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REVIEW

Obinutuzumab in kidney transplantation: Past, present, and future

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Abstract

Antibody-mediated rejection (ABMR) and recurrent primary renal disease (PRD) represent major causes of kidney transplant (KT) loss. The standard of care for desensitization, ABMR, and relapsing autoimmune glomerulopathies or nephrotic syndrome includes apheresis for antibody removal and polyclonal immunoglobulin for antibody blockage. Although frequently used to achieve B-cell depletion, the administration of the type 1 anti-CD20 monoclonal antibodies (mAb) rituximab (RTX) or ofatumumab (OFA) has failed to demonstrate a significant survival benefit. Obinutuzumab (OBI) is a humanized glycoengineered type 2 anti-CD20 mAb. Compared to RTX or OFA, OBI-induced B-cell depletion is not related to complement-dependent cytotoxicity, mostly operating through antibody-dependent cell-mediated cytotoxicity, antibody-dependent phagocytosis, and direct cell death. These characteristics could play a pivotal role in the development of new anti-rejection strategies, enabling the simultaneous administration of complement inhibitors and B-cell-depleting agents. OBI has also demonstrated more powerful peripheral and central B-cell depletion capacities than RTX, with enhanced effects on memory B cells and plasmablasts. In patients with autoimmune glomerulopathies or multidrug-dependent nephrotic syndrome, OBI has shown encouraging results, representing a potential evolution of the treatment of post-transplant relapsing PRD. The present review summarizes the current knowledge on OBI use in KT setting.

Key Words: Obinutuzumab; Rituximab; Kidney transplantation; Desensitization; Antibody-mediated rejection; Glomerulopathies; Nephrotic syndrome; Recurrence; Review

Core Tip: Antibody-mediated rejection and recurrent primary renal diseases remain major causes of kidney transplant loss. Obinutuzumab (OBI) is a type 2 anti-CD20 monoclonal antibody with enhanced peripheral and central B-cell depletion capacities compared to type 1 anti-CD20 monoclonal antibodies. Compared to other B-cell-targeted agents, OBI-induced B-cell depletion is marginally affected by complement function, primarily operating through antibody-dependent cell cytotoxicity, antibody-dependent cell phagocytosis, and direct cell death. These characteristics suggest that OBI might represent a game-changer in the management of highly sensitized transplant candidates, humoral rejection, and relapsing renal diseases. This review summarizes the current knowledge on OBI use in kidney transplantation.

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INTRODUCTION

Kidney transplantation is considered the gold standard treatment for patients with end-stage renal disease (ESRD), because it provides longer life expectancy and better quality of life compared to dialysis[1]. Although there have been encouraging advancements in deceased donors management, organs preservation technologies, peri-operative surgical care, and maintenance immunosuppression in the last decades, long-term kidney transplant (KT) outcomes have not substantially changed[2-5]. Compared to the past, we have witnessed a progressive reduction in primary non-function, technical graft loss, and T-cell-mediated rejection (TCMR) rates. However, we are still losing organs due to antibody-mediated rejection (ABMR)[6,7] and recurrent primary renal disease (PRD)[8-10].

Current desensitization and ABMR protocols include apheresis for antibody removal, intravenous human polyclonal immunoglobulin (IVIg) for antibody blockage or clearance, and the first-generation type 1 anti-CD20 monoclonal antibody (mAb) rituximab (RTX) to obtain B-cell depletion and further down-regulation of antibody production[11-13]. Aphaeretic techniques and RTX also represent the mainstay of treatment of post-transplant recurrence of several autoimmune glomerulopathies and steroid-resistant nephrotic conditions[8,14,15]. The main limitation of this multi-modality strategy is the inability to rapidly halt or reverse the mechanisms causing graft injury, as well as to determine a sustained inhibition of antibody production[16-18]. Indeed, the effects of apheresis on circulating antibodies or soluble molecules are strictly dose-dependent (therefore requiring prolonged or repeated sessions) and transient, with frequent development of rebounds. Apheresis is also logistically demanding and expensive, with relevant discomfort and risks for the patient[19,20]. In this setting, the rationale for using high-dose IVIg is that they can easily compensate for the non-selective antibody depletion caused by the aphaeretic procedures while acting on undesired molecules or antibodies *via* multiple mechanisms, including their binding to the Fragment crystallizable (Fc) receptor (FcγR) for immunoglobulin G (IgG) and direct inhibition of myeloid dendritic cells[13,21,22]. Nevertheless, the highly variable pharmacokinetics (PK), the lack of specificity, and the frequent occurrence of infusion-related reactions (IRR) make IVIg a relatively ineffective agent[22].

CD20+ B lymphocytes play a critical role in graft-specific alloreactivity, directly contributing to the development and progression of ABMR[23,24] and, perhaps, TCMR[25,26]. CD20+ B cells are also involved in the pathogenesis of antibody-mediated PRDs, like membranous nephropathy (MN) or lupus nephritis (LN), as well as some proteinuric diseases of uncertain origin, including focal segmental glomerulosclerosis (FSGS) or minimal change disease (MCD)[27,28]. Since the release into the market of RTX in the late nineties, there has been an expanding interest in the use of B-cell depleting strategies in clinical practice, embracing different specialties and diseases. Primarily developed for the treatment of B-cell malignancies, RTX is a first-generation type 1 anti-CD20 chimeric mAb (unconjugated IgG1κ) resulting from a murine Ig variable region mounted on a human Ig heavy chain[29]. After infusion, B cells are mostly depleted through immune-mediated mechanisms involving the Fc portion of the mAb and the FcγRs on effectors cells [natural killer (NK) cells, macrophages, neutrophils, dendritic cells], such as complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), and antibody-dependent cell phagocytosis (ADCP). Much less effectively, the binding of the Fragment antigen binding (Fab) of RTX to CD20 on target cells also induces growth inhibition and classic apoptosis (caspase-dependent)[30]. The reduction of the peripheral B-cell count starts within few weeks of administration, and it is diluted over time, generally lasting from 6 to 12 months[30]. Inhibition of antibodies production through B-cell depletion is the desired and expected effect of RTX in the setting of desensitization, ABMR, and post-transplant relapsing antibody-mediated renal diseases. Nonetheless, the reported efficacy of RTX in some cases of non-antibody-mediated renal diseases suggests that it might interact with other cell types, including podocytes and regulatory T cells[31].

While RTX is a well-consolidated therapeutic option in kidney transplantation, the recognition of RTX-resistant autoimmune glomerulopathies and the limited results obtained in desensitization or long-term control of ABMR have forced the international transplant community to investigate alternative strategies targeting CD20+ B cells and antibody production[8,32]. Therefore, there is mounting interest in research projects focusing on second-generation type 1 anti-CD20 mAbs ofatumumab (OFA), ocrelizumab (OCR), or ublituximab (UBL), and type 2 anti-CD20 mAb obinutuzumab (OBI). OBI could offer several advantages over type 1 anti-CD20 compounds, including enhanced ADCC, ADCP, and direct cell death (DCD)[33]. Relevantly, CDC appears as a marginal mechanism of action for OBI, giving the unique opportunity to explore the synergistic effects of concomitant complement inhibition and B-cell depletion in real-life scenarios[33-36]. Furthermore, data are showing faster, wider, and more sustained B-cell depletive properties, with a potential impact on centrally located memory B cells and plasmablasts[37,38].

In the present review, we summarize the current knowledge on OBI use in kidney transplantation, discussing the rationale for future applications.

RATIONALE FOR CD20-TARGETED THERAPIES IN KIDNEY TRANSPLANTATION

CD20 is a non-glycosylated surface molecule belonging to the membrane-spanning 4-domains sub-family A proteins[39,40]. It consists of four hydrophobic transmembrane domains, mostly existing as homo-dimeric or homo-tetrameric oligomers associated with other signal-transducing proteins. Relevantly, CD20 appears as physically coupled to class II major histocompatibility complex, B-cell receptor (BCR), and CD40[39,41-43]. As a general B-cell marker, CD20 is expressed in pre-B cells, naïve B cells, memory B cells, and plasmablasts, being lost in long-lived plasma cells[25]. This wide expression pattern makes CD20 a strategic target for B-cell depleting or immunomodulatory therapies primary aimed at mitigating ongoing antibody production while preserving the anamnestic response[25]. However, the exact function of CD20 in B cells has not yet been clarified[39]. Interestingly, it has been observed that individuals with congenital CD20 deficiency exhibit normal central B-cell differentiation, peripheral B-cell number, and IgM production, but they have fewer circulating memory B cells, impaired isotypic switch, and reduced IgG levels[44]. In line with these findings, data from animal models suggest that CD20 could be essential for the optimization of both T-cell-independent and T-cell-dependent humoral immunity[45-47]. Due to its coupling and its interactions with the BCR, it has been postulated that CD20 might take part in the processes leading to effective BCR signaling and B-cell activation[39,48-50]. It is now accepted that the role of CD20+ B cells in kidney transplantation extends beyond their function as mere precursors to plasma cells. In addition to producing antibodies potentially causing ABMR or relapsing PRD, CD20+ B cells routinely operate as professional antigen-presenting cells, priming alloreactive T cells and thereby amplifying the alloimmune cascade. In this regard, it is worth mentioning that a subset of CD20+ T cells with proinflammatory and immunomodulatory properties has been recently identified, likely extending the spectrum of action of CD20-targeted therapies[25]. Finally, the importance of CD20+ memory B cells, representing a critical reservoir for rapid recall responses following antigen re-exposure, in the pathogenesis of ABMR[26,51,52] and some recurrent graft nephropathies[53-55] should not be neglected.

OBI PHARMACODYNAMICS AND PK

OBI is a humanized, glycoengineered, IgG1, type 2 anti-CD20 mAb exhibiting a unique pharmacological profile compared to type 1 anti-CD20 mAbs, such as RTX, OFA, OCR, or UBL. OBI targets the type 2 epitope of CD20, constitutively expressed on both pre-mature and mature B cells as well as plasmablasts. Similarly to RTX, OBI operates through two types of binding: (1) Specific, between the mAb Fab region and the target CD20 epitope on B cells; and (2) Non-specific, between the mAb Fc region and the FcγRs on effector cells, neonatal FcR (FcRn) on different cell lineages, or C1q. Both type 1 and type 2 anti-CD20 mAbs bind bivalently to CD20 (RTX affinity: 4.5 nM *vs* OBI affinity: 4.0 nM), but they generate different effects. Precisely, RTX determines CD20 stabilization by forming tetramers in lipid rafts whereas OBI does not induce CD20 cross-linking so that it remains dispersed on the cell surface. As a result, OBI has lower complement-binding capacity, but higher cell-to-cell interaction and DCD induction capabilities than RTX[30,33]. OBI-CD20 complexes persist longer on the cell surface compared to RTX, limiting antigenic modulation and increasing the chances of effective ADCC and ADCP[56,57]. OBI cell-to-cell interaction is further enhanced by the presence of a glycosylated Fc segment, which can increase the affinity for the FcγRIIIA and FcγRIIIB located on macrophages, NK cells, neutrophils, and dendritic cells. The glycosylation of the Fc segment (removal of fucose on asparagine 297 within the CH2 domain) substantially improves OBI ADCC and ADCP through FcγRIIIA/B-induced NK cells degranulation and macrophages phagocytosis, enabling a faster and wider depletion of both circulating and centrally located B cells, including those constituting the memory-B-cell compartment. Unlike RTX, the OBI glycoengineered Fc segment can stimulate B-cell phagocytosis by Kupffer cells in the liver, another important mechanism of B-cell depletion *in vivo*[58]. The increased affinity for the FcγRIIIA reduces the inhibitory effects exerted by the presence of excessive IgG plasma concentrations on ADCC or ADCP, making OBI a preferred option over type 1 anti-CD20 mAbs in case of administration of high-dose IVIg. OBI higher affinity for the FcRn offers an additional benefit in the presence of excessive levels of circulating IgG because it protects (*via* competitive binding) the mAb from cell degradation, thus slowing down the overall clearance of the compound[30,33]. A lower induction of CD20 shaving (trogocytosis) on target cells has been recently demonstrated, further increasing the potential efficacy of OBI over RTX or other anti-CD20 agents[31]. Relevantly, OBI can induce caspase-independent DCD operating with mechanisms involving lysosomal membrane permeabilization and homotypic adhesion[33,59]. Also, it shows superior peripheral B-cells growth inhibition than RTX [33]. Therefore, it remains less dependent on CDC than type 1 anti-CD20 (RTX, OFA, OCR, UBL), anti-CD52 (alemtuzumab), or anti-CD38 [daratumumab (DAR)] mAbs. This characteristic is particularly relevant because complement components consumption or iatrogenic complement blockage can significantly impair the efficacy of targeted-cell-targeted agents[32]. On the contrary, as recently demonstrated *in vivo* by our group, OBI-induced B-cell depletion is not affected by the concomitant inhibition of the terminal complement cascade, resulting in fast, full, and sustained peripheral B-cell depletion, regardless of residual complement activity[35,36,60].

In healthy volunteers, patients with hematologic malignancies, individuals with chronic kidney disease, ESRD KT candidates, and KT recipients[32,33,35-37], OBI exhibited greater potency and efficacy than RTX in terms of absolute B-cell depletion and efficacy against memory B cells and plasmablasts[60,61]. According to the THEORY study (multicenter, phase 1b, open label, sequential, 2-cohort trial), most of the KT candidates who had received OBI as a part of their desensitization strategy had undetectable peripheral CD19+ B cells by week 3 after infusion (60% in the group treated with a single dose of OBI and 100% in the cohort administered two or more doses). By week 24, signs of peripheral B-cell reconstitution could be detected in 80% and 10% of the patients in the two cohorts, respectively. Of note, OBI administration was also associated with reduced levels of CD19+ B cells in retroperitoneal lymph nodes[37]. Further investigations have shown that OBI determined profound depletion of several peripheral B-cell subsets including naïve B cells, switched and unswitched memory B cells, IgD+ transitional B cells, double negative B cells, and plasmablasts/plasma cells (paired t tests between levels at baseline and 52 weeks after infusion; $P < 0.05$)[62]. As previously demonstrated in patients with chronic lymphocytic leukemia[63], ESRD patients receiving OBI prior KT exhibited significantly lower lymph nodes total B-cell (median: 0.14% *vs* 32%), naïve B-cell (median: 0% *vs* 10.6%), memory B-cell (median: 0.08% *vs* 15.9%), and plasmablasts (median: 0% *vs* 0.06%) counts than controls (unpaired 2-group t test between levels in OBI treated patients and controls; $P < 0.001$)[62]. Tissue memory B cells and plasmablasts have been traditionally considered resistant to conventional B-cell targeted therapies and they could justify further OBI evaluation in ABMR and autoimmune glomerulopathies affecting native kidneys or renal grafts[62]. Similarly, excellent results were observed by NasrAllah *et al*[38], with 5/5 of the KT candidates treated with OBI achieving a median drop in peripheral CD19+ B cells of 98% two weeks after infusion. A fast (within 24-48 hours), full, and long-lasting (> 1 year) depletion of peripheral CD19+ B cells has been confirmed by our group using OBI as an induction agent in 10 high immunological risk deceased donor KT recipients (preliminary results presented at the American Transplant Congress 2023; research article in progress)[60] or as a salvage therapy in 2 patients with ABMR[36].

The experience gathered in hematology indicates that RTX follows a 2-compartment open PK model with first-order elimination. In particular, the binding between RTX and CD20 primarily determines RTX distribution and elimination [64]. In similar settings, OBI appears to follow a 2-compartment linear PK model with both time-independent and time-dependent clearance components whereby the extent of B-cell depletion can influence the distribution and half-life of the mAb[30,61]. To date, there is a lack of information regarding OBI PK in immune-mediated glomerular diseases (MN, LN, MCD, FSGS)[31]. PK analyses carried out during the THEORY study suggest that the concentration-time course of OBI in ESRD patients might not be relevantly different to that observed in other populations. Furthermore, in this group of patients, OBI clearance and volume of distribution remained body weight-dependent and sex-dependent[37]. As already demonstrated with RTX, it is possible that nephrotic syndrome and non-selective proteinuria might alter OBI PK, thus affecting overall clearance, levels, and efficacy[65]. However, waiting for the results of ongoing clinical trials, it is reasonable to assume that OBI unique characteristics, such as enhanced FcγRIIIA or FcRn affinity, and reduced CD20 shaving could mitigate the expected effects of the increased urinary loss[31]. Most relevant characteristics of OBI and other B-cell targeted agents are summarized in Table 1.

OBI IN DESENSITIZATION, INDUCTION, AND ABMR

In the last 20 years, there has been a continuous increase in the number of heavily sensitized patients engulfing the KT waiting lists, now representing up to 20% of transplant candidates worldwide[66]. As a matter of fact, the implementation of organ allocation strategies has not determined a substantial improvement in negative-crossmatch transplant rates[67]. Furthermore, current desensitization and induction protocols in patients with high-level preformed anti-HLA donor-specific antibodies (DSA) are associated with an excessive risk of early ABMR and premature transplant failure[68]. Two types of ABMR due to anti-HLA antibodies have been recognized. Type 1 ABMR occurs in patients with previous immunization, thus exhibiting circulating preformed DSA or rapid anti-donor B-cell response at the time of transplant; type 2 ABMR is caused by the development of de novo DSA at a later stage. There is evidence that KT recipients with type 1 ABMR are more likely to respond to apheresis, IVIg, and RTX, showing better long-term graft survival than those diagnosed with type 2 ABMR. The reason behind this difference is poorly understood. However, most authors agree that the ideal anti-rejection regimen should guarantee effective complement inhibition, complete B-cell depletion (including memory B cells and long-lived plasma cells), and sustained anti-HLA antibody production blockage[32]. Although there are studies showing that KT patients receiving RTX induction exhibit lower 1-year ABMR rates and superior short-term graft function than those treated with apheresis and IVIg[69,70], episodes of ABMR due to rebound preformed DSA or de novo DSA can frequently occur, with deleterious effects on transplant survival. Indeed, the positive results observed using RTX for desensitization or induction have not been confirmed in the setting of ABMR, where RTX has failed to add substantial benefit to the standard of care[36]. It has been postulated that OBI (acting on centrally located memory B cells and plasmablasts) can lead to improved desensitization and anti-rejection outcomes. Furthermore, not relying on CDC and effectively operating in case of IVIg blocking, OBI can be integrated into multimodality regimens including high-dose IVIg and complement inhibitors[32]. Available literature and ongoing clinical trials exploring OBI use in desensitization or ABMR are summarized in Tables 2 and 3[35-38,71,72].

Desensitization

In the THEORY trial, heavily sensitized KT candidates were allocated into two groups. Cohort 1 ($n = 5$) received a single infusion of OBI (1000 mg) on day 1, followed by IVIg (2 g/kg) at weeks 3 and 6; cohort 2 ($n = 20$) was given OBI (1000 mg) on day 1 and 15, and an optional administration at week 24, with similar IVIg timing and dosing. Patients who were

Table 1 Main anti-B-cell agents with potential use in kidney transplantation

Drug	Approval	Target	Structure	CDC	ADCC	ADCP	DCD	Notes/unique properties
Rituximab	1997 (FDA/EMA)	Type 1 anti-CD20	Chimeric IgG1κ (mouse-human)	+++	++	++	±	First approved anti-CD20 monoclonal antibody; complement-dependent; widely used
Obinutuzumab	2013 (FDA); 2014 (EMA)	Type 2 anti-CD20	Glycoengineered humanized IgG1	+	+++	++	+++	Enhanced ADCC, ADCP and DCD; low CDC; resistant to complement inhibition, high-dose IgG, and trogocytosis
Ofatumumab	2009 (FDA)	Type 1 anti-CD20	Fully human IgG1κ	++++	+	+	-	Strong CDC; high affinity for CD20 membrane-proximal epitope
Ocrelizumab	2017 (FDA/EMA)	Type 1 anti-CD20	Humanized IgG1	++	++	+	±	Reduced immunogenicity *vs* RTX
Ublituximab	2022 (FDA)	Type 1 anti-CD20	Glycoengineered chimeric IgG1	++	+++	++	±	Enhanced FcγRIIIA binding; increased ADCC
Inebilizumab	2020 (FDA)	Anti-CD19	Humanized IgG1	++	++	++	±	CD19-depleting agent; long-lived plasma cells modulation
Belimumab	2011 (FDA/EMA)	BLyS-inhibitor	Human IgG1λ	-	-	-	-	Inhibits B-cell survival factor B-cell activating factor
Daratumumab	2015 (FDA); 2016 (EMA)	Anti-CD38	Human IgG1κ	+++	+++	+++	++	Targets CD38 on plasma cells and activated B cells/T cells; depletes donor-specific anti-HLA antibodies-producing clones; synergizes with anti-CD20

+ to ++++: Reflects relative strength of activity; ±: Variable or minimal activity; –: Absent activity; ADCC: Antibody-dependent cell-mediated cytotoxicity; ADCP, antibody-dependent cell phagocytosis; CDC: Complement-dependent cytotoxicity; DCD: Direct cell death; EMA: European Medicines Agency; FcγR: Fragment crystallizable receptor; FDA: Food and Drug Administration; IgG: Immunoglobulin G; RTX: Rituximab.

transplanted during the follow-up (n = 7) received two additional OBI infusions. The primary endpoint was to assess OBI safety in ESRD patients whereas the secondary endpoints were PK and pharmacodynamics (PD) analyses. The impact on sensitization status was also evaluated. Incidence and severity of IRRs and serious adverse events (SAE) were acceptable. As previously discussed, OBI was extremely effective in reducing peripheral and centrally located B cells, including memory B cells and plasmablasts. Higher OBI doses were associated with increased B-cell depletion and slower B-cell reconstitution, suggesting that 2000 mg total-dose might reliably ensure full and long-lasting B-cell depletion, without compromising safety. On the contrary, OBI effects on anti-HLA antibody levels [expressed as mean fluorescence intensity (MFI)] were inconsistent and modest. Changes in the number of unacceptable antigens or calculated panel reactive antibody (cPRA) score were also marginal[37]. In line with the THEORY trial, effective B-cell depletion but neglectable impact on pre-transplant crossmatch results were observed by NasrAllah *et al*[38] in a small group (n = 5) of KT candidates.

These findings confirm OBI enhanced CD20+ B-cell depletion capacities as well as the role of long-lived (CD20-) plasma cells in the production of anti-HLA antibodies and ABMR. They also highlight the lack of efficacy of OBI on this specific cellular subset. However, the disappointing results observed with the proteasome inhibitor bortezomib, despite its depletive effects on central plasma cells, indicate that memory B-cell compartment (actively replenishing donor-specific plasma cells) remains a primary target for next-generation anti-rejection protocols. In this regard, it would be worth evaluating a desensitization strategy with OBI and DAR for total B-cell depletion[32].

Induction

In patients with preformed DSA at the time of transplant, ABMR rates as high as 50% have been reported. There is mounting evidence that eculizumab (ECU) can reduce the incidence of early ABMR, temporarily protecting the graft from CDC and ADCC. Taking advantage of OBI unique mechanisms of action, our group developed a multimodality induction scheme with ECU and OBI for the prevention of ABMR in sensitized deceased donor KT recipients. The safety and efficacy of this novel immunosuppressive protocol were evaluated in a single-center exploratory trial presented at the American Transplant Congress 2023. Ten consecutive high-immunological risk (maximal class I and/or class II cPRA > 95% and/or circulating DSA > 1000 MFI) KT candidates received the following regimen: (1) Pre-operative plasma exchange (PEX); (2) ECU (900 mg) prior reperfusion; (3) Thymoglobulin (5 mg/kg total-dose) from day 0 to day 4; (4) Intermittent PEX between day 5 and day 14; (5) IVIg (2 g/kg total-dose) after PEX; and (6) OBI (1000 mg) two weeks after the last IVIg administration. As maintenance, we used LCP-tacrolimus, mycophenolate mofetil (MMF), and steroid. After two years, all patients were alive with a functioning graft. Despite complement inhibition, OBI infusion rapidly led to complete and long-lasting peripheral B-cell depletion. Remarkably, no episodes of ABMR were recorded and no signs of active or chronic ABMR were detected on protocol histology. Overall, anti-HLA antibody levels showed mixed results, with high-degree interpatient variability. However, none of the recipients developed de novo DSA. IRR and SAE rates

Table 2 Current literature on obinutuzumab use in kidney transplantation

Ref.	Year	Focus	Study design	Population	Treatment scheme	Main outcomes	IRR	SAE	FU
Redfield *et al*[37]	2019	Desensitization in highly sensitized KT candidates	Phase 1b, open label	25 ESRD patients (cPRA ≥ 98%); 5 received 1 OBI dose, 20 received 2 OBI doses	OBI 1 gon days 1 and 15 (± week 24) + IVIg 2 g/kg on days 22 and 43	> 90% peripheral CD19+ B-cell depletion; modest anti-HLA MFI reduction; 8/25 candidates proceeded to transplant	Mild–moderate IRRs in 52% (mainly chills, nausea, hypotension after first infusion)	44% had infections (11 SAEs in 9 patients), including pneumonia and nocardiosis	12 months
Zhang *et al*[72]	2021	B-cell depletion and CDC crossmatch	Observational cohort	12 sensitized KT candidates (6 OBI *vs* 6 RTX)	OBI 1 g *vs* RTX	Obinutuzumab achieved a median of 98% CD19+ B-cell reduction; CDC crossmatch results not influenced by OBI (unlike RTX)	Not reported	Not reported	2 weeks
Zhang *et al*[72]	2021	Lymphoid-tissue B-cell depletion	Sub study of Phase 1b trial	7 KT recipients	Same OBI + IVIg regimen as Redfield *et al*[37]	Significant reduction in CD20+ B-cell frequency in retroperitoneal lymph nodes *vs* non- OBI controls; depletion of naïve B cells, memory B cells, and plasmablasts	Not specified	Not specified	Up to 24 weeks
Favi *et al* [35]	2022	Induction in DEAP-HUS	Case report	1 high-risk KT recipient with CFHR1/CFHR3 deletion and anti-CFH antibody	Eculizumab 900 mgon days 0, and 30 + OBI 1 g on day 6	Complete complement blockade; rapid, full, and sustained CD20+ B-cell depletion; undetectable anti-CFH antibody; stable graft function	None	None	1 year
NasrAllah *et al*[38]	2022	OBI *vs* RTX: B-cell depletion and CDC-crossmatch	Comparative cohort	12 highly sensitized KT candidates/recipients (6 OBI, 6 RTX)	OBI 1 g or RTX 375 mg/m^2 with B-cell count and CDC-crossmatch assessed pre- and 2 weeks post-infusion	OBI induced a 98% median reduction in CD19+ B cells; unlike RTX, OBI did not cause false positive CDC-crossmatch	Not reported	Not reported	Not applicable
Favi *et al* [36]	2024	Treatment of ABMR	Case series	2 high-risk KT recipients with early active ABMR refractory to conventional therapy	Eculizumab 900 mg followed by OBI 1 g	Complement inhibition with clearance of intra-graft C4d and C5b-9 depositions; durable peripheral B-cell depletion; preformed and de novo DSA decline; preserved graft function with no signs of ABMR after 3 years	Nausea, vomiting, tachycardia,	CMV viremia, SARS-CoV2 infection, leukopenia	3 years
Ravani *et al*[71]	2024	Recurrent FSGS	Case series	2 KT recipients with early, RTX-resistant recurrent FSGS	OBI 1 g and DAR 16 mg/kg (two doses)	Rapid and complete remission of proteinuria;	Not reported	None reported	≥ 12 months

plasmapheresis discontinued; sustained albumin normalization; no further relapses

ABMR: Antibody-mediated rejection; CDC: Complement-dependent cytotoxicity; CFHR: Complement factor H-related plasma proteins; cPRA: Calculated Panel Reactive Antibody; DAR: Daratumumab; DEAP-HUS: Deficiency of complement factor H-related plasma proteins and autoantibody positive form of hemolytic uremic syndrome; DSA: Donor-specific antibodies; ESRD: End-stage renal disease; FSGS: Focal segmental glomerulosclerosis; FU: Follow-up; KT: Kidney transplant; IRR: Infusion-related reaction; IVIg: Intravenous human polyclonal immunoglobulin; MFI: Mean fluorescence intensity; OBI: Obinutuzumab; RTX: Rituximab; SAE: Serious adverse event.

were acceptable[60]. Following these encouraging results, we are testing an ECU, thymoglobulin, IVIg, and OBI induction scheme without peri-operative PEX. DAR administration will be considered in case of persistently elevated or rebound preformed DSA.

ABMR

In a recent proof of concept study, our group used ECU and OBI to treat two heavily sensitized KT recipients with early refractory ABMR due to C1q-fixing class I and class II DSA. After ECU (900 mg) and OBI (1000 mg) administration, both patients showed effective complement blockage, full peripheral CD20+ B-cell depletion, and prolonged inhibition of preformed and de novo DSA production (both class I and class II). Remarkably, graft histology demonstrated complete clearance of intra-graft C4d deposition and progressive resolution of microvascular inflammation. Renal function rapidly recovered, remaining stable up to three years of follow-up[36]. The preferred use of OBI over other anti-B-cell agents for the treatment of active ABMR recognizes several reasons. First, OBI does not require CDC for B-cell depletion. Therefore, it can be administered with complement inhibitors without losing efficacy. Second, being resistant to IVIg blockage and shaving, OBI remains effective at very high IgG concentrations. Third, OBI enhanced activity on memory B cells and plasmablasts can reduce ongoing anti-HLA antibodies production while limiting long-term plasma cells replacement. Larger studies are needed to confirm these positive findings.

OBI IN POST-TRANSPLANT RELAPSING PRD

The management of autoimmune glomerulopathies and nephrotic syndrome of uncertain origin, such as LN, MN, FSGS, or MCD, represents an unmet clinical need. Although the widespread use of RTX has significantly improved the outcomes of patients who fail to respond to conventional immunosuppressive therapies, the frequent observation of RTX-resistance prompts the development of alternative treatment strategies[73]. Successful OFA administration has been anecdotally described in a case of MN with anti-phospholipase A2 receptor (PLA2R) antibody resistant to RTX[74], and in small case series of pediatric patients with multidrug-dependent nephrotic syndrome[75-77]. However, results from larger studies and experience in KT setting do not support OFA use due to limited benefits and safety concerns[71,78]. Interestingly, encouraging response rates have been observed with OBI in patients with multidrug-dependent nephrotic syndrome, FSGS, MN, or LN[73]. Available literature and ongoing clinical trials exploring OBI use in autoimmune glomerulopathies, multidrug-resistant nephrotic syndrome, and post-transplant relapsing PRD are summarized in Tables 2 and 3, respectively[35-38,71,72].

FSGS

FSGS is a heterogeneous clinicopathologic entity, better defined as a pattern of histologic injury involving podocytes and evolving in complex damage to glomerular capillaries[20]. Currently, it represents the leading cause of nephrotic syndrome in several countries. Among the multiple forms of the disease, primary or idiopathic FSGS certainly represents the most challenging, with overall post-transplant recurrence rates ranging from 30% to 50% and an exceedingly high risk of graft loss. To date, the exact pathogenesis of primary FSGS remains uncertain. The most widely accepted theory is that podocytes injury is initiated by a not yet identified circulating factor, such as the soluble urine-type plasminogen activator receptor (suPAR) and/or B-cell-derived molecules, including antibodies[20,79]. Well-recognized risk factors for relapses are Caucasian ethnicity, young age at onset, rapid progression to ESRD, and previous KT failure due to recurrence[20]. The management of post-transplant relapsing primary FSGS is still debated, and it is generally based on intensified plasmapheresis (PP) with or without anti-CD20 agents like RTX or OFA[20,79]. Although there are studies showing higher response rates following type 1 anti-CD20 mAbs administration, overall outcomes are disappointing, with up to 50% of patients remaining PP-dependent or experiencing graft loss due to recurrence. Similarly, there is no consensus regarding possible prophylactic protocols as most of the schemes have failed to demonstrate a substantial reduction in recurrence or long-term transplant failure[80]. Aiming to explore alternative anti-B-cell strategies, immunosuppressive regimens containing OBI have been recently proposed for the treatment of multidrug-resistant or frequently relapsing FSGS in native kidneys, with interesting outcomes[80,81].

To date, experience in KT setting is limited to three cases. In a pediatric patient (2-year-old, female) with early relapsing primary FSGS refractory to steroid pulses and intensive immunoadsorption, remission was achieved with

Table 3 Ongoing studies with Obinutuzumab in nephrology settings

NCT number	Study title	Type	Phase	Condition(s) studied	Summary	Status	Sponsor
NCT02550652	A Study to Evaluate the Safety and Efficacy of Obinutuzumab in Patients with Lupus Nephritis	I	II	LN	Compare efficacy and safety of OBI plus MMF/MPA with placebo plus MMF/MPA in patients with proliferative LN	Completed	Hoffmann-La Roche
NCT04629248	A Study Evaluating the Efficacy and Safety of Obinutuzumab in Participants with Primary Membranous Nephropathy (MAJESTY)	I	II	pMN	Evaluate efficacy, safety, PD/PK of OBI compared with tacrolimus in pMN	Active, not recruiting	Hoffmann-La Roche
NCT05050214	Obinutuzumab in primary MN (ORION)	I	II	pMN		Active, not recruiting	Mario Negri Institute for Pharmacological Research
NCT05845762	Obinutuzumab in the management of Idiopathic Membranous Nephropathy	O		Idiopathic MN		Not yet recruiting	Qianfoshan Hospital
NCT06120673	REmission in Membranous Nephropathy International Trial (REMIT)	I	III	pMN	Multi-centre, prospective, randomized, open-label, parallel-group trial: 224 adult participants will be recruited to receive either CCS and CP or OBI	Not yet recruiting	The University of Queensland
NCT02586051	A Study of Obinutuzumab to Evaluate Safety and Tolerability in Hypersensitized Adult Participants with End Stage Renal Disease Awaiting Transplantation	I	Ib	End-stage renal disease awaiting KT	Assessment of safety and tolerability of OBI regimen (1 infusion *vs* 2 infusions) at week 24 of desensitization phase and week 28 post-KT	Completed	Hoffmann-La Roche
NCT06781944	OBINUTUZUMAB Versus Cyclophosphamide + Glucocorticoids in Primary Membranous Nephropathy (Blossom Study)	I	III	pMN	Compare OBI against CP combined with CCS in pMN patients. Primary endpoint: Non-inferiority	Recruiting	Huashan Hospital
NCT06295770	Obinutuzumab in Treatment of Fibrillary Glomerulonephritis	I	II	FGN	Efficacy and safety in FGN	Recruiting	Mayo Clinic
NCT04983888	Obinutuzumab in Primary FSGS	I	II	FSGS	Safety and efficacy in inducing complete or partial remission of proteinuria	Active, not recruiting	Mayo Clinic
NCT05786768	Efficacy and Safety of Obinutuzumab Versus Rituximab in Childhood Steroid-Dependent and Frequently Relapsing Nephrotic Syndrome (OBIRINS)	I	II–III	FRNS, SDNS	Assess efficacy and safety of a single infusion of low-dose OBI compared to a single infusion of RTX in children with FRNS/SDNS	Recruiting	Assistance Publique-Hôpitaux de Paris
NCT04221477	A Study to Evaluate The Efficacy And Safety Of Obinutuzumab In Patients With ISN/RPS 2003 Class III Or IV Lupus Nephritis (REGENCY)	I	III	LN	Evaluate efficacy, safety, and PK of OBI compared with placebo in patients with ISN/RPS class III or IV LN when added on to standard-of-care therapy (MMF + CCS)	Active, not recruiting	Hoffmann-La Roche
NCT06265220	AB-101 in Combination With B-Cell Depleting mAb in Patients Who Failed Treatment for Class III or IV Lupus Nephritis or Other Forms of Refractory Systemic Lupus Erythematosus	I	I	LN	Assess safety, tolerability, and preliminary activity of AB-101 plus a B-cell depleting mAb after CP and fludarabine in adult with relapsed/refractory LN class III/IV	Recruiting	Artiva Biotherapeutics, Inc.
NCT05039619	A Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Obinutuzumab in Adolescents with Active Class III or IV Lupus Nephritis and the Safety and PK of Obinutuzumab in Pediatric Participants (POSTERITY)	I	II	LN	Evaluate safety, efficacy and PK of OBI in adolescent aged 12-17 years with biopsy-confirmed proliferative LN and pediatrics aged 5-11 years with LN	Recruiting	Hoffmann-La Roche
NCT05627557	A Study to Evaluate the Efficacy and Safety of Obinutuzumab Versus MMF in Participants with	I	III	INS, FRNS, SDNS	Assess efficacy, safety, and PK/PD of OBI compared with MMF in patients with FRNS	Active, not recruiting	Hoffmann-La Roche

	Childhood Onset Idiopathic Nephrotic Syndrome (INShore)				SDNS		
NCT04702256	Induction Therapy for Lupus Nephritis With no Added Oral Steroids: A Trial Comparing Oral Corticosteroids Plus Mycophenolate Mofetil (MMF) Versus Obinutuzumab and MMF (OBILUP)	I	III	LN	Demonstrate that a regimen free of additional oral CCS but with OBI (and MMF) is not inferior to a regimen based on oral CCS and MMF in achieving complete renal response at week 52 without receiving CCS above a prespecified dose	Recruiting	Assistance Publique-Hôpitaux de Paris

CCS: Corticosteroids; CP: Cyclophosphamide; FGN: Focal glomerulonephritis; FRNS: Frequently relapsing nephrotic syndrome; FSGS: Focal segmental glomerulosclerosis; ISN/RPS: International Society of Nephrology/Renal Pathology Society; KT: Kidney transplant; LN: Lupus nephritis; mAb: Monoclonal antibodies; MMF/MPA: Mycophenolate mofetil/mycophenolic acid; MN: Membranous nephropathy; OBI: Obinutuzumab; PD: Pharmacodynamics; PK: Pharmacokinetics; SDNS: Steroid-dependent nephrotic syndrome.

repeated (every week for four consecutive weeks) OBI (1000 mg/1.73 m^2) and DAR administrations, followed by additional infusions in case of peripheral B-cell reconstitution or increasing proteinuria. The rationale behind this combination strategy was to obtain global B-cell depletion (and antibody production blockage) with a synergistic effect on both peripheral and centrally located CD20+ and CD38+ B cells. A significant reduction in urine protein/creatinine ratio (UPCR) was noted after a few weeks of induction, and it was maintained below the nephrotic range up to 18 months of follow-up. As expected, considering the total doses of anti-CD20 and anti-CD38 mAbs given, several SAEs occurred, including opportunistic pneumonia, cytomegalovirus (CMV) reactivation, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, and chronic hypogammaglobulinemia[82]. Similar results with OBI and DAR were obtained by Randone *et al*[83] in two very recent episodes of post-transplant relapsing primary FSGS unresponsive to intensive PEX, RTX, and anti-interleukin (IL)-1 receptor antagonist anakinra. In both the recipients treated (a 22-year-old male and a 15-year-old female), the authors used a single dose of OBI (1000 mg/1.73 m^2), administering DAR according to peripheral CD38+ cells count. Treatment led to improved renal function, decreased proteinuria, and PEX withdrawal. OBI was not associated with relevant IRRs or SAEs. No graft losses were reported after 14 and 21 months of follow-up[83]. Overall, these preliminary data suggest that OBI might represent a better option over RTX for the treatment of post-transplant refractory primary FSGS because it provides wider and more sustained B-cell depletion. Relevantly, these reports demonstrate that OBI can be coupled with DAR to achieve global B-cell control and sustained FSGS remission. It can be argued that, given the limited information available, we cannot assess the specific contribution of OBI or DAR. In this regard, it would be helpful to investigate the effects of type 2 anti-CD20 and anti-CD36 mAbs monotherapies. However, the lack of efficacy of current protocols prompts the utilization of alternative treatment strategies. In line with Angeletti *et al*[84], we believe that first-line anti-CD20 and anti-CD38 agents should be offered to all KT recipients experiencing post-transplant FSGS recurrence. A similar prophylactic scheme could be proposed to patients at high risk of recurrence[84].

MN

Primary MN, histologically characterized by immune complex deposition along the subepithelial region of the glomerular basement membrane and ultrastructural podocyte injury, represents a leading cause of nephrotic syndrome [85,86]. It has been demonstrated that podocytes injury is mediated by complement activation and autoantibodies against the PLA2R or thrombospondin type 1 domain-containing 7A. Although spontaneous remission can occur, about 30% of patients progress to ESRD, eventually requiring renal replacement therapy over 5-10 years[86,87]. Current international guidelines recommend RTX as first-line treatment of primary MN at high risk of progression or with persistent nephrotic-range proteinuria under standard immunosuppression[88]. However, RTX-resistance has been reported in 1/3 of the cases[89]. After KT, signs of recurrence can be detected in up to 50% of recipients, often within the first post-transplant year. The main determinant of graft recurrence is the presence of circulating anti-PLA2R antibody at the time of transplant. As observed in the non-transplant population, a significant proportion of recipients fail to respond to conventional therapies or RTX, eventually losing their transplant[85]. Recent studies suggest that OBI may be more effective than RTX in managing refractory primary MN as it shows greater B-cell depletion capacity and enhanced activity against memory B cells. Furthermore, primarily operating through complement-independent mechanisms, OBI is not affected by complement dysfunction or exhaustion[31,87].

In a retrospective case series, Lin *et al*[80] evaluated the outcomes of 18 patients with refractory MN (66.6% following RTX) who had been treated with OBI as a rescue therapy. OBI (1000 mg) was administered, aiming to achieve full peripheral CD19+ B-cell depletion, with repeated infusions (1000 mg every two weeks) in case of B-cell persistence or reconstitution. After a median follow-up of 13.6 months, signs of remission were observed in 94.4% of patients [Cox proportional hazards model, log-rank test, and Kalan-Meier survival analysis: (1) Partial remission: 66.7%; and (2) Complete remission: 27.8%]. There was a significant reduction in median UPCR (P = 0.003) and a significant increase in median serum albumin levels (P < 0.001) at 12 months. IRRs and SAEs were minimal[90]. Positive results were also reported by a larger retrospective study assessing the efficacy of OBI (n = 20) *vs* RTX (n = 31) in patients with refractory MN. Overall response rate was strikingly higher in the group treated with OBI (90%) compared to the one receiving RTX (38.7%), with a significant difference in the likelihood of remission [hazard ratio (HR): 4.91; 95%CI: 2.25-10.73; P < 0.001]. After six months, anti-PLA2R antibody negativity was achieved in 87.5% of patients in the OBI group and 21.4% in the RTX group. Safety outcomes were similar, confirming OBI tolerability in heavily immunosuppressed patients[91].

Interestingly, successful treatment of patients with primary MN and anti-RTX antibody has been recently described by an international retrospective multicenter study[92]. Two more studies, a phase 2 (ORION, NCT-05050214: OBI *vs* tacrolimus) and a phase 3 (MAJESTY, NTC-04629248: OBI *vs* RTX) trial are actively recruiting patients.

The first report describing OBI use in KT recipients with MN was published in 2020. Four patients (three with relapsing primary MN and one with de novo MN) received OBI (2000 mg total dose) following an unsuccessful course of tacrolimus or RTX. During the follow-up (between 9 and 24 months), all patients achieved remission (complete or partial), showing substantial improvements in UPCR, serum albumin concentration, and circulating anti-PLA2R antibody level. Overall, graft function remained stable. Reported SAEs included leukopenia, hypogammaglobulinemia, and CMV viremia[85]. In a very recent single-center case series from Australia, five patients with refractory or recurrent MN received OBI (100 mg on day 1, 900 mg on day 2, and 1000 mg on day 15) as a rescue therapy. Among these patients, a KT recipient with relapsing MN was included. Three out of five subjects (precisely, those with PLA2R-associated MN) achieved complete clinical and immunological remission, with sustained anti-PLA2R antibody negativity. Despite OBI, the KT recipient did not show signs of remission, eventually losing the graft due to recurrence[93]. There is mounting evidence that OBI could represent a game-changer in the management of patients with primary MN. In our opinion, the positive findings observed in native kidneys support OBI use in KT setting, particularly in case of refractory or frequently relapsing MN with circulating anti-PLA2R antibody. Aiming to reduce the cumulative burden of immunosuppression, first-line attempts with OBI might be considered in selected cases.

MCD

MCD is a major cause of idiopathic nephrotic syndrome. The pathological hallmark of the disease is the presence of podocytes diffuse foot processes effacement and loss of slit diaphragms, without electron-dense deposits[94]. T-cell dysfunction plays a critical role in the development of MCD, but there is now evidence that B cells and anti-nephrin antibody represent important contributing factors[95]. Current international guidelines recommend steroid administration as first-line treatment, progressively escalating to calcineurin inhibitors, MMF, and cyclophosphamide (CP) in case of resistance or relapse[96]. However, chronic tacrolimus or CP do not guarantee long-term remission, and they are frequently associated with metabolic complications and nephrotoxicity. Following the recognition of anti-nephrin antibody as a possible cause of steroid-resistant MCD, RTX has emerged as a promising therapeutic option[97]. Further benefits of RTX in the setting of MCD include T-cell modulation (with reduction of T helper 17 cells and restored T-cell homeostasis) and podocytes protection through multiple mechanisms (namely, sphingomyelinase-like phosphodiesterase 3b-mediated stabilization, IL-4 signaling modulation, direct cytoskeletal effects, and improved podocytes response to oxidative stress)[95]. Although there are several studies describing successful RTX use in de novo, refractory, or frequently relapsing MCD[95], an increasing number of patients with RTX-resistant MCD has been reported[80,81]. Relevantly, cases of de novo or recurrent MCD can be observed after KT[98,99]. Recipients with older age at native kidney disease onset or steroid-resistant MCD show the highest risk of recurrence, and they might not respond to conventional treatments[100].

In non-transplant patients, positive response rates have been observed with rescue OBI administration in both adults and children[80,81,101,102]. According to Wang *et al*[101], complete remission was obtained following OBI use in a 37-year-old woman with a long history of frequently relapsing MCD unresponsive to RTX. In a small case series, six patients (median age: 30.4 years) with steroid-resistant, RTX-resistant, or frequently relapsing MCD were treated with OBI. Within a few weeks, 84% of subjects achieved complete remission. Renal function improved in all cases, with 50% of patients rapidly returning to baseline. No relapses, severe IRRs, or SAEs were observed during a mean follow-up of 12.5 months [102]. Excellent response rates were also described by a larger retrospective study in pediatric patients (n = 41) with RTX-resistant nephrotic syndrome[81]. Further studies are needed to confirm the superiority of OBI over RTX in MCD, before and after transplant. Above all, it will be necessary to establish which subgroup of patients can benefit the most from a more powerful and wider B-cell depletion.

LN

LN affects 30%-60% of patients with systemic lupus erythematosus (SLE), representing a leading cause of ESRD in young women. LN is characterized by autoantibody production and immune complex deposition in the kidney, progressively leading to glomerulonephritis, tubulointerstitial inflammation, and fibrosis. Despite significant advances in immunosuppressive therapies, up to 30% of LN eventually require renal replacement therapy[103]. After KT, recurrence rates as high as 40% have been reported, with increased morbidity and poor graft survival. Recipients with prolonged disease activity before transplant and those with persistently high anti-dsDNA antibody levels exhibit the highest risk of recurrence, with early onset and rapid progression to graft failure[104]. As for other autoimmune glomerulopathies with autoantibody production, RTX use is endorsed by current international guidelines in case of aggressive or refractory LN[105]. Improved outcomes compared to the standard of care have been recently observed following OBI administration.

In the NOBILITY trial (phase 2, randomized, double-blind, placebo-controlled), 125 patients with proliferative LN on MMF and steroid were randomized to receive multiple OBI doses (1000 mg at weeks 0, 2, 24, and 26) or placebo. Complete renal response (*i.e.*, UPCR < 0.5, stable serum creatinine, and inactive urinary sediment) rate was significantly higher in the OBI group: 41% *vs* 23% (P = 0.026). Relevantly, OBI administration was associated with a slower deterioration of renal function (slope advantage: 4.1 mL/minute/1.73 m^2; P = 0.043), and a reduced risk of LN flare (HR: 0.43; 95%CI: 0.20-0.95)[106]. The REGENCY study (phase 3, randomized, double-blind, placebo-controlled) investigated the efficacy of OBI in adult patients with severe LN. In addition to standard immunosuppression (MMF and steroid), the participants received a placebo or two different OBI schemes (1000 mg on day 1, 2, 24, 26, and 52 or 1000 mg on day 1, 2, 24, 26, 52, and week 50). The primary endpoint of the study was the achievement of a complete renal response (namely, UPCR < 0.5, estimated glomerular filtration rate ≥ 85% from baseline, and no intercurrent events) by week 76. Key secondary endpoints included the maintenance of a complete renal response with a daily prednisone dose ≤ 7.5 mg between weeks 64 and 76, and a UPCR < 0.8 without intercurrent events. A total of 271 subjects were enrolled: 135 were treated with OBI while 136 received a placebo. According to results, 46.4% of the patients who had received OBI exhibited complete renal response at week 76, compared to 33.1% in the placebo group ($P = 0.02$). In 42.7% of OBI-treated patients, complete renal response was maintained with a prednisone daily dose ≤ 7.5 (30.9% in the placebo group; $P = 0.04$). OBI administration was also associated with a significant reduction in UPCR (55.5% *vs* 41.9%; $P = 0.02$). Although the incidence of SAEs was higher in the OBI arm (especially infectious complications), OBI safety profile remained acceptable [107]. Two more randomized clinical trials investigating OBI in LN are in progress (ALLEGORY, NTC-04963296 and OBILUP, NTC-04702256). Overall, current literature seems to support future OBI use in KT recipients with aggressive or refractory LN. Moreover, considering the specific characteristics of SLE and LN, OBI unique mechanism of action could favor the development of more effective integrated anti-CD20 and anti-complement strategies.

Atypical hemolytic uremic syndrome

Primarily acting through complement-independent B-cell-depleting mechanisms, OBI can be administered in combination with complement-inhibitors in case of relapsing PRDs due to abnormal complement activity and antibody production[35]. The widespread use of the anti-C5 mAb ECU has changed the management of patients with atypical hemolytic uremic syndrome (aHUS)[108]. However, some rare disease variants remain difficult to treat[35]. KT candidates with deficiency of complement factor H (CFH)-related plasma proteins and autoantibody positive form of hemolytic uremic syndrome (DEAP-HUS) exhibits a dangerous combination of genetic and acquired predisposing factors for relapsing thrombotic microangiopathy after transplant. Therefore, they require specific interventions to prevent anti-CFH production and/or block the complement cascade[109,110]. The recommended strategy is repeated pre-transplant and post-transplant PEX with life-long ECU administration. In fact, it has been shown that high-risk recipients usually experience anti-CFH antibody rebound and relapsing aHUS as soon as PEX is interrupted, or ECU is withdrawn. To reduce the burden of anti-CFH antibody, peri-transplant administration of RTX has also been considered, but experience remains limited to four patients with a relatively low risk of recurrence and short-term follow-up[35,111,112]. Following the same rationale while taking advantage of OBI unique characteristics, our group has recently described an alternative prophylactic strategy for high-risk DEAP-HUS KT candidates. Rather than multiple PEX sessions and chronic complement inhibition, we opted for peri-transplant administration of ECU and OBI, achieving temporary complement inhibition (15-30 days), sustained B-cell depletion (up to 12 months), and long-lasting anti-CFH antibody production blockage (undetectable anti-CFH antibody during the entire follow-up). This OBI-based prophylaxis scheme could simplify the management of KT patients with DEAP-HUS, enabling deceased donor’s allocation and recipient’s optimization with excellent transplant outcomes and reduced costs[35].

Cryoglobulinemia

Cryoglobulins are plasma Ig precipitating at temperatures < 37 °C. Cryoglobulinemia can be associated with several symptoms and signs overall referred to as cryoglobulinemic vasculitis (CV). The kidney is involved in about 30% of cases, with the occurrence of acute nephritic syndrome or nephrotic range proteinuria (mostly, membranoproliferative glomerulonephritis), eventually leading to dialysis or transplantation. Etiology varies and it may include B-cell malignancies and chronic hepatitis C infection[113]. Treatment is generally tailored on the specific characteristics and needs of the patient, but severe forms of the disease often require apheresis, high-dose steroid, CP, and B-cell depletion for effective control of circulating cryoglobulins[113-115]. Currently, RTX represents the preferred anti-B-cell agent in the setting of CV, because it directly reduces the amount of CD20+ B lymphocytes producing cryoglobulins. Several studies have demonstrated that RTX use is associated with a significant improvement in both clinical and laboratory parameters (up to 80% response rate) [115,116]. However, repeated RTX administrations are costly, may lead to resistance due to the development of anti-RTX antibody, and greatly increase the risk of IRRs or SAEs. Urgent apheresis is still recommended in individuals with refractory forms of CV affecting multiple organs and causing hyper viscosity syndrome[117]. To date, data regarding the use of other type 1 anti-CD20 mAbs in the setting of CV are lacking. Encouraging results have been obtained with the anti-B-cell activating factor (BAFF) mAb belimumab[118,119].

Interestingly, there are three case reports describing OBI-based rescue therapies in patients with RTX-resistant and bortezomib-resistant mixed cryoglobulinemic membranoproliferative glomerulonephritis[120,121], or RTX allergy[122]. These positive findings could further expand post-transplant indications to OBI administration.

OBI SAFETY AND COSTS

IRRs

Assessing the safety profile of OBI in ESRD and KT patients represents a major issue, and it should be a critical endpoint for future research projects. Indeed, considering OBI effects on peripheral and central CD20+ B cells as well as CD4+ and CD8+ T cells or NK cells, the risk of IRRs and SAEs remains substantial[123].

The experience gained treating hematologic malignancies demonstrates that OBI safety is overall like that of RTX. Indeed, recent studies evaluating the occurrence of IRRs in the real world have shown that the cumulative incidence of IRRs is about 25%, but less than 2% of the patients experience severe complications[124]. As for other cell-depleting mAbs, IRRs are mostly non-allergic and caused by massive cytokine release and/or inflammation, primarily triggered by the binding of the compound to the designed target on the cell surface. Accordingly, they occur within a few hours of infusion and can be mitigated by the concomitant use of premedication (steroid, antihistamines, paracetamol, and antiemetics), hypertension medications withdrawal, or splitting the total dose of OBI in two or more administrations[124]. IRRs can be extremely variable, with symptoms and signs of systemic or, more often, localized involvement[124]. To date, clinical or laboratory characteristics that may reliably predict the risk of OBI IRRs have not been identified[124]. Furthermore, the potential generalizability of the information acquired in hematology setting remains questionable as patients with leukemias or lymphomas may greatly differ from those with ESRD or KT.

The results from the THEORY trial and the small case series or case reports currently available show that the cumulative incidence of IRRs is about 50%, with most patients experiencing mild-to-moderate symptoms, such as chills, nausea, vomiting, tachycardia, or hypotension. Relevantly, no life-threatening reactions[35-38] were recorded and there were no patients requiring OBI withdrawal[60,83,85,93]. At our institution, we administer OBI 1000 mg diluted into a 250 mL 0.9% sodium chloride bag. The infusion starts at 50 mg/hour, and the rate of infusion is progressively increased by 50 mg/hour increments every 30 minutes (to a maximum of 400 mg/hour). Patients always receive premedication with glucocorticoid, acetaminophen, antihistamine, and metoclopramide. They are closely monitored, and the infusion is slowed down or temporarily interrupted in case of IRRs. Previous ECU administration did not increase the risk of OBI IRRs[35,36,60].

SAEs

The occurrence of drug-related adverse events is a frequent complication following the administration of anti-CD20 mAbs. It is well-known that RTX use is mostly associated with leukopenia and infections[125]. Although in clinical trials OBI has demonstrated a similar safety profile, the cumulative incidence of adverse events was higher than RTX, suggesting increased toxicity[126,127]. A recent systematic review and meta-analysis focused on patients with B-cell lymphoproliferative disorders (n = 4247) has evaluated the incidence and severity of adverse events for OBI-based and RTX-based regimens. Patients treated with OBI were at higher risk of SAEs (grade 3 and 4) compared to those receiving RTX [risk ratio (RR) = 1.15; 95%CI: 1.09-1.2]. OBI administration was more often complicated by clinically relevant thrombocytopenia (RR = 2.8; 95%CI: 1.92–4.06) and cardiac events (RR = 1.65; 95%CI: 1.11–2.46). Rates of moderate-to-severe neutropenia, anemia, and secondary malignancies were similar. Nonetheless, a nearly significant increase in infections rate was noticed after OBI use (RR = 1.17; 95%CI: 1.0–1.36)[126]. A possible explanation is that OBI profound peripheral and central B-cell depletion (also involving memory B cells and plasmablasts) might have a greater impact on B-cell immunity, thus increasing the overall risk of infections. Similarly, the higher incidence of thrombocytopenia and cardiac events might be reasonably explained by the stronger cytokine release syndrome associated with B-cell depletion [128].

Available data show that the risk of adverse events after OBI infusion is high also in patients with ESRD and KT recipients. According to the THEORY study, the incidence of adverse events in KT candidates desensitized with OBI was 36%, with the occurrence of life-threatening episodes of pneumonia, nocardiosis, and sepsis[37]. Two deaths due to mucormycosis and SARS-CoV-2 were reported by NasrAllah *et al*[38] in a similar subset of patients. Among KT recipients treated for relapsing MN, there was a death due to glioblastoma[85]. Overall, frequently observed SAEs[35-38] included grade 3-4 Leukopenia, SARS-CoV-2 infection, and CMV infection[60,83,85,93]. In our experience, OBI use was not associated with higher complication rates than RTX. Intermittent leukopenia was easily managed with MMF minimization or temporary withdrawal; CMV and SARS-CoV-2 infections resolved with immunosuppression reduction and antiviral therapy. Remarkably, the concomitant administration of ECU did not increase the risk of SAEs[35,36,60]. In this regard, it is relevant to say that we routinely vaccinate all KT candidates for measles, chickenpox, SARS-CoV-2, influenza, and HBV. Heavy sensitized recipients and patients with aHUS also receive pre-transplant meningitis vaccination and a multi component serogroup B vaccine. We provide CMV universal prophylaxis (valganciclovir) and pneumocystis prophylaxis (trimethoprim/sulfamethoxazole) for six months. Considering the net state of immunosuppression of the patients treated with OBI in KT setting (heavy sensitization, refractory PRD, previous exposure to several immunosuppressants and mAbs), it remains difficult to rule out the contribution of other immunosuppressive agents. Nevertheless, the predictable consequences of profound and sustained B-cell depletion, particularly regarding hypogammaglobulinemia and secondary immunodeficiency, warrant continued and careful monitoring, necessitating individualized risk assessments and prophylactic strategies.

Costs

The economic implications of integrating novel therapeutics, such as OBI, into current KT practice clearly extend beyond the clinical efficacy of the proposed agent, necessitating a detailed cost analysis that should consider local variations in health care organizations, tariffs, and reimbursements. Table 4 offers a comprehensive cost comparison between the main B-cell, T-cell, antibody-targeted, and complement-targeted therapies available in Italy with a potential application in KT. These numbers refer to a very specific context; precisely a country in which operates a fully nationalized health care system, providing complete support to all citizens regardless of their social status, income, or insurance coverage. The national health systems in France, Spain or United Kingdom are very similar to the Italian one. Many other European countries like Germany or Holland apply centralized pricing and negotiated reimbursement models that ultimately help lowering the final cost of treatment. In contrast, the United States exhibit higher acquisition costs due to market-based pricing, and greatly rely on private insurance coverage, which may pose significant barriers to the adoption of more expensive immunosuppressive regimens, especially outside formal approval (off-label use).

As pointed out by our group when discussing the perceived increase in cost associated with the use of ECU and OBI for the treatment of ABMR, the financial burden of new protocols should be carefully weighed against the potential savings generated by prolonged kidney graft survival compared to dialysis or retransplant[36]. Furthermore, as suggested when proposing an alternative OBI-based management strategy for KT candidates with DEAP-HUS, a wider analysis of the collateral costs associated with current standard of care could disclose hidden, yet substantial, long-term

Table 4 Cost of main B-cell, T-cell, and complement-targeted therapies in Italy

Active substance	Dosage form	Trade name	Manufacturer brand	Price per unit (€)
Rituximab	500 mg, 50 mL	Mabthera	Roche	2067
Ofatumumab	20 mg, 0.4 mL	Kesimpta	Novartis	2035
Ocrelizumab	300 mg, 10 mL	Ocrevus	Roche	9309
Ublituximab	150 mg, 6 mL	Briumvi	Neuraxpharm	5067
Obinutuzumab	1000 mg, 40 mL	Gazyvaro	Roche	4668
Daratumumab	1800 mg, 15 mL	Darzalex	Janssen-Cilag	8418
Bortezomib	3.5 mg	Bortezomib BV	Sandoz	1277
Alemtuzumab	12 mg, 1 mL	Lemtrada	Sanofi	13126
Thymoglobulin	50 mg, 10 mL	Thymoglobuline	Sanofi	239
Basiliximab	20 mg, 5 mL	Simulect	Novartis	1515
Belimumab	400 mg	Benlysta	GlaxoSmithKline	726
Eculizumab	300 mg, 30 mL	Soliris	Alexion	6852
Ravulizumab	100 mg, 11 mL	Ultomiris	Alexion	27407
Imlifidase	11 mg	Idefirix	Hansa Biopharma	245084
Intravenous human polyclonal immunoglobulin	10 g, 200 mL	Ig vena	Kedrion	1073
Fresh-frozen plasma	200 mL	Octaplas	Octapharma	75

savings with OBI[35].

OBI INDICATIONS, LIMITATIONS, AND FUTURE PERSPECTIVES

The clinical rationale for OBI use in current and future prophylactic or therapeutic protocols is compelling. However, considering the limited experience in patients with ESRD or KT recipients, OBI administration must be guided by a thorough evaluation of potential benefits and risks.

OBI can offer a faster, deeper, and wider B-cell depletion compared to type 1 anti-CD20 mAbs, effectively acting on both peripheral and central memory B cells and plasmablasts. The unique characteristics of the type 2 anti-CD20 Fab region and the glycoengineered Fc segment ensure enhanced ADCC, ADCP, and DCD while limiting the negative effects of excessive plasma IVIg concentrations, complement dysfunction, and trogocytosis. Therefore, OBI can reasonably be considered as a rescue therapy for patients who fail to respond to RTX or with documented anti-RTX antibodies. It might also represent a preferred option over type 1 anti-CD20 mAbs in the case of simultaneous administration of high-dose IVIg or complement inhibitors.

Although encouraging, the results from the THEORY trial do not seem to support routinary OBI inclusion in standard (apheresis, IVIg, anti-CD20 mAb) desensitization protocols, unless there is a previous history of RTX-induced SAEs, RTX-resistance, or anti-RTX antibody. In fact, despite the remarkable B-cell depletion capacities, OBI did not show a clinically relevant impact on pre-transplant circulating anti-HLA antibodies and negative crossmatch transplant rates[37]. The different efficacy observed with anti-HLA antibodies compared to autoantibodies in autoimmune diseases might be explained by the fact that autoantibodies are mostly produced by plasmablasts (CD20+) whereas preformed DSA are primarily produced by long-lived plasma cells (CD20-). Accordingly, next desensitization protocols might consider combining OBI with anti-CD38 mAbs (DAR), proteasome inhibitors (bortezomib, carfilzomib), or compounds targeting IL-6 (tocilizumab, clazakizumab), and BAFF (belimumab)[32,129]. OBI integration in IgG degrader imlifidase-containing protocols for HLA-incompatible KT candidates is currently under investigation in our institution, aiming to reduce rebound anti-HLA antibody levels and early AMBR rates[130]. The theoretical lack of effects of OBI on CDC crossmatch tests (due to the lower complement-binding capacity) could represent an unexpected benefit as RTX-based desensitization regimens have been associated with the frequent occurrence of false positive results[38]. However, this hypothesis requires further validation, and it may not justify a change in clinical practice[72].

Preliminary experience using ECU and OBI in a multimodality induction regimen for high immunological risk deceased donor KT recipients demonstrated effective complement blockage and peripheral B-cell depletion, but mixed activity on preformed DSA. Although there was a certain degree of intra-patient and inter-patient variability in preformed DSA titers, no episodes of ABMR were recorded and there was no evidence of de novo DSA production after one year of follow-up[60]. These findings appear extremely positive, supporting OBI administration as a first-line anti-CD20 induction agent in heavily sensitized deceased donor KT patients receiving ECU. However, long-term graft function and histology data are warranted to confirm the benefits observed in the short run.

Observed outcomes of ECU and OBI in the treatment of refractory active ABMR in patients with high-level preformed class I and class II DSA undoubtedly prompt further investigations as they could promote a substantial change in the management of ABMR[36]. Waiting for more robust data, we believe that OBI use should be cautiously restricted to KT recipients with early or late active ABMR and anti-RTX antibody, those who have failed to respond to conventional anti-rejection treatments, and patients on complement inhibitors.

Even though the results observed in patients with autoimmune glomerulopathies in the native kidneys are extremely positive, the information acquired in KT setting is scant. Therefore, OBI should be primarily considered as a salvage option for recipients with refractory or frequently relapsing primary FSGS and anti-PLA2R-associated MN. In this regard, it might be worth considering extending the spectrum of B-cell depletion combining OBI with DAR as an adjuvant induction or maintenance agent. At the same time, KT recipients with refractory or recurrent PRD and circulating anti-RTX antibody might represent ideal candidates for first-line OBI administration. Considering the lack of validated prophylactic protocols and the scarce efficacy of current treatment strategies, OBI-based prophylaxis could reasonably be offered to patients at high risk of recurrence and with very limited chances of retransplant. The much-anticipated results of ongoing clinical trials will further elucidate the role of OBI in antibody-mediated renal diseases and multidrug-resistant nephrotic syndrome, including LN and MCD.

Future research exploring possible OBI applications in KT will require larger populations, extended follow-up, and rigorous methodology. Prospective, multicenter, randomized, trials are certainly warranted, and they should compare OBI monotherapy and/or OBI-based regimens with the standard of care (or alternative emerging protocols) in relapsing PRD, desensitization, and ABMR. In addition to evaluating the specific efficacy of OBI, these studies should refine dosing, timing, and optimal combination strategies. The possibility of integrating OBI unique B-cell depletion properties with anti-plasma cell agents (DAR) or complement inhibitors (ECU) represents an unprecedented opportunity, and it might drive a paradigm shift in clinical immunosuppression. However, the expected increase in IRRs and SAEs prompts further safety evaluations and the development of dedicated risk mitigation strategies. Translational and mechanistic studies are of utmost importance to better understand OBI PD and PK in ESRD and KT patients. Relevantly, investigating OBI effects on distinct peripheral and centrally located B-cell subsets as well as different autoantibody patterns could help define unrecognized predictors of clinical response or resistance. Given the rarity of the conditions and the heterogeneity of the patients (including the complex immune milieu), creating national and international registries could facilitate data aggregation, outcome assessments, and cost-effectiveness analyses.

CONCLUSION

OBI is a type 2 anti-CD20 mAb with enhanced ADCC, ADCP, and DCD compared to type 1 anti-CD20 mAbs. Unlikely type 1 anti-CD20, anti-CD52, and anti-CD38 mAbs, OBI-induced B-cell depletion is marginally dependent on CDC, and it is not affected by the presence of high-level IVIg or trogocytosis. Preliminary experience with OBI in ESRD patients and KT recipients highlights the potential advancements achievable in the prevention and treatment of ABMR and relapsing PRD, such as autoimmune glomerulopathies, nephrotic syndrome, and DEAP-HUS. Theoretically, OBI unique characteristics could address several limitations of current targeted-cell-targeted therapies, including the limited effects on peripheral and centrally located memory B cells, as well as the reduced efficacy in case of complement dysfunction or excessive antibody concentrations. The possibility of combining OBI with anti-complement agents, proteasome inhibitors, anti-CD38 mAbs, or anti-B-cell activating factor represents an unprecedented opportunity. However, considering the lack of long-term safety and efficacy data, OBI indications should be carefully evaluated and strictly personalized, balancing potential benefits and risks. Properly designed clinical trials are needed to confirm the role of OBI in KT.

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