Rituximab in Kidney Tranplantation

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outline

- RTX in :

1)HLA incompatible recipients

2)ABO incompatible recipients

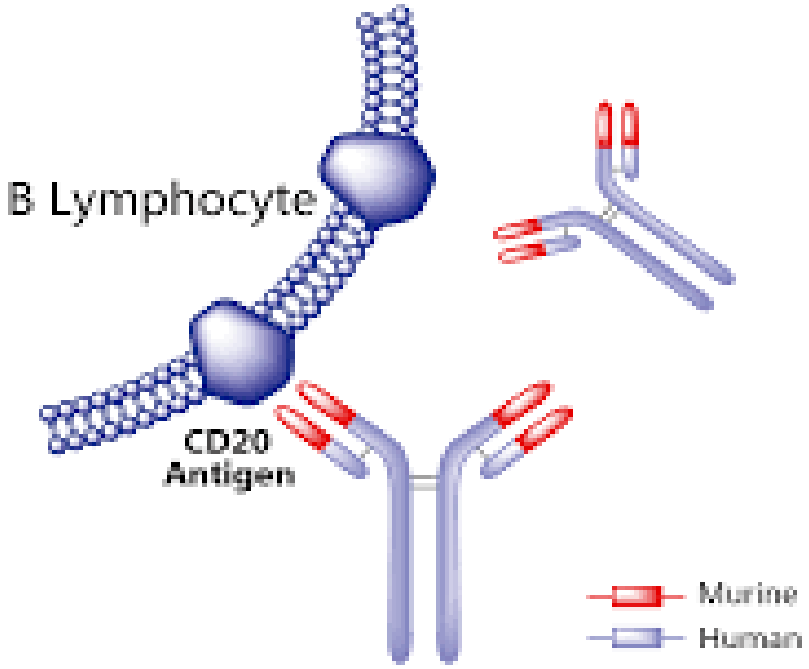
3) Acute and chronic rejection

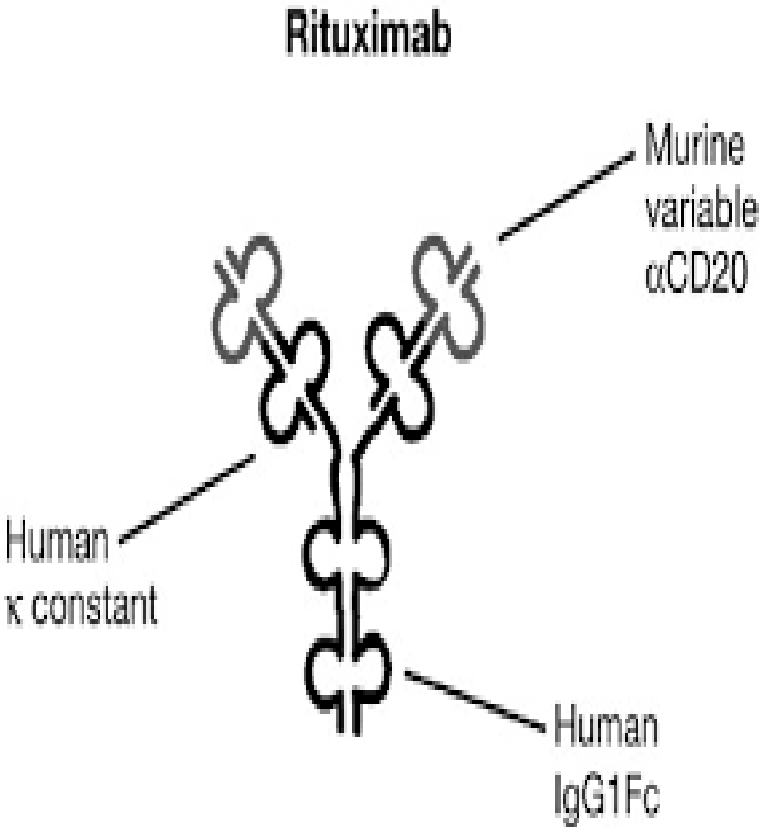
4) Recurrent GN after transplant

5) PTLD

Rituximab

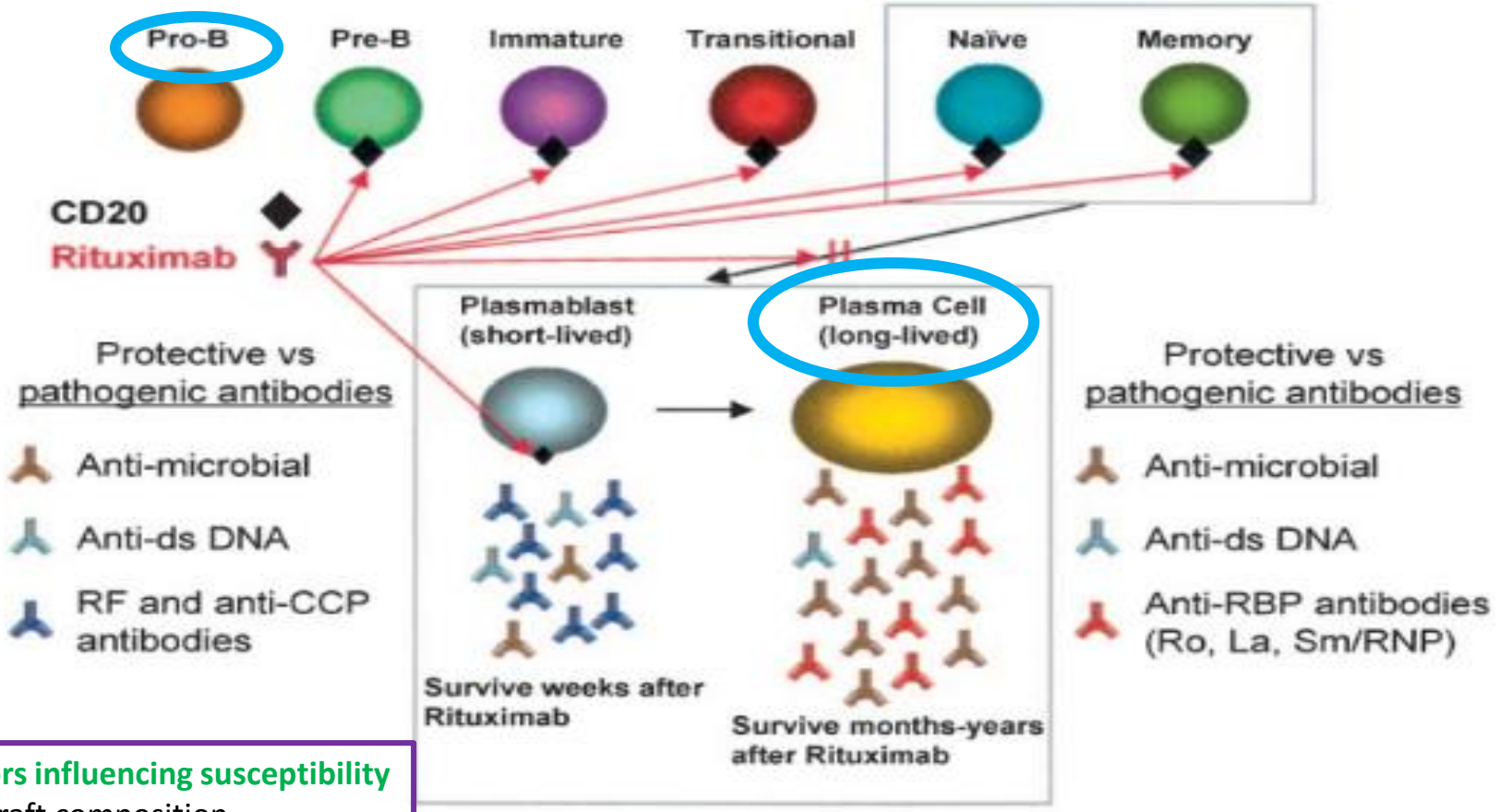
1997- FDA approved





Smith, *Oncogene* 22, 7359–7368 (2003).

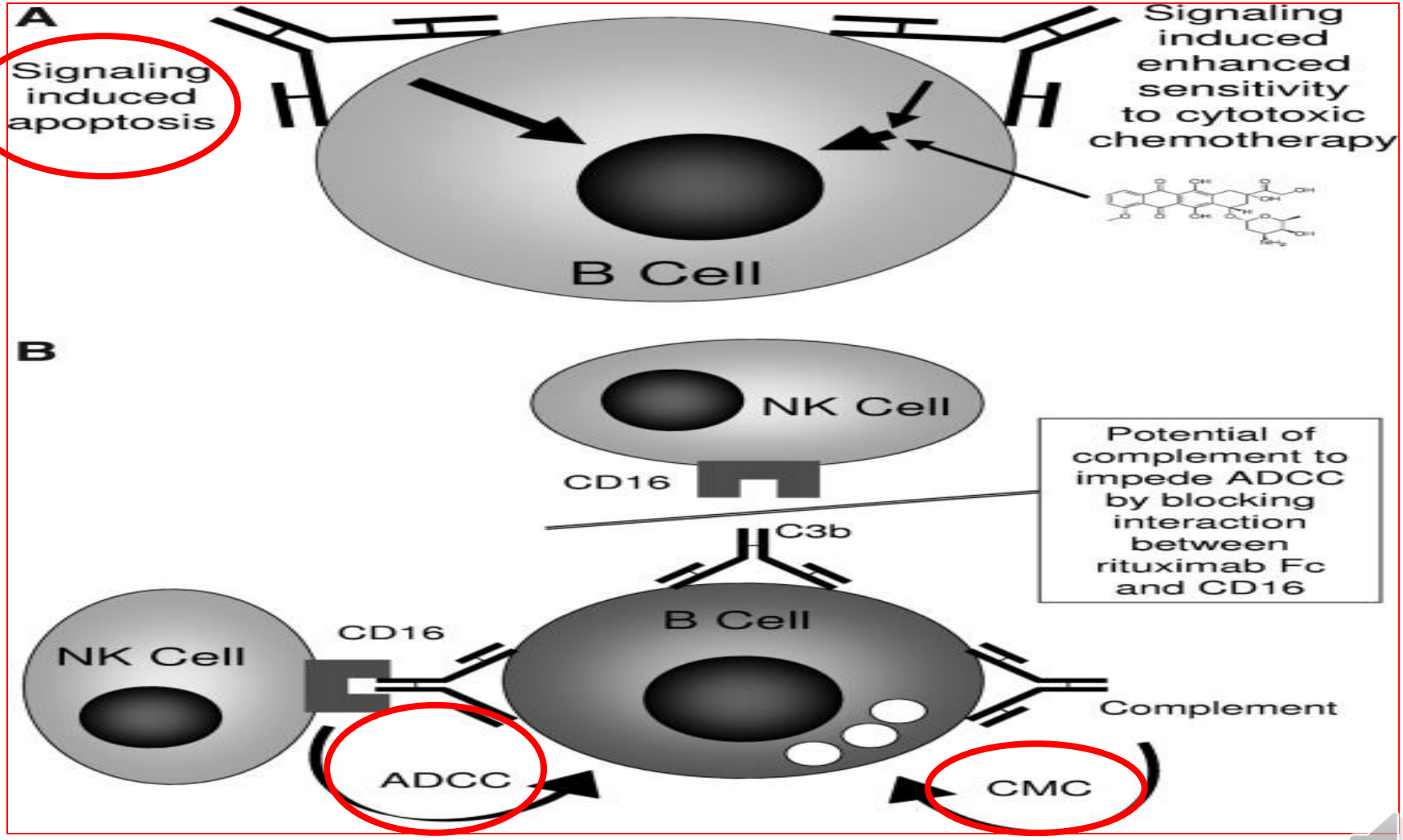
Targets of Rituximab



factors influencing susceptibility
lipid raft composition
Compelement reg pro
FCγRIIIA polymorphisms
FCγRIIB expression

Loony et al, American College of Rheumatology, 2008,58(1)

Mechanism of action



George J.Seminars in Hematology, 47(2),2010

B cells function in Transplantation

- Effective antigen presenting cells(APC)
- Ab secretion, CK production, lymphoid architecture organization
- presence of B-cell aggregates contribute to local immune response in acute or chronically rejecting grafts.
- CK TNF-α and IL-10 is also described in renal allograft injury
- Costimulatory molecules that promote activated T-cell transition to cytotoxic T cells

RTX in kidney transplantation

A: Desensitization protocols for highly sensitized recipients before or concurrent with kidney Tx, and in ABO incompatible kidney Tx

B: Treatment of acute and chronic Ab-Mediated rejection

C:Treatment of recurrent and de novo glomerular diseases

D: Treatment of PTLD

RTX in kidney transplantation

A: **Desensitization protocols for highly sensitized recipients before or concurrent with kidney Tx, and in ABO incompatible kidney Tx**

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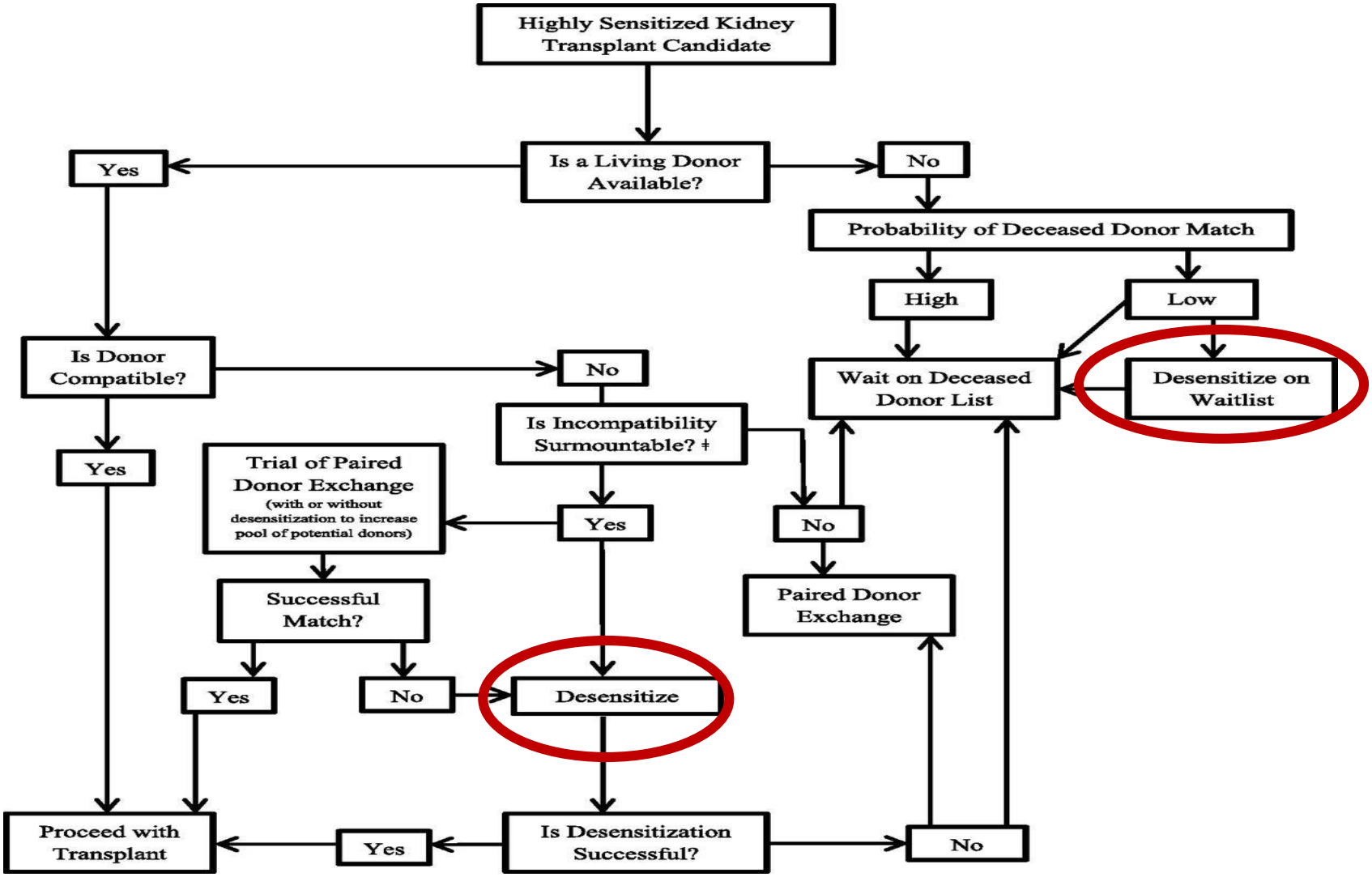
- Approximately 30% of the patients on the United Network for Organ Sharing (UNOS) wait list are considered highly sensitized.
- Eurotransplant, the percentage of patients with a Panel Reactive Antibody (PRA) level of ≥85% increased from 2.0% to 5.6% from 2011 to 2019.
- temporarily remove circulating antibodies and/or antibody production by desensitization
- Recent studies showed improved patient and graft survival in HS patients use of desensitization protocols (B cell reducing agents (rituximab), (IVIG) and plasmapheresis)

Heidt et al.Front Immunol, 25 June 2021

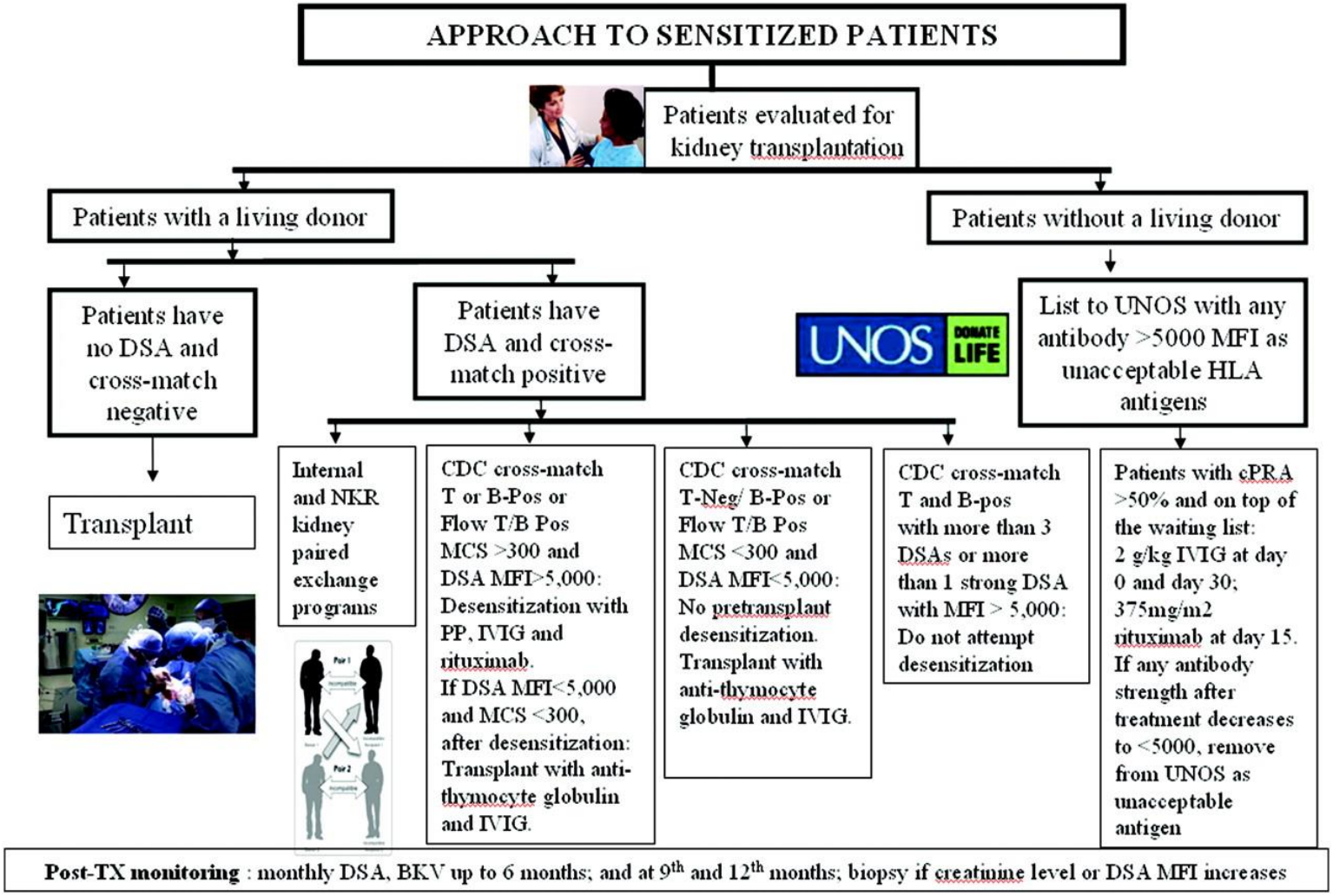
Algorithm for the management of the highly sensitized patient seeking kidney transplant.



Douglas S. Keith, and Gayle M. Vranic CJASN 2016;11:684-693

CJASN
Clinical Journal of the American Society of Nephrology

Algorithmic approach to sensitized patients.



Kwaku Marfo et al. CJASN 2011;6:922-936

CJASN
Clinical Journal of the American Society of Nephrology

Treatment options for sensitized patients

1. **Removal of antibodies**
   Plasmaphresis
   Immunoadsorption

2. Inhibition of antibody production

a. Anti-B cell agents: rituximab (anti-CD20)

b. Plasma cell inhibitors: bortezemib (proteosome inhibitor)

3. Inhibition of complement cascade: eculizumab (anti-C5a)

4. IVIG

a. Neutralization of circulating anti-HLA antibodies through anti-idiotypic antibodies
b. Inhibition of complement activation by binding C3b and C4b and neutralization of C3a and C5a
c. Blockage of immune activation and enhancing the clearance of anti-HLA antibodies by competing for activating FcRs
d. Inhibits the expression CD19 on activated B cells and induces apoptosis of B cells
e. Induces the expression of FcIIB, which is a negative regulatory receptor on immune cells
f. Inhibitory effects on cellular immune responses and nonspecific inhibitory effects on the immune system by binding to Fc receptors on macrophages, neutrophils, platelets, mast cells, and natural killer cells and inhibiting cytokine, chemokine, adhesion molecules, and endothelial cell activity

5. Splenectomy

(removes a major source of lymphocytes, including antibody-secreting B cells, B cell precursor cells, and plasma cells)

Clin J Am Soc Nephrol 6: 922–936, April, 2011

Desensitization therapies in kidney transplantation

Drug class	Name	Mechanism of Action	Previous and ongoing studies	Key Features
Plasmapheresis	NA	Removal of circulating immunoglobulin	Stegall et al. (28)	
Intravenous Immunoglobulin	NA	Exact mechanism unknown. Multiple Immunomodulatory mechanisms.	Glotz et al. (34) Jordan et al. (35) Stegall et al. (28)	
Anti-CD 20 monoclonal antibodies	Rituximab	Depletes B cells	Jordan et al. (36) Vo et al. (31) Jackson et al. (37)	
	Obinutuzumab		Redfield et al. (38)	3rd generation anti-CD20 dependent on ADCC. Used in for relapsed hematologic malignancies.
Proteosome inhibitors	Bortezomib	Accumulation of unwanted cellular protein and apoptosis.	Woodle et al. (39) Moreno Gonzalez et al. (40)	Reversible proteasome inhibitor
	Carfilzomib		Tremblay et al. (41)	Irreversible proteasome inhibitor. Less neurotoxicity than bortezomib.
	Ixazomib		Ongoing ClinicalTrials.gov Identifier: NCT03213158	First oral proteasome inhibitor
Anti-CD38 monoclonal antibodies	Daratumumab	Depletes plasma cells	Kwun et al. (42)	Studied in nonhuman primate model and was associated with increased in T cell mediated rejection.
	Isatuximab		Ongoing ClinicalTrials.gov Identifier: NCT04294459	
Cysteine protease	Imlifidase	Cleaves heavy chains of human IgG (all subclasses) and eliminates IgG effector functions	Jordan et al. (43) Jordan et al. (44)	Rebound of DSA at Day 7. Retreatment with imlifidase often ineffective because of the development of neutralizing antibodies.
Interleukin-6 Blockade	Tocilizumab	IL-6 receptor inhibitor	Vo et al. (45)	
Complement inhibitors*	Eculizumab	Terminal complement blockade to protect against antibody mediated rejection.	Stegall et al. (46) Marks et al. (47) Glotz et al. (48)	

*Does not deplete antibody and therefore not a "desensitization" agent.

Front. Immunol., 2021 | https://doi.org/10.3389/fimmu.2021.686271

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Rituximab and Intravenous Immune Globulin for Desensitization during Renal Transplantation

- 20 recipients / 16 transplanted (80%)
- IVIG 2 g/kg on day 0 and day 30
- Rituximab twice (1 g on day 7 and day 22)
- Immunologic markers : on day 0, at weeks 1, 2, 4, and 6, and at months 3, 6, and 12

- Result: reduction in mean time to transplant from 144 ± 89months to 5 ± 6 months
- 1-year graft and patient survival of 94% and 100%

N Engl J Med. 2008;359(3):242– 51

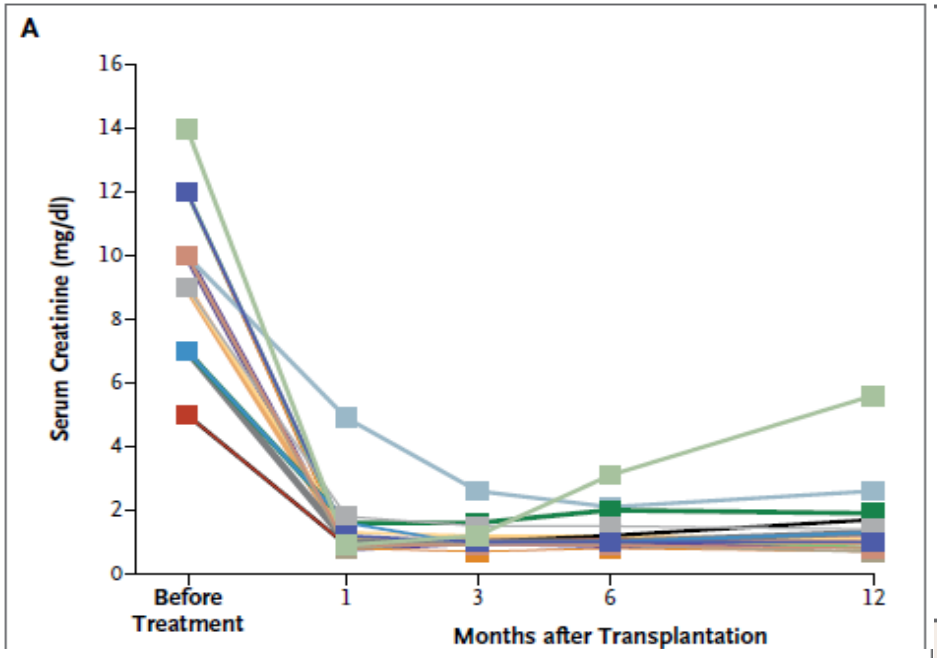


Figure 3. Serum Creatinine Values in the 16 Patients Who Received a Kidney Transplant after Desensitization.

Individual creatinine values (Panel A) and mean values (Panel B) are shown before treatment and through 12 months after transplantation. To convert values for creatinine to micromoles per liter, multiply by 88.4. I bars denote standard deviations.

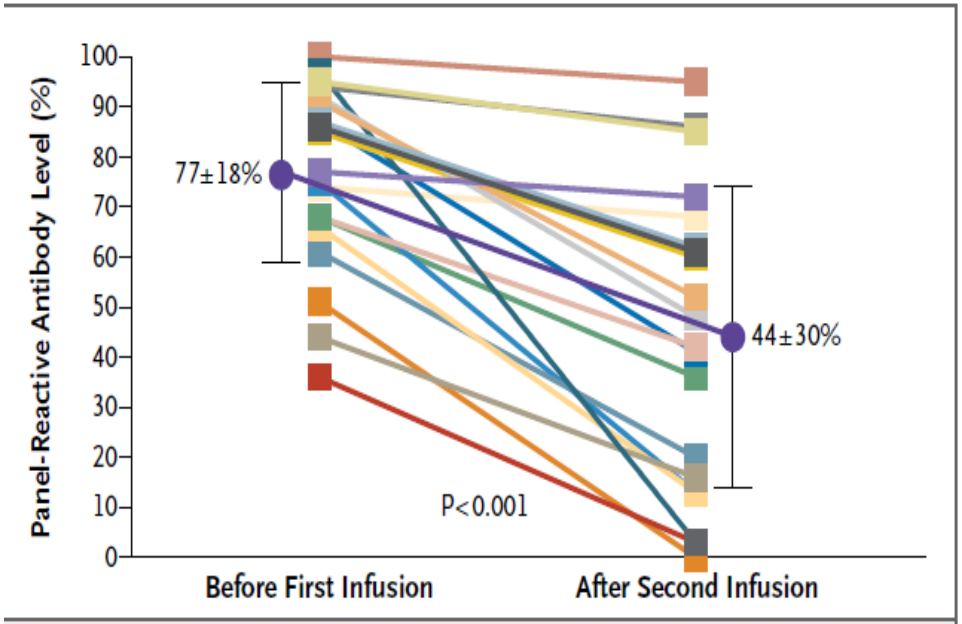


Figure 1. Panel-Reactive Antibody Levels in the 20 Study Patients.

Individual data are shown for patients before the first infusion of intravenous immune globulin and after the second infusion. The pretreatment and post-treatment means are also shown, as determined with the T-cell complement-dependent cytotoxicity panel-reactive antibody assay. The means were significantly different (P<0.001). I bars denote standard deviations.

- No important infectious complications
- 1)Rituximab has no effect on plasma cells,primary source of acute antibody production.
- 2)Rituximab has no immediate effect on circulating antibody levels.

Transplantation

Efficacy, Outcomes, and Cost-Effectiveness of Desensitization Using IVIG and Rituximab

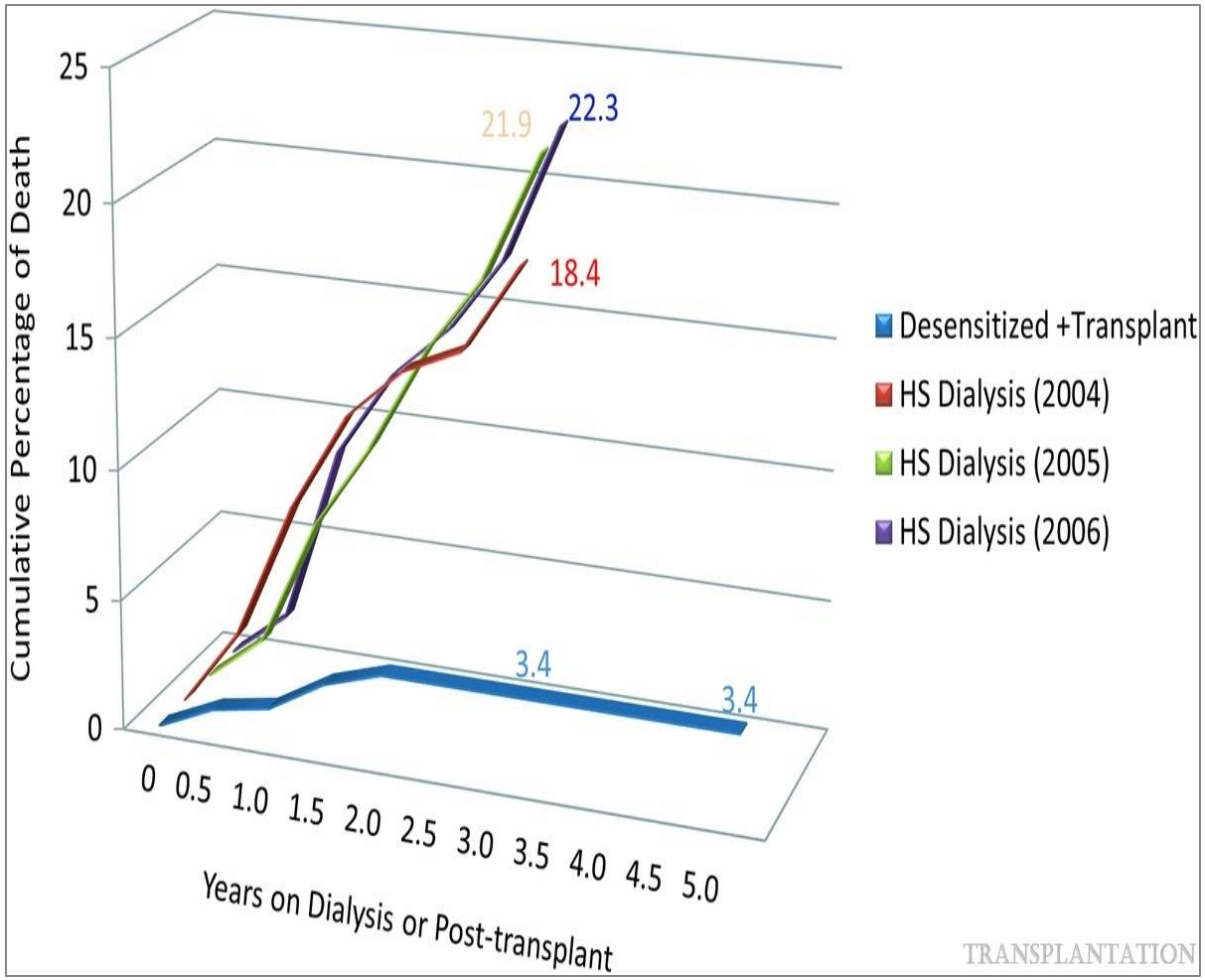
Vo, Ashley A.[1,6]; Petrozzino, Jeffrey[2,3]; Yeung, Kai[1]; Sinha, Aditi[4]; Kahwaji, Joseph[1]; Peng, Alice[1]; Villicana, Rafael[1]; Mackowiak, John[5]; Jordan, Stanley C.[1]

- 2006 - 2011
- N= 207 HS (56 living donors/151 deceased donors) patients (DSA positive, PRA>80%)
- IVIG 2 g/kg on day 1 and day 30
- Rituximab twice (1 g on day 15)
- 146 (71%) transplanted.
- At 48 months: patient and graft survival were 95% and 87.5%
- reduction in mean time to transplant from 114 ± 56months to 4.4 ± 4.9 months
- 29 % of treated patients experienced acute rejections (22% ABMR and 7% cell-mediated rejection)

Efficacy, Outcomes, and Cost-Effectiveness of Desensitization Using IVIG and Rituximab

Transplantation95(6):852-858, March 27, 2013.

doi: 10.1097/TP.0b013e3182802f88



Probability of death after desensitization and transplantation in 146 patients (3.4% at 3 years) compared with a large cohort of patients (n=3754) who were wait listed for transplants, of similar age (45–65 years) and antibody characteristics (PRA>80%), and remained on dialysis during the observation period. The mortality shown is calculated based on UNOS reported data at 1 and 3 years of listing for transplantation. PRA, panel reactive antibody; UNOS, United Network for Organ Sharing.

Efficacy, Outcomes, and Cost-Effectiveness of Desensitization Using IVIG and Rituximab

Outcomes	Year 1 (n)	Year 1 (%)	Year 1 cost[a]	Year 2 (n)	Year 2 (%)	Year 2 cost[a]	Year 3 (n)	Year 3 (%)	Year 3 cost[a]
Transp.+AR	34	16.4	$165	34	16.4	$19	34	16.4	$19
Transp.+AR and DWFG	0	0	$0	1	0.5	$0	1	0.5	$0
Transp.+AR and graft loss	8	3.9	$249	7	3.4	$85	7	3.4	$85
Transp.−AR and DWFG	0	0	$0	4	1.9	$0	4	1.9	$0
Transp.−AR and graft loss	2	1.4	$196[b]	2	1.4	$85	3	1.49	$85
Transp.−AR and no graft loss	102	49.3	$140	98	47.3	$19	97	46.9	$19
Never transp.+dialysis	61	29.5	$113	57	27.5	$85	53	25.6	$85
Deaths+dialysis	0	0	$0	4	1.9	$0	8	3.9	$0
Desensitize cohort cost	207	100	$142	207	100	$39	207	100	$38
3% Discount			$142			$40			$38
4.06% Inflation						$41			$41
Dialysis cohort cost		100	$85		93	$79		86	$73
3% Discount			$85			$80			$74
4.06% Inflation						$82			$79
Total cost desensitize and transp.									$219 per patient
Total cost dialysis only									$239 per patient

[a] Costs are defined as thousands $US per patient.
[b] Derivation of costs are described in detail in the Patients and Methods section.
AR, allograft rejection; DWFG, death with functioning graft.

TRANSPLANTATION

Transplantation95(6):852-858, March 27, 2013.
doi: 10.1097/TP.0b013e3182802f88

Base case costs, apportioned by time and outcomes over the 3-year observation period, and based on 7% mortality rate for dialysis patients

total 3-year cost for patients treated in the desensitization arm was $219,914 per patient compared with $238,667 per patient treated in the dialysis arm.($18,753)

- Marfo et al prospectively desensitized 11 patients with cPRA > 50% (waiting list for more than 5 years),
- IVIg 2 g/kg (days 0 and 30 and single-dose Rituximab 375 mg/m2 on day 15).
- Only 2 of 11 patients transplanted
- Desensitization therapy did not lead to significant reduction in cPRA, the number of unacceptable antigens or their mean florescent intensity (MFI) values
- Kozlowski and Andreoni desensitized 5 patients with c-PRA >85% , noted only transient depletion in antibody was not enough to facilitate transplantation.

Desensitization at the Time of Transplantation for Highly Sensitized Recipients

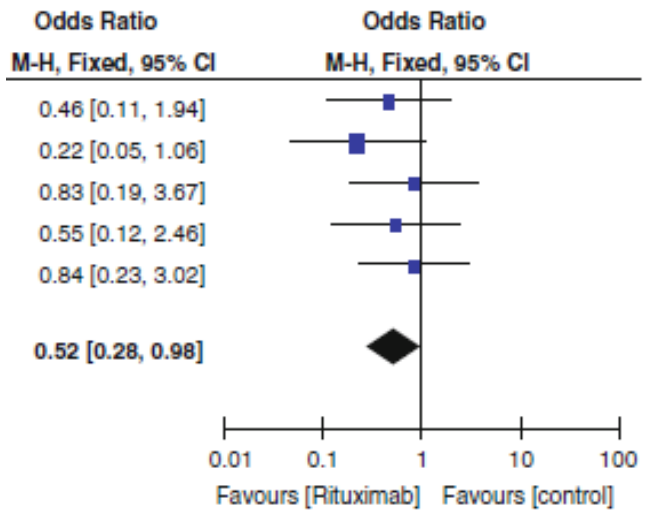
Nephrology - Original Paper | Published: 17 November 2013

Clinical efficacy of rituximab for acute rejection in kidney transplantation: a meta-analysis

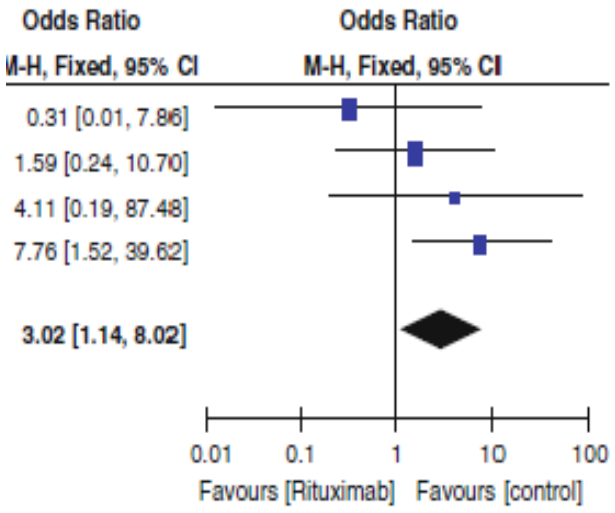
Yu-gang Zhao, Bing-yi Shi, Ye-yong Qian, Hong-wei Bai, Li Xiao & Xiu-yun He

- 589 patients
- 312 pts without RTX/ 277 pts with RTX.
- dosing of RTX ranged from 100 to 1,000 mg.
- IVIg, PP, MMF, Tac, TG.

Desensitization at the Time of Transplantation for Highly Sensitized Recipients



Forest plot of meta-analysis on AMR episodes



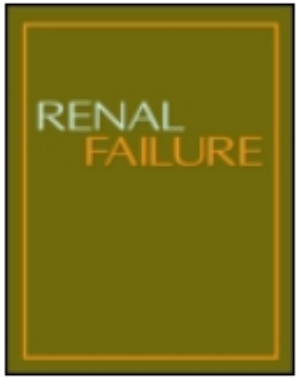
Forest plot of meta-analysis on graft survival rates

Meta analysis:

Rituximab could significantly decrease AMR and increase graft survival rates in sensitized patients

Rituximab as Induction therapy?

- Rituximab has been used for positive cytotoxic/flow cytometric crossmatch, positive DSA , and in high PRA/high immunological risk patients



Renal Failure

ISSN: 0886-022X (Print) 1525-6049 (Online) Journal homepage: https://www.tandfonline.com/loi/irnf20

The effectiveness and safety of rituximab as induction therapy in ABO-compatible non-sensitized renal transplantation: a systematic review and meta-analysis of randomized controlled trials

Rituximab as Induction therapy?

- ABO compatible, non-sensitised recipients.
- 11 records(4 RCT= 480 patients)

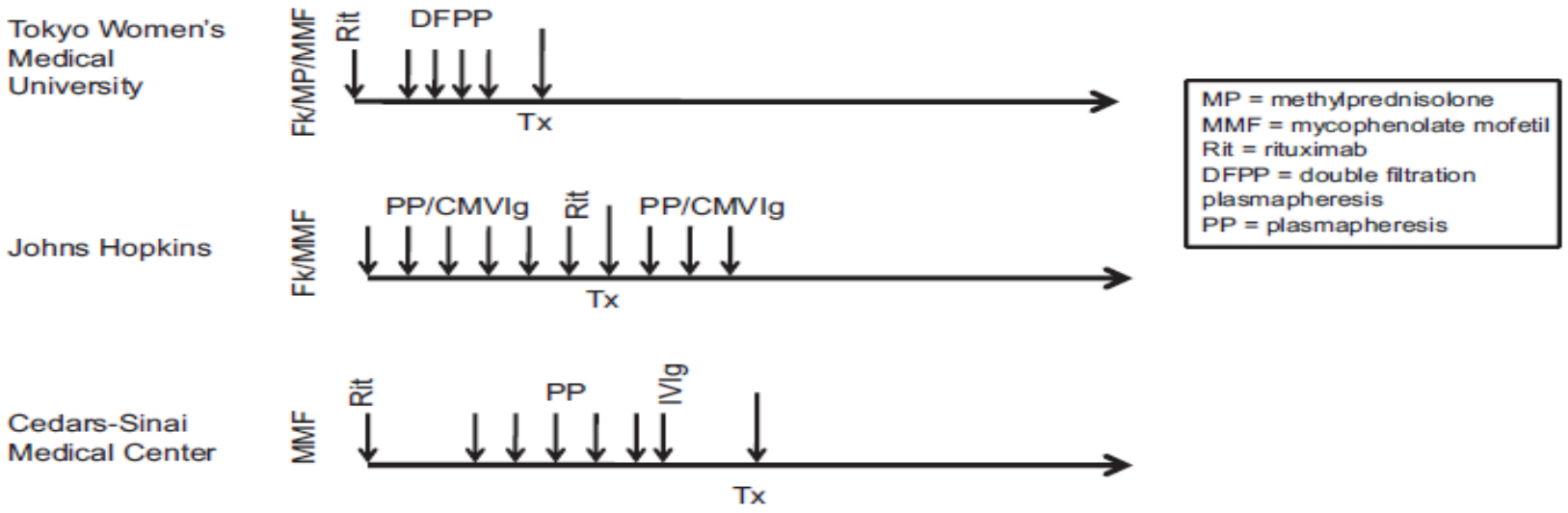
Tydén	PRA ≤50%	RTX/Placebo
van den	PRA ≤85%	RTX/Placebo
Tsai	PRA <20%	RTX + MMF/RTX/MMF TAC + CS
Clatworthy	-	RTX + CS/DAC MMF + TAC

- **No significant improvements in patient and graft survival or acute rejection rates were identified with rituximab induction**

- risk of leukopenia is 8.22-fold increased in rituximab therapy
- Tyden : significant increase in mortality at 3-year follow-up

Rituximab for ABO Incompatible Transplantation

- ABOi kidney transplants were introduced in Japan in 1989.
- Until year 2002, preoperative desensitization with combination PP, IVIg and splenectomy formed the backbone of ABOi transplant success



Pre-conditioning protocols for ABOi transplantation

Kahwaji et al,Transplant Research and Risk Management 2009

TABLE 1. Outcomes of studies of rituximab for desensitization in ABO-incompatible recipients

Study (yr) country	No. of patients (RTX/non-RTX)	Study period, mo	Treatment regimen (RTX/non-RTX)	Baseline IS	T-cell induction therapy	Patient survival
Retrospective cohort studies						
Hyodo (2011)* Japan (*34*)	122 (29/31/62)	60	RTX+MMF/SPX+MMF/SPX+AZA	Not fully reported	Not reported	Not reported
Aikawa (2011)* Japan (*35*)	111 (16/95)	36	RTX+PE or PP/SPX+PE or PP	TAC or CsA, MMF or AZA+CS	BXM[c]	No difference
Tanabe (2007) Japan (*17–21, 36–41*)	102 (57/45)	24	RTX+PP/SPX+PP	TAC, MMF+CS	BXM	No difference[d]
Ashimine (2014) Japan (*22*)	81 (30/51)	36	RTX+PP/SPX+PP	TAC or CsA+MMF or MZR	BXM	No statistical comparison
Harada (2013)* Japan (*42*)	70 (46/24)	60	RTX+PP/SPX+PP	TAC, MMF, or AZA+CS	BXM or ALG	No statistical comparison
Charif (2013)* UK (*43*)	63 (24/39)	36	RTX+PE/ALZ+PE	TAC+CS±MMF[g]	DAC (RTX group only)	No difference
Nakagawa (2011)* Japan (*44*)	61 (42/19)	36	RTX/SPX	TAC or CsA, MMF+CS[h]	BXM (RTX group only)	No difference
Montgomery (2009) USA (*23*)	60 (3/15/14/28)	60	RTX, IVIg, PP+SPX/RTX, IVIg+PP/SPX, IVIg+PP/	TAC, MMF+CS	DAC	Not reported
Gloor (2005) USA (*24*)	34 (11/23)	24	RTX, IVIg+PP/SPX, IVIg+PP	TAC, MMF+CS	ATG	No difference
Waigankar (2013) India (*25*)	26 (7/19)	12–18	RTX, PP+IVIg/SPX, PP+IVIg	TAC, MMF+CS	Not reported	No statistical comparison

Rituximab was found to be equivalent to splenectomy, indicating that this invasive surgical procedure is not necessary

Points of RTX use

- the AUC for Rituximab is reduced by up to 26% when PP is performed less than 3 days after infusion
- can be detected in the serum for many months after the dose of drug.
- Rituximab is cytotoxic in the presence of complement, sera that contain Rituximab would produce a positive B cell cytotoxic-positive crossmatch
- Human portion of the IgG1would provide a target for the antihuman Ig fluorochromes used in flow cytometric crossmatches again resulting in a false positive B cell crossmatch
- elimination of the cell surface CD20 by pronase treatment of the cells or removal of the circulating rituximab by immunomagnetic bead absorption.

RTX in kidney transplantation

A: Desensitization protocols for highly sensitized recipients before or concurrent with kidney Tx, and in ABO incompatible kidney Tx

B: Treatment of acute and chronic Ab-Mediated rejection

C:Treatment of recurrent and de novo glomerular diseases

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Treatment of Acute AMR

- The incidence of AMR ranges from 5.6% to 23% in unselected populations to 30% to 60% in patients undergoing preconditioning for ABO or HLA-incompatible transplants
- modalities used to prevent and treat AMR vary across centers

- Hychko conducted a meta-analysis of studies of Rituximab use in AMR, included 249 patients and reported a pooled ratio of response to Rituximab defined by at least partial improvement in graft function (OR 3.16, 95% CI: 1.75-5.70)

- Power was limited by paucity of randomized control trial (RCTs) and prospective studies

A Systematic Review and Meta-Analysis of Rituximab in Antibody-mediated Renal Allograft Rejection

Table2: Characteristics of individual studies

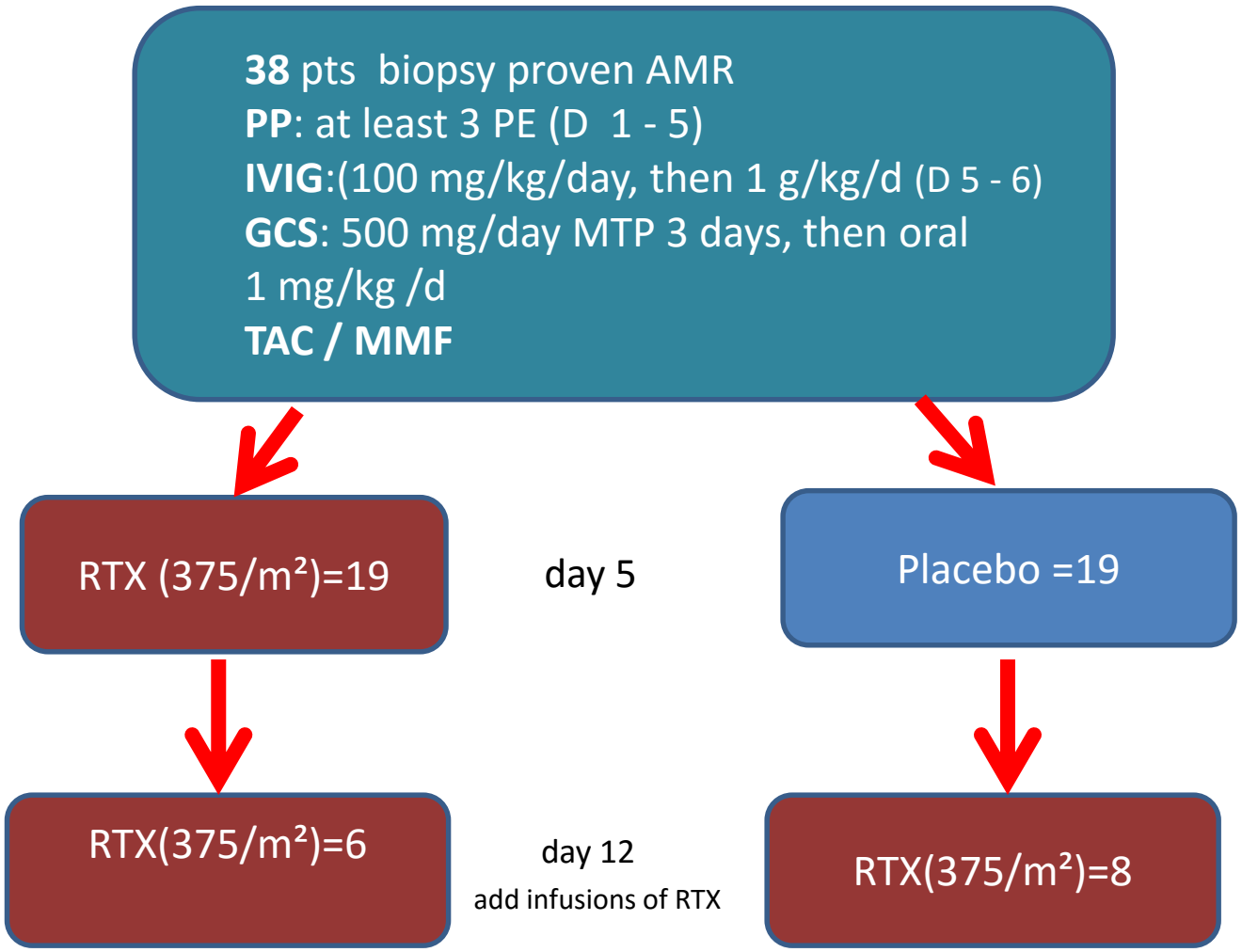
Study	Publication Year	Design	Study Outcome(s)	n	Follow-up (months)
Becker [16]	2004	Prospective*	graft survival	27	24
Faguer [17]	2007	Prospective	B cell depletion; graft function	8	10
Steinmetz [18]	2007	Retrospective; comparative	B cell depletion; creatinine; Bx**	16	3
Bett [19]	2008	Retrospective	Creatinine	9	46
Zarkhin [20]	2008	Prospective; comparative; pediatric	B cell depletion; graft survival; Bx; DSA@	20	12
Mulley [21]	2009	Prospective*	B cell depletion; creatinine	7	21
Kaposztaz [22]	2009	Retrospective; comparative	graft survival; graft function; Bx; creatinine	54	24
Ferrero [23]	2010	Prospective; comparative	Creatinine	8	10
Hurley [24]	2010	Prospective*	graft survival; creatinine	36	24
Scemla [28]	2010	Retrospective	graft survival	64	25

Hychko et al, Int J Org Transplant Med 2011; Vol. 2 (2)

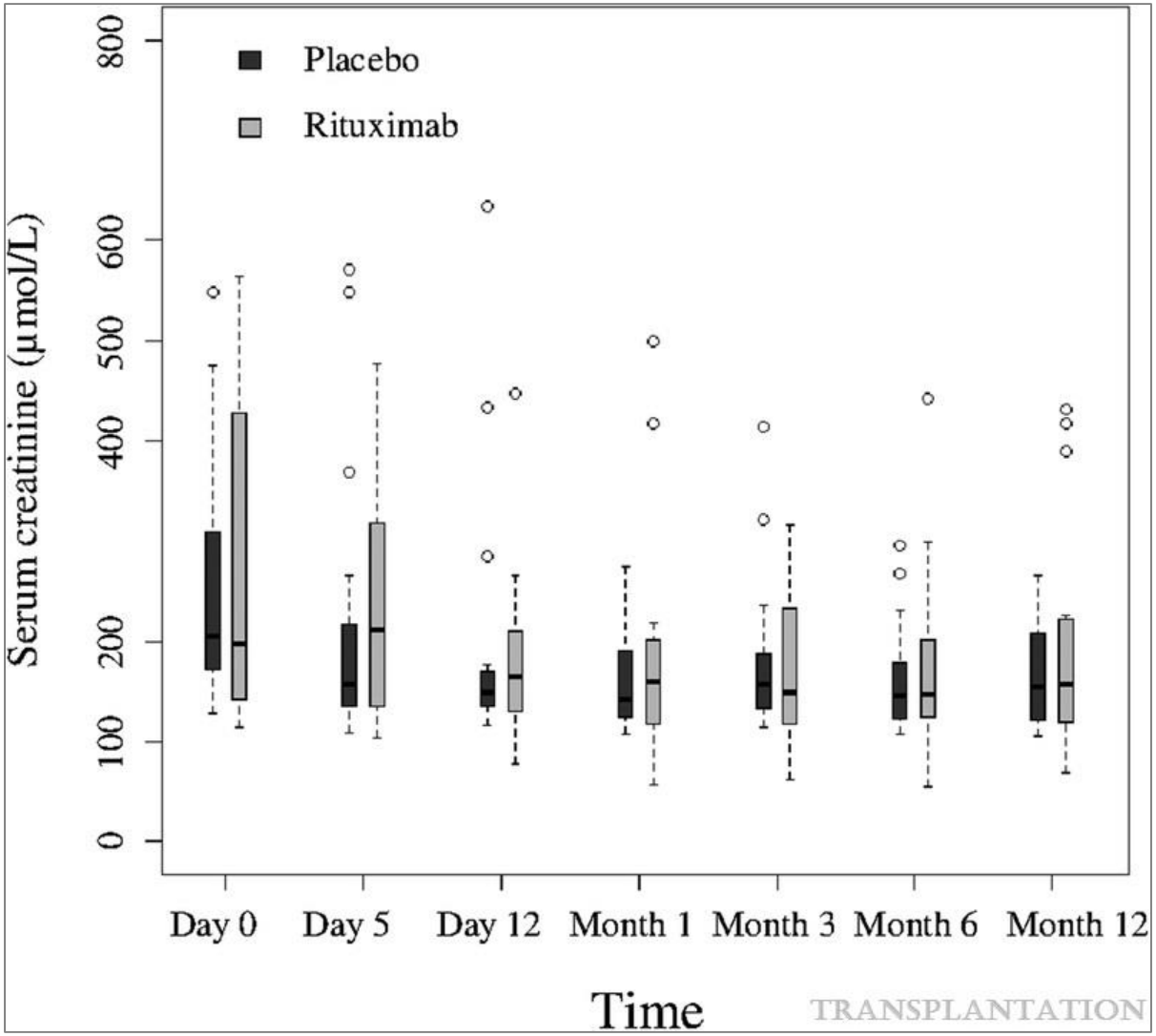
Official Journal of The Transplantation Society & International Liver Transplantation Society
Transplantation

RITUX –ERAH

(multicenter randomized clinical trial)



Sautenet B, Transplantation2016 Feb;100(2):391-9



[One-year Results of the Effects of Rituximab on Acute Antibody-Mediated Rejection in Renal Transplantation: RITUXERAH, a Multicenter Double-blind Randomized Placebo-controlled Trial]

Sautenet, Transplantation100(2):391-399, February 2016.
doi: 10.1097/TP.0000000000000958

ITT analysis of serum creatinine level (µmol/L) over 1 year in the rituximab and placebo groups. Box height indicates the IQR with the lower and upper edges of the box representing the 25th and 75th percentiles, respectively. The horizontal line is the median. The lower whisker represents the 25th percentile minus 1.5 times the IQR and the upper whisker the 75th percentile plus 1.5 times the IQR. Values outside the whiskers are outliers. IQR indicates interquartile range.

(95% CI, –95.53 to 45.05; *P* = 0.480)

no additional effect of rituximab

underpowered

Transplant International

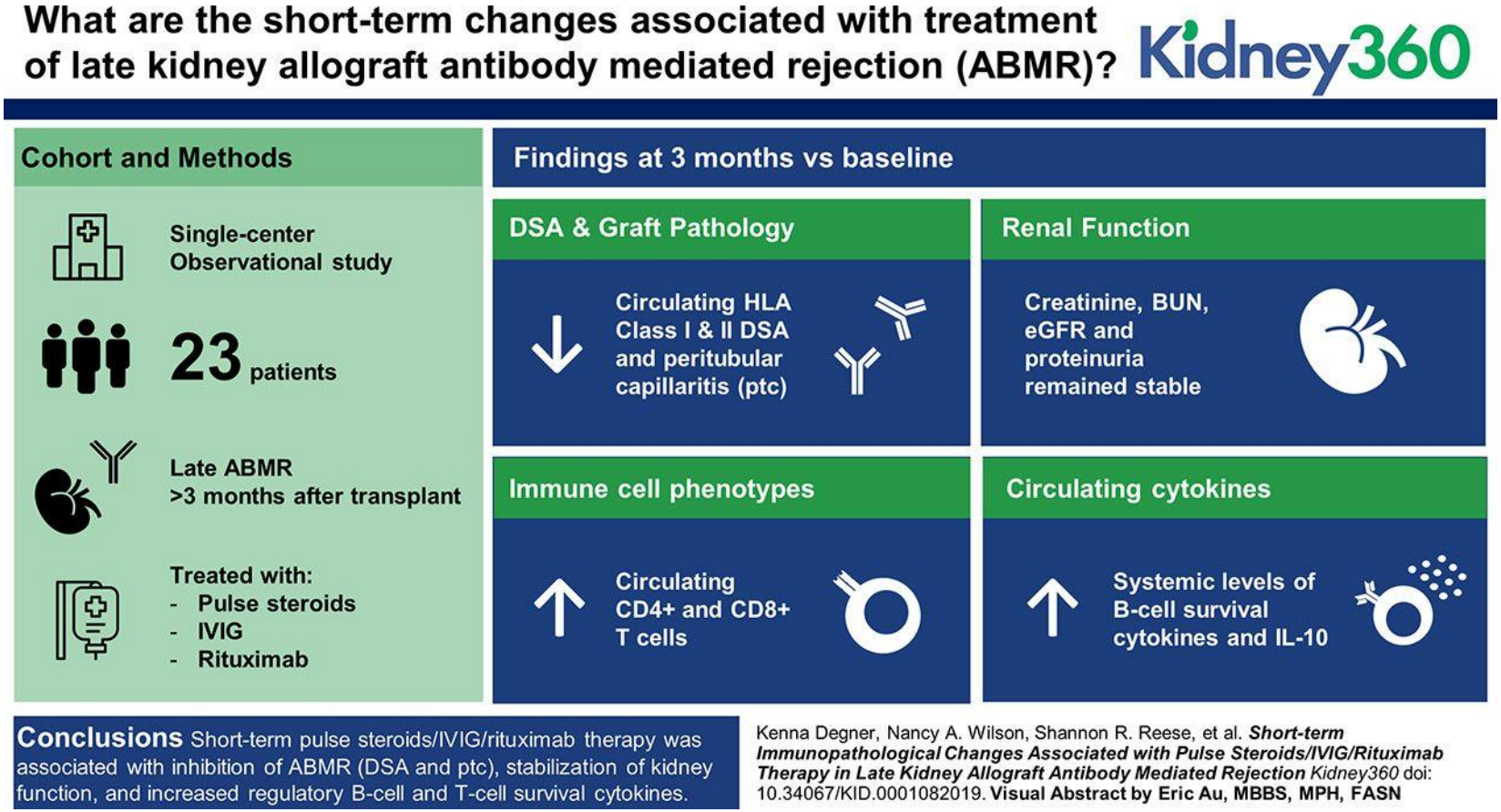
Original article | Free Access

An extension of the RITUX-ERAH study, multicenter randomized clinical trial comparing rituximab to placebo in acute antibody-mediated rejection after renal transplantation

Elodie Bailly, Simon Ville, Gilles Blancho, Emmanuel Morelon, Jamal Bamoulid, Sophie Caillard, Valérie Chatelet, Paolo Malvezzi, Jérôme Tourret, Vincent Vuiblet, Dany Anglicheau ... See all authors

First published: 12 April 2020 | https://doi.org/10.1111/tri.13613 | Citations: 6

- Evaluation of the 7-year outcomes of the RITUX-ERAH study patients
- there was no benefit 7 years after ABMR of rituximab in addition to plasma exchanges, intravenous immunoglobulins, and steroids.



Kenna R. Degner et al. Kidney360 2020;1:389-398

Kidney360®

Treatment of chronic AMR

American Journal of TRANSPLANTATION

AST AMERICAN SOCIETY OF TRANSPLANTATION ASTS

ORIGINAL ARTICLE | Free Access

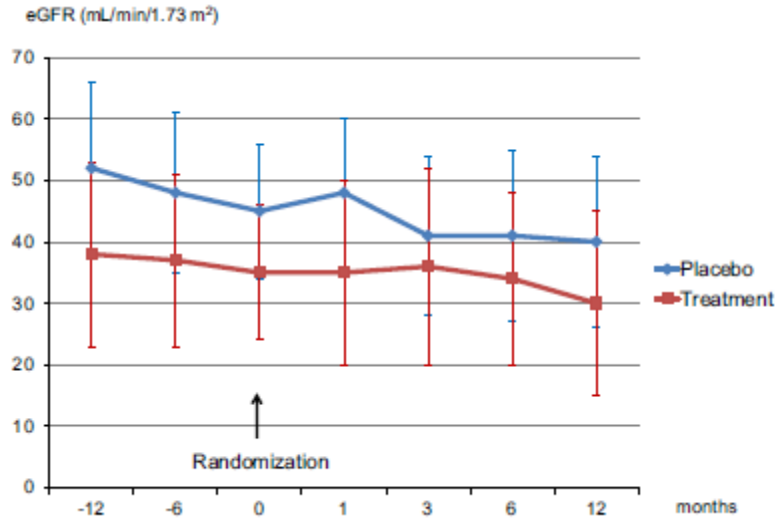
Treatment of chronic antibody mediated rejection with intravenous immunoglobulins and rituximab: A multicenter, prospective, randomized, double-blind clinical trial

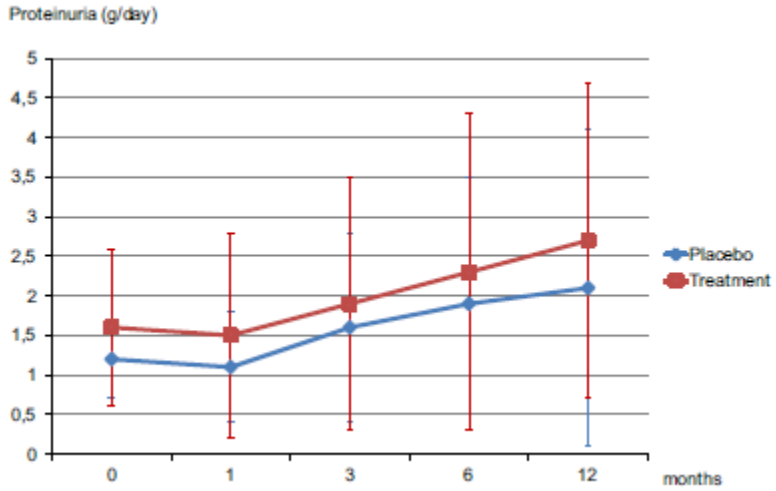
- six renal transplant units in Spain
- Patients with transplant glomerulopathy and anti-HLA donor-specific antibodies (DSA) were eligible.
- Patients with GFR< 20 cc/m and/or sever IFTA excluded.
- Patients were randomized:

  IVIG (4 doses of 0.5 g/kg) and RTX (375 mg/m^2)

  or isovolumetric saline infusion

Treatment of chronic AMR





- There were no differences between the treatment and placebo groups in eGFR decline (−4.2 ± 14.4 vs. −6.6 ± 12.0 mL/min per 1.73 m^2, *P*-value = .475), increase of proteinuria (+0.9 ± 2.1 vs. +0.9 ± 2.1 g/day, *P*-value = .378), Banff scores at one year and MFI of the immunodominant DSA.

Treatment of chronic AMR

- Chung *et al* conducted Retrospective cohort study:

RTX

- 25 patients CAMR
- Rituximab 375mg/m2
- high-dose steroids
- IVIG 400 mg/kg 4

control

- 29 historic controls
- received low-dose pulse steroids

- ΔeGFR was significantly decreased in the RTX group compared with HC group after 6 months ($P < 0.05$).
- overall allograft survival rate in the RTX group was significantly higher
- limitation

RESEARCH ARTICLE Open Access

Rituximab, plasma exchange and immunoglobulins: an ineffective treatment for chronic active antibody-mediated rejection

Gastón J Piñeiro[1,2], Erika De Sousa-Amorim[1], Manel Solé[3], José Ríos[4,5], Miguel Lozano[6], Frederic Cofán[1],

Results: We identified 62 patients with active c-aABMR and TG (cg ≥ 1). Twenty-three patients were treated with the combination therapy and, 39 patients did not receive treatment and were considered the control group. There were no significant differences in the graft survival between the two groups. The number of graft losses at 12 and 24 months and the decline of eGFR were not different and independent of the treatment. A decrease of eGFR≥13 ml/min between 6 months before and c-aABMR diagnosis, was an independent risk factor for graft loss at 24 months (OR = 5; $P = 0.01$). Infections that required hospitalization during the first year after c-aABMR diagnosis were significantly more frequent in treated patients (OR = 4.22; $P = 0.013$), with a ratio infection/patient-year of 0.65 and 0.20 respectively.

Conclusions: Treatment with rituximab, PE, and IVIG in kidney transplants with c-aABMR did not improve graft survival and was associated with a significant increase in severe infectious complications.

Trial registration: Agencia Española de Medicametos y Productos Sanitarios (AEMPS): 14566/RG 24161. Study code: UTR-

KDIGO guideline

- **Antibody-Mediated Acute Rejection:**
- We suggest one or more of the following alternatives, with or without corticosteroids (**2C**):
- plasma exchange
- intravenous immunoglobulin
- **anti-CD20 antibody**
- lymphocyte-depleting antibody
- **Chronic Allograft Injury:**
- For patients with CAI and histological evidence of CNI toxicity, we suggest reducing, withdrawing, or replacing the CNI. (**2C**)
- For patients with CAI, eGFR 40 ml/min/1.73 m2 , and urine total protein excretion >500 mg per gram creatinine we suggest replacing the CNI with a mTORi. (**2D**)

Treatment of AMR

- There is **no consensus** on role of Rituximab in the treatment of acute and chronic AMR and larger multicenter RCTs are required.

RTX in kidney transplantation

A: Desensitization protocols for highly sensitized recipients before or concurrent with kidney Tx, and in ABO incompatible kidney Tx

B: Treatment of acute and chronic Ab-Mediated rejection

C:Treatment of recurrent and de novo glomerular diseases

D: Treatment of PTLD

Recurrent Membranous Nephropathy

- is observed with an incidence of 7% to 51% and progression related to degree and duration of proteinuria.
- Presentation: early
  late
  de novo (most common)
- Regime: 4 weekly doses of 375 mg/m2
  or 2 doses of 1000 mg iv given 2 weeks apart
- PLA2R : posttransplant recurrence rate in PLA2R positive and negative patients (83% and 58% respectively)
- routine laboratory monitoring PLA2R Ab levels.

Recurrent FSGS

- Recurrence of primary FSGS occurs in 30% to 50% of transplanted patients (80% in second Tx)
- case reports/series of partial or complete remission of FSGS with Rituximab (alone or in combination with PP)
- Audard et al reported 4 cases: Rituximab alone or with PP was successfully used in prophylaxis of FSGS recurrence in second transplants after loss of first graft to FSGS recurrence.
- Currently, there is more data supporting Rituximab use in documented recurrence than its use in prevention of FSGS recurrence in high-risk patients

Other Recurrent GN

- **Recurrent ANCA vasculitis:** case reports +
- **Recurrent IgA nephropathy:** case reports +/-
- **Recurrent MPGN:** case reports +/-
- **Recurrent Lupus Nephritis:** no data

- utility of Rituximab in recurrent MN appears promising
- for recurrent FSGS may be beneficial through nonspecific activity in stabilizing glomerular cytoskeleton.
- in allograft vasculitis appears to be beneficial
- there is no evidence to support Rituximab in patients with recurrent MPGN, IgAN or lupus recurrence posttransplant

RTX in kidney transplantation

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Treatment of PTLD

- PTLD is a spectrum of lymphoproliferative disorders ranging from benign to neoplastic B cell (occasionally T cell) processes
- 1.58 cases/1000 patient years in adults

- RF: EBV status, type of organ transplanted and intensity of immunosuppression
- first-line therapy for PTLD is reduction in IS
- cessation of MMF or Azathioprine with reduction in CNI (50%)

- Therapies against B cells, chemotherapy , adoptive T-cell therapy and surgical resection have all been used in cases where reduction in IS alone is not sufficient

Role of Rituximab in the treatment of PTLD

PTLD lesion type	Initial management	Further treatment/no complete response (CR)
Early lesion—plasmacytic hyperplasia or infectious mononucleosis like picture	Reduction in IS	Localized surgery/XRT Advanced **Rituximab** No chemotherapy
Polymorphic/monomorphic CD20+ PTLD	Reduction in IS and **Rituximab**	No response or partial response with IPI >3, sequential R-CHOP
Polymorphic/monomorphic CD20- PTLD	Reduction in IS ± chemo/XRT	**Rituximab is not indicated**
Primary CNS lymphoma	Reduction in IS and treatment similar to immunocompetent host	**Rituximab is not indicated**

conclusion

- Rituximab is used in various clinical scenarios in kidney transplant recipients
- its evidence-based use there remains limited due to lack of controlled studies, limited sample size, short follow-up.

- Rituximab is indicated for CD20+ PTLD

- may be beneficial for treating recurrent MN and recurrent ANCA vasculitis and possibly for recurrent FSGS.

Conclusion…

- Rituximab, in combination with IVIg/plasmapheresis, appears to decrease antibody level and increase the odds of transplantation in sensitized recipients.

- Role of Rituximab in ABOi transplant remains unclear although replaced splenectomy.

- There is **no consensus** on role of Rituximab in AMR .

Thank you