model Random effects mode Heterogeneity: $l^2 = 0\%$, τ	9 2 8 2 4	4	0.33 0.37	[0.21; 0.64] [0.16; 0.55] [0.24; 0.52] [0.24; 0.52]
Fixed effect model Random effects mode Heterogeneity: <i>I</i> ² = 88%,				[0.48; 0.55] [0.31; 0.55]

FIGURE 3 | Forest plots of CRR at any time (A) and 1 month (B) after treatment with IL-2RAs.

FIGURE 2 | Forest plots of ORR at any time (A) and 1 month (B) after treatment with IL-2RAs.

0.65 [0.62; 0.68] 0.68 [0.56; 0.77]



be included in the analysis of prospective unrandomized studies, and the OS rate was 54.7%, 40.0% and 10.0%, respectively. The OS rate of the unique RCT about inolimomab was 46.9% (33).

DISCUSSION

In this meta-analysis, basiliximab seemed to have the highest response rate, particularly in the gut and liver GVHD, and inolimomab treatment showed a higher infection rate. However, the survival seemed to be comparable among basiliximab, daclizumab, and inolimomab. This was the first meta-analysis comparing the efficacy and safety of different IL-2RAs, which provided valuable information for the treatment of SR-aGVHD.

Activation of T lymphocytes mediates one of the major pathophysiological mechanisms of aGVHD, which exclusively expresses the IL-2R alpha chain (46). IL-2RAs prohibit T-cell proliferation (47); however, in *in vitro* experiments, the ability of inhibiting T lymphocytes varied among different IL-2RAs. Kircher et al. (48) separated peripheral blood mononuclear cells from heparinized peripheral blood of healthy volunteers and then incubated them with 100 μ g/Ml anti-CD3 monoclonal antibody. They set the level of proliferation in the absence of the compounds as 100%. At the concentrations of 0.001, 0.01, and 0.1 μ g/Ml, basiliximab seemed to be stronger in terms of suppressing T-cell proliferation compared with daclizumab. Particularly, at the concentration of 0.1 μ g/Ml, basiliximab could reduce T-cell proliferation from 100% to 41%, while daclizumab could reduce it only from 100% to 69%. However, at higher concentrations (e.g., 1 and 10 μ g/Ml), both of them inhibited T-cell proliferation to a similar degree. Thus, T cells were more sensitive to inhibition by basiliximab in this study.

Similarly, Baan et al. (49) identified the inhibitory effect of different IL-2RAs (basiliximab, daclizumab, and inolimomab) on T-cell proliferation induced by IL-2, IL-7, and IL-15. At lower concentrations (0.1, 0.5, and 1.0 µg/Ml), basiliximab occupied the dominant position for suppressing T-cell proliferation induced by IL-2, followed by daclizumab and inolimomab ranking the last. For suppressing T-cell proliferation induced by IL-7, daclizumab seemed to be stronger than basiliximab at concentrations of 0.1 and 0.5 µg/Ml, while basiliximab seemed to be better at other concentrations (1.0, 5.0, and 10.0 μ g/Ml). Irrespective of the concentration, T cells appeared to be minimally inhibited by inolimomab. In IL-15-driven T-cell proliferation, daclizumab performed better than basiliximab at concentrations higher than 0.5 µg/Ml, while the function of inolimomab was still the weakest. These results might also partly explain the fact that inolimomab was less effective than basiliximab and daclizumab in SR-aGVHD treatment. Among these three cytokines (i.e., IL-2, IL-7 and IL-15), IL-2 showed the preferential protective effects on T cells against glucocorticoidinduced apoptosis (50). Therefore, basiliximab exhibited the best efficacy in treating SR-aGVHD.

From the perspective of structure, inolimomab was a murine anti-human monoclonal antibody (7), basiliximab was a murine chimeric monoclonal antibody (8), and daclizumab was a humanized monoclonal antibody (9). The human immune system can produce its own antibodies to clear rodent antibodies rapidly because they are foreign proteins, leading to reduced efficacy (51, 52). An increased risk of an infusion reaction may exist as well (53). Moreover, a longer half-life may help to inhibit T cells more effectively. The half-lives of basiliximab and daclizumab are 7 days and 21–25 days (8, 9), respectively, while the half-life of inolimomab is only 44.5 h (7). It might partially explain the higher ORRs of basiliximab (81%) and daclizumab (71%), while that of inolimomab was only 50%.

It is reported that IL-2RA may suppress regulatory T cells (54) which possibly leads to chronic GVHD after treatment (55, 56). However, aGVHD was a significant risk factor of cGVHD, and more than 65% of patients with grades II to IV aGVHD would develop cGVHD (57–59). This was similar to the rate of cGVHD in the present study. Thus, it was suggested that the suppression of regulatory T cells caused by IL-2RA might have an influence on cGVHD, however, the incidence of cGVHD could also be driven by the prior SR-aGVHD, which needs to be further explored by prospective RCTs.

In this study, basiliximab, daclizumab, inolimomab, and denileukin diffitox were found to have similar efficacy in aGVHD of the skin, while basiliximab seemed to be better in aGVHD of the gut and liver. Clinically, aGVHD of the gut and liver significantly increased the risk of transplant-related mortality (60). Therefore, basiliximab could improve the prognosis to a much greater extent, especially in severe SR-aGVHD.

This study had several limitations. First, the generalizability of this meta-analysis was limited by various circumstances due to the heterogeneity originating from different study designs and the process of conducting and analyzing, which might influence the accuracy of our results. Second, the time frame for the evaluation of the response rate at 1 month after IL-2RA treatment was prolonged because different studies had different time points. That is, the earliest studies evaluating at 3 weeks while the latest studies evaluating at 6 weeks after treatment with IL-2RAs were enrolled in this analysis, which might have influenced the study outcomes. Third, one more drawback was the lack of prospective RCTs to compare distinct categories of IL-2RA directly. Instead, most studies that could be used for analysis were retrospective studies with relatively limited sample sizes. Finally, several biases might have been introduced into this metaanalysis, including unbalanced medical resources from different time points or areas. Thus, the superiority of basiliximab over other IL-2RAs in patients with SR-aGVHD needs to be validated by further studies.

CONCLUSION

In conclusion, the efficacy and safety of different IL-2RAs varied. The response rate of basiliximab seemed to be the highest, followed by daclizumab. More prospective RCTs are needed to compare the efficacy and safety of different IL-2RAs.

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DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

Two reviewers J-XL and M-ZS conducted the study selection and data extraction independently. A third reviewer X-DM arbitrated when the former two reviewers had diverse opinions X-DM and X-JH designed the study. J-XL, M-ZS, L-PX, X-HZ, YW, and K-YL collected the data. J-XL, M-ZS, and S-DH analyzed the data and drafted the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2021. 749266/full#supplementary-material

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