Diagnosis and Management of Acute and Chronic Humoral Rejection

Lars Pape

Medizinische Hochschule Hannover
Immunosuppression

Acute rejection
Chronic rejection

Side effects
Infections
Nephrotoxicity
Adult population

- Nearly all late rejection-related graft losses involved antibody mediated rejections (Sellares et al., AJT 2012)
- Younger age seems to be associated with higher risk to develop donor specific antibodies (Everly et al., Transplantation 2013)
Diagnosis of humoral rejection

- Transplant kidney biopsy
- Detection of Donor Specific Antibodies (DSA)
- Cross-match donor/recipient (living donation)
BANFF-Classification of transplant biopsy

Table 1: Banff 97 diagnostic categories for renal allograft biopsies—Banff ’09 update

1. Normal
2. Antibody-mediated changes (may coincide with categories 3, 4 and 5 and 6)
   Due to documentation of circulating antidonor antibody, C4d, and allograft pathology
   C4d⁺, presence of circulating antidonor antibodies, no signs of acute or chronic TCMR or ABMR (i.e. g0, cg0, ptc0, no ptc lamination (<5 layers by electron microscopy), no ATN-like minimal inflammation). Cases with simultaneous borderline changes are considered as indeterminate
Acute antibody-mediated rejection²
   C4d⁺, presence of circulating antidonor antibodies, morphologic evidence of acute tissue injury, such as (Type/Grade)
   I. ATN-like minimal inflammation
   II. Capillary and or glomerular inflammation (ptc/g > 0) and/or thromboses
   III. Arterial – v3
Chronic active antibody-mediated rejection²
   C4d⁺, presence of circulating antidonor antibodies, morphologic evidence of chronic tissue injury, such as glomerular double contours and/or peritubular capillary basement membrane multilayering and/or interstitial fibrosis/tubular atrophy and/or fibrous intimal thickening in arteries
IVIG

Apheresis for antibody depletion:
- Plasmapheresis
- IVIG
- Immunoabsorption

Modulation of adaptive or innate immunity:
- IVIG
- Rituximab
- ATG
- Bortezomib
- Eculizumab
- Splenectomy
Acute humoral rejection
Therapy of acute humoral rejection

6 (?) Steroid pulses
IVIG-Administration
3-6 Plasmaphereses or Immunoadsorptions,
Discuss Rituximab
Increase underlying immuosuppressive therapy
Monitor DSA
Acute antibody-mediated rejection in paediatric renal transplant recipients

Birgitta Kranz · Reinhard Kelsch · Eberhard Kuwertz-Bröking · Verena Bröcker · Heiner H. Wolters · Martin Konrad

In conclusion, the intense therapy with steroid pulses, TAC, MMF, plasmapheresis, IVIG and rituximab led to a favourable outcome in 3 out of 4 episodes of aAMR. In these cases a single dose of rituximab had been sufficient, although it was followed by plasmapheresis sessions starting the following day. In the episode that could not be controlled by this therapy the only obvious difference was that rituximab was administered rather late, after 10 PEs had failed. The documented B-cell depletion lasted at least 3 months, in the third patient it is still ongoing after 18 months.

Currently, it is impossible to distinguish which therapy element is the most effective and whether this multimodal therapy might be adjusted individually.
Immunoabsorption in Severe C4d-Positive Acute Kidney Allograft Rejection: A Randomized Controlled Trial


ularly poor prognosis (1–3). Mainly based on small uncontrolled series, distinctly ‘anti-humoral’ treatment modalities have been proposed to be effective in reversing AMR, including extracorporeal strategies for the removal of dele-
Eculizumab Treatment of Acute Antibody-Mediated Rejection in Renal Transplantation: Case Reports

F. González-Roncero, M. Suñer, G. Bernal, V. Cabello, M. Toro, P. Pereira, and M. Angel Gentil
Special cases

• Transplantation against „forbidden antigens“ → desensitization protocols (i.e. Rituximab / Immunoabsorption / IgG / immunosuppression prior to Tx / Induction therapy)

• High Panel reactive antibodies prior to Tx

• ABO incompatible Tx (antigen specific immunoabsorption / Rituximab / IgG / Immunosuppression before Tx)

• Non-HLA-antibodies
Chronic humoral rejection
Chronic changes in protocol biopsy

**early:** tubulointerstitial damage

**late:** microvascular / Glomerular damage

Nankivell et al, NEJM 349: 2326, 2003
Birk et al, Transplantation 15: 334, 2010
Increasing Prevalence of IF/TA
(Pediatric Recipients, Antibody/Tac/MMF/Pred)

Birk et al, Transplantation 89: 334, 2010
Meaning of fibrosis and inflammation

“In late biopsies all infiltrates … were associated with increased future graft loss …. The impact of inflammation on survival reflects the association of progressing disease with inflammation.”
Meaning of fibrosis and inflammation

- 1-yr protocol biopsies
  - 1.) normal histology (n=86)
  - 2.) fibrosis (n=45)
  - 3.) fibrosis und inflammation (n=20)

Park et al, JASN 2010
Stages of Antibody Mediated Rejection

I
II
III
IV

Graft dysfunction
Pathology in graft
C4d in graft
Alloantibody in circulation

Graft Failure

Time post-transplant

0
The Clinical Impact of Humoral Immunity in Pediatric Renal Transplantation

Abanti Chaudhuri,* Mikki Ozawa,† Matthew J. Everly,† Robert Ettenger,‡ Vikas Dharnidharka,§

Diagram: Flowchart showing the distribution of samples:
- n=124
- Steroid free: n=60
  - Unique Serum Samples: 215
  - Unique Biopsy Samples: 215
  - Total samples: 440
- Steroid based: n=64
  - Unique Serum Samples: 225
  - Unique Biopsy Samples: 225
  - Total samples: 440
- Total samples: 880

Legend:
- Time 0: Pre transplant Serum Sample
- 6 months: Post transplant Serum Sample
- 12 months: Post transplant Serum Sample
- 24 months: Post transplant Serum Sample

* and † indicate author contributions, with † indicating equal contribution.
Figure 2. *De novo* antibody titers in SF versus SB immunosuppression. Antibody titers. The highest MFIs are shown for DSA, NDS, Cw, DQ, and DP (where donor typing for these antigens were not available), and MICA antigens.
Figure 6. Significant association of Ab positivity and graft loss. Anti-HLA DSA and anti-MICA Ab positivity in patients associates with greater risk of graft loss over the course of the SNSO1 study, even in low-risk pediatric renal transplant recipients.
Association of *de novo* DSA with late graft failure

Figure 6: Probability of graft survival curves in patients who underwent a late biopsy and were assessed for DSA.
Association of DSA positivity with graft survival

4 year graft survival

\[
\text{DSA +} \quad 45% \\
\text{DSA -} \quad 87%
\]

\[p = 0.002, \text{ log-rank test}\]

Courtesy of Alexander Fichter, Heidelberg - Germany
Association of C1q-binding DSA with graft survival

p = 0.009

4 year graft survival

- DSA+ / C1q + 11%
- DSA+ / C1q - 82%
- DSA - 87%

p < 0.001, log-rank test

Courtesy of Alexander Fichter, Heidelberg - Germany
Molecular Microscope Strategy to Improve Risk Stratification in Early Antibody-Mediated Kidney Allograft Rejection

Alexandre Loupy,† Carmen Lefaucheur,†‡ Dewi Vernerey,†§ Jessica Chang,‖ Luis G. Hidalgo,¶ Thibaut Beuscart,† Jerome Verine,** Olivier Aubert,† Sébastien Dubleumortier,†‡ Jean-Paul Duong van Huyen,†‡‡ Xavier Jouven,† Denis Glotz,†‡ Christophe Legendre,*† and Philip F. Halloran‖§§
<table>
<thead>
<tr>
<th>Parameters</th>
<th>HR</th>
<th>95% CI</th>
<th>P Value</th>
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<tr>
<td>Recipient age, yr</td>
<td>1.02</td>
<td>0.98 to 1.06</td>
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<td>Cold ischemia time, min</td>
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<td>Donor age, yr</td>
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<tr>
<td>&lt;60</td>
<td>1</td>
<td>—</td>
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<tr>
<td>≥60</td>
<td>3.58</td>
<td>1.45 to 8.87</td>
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<td>Proteinuria at biopsy, g/L</td>
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<td>&lt;0.15</td>
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<tr>
<td>≥0.15</td>
<td>1.52</td>
<td>0.82 to 2.81</td>
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<td>Immunologic parameters</td>
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<tr>
<td>Immunodominant DSA MFI at the time of rejection</td>
<td>1.00</td>
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<td>Functional parameters</td>
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<td>eGFR at 1 yr</td>
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<tr>
<td>eGFR≥30</td>
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<td>eGFR&lt;30</td>
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<td>Arterial fibrous intimal thickening score</td>
<td>0.96</td>
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<td>Interstitial inflammation score</td>
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<td>Tubulitis score</td>
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<td>1.20</td>
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<td>C4d Banff score</td>
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<td>1.03 to 2.08</td>
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<td>Humoral histologic score</td>
<td>1.36</td>
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<td>Molecular parameters</td>
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<td>ABMR Molecular Score</td>
<td>8.82</td>
<td>1.82 to 42.73</td>
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<td>Endothelial DSA-selective transcripts</td>
<td>2.94</td>
<td>1.00 to 8.69</td>
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<td>NK transcripts</td>
<td>1.61</td>
<td>0.81 to 3.22</td>
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<td>T-cell transcripts</td>
<td>0.93</td>
<td>0.50 to 1.73</td>
<td>0.83</td>
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<td>AKI score</td>
<td>1.17</td>
<td>0.63 to 2.18</td>
<td>0.61</td>
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* eGFR using the Modification of Diet in Renal Disease formula.
* Note that all ABMR episodes with v lesions in the present study were treated by antibody-targeting strategies.
* Humoral histologic score defined by g+ptc+v+c+C4d Banff scores.
Successful Treatment of Chronic Antibody-Mediated Rejection With IVIG and Rituximab in Pediatric Renal Transplant Recipients

Heiko Billing,¹ Susanne Rieger,¹ Jörg Ovens,² Caner Süşal,² Anette Melk,¹ Rüdiger Waldherr,³ Gerhard Opelz,² and Burkhard Tönshoff¹,⁴

(Months)

GFR (ml/min/1.73 m²)

IVIG / rituximab

Biopsy

(Months)

(Transplantation 2008;86: 1214–1221)
IVIG and rituximab for treatment of chronic antibody-mediated rejection: a prospective study in paediatric renal transplantation with a 2-year follow-up

Heiko Billing,1 Susanne Rieger,1 Caner Süsal,2 Rüdiger Waldherr,3 Gerhard Opelz,2 Elke Wühl1 and Burkhard Tönshoff1
Bortezomib as the Sole Post-Renal Transplantation Desensitization Agent Does Not Decrease Donor-Specific Anti-HLA Antibodies

R. Sbero-Soussan, J. Zuber, C. Suberbielle-Boissel, S. Candon, F. Martinez,

Received 07 July 2009, revised 22 October 2009 and accepted for publication 04 November 2009

Bortezomib Provides Effective Therapy for Antibody- and Cell-Mediated Acute Rejection


(Transplantation 2008;86: 1754–1761)
Immune Response of Pediatric Renal Transplant Recipients challenged by Sensitization, Vaccination or Non-Adherence: Cross-Sectional and Prospective Analyses of the International CERTAIN Registry Cohort
Design

Nested case-control study

Identification of cases and controls from CERTAIN

Blood/urine collection and analysis at 1 time-point

Statistical analysis of nested case-control study

40 cases - 120 controls

Identification of controls locally and via CERTAIN registry
Design

Prospective longitudinal study

Renal Tx (7/15-12/16)

- 7d
- 30d
- 6mo
- 1y
- 2y

blood + urine collection (analysis at marked time points and in case of indication biopsy)

180 patients to be followed
Marker

- Cytokines (Falk)
- Senescence markers (Melk)
- Urinary Proteomics (Pape)
- Complement in Urine and Plasma (Heindl-Rusai)
- Free DNA (Schütz)
- Complement fixing DSA (Fichtner)
- Virus-specific T cells (Pape)
Diagnosis of humoral rejection is a combination of detection of circulating DSA and histology. Complement fixing DSA might be the future diagnostic mean.

Acute humoral rejection is a rare condition in pediatric renal transplantation and can be treated successfully in most cases.

Fibrosis is a scar and stable; inflammation with fibrosis is signalling progressive disease and bad prognosis.
Conclusions II

Chronic humoral rejection is the main cause for long-term graft loss.

Chronic humoral rejection might be treated successfully if detected early enough.

Treatment consists of IgG, Rituximab, increase of underlying immunosuppression and eventually Immunoadsorption / Plasmapheresis.

The role of Bortezomib is to be determined.