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Review

Novel Therapies for the Treatment of Antibody Mediated Rejection in Solid Organ Transplantation: A Systematic Review

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Abstract

Antibody mediated rejection (AMR) is a considerable cause of late allograft failure in solid organ transplantation. Conventional approaches, using plasmapheresis, intravenous immunoglobulin, rituximab, bortezomib, and eculizumab have been unsuccessful in improving graft survival. This review aims to assess emerging therapies for AMR treatment across all organs. Using a PubMed search, literature published up to July 20, 2025 regarding tocilizumab, clazakizumab, carfilzomib, daratumumab, imlifidase, felzartamab, and obinutuzumab were reviewed. Articles were included if available in English, full-text, and reported clinical efficacy outcomes, and excluded if they discussed non-AMR indications or were review articles, single case reports, opinion pieces, protocols, animal studies, or *in vitro* studies. A total of 28 studies were included, and grouped by drug, organ, and indication. Quality was rated with the Newcastle-Ottawa Scale. The majority of evidence was with single-center retrospective studies and kidney transplantation. Tocilizumab demonstrated the most promise for stabilizing graft function in kidney chronic active AMR (cAMR). Clazakizumab failed to meet its primary efficacy outcome in its cAMR phase III study despite encouraging findings in earlier

trials. Carfilzomib may be considered in acute AMR when toxicities preclude use of bortezomib, but comes with risks of nephrotoxicity. Evidence to support daratumumab's utility in acute AMR is limited to highly heterogenous case series. Imlifidase, felzartamab, and obinutuzumab are not widely studied but may be potential therapies in the future. Studies comparing these therapies to standard of care are needed to establish the place in therapy of these agents. Additionally, there is a need to identify patient characteristics most predictive of clinical success.

Keywords
Antibody mediated rejection; solid organ transplantation; kidney transplant; liver transplant; lung transplant; heart transplant

1. Introduction

Antibody mediated rejection (AMR) remains a therapeutic challenge in solid organ transplantation and is a major cause for late allograft loss across all organ groups [1-5]. In kidney transplantation, there is a 4.7-fold increased risk of graft loss in patients experiencing AMR in comparison to those who do not [1]. Similarly, C4d positive staining and the presence of donor specific antibodies (DSA) in both pancreas and liver transplantation are associated with a significantly increased risk of graft loss [2, 3]. In cardiothoracic transplantation, AMR portends a poor prognosis, with a 5.4-fold increased risk of developing cardiac allograft vasculopathy (CAV) in heart transplantation and an 8.7-fold increased risk of developing chronic lung allograft dysfunction (CLAD) in lung transplantation [6-8].

Allograft injury resulting from acute AMR is driven predominantly by production of donor-specific human leukocyte antigen (HLA) antibodies, which results in inflammation and endothelial cell injury, complement activation, and infiltration of innate immune cells into the endothelium. Repeated allograft injury and uncontrolled repair responses can result in transplant vasculopathy and irreversible fibrosis, characteristic of chronic active AMR (cAMR) [9]. Conventional therapy for AMR includes a combination of plasmapheresis (PLEX) and intravenous immunoglobulin (IVIg) for removal and neutralization of DSA. In the past decade, adjunctive therapies such as rituximab targeting B cells, bortezomib targeting plasma cells, and eculizumab targeting the complement system have been used [10, 11]. Yet, these approaches have been unsuccessful in improving clinical outcomes and long-term survival in kidney transplantation. In a randomized controlled trial, addition of rituximab to PLEX and IVIg failed to show any differences from placebo in graft loss, renal function, Banff histologic scores, or DSA strength [12]. Additionally, long-term death-censored graft survival at 7 years remained not different from placebo [13]. Given that rituximab targets CD20 without any effect on antibody-producing plasma cells, bortezomib, a 26S proteasome inhibitor has been explored as a potential therapeutic option. However, bortezomib also failed to show benefits in comparison to placebo in estimated glomerular filtration rate (eGFR) slope, graft survival, Banff histology or DSA strength [14]. Eculizumab, which targets the C5 complement protein, preventing formation of the membrane attack complex, has also been studied as a potential treatment option. In a randomized control trial where eculizumab was compared to placebo for cAMR, there was no

improvement in kidney function or endothelial cell-associated transcripts [15]. A subsequent case series of 15 kidney transplant recipients found improvements in eGFR in early acute AMR (within 30 days of transplant). However, this study lacked a comparator group, and therefore these findings do not confirm the definitive benefit of eculizumab [16]. With these therapies, the management of acute AMR and attenuating the progression towards chronic, irreversible allograft injury remains challenging.

Thus, there have been recent efforts in identifying new therapeutic targets for the treatment of AMR. The goal of this review is to assess the available data for tocilizumab, clazakizumab, carfilzomib, daratumumab, imlifidase, felzartamab, and obinutuzumab for use in the treatment of AMR across all solid organ transplant types.

2. Methods

2.1 Protocol and Ethics Statement

Reporting followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [17]. The protocol was registered with the PROSPERO registry (CRD420251072841). This review was screened for Institutional Review Board criteria, and did not require approval through an ethics committee.

2.2 Search Strategy

Emerging therapeutic agents for AMR were identified from published review articles [18-28]. A PubMed search was conducted to identify studies assessing the use of tocilizumab, clazakizumab, carfilzomib, daratumumab, imlifidase, felzartamab, obinutuzumab, belimumab, ofatumumab, inebilizumab, and isatuximab for the treatment of AMR. Studies published up to July 20, 2025 were assessed for inclusion. The database was searched using the drug name AND (“antibody mediated rejection” OR “antibody-mediated rejection”) AND (kidney transplantation [MeSH Terms] OR “kidney transplant*” OR pancreas transplantation [MeSH Terms] OR “pancreas transplant*” OR liver transplantation [MeSH Terms] OR “liver transplant*” OR lung transplantation [MeSH Terms] OR “lung transplant*” OR heart transplantation [MeSH Terms] OR “heart transplant*” OR organ transplantation [MeSH Terms] OR “organ transplant*”).

2.3 Study Selection

Articles were included if they were available in English, full-text and reported clinical efficacy outcomes of the drug of interest. Articles were excluded if they discussed the drug therapy for non-AMR indications, if they were review articles, single case reports, opinion pieces, study protocols, animal studies, or *in vitro* studies. The final search results were exported, and an eligibility assessment was independently performed by the authors. Differences were resolved by consensus. Additional articles were included as appropriate if they were identified through the bibliography of articles that came from the PubMed search.

2.4 Data Extraction and Bias Assessment

Data were independently extracted by both authors. Subsequently results were discussed, and inconsistencies in charting were resolved by consensus. The following data were extracted from the studies: organ type, indication, study design (study type, number of centers, country), number of patients, inclusion/exclusion criteria, timing of rejection, baseline graft function [serum creatinine (SCr)/eGFR, liver function tests (LFTs), forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC), left ventricular ejection fraction (LVEF)], baseline histology/AMR classification, baseline DSA, treatment regimen and timing of initiation, follow-up duration, efficacy outcomes (graft survival, patient survival, graft function, histology, and DSA), and safety outcomes [adverse effects (AEs), treatment discontinuations]. Studies were grouped by drug, organ type, and indication.

Both authors independently assessed and rated study quality following the Newcastle-Ottawa Scale (NOS) for cohort studies [29]. The total NOS score ranges from 0-9, with the following criteria: quality of patient selection (S: 0-4 points), comparability of cohorts (C: 0-2 points), and assessment/follow-up of outcomes (O: 0-3 points).

3. Results

3.1 Identified Studies

The search strategy yielded 156 results which were then filtered to exclude 3 non-English articles and 1 non-full text article. After screening titles and abstracts, 126 articles were excluded for non-AMR indications (n = 22) and article types (n = 104). After assessing full-text articles for exclusion criteria and the addition of studies through bibliographies, 28 studies were included in the final review (Figure 1). Belimumab, ofatumumab, inebilizumab, and isatuximab were included in the initial search strategy because they were proposed as potential treatment options for AMR in published review articles [18-28]. However, our literature search yielded five reports for belimumab, but none of them met the inclusion criteria (three review articles and two case reports for non-AMR indications). No studies for ofatumumab, inebilizumab, and isatuximab were found on our literature search.

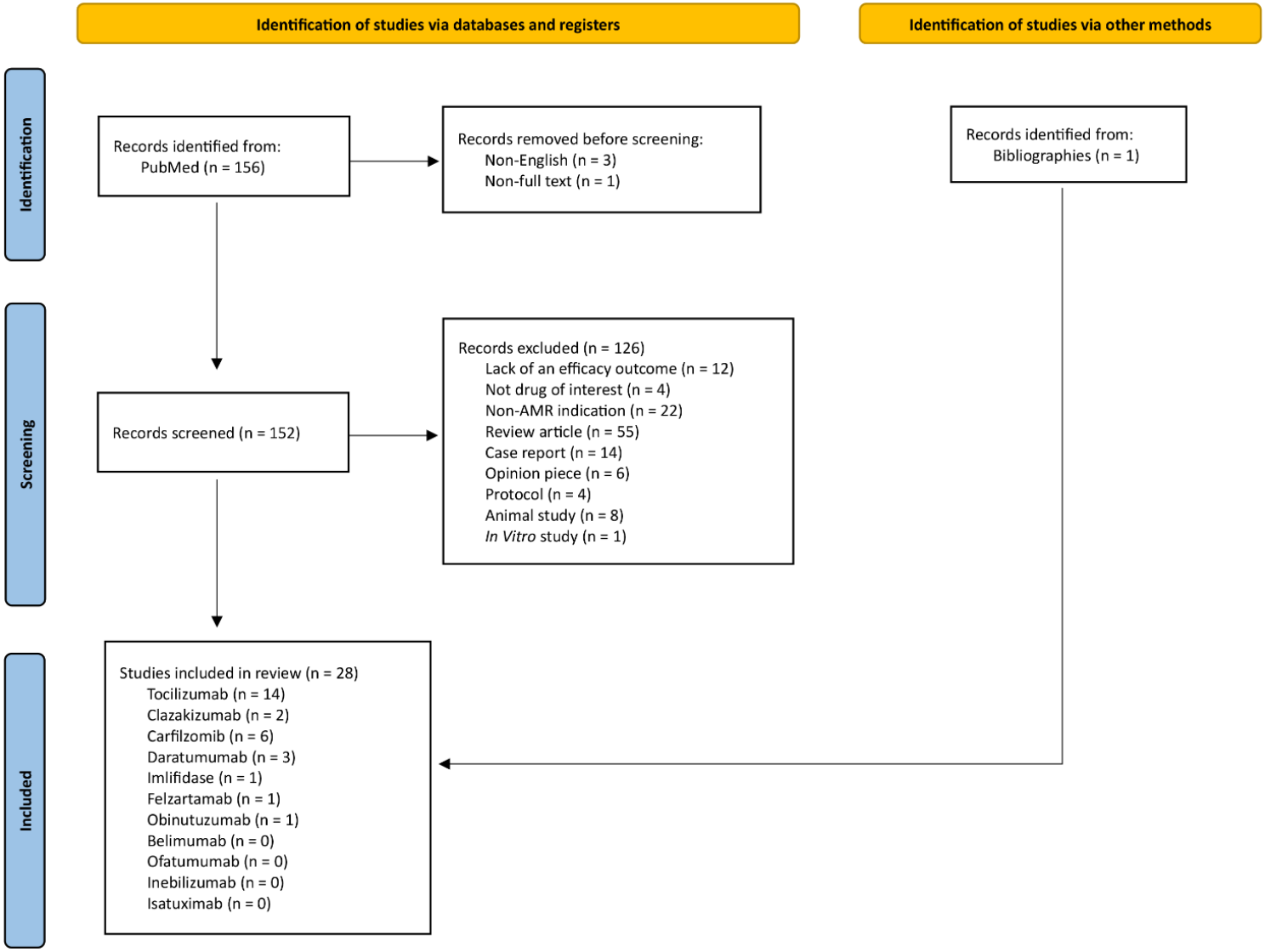

Figure 1 PRISMA Flow Diagram.

3.2 Study Characteristics

The included studies are grouped by agent, organ type, and indication. No studies assessed the treatment of AMR in pancreas transplantation. The majority of studies were retrospective case series, with only three studies being prospective studies. Six studies included a comparator group, of which three were retrospective studies and three were randomized controlled trials. Overall, NOS selection scores ranged from 3-4, comparability scores ranged from 0-1, and outcome scores ranged from 2-3, with a total NOS score range of 5-8. In the selection category, all studies received at least 3 points given representativeness of the exposed cohort to the average population, ascertainment of the exposure from secure records, and demonstration that the outcome of interest was not present at the start of the study. The three retrospective comparative studies received an additional point in the selection category for having the non-exposed cohort drawn from the same community as the exposed cohort, and an additional point in the comparability category for including a control for comparison. No studies received the full 2 points in the comparability category due to lack of additional controls. In the outcome category, all studies had at least 2 points given for independent blind assessment of outcomes and >80% of subjects included at follow-up. Seventeen of the studies had an additional point for the outcome category for a follow-up period ≥1 year when considering efficacy outcomes. Table 1 summarizes the study design and baseline characteristics, and Table 2 summarizes the efficacy and safety outcomes.

Table 1 Study Design and Baseline Characteristics.

Reference	Design	Organ	Indication	NOS score	Follow-up	Baseline Characteristics				
						Timing of Rejection	Timing of Therapy	Graft Function	Banff Histology (kidney) ISHLT/AHA classification (lung/heart)	DSA
Tocilizumab (TCZ)										
Pottebaum, et al. [30] (n = 7)	Single-center, retrospective case series in the United States	Kidney	**Acute AMR**	5 (S3, C0, O2)	Median (IQR) 3 months (3-6)	Approximate range of 12 days to 91 months post-transplant	--	Median SCr (IQR) 2.3 mg/dL (1.7-5.4)	**Banff Criteria used not reported** • g score, range: 0-2 • ptc score, range: 0-3 • C4d positive, n (%): 3/7 (43%) • cg score, range: 0-1	7/7 (100%) had HLA-DSAs Median iDSA MFI (IQR) 12,662 (4,960-24,042)
Pearl, et al. [31] (n = 25)	Two center retrospective case series in the United States	Kidney (Pediatric)	**Acute AMR** (n = 16) **cAMR** (n = 9) Refractory to IVIg ± RTX, pulse steroids, PLEX ± BTZ	6 (S3, C0, O3)	Median (IQR) 15.8 months (8.4-35.7)	Median (IQR) 41.4 months post-transplant (24.3-67.7)	Median (IQR) 10.6 months from diagnosis (8.3-17.6)	--	**Banff 2017 Criteria** • 13/25 (52%) C4d+ at time of 1st TCZ	23/25 (92%) had HLA-DSA 2/25 (8%) had AT1R-Ab

Choi, et al. [32] (n = 36)	Single-center, prospective open-label case series in the United States	Kidney	**cAMR** Refractory to a combination of IVIg + RTX ± PLEX	6 (S3, C0, O3)	Median (IQR) 3.26 years (1.82-3.81)	--	Mean (SD) 6.72 years post-transplant (4.63)	Mean eGFR (SD) 48.4 mL/min/ 1.73 m^2 (34.56)	**Banff 2013 Criteria** • g score, mean (SD): 1.67 (1.11) • ptc score, mean (SD): 1.78 (0.58) • C4d deposition, mean (SD): 1.54 (1.50) • cg score, mean (SD): 1.57 (1.03) • IF/TA score, mean: 0.93 (0.72)	33/36 (91.7%) had HLA-DSAs: mean iDSA MFI > 10,000 3/36 (8.3%) had AT1R Ab
Lavacca, et al. [33] (n = 15)	Single-center, prospective open-label case series in Italy	Kidney	**cAMR** 1st line therapy	6 (S3, C0, O3)	Median (IQR) 20.7 months (18.0-27.8)	Median (IQR) 5.9 years post-transplant (4.6-14.0)	Median (IQR) 100 days post-biopsy (79-137.5)	Median eGFR (IQR) 54.5 mL/min/ 1.73 m^2 (47.5-56.8) Median proteinuria (IQR) 1.10 g/day (0.60-1.52)	**Banff 2017 Criteria** • g score, median (IQR): 2 (0-2) • ptc score, mean (IQR): 2 (1-2) • g+ptc score, median (IQR): 3 (2-4) • C4d score, median (IQR): 1 (0-2) • cg score, median (IQR): 3 (2-3) • IF/TA score, median (IQR): 1 (1-1)	15/15 (100%) had HLA-DSAs: median iDSA MFI (IQR) 22,600 (21,700-3,700) 11/15 (84.6%) had AT1R Ab: median AT1R Ab level (IQR) 15.8 U/mL (12.5-16.6)

Kumar, et al. [34] (n = 10)	Single-center retrospective case series in the United States	Kidney	**cAMR** Refractory to a combination of PLEX, IVIg ± RTX or BTZ	6 (S3, C0, O3)	Median (range) 12 months (8-24)	--	Median (range) 31 months post-transplant (13-115)	Mean eGFR (SD) 42 mL/min/ 1.73 m^2 (19) Mean proteinuria (SD) 1.5 g/g (1.14)	**Banff 2017 Criteria** • g+ptc score, mean (SD): 4.8 (1.4) • IF/TA score, mean (SD): 2.5 (0.84)	8/10 (80%) had HLA-DSAs Mean total DSA MFI (SD) 7,272 (6,698)
Massat, et al. [35] (n = 9 TCZ + SOC vs. n = 37 SOC)	Single-center retrospective cohort study in France	Kidney	**cAMR** (n = 6) **Mixed AMR/ACR** (n = 4) Refractory to unspecified SOC	8 (S4, C1, O3)	1 year	Median (range) post-transplant: 25 months (4-164) in TCZ + SOC vs. 29 months (2-270) in SOC	--	--	**Banff 2017 Criteria** • cg, g+ptc, C4d deposition, and IF/TA score not different between the TCZ and non-TCZ groups (not numerically reported) • t+i score, mean (SD): 1.78 (1.40) in TCZ vs. 0.75 (1.25) in non-TCZ (p = 0.05)	Pre-formed DSAs: 6/9 (66.6%) in TCZ + SOC vs. 12/37 (32.4%) in SOC (p = 0.12) dnDSAs: 3/9 (33.4%) in TCZ + SOC vs. 25/37 (67.6%) in SOC (p = 0.12) Mean iDSA MFI (SD): 7,321 (6,774) in TCZ + SOC vs. 5,623

										(3,773) in SOC (p = 0.81)
Noble, et al. [36] (n = 40)	Single-center retrospective case series in France	Kidney	**cAMR** 1st line therapy (n = 7) Refractory to a combination of RTX ± PLEX ± steroids ± rATG (n = 33)	5 (S3, C0, O2)	Median (range) 7 months (4-13)	Median (range) 18.9 months post-transplant (6-55)	Median (range) 34 days post-biopsy (23-155)	Mean eGFR (SD) 43 mL/min/ 1.73 m^2 (17)	**Banff 2019 Criteria** • g ≥2: 20/40 (50%) • ptc ≥2: 20/40 (50%) • cg ≥2: 10/40 (25%) • IF/TA ≥2: 7/40 (18%)	22/40 (55%) had HLA-DSAs
Khairallah, et al. [37] (n = 38)	Single-center retrospective case series in the United States	Kidney	**cAMR** Refractory to steroids ± IVIg ± PLEX	6 (S3, C0, O3)	Median (IQR) 21 months (21-50)	--	Median (IQR) 3.2 years post-transplant (1.7-6.4)	Mean eGFR (SD) 34 mL/min/1.73 m^2 (16)	**Banff 2019 Criteria** • g score, median (IQR): 1 (0-1) • ptc score, median (IQR): 2 (1-2) • C4d score, median (IQR): 0 (0-0.5) • t score, median (IQR): 1 (1-2) • i score, median (IQR): 1 (0-1)	31/38 (82%) had DSAs: median MFI (IQR) 3,450 (1,350-8,875)

Boonpheng, et al. [38] (n = 11)	Single-center retrospective case series in the United States	Kidney	**cAMR** 1st line therapy (n = 4) Previous treatment for acute AMR or cAMR with RTX ± IVIg (n = 7)	6 (S3, C0, O3)	Up to 18 months (iDSA, eGFR) 16 months (histologic assessment) Up to 12 months (proteinuria)	Median (range) 90 months post-transplant (14-224)	--	Mean eGFR (SD) 57 mL/min/ 1.73 m^2 (18) Mean proteinuria (SD) 1.5 g/g (1.3)	**Banff 2019 Criteria** • g score, median (IQR): 2 (2-3) • ptc score, median (IQR): 2 (1.5-3) • cg score, median (IQR): 2 (1-3) • ci score, median (IQR): 1 (0-1) • ct, median (IQR): 1 (1-1) • C4d positive, n (%): 5/11 (45%)	Median iDSA MFI (range) 10,700 (4,200-27,000)
Chamoun, et al. [39] (n = 5)	Single-center retrospective case series in Spain	Kidney	**cAMR** Refractory to initial treatment with PLEX + IVIG ± RTX	5 (S3, C0, O2)	--	Mean (SD) 13.8 months post-transplant (10.5)	Mean (SD) 47 days from biopsy (52)	Mean eGFR (SD) 46 mL/min/ 1.73 m^2 (15)	**Banff 2019 Criteria** • g+ptc score, mean (SD) 4.2 (0.8) • cg score, mean (SD): 1.2 (0.4)	1/5 (20%) had HLA-DSA
Sangermano, et al. [40] (n = 6)	Single-center retrospective case series in Italy	Kidney (Pediatric)	**cAMR** Refractory to PLEX + RTX ± pulse steroids ± BTZ	5 (S3, C0, O2)	6 months	Mean (SD) 5.7 years post-transplant (4.3)	--	--	**Banff 2017 Criteria** • Baseline scores not reported	3/6 (50%) patients had HLA-DSA: mean total DSA MFI (SD) 19,153 (1,083) 2/6 (33.3%) patients had

										elevated levels of AT1R-Ab
Noble, et al. [41] (n = 45 cAMR, n = 19 MVI without DSA or C4d deposition)	Two center retrospective case series in France and Italy	Kidney	**cAMR** 1st line therapy	6 (S3, C0, O3)	1 year	Median (IQR) 58 months post-transplant (16-130)	--	Mean eGFR (SD) 39.4 (16) mL/min/1.73 m^2	**Banff 2022 Criteria** • cg score ≥1: 53.1% • g score ≥1: 81.2% • ptc score ≥1: 82.3% • C4d positive: 26.5%	40/64 (62.5%) patients had DSA Median iDSA MFI (IQR) 9,537 (1,426-15,075)
January, et al. [42] (n = 9 TCZ vs. n = 18 non-TCZ)	Single-center, retrospective cohort study in the United States	Lung	**Acute AMR** 1st line therapy	8 (S4, C1, O3)	Mean 211 days in TCZ vs. 261 days in non-TCZ (p = 0.409)	--	Mean (SD) 402 days (341) in TCZ vs. 856 days (499) in non-TCZ (p = 0.068)	Mean FEV1 (SD) 2.31 L (0.8) in TCZ vs. 2.31 L (0.86) in non-TCZ (p = 0.689) Mean FVC (SD) 2.80 L (0.81) in TCZ vs. 2.87 L (0.97) in non-TCZ (p = 0.857)	**ISHLT 2016 Criteria** • TCZ: 7/9 (78%) probable AMR, 2/9 (22%) definite AMR • Non-TCZ: 1/18 (5%) possible AMR, 12/18 (67%) probable AMR, 5/18 (28%) definite AMR **CLAD** • 3/9 (33.3%) in TCZ vs. 3/18 (16.7%) in non-TCZ	Mean iDSA MFI: 7,763 in TCZ vs. 8,199 in non-TCZ (p = 0.878)

Pottebaum, et al. [43] (n = 7)	Single-center retrospective case series in the United States	Heart	**Acute AMR** 1st line (n = 3) Refractory to PLEX + IVIg + RTX (n = 4)	6 (S3, C0, O3)	Duration of TCZ: median (IQR) 15 months (10-21) Outcomes: at 4-6 months	Median (IQR) 22 months post-transplant (11-40)	Median (IQR) 25 months post-transplant (11.5-42)	Median LVEF 47%	**AHA 2015 Criteria** pAMR • 0/7 (0%) pAMR0 • 2/7 (28.6%) pAMR1, H+ • 1/7 (14.3%) pAMR1, I+ • 4/7 (57.1%) pAMR2 CAV grade • 2/7 (28.6%) with 0 • 2/7 (28.6%) with 1 • 1/7 (14.3%) with 2-3 • 2/7 (28.6%) with no assessment	5/7 (71%) had HLA-DSAs: median iDSA MFI 19,038 1/7 (14%) had AT1R-Ab 0/7 (0%) had no antibodies
Clazakizumab (CLAZ)										
Doberer, et al. [44] (n = 20)	Phase 2 randomized double-blind, placebo-controlled pilot trial in Austria & Germany	Kidney	**Active AMR** (n = 2 CLAZ) **cAMR** (n = 8 CLAZ, n = 10 in placebo)	N/A (RCT)	52 weeks	--	Median (IQR) 10.6 years post-transplant (4.4-16.2)	Median eGFR (IQR) 39.3 mL/min/1.73 m^2 (33.6-49.7)	**Banff 2017 Criteria** • C4d positive, n (%): 7/20 (35%)	4/20 (20%) had HLA-DSAs Median peak DSA MFI (IQR) 11,708 (1,947-17,709) Median MFI sum of detected DSA (IQR) 13,130 (2,137-18,962)

Jordan, et al. [45] (n = 10)	Phase 2, single-center, open-label study in the United States	Kidney	**cAMR** Previously treated (n = 8) Not previously treated (n = 2)	6 (S3, C0, O3)	Study follow-up: 12 months Long-term extension period follow-up: >2.5 years	Mean (range) 2997 days post-transplant (1,126-8,113)	--	Mean eGFR (SD) 41.9 mL/min/ 1.73 m^2 (12.09)	**Banff 2017 Criteria** • G+ptc, mean: 4.38 • Cg, mean: 2.38 • C4d, mean: 1.26 • i-IFTA, mean: 0.813	Mean DSA MFI (SD) 9,625 (5,745) • DQ: 8/10 (80%) • DR: 1/10 (10%) • DP: 1/10 (10%)
					Carfilzomib (CFZ)					
Cody, et al. [46] (n = 2)	Single-center retrospective case series in the United States	Kidney (Pediatric)	**Acute AMR** Intolerance to BTZ	6 (S3, C0, O3)	Approximately 1 year	Patient 1: 36 days post-transplant Patient 2: 3 years post-transplant	Patient 1: 47 days from biopsy Patient 2: 20 days from biopsy	Patient 1: SCr 0.3 mg/dL Patient 2: SCr 0.81 mg/dL	**Criteria not specified** • Patient 1: focally prominent peritubular capillaritis suggestive of AMR • Patient 2: significant peritubular capillaritis, some glomerulitis, C4d+ staining	Patient 1: DR53 MFI 3,900, DR15 MFI 2,200, DR51 MFI 1,900 Patient 2: DQ6 & DQA*01 (MFI not reported)

Jamal, et al. [47] (n = 2)	Single-center retrospective case series in the United States	Liver	**Acute AMR** Refractory to steroids + IVIg + RTX	5 (S3, C0, O2)	--	Patient 1: 10 days post-transplant Patient 2: 158 days post-transplant	Patient 1: ~2 months post-transplant Patient 2: ~7 months post-transplant	--	**Criteria not specified** • Patient 1: biopsy suggestive of AMR • Patient 2: biopsy with ACR and no evidence of AMR, but patient had elevated DSAs	Patient 1: A1 MFI 1,280, A2 MFI 5,863, B8 MFI 7,891, B18 MFI 2,119, Cw5 MFI 3,588, Cw7 MFI 1,266, DQ2 MFI 29,907, DP3 MFI 653 Patient 2: DQ2 MFI 9,519, DQ4 MFI 24,780, DP1 MFI 2,266
Ensor, et al. [48] (n = 14)	Single-center retrospective case series in the United States	Lung	**Acute AMR**	5 (S3, C0, O2)	--	Median time to DSA (IQR) 126 days post-transplant (30-567) Median time to AMR after DSA (IQR) 121 days (42-385)	--	Mean FEV1 fell from 2.11 L pre-AMR to 1.92 L at AMR (p = 0.04)	**ISHLT 2012/2016 AMR Criteria** • 6/14 (42.9%) definitive • 8/14 (57.1%) probable **ISHLT 2014 CLAD Criteria** • 9/14 (64.3%) CLAD stage 0 • 1/14 (7.1%) CLAD stage 1 • 2/14 (14.3%) CLAD stage 2	Median iDSA MFI at AMR (IQR) 10,914 (5,297-13,832)

									• 2/14 (14.3%) CLAD stage 3	
Pham, et al. [49] (n = 28)	Single-center retrospective case series in the United States	Lung	**Acute AMR**	5 (S3, C0, O2)	--	Median time to dnDSA (IQR) 105 days post-transplant (30-573)	Median time to CFZ (IQR) 266 days post-transplant (76-764)	Estimated mean decline in % FEV1 before CFZ -0.75% per month (95% CI -1.29 to -0.21)	**ISHLT 2016 AMR Criteria** • 8/28 (28.6%) possible clinical AMR • 18/28 (64.3%) probable clinical • 3/28 (10.7%) definite clinical AMR • 1/28 (3.6%) possible subclinical • 1/28 (3.6%) probable subclinical	Median class I iDSA MFI (IQR) 3,540 (2,378-5,490) Median class II iDSA MFI (IQR) 8,291 (6,875-10,628)
Razia, et al. [50] (n = 17 CFZ, n = 36 RTX)	Single-center retrospective cohort study in the United States	Lung	**Acute AMR**	7 (S4, C1, O2)	--	Median time to DSAs (IQR) 3 months post-transplant (1-24)	Median time to treatment (IQR) 4.5 months post-transplant (2-25)	Median % predicted FEV1 when DSA elevated (IQR) 67% (48-81)	**Not reported** • 6/44 (13.6%) no AMR • 0/44 (0%) definite AMR • 1/44 (2.3%) probable AMR • 37/44 (84.1%) possible AMR	Median pre-CFZ DQ (IQR) 12,789 (5,518-15,015) Median pre-CFZ DR (IQR) 1,880 (508-6,613) Median pre-RTX DQ (IQR) 10,397 (5,750-16,300) Median pre-RTX DR (IQR) 3,439 (1,760-8,159)

Horn, et al. [51] (n = 8 CFZ, n = 2 BTZ)	Single-center retrospective case series in the United States	Heart	**Acute AMR**	6 (S3, C0, O3)	1 year	Median (range) 705 days post-transplant (186-1,345)	--	Median EF (IQR) 28% (19-60) 6/10 (60%) patients presented with graft dysfunction	**AHA 2019 Criteria** • 5/10 (50%) pAMR2 • 2/10 (20%) pAMR1 • Of the remaining 3 patients that were treated, 2 presented with graft dysfunction & positive DSA, 1 presented with cardiac MRI findings consistent with rejection & ISHLT ACR grade 1 rejection	10/10 (100%) had ≥1 strong DSA (MFI >8,000) in undiluted serum • 20/21 (95%) of DSAs were class II • Median iDSA baseline MFI (IQR) 22,512 (15,040-25,633) (undiluted) • Median iDSA baseline (IQR) 17,550 (7,865-20,525) (diluted 1:16)

						Daratumumab (DARA)				
Zhu, et al. [52] (n = 2)	Single-center retrospective case series in China	Kidney	**cAMR** (patient 1) **Acute AMR** (patient 2)	6 (S3, C0, O3)	Patient 1: 20 months Patient 2: 15 months	Patient 1: 2.5 years post-transplant Patient 2: 19 months post-transplant	Patient 1: ~4 months after biopsy Patient 2: ~33 days after biopsy	Patient 1: Not reported Patient 2: Scr 2.67 mg/dL	**Banff 2017 Criteria** (patient 1) • g1, ptc1-2, C4d1, cg1 **Banff 2019 Criteria** (patient 2) • g1, ptc2, C4d3, cg0	Patient 1 MFI: DQ7 15,237 Patient 2 MFI: DQ7 18,548
Lemal, et al. [53] (n = 3)	Single-center retrospective case series in France	Kidney	**Acute AMR** (n = 3)	6 (S3, C0, O3)	Patient 1 and 2: 36 months Patient 3: 1 month	--	--	--	**Banff Criteria - year not reported** • Patient 1 and 2: C4d positive	--
Osmanodja, et al. [54] (n = 2)	Single-center retrospective case series in Germany	Kidney	**Acute AMR** (n = 2)	6 (S3, C0, O3)	18 months	Patient 1: 6 weeks post-transplant Patient 2: 9 days post-transplant	Patient 1: 9 months post-transplant Patient 2: 12 months post-transplant	Patient 1: SCr ~1.7 mg/dL Patient 2: SCr ~2.1 mg/dL	**Banff Criteria - year not reported** • Patient 1: g3, ptc 3, cg3, IF/TA 0 • Patient 2: g3, ptc 2, cg2, IF/TA 0	Patient 1 MFIs: DR7: 194, DQ2: 9, B44: 0 Patient 2 MFIs: DP2: 5,849, Cw6: 397

Imlifidase (IdeS)										
Halleck, et al. [55] (n = 18 IdeS vs. n = 10 PLEX)	Randomized open-label, multicenter, multinational trial at 14 transplant centers	Kidney	**Acute AMR** (n = 9) **cAMR or mixed rejection** (n = 19)	N/A (RCT)	6 months	Median time post-transplant (range) 4 years (0.1-25.5) in IdeS vs. 1.1 years (0-13) in PLEX	Median time from biopsy to treatment (range) 5 days (2-10) in IdeS vs. 2.5 days (1-8) in PLEX	Median eGFR (range) 30.2 mL/min/1.73 m^2 (0-54.4) in IdeS, vs. 20.2 mL/min/1.73 m^2 (10-37.3) in PLEX (p = 0.208)	**Banff 2017 Criteria** • Chronicity score (ci + ct + cv + cg), median (IQR): 5 (1-2), n = 16 in IdeS vs. 4 (1-9), n = 9 in PLEX	Pre-treatment DSA (sum of MFI), median (range): 11,039 (2,378-39,850) in IdeS vs. 18,922 (530-45,053) in PLEX Pre-treatment DSA (sum of MFI), 1:16 dilution, median (range): 4,795 (425-36,795) in IdeS vs. 10,228 (167-56,915) in PLEX
Felzartamab (FELZ)										
Mayer, et al. [56] (n = 11 FELZ vs. n = 11 placebo)	Phase 2, double-blind, randomized, placebo-controlled trial in Vienna & Berlin	Kidney	**Acute AMR** (n = 7) **cAMR** (n = 15)	N/A (RCT)	1 year	Median time (IQR) 9 years post-transplant (5-18)	--	Median eGFR (IQR) 60 mL/min/1.73 m^2 (35-69) in FELZ vs. 36 mL/min/1.73 m^2	**Banff 2019 Criteria** • g score, median: 1 in FELZ vs. 2 in placebo • ptc score, median: 2 in FELZ vs. 2 in placebo • cg score, median: 1 in FELZ vs. 1 in placebo	13/22 (59%) had class II DSA 8/22 (36%) with mean MFI of DSA >10,000

								(31-43) in placebo		
Obinutuzumab (OBTZ)										
Favi, et al. [57] (n = 2)	Single-center retrospective case series in Italy	Kidney	**Acute AMR**	6 (S3, C0, O3)	3 years	Patient 1: POD 6 Patient 2: POD 13	Patient 1: POD 41 Patient 2: POD 21	Patient 1: SCr 4.4 mg/dL Patient 2: SCr 2.2 mg/dL	**Banff 2019 Criteria** • Patient 1: g2, ptc2, C4d3, cg0, i-IFTA0 • Patient 2: g1, ptc2, C4d3, cg0, i-IFTA0	Patient 1: median MFI (IQR) 10,299 (2,171-14,768) Patient 2: median MFI (IQR) 18,809 (5,981-19,519)

NOS = Newcastle-Ottawa Scale; ISHLT = International Society for Heart and Lung Transplantation; AHA = American Heart Association; DSA = donor specific antibodies; TCZ = tocilizumab; AMR = antibody mediated rejection; IQR = interquartile range; -- = not reported by study; SCr = serum creatinine; g = glomerulitis; ptc = peritubular capillaritis; cg = glomerular basement membrane double contours; HLA = human leukocyte antigen; MFI = mean fluorescence intensity; iDSA = immunodominant donor specific antibodies; cAMR = chronic active AMR; IVIg = intravenous immunoglobulin; RTX = rituximab; PLEX = plasmapheresis; SD = standard deviation; eGFR = estimated glomerular filtration rate; IF/TA = interstitial fibrosis and tubular atrophy; AT1R Ab = angiotensin II type 1 receptor antibodies; BTZ = bortezomib; SOC = standard of care; ACR = acute cellular rejection; t = tubulitis; i = interstitial inflammation; dnDSAs = de novo DSAs; rATG = rabbit anti-thymocyte globulin; ci = interstitial fibrosis; ct = tubular atrophy; MVI = microvascular inflammation; FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; CLAD = chronic lung allograft dysfunction; LVEF = left ventricular ejection fraction; pAMR = pathological antibody mediated rejection; CAV = cardiac allograft vasculopathy; CLAZ = clazakizumab; N/A = not applicable; RCT = randomized controlled trial; CFZ = carfilzomib; MRI = magnetic resonance imaging; DARA = daratumumab; IdeS = imlifidase; cv = vascular narrowing; FELZ = felzartamab; OBTZ = obintuzumab; POD = post-operative day.

Table 2 Efficacy and Safety Outcomes.

Reference Organ-Indication	Graft Survival	Patient Survival	Efficacy			Safety	
			Graft function	Histology	DSA	AEs	Discontinuations
				Tocilizumab (TCZ)			
Pottebaum, et al. [30] (n = 7) Kidney - Acute AMR	71.4% at a median follow-up of 3 months	--	SCr remained stabilized or improved Median SCr change (IQR) -0.6 mg/dL (-2.1 to 0.05)	--	4/6 (67%) patients had ≥50% reduction in iDSA MFI 2/6 (33%) patients had iDSA stabilization Median (IQR) change of iDSA MFI -3,576 (-12,895 to -1,095)	2/7 (29%) had AEs • CMV esophagitis (n = 1) • Potential hypersensitivity (n = 1)	7/7 (100%) patients • Completion of therapy (n = 3) • CMV esophagitis (n = 1) • Potential hypersensitivity (n = 1) • Multiple comorbidities (n = 1) • Malignancy (n = 1)
Pearl, et al. [31] (n = 25) Kidney (Pediatric) - Acute AMR and cAMR	96%	--	Renal function remained stable Mean eGFR change (95% CI): -3.12 mL/min/1.73 m^2/year (-6.36 to 0) pre-TCZ vs. -1.43 mL/min/1.73 m^2/year (-5.57 to 2.72) post-TCZ	19/25 (76%) patients had a biopsy at a median (IQR) 396 days post-TCZ (396-412.5) • Reduction in ptc (p = 0.015) and C4d scoring (p = 0.009) • No significant impact on scores for glomerulitis • Statistically significant increase in cg score (p = 0.018) over the	No significant decrease in iDSA MFI in all 25 patients On a subset analysis of the 18 patients with DSA at the start of TCZ, there was a significant decrease in iDSA strength (p = 0.049)	4/25 (16%) had quantifiable viremias • EBV (n = 1) • BK (n = 3) 21/25 (84%) had blood count abnormalities • Anemia (n = 9) • Thrombocytopenia (n = 1) • Neutropenia (n = 2)	10/25 (40%) patients • Not AEs (n = 5) • AEs (n = 3) • Graft loss (n = 1) • On hold due to JC viremia (n = 1)

				follow-up period, but no increase in IF/TA score		3/25 (12%) with liver enzyme elevations that were transient	
Choi, et al. [32] (n = 36) Kidney - cAMR	80% at 6 years	91% at 6 years	eGFR remained stable post-treatment over 36 months in adults, and over 18 months in pediatrics (6-17 years of age) Numerical values not reported	Obtained pre- & post-TCZ for 9/36 (25%) patients • Significant reductions in C4d+ deposition (p = 0.0318) and g+ptc scores (p = 0.0175) after treatment	iDSA declined significantly beginning at 24 months (p = 0.043)	13/36 (36%) had infectious AEs • CMV (n = 5) • BK (n = 2) • Trichodysplasia spinulosa (n = 1) • Bacterial infections (n = 7) 3/36 (8%) had cardiovascular complications • Stroke (n = 1) • NSTEMI (n = 2) 8/36 (22%) developed HGG (IgG <600 mg/dL)	4/36 (11%) patients • Medical reasons (n = 1) • Financial reasons (n = 3)

Lavacca, et al. [33] (n = 15) Kidney - cAMR	93.3% at a median follow-up of 20.7 months	--	eGFR and proteinuria stabilized Median eGFR decline -10.5 mL/min/1.73 m^2/year before cAMR diagnosis vs. -4.4 mL/min/1.73 m^2/year after diagnosis Proteinuria at diagnosis 1.1 g/day vs. 1 g/day at 12 months	Significant reduction in microvascular inflammation • Median g+ptc score (IQR): 3 (2-4) pre-TCZ vs. 2 (1-2.5) post-TCZ (p = 0.014) No transplant glomerulopathy, C4d deposition or IF/TA progression	Significant reduction of DSAs Median iDSA MFI (IQR): 22,600 (21,700-23,700) pre-TCZ vs. 18,200 (12,650-22,150) post-TCZ (p = 0.002)	5/15 (33%) had bacterial infections • Urinary tract infection (n = 4) • Lower respiratory tract infection (n = 1) 4/15 (27%) developed HGG (IgG <450 mg/dL) 3/15 (20%) had asymptomatic mild alterations in liver enzymes	1 patient discontinued TCZ (due to development of interstitial lung disease) Unclear if any other patients discontinued TCZ as not reported explicitly
Kumar, et al. [34] (n = 10) Kidney - cAMR	80% at median follow-up of 12 months	90% at median follow-up of 12 months	Mean eGFR (SD) remained stable: 42 mL/min/1.73 m^2 (18) to 37 mL/min/1.73 m^2 (24) (p = 0.27) Mean proteinuria (SD) remained unchanged: 1.6 g/g (1.1) to 1.9 g/g (2.3) (p = 0.70)	No improvement in mean g+ptc scores (SD): 4.8 (1.4) to 4.2 (2.0) (p = 0.39) Numerical worsening of mean ci+ct scores (SD): 2.5 (0.8) to 3.3 (1.7) (p = 0.38)	Mean DSA MFI (SD) unchanged pre- and post-therapy: 7,272 (6,698) to 6,273 (8,480) (p = 0.63)	9/10 (90%) had AEs • Infection (n = 4) • Leukopenia (WBC < 4 × 10^3 cells/mm^3) (n = 5)	4 patients discontinued/interrupted TCZ due to infection Unclear if any other patients discontinued TCZ as not reported explicitly

Massat, et al. [35] (n = 9 TCZ + SOC vs. n = 37 SOC) Kidney - cAMR	1 year graft survival: 66.7% in TCZ + SOC vs. 81.1% SOC (log rank p = 0.26)	100%	Median eGFR decline (range) not different between groups: -4.0 mL/min/1.73 m^2/year (5.0 to -33.0) in TCZ + SOC vs -2.9 mL/min/1.73 m^2/year (30.0 to -45.0) in SOC (p = 0.18)	Follow biopsies available for 7/9 (78%) in TCZ + SOC & 14/37 (38%) in SOC • Mean t+i scores (SD) decreased with TCZ: 1.78 (1.40) to 0.57 (0.79) (p = 0.07) and remained stable with non-TCZ: 0.75 (1.25) to 1.0 (1.30) (p = 0.47)	Mean change of DSA (SD): -48% (44) in TCZ + SOC vs. +107% (94) in SOC for class I (p = 0.03) and -50% (20) in TCZ + SOC vs. +158% (38) in SOC for class II (p = 0.01)	Infection: 6/9 (67%) in TCZ + SOC vs. 17/37 (46%) in SOC (p = 0.46)	--
Noble, et al. [36] (n = 40) Kidney - cAMR	85% at a median follow-up of 7 months Patients who lost their graft had more severe cAMR at time of TCZ initiation	--	eGFR remained stable from baseline: mean eGFR at 12 months (SD) 41.6 mL/min/1.73 m^2 (17) (p = 0.102)	38/44 (70%) patients had a biopsy after TCZ therapy • Number of biopsies with a cg score ≥2 significantly increased over time (p = 0.037) • Mean cg score (SD) was higher in >17-month biopsies vs. baseline: 2.4 (0.8) vs. 1.5 (0.9) (p = 0.053)	--	--	--

				• Mean IF/TA score (SD) decreased in 9-12-month biopsies vs. baseline: 0.6 (0.6) vs. 1.1 (0.8) (p = 0.053)			
Khairallah, et al. [37] (n = 38) Kidney - cAMR	95% at a median follow-up of 21 months	--	eGFR remained stable from baseline: mean eGFR at 6 months (SD) 36 mL/min/1.73 m^2 (15) Difference of eGFR slope between pre-/post-TCZ in patients with DSA at time of TCZ initiation: +2.5 mL/min/1.73 m^2/month (p = 0.02) No significant change in mean proteinuria (SD): 0.6 g (0.5) pre-TCZ vs 1.5 g (2) post-TCZ (p = 0.07)	19/38 (50%) patients had a biopsy at a median (IQR) of 5.1 months post-TCZ initiation (2-9.8) • Significant improvement in mean interstitial inflammation scores (IQR): 1 (0-1) to 0 (0-1) (p = 0.03) • Other scores (C4d+, ptc, arteritis, glomerulitis, tubulitis) remained stable	No significant change in DSA	12/38 (32%) had infections • BK viremia (n = 3) • CMV viremia (n = 3) • EBV viremia (n = 1) • Zoster (n = 1) • Cellulitis with bacteremia (n = 1) • Pneumonia n = 1) • Pyelonephritis (n = 3) 15/38 (39%) had leukopenia (WBC <3 × 10^9/L) 16/38 (42%) had thrombocytopenia	18/38 (47%) patients after a median administration time (IQR) of 10.4 months (4.9-15.8) • Kidney function stabilized (n = 3) • HPV positive tonsillar cancer (n = 1) • Infection (n = 4) • Patient preference (n = 3) • Diverticulitis (n = 1) • Non-compliance (n = 1) • Insurance coverage (n = 1) • Recurrent rejection (n = 2) • Graft failure (n = 2)

						(PLT <150 × 10^3 PLT/microL) 7/38 (18%) with liver enzyme elevations, 1 of which had >2.5× ULN	
Boonpheng, et al. [38] (n = 11) Kidney - cAMR	100% at 18 months	--	eGFR remained stable from baseline: mean eGFR (SD) 56 ml/min/1.73 m^2 (17) at 6 months (p = 0.25) Of the 6 patients who completed ≥12 months of TCZ, there was no significant difference between mean pre-TCZ eGFR (SD): 63 ml/min/1.73 m^2 (20), eGFR at 6 months: 59 ml/min/1.73 m^2 (18) (p = 0.29) and eGFR at 12 months: 60 ml/min/1.73 m^2 (24) (p = 0.48)	2/11 (18%) patients had biopsies at 16 months after TCZ therapy • g+ptc score decreased in both patients (4 to 3, and 5 to 0)	Of the 6 patients with follow-up data, iDSA MFI decreased on average 8% at 6 months (p = 0.13) Of the 4 patients who completed ≥12 months of TCZ, iDSA MFI decreased on average 7% at 6 months (p = 0.17) and 29% at 12 months (p = 0.047)	2/11 (18%) with moderate-severe infections • Severe herpes zoster and uncomplicated diverticulitis (n = 1) • Mild SARS-CoV-2 infection 3-4 months after TCZ, and then uncomplicated C. difficile colitis (n = 1)	--

			Proteinuria decreased 41% and 17% from baseline at 3 months (p = 0.07) and 6 months (p = 0.35) respectively Of the 6 patients who received ≥12 months of TCZ, average proteinuria decreased from baseline 1.19 g/g to 0.97 g/g at 12 months (p = 0.70)				
Chamoun, et al. [39] (n = 5) Kidney - cAMR	80%	80%	eGFR and proteinuria worsened Mean eGFR (SD) 46 mL/min/1.73 m^2 (15) pre-TCZ vs. 36 mL/min/1.73 m^2 (16) post-TCZ Mean proteinuria (SD) 3.2 g/g (4.0) pre-TCZ vs. 6.9 g/g (11.0) post-TCZ	4/5 (80%) patients had biopsy results post-TCZ initiation • Mean g+ptc scores (SD): 4.2 (0.8) pre-TCZ vs. 4.3 (1.0) post-TCZ (p = 0.936) • Mean cg scores (SD): 1.2 (0.4) pre-TCZ vs. 1.8 (1.0) post-TCZ (p = 0.287)	Not assessed; 4/5 (80%) patients did not have DSAs at time of AMR diagnosis	1/5 (20%) with severe cytopenia/CMV viremia	2/5 (40%) patients • Severe cytopenia/CMV viremia (n = 1) • Graft failure (n = 1)

Sangermano, et al. [40] (n = 6) Kidney (Pediatric) - cAMR	50%	--	eGFR remained stable at 6 months post-TCZ, but 3 patients had graft loss Mean proteinuria 1.3 g/24 h pre-TCZ vs. 1 g/24 h post-TCZ	4/6 (67%) patients had biopsy at a median of 7.5 months from TCZ initiation • No significant improvement in microvascular inflammation scores (g+ptc) • Worsening in overall chronicity (ci, ct, cg, cv, IF/TA)	No impact on DSA: mean MFI (SD) 18,620 (594) post-TCZ	1 case of uncomplicated pneumonia	--
Noble, et al. [41] (n = 45 cAMR, n = 19 MVI without DSA or C4d deposition) Kidney- cAMR, MVI without DSA or C4d deposition	93.7% at 1 year	98.4% at 1 year	eGFR trajectory significantly decreased after TCZ: -1.2 ± 0.2 mL/min/1.73 m^2/month pre-TCZ vs. 0.03 ± 0.2 mL/min/1.73 m^2/month post-TCZ (p = 0.001) • This difference remained statistically significant in the subgroup analysis of both cAMR patients (p = 0.038)	Only at the France center, surveillance biopsies were performed 1 year after starting TCZ (n = 39) • A significant decrease was observed in the g score (p = 0.014) but not in the ptc, g+ptc, c4d and cg scores • 29.3% had a g score = 3 pre-TCZ vs. 22% at 1-year	The percentage of patients with DSA decreased from 63.9% to 38.9% (p < 0.001) Median MFI (IQR) decreased from 9,537 (1,426-15,075) to 7,250 (3,100-14,975) (p = 0.001)	5/64 (7.8%) with infections • Peritonitis (n = 1) • Cryptococcosis disease (n = 1) • CMV disease (n = 1) • Tuberculosis (n = 1) • Campylobacter infection (n = 1) 1/64 (1.6%) with transaminase elevations (AST/ALT >4× ULN)	13/64 (20.3%) patients • Histological or clinical stabilization (n = 7) • Infection (n = 5) • Transaminase elevations (n = 1)

			and MVI without DSA C4d deposition patients (p = 0.007) Urine albumin-to-creatinine ratio declined from 1.0 ± 1.3 g/g pre-TCZ to 0.6 ± 0.7 at 1-year post-TCZ (p = 0.033)	post-TCZ (p = 0.032)			
January, et al. [42] (n = 9 TCZ vs. n = 18 non-TCZ) Lung – Acute AMR	88.9% in TCZ vs. 50% in non-TCZ (p = 0.049) Mean follow-up of 211 days in TCZ vs. 261 days in non-TCZ	--	Mean FEV1 (SD) 1.24 L (0.81) TCZ vs. 1.45 L (0.83) non-TCZ (p = 0.686) Mean FVC (SD) 1.90 L (0.78) TCZ vs. 2.08 L (0.88) non-TCZ (p = 0.818)	--	TCZ resulted in more clearance of DSA, lower recurrence of new DSA, development of new DSA, and less progression (not statistically significant)	Infection • 5/9 (56%) in TCZ vs. 11/18 (61%) in non-TCZ Transaminase Elevations • 2/9 (22%) in TCZ vs. 2/18 (11%) in non-TCZ, resolved without intervention	5/9 (55.5%) patients • Reason for discontinuation not reported
Pottebaum, et al. [43] (n = 7) Heart - Acute AMR	85.7% Duration of TCZ:	--	LVEF improved to a median of 60% (p < 0.05)	pAMR • 3/7 (42.9%) pAMR0 • 0/7 (0%) pAMR1 • 0/7 (0%) pAMR 2	iDSA improved to median MFI of 21,175, but no consistent effect on DSAs was observed	7/7 (100%) had AEs after TCZ • Leukopenia (WBC <3,000 cells/uL) (n = 1)	3/7 (42.8%) patients • None discontinued TCZ due to AEs

	median (IQR) 15 months (10-21) Outcomes: at 4-6 months			• 4/7 (47%) no assessment CAV grade • 2/7 (28.6%) with 0 • 0/7 (0%) with 1 • 5/7 (71.4%) with 2-3		• Neutropenia (ANC <1,500 cells/uL) (n = 1) • Thrombocytopenia (PLT <100,000 cells/uL) (n = 3) • Mild transaminase elevations (AST/ALT ≤ ULN) (n = 1)	
				Clazakizumab (CLAZ)			
Doberer, et al. [44] (n = 20) Kidney - Late active or cAMR	100%	--	Part A (double-blind 12-week period): mean eGFR slope (95% CI) -0.96 mL/min/1.73 m^2 (-1.96 to 0.03) CLAZ vs. -2.43 mL/min/1.73 m^2 (-3.40 to -1.46) placebo (p = 0.04) Part B (open-label 40-week period): patients switched from placebo to CLAZ showed significant improvement in the	20 index, 20 11-week follow-up, and 18 51-week follow-up biopsies performed; no indication biopsies performed 11-week biopsies: no significant inter-group differences in rejection-related molecular and morphologic scores; no meaningful changes in AMR phenotypes	Part A: median DSA MFI (IQR) decreased to 77% (63-101) from baseline in CLAZ vs. 103% (94-104) in placebo (p = 0.035) Part B: led to a further decrease of DSA levels (p < 0.001)	Part A: 3 serious AEs in CLAZ vs. 1 serious AE in placebo Part B: 9 serious AEs, including 5 infections Overall, 9/20 (45%) patients had colon diverticulosis, among them, 2 patients who developed diverticulitis	2/20 (10%) patients withdrew in CLAZ arm due to diverticulitis

			eGFR slope ($p < 0.001$); patients in CLAZ continuation had no significant change in the mean eGFR slope (95% CI): -0.29 mL/min/1.73 m^2/month (-0.85 to 0.26) vs. -0.64 mL/min/1.73 m^2/month (-1.13 to -0.14) ($p = 0.37$)	51-week biopsies: significant decrease in molecular AMR ($p = 0.020$) and "all rejection" scores ($p = 0.037$); ACR scores remained negative at all time points • 3/4 (75%) patients who had resolution of AMR activity at 51-weeks were C4d negative and had g+ptc sum score ≤3 at baseline			
Jordan, et al. [45] (n = 10) Kidney - cAMR	80%	--	Mean eGFR (SD) stabilized at 41.6 mL/min/1.73 m^2 (14) and 38.1 mL/min/1.73 m^2 (20.3), at 12 and 24 months respectively	Patients who completed the first 6 months of therapy underwent 6-month protocol biopsy (n = 9) • g+ptc 4.38 to 3.25 ($p = 0.080$) • cg 2.38 to 2.00 ($p = 0.518$) • C4d 1.26 to 1.00 ($p = 0.678$) • i-IF/TA 0.813 to 1.75 ($p = 0.07$)	Mean DSA MFI (SD): • 0 months: 9,625 (5,745) (n = 10) • 12 months: 5,469 (7,675) ($p = 0.21$, n = 8) • 24 months: 4,167 (7,188) ($p = 0.12$, n = 7)	14 infections (42% of the AEs reported); 2 with sepsis requiring hospitalization	No patients discontinued CLAZ due to AEs

Carfilzomib (CFZ)							
Cody, et al. [46] (n = 2) Kidney - Acute AMR (Pediatric)	100%	100%	Patient 1: SCr returned to baseline Patient 2: SCr stable at 1.2-1.3 mg/dL	Patient 1: histology improved prior to CFZ Patient 2: histology improved after CFZ	Patient 1: POD 139 (40 days after CFZ) DSAs were below detection threshold Patient 2: ~1-year post-AMR diagnosis, low levels of two class II DSA remained with MFI between 2,000-2,600	Patient 1 • Stage 1 AKI with 1st two CFZ cycles (doses 1-4), that resolved with fluid administration • Given IV fluids (10 mL/kg) pre & post-CFZ with N-acetylcysteine (10 mL/kg) (q12h for 4 doses) with the 3rd cycle (doses 5-6), and no AKI was observed Patient 2 • Stage 1-2 AKI with the 2nd cycle (doses 3-4), with SCr increase from 0.95 mg/dL during 1st round to 1.68 mg/dL • Admitted for IV fluids with	Patient 2 did not complete all 6 doses of CFZ due to AKI

						improvement in SCr to 1.46 mg/dL on discharge	
Jamal, et al. [47] (n = 2) Liver - Acute AMR	50%	100%	Patient 1: LFTs normalized Patient 2: LFTs did not show improvement	--	Patient 1: DSAs significantly reduced • Post-PLEX (obtained 1 month after final procedure): negative Patient 2: DSAs marginally reduced • Post-PLEX (obtained 2 weeks after final procedure): DQ2 MFI 2,091, DQ4 MFI 23,474, DP1 MFI 1,260	Patient 1 • Mild pneumonia Patient 2 • Not reported	Patient 1 did not complete the final two sessions of cycle 2 due to a mild pneumonia Patient 2 discontinued treatment after 10 sessions and was referred for repeat liver transplantation
Ensor, et al. [48] (n = 14) Lung - Acute AMR	--	100% at 120 days 50% at post-CFZ therapy (follow-	Mean FEV1 was unchanged after CFZ at 1.91 L and subsequently rose to a maximum of 2.13 L (p = 0.01)	--	Median DSA MFI (IQR) fell from 7,665 (3,230-11,874) to 1,878 (653-7,791) after therapy	2/14 (14.3%) patients experienced AKI • Full recovery seen in 1 patient; the other patient had multiple	12/14 (85.7%) patients completed the full course of CFZ based therapy 2/14 (14.3%) required either CFZ dose

		up period not reported)	Responders had less CLAD development or progression vs. non-responders: 25% vs. 83% (p = 0.04)		(p = 0.001) and to 1,400 (850-8,287) 2 weeks later (p = 0.001) Median DSA C1q MFI fell from 3,596 (714-14,405) to <30 after therapy (p = 0.01) and remained <30 2 weeks later (p = 0.02) Non-responders had significantly more high-titer DSAs (p = 0.001) pre-CFZ and had longer time after DSA detection to CFZ-based therapy (p = 0.05)	additional sources of nephrotoxicity and developed end-stage renal disease 7/14 (44%) patients developed thrombocytopenia, which recovered fully • 1 patient had severe thrombocytopenia (PLT < 5,000) after dose 2, requiring discontinuation of further CFZ	adjustment or delayed time to administration for AEs
Pham, et al. [49] (n = 28) Lung - Acute AMR	--	42.9% Median time from CFZ to death (IQR) 0.8 years (0.4-2.0)	Mean decline in %FEV1 (95% CI) -0.75% per month (-1.29 to -0.21) pre-CFZ	--	11/14 (78.6%) with class I dnDSA had complete resolution of DSA 6/28 (21.4%) with class II dnDSA had	8/28 (28.5%) developed AKI within 7 days of receiving CFZ • SCr increased by a median of 0.5 mg/dL	7/28 (25%) did not complete all 6 doses of CFZ due to active infection, clinical decompensation or withdrawal of care

		1 year patient survival: 78.0% CFZ-responders vs. 20.0% CFZ non-responders (p = 0.004)	Mean decline in %FEV1 (95% CI) -0.59% per month (-0.35 to 1.52) post-CFZ		complete resolution of DSA Class I DSA MFI decreased from median (IQR) 3,540 (2,378-5,490) with a median MFI reduction of 2,815 (2,284-4,297) (79.5% reduction, p = 0.01) Class II DSA MFI decreased from median (IQR) 8,291 (6,875-10,628) to 5,120 (2,190-8,074) (37.1% reduction, p = 0.01)	• All patients achieved renal recovery without intervention 15/28 (53.5%) experienced a bacterial infection	
Razia, et al. [50] (n = 17 CFZ, n = 36 RTX) Lung - Acute AMR	--	Cumulative 1-year survival: 87.5% (single CFZ event), 93.1% (single RTX event), 100% (≥2 drug events), p = 0.657	CFZ group: Mean % predicted FEV1 (SD) did not improve significantly at 3 months [54 (34-75) vs. 42 (35-68), p = 0.135] or 6 months after	--	Median MFI (IQR) at DQ and DR loci significantly decreased after treatment with CFZ or RTX • Pre- and post-CFZ DQ: 12,789 (5,518-15,015) vs. 2,948	2/17 (12%) developed reversible CFZ-induced pneumonitis Prevalence of renal failure within 1 month of administration was	--

	treatment [50 (37-59) vs. 42 (35-68), p = 0.865] compared to FEV1 at the time of DSA elevation RTX group: Mean % predicted FEV1 (SD) improved significantly at 3 months [78 (62-87) vs. 67 (47-83), p = 0.003] and 6 months after treatment [76 (62-94) vs. 67 (47-83), p < 0.001] compared to FEV1 at the time of DSA elevation % predicted ΔFEV1 at 6 months after treatment was significantly higher in RTX vs. CFZ (12% vs. 2%, p = 0.002)			
Cumulative 3-year survival: 75% (single CFZ event), 82.8% (single RTX event), 85.7% (≥2 drug events), p = 0.43			(707-6,740), p < 0.0001 and DR: 1,880 (508-6,613) vs. 652 (538-1,280), p = 0.19 • Pre- and post-RTX DQ: 10,397 (5,750-16,300) vs. 1,171 (543-4,567), p < 0.0001 and DR: 3,439 (1,760-8,159) vs. 888 (0-2,117), p < 0.0001 The median ΔMFI (IQR) at DP, DQ, and DR loci was comparable between CFZ and RTX • ΔDP: 953 (953-953) vs. -450 (-619 to -281), p = N/A • ΔDQ: -9,139.5 (-11,712.5 to -3,770) vs. -6,805 (-11,610 to -2,719), p = 0.39	comparable between CFZ and RTX groups (17.6% vs. 5.6%, p = 0.313)

					• ΔDR: -830 (-6,291 to 541.5) vs. -2,064 (-5,696 to -521), p = 0.63		
Horn, et al. [51] (n = 8 CFZ, n = 2 BTZ) Heart - Acute AMR	90% at 1-year post-AMR treatment	--	Median LVEF post-AMR (IQR) 55% (39-63) with median change in LVEF post-AMR (IQR) 8% (2-32) 4/6 (66.7%) patients with graft dysfunction had recovered LVEF >40%	pAMR resolved in 5/7 (71.4%) patients at 1 year after treatment	MFI of strong DSAs had a median reduction (IQR) of 56% (13-89) in undiluted serum and 92% (53-95) at 1:16 dilution DSA with MFI >8,000 at 1:16 dilution was less responsive to treatment	7/8 (90%) experienced AKI • All episodes resolved after therapy was completed and prior to subsequent doses being administered 3/8 (38%) experienced thrombocytopenia but did not require a reduction in subsequent doses 1/8 (13%) experienced bacteremia prompting cessation of therapy	2/8 (25%) patients switched from CFZ to BTZ due to AKI in setting of cardiogenic shock

Daratumumab (DARA)							
Zhu, et al. [52] (n = 2) Kidney - cAMR (patient 1), Acute AMR (patient 2)	100%	--	Patient 1: SCr remained stable Patient 2: SCr remained stable (2.64 mg/dL at follow-up)	Patient 1: no follow-up histology Patient 2: g0, ptc1, cg1; had progression to mild cAMR	Patient 1: DSA MFI ~5000 at 1:4 diluted serum (unclear change, since baseline DSA was not reported as undiluted serum) Patient 2: DSA MFI 16,759 (decreased from baseline)	Mild flu-like symptoms in both patients Patient 2 had mild leukopenia (WBC 3-4 × 10^9/L), and Banff IA AMR at day 346 of treatment (tacrolimus level was 3.7 ng/mL)	Patient 1: discontinued DARA after 20 months Patient 2: discontinued DARA since DSA remained elevated, and SCr unchanged
Lemal, et al. [53] (n = 3) Kidney - Acute AMR	100%	--	SCr decreased in all patients, not numerically reported	Resolution of AMR on histology; Banff scores not reported	Decreased in all patients, not reported numerically	Mild infusion reactions	No patients required discontinuation of DARA
Osmanodja, et al. [54] (n = 2) Kidney - Acute AMR	100%	--	Remained stable in both patients Patient 1: SCr 1.5 mg/dL Patient 2: SCr 1.7 mg/dL	Partial response seen in patient 1: g2, ptc1, cg3, IF/TA0 Full response seen in patient 2: g0, ptc1, cg2, IF/TA1	DSA decreased or stabilized in both patients Patient 1: DR7: 5, DQ2: 0, B44: 0 Patient 2: DP2: 5269, Cw6: 511	Mild infusion reactions (nausea, vomiting), HGG, and leukopenia occurred in both patients Patient 1 developed SARS-CoV-2 infection & was treated with remdesivir × 3 days	No patients required discontinuation of DARA

				Imlifidase (IdeS)			
Halleck, et al. [55] (n = 18 IdeS vs. n = 10 PLEX) Kidney - Acute AMR (n = 9), cAMR or mixed rejection (n = 19)	77.8% IdeS vs. 90% PLEX	94.4% IdeS vs. 100% PLEX	Overall mean difference of 6 mL/min/1.73 m^2 in eGFR between the groups (p = 0.816)	Biopsies at 6 months (n = 13 IdeS, n = 10 PLEX) • Overall, no improvement in histology except for 1 patient in IdeS and 2 patients in PLEX with resolution of AMR	Reduction in DSA (range) 5 days following start of treatment: 97% (85-98) IdeS vs. 42% (5-82) PLEX Median time (range) to maximum DSA reduction: 5 hours (2-72) IdeS vs. 9 days (2-180) PLEX	No differences between the groups 1 patient in IdeS required PLEX for AKI AE related to IdeS 1 death of unknown cause in IdeS (not related to IdeS)	--
				Felzartamab (FELZ)			
Mayer, et al. [56] (n = 11 FELZ vs. n = 11 placebo) Kidney - Acute AMR (n = 7), cAMR (n = 15)	100% FELZ vs. 91% placebo	100% for both groups	1-year mean eGFR slope (95% CI) -0.39 mL/min/1.73 m^2 (-5.47 to 4.69) FELZ vs. -4.53 mL/min/1.73 m^2 (-9.83 to 0.77) placebo	Resolution of morphologic AMR at week 24: 9/11 (82%) in FELZ vs. 2/10 (20%) in placebo, difference of 62% (95% CI 19-100), risk ratio of 0.23 (95% CI 0.06-0.83) Recurrence of AMR at week 52 in 3/9 (33.3%) patients who had a response to FELZ	Modestly lower values for the MFI of peak DSA with FELZ treatment	Mild or moderate infusion reactions during the 1st infusion in 8 FELZ patients vs. none in placebo (p = 0.001) Drug-related AEs: 27 in FELZ vs. 11 in placebo Infection: 10/11 (91%) FELZ vs. 7/11	No patients discontinued due to AEs

						(64%) placebo (p = 0.31)	
Obintuzumab (OBTZ)							
Favi, et al. [57] (n = 2) Kidney - Acute AMR	100%	--	Patient 1: SCr 1.3 mg/dL Patient 2: SCr 1.9 mg/dL	Patient 1 (9 months): g1, ptc1, C4d0, cg0, i-IF/TA0 Patient 2 (6 months): g0, ptc0, C4d0, cg0, i-IF/TA0	Patient 1: All DSA undetectable except DP13 (MFI 1700) Patient 2: not reported	Patient 1: infusion related reactions (nausea, vomiting, tachycardia), camphylobacter jejuni infection, asymptomatic CMV viremia, asymptomatic SARS-CoV-2, intermittent leukopenia Patient 2: infusion related reactions (nausea, tachycardia), asymptomatic CMV viremia, SARS-CoV-2 infection, intermittent leukopenia	No patients discontinued due to AEs

DSA = donor specific antibodies; AEs = adverse effects; TCZ = tocilizumab; AMR = antibody mediated rejection; SCr = serum creatinine; IQR = interquartile range; iDSA = immunodominant donor specific antibodies; MFI = mean fluorescence intensity; CMV = cytomegalovirus; cAMR = chronic active AMR; eGFR = estimated glomerular filtration rate; g = glomerulitis; ptc = peritubular capillaritis; NSTEMI = non-ST segment elevation myocardial infarction;

HGG = hypogammaglobulinemia; IF/TA = interstitial fibrosis and tubular atrophy; SD = standard deviation; ci = interstitial fibrosis; ct = tubular atrophy; WBC = white blood cells; SOC = standard of care; t = tubulitis; i = interstitial inflammation; cg = glomerular basement membrane double contours; EBV = Epstein-Barr virus; PLT = platelets; ULN = upper limit of normal; HPV = human papillomavirus; cv = vascular narrowing; MVI = microvascular inflammation; FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; LVEF = left ventricular ejection fraction; pAMR = pathological antibody mediated rejection; CAV = cardiac allograft vasculopathy; ANC = absolute neutrophil count; AST = aspartate aminotransferase; ALT = alanine transaminase; CLAZ = clazakizumab; ACR = acute cellular rejection; CFZ = carfilzomib; AKI = acute kidney injury; LFTs = liver function tests; CLAD = chronic lung allograft dysfunction; dnDSAs = de novo DSAs; RTX = rituximab; BTZ = bortezomib; DARA = daratumumab; IdeS = imlifidase; PLEX = plasmapheresis; FELZ = felzartamab; OBTZ = obintuzumab.

3.3 Tocilizumab

3.3.1 Kidney – Acute AMR

Two retrospective case series described tocilizumab primarily for the treatment of acute AMR in 32 kidney transplant recipients. Four patients had mixed acute AMR and acute cellular rejections (ACR), 18 had acute AMR alone, and 10 had cAMR. Tocilizumab 8 mg/kg IV monthly was given for 1-6 months in addition to conventional therapies (which included combinations of steroids, PLEX, IVIg, rituximab, or bortezomib) in Pottebaum, et al., and for a median of 12 months for patients who were refractory to combinations of IVIg, rituximab, steroids, PLEX, or bortezomib in Pearl, et al. 17/32 (53%) of patients discontinued tocilizumab, with nine discontinuing due complications. Patients were followed for a median of 3 months (IQR 3-6) post-tocilizumab in Pottebaum, et al., while follow-up period was not reported in Pearl, et al.; graft survival was 71.4% and 96% respectively. Renal function improved or stabilized during tocilizumab therapy in both studies. For Pottebaum, et al., a ≥50% reduction in immunodominant donor specific antibodies (iDSA) was observed in four patients with DSAs, iDSA stabilized in two patients, and one patient did not have DSAs checked after therapy. Pearl, et al., found a significant decrease in iDSA strength in the subset of patients who had DSAs at tocilizumab initiation. Follow-up histology was not reported in either of the studies. Given the small sample size, inclusion of cAMR patients, lack of a control, and heterogeneity of regimens used with tocilizumab, it is difficult to determine if tocilizumab significantly altered the course of acute AMR in kidney transplant recipients. It is also unclear if the complications observed were associated with tocilizumab [30, 31].

3.3.2 Kidney – Chronic Active AMR

Ten studies reported tocilizumab for treatment of cAMR and/or refractory AMR in kidney transplant recipients [32-41]. Of these studies, two were prospective open-label case series, seven were retrospective case series, and one study was a retrospective cohort study comparing tocilizumab plus standard of care (SOC) to historical SOC. Tocilizumab was added as rescue therapy for refractory cAMR in six studies, two focused on tocilizumab as first line therapy in cAMR, and two discussed tocilizumab in both first line and rescue therapy. The majority of patients were treated with tocilizumab 8 mg/kg IV monthly for 3-25 months. One study also examined subcutaneous dosing with 162 mg every 15 days.

Overall graft survival with tocilizumab therapy was 50-100%, with median follow-up of 5.8-20.7 months. Renal function remained stable in seven studies, worsened in two studies, and was not different between the tocilizumab and the non-tocilizumab groups in the cohort study. The effect of tocilizumab on DSA was variable, with three studies reporting a statistically significant decline in DSA, and the other seven studies reporting either a DSA change of unknown significance or non-significant change in DSA. A reduction in microvascular inflammation (g+ptc score) was reported in four studies, with two studies finding statistical significance. No other trends were seen among other histological parameters. In the studies that reported the following specific safety outcomes, 49/194 (25.3%) experienced infection, 21/53 (39.6%) experienced leukopenia, 12/51 (23.5%) experienced hypogammaglobinemia, and 11/117 (9.4%) experienced asymptomatic liver enzyme elevations, which were potentially secondary to tocilizumab [32-41].

Both Choi, et al. and Lavacca, et al. found favorable results where renal function was stabilized, microvascular inflammation was significantly reduced, and DSA strength was significantly decreased [32, 33]. In contrast, a subsequent study from Kumar, et al. failed to find any improvement in microvascular inflammation or DSA strength but found that renal function remained stable. This finding could be secondary to higher baseline microvascular inflammation in comparison to the two proceeding studies [34]. Massat, et al. evaluated tocilizumab as add-on therapy in comparison to SOC and did not find any differences in graft survival or decline in eGFR between the two groups despite the serological and histological improvements in tocilizumab patients [35]. Noble, et al. (2021) found that patients who lost their allograft had both lower eGFR (mean ± SD: 24.5 ± 16 vs. 46.3 ± 15 mL/min/1.73 m^2, p = 0.006) and higher proteinuria (mean ± SD: 1.8 ± 1 vs. 0.8 ± 0.9 g/L, p = 0.022) at the time of AMR diagnosis in comparison to those who did not. As expected, patients who had more severe histology (ct = 3, ci = 3, v =2) were more likely to lose their graft in comparison to those who did not ($p < 0.05$) [36]. Khairallah, et al. found that tocilizumab stabilized renal function, with significant improvement in interstitial inflammation, and no significant effect on DSA [37]. Similarly, Boonpheng, et al. found stabilization of renal function, numerical improvements in microvascular inflammation, and no significant effect on DSA [38]. Chaumon, et al. and Sangermano et al. found worsened renal function, and no differences in histology [39, 40]. A subsequent study from Noble, et al. (2025), examined tocilizumab in both cAMR and those with microvascular inflammation (MVI) without DSA or C4d deposition. Renal function was stabilized with tocilizumab in both patient groups, with significant decreases in the g score in those who had surveillance biopsies at 1 year. In this study, younger age (OR = 0.95, p = 0.02), MVI without DSA or C4d deposition (OR = 5.1, p = 0.01) and lower chronic glomerulopathy score (OR = 4.5, p = 0.02) were associated with treatment response (defined as eGFR stabilization or improvement). Subcutaneous administration was also not associated with a reduced treatment response (p = 0.421) [41]. Synthesizing these findings, tocilizumab in cAMR seemed to generally stabilize renal function, with variable effect on histological parameters and DSA strength. Patients with cAMR were more likely to benefit from tocilizumab if baseline microvascular inflammation was lower. Interestingly, one study's results suggested that tocilizumab may also have utility in earlier stages of graft inflammation even without the presence of DSA or C4d staining. However, the majority of studies that examined tocilizumab in cAMR in kidney transplantation were case series without a comparator.

3.3.3 Lung – Acute AMR

One single-center cohort study assessed tocilizumab in the treatment of acute AMR in lung transplant recipients. Patients who received combination therapy containing tocilizumab (n = 9) were compared to patients who received a non-tocilizumab regimen (n = 18). Therapies that were used in combination regimens included rituximab, carfilzomib, bortezomib, rabbit anti-thymocyte globulin (rATG), IVIg, extracorporeal photopheresis, and PLEX. Mean duration of tocilizumab therapy was 6 months (range 2-12). At an average follow up of 211 days (tocilizumab group) and 261 days (non-tocilizumab group), improved graft survival was observed with tocilizumab therapy in comparison to non-tocilizumab regimens (88.9% vs. 50%, p = 0.049). Non-statistically significant improvements in average FEV1 and FVC were also observed with tocilizumab therapy. Tocilizumab resulted in more clearance of DSA, lower recurrence of DSA, and lower development of de novo DSA, but none of these findings were statistically significant. Post-treatment infection rate was

similar between the tocilizumab and non-tocilizumab groups (56% vs. 61%). Of note, at this institution, no patients who received tocilizumab received PLEX vs. 38.9% of patients who received non-tocilizumab regimens received PLEX, and in general more therapies were given to non-tocilizumab treated patients. However, given that there was a favorable change in DSA strength in the tocilizumab treated patients, this was less likely to be a significant confounder. Tocilizumab may be considered as an adjunctive therapy in lung acute AMR due to its favorable impact on graft survival in comparison to non-tocilizumab regimens, but given the wide range of therapies that were given in conjunction to tocilizumab, the treatment effect of tocilizumab cannot be definitively ascertained from the findings of this study [42].

3.3.4 Heart – Acute AMR

One single-center case series assessed tocilizumab for acute AMR in heart transplantation. Of the seven patients included, four patients had refractory AMR, who all received PLEX, IVIg and rituximab prior to initiation of tocilizumab, and the other three patients received tocilizumab in conjunction with PLEX and IVIg for first line therapy. Median duration of tocilizumab therapy was 15 months (IQR 10-21), and patients were followed up at a range of 5-54 months after tocilizumab therapy initiation, at which graft survival was 85.7%. The one patient who expired had an autopsy that showed severe CAV. LVEF improved in all patients post-tocilizumab therapy with a median change of +17% (IQR 11-18), and all patients reported an improvement in functional capacity as measured by the New York Heart Association Functional Classification. Median change in LVEF for those who received tocilizumab for rescue therapy was similar to that of those who received tocilizumab as first line therapy (+17% vs. +15%). Three patients that had follow-up biopsy results showed an improvement from pre-tocilizumab biopsy findings. International Society for Heart and Lung Transplantation (ISHLT) CAV grade generally worsened with two patients having CAV grade 2-3 at baseline, to five patients having CAV grade 2-3 at follow-up. No consistent effect was observed on DSA. Tocilizumab as both first line and rescue therapy in this case series improved both echocardiographic measurements and functional capacity but failed to decrease risk of progression of CAV, demonstrating the difficulties with preventing the progression and development of CAV in patients who experience AMR [43].

3.4 Clazakizumab

3.4.1 Kidney – Late AMR

Two phase II studies to date have been published examining the use of clazakizumab for AMR in solid organ transplantation [44, 45]. Doberer, et al. conducted a randomized, double-blind, placebo-controlled pilot trial, where kidney transplant recipients with late acute or cAMR were randomized 1:1 to receive clazakizumab 25 mg SQ every 4 weeks (n = 10) or placebo (n = 10) for 12 weeks (part A), followed by a 40-week open-label extension during which all patients received clazakizumab (part B) with the last trial visit conducted at week 52 [44]. Jordan, et al. conducted an open-label single-arm trial of kidney transplant recipients with cAMR who received clazakizumab 25 mg SQ every 4 weeks for 12 months (n = 10). At 12 months, patients were provided the option to enter a long-term extension where they received clazakizumab 25 mg SQ every other month [45]. In the two studies, patients were enrolled at a median range of 8.2-10.6 years post-transplant, with 2/30

(6.7%) patients having acute AMR, and 28/30 (93.3%) patients having cAMR. In Doberer, et al., prior treatments for patients who had cAMR were not reported, but patients who had acute rejection treatment <3 months prior to screening were excluded from the trial [44]. In Jordan, et al., 8/10 (80%) patients had received previous therapies, all with a combination of either ritixumab and/or obinutuzumab with IVIg; additionally, 3/8 of these patients also received tocilizumab for 6 months [45]. Graft survival was not explicitly reported in Doberer, et al., and was 80% in Jordan, et al. Both studies demonstrated either stabilization or improvement of renal function and DSA, with the improvements reaching statistical significance in Doberer, et al. With extension of clazakizumab therapy beyond 12 weeks in Doberer, et al., and beyond 12 months with Jordan, et al., DSA was reduced further. In terms of histology, the 51-week biopsies demonstrated a significant decrease in molecular AMR ($p = 0.020$) and all rejection scores ($p = 0.037$) in Doberer, et al., and the 6 months biopsies demonstrated significant decreases in g+ptc score in Jordan, et al. In terms of safety, 9/20 (45%) of patients developed diverticulitis in Doberer, et al., with no patients experiencing this complication in Jordan, et al. Overall, 19/30 (63.3%) of patients experienced an infection under clazakizumab therapy. Given that clazakizumab demonstrated beneficial effects on DSA, histology, and eGFR decline, it showed some promise in altering the course of patients experiencing late AMR, meeting an unmet need [44, 45].

The subsequent phase III trial examining clazakizumab for kidney transplant recipients experiencing cAMR aimed to recruit approximately 350 kidney transplant recipients, randomized 1:1 to clazakizumab or placebo [58]. Unfortunately, in the interim analysis of 100 participants who completed 1-year of the study, investigators found that the study was unlikely to meet the primary efficacy outcome (time to composite of all-cause allograft loss or irreversible loss of allograft function), and the data and safety monitoring board recommended discontinuation of the study. The final analysis after the 1-year interim analysis of eGFR found no difference in Least Squares mean change from baseline eGFR at week 52 for clazakizumab in comparison with placebo, confirming that clazakizumab does not seem to attenuate renal function decline in cAMR [59].

Timing of rejection/therapy initiation was approximately 8-10 years post-transplant for the phase II trials but not reported in the phase III trial. Outcomes examined were similar among all three studies. In terms of follow-up, all studies utilized a follow-up period of 52 weeks or 12 months. Notably, baseline microvascular inflammation and chronicity scores were only reported in one of the studies. Therefore, baseline degree of cAMR progression cannot be compared among the studies, which would have had an important factor in interpretation of findings. Additionally, the number of participants included in the phase III study was significantly greater than that of the phase II studies, which may point to the possibility of a type II error found in the phase II studies.

3.5 Carfilzomib

3.5.1 Kidney – Acute AMR

In a case series of two pediatric kidney transplant recipients with AMR, carfilzomib was used in the setting of bortezomib intolerance. Patient 1 underwent treatment with rituximab, IVIg, and then PLEX and bortezomib, which was limited by thrombocytopenia and peripheral neuropathy. Patient 2 underwent treatment with PLEX and bortezomib, which was limited by peripheral neuropathy. Both were switched to carfilzomib, which resulted in a decrease in DSA MFI (Patient 1 cleared all three class II DSA; patient 2 cleared one class I DSA but continued to have low levels of two class II

DSA). Patient 1 already had histological improvements prior to carfilzomib treatment, while patient 2 experienced improvements after carfilzomib treatment. Both patients experienced acute kidney injury (AKI) under carfilzomib, which was treated with N-acetylcysteine and IV fluids pre- and post-therapy. Patient 1 finished six doses of carfilzomib 20 mg/m^2 (days 1, 2, 8, 9, 15, and 16), whereas patient 2 discontinued after four doses of carfilzomib given that SCr remained elevated even with IV fluid administration. After a follow-up period of approximately 1 year, SCr returned to pre-AMR baseline in patient 1, and SCr in patient 2 decreased but not back to the pre-AMR baseline. Since both patients underwent prior proteasome inhibition with bortezomib, it is difficult to differentiate if the improvement in DSA and SCr at the follow-up was due to carfilzomib vs. bortezomib. Additionally, carfilzomib is known to be associated with AKI, and there were differing effects of IV fluids and N-acetylcysteine in preventing AKI. Thus, carfilzomib should be used with caution in the solid organ transplant population [46].

3.5.2 Liver – Acute AMR

In a case series of two liver transplant recipients, carfilzomib 20 mg/m^2 (days 1, 2, 8, 9, 15, and 16) with PLEX for 2 cycles was utilized in patients with acute AMR refractory to steroids, IVIg and rituximab. Patient 1 presented with AMR features on biopsy at 10 days post-transplant, whereas patient 2 presented with ACR on biopsy and no evidence of AMR, but positive DSAs at 158 days post-transplant. Only patient 1 had demonstrated clinically significant normalization of LFTs and DSAs. Patient 2 later required repeat liver transplantation. Patient 1 discontinued carfilzomib early given a mild pneumonia that later resolved. Patient 2 discontinued treatment at the time of referral for retransplantation. Other specific adverse effects were not reported in this study. This case series shows that carfilzomib may be a potential therapy option used in acute AMR in liver transplantation, and treatment response may be improved with earlier recognition and treatment of AMR. Given that AMR occurs infrequently in liver transplantation, there are difficulties in timely diagnosis, and treatment strategies remain unclear in this population [47].

3.5.3 Lung – Acute AMR

Three single-center retrospective case series reported the use of carfilzomib for treatment of acute AMR in lung transplant recipients, with one of the three studies comparing carfilzomib therapy to rituximab therapy [48-50]. Number of carfilzomib cycles administered was not reported in any of the studies. Carfilzomib was administered in addition to PLEX and IVIg in Ensor, et al. and Pham, et al., and in addition to IVIg ± PLEX in Razia, et al. In Ensor, et al. and Razia, et al., carfilzomib was utilized as initial therapy, whereas in Pham, et al., 6/28 (21.4%) patients were given rituximab prior to carfilzomib, and 7/28 (25%) patients were given rATG prior to carfilzomib. As expected, AKI was associated with carfilzomib, occurring in 12/44 (27.2%) patients. FEV1 or % predicted FEV1 rose after carfilzomib therapy in one study and was unchanged in two studies [48-50]. The study that compared rituximab to carfilzomib found that % predicted ΔFEV1 at 6 months after treatment was significantly higher in the rituximab group than in the carfilzomib group (12% vs. 2%, $p = 0.002$) [50]. Carfilzomib significantly decreased DSA in all three studies, and in the two studies that looked at C1q fixing ability, carfilzomib also had significant effects in suppressing C1q fixing ability of DSAs [48-50]. The study that compared rituximab to carfilzomib found that median change in MFI was comparable, but carfilzomib had a shorter median interval to DSA rebound in comparison to

rituximab (4.8 vs. 15.6 months, p = 0.015) [50]. Ensor, et al. found that patients who had loss of C1q fixing ability of iDSA were less likely to develop CLAD or have progression of CLAD in comparison to those who did not (25% vs. 83%, p = 0.04) [48]. Razia, et al. found that cumulative CLAD free survival was similar between those who received carfilzomib in comparison to those who received rituximab (75% vs. 86.2%, p = 0.339) [50]. Follow-up histology was not reported in any of the studies.

Graft survival at last follow-up in Ensor, et al. and Pham, et al. were similar at 50% (post-carfilzomib therapy, follow-up period not reported) and 42.9% (median time to death was 0.8 years, IQR 0.4-2.0), respectively. Razia, et al. reported higher graft survival rates with carfilzomib: 87.5% at 1 year and 75% at 3 years. In terms of ISHLT AMR classification, the majority of patients had probable AMR in Ensor, et al. (50%) and Pham, et al. (64.3%), whereas the majority of patients had possible AMR in Razia, et al. (84.1%), suggesting that the former two studies had included more patients who had a higher likelihood of true AMR, which could have contributed to these findings. Baseline pulmonary function testing among the three studies did not demonstrate any association with outcomes.

Across all studies, DSA MFI significantly decreased with carfilzomib therapy, confirming the efficacy of carfilzomib in reduction of DSAs in acute AMR. Ensor, et al. found that non-responders had significantly more high-titer DSA pre-carfilzomib and longer time from DSA detection to therapy, showing that early initiation of carfilzomib may result in improved reduction of DSA. However, despite significant reductions in DSAs found with carfilzomib, altering the course of AMR and improving long term graft survival remains a challenge [48-50].

3.5.4 Heart – Acute AMR

In a single-center retrospective case series of heart transplant recipients treated with PLEX and proteasome inhibitors (n = 8 carfilzomib, and n = 2 bortezomib) for initial treatment of acute AMR, graft survival was 90% at 1 year after AMR diagnosis. Of the ten patients included, six presented with graft dysfunction at the time of AMR diagnosis. With proteasome inhibition, 4/6 (66.7%) patients had a recovered EF to >40% after treatment, with five of these patients being treated with carfilzomib. Pathologic AMR resolved in 5/7 (71.4%) patients within 1 year after treatment. Proteasome inhibition also resulted in reductions in MFI of strong DSAs in both undiluted serum and at a 1:16 dilution, with a median reduction of 56% (IQR 13-39), and 92% (IQR 53-95) respectively. All non-responders (patients who did not have an MFI reduction in the strong DSA) had DSA with MFI of >8,000 at 1:16 dilution. Increased number of proteasome inhibitor cycles, and earlier treatment was associated with treatment responsiveness, as some DSA with MFI >8,000 at a 1:16 dilution responded to early and multiple treatment cycles. In summary, this retrospective case series shows that proteasome inhibition as initial therapy can effectively reduce DSAs in heart transplant recipients presenting with acute AMR, but given that both bortezomib and carfilzomib were included, and the lack of a sub-group analysis examining the differences in efficacy, the preferred therapy for AMR cannot be clearly identified [51].

3.6 Daratumumab

3.6.1 Kidney – Acute AMR and Chronic Active AMR

Three single-center retrospective case series have been published reporting the use of daratumumab for treatment of seven acute AMR cases and one cAMR case. Zhu, et al. used an intensive dosing phase where daratumumab 400-500 mg IV once a weekly was given until DSA MFI fell <5000, after which daratumumab 400-500 mg IV once weekly was given until DSA disappeared [52]. Lemal, et al. administered daratumumab 16 mg/kg IV as a one-time dose, and Osmanodja, et al. administered daratumumab 16 mg/kg IV monthly for 9 months [53, 54]. Daratumumab was utilized as rescue therapy after a combination of rituximab and/or carfilzomib + PLEX/IVIg in Zhu et al., after PLEX in Lemal, et al., and after PLEX/IVIg in Osmanodja, et al. Follow up ranged from 1-35 months, with a graft survival of 100%. Renal function remained stable or improved in all patients, histological parameters improved in 5/6 (83.3%) patients who had follow-up biopsies, and DSA MFI decreased or stabilized in all patients. Baseline Banff histology scores were worse in Osmanodja, et al. in comparison to Zhu, et al., but were not reported by Lemal, et al. Given the wide heterogeneity of patients included, and the variability in both daratumumab dosing regimens used and duration of therapy, it is difficult to draw conclusions regarding the efficacy of daratumumab for the indications of both acute AMR and cAMR, and the patients who would benefit most from daratumumab therapy [52-54]. Additionally, there have been concerns for increased risk of ACR with daratumumab, as seen in a few case reports, given its effect on enhancing effector T-cell functions [60-62]. One patient in the published case series did present with ACR after daratumumab therapy, although tacrolimus levels were also subtherapeutic at time of presentation [52]. Thus, if utilizing daratumumab in AMR, managing treatment of AMR, while balancing the risk of ACR is an important consideration.

3.7 Imlifidase

Imlifidase, which has been used for desensitization for kidney transplantation, has also been studied in the context of AMR in kidney transplant recipients. In a randomized, open-label, multicenter, multinational trial, patients were randomized 2:1 to receive either a single IV infusion of imlifidase 0.25 mg/kg (n = 18) or 5-10 sessions of PLEX (n = 10). All patients in the study received methylprednisolone 500 mg IV for 3 days prior to the first treatment, IVIg 2 g/kg 3 days after imlifidase or directly after the last PLEX session, and a single dose of rituximab 375 mg/m^2 IV 5 days after IVIg infusion. 4/18 (22%) patients in the imlifidase arm and 1/10 (10%) patients in the PLEX arm had previous AMR. 19/28 (68%) had cAMR or mixed rejection and only 9/28 (32%) had active AMR. Imlifidase demonstrated superiority in both magnitude and time to reduction of DSA in comparison to PLEX. Reduction in DSA 5 days following start of treatment was 97% (range 85-98) for imlifidase vs. 42% (range 5-82) for PLEX (95% CI 37-66), and median time to maximum DSA reduction was 15 hours (range 2-72) in the imlifidase arm vs. 9 days (range 2-180) in the PLEX arm. After antibody rebound in the imlifidase arm (approximately 6-12 days), both arms had similar reductions in DSA. Despite this, imlifidase did not demonstrate any meaningful clinical benefits at the 6-month follow-up, given that graft survival was 77.8% and 90% in the imlifidase and PLEX arms respectively. All graft losses within the imlifidase arm were with concurrent ACR which brings the question of determining if imlifidase or mixed rejection was the greater contributing factor to graft

loss. Approximately 50% of all patients had cAMR, thus antibody elimination through imlifidase may not be effective in preventing graft loss once patients have developed significant histopathological changes on biopsy as seen in cAMR. Additionally, median time since transplantation in the imlifidase arm was numerically greater than that of the PLEX arm (4 vs. 1.1 years) [55]. A chronicity score of ≥4 has been associated with graft loss in kidney transplant recipients with AMR; median chronicity score in this trial was 4-5 overall (n = 25), suggesting that all patients, regardless of indication, had more advanced disease at the time of inclusion [63]. Mechanistically, imlifidase may have greater benefit in early acute AMR where prompt DSA removal can serve as a bridge to initiation of other combination therapies. The authors comment on this, stating that if imlifidase is to be explored for AMR in future trials, defining maximum time from transplantation, maximum degree of chronic damage, the clear presence of DSA, and excluding mixed rejection should be considered [55].

3.8 Felzartamab

Recently, a phase II trial examined felzartamab in late acute AMR and late cAMR (n = 22). Patients were randomized 1:1 to receive felzartamab or placebo for 6 months, followed by an observational period of 6 months. Patients who had previous treatment with anti-CD38 monoclonal antibodies at any point, or previous treatment with other immunomodulatory monoclonal/polyclonal antibodies within 3 months of study treatment were excluded from this trial. The trial met its primary outcome of safety as felzartamab showed an acceptable safety profile. At 1 year, one graft loss occurred in the placebo group due to persistent cAMR, and patient survival was 100% in both trial groups. Biopsies were performed at 24 weeks and 52 weeks per study protocol. At 24 weeks, resolution of morphologic AMR was more frequent with felzartamab (9/11) than with placebo (2/10) with a difference of 62% (95% CI 91-100), and a risk ratio of 0.23 (95% CI 0.06-0.83). Median microvascular inflammation score was lower in the felzartamab group than in the placebo group (0 vs. 2.5) for a mean difference of -1.95 (95% CI -0.97 to -0.92). Of note, the effect of felzartamab did not persist after treatment discontinuation, as recurrence of AMR was reported in 3/9 (33.3%) patients who had a response to felzartamab at week 52, suggesting that continuation of therapy may be necessary to stabilize graft function in the setting of late AMR. However, at week 52, median scores for microvascular inflammation remained lower in the felzartamab group (1, IQR 0-2) than in the placebo group (2, IQR 2-3.5) for a median difference between groups of -1.58 (95% CI -2.70 to -0.45). eGFR slope at 1 year was -0.39 mL/min/1.73 m^2 (95% CI -5.47 to 4.69) in the felzartamab group and -4.53 mL/min/1.73 m^2 (95% CI -9.83 to 0.77) in the placebo group with a difference of 4.14 mL/min/1.73 m^2 (95% CI -3.20 to 11.48), indicating that felzartamab may potentially stabilize graft function. There were modestly lower values for iDSA with felzartamab treatment (not reported numerically) [56]. These results show promise for utilization of felzartamab in the setting of late AMR, thus the two phase III trials for felzartamab in cAMR with and without DSA are planned [64, 65].

3.9 Obinutuzumab

Obinutuzumab, an anti-CD20 monoclonal antibody, has been used in a case series of two kidney transplant recipients with AMR on biopsy at post-operative day (POD) 6 and POD 13. Both patients had persistent histological features of active AMR refractory to PLEX, IVIg, and eculizumab prior to receiving obinutuzumab. Patient 1 received eculizumab on POD 37, followed by obinutuzumab on

POD 41, and patient 2 received eculizumab on POD 18 followed by obinutuzumab on POD 21. SCr in both patients decreased from time of AMR to last follow-up at 3 years, from 4.4 mg/dL to 1.3 mg/dL for patient 1, and from 2.2 mg/dL to 1.9 mg/dL for patient 2. Histological improvements were also seen on follow-up biopsies for both patients, but no consistent effect on specific Banff scores was seen. DSA overall decreased in both patients. At 3 years, no signs of active AMR or rebound DSA were detected. This case series suggests that obinutuzumab may be a viable treatment option; however, these findings need to be confirmed in larger studies [57].

4. Discussion

Evidence regarding emerging therapies for AMR is limited mostly to smaller retrospective case series lacking a comparator arm, which introduces selection bias, and limits both generalizability and the ability to control for confounding factors. Additionally, there was wide heterogeneity in prior and concomitant therapies used for the treatment of AMR and substantial variation in duration of treatment and dosing regimens used which confounds interpretation of efficacy outcomes. Given the need for effective therapies in AMR, publication bias may have also played a role in the available reports in literature. Although 17/25 studies had a follow-up period of more than 1 year, long-term graft function cannot be assessed with the available data as only three of these studies reported an actual or median follow-up period of >3 years. As expected, the majority of literature was in kidney transplantation. In kidney AMR, there are clear criteria for active and cAMR, and more granularity with histological scoring, which is not found in diagnostic criteria of AMR in other solid organs [66-71]. Given notable differences in AMR definitions and diagnostic criteria across organs, histological and graft function outcomes found in kidney transplantation data cannot be effectively generalized to other organ types.

4.1 Tocilizumab

Tocilizumab is a humanized monoclonal antibody that competitively inhibits the binding of interleukin-6 (IL-6) to the IL-6 receptor. IL-6 is a proinflammatory cytokine involved in activation of T-helper 17 cells, inhibition of regulatory T cells, and differentiation of plasma cells [72]. Elevated levels of IL-6 have been associated with both AMR and chronic allograft dysfunction, thus tocilizumab may potentially have utility in both acute AMR and cAMR [45, 73]. The majority of published literature for tocilizumab is in cAMR of the kidney, where use of tocilizumab was generally associated with stabilization of renal function, and variable effects on graft survival, DSA MFI reduction, and histological changes [32-41]. In terms of histology, reduction in microvascular inflammation was most commonly seen with tocilizumab; however, tocilizumab failed to prevent progression of chronicity. This suggests that tocilizumab stabilizes graft function through reduction of inflammation, without significant effect on disease progression. Baseline chronicity and degree of renal dysfunction may possibly be associated with the benefit patients would experience with tocilizumab therapy, but optimal timing of initiation cannot yet be inferred from the literature available.

4.2 Clazakizumab

Clazakizumab is another humanized monoclonal antibody against IL-6, which exhibits increased potency and duration of action in comparison to tocilizumab [74, 75]. It is thought that clazakizumab is not associated with the rebound phenomenon as seen with IL-6 accumulation in tocilizumab, thus there was interest in its use in late AMR [32, 76]. Despite encouraging results in two phase II studies published in its use in late acute or cAMR, where clazakizumab resulted in a stabilization or improvement of renal function, DSA MFI, and histology, the subsequent phase III study in cAMR was terminated early given failure to find benefit in its primary efficacy outcome [44, 45, 59]. Thus, at present, there are no known further efforts in exploring clazakizumab as a therapy in AMR.

4.3 Carfilzomib

Carfilzomib is a tetrapeptide epoxyketone that irreversibly binds to the 26S proteasome, resulting in accumulation of ubiquinated proteins and plasma cell apoptosis. Its effective half-life is greater than that of bortezomib, which demonstrates reversible inhibition [77, 78]. Carfilzomib also demonstrates specificity of the NH_2-terminal threonine residue, which decreases potential for off-target activity with cellular proteases, which may result in improved tolerability in comparison to bortezomib [79]. Carfilzomib was found to decrease DSA MFI in a case series of kidney transplant recipients, with no consistent effect on histology [46]. There has been one published report to date of carfilzomib use in liver transplant recipients, with variable effect on DSA and graft function, showing the complexity of liver transplant AMR [47]. In lung transplant recipients, carfilzomib either improved or stabilized FEV1, and decreased DSA in all studies. Despite these findings, graft survival remained poor at 42.9-50% with carfilzomib use in lung transplant AMR [48-50]. In heart transplant, the majority of patients treated with carfilzomib had recovered LVEF, and most patients had resolved pathologic AMR 1-year post-transplant [51]. In both the lung and heart transplant data, longer time from DSA detection and higher DSA MFI was associated with non-response, suggesting earlier initiation of therapy would predict treatment success. As expected, patients across all organ groups experienced AKI with carfilzomib, with the majority of patients recovering. Thus, carfilzomib may be considered in cases where bortezomib use is precluded by thrombocytopenia and peripheral neuropathy; however, caution must be exercised given the known risk of AKI, especially in kidney transplant population. Currently, reported use of carfilzomib outside lung transplant population is limited.

4.4 Daratumumab

Daratumumab is a humanized monoclonal antibody against CD38, which results in apoptosis of plasma cells through Fc mediated crosslinking, leading to complement dependent cytotoxicity, antibody dependent cell mediated cytotoxicity, and antibody dependent cellular phagocytosis [80]. Despite the earlier single case reports in pediatric heart transplantation, the studies that met inclusion criteria were in kidney transplantation for both acute AMR and cAMR [81, 82]. Renal function and DSA MFI stabilized or improved in all patients, and histology improved in the majority of patients [52-54]. Given the wide variability in dosing regimens used and the heterogeneity of patients included, the utility of daratumumab for AMR cannot be confirmed with the available

evidence. Furthermore, the potential for increased effector T-cell functions and risk of subsequent ACR is an important concern when utilizing daratumumab in solid organ transplantation.

4.5 Imlifidase, Felzartamab, Obinutuzumab

Data for imlifidase, felzartamab, and obinutuzumab are limited to single studies, thus no definitive conclusions can be drawn in terms of their place in therapy in AMR [55-57].

5. Conclusions and Future Directions

AMR is a significant contributor to late allograft loss in solid organ transplantation. Optimizing treatment of AMR remains difficult given the various mechanisms for DSA-mediated allograft injury. Although there are several potential targets with novel drug therapies on the market, long-term efficacy and safety is not yet known. Optimal timing of therapy, and identification of patients who are likely to benefit most from initiation of therapy also needs to be defined. The majority of studies were case series without a comparator. Prospective, randomized controlled studies with comparisons to standard of care and endpoints predictive of long-term graft survival are needed to better identify the place in therapy of these novel agents.

Author Contributions

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Competing Interests

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