Traitement du rejet humoral

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Antibody-mediated rejection
Strategies

Meeting Report

Antibody-Mediated Rejection — An Ounce of Prevention Is Worth a Pound of Cure

J. A. Bradley*, W. M. Baldwin*, A. Bingaman*, C. Ellensfeder*, H. M. Gebel*, D. Glotz† and A. D. Kirk‡

Key words: Alloantibody, antibody-mediated rejection, desensitization, immune monitoring, kidney paired donation

« The current consensus is that ABMR should be prevented rather than cured »
Antibody-mediated rejection

Prevention

- Avoid pretransplant DSAs
  - Optimize HLA matching / limit epitope mismatching
  - Acceptable mismatches in highly sensitized patients
  - Paired kidney donation/exchange in sensitized patients
  - Pre- and/or post-transplantation desensitization in highly sensitized DSA-positive patients
- Avoid under-immunosuppression
- Prevent acute TCMR

Treatment

Adapted from Fehr T & Gaspert A. Transplant int 2012
Plasma exchanges and IVIG

I Schwab et al., Nat Rev Immunol 13

Plasma exchanges and IVIG

Titre des DSA significativement plus bas à 3 mois dans le groupe B

C Lefaucheur et al, Am J Transplant 2009
**Traitemen du rejet aigu humoral DSA+/v+**

![Graph showing graft survival](image)

- **New approach** (n = 22)
- **Classical Banff approach** (n = 42)

**Log rank**: p = 0.035

<table>
<thead>
<tr>
<th>Time post rejection (months)</th>
<th>PE/IVlg/Ritux</th>
<th>OKT3</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>12</td>
<td>90</td>
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<td>60</td>
<td>50</td>
<td>50</td>
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<tr>
<td>72</td>
<td>40</td>
<td>40</td>
</tr>
</tbody>
</table>

**Number at risk**

- **New approach**
  - 42
  - 22
  - 20
  - 16
  - 13
  - 10
  - 5
  - 3

- **Classical Banff approach**
  - 42
  - 34
  - 29
  - 22
  - 14
  - 9
  - 7


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**Plasma exchanges and IVIG**

**TABLE 3. Evidence for use of plasma exchange and intravenous immune globulins as SOC in active AMR**

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Evidence</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biological rationale</td>
<td>Anti-HLA antibodies activate complement and interact with Fc receptors and endothelium. Removal of anti-HLA Ab via plasma exchange correlates with better clinical response in kidney transplant recipients.</td>
<td></td>
</tr>
<tr>
<td>Benefit in clinical (international) studies</td>
<td>Humoral rejection treated with PE/IVIG results in improved renal function.</td>
<td></td>
</tr>
<tr>
<td>International recommendations</td>
<td>The combination PE/IVIG leads to better removal of anti-HLA antibodies and correlates with better graft survival.</td>
<td></td>
</tr>
<tr>
<td>Most used combination in clinical practice</td>
<td>American Society of Transplantation survey: Most centers utilize a combination of IVIG and plasmapheresis for treatment.</td>
<td></td>
</tr>
</tbody>
</table>

Ab, antibody; AMR, antibody-mediated rejection; Fc, fragment crystallizable; IVIG, intravenous immune globulins; PE, plasma exchange; FDA, Federal Drug Administration; KDIGO, Kidney Disease Improving Global Outcomes; SOC, standard of care.

Transplantation. 2020 May;104(5):911-922
Rituximab in acute ABMR?

One-Year Results of the Effects of Rituximab on Acute Antibody-Mediated Rejection in Renal Transplantation

RITUXERA-A, a multicenter double-blind randomized placebo-controlled trial

Sautenet B et al, Transplantation 2015

- A phase III, French, multicenter, randomized study
- 64 patients with acute ABMR
- Primary endpoint: a composite one combining:
  - Graft loss
  - Impaired renal function recovery
  - PE + IVIg + Steroids ± anti-CD20, Rituximab in acute ABMR?

Am J Transplant. 2018 Apr;18(4):927-935

Rituximab in chronic ABMR?

- Treatment group (n=13) vs controls (n=12):
  - IVIG (4 doses of 0.5 g/kg) + rituximab 375 mg/m²
  - Exclusion: eDGF <20 ml/min an severe IFTA

Am J Transplant. 2018 Apr;18(4):927-935
After kidney transplantation, the use of rituximab is associated with a high risk of infectious disease and death related to infectious disease.

There was no statistically significant difference in the incidence of infectious or neoplastic complications, but to be noted, seven cancers developed in six patients treated with rituximab.

No benefit of rituximab at 7 years.

Eculizumab?
Complement and ABMR

Evidences supporting the role of complement in AMR

C4d capillary staining and C1q-binding DSA are correlated with poor outcome


Complement crosstalk with immune cells

Ricklin Nat Rev Nephrol 2016
Eculizumab in acute ABMR?

- 15 DSA+ patients with early ABMR
- Eculizumab +/- PE

### Table 2

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>DSA</th>
<th>CRP</th>
<th>FSG</th>
<th>Age</th>
<th>Follow-up Biopsy</th>
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<tr>
<td>1</td>
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<td>11</td>
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</tbody>
</table>

*Table 2: Individual cases of AMR.

### Follow-up Biopsy

- At 6 months: 14/15 patients had a normal biopsy.
- At 12 months: 13/15 patients had a normal biopsy.

*Table modified from the original text for clarity.*
Eculizumab in chronic ABMR?

- 5 controls vs 10 treatments (6 months of eculizumab)
- Pas d’effet sur la fonction
- Pas d’effet sur les ENDATs

American Journal of Transplantation 2017; 17: 682–691

Traitement curatif du rejet aigu humoral

C1-inhibiteur

Rescue

Viglieti D, Gosset C et al. AJT 2016
**Traitement curatif du rejet aigu humoral**

**Rescue**

No improvement of the g + ptc histological scores

<table>
<thead>
<tr>
<th>Characteristics of anti-HLA DSA</th>
<th>M0</th>
<th>M+6</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number, mean ± SD</td>
<td>2.0 ± 0.6</td>
<td>2.0 ± 0.6</td>
<td>–</td>
</tr>
<tr>
<td>HLA class specificity, n (%)</td>
<td>2 (33.3)</td>
<td>2 (33.3)</td>
<td>–</td>
</tr>
<tr>
<td>HLA class I</td>
<td>3 (50.0)</td>
<td>3 (50.0)</td>
<td>–</td>
</tr>
<tr>
<td>HLA class II</td>
<td>1 (16.7)</td>
<td>1 (16.7)</td>
<td>–</td>
</tr>
<tr>
<td>MFI sum, means ± SE</td>
<td>17 469.0 ± 3833.7</td>
<td>14 872.2 ± 3307.9</td>
<td>0.0277</td>
</tr>
<tr>
<td>MFI mean, mean ± SE</td>
<td>9806.4 ± 2472.6</td>
<td>10 395.6 ± 3071.1</td>
<td>0.9165</td>
</tr>
</tbody>
</table>

Clinical characteristics:
- sGFR (mL/min/1.73 m²), mean ± SD: 38.7 ± 17.9 vs 45.2 ± 21.3 (0.0277)
- Proteinuria (g/d), mean ± SD: 0.9 ± 0.4 vs 0.7 ± 0.8 (0.2066)

Histological characteristics (Ibori scores): g + ptc score, mean ± SD: 3.7 ± 1.0 vs 3.0 ± 1.1 (0.1685)
- v score, mean ± SD: 0.3 ± 0.8 vs 0.0 (0.3173)
- vG score, mean ± SD: 0.3 ± 0.5 vs 0.5 ± 0.5 (0.3173)
- FTA score, mean ± SD: 1.2 ± 0.4 vs 1.7 ± 1.0 (0.4235)
- C4d deposition, n (%): 5 (83.3) vs 1 (16.7) (0.0465)

DSA C1q status decreased from 6/6 (100%) positive at enrollment to 1/6 (16.6%) at M+6

**Viglietti D, Gosset C et al. AJT 2016**

**Traitement curatif du rejet aigu humoral**

**First-line**

- ClinicalTrials.gov Identifier: NCT01147302

Primary Outcome Measures: change from baseline in histopathology endpoints
- First qualifying episode of biopsy-proven ABMR within the 1st year post-Tx (C4d or ptc or g)
- Concurrent DSA ≥ 40 mL/mn within the first 4 weeks

**Randomization**

- Exclusion
  - ah, ci, ct ≥ 2
  - Severe oliguric ABMR
  - History of bleeding/clotting

- n=9

**Plasma-Derived C1 Esterase Inhibitor for Acute Antibody-Mediated Rejection Following Kidney Transplantation: Results of a Randomized Double-Blind Placebo-Controlled Pilot Study**

- n=9

**Primary Outcome Measures**

- Exclusion
  - ah, ci, ct ≥ 2
  - Severe oliguric ABMR
  - History of bleeding/clotting

- n=9

**Montgomery R et al. AJT 2016**
Creatinine clearance levels peaked at day 13 and were sustained through day 90 for the C1 INH cohort. In the placebo group, there was a trend toward reduction of creatinine clearance.

14/18 were transplanted at JHMI and underwent a SOC 6-month screening biopsy.

0/7 C1 INH subjects had TG
3/7 placebo subjects had TG

Montgomery R et al. AJT 2016
Bortezomib

Figure 1 | 26S Proteasome structure.

Antigen processing for MHC class I presentation
Regulation of NF-κB-mediated cytokine production
Induction of cell-cycle arrest and apoptosis
Induction of ER stress and terminal UPR

RC Walsh et al, Kidney Int 2012

Molecules of equivalent soluble fluorescence (MESF)

PTD

- Rituximab
- Bortezomib
- Plasmapheresis
- Corticosteroids

RC Walsh et al, Kidney Int 2012
Bortezomib in chronic ABMR?

**Borteject Study**

<table>
<thead>
<tr>
<th>21 received</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 cycles bortezomib, intravenously (4 x 1.3 mg/ml over 2 weeks)</td>
</tr>
<tr>
<td>oral valsartan (1 week per cycle)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>23 received</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 cycles placebo, intravenously (4 x 1.3 mg/ml over 2 weeks)</td>
</tr>
<tr>
<td>oral placebo (1 week per cycle)</td>
</tr>
</tbody>
</table>

2 received no or incomplete second cycle (SAE considered possibly related to treatment) 2 died 21 were analyzed after 24 months

→ Bortezomib did not affect the slope of eGFR
→ No difference in secondary endpoints
→ More adverse effects

*Tocilizumab in chronic ABMR?*

- N=36 pts with DSA-positive TG
- Monocenter, uncontrolled trial
- Rescue therapy after PE, IVIG, rituximab
- Monthly infusions of tocilizumab

**Assessment of Tocilizumab (Anti-Interleukin-6 Receptor Monoclonal) as a Potential Treatment for Chronic Antibody-Mediated Rejection and Transplant Glomerulopathy in HLA-Sensitized Renal Graft Recipients**

- Mean score
  - Pre TGZ: 2.0
  - Post TGZ: 1.5

Graft survival: 80% at 6 yrs

*American Journal of Transplantation 2017; 17: 2381-2389*
Clazakizumab in chronic ABMR?

- Phase 2 randomized pilot trial

A Randomized Clinical Trial of Anti–IL-6 Antibody Clazakizumab in Late Antibody-Mediated Kidney Transplant Rejection

- Decreased DSA levels under clazakizumab

- Slower mean eGFR decline under clazakizumab
Clazakizumab in chronic ABMR?

A Randomized Clinical Trial of Anti–IL-6 Antibody Clazakizumab in Late Antibody-Mediated Kidney Transplant Rejection

Kostis D. Grintzalis,1,* Michael Gouw,1 Toby J. Hulcher,7 Frédéric Lavallée,1 Klenoro Studer,7 Herve Fournier,7 Jeff Rees7 and Nicole Kadowaki,1 Renée Read,8 Swathi Sridevi,1* Carmen Arroyo,8 Fady Younan,8 Maria Sesma,9 Caterina Guazzi,9 Albert Lin,9 Sabina Svoboda,9 Christian Fabry,1 Jakub Milewski,1 Georg Delporte,9 Thomas Prieur,9* Markus Walther,9 Alexander Krei,9 Fabien Néel,9 Fabien Holack,9 Grigori Bovlot,9 Edward Chang,9* Bernd Arico,9 and Gunay A. Bilbao9

Table 2. Serious treatment emergent adverse events by system organ class

<table>
<thead>
<tr>
<th>Serious Adverse Events, n (%)</th>
<th>Part A*</th>
<th>Part B</th>
<th>Clazakizumab (n=10)</th>
<th>Placebo (n=10)</th>
<th>Clazakizumab (n=19)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>0</td>
<td>0</td>
<td>5 (5.3)</td>
<td></td>
<td></td>
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<tr>
<td>Pneumonia</td>
<td>0</td>
<td>0</td>
<td>1 (10.3)</td>
<td></td>
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<tr>
<td>Pyelonephritis</td>
<td>0</td>
<td>0</td>
<td>1 (5.3)</td>
<td></td>
<td></td>
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<tr>
<td>Ovarian abscess</td>
<td>0</td>
<td>0</td>
<td>1 (5.3)</td>
<td></td>
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<tr>
<td>Appendicitis</td>
<td>0</td>
<td>0</td>
<td>1 (5.3)</td>
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<tr>
<td>Gastrointestinal disorders</td>
<td>1 (10)</td>
<td>0</td>
<td>1 (5.3)</td>
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<tr>
<td>Diuretics</td>
<td>1 (100)</td>
<td>0</td>
<td></td>
<td>1 (10)</td>
<td></td>
</tr>
<tr>
<td>General disease and administration site conditions</td>
<td>0</td>
<td>1 (10)</td>
<td>0</td>
<td>1 (10)</td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td>1 (10)</td>
<td>0</td>
<td>1 (5.3)</td>
<td></td>
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<tr>
<td>Pleural effusion</td>
<td>1 (10)</td>
<td>0</td>
<td>1 (5.3)</td>
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<tr>
<td>Surgical and medical procedures</td>
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<td>0</td>
<td>1 (5.3)</td>
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<tr>
<td>Nephrosis</td>
<td>0</td>
<td>0</td>
<td>1 (5.3)</td>
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<tr>
<td>Permanent thorax cavity drainage</td>
<td>0</td>
<td>0</td>
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<td>1 (10)</td>
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<tr>
<td>Renal and urinary disorders</td>
<td>1 (10)</td>
<td>0</td>
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<tr>
<td>Acute renal injury</td>
<td>1 (10)</td>
<td>0</td>
<td>0</td>
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</tr>
</tbody>
</table>

Traitement curatif du rejet chronique humoral

- Clazakizumab : anti-CD38 ciblant les plasmocytes
- Plerixafor : anti-CXCR4

Daratumumab In Sensitized Kidney Transplantation: Potentials and Limitations of Experimental and Clinical Use

Joan Kwan,2* Marie-Mariette4,5 Martin Masood,4,5 Soualif Guenounou,2 Vincent Aslam,2 David Kowalski,2* Don Paulson2 Cédric Guadagnini4,5 Éric Guegan,2 Omer Bodur,2 Wilfried Dany,2 Laurine Faure2,4,5 Gabiela Menasch4,5 Songhong Yuan,2,4,5 Jennifer Park2,4,5 Kruno Banković,2,4,5 Youngki Choi2,4,5 Hyunjoo Kim2,4,5 Bradley Collins2,4,5 Mark Hoppe2,4,5 Allen B. Jantz,2* Stuart Knoblaich,2 and Philippe Greffard2

Traitement curatif du rejet chronique humoral

Patient #1: traitement de réfractaires cœur et rein ABMR

Daratumumab in Sensitized Kidney Transplantation: Potentials and Limitations of Experimental and Clinical Use


Recommended Treatment for Antibody-mediated Rejection After Kidney Transplantation: The 2019 Expert Consensus From the Transplantation Society Working Group

Carrie A. Schinstock, MD,1 Roslyn B. Mannon, MD,2 Klemens Budge, MD,3 Anita S. Chong, PhD,4 Mark Haas, MD,6 Stuart Knoechle, MD,3 Carmen Lefaveau, MD, PhD,2 Robert A. Montgomery, MD,8 Peter Nickerson, MD,9 Stefan G. Tulius, MD, PhD,9 Curie Ahn, MD, PhD,10,11 Medhat Asear, MD, PhD,12 Marta Crespo, MD, PhD,13 Steven J. Chadban, PhD,14 Sandy Fang, MD, PhD,15 Stanley C. Jordan, MD,16 Kwan Man, PhD,17 Michael Mangol, MD,18 Randall E. Morris, MD,19 Inish D’Oherny, PhD,18 Binnaz H. Ozdemir, MD,20 Daniel Seron, MD, PhD,20 Anat R. Tambur, PhD,20 Kazunari Tanabe, MD, PhD,21 Jean-Luc Taupin, PhD,22,23 and Philip J. O’Connell, PhD24

Transplantation. 2020 May;104(5):911-922
## Antibody-mediated rejection

### Summary

<table>
<thead>
<tr>
<th>Timing</th>
<th>DSA</th>
<th>Histology (Banff 2017)</th>
<th>Standard of care</th>
<th>Consider additional therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early/late acute (&lt;30 days posttransplant)</td>
<td>Preexisting DSA (or nonimmunologically naive)</td>
<td>Active AMR</td>
<td>Plasmapheresis (daily or alternative day × 6 based on DSA titer) (1C)</td>
<td>Complement inhibitors (2B)</td>
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<td>Rituimen 375 mg/m² (2B)</td>
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<td>Splenectomy (3C)</td>
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<tr>
<td></td>
<td></td>
<td>Active AMR</td>
<td>Plasmapheresis (daily or alternative day × 4–6 based on DSA titer) (2C)</td>
<td>Rituimen 375 mg/m² (2B)</td>
</tr>
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<td></td>
<td>MPA (3C)</td>
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<tr>
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<td></td>
<td>Chronic AMR</td>
<td>Optimize baseline immunosuppression (e.g., add steroids if on a steroid-free regimen) (1C)</td>
<td>MPA (3C)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>De novo DSA</td>
<td>Optimize baseline immunosuppression (e.g., add steroids if on a steroid-free regimen) (1C)</td>
<td>Plasmapheresis and MPA (3C)</td>
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<tr>
<td></td>
<td></td>
<td>Chronic AMR</td>
<td>Evaluate and manage nonadherence</td>
<td>Rituimen (3C)</td>
</tr>
</tbody>
</table>

*For all cases, treatment of concordant T cell-mediated rejection (undefined) and optimizing immunosuppression is recommended. Optimizing immunosuppression includes the use of tacrolimus with prednisolone of 5-10 mg and use of maintenance steroid equivalent to prednisone 5 mg daily.

*Fresh frozen plasma to be used for replacement fluid for plasmapheresis if a biopsy was performed within 24–48 hours. The codes for grades of evidence have been taken from HOSG, 2021 AMR, antibody-mediated rejection; DSA, donor-specific antibody; ELS, expert opinion; MPA, intravenous immune globulin; HOOS, Kidney Disease Improving Global Outcomes.
Antibody-mediated rejection

Summary

**Antibody-mediated rejection**

Strategies

The current consensus is that ABMR should be prevented rather than cured.