Rituximab in Kidney Transplantation

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TUMS

Rituximab (Rituxan)

- **Rituximab** is a chimeric monoclonal antibody that targets the CD20 B-cell antigen.
- This antigen is expressed on 90% of B-cell neoplasms
- The precise biological functions of CD20 are uncertain, but the antibody is believed to function by flagging the B-cells for destruction by the body's own immune system, including ADCC, CDC, and apoptosis.
- This antibody thus leads to the elimination of all B-cells from the body (including cancerous ones), allowing new, healthy B-cells to be produced from lymphoid stem cells.

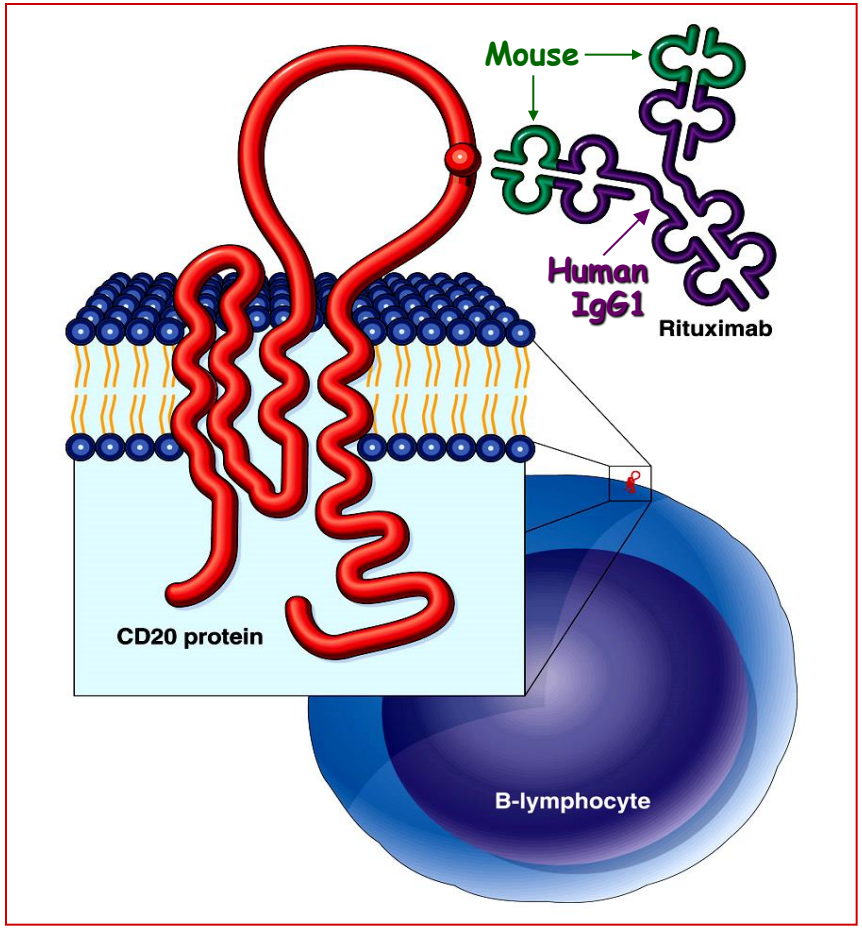
Anti- CD20 mAb

first FDA-approved monoclonal antibody (mAb)

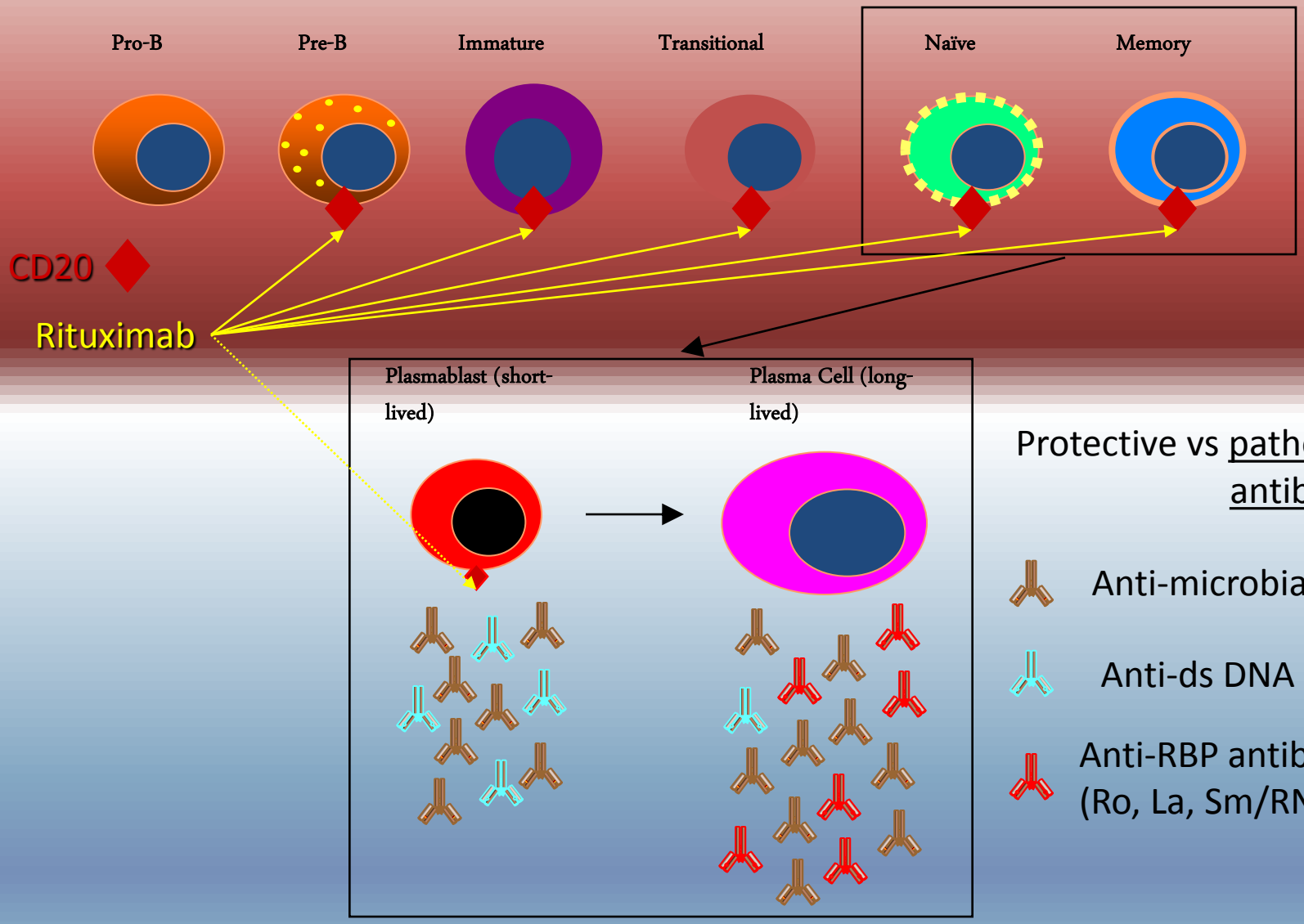
Rituximab (chimeric anti-CD20 mAb) for the treatment of B-NHL cells

Subsequently, over 20 approved mAbs have been in use clinically for the treatment of various cancers and several non-cancer related diseases.

Rituximab targets CD20 specifically expressed on the surface of B-cells



Rituximab targets. Plasma cells are spared

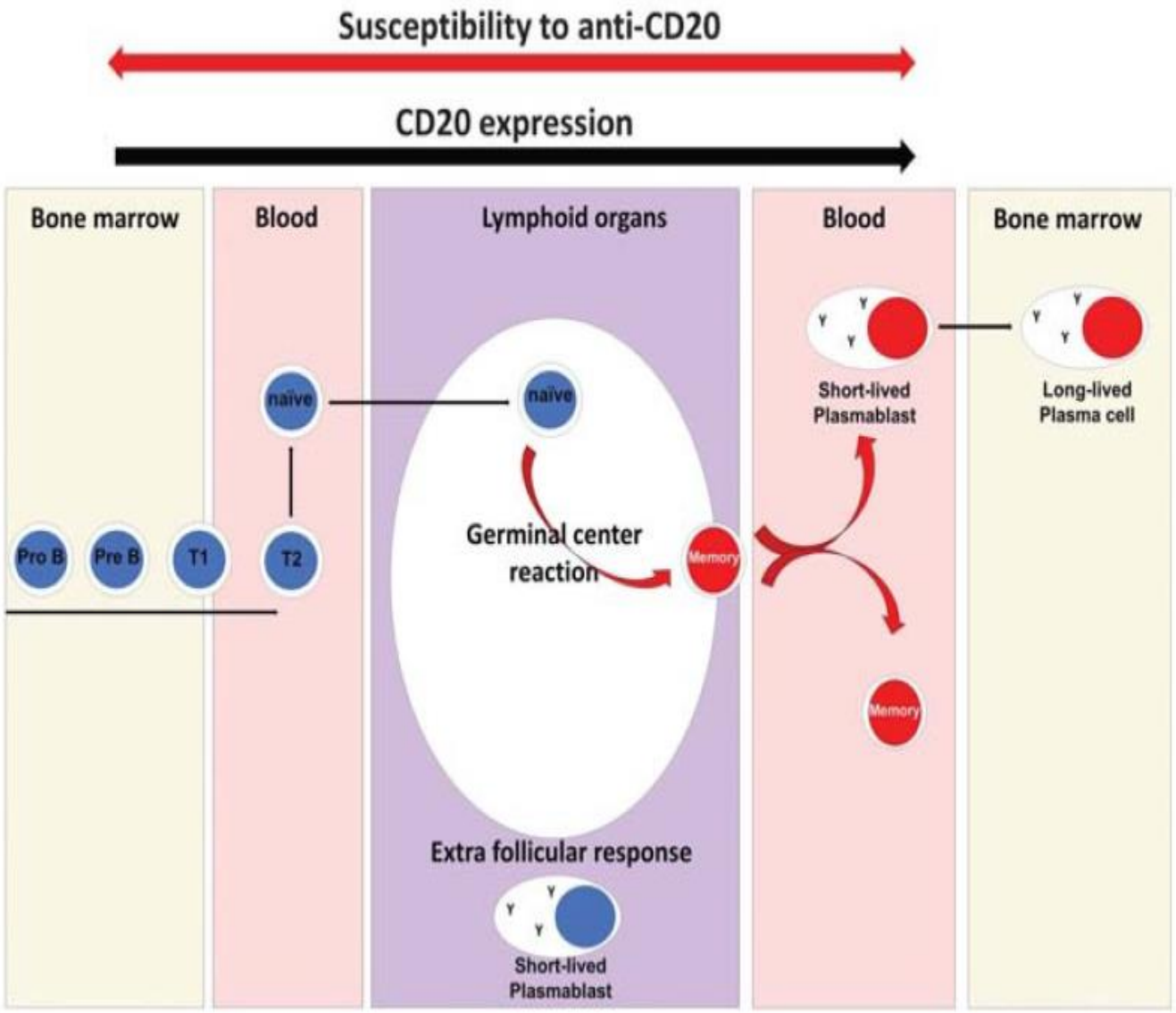


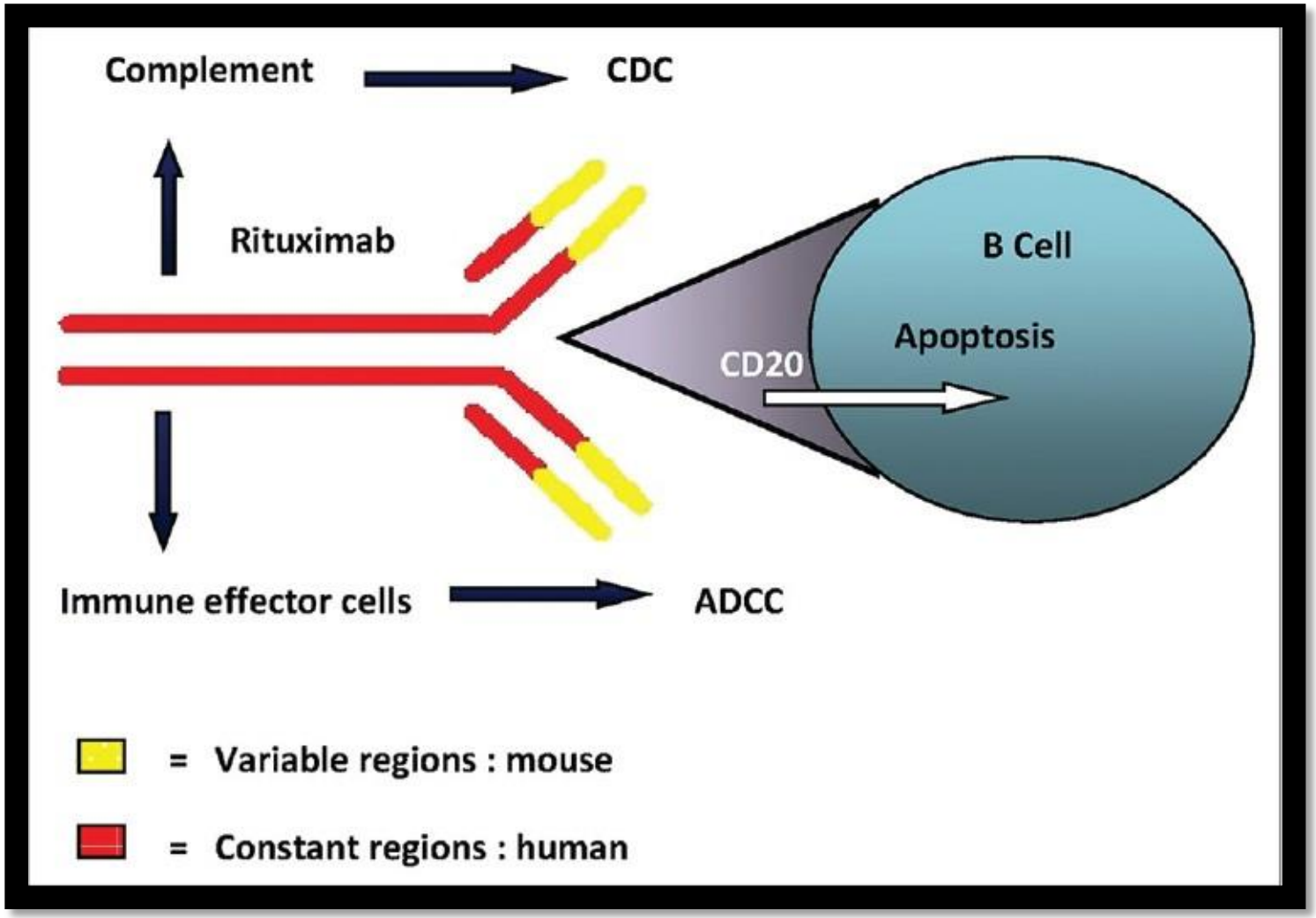
Protective vs <u>pathogenic antibodies</u>

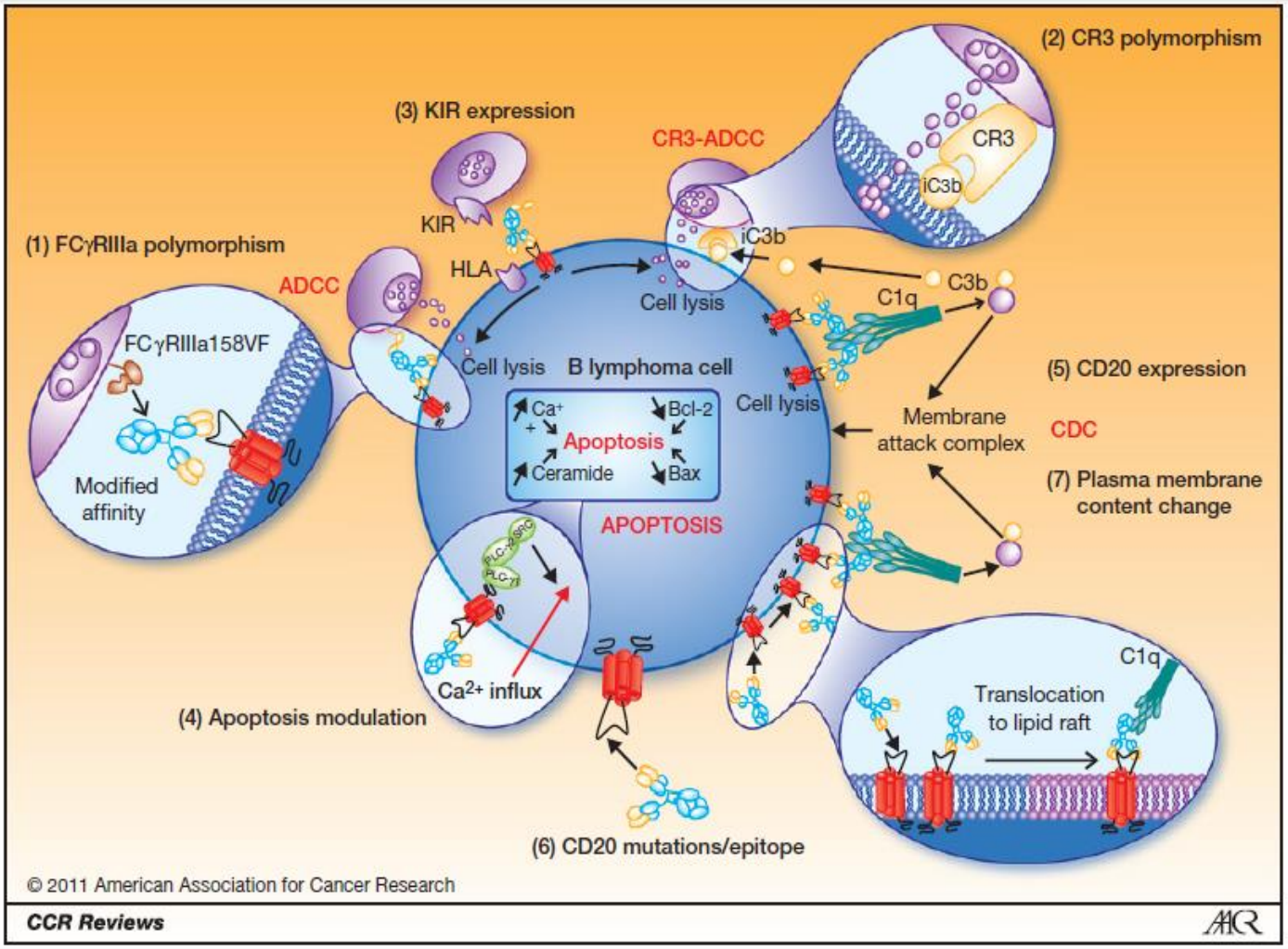
- Anti-microbial
- Anti-ds DNA
- Anti-RBP antibodies (Ro, La, Sm/RNP)

Factors influencing susceptibility:

1. Lipid raft composition
2. Complement regulatory proteins
3. FCγRIIIA polymorphisms
4. FCγRIIB expression




Complement
CDC
Rituximab
B Cell
Apoptosis
CD20
Immune effector cells
ADCC
= Variable regions : mouse
= Constant regions : human


(2) CR3 polymorphism
CR3
iC3b
(3) KIR expression
CR3-ADCC
KIR
HLA
iC3b
(1) FCγRIIIa polymorphism
ADCC
Cell lysis
C1q
C3b
FCγRIIIa158VF
Cell lysis
B lymphoma cell
(5) CD20 expression
Cell lysis
Membrane attack complex
CDC
Ca+ + Bcl-2
Apoptosis
Ceramide Bax
Modified affinity
APOPTOSIS
(7) Plasma membrane content change
C1q
Translocation to lipid raft
Ca2+ influx
(4) Apoptosis modulation
(6) CD20 mutations/epitope
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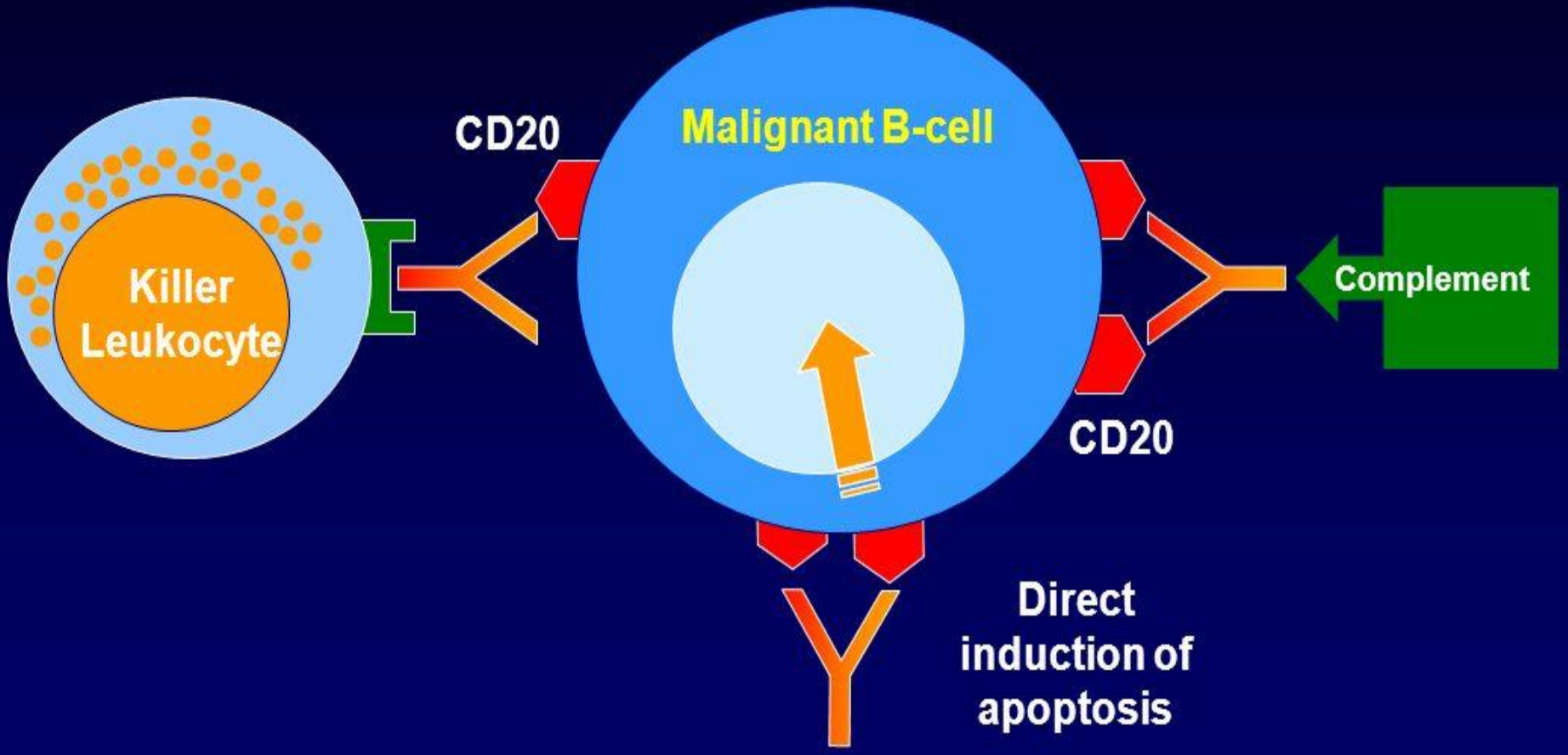
CCR Reviews
AACR

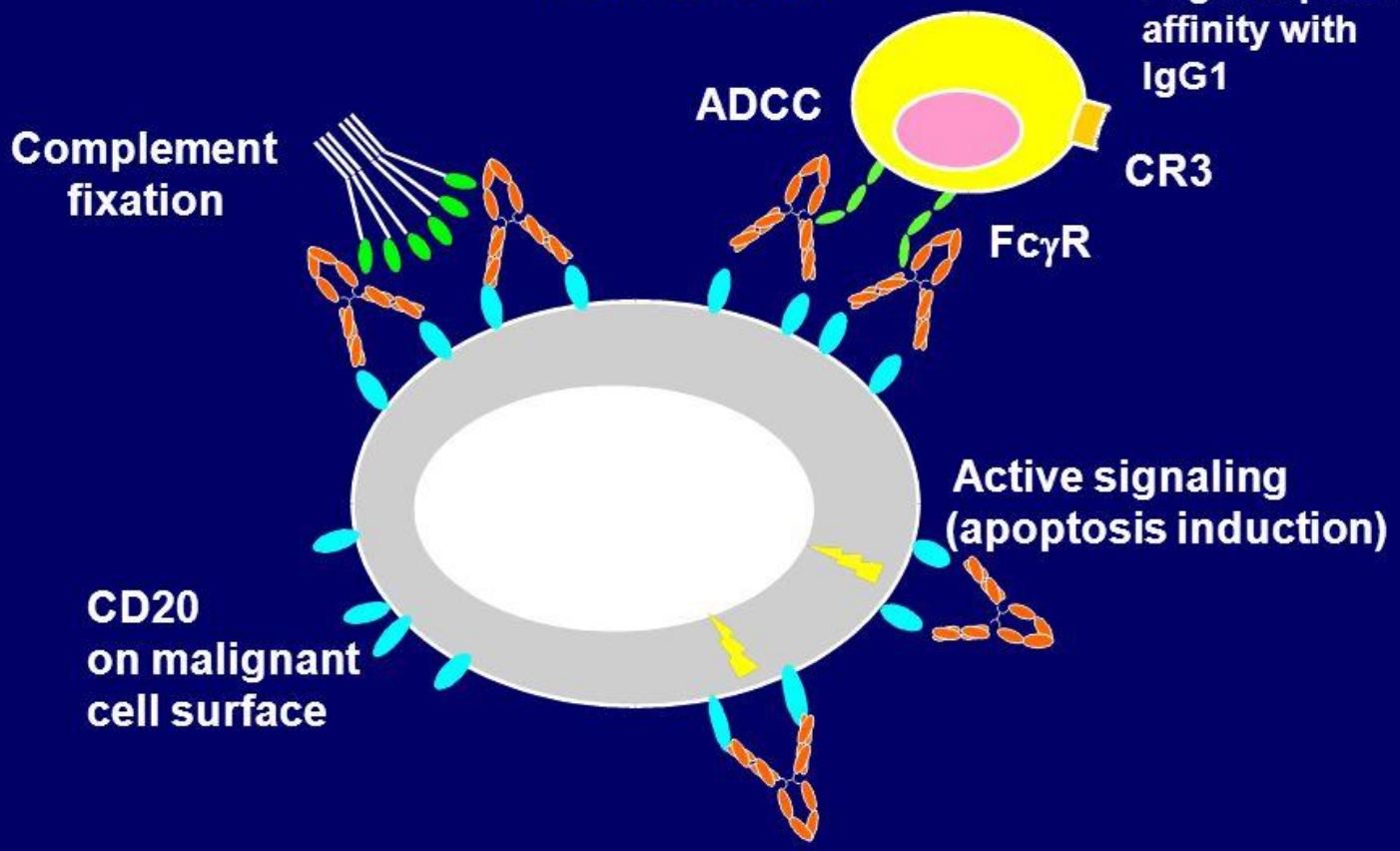
Anti-CD20 (Rituximab= Mabthera®)

mechanism of action



Adapted from Male D, *et al., Advanced Immunology* 1996: 1.1–1.16

Rituximab : Proposed Mechanisms of Action



Review

Anti-CD20 Blocker Rituximab in Kidney Transplantation

Puneet Sood, MD, MPH[1] and Sundaram Hariharan, MD[1]

Abstract: Rituximab is a chimeric anti-CD20 monoclonal protein used in various clinical scenarios in kidney transplant recipients. However, its evidence-based use there remains limited due to lack of controlled studies, limited sample size, short follow-up and poorly defined endpoints. Rituximab is indicated for CD20+ posttransplant lymphoproliferative disorder. It may be beneficial for treating recurrent membranous nephropathy and recurrent allograft antineutrophilic cytoplasmic antibody vasculitis and possibly for recurrent focal segmental glomerulosclerosis. Rituximab, in combination with IVIg/plasmapheresis, appears to decrease antibody level and increase the odds of transplantation in sensitized recipients. The role of Rituximab in ABOi transplant remains unclear, as similar outcomes are achieved without its use. Rituximab is not efficacious in antibody-mediated rejection/chronic antibody-mediated rejection. Strict randomized control trials are necessary to elucidate its true role in these settings.

(*Transplantation* 2018;102: 44–58)

Effect on B-cell populations

Rituximab causes a profound and sustained depletion in the number of circulating B-cells. It also decreases B-cell populations in the lymph nodes and spleen. A recent study by Genberg and colleagues evaluated the pharmacodynamics after a single dose of rituximab (375 mg/m^2) in renal transplant recipients.[23] Elimination of B-cells was rapid, and occurred over one to three days in the peripheral blood. It was also prolonged. B-cell populations did not begin to reemerge until after one year and remained suppressed for two years. This is longer than what is observed in patients with lymphoma or rheumatoid arthritis. It is notable that B-cell lymphopenia was present at baseline in the renal transplant population. It is possible that the delayed recovery of B-cells was related to the maintenance immunosuppression. Rituximab also leads to a significant reduction of B-cells in lymph nodes, although they were not completely eliminated. It is suggested that the densely populated lymph node is more difficult to penetrate and may require a higher dose of rituximab.

Rituximab in Kidney Tx

(A) Desensitization protocols for highly sensitized recipients before or concurrent with kidney transplantation, and in ABO incompatible kidney transplantation

(B) Treatment of Acute and Chronic Antibody-Mediated Rejection

(C) Treatment of Recurrent and de novo Glomerular Diseases after kidney transplant, and

(D) Treatment of Posttransplant Lymphoproliferative Disorder (PTLD).

Pre-transplant immunologic assessment

Approximately 30-35% of the patients on waiting list have evidence of sensitization in the form of alloantibodies.

What if the donor and the recipient are not compatible?

Pre-Transplant Assessment of Donor-Reactive, HLA-Specific Antibodies in Renal Transplantation: Contraindication vs. Risk

Howard M. Gebel[a,*], Robert A. Bray[a] and Peter Nickerson[b]

[1]*Department of Pathology, Emory University Hospital, Atlanta, GA*
[2]*Faculty of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada*
[*]*Corresponding author: Howard M. Gebel, hgebel@emory.edu*

Recommendations to evaluate the 'sensitized' patient:

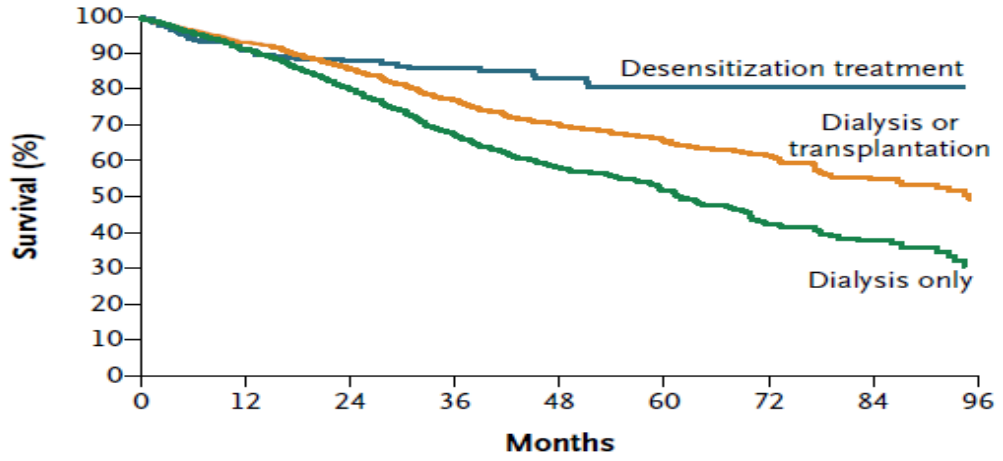
- To optimize detection of low titer HLA antibodies, monitoring should be performed using sensitive solid-phase assays.
- Monitoring should include evaluation for both antibodies to class I and class II HLA antigens.
- A crossmatch test must be performed before transplantation using, as a minimum, an enhanced CDC technique.
- The final crossmatch technique should be of equal sensitivity to the solid-phase assay used to screen for the presence of HLA antibody.
- A B-cell crossmatch should be included in the final crossmatch.
- Peak sera should be included in the final crossmatch.
- Auto-crossmatches should be utilized to aid in the interpretation of allo-crossmatches.

Previously, a positive DSA or a positive cross match was considered a contraindication to transplantation.

Recently, many advances have made and transplantation of sensitized patients are possible.

There are different desensitization protocols & **K**idney transplantation through desensitization protocols has been shown to improve survival for some patients compared to remaining on dialysis therapy.

N Engl J Med 2011;365:318-26.



No. at Risk									
Desensitization treatment	210	170	143	110	75	58	42	28	14
Dual therapy	1027	854	688	497	321	230	157	96	41
Dialysis only	1012	822	626	419	250	159	93	54	17

Figure 1. Survival Benefit of Desensitization in HLA-Incompatible Kidney Recipients.

Kaplan–Meier estimates of patient survival are shown for patients who underwent desensitization treatment before kidney transplantation (treatment group), as compared with two matched control groups of patients on a kidney waiting list who continued to receive dialysis (dialysis-only group) or who either continued to undergo dialysis or underwent HLA-compatible transplantation (dialysis-or-transplantation, or dual therapy, group). There were 35 deaths in the treatment group. The most common cause of death was cardiac disease (ischemic or valvular), which accounted for 15 deaths (43%). Infections, primarily opportunistic pneumonias, were responsible for 6 deaths (17%). The other causes of death were hemorrhage in 3 patients, bowel perforation or loss of vascular access in 2 patients each, and pancreatitis, cancer, motor vehicle accident, hypoglycemia, pulmonary embolism, pulmonary venous occlusion, and airway obstruction in 1 patient each.

APPROACH TO SENSITIZED PATIENTS

Patients evaluated for kidney transplantation

Patients with a living donor

Patients have no DSA and cross-match negative

Transplant

Patients have DSA and cross-match positive

Internal and NKR kidney paired exchange programs

CDC cross-match T or B-Pos or Flow T/B Pos MCS >300 and DSA MFI>5,000: Desensitization with PP, IVIG and rituximab. If DSA MFI<5,000 and MCS <300, after desensitization: Transplant with anti-thymocyte globulin and IVIG.

CDC cross-match T-Neg/ B-Pos or Flow T/B Pos MCS <300 and DSA MFI<5,000: No pretransplant desensitization. Transplant with anti-thymocyte globulin and IVIG.

CDC cross-match T and B-pos with more than 3 DSAs or more than 1 strong DSA with MFI > 5,000: Do not attempt desensitization

Patients without a living donor

UNOS DONATE LIFE

List to UNOS with any antibody >5000 MFI as unacceptable HLA antigens

Patients with cPRA >50% and on top of the waiting list: 2 g/kg IVIG at day 0 and day 30; 375mg/m2 rituximab at day 15. If any antibody strength after treatment decreases to <5000, remove from UNOS as unacceptable antigen

Post-TX monitoring : monthly DSA, BKV up to 6 months; and at 9th and 12th months; biopsy if creatinine level or DSA MFI increases

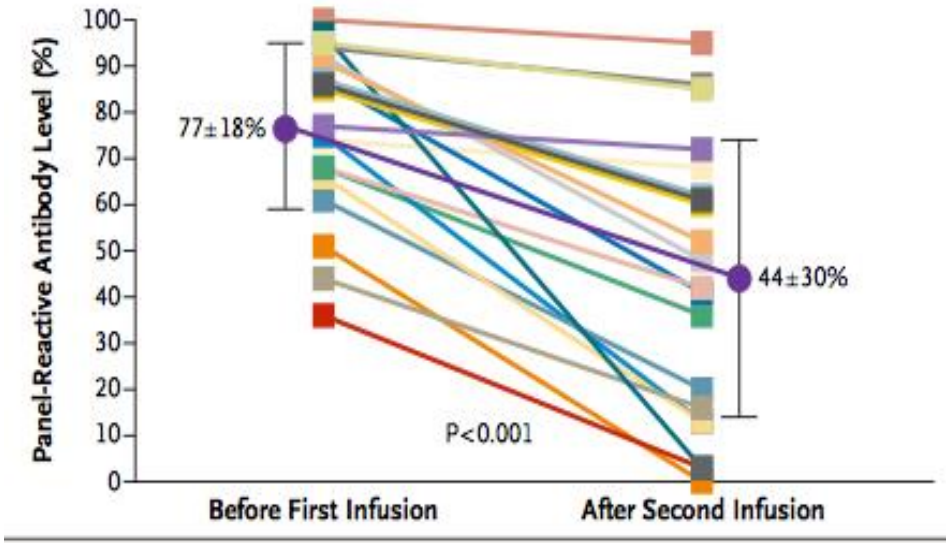
Box 1. Agents Used in Desensitization Protocols of Kidney Transplant Recipients

1. Removal of anti-HLA antibodies
   a. Plasmapheresis
   b. Immunoadsorption
   c. IdeS
2. Depletion of antibody-producing cells
   a. Naïve and memory B cells: rituximab (anti-CD20)
   b. Plasma cells: bortezomib (proteosomal inhibitor)
3. Inhibition of antibody and complement-system cascade
   a. IVIg
   b. Complement inhibitors
      i. Eculizumab (C5a inhibitor)
      ii. C1 inhibitor
4. Inhibition of cytokines and inflammation
   a. IVIg
   b. Tocilizumab (anti–IL-6 receptor blocker)

Abbreviations: IdeS, immunoglobulin G-degrading enzyme of *Streptococcus pyogenes*; IL-6, interleukin 6; IVIg, intravenous immune globulin.

Rituximab

- In sensitized patients awaiting renal transplantation, the use of rituximab in combination with IVIg significantly reduced PRA and wait time to transplant, and was associated with excellent graft and patient survival at 12 months.



Individual data for patient before the first infusion of intravenous immune globulin and after the second infusion.

N Engl J Med. 2008;359(3):242– 51.

N Engl J Med. 2008;359(3):242– 51.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Rituximab and Intravenous Immune Globulin for Desensitization during Renal Transplantation

Ashley A. Vo, Pharm.D., Marina Lukovsky, Pharm.D., Mieko Toyoda, Ph.D., Jennifer Wang, M.D., Nancy L. Reinsmoen, Ph.D., Chih-Hung Lai, Ph.D., Alice Peng, M.D., Rafael Villicana, M.D., and Stanley C. Jordan, M.D.

The study used an open-label design to examine whether human polyclonal **intravenous immune globulin** (10% formulation) given twice (2 g per kilogram of body weight on day 0 and day 30), plus **rituximab** given twice (1 g on day 7 and day 22), could reduce the rate of, or eliminate, a positive cross-match in highly HLA-sensitized patients awaiting transplantation at Cedars–Sinai Medical Center.

Table 1. Baseline Characteristics of the 20 Study Patients.

Characteristic	Value
Sex — no. (%)	
Male	7 (35)
Female	13 (65)
Receipt of transplant during the study — no. (%)	16 (80)
From deceased donor	6 (38)
From living donor	10 (62)
Age range at time of transplantation — yr	22–61
Mean duration of follow-up after treatment ≥12 mo — %	100
Race or ethnic group — %*	
White	26
Black	11
Hispanic	58
Other	5
Cause of end-stage renal disease — %	
Diabetes or hypertension	32
Focal or segmental glomerulosclerosis	16
Systemic lupus erythematosus	16
Other (glomerulonephritis, Alport's syndrome, obstructive uropathy, or chronic interstitial nephritis)	36

* Race or ethnic group was self-reported.

Table 2. Immunologic Findings and Infectious Complications of the 16 Patients Who Received a Transplant.*

Characteristic	Patients
	no. (%)
Panel-reactive antibody level at study entry	
<20%	4 (25)
Transplant from deceased donor	1
Transplant from living donor	3
20–50%	2 (13)
Transplant from deceased donor	1
Transplant from living donor	1
>50%	10 (62)
Transplant from deceased donor	4
Transplant from living donor	6
Previous transplants	
0	6 (38)
1	6 (38)
≥2	4 (25)
Cross-match at time of transplantation†	
CDC+, FCMX+	3 (19)
CDC+, FCMX–‡	2 (12)
CDC–, FCMX+	8 (50)
CDC–, FCMX–	3 (19)
Complications of infection	
Viral	
Polyomavirus BK	0
Cytomegalovirus	0
Parvovirus B-19	0
Epstein–Barr virus	0
Bacterial (asymptomatic urinary tract infection)	7 (44)
HLA mismatches	
6-Antigen mismatch	4 (25)
5-Antigen mismatch	3 (19)
≤4-Antigen mismatch	9 (56)

* CDC denotes complement-dependent cytotoxicity asay, and FCMX flow-cytometric cross-matching.
† The CDC+ result was at a 1:1 dilution, and the CDC– result was at a 1:2 dilution, of the serum in saline.
‡ The cross-match result reflects a probable IgM donor antigen.

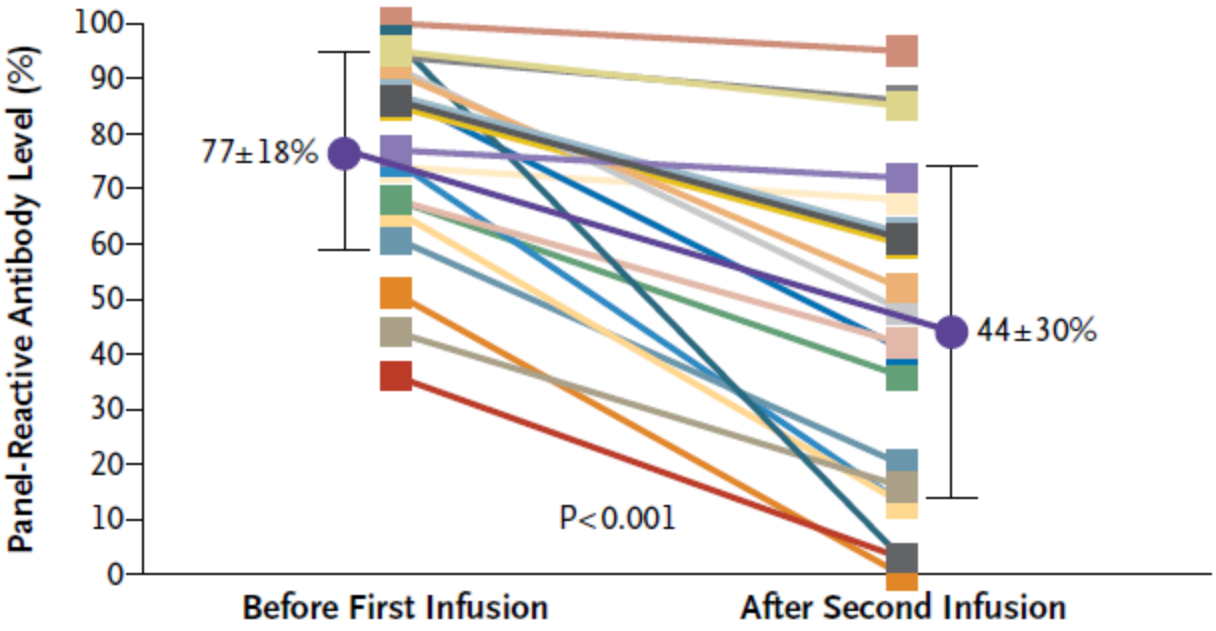


Figure 1. Panel-Reactive Antibody Levels in the 20 Study Patients.

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.

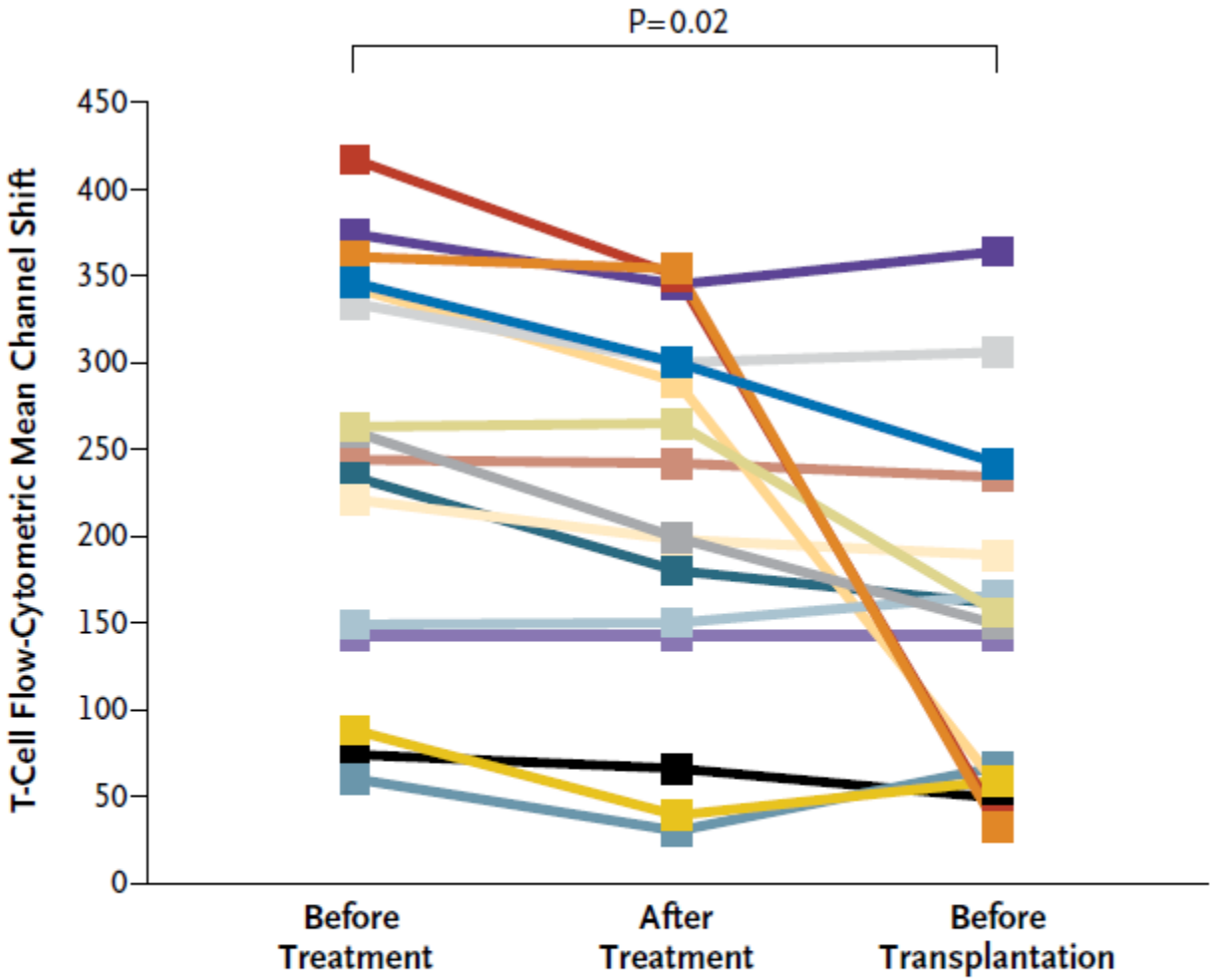


Figure 2. Mean Channel Shifts from T-Cell Flow-Cytometric Cross-Matching of the 16 Study Patients with Donors.

The mean (±SD) channel shifts (the numbers of binding fluorescent units above the background number) were 212±95 before treatment (P=0.30), 245±104 immediately after treatment (P=0.15), and 149±97 immediately before transplantation.

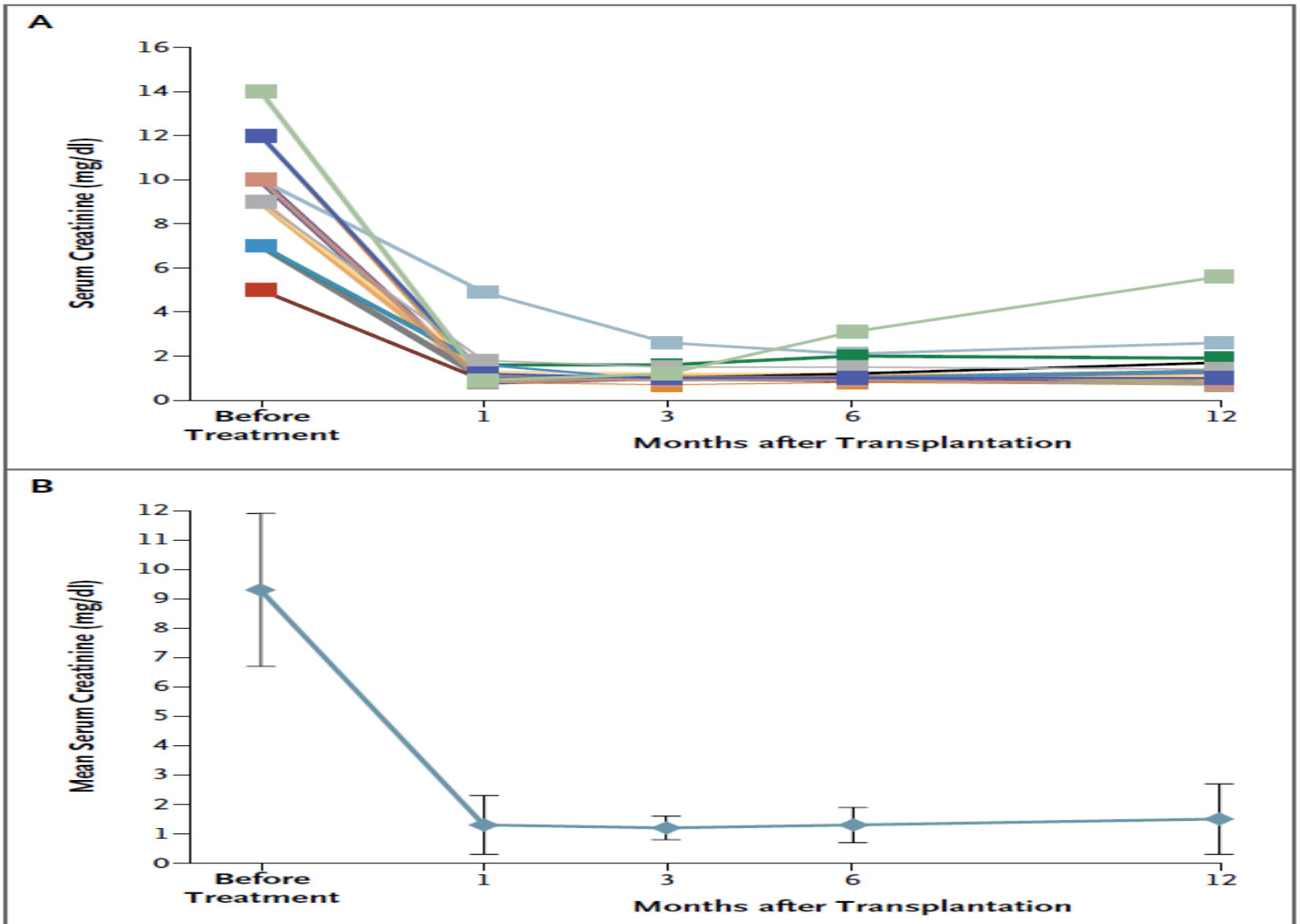


Figure 3. Serum Creatinine Values in the 16 Patients Who Received a Kidney Transplant after Desensitization.

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.

Conclusion

In this nonrandomized study, transplantation was accomplished in 80% of the patients, and treatment time was reduced from 16 weeks to 5 weeks. In addition, our patients who received a transplant from a deceased donor had been on a waiting list for a mean of 12 years (range, 5 to 27) but received transplants within 5 to 6 months after treatment with intra
venous immune globulin plus rituximab.

Transplant Research and Risk Management

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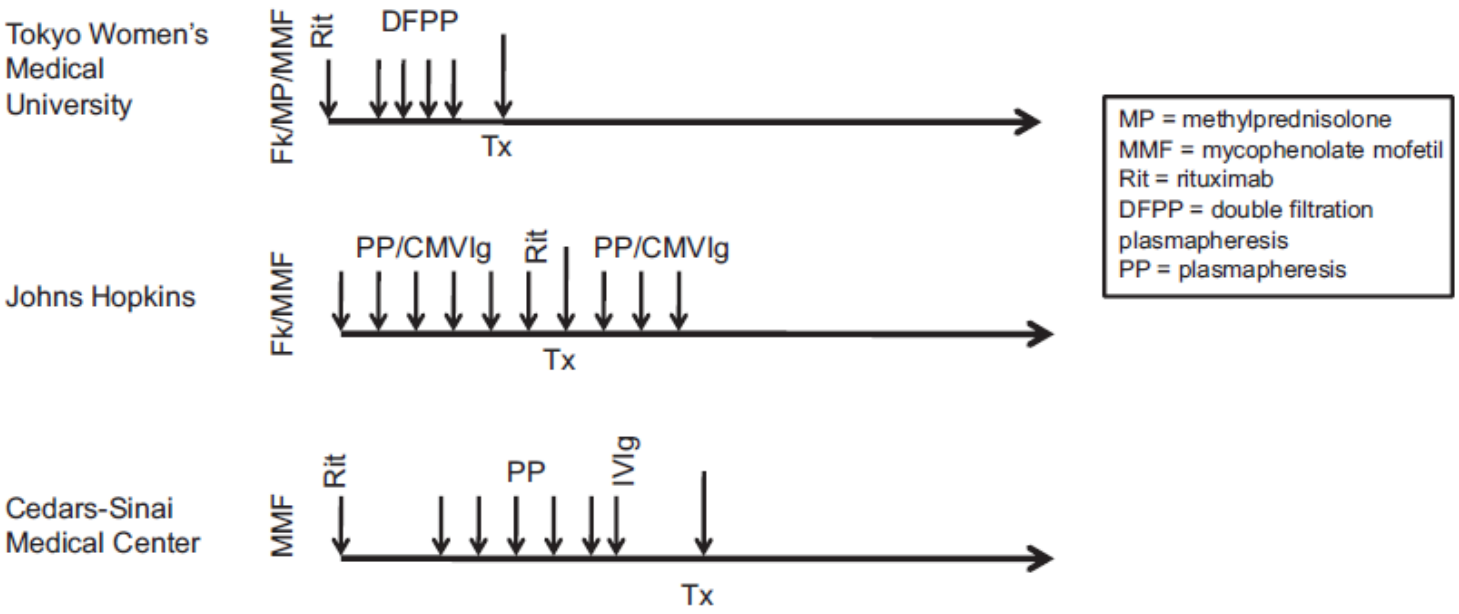
REVIEW

Rituximab: An emerging therapeutic agent for kidney transplantation



Pre-conditioning protocols for ABOi transplantation

SPECIAL FEATURE

A Systematic Review of the Use of Rituximab for Desensitization in Renal Transplantation

Philip S. Macklin,[1] Peter J. Morris,[1,2] and Simon R. Knight[1,2,3]

TABLE 2. Outcomes of studies of rituximab for desensitization in recipients with a positive complement-dependent cytotoxicity cross-match (CDC-XM)

Study (yr) country	Inclusion criteria	No. of patients (RTX/non-RTX)	Study period, mo	Treatment regimen (RTX/non-RTX)	Baseline IS	T-cell induction therapy
Retrospective cohort studies						
Stegall (2006) USA (*26*)	+ve T-AHG CDC-XM	61 (16/32/13)[a]	6	RTX, LD IVIg+PP/RTX, LD IVIg, PP±SPX/ HD IVIg	TAC, MMF+CS	ATG in group 1 only
Umanath (2012)* USA (*45*)	+ve CDC-XM	27 (15/12)	12	RTX+IVIg/IVIg	TAC, MMF+CS	ALZ or ATG[b]

All outcomes are reported for the end of the study period unless stated otherwise.

* Abstract only.

[a] Only patients who achieved a negative CDC-XM underwent transplantation, therefore the number of patients analysed in each group were 14, 30 (including 3 high-dose IVIg nonresponders who were changed to this protocol) and 5, respectively.

[b] 17 patients received ALZ and 10 received ATG.

[c] Final pre-transplant CDC-XM was negative in all patients.

ALZ, alemtuzumab; ATG, anti-thymocyte globulin; CS, corticosteroids; HD, high dose; IS, immunosuppression; IVIg, intravenous immunoglobulin; LD, low dose; MMF, mycophenolate mofetil; No., number; PP, plasmapheresis; RTX, rituximab; SPX, splenectomy; TAC, tacrolimus; (T-AHG) CDC-XM, (T-cell antiglobulin enhanced) complement-dependent cytotoxicity cross-match; USA, United States of America.

Background. Rituximab is a B lymphocyte–depleting agent used to treat lymphoma and autoimmune diseases. Recently, it has been used for desensitization therapy in ABO-incompatible and highly sensitized recipients undergoing renal transplantation.

Methods. A systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. Four databases and three trial registries were searched for studies comparing rituximab with non-rituximab desensitization protocols. A lack of randomized evidence precluded meta-analysis, and thus a narrative review was conducted.

Results. Forty-five records met the inclusion criteria, relating to 21 individual studies (two randomized controlled trials and 19 retrospective cohort studies). Ten studies investigated the use of rituximab in ABO-incompatible patients; most found no significant differences in patient and graft outcomes when compared most frequently to splenectomy-based protocols. Nine studies of limited quality focused on highly sensitized recipients (positive cross-match, donor-specific antibody, and elevated panel reactive antibody) and demonstrated some benefits in graft survival, acute and chronic rejection, and sensitization levels with rituximab. The remaining two studies combined ABO-incompatible and highly sensitized recipients and found no statistically significant increase in infectious complications with rituximab.

Conclusion. Evidence of limited quality was identified to support the use of rituximab desensitization in highly sensitized recipients. Among ABO-incompatible recipients, rituximab was found to be equivalent to splenectomy, indicating that this invasive surgical procedure is not necessary. Further randomized controlled trials are required to better define the efficacy, long-term safety, and optimal dosing regimen of rituximab in this setting.

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

All outcomes are reported for the end of the study period unless stated otherwise.

* Abstract only.

[a] No difference in graft survival between RTX+MMF and SPX+MMF groups; SPX+AZA group had a significantly poorer graft survival compared to the other two groups.

[b] Only given to patients after the year 2000.

[c] No difference in patient survival between groups at 6 years.

[d] No difference in graft survival between groups at 5 years.

[e] Higher incidence of leukopenia with RTX at 6 years but lower incidence of CMV infection with RTX at 5 years.

[f] The RTX group received TAC, MMF+CS whereas the non-RTX group received TAC+CS only; both groups received a CS sparing regimen (prednisolone 1 mg/kg for 4 days, 0.5 mg/kg for 3 days, then stopped).

[g] The RTX group received a low dose CS protocol whereas the non-RTX group received a standard dose CS protocol.

[h] P=0.05 and therefore not considered to be statistically significant.

[i] Less posttransplant diabetes mellitus and peptic ulcer disease in RTX group because of low dose CS protocol.

[j] At a mean follow-up of 399 and 1056 days for the RTX and non-RTX groups, respectively.

ALG, antilymphocyte globulin; ALZ, alemtuzumab; ATG, antithymocyte globulin; AZA, azathioprine; BXM, basiliximab; CS, corticosteroids; CsA, cyclosporin A; DAC, daclizumab; IS, immunosuppression; IVIg, intravenous immunoglobulin; MMF, mycophenolate mofetil; MZR, mizoribine; No., number; PE, plasma exchange; PP, plasmapheresis; RTX, rituximab; SPX, splenectomy; TAC, tacrolimus; UK, United Kingdom; USA, United States of America.

The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med 2017;377:442-53.
DOI: 10.1056/NEJMoa1612567

ORIGINAL ARTICLE

IgG Endopeptidase in Highly Sensitized Patients Undergoing Transplantation

S.C. Jordan, T. Lorant, J. Choi, C. Kjellman, L. Winstedt, M. Bengtsson, X. Zhang, T. Eich, M. Toyoda, B.-M. Eriksson, S. Ge, A. Peng, S. Järnum, K.J. Wood, T. Lundgren, L. Wennberg, L. Bäckman, E. Larsson, R. Villicana, J. Kahwaji, S. Louie, A. Kang, M. Haas, C. Nast, A. Vo, and G. Tufveson

AJKD

In the Literature

A New Treatment Option for Highly Sensitized Patients Awaiting Kidney Transplantation

Enver Akalin

Rituximab in Kidney Tx

(A) Desensitization protocols for highly sensitized recipients before or concurrent with kidney transplantation, and in ABO incompatible kidney transplantation

(B) Treatment of Acute and Chronic Antibody-Mediated Rejection

(C) Treatment of Recurrent and de novo Glomerular Diseases after kidney transplant, and

(D) Treatment of Posttransplant Lymphoproliferative Disorder (PTLD).

Treatment of Biopsy-Proven Acute Antibody-Mediated Rejection Using Thymoglobulin (ATG) Monotherapy and a Combination of Rituximab, Intravenous Immunoglobulin, and Plasmapheresis: L...

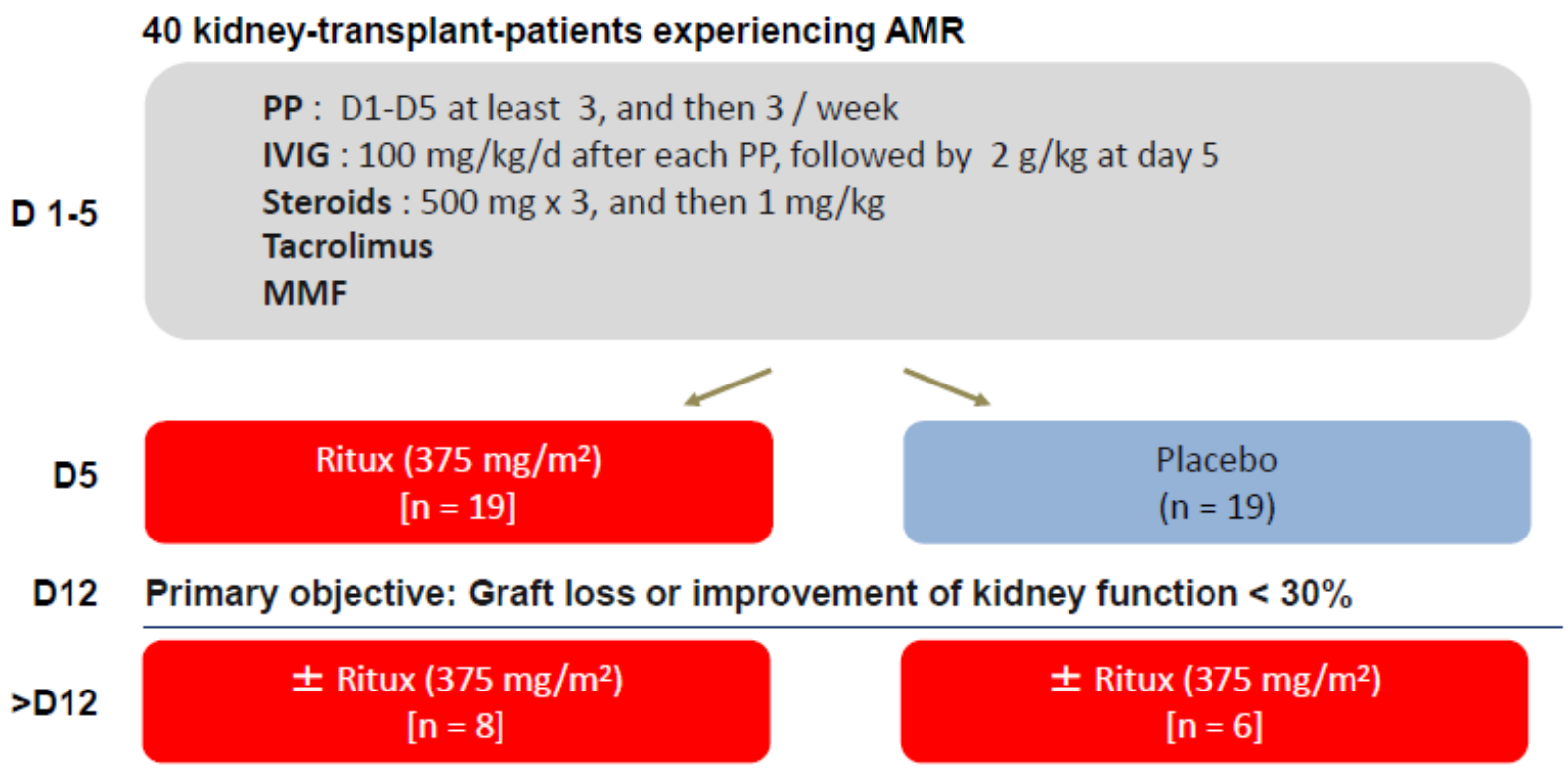
Article *in* Clinical transplants · January 2014

Table 1 Overview of rituximab for AMR

Author	Study type	Subjects	Protocol	Results
Becker et al 2004	Case series	N = 27 Adults Rejection (TMA or endothelitis without cellular infiltrate) refractory to steroids or ATG/PP	Single dose of RIT (375 mg/m^2)	89% Graft survival Average Cr 0.95 at discharge
Wade et al 2006	Case series	N = 3 Adults AMR	RIT given with various combinations of PP, steroid, OKT3, and IVIG	1 of 3 responded to treatment
Faguer et al 2007	Case series	N = 8 Adults AMR	RIT (375 mg/m^2 weekly × 4) with steroids and PP + various additional treatments	10 m average follow-up Graft survival 75% Cr improved ($P = 0.04$)
Zarkin et al 2008	Randomized, prospective trial	N = 20 Pediatrics CD20$^+$ rejection	Patients randomized to standard care or standard care plus RIT 375 mg/m^2 × 4 doses	12 m Follow-up Improved Cr in RIT group ($P = 0.026$)
Mulley et al 2009	Pilot study	N = 7 Adults AMR	Single-dose rituximab (500 mg) for AMR refractory to PP/low dose IVIG	20 m average follow-up Cr improved ($P = 0.49$) 100% allograft survival
Kasposztas et al 2009	Retrospective case-control	N = 54 Adults AMR	PP plus RIT ± IVIG vs PP alone ± IVIG	24 m follow-up Graft survival 90% (ritux) vs 60% (control) ($P = 0.005$) Mean GFR no change ($P = 0.42$)
Tanriover et al 2008	Pilot study	N = 7 Adults AMR	RIT (375 mg/m^2) with IVIG (2 g/kg)	24 m follow-up 86% one-year allograft survival 58% two-year allograft survival
Billing et al 2008	Pilot study	N = 6 Pediatric (one adult) Chronic AMR	IVIG (1 g/Kg) weekly × 4 doses followed by RIT 375 mg/m^2 × 1 dose	12 m follow-up GFR stabilized in 4/6 patients

Abbreviations: AMR, antibody-mediated rejection; ATG, antithymocyte globulin; Cr, creatinine; IVIg, intravenous immunoglobulins; m, month; PP, plasmapheresis; RIT, rituximab; TMA, thrombotic microangiopathy.

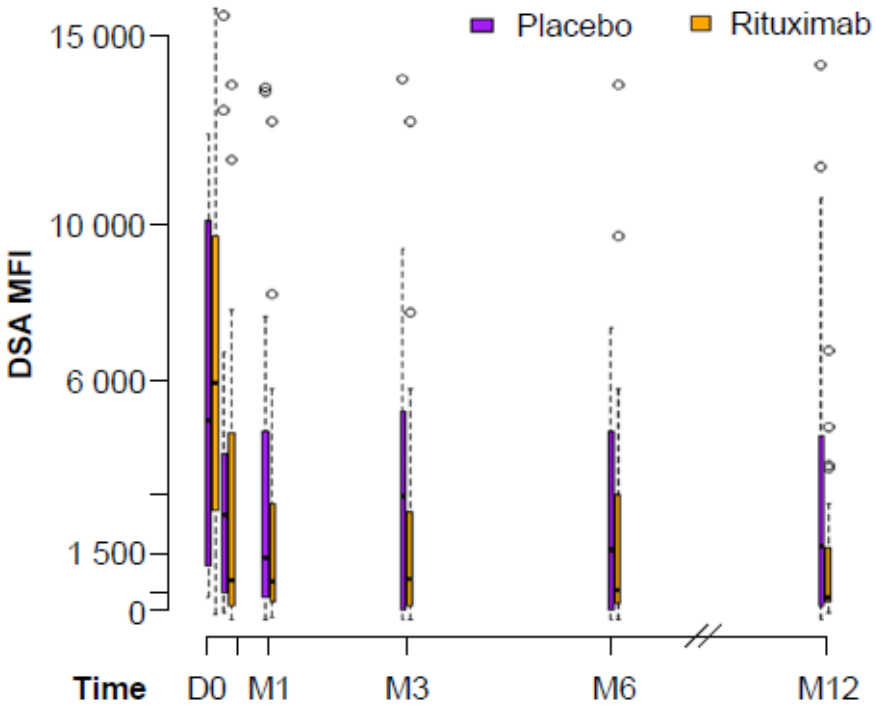
RITUX-ERAH: A prospective study(1)



Sautenet B. et al., Transplantation. 2015 Nov 9.

	Placebo (n = 19)	Rituximab (n = 19)
Mean Age (years)	46.7 (16.2)	44.6 (16.8)
PRA at transplantation, n (%)	9 (47.3)	12 (63.1)
Median time to AMR	74.0 (14.0 ; 178.0)	17.0 (12.0 ; 261.0)
Median Creatinine level at AMR (µmol/L)	204.0 (167.0 ; 324.0)	197.0 (139.2 ; 489.0)
Median MFI at AMR	5 538 (1 400 ; 9 800)	6 000 (2 840 ; 10 500)
Patient survival (%)	**100**	**100 (NS)**
Graft survival (%)	**94.7**	**94.7 (NS)**
Primary objective at day 12 : graft loss or improvement of kidney function < 30 %)	**52.6 %**	**57.9 % (NS)**
Creatinnine level at 1 year (µmol/L)	**197**	**204 (NS)**
Persistance of AMR signs at month 6 kidney biopsy (%)	**31.3**	**41.7 (NS)**

Sautenet B. et al., Transplantation. 2015 Nov 9.



	Placebo (n = 15)	Rituximab (n = 17)
MFI < 2 000 at M12	6 (40 %)	13 (76.5 %)

p < 0.04

Sautenet B. et al., Transplantation. 2015 Nov 9.

Rituximab in Kidney Tx

(A) Desensitization protocols for highly sensitized recipients before or concurrent with kidney transplantation, and in ABO incompatible kidney transplantation

(B) Treatment of Acute and Chronic Antibody-Mediated Rejection

(C) Treatment of Recurrent and de novo Glomerular Diseases after kidney transplant, and

(D) Treatment of Posttransplant Lymphoproliferative Disorder (PTLD).

Recurrent glomerulonephritis after kidney transplantation: risk factors and allograft outcomes

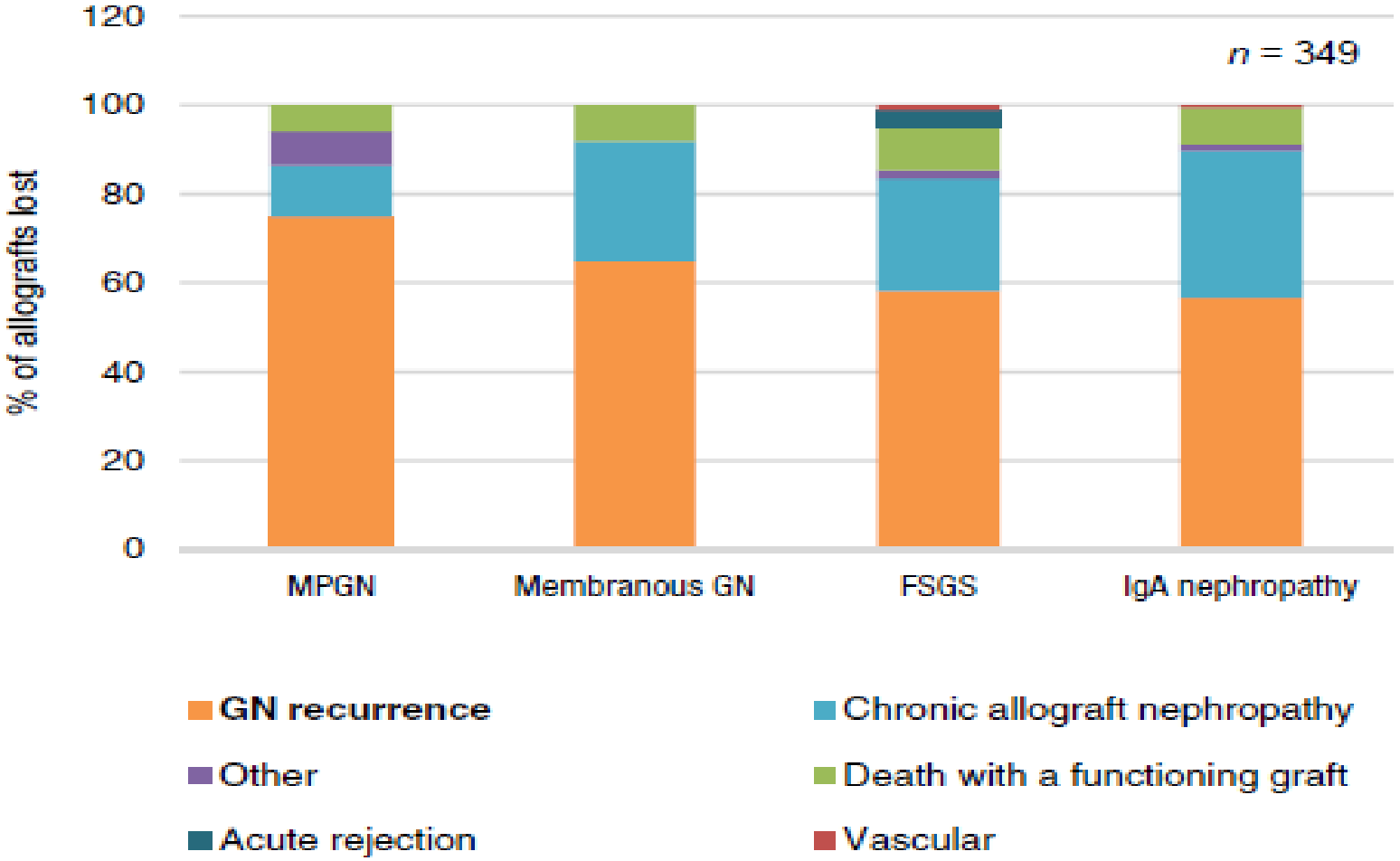
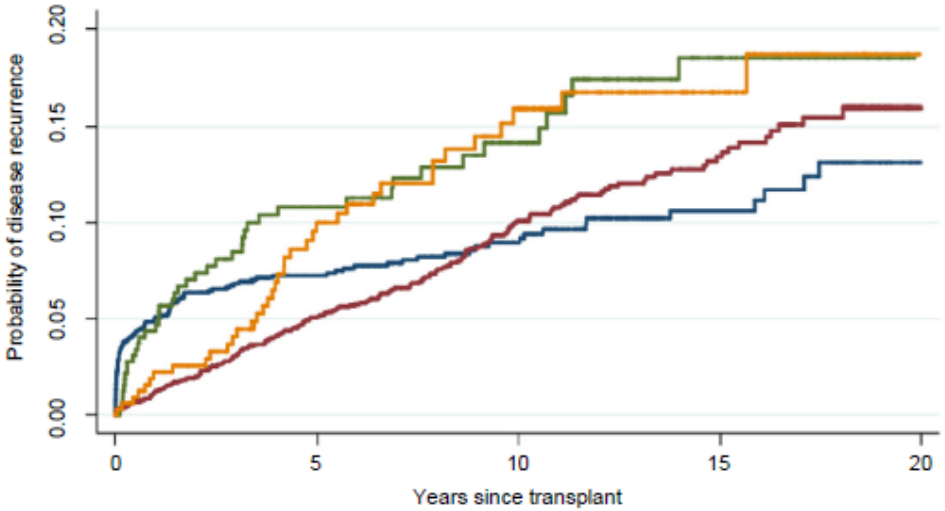
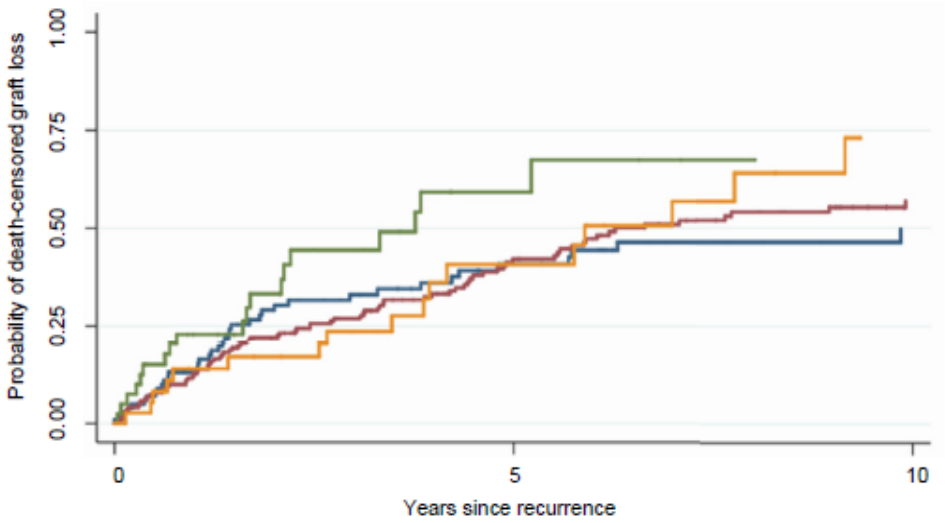


Figure 5 | Causes of allograft loss in recipients with recurrent glomerulonephritis (GN). FSGS, focal segmental glomerulosclerosis; MPGN, membranoproliferative glomerulonephritis.



Number at risk					
FSGS	1653	769	412	194	67
IgA nephropathy	2451	1543	836	365	115
MPGN	352	201	122	63	35
Membranous	340	194	121	51	13

Figure 2 | Kaplan–Meier estimates of disease recurrence, stratified by glomerulonephritis (GN) types: focal segmental glomerulosclerosis (FSGS), IgA nephropathy, membranoproliferative glomerulonephritis (MPGN), and membranous GN.



Number at risk			
FSGS	103	35	15
IgA nephropathy	195	70	26
MPGN	41	5	1
Membranous	37	13	2

Figure 6| Allograft survival after recurrence, stratified by glomerulonephritis (GN) type: focal segmental glomerulosclerosis (FSGS), IgA nephropathy, membranoproliferative glomerulonephritis (MPGN), and membranous GN.

NDT Plus (2009) 2: 395–397
doi: 10.1093/ndtplus/sfp071
Advance Access publication 17 June 2009

Case Report

NDT PLUS
Nephrology Dialysis Transplantation

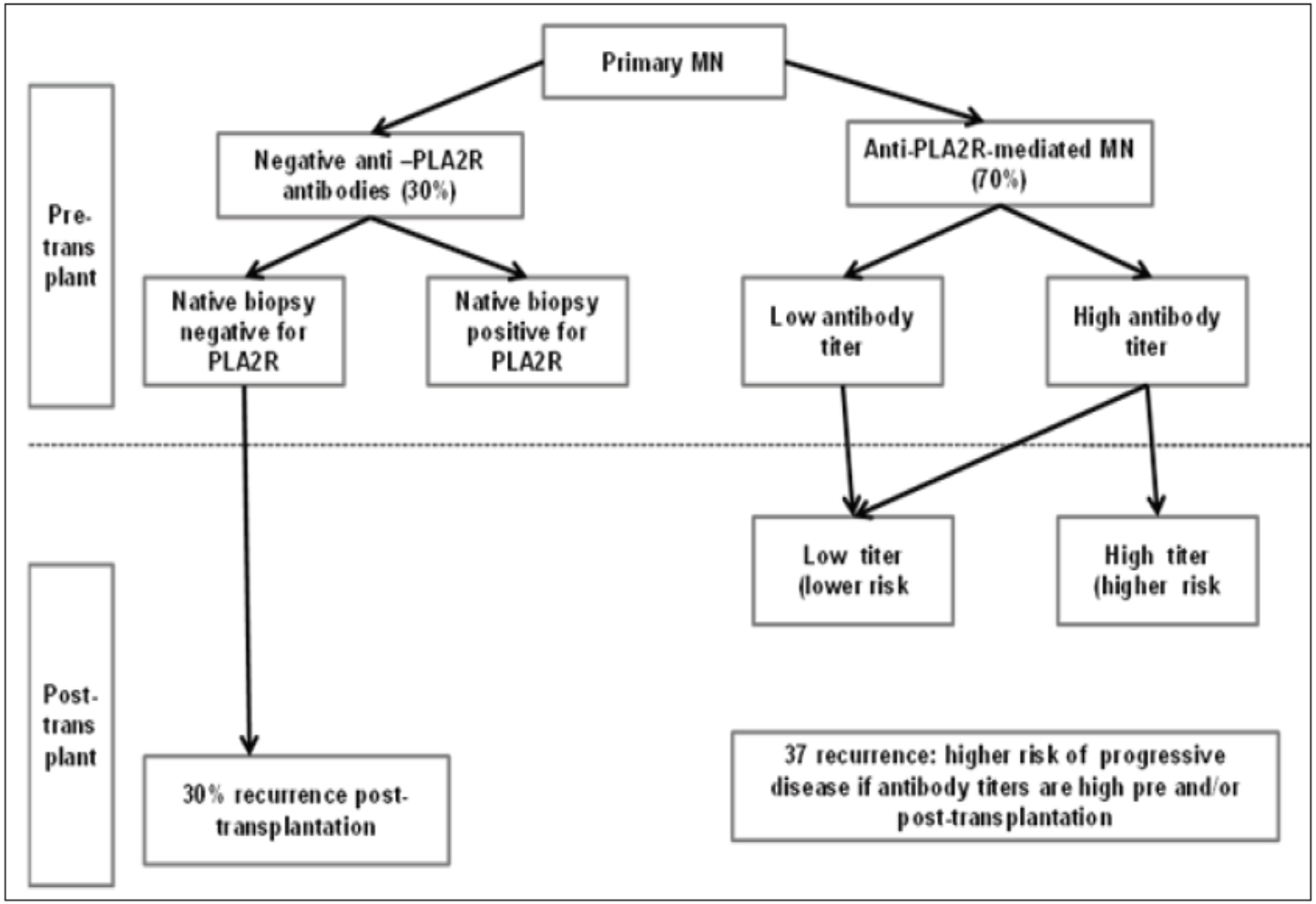
Recurrent idiopathic membranous nephropathy in the renal allograft: successful treatment with the anti-CD20 monoclonal antibody rituximab

Marco Ladino and David Roth

Published in final edited form as:

Am J Transplant. 2015 May ; 15(5): 1349–1359. doi:10.1111/ajt.13133.

Anti-Phospholipase A_2 Receptor Antibodies in Recurrent Membranous Nephropathy


Primary MN
Negative anti –PLA2R antibodies (30%)
Anti-PLA2R-mediated MN (70%)
Pre-trans plant
Native biopsy negative for PLA2R
Native biopsy positive for PLA2R
Low antibody titer
High antibody titer
Low titer (lower risk
High titer (higher risk
Post-trans plant
30% recurrence post-transplantation
37 recurrence: higher risk of progressive disease if antibody titers are high pre and/or post-transplantation

Nephrol Dial Transplant (2008) 23: 2091–2094
doi: 10.1093/ndt/gfn099
Advance Access publication 4 March 2008

NDT
Nephrology Dialysis Transplantation

Exceptional Case

Rituximab therapy in early recurrent focal segmental sclerosis after renal transplantation

Terje Apeland[1] and Anders Hartmann[2]

Rituximab in Kidney Tx

(A) Desensitization protocols for highly sensitized recipients before or concurrent with kidney transplantation, and in ABO incompatible kidney transplantation

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American Journal of Transplantation 2005; 5: 2901–2906
Blackwell Munksgaard

doi: 10.1111/j.1600-6143.2005.01098.x

Effect of Anti-CD 20 Antibody Rituximab in Patients with Post-Transplant Lymphoproliferative Disorder (PTLD)

The incidence of **PTLD** varies from 1.3% in kidney transplant recipients to 8.2% in lung transplant recipients.

Risk factors for PTLD include Epstein–Barr virus (EBV) status, type of organ transplanted and intensity of immunosuppression. EBV positivity has ranged from 29% to 100% in patients who developed PTLD.62

The majority of these tumors are CD20+ B-cell clones; mostly diffuse large cell lymphomas.

American Journal of Transplantation 2011; 11: 1058–1063
Wiley Periodicals Inc.

Monitoring Infection with Epstein–Barr Virus among Seromismatch Adult Renal Transplant Recipients

Twenty (60.6%) of the 34 recipients developed viremia during the first year post-transplant.

Of the recipients who became viremic, six (30%) received rituximab. None of the six who received rituximab-developed PTLD.

RITUXIMAB THERAPY FOR AUTOIMMUNE HEMATOLOGICAL DISEASES

Bon Appétit!