Desensitization: Increasing Access to Transplantation for Highly-HLA Sensitized Patients

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Cedars-Sinai Medical Center
I have grants from Hansa Medical, Roche-Genentech, Vitaeris, Novartis and CSL-Behring. I am a consultant for Hansa Medical, Roche-Genentech, Vitaeris and CSL-Behring

AND

My presentation does include discussion of off-label or investigational use.
Sir Peter Medwar, Nobel Prize in Medicine 1960

Champion of T-cell centric view of transplantation
And proponent of Tolerance

Paul Terasaki, PhD

Champion of the Humoral Theory of Transplantation
Allo-sensitization & Donor Specific Antibodies: Enemies of Allograft Survival

Donor Specific Anti-HLA Antibodies = allograft rejection in transplant patients
Patients With De Novo DSA Have Early (0-6 mo) TCMR With More Intense PTC Inflammation

<table>
<thead>
<tr>
<th>TCMR PTC Score</th>
<th>de novo DSA</th>
<th>No DSA</th>
<th>$P &lt; .05$</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.0</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>1.0</td>
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</tbody>
</table>

IFN: interferon.

Source: Peter Nickerson
Mechanisms of Donor-Specific Antibody-Mediated Endothelial Injury in Renal Allografts

Model Linking TCMR, dnDSA, and AMR With Graft Loss


Source: Peter Nickerson
Complement Fixing (C1q+) DSAs Have the Greatest Potential to Injure and Destroy Allografts

Rituximab +IVIG significantly lowered PRA levels and improved transplant rates For HS patients.
Desensitization for Kidney Transplantation

• Patient underwent desensitization with IVIG + Rituximab without successful reduction of DSAs. After 6M, the patient received PLEX/IVIG/Rituximab and was transplanted with TCMX: 200, BCMX 283. Patient received induction with Campath 1H and maintained on Pred/Tacro/MMF.

• At 1M post-transplant, the only DSA present was a weak DQ7. DSAs have subsequently disappeared. Patient is now 5 years post-transplant with SCr 0.9mg/dl. Biopsy showed no evidence of ABMR or TG.
Freedom from Allograft Rejection & Infection Post-Desensitization (#372) v. Normal (#578)

(a) Allograft rejection (ABMR or CMR)
(b) ABMR
(c) CMR

(p = 0.08)
(p < 0.001)
(p = 0.04)
(p = 0.01)
(p = 0.27)
(p = 0.72)

(Freedom from CMR)
(Freedom from CMV-viremia)
(Freedom from EBV-viremia)
(Freedom from BKV-viremia)
Patient & Graft Survival for Desensitized (#372) v. Normal(#578) at 5 Years

(a) Graft loss (death-censored)  
(b) Patient survival

$p = 0.22$  
$p = 0.77$
Factors Predicting Risk for Antibody-mediated Rejection and Graft Loss in Highly Human Leukocyte Antigen Sensitized Patients Transplanted After Desensitization

Ashley A. Vo,1 Aditi Sinha,2 Mark Haas,3 Jua Choi,1 James Mirocha,4 Joseph Kahwaji,1 Alice Peng,1 Rafael Villicana,1 and Stanley C. Jordan1

Background. Desensitization with intravenous immunoglobulin and rituximab (I+R) significantly improves transplant rates in highly sensitized patients, but antibody-mediated rejection (ABMR) remains a concern. Patients and Methods. Between July 2006 and December 2012, 226 highly sensitized patients received transplants after desensitization. Most received alemtuzumab induction and standard immunosuppression. Two groups were examined: ABMR+ (n = 181) and ABMR− (n = 45, 20%). Risk factors for ABMR, pathology, and outcomes were assessed. Results. Significant risks for ABMR included previous transplants and pregnancies as sensitizing events, donor-specific antibody (DSA) relative intensity scores greater than 17, presence of both class I and II DSAs at transplant and time on waitlist. The ABMR− showed a significant benefit for graft survival and glomerular filtration rate at 5 years (P < 0.0001). Banff pathology characteristics for ABMR+ patients with or without graft loss did not differ. C4d+ versus C4d− ABMR did not predict graft loss (P = 0.086). Thrombotic microangiopathy (TMA+) significantly predicted graft failure (P = 0.045). The ABMR episodes were treated with I+R (n = 25), or, in more severe ABMR+, plasma exchange (PLEX)+I+R (n = 20). Graft survival for patients treated with I+R was superior (P = 0.028). Increased mortality was seen in ABMR+ patients experiencing graft loss after ABMR treatment (P = 0.004). The PLEX + Eculizumab improved graft survival for TMA+ patients (P = 0.036). Conclusion. Patients desensitized with I+R who remain ABMR− have long-term graft and patient survival. The ABMR+ patients have reduced graft survival and glomerular filtration rate at 5 years, especially TMA+. Severe ABMR+ episodes benefit from treatment with PLEX + Eculizumab. The DSA-relative intensity scores at transplant was a strong predictor
Risk for ABMR after Desensitization

**DSA Number & Strength are Strong Predictors of Risk for ABMR**

**DSA Relative Intensity Scale (RIS) at Transplant by ABMR Status**

*Figure 1C*

**Positive Predictive Value (PPV) of RIS for ABMR Episodes**

*Figure 1D*

Vo et al Transplantation 2014
Efficacy of Desensitization: Rituximab + IVIg 2017-2018

3 Patients Transplanted with cPRA <90
13 Patients Transplanted cPRA 95-98%
10 Patients Transplanted cPRA 99-100%
Survival Benefits of HLAi Transplantation After Desensitization

**ABSTRACT**

A report from a high-volume single-center indicated a survival benefit of receiving a kidney transplant from an HLA-incompatible live donor as compared with remaining on the waiting list, whether or not a kidney from a deceased donor was received. The generalizability of that finding is unclear.

**METHODS**

In a 22-center study, we estimated the survival benefit for 2010 recipients of kidney transplants from HLA-compatible live donors who were matched with controls who remained on the waiting list or received a transplant from a deceased donor (waiting-list or transplant control group) and controls who remained on the waiting list but did not receive a transplant (waiting-list-only control group). We analyzed the data with and without patients from the highest-volume center in the study.

**RESULTS**

Recipients of kidney transplants from incompatible live donors had a higher survival rate than either control group at 1 year (95.0% vs. 94.0% for the waiting-list or transplant control group and 89.0% for the waiting-list-only control group), 3 years (84.0% vs. 83.0% and 79.0%, respectively), 5 years (80.0% vs. 79.4% and 74.2%, respectively), and 8 years (76.5% vs. 76.9% and 43.9%, respectively). For all comparisons with the control group, the survival benefit was significant at 8 years across all levels of donor-specific antibody 89.0% for recipients of kidney transplants from incompatible live donors who had a positive Lumines assay for anti-HLA antibody but a negative flow-cytometric cross-match versus 66.0% for the waiting-list or transplant control group and 60.0% for the waiting-list-only control group. 86.0% for recipients with a positive flow-cytometric cross-match but a negative cytotoxic cross-match versus 63.6% and 43.1%, respectively, and 72.1% for recipients with a positive cytotoxic cross-match versus 67.5% and 41.7%, respectively. The findings did not change when patients from the highest-volume center were excluded.

**CONCLUSIONS**

This multicenter study validated single-center evidence that patients who received kidney transplants from HLA-incompatible live donors had a substantial survival benefit as compared with patients who did not undergo transplantations and those who waited for transplants from deceased donors. (Funded by the National Institute of Diabetes and Digestive and Kidney Diseases.)
Therapeutic Options for AMR

IdeS (IgG Endopeptidase): A Potent IgG Degrading Enzyme

Steptococcus Pyogenes

IgG Endopeptidase

IgG → 1st → sclIgG → 2nd → F(ab')2 & Fc
Solutions to remove pathogenic IgG in Patients

IdeS treatment

Therapeutic plasma exchange/Immunoadsorption
IgG Endopeptidase in Highly Sensitized Patients Undergoing Transplantation


BACKGROUND
Donor-specific antibodies create an immunologic barrier to transplantation. Current therapies to modify donor-specific antibodies are limited and ineffective in the most highly HLA-sensitized patients. The IgG-degrading enzyme derived from Streptococcus pyogenes (IdeS), an endopeptidase, cleaves human IgG into F(ab')2, and Fc fragments inhibiting complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity, which suggests that IdeS might be useful for desensitization. We report on the combined experience of two independently performed open-label, phase 1–2 trials (conducted in Sweden and the United States) that assessed the efficacy of IdeS with regard to desensitization and transplantation of a kidney from an HLA-incompatible donor.

METHODS
We administered IdeS to 25 highly HLA-sensitized patients (11 patients in Uppsala, Sweden, and 14 in Minneapolis, Minnesota) at doses ranging from 0.01 to 1.0 mg, in 12-hourly intervals, 2 weeks before transplantation. The primary end point was the occurrence of acute cellular rejection or a rapid rise in cold ischemia time. The secondary end point was the rate of successful transplantation.

RESULTS
Rejection occurred in only 2 of 25 patients (8%). The mean cold ischemia time was 30.9 minutes, and 21 (84%) of the patients received a kidney transplant. The incidence of rejection did not correlate with the prior number of sensitization reactions, donor specificities, or doses.

CONCLUSIONS
IgG Endopeptidase may be useful for desensitization before kidney transplantation.
Mechanism of Action of IdeS with Implications for CDC and ADCC

IgG

| Complement(+) | FcγR(+) | CDC(+) | ADCC(+) |

sclgG

| Complement(-) | FcγR(+/-) | CDC(-) | ADCC(+/-) |

F(ab´)2 & Fc

| Complement(-) | FcγR(-) | CDC(-) | ADCC(-) |

Impact of IdeS on Luminex SAB and C1q Assays

HLA - 6 h after IdeS treatment

C1q - 1 h after IdeS treatment
Fig. 6

CD4+ T Cells

Blood only

Blood + CMV lysate

Blood + CMV lysate + IdeS

Blood + PHA (+Control)

CD56+NK Cells

(A)  

(B)  

(C)  

(D)  

(E)  

(F)  

(G)  

(H)  

CD107a

CD107a

CD107a

CD107a

NK

NK

NK

NK

IFNγ

Blood

+ CMV lysate

Blood

+ CMV lysate

Blood

+ CMV lysate

Blood

+ PHA

Control

Blood

only
 Protocol

- 11 patients in Swedish cohort and 14 in US
- DSA detected with solid-phase assay
- Samples obtained before IdeS administration
  - DSA and flow-cytometric cross-match
- Cross-match and DSA tests done at 6 hours, 24 hours, and days 7, 30, 60, 90 (US only), 180 (US only)
- Biopsies performed to assess ABMR when allograft dysfunction noted
- Protocol biopsy at 6 months
  - C4d staining and Banff 2013 criteria
- IdeS and IgG levels assessed with SDS-PAGE and Western blot
- Cleavage and clearance of Fc and F(ab')\textsubscript{2} fragments analyzed with ELISA
- Routine lab tests, vital signs, adverse events
Impact of IdeS on Circulating IgG Levels in HS Patients

P<0.001

IgG conc. in serum (g/L)
SDS-Page and Western Blot Analysis of Serum Pre and Post IdeS Treatment

Serum Cr Values Over the First 6 Months Post-Transplant
(1) ABMR Biopsy Banff Scoring US vs Sweden

G + ptc vs C4d

Mean Banff Score

p = 0.0246

US: N=7
Sweden: N=4

(2) Protocol Biopsy Banff Scoring US vs Sweden

G + ptc vs C4d+

Mean Banff Score

US: N=7
Sweden: N=9
Immunoglobulin G–Degradation Enzyme of \textit{Streptococcus pyogenes} (IdeS), Desensitization, and the Kidney Allocation System

Complementary Approaches to Increase Transplantation in Highly HLA Sensitized Patients

Edmond Huang and Stanley C. Jordan

In a recent Perspective article in the Clinical Journal of the American Society of Nephrology, Formica and Kulikowski (1) contextualize the use of the IgG-degrading enzyme of \textit{Streptococcus pyogenes} (IdeS) for desensitization in the era of the new kidney allocation system (KAS). Since the KAS, more highly sensitized kidney candidates have received transplants than before. Therefore, it was suggested that the allocation priority for highly sensitized candidates in the new KAS diminishes the need for desensitization and that waiting for a suitable matched donor is preferable to undergoing an incompatible transplant.

As previously reported, the median waiting time for patients with calculated panel reactive antibodies (PRA) > 50% has fallen from >10 years pre-KAS to 3.2 years post-KAS (2). Therefore, it was stated that, if a sensitized patient can receive a compatible transplant quickly, there is "no clinical justification for desensitization" (1). Although it is true that more patients with calculated panel reactive antibodies (PRA) > 50% were transplanted since the KAS, not all highly sensitized patients benefited to the same degree. Patients with calculated panel reactive antibodies > 99.9% accounted for 34.0% of candidates with calculated panel reactive antibodies > 99% in the United States (3). However, only 8% of the transplants for those with calculated panel reactive antibodies > 99% in the first year after the KAS was implemented (3). For any given calculated panel reactive antibodies percentage, the probability of finding an acceptable match can be estimated with the following formula: 1 – (calculated panel reactive antibodies percentage) 100. Using this formula, candidates with calculated panel reactive antibodies of 99.9% would need approximately 6000 matches to have a 95% probability of an acceptable crossmatch. This estimate increases approximately 12,000 donors; however, clearly, a significant number of highly sensitized candidates will not benefit from the KAS and are unlikely to receive a transplant without desensitization.

Although highly sensitized candidates have received transplants more frequently after the KAS, it is unknown how many received transplants with a negative crossmatch. One cannot assume that the increased number of transplants was performed with a negative crossmatch and without donor-specific antibodies. Hoog et al. (3) reported that 56% of transplants performed among candidates with calculated panel reactive antibodies of 99%–100% at Johns Hopkins after the KAS was implemented were in the presence of donor-specific antibodies (18 of 30 in 2013 and eight of 17 in 2016), and they noted that 48–42% of their highly HLA-sensitized list could not be transplanted under the KAS and required desensitization. Here, the authors noted that, before KAS implementation, patients with calculated panel reactive antibodies > 99% defined by cytotoxicity assays could be "converted" to calculated panel reactive antibodies of 100% by using more sensitive Luminex assays and setting mean fluorescence intensities at or below the threshold of detection, thus increasing their chances for early transplantation in the KAS. These patients are not immunologically challenging as the highly and broadly sensitized patients who have calculated panel reactive antibodies of 100% and are less likely to need desensitization.

The Perspective article cautioned against the use of desensitization, because HLA-incompatible transplants have lower graft survival compared with compatible transplants. This may not be a valid comparison. As discussed above, a large number of patients are so broadly sensitized that their chances of finding a compatible donor are remote. Additionally, it was
Outcomes of cPRA 99.9% ESRD Patients Awaiting Transplant in KAS Era

More Patients Died or Were Delisted, Presumably Due to Health Reasons, Than were Transplanted Under KAS
AMR: STILL THE MAIN CAUSE OF ALLOGRAFT LOSS

4 French centers: 4,921 kidney recipients and 10,293 kidney allograft biopsies

739 graft losses

Unpublished results
HETEROGENEITY OF CHRONIC AMR: ARCHETYPES IDENTIFY DISTINCT ALLOGRAFT SURVIVALS

Archetype 1

Archetype 2

Archetype 3

Archetype 4

Archetype 5

Abstract FR-OR136
PRE-EXISTING / RECURRENT VERSUS DE NOVO DSA: HOW THESE PROCESSES COMPARE?

Antibody-Mediated Rejection Due to Preexisting versus De Novo Donor-Specific Antibodies in Kidney Allograft Recipients

Olivier Aubert, Alexandre Loupy, Luis Hidalgo, Jean-Paul Duong van Huyen, Sarah Higgins, Denis Viglietti, Xavier Jouven, Denis Glotz, Christophe Legendre, Carmen Lefaucheur, and Philip F. Halloran

Antibody-mediated rejection (AMBR) of renal allografts occurs in two forms. Type 1 AMBR results from persistence and/or a rebound of preexisting donor-specific antibodies in sensitized patients and usually occurs early post-transplantation. Type 2 AMBR is associated with de novo donor-specific antibodies and usually occurs one year post-transplantation. It is generally accepted that types 1 and 2 also differ with regard to certain pathological features including the frequencies of C4d positivity and concurrent cell-mediated rejection. However, direct comparison of pathologic, serologic, and clinical features of types 1 and 2 AMBR is lacking. Here we compared these features in 80 cases of AMBR (37 type 1, 43 type 2) diagnosed at our center. Compared with type 1, type 2 AMBR occurred later post-transplantation, was more often associated with donor-specific antibodies against Class II HLA, and was associated with more interstitial fibrosis/tubular atrophy and more frequent cell-mediated rejection, although these did not differ with respect to C4d positivity. By univariate analysis, graft survival was lower with type 2 than type 1 AMBR with borderline significance. Still, among these 80 patients, all but one treated for AMBR following diagnosis of type 2, the two only independent predictors of graft failure were at least moderate interstitial fibrosis/tubular atrophy and failure of the donor-specific antibody relative intensity scale score, a measure of the combined strength of all donor-specific antibodies present, to decrease in response to therapy.

Antibody-mediated rejection (AMBR) is a major cause of renal allograft failure. Active AMBR is manifested morphologically as microvascular inflammation (MI), primarily glomerulitis and peritubular capillaritis. If unrecognized or not successfully treated by measures including the removal of donor-specific antibodies (DSAs), acute AMBR leads to chronic allograft damage, including transplant glomerulopathy (TG), arterial intimal fibrosis, and interstitial fibrosis/tubular atrophy (IFTA). TG in particular is strongly associated with increased rates of graft loss. Historically, AMBR has been under-recognized in renal allografts for reasons. First, it may be subclinical and lead to chronic damage, including TG, before a detectable rise in serum creatinine occurs. Second, it was not until 2009 that evidence began to appear indicating that AMBR may occur in the absence of complement deposition in the microcirculation, and prior to the most recent Banff classification for AMBR complement deposition, in the form of C4d staining within peritubular capillaries (pTC), was a requirement for diagnosis of AMBR in renal allograft biopsies.

AMBR of renal allografts occurs in the following 2 forms: type 1, resulting from persistence and/or a rebound of pre-existing DSA in sensitized patients, and type 2, associated with de novo DSA. It is generally accepted that type 1 AMBR usually occurs early after transplantation, whereas type 2 AMBR most often occurs at least 1 year after transplantation.
Factors Associated with Graft Loss in ABMR Patients

Table 3 | Predictors of death-censored graft loss

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Univariate analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.01 (0.99–1.04)</td>
<td>0.33</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.74 (0.32–1.70)</td>
<td>0.33</td>
</tr>
<tr>
<td>Live donor</td>
<td>1.97 (0.85–4.56)</td>
<td>0.12</td>
</tr>
<tr>
<td>Biopsy indication: progressive dysfunction</td>
<td>1.48 (0.64–3.46)</td>
<td>0.36</td>
</tr>
<tr>
<td>Interval transplant to biopsy ≥ 84 months</td>
<td>2.56 (1.05–6.22)</td>
<td>0.038</td>
</tr>
<tr>
<td>Type 2 versus type 1 ABMR</td>
<td>2.51 (0.98–6.43)</td>
<td>0.054</td>
</tr>
<tr>
<td>C4d score 2-3 versus 0-1</td>
<td>1.16 (0.43–3.15)</td>
<td>0.77</td>
</tr>
<tr>
<td>cg score ≥ 1</td>
<td>2.31 (0.98–5.42)</td>
<td>0.054</td>
</tr>
<tr>
<td>Chronic, active versus acute/active ABMR</td>
<td>1.97 (0.84–4.63)</td>
<td>0.12</td>
</tr>
<tr>
<td>(ci + ct) ≥ 3</td>
<td>3.88 (1.67–9.05)</td>
<td>0.002</td>
</tr>
<tr>
<td>CMR, Banff grade 1a or higher</td>
<td>2.48 (1.07–5.75)</td>
<td>0.037</td>
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<tr>
<td>TMA</td>
<td>2.58 (0.75–8.84)</td>
<td>0.13</td>
</tr>
<tr>
<td>Presence of anti-HLA DQ DSA</td>
<td>1.53 (0.62–3.76)</td>
<td>0.36</td>
</tr>
<tr>
<td>Decrease in RIS score &gt; 2</td>
<td>0.21 (0.06–0.70)</td>
<td>0.012</td>
</tr>
<tr>
<td>B. Multivariable analysis</td>
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<tr>
<td>Predictor</td>
<td>Hazard ratio</td>
<td>95% CI</td>
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<tr>
<td>(ci + ct) ≥ 3</td>
<td>2.98</td>
<td>1.26–7.06</td>
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<tr>
<td>Decrease in RIS score &gt; 2</td>
<td>0.23</td>
<td>0.07–0.79</td>
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<tr>
<td>CMR, Banff grade 1a or higher</td>
<td>2.19</td>
<td>0.93–5.15</td>
</tr>
</tbody>
</table>
**Characterization of anti-HLA DSA to better assess:**

- Rejection phenotypes
- Operating biological processes
- Allograft loss profiles
- Response to therapy

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ABMR TREATMENT OPTIONS: WHAT’S NEW?

B-cell Therapeutics

Loupy et al. NEJM 2018.
IL-6: A Pleiotropic Cytokine Impacting Multiple Organ Systems

**Immune cells**
1. Stimulate B-cell differentiation to antibody producing plasma cells
2. Plasma cell & myeloma cell growth factor
3. Maintains Th1 & Th2 cell activities
4. Increases Th17 and Tfh cells
5. Decreases Tregs

**Skin**
1. Increase Keratinocytes
2. Increase dermal fibroblast collagen
3. May be primary factor in scleroderma

**Liver**
1. Increase CRP
2. Increase Serum Amyloid A
3. Increase Fibrinogen
4. Increase Hepcidin (anemia of chronic disease)
5. Decreases albumin & transferrin

**Cardiac**
1. Increase VEGF to increase angiogenesis
2. Increase risk for coronary artery disease
3. Increases mortality from cardiovascular disease in ESRD patients

**Kidney**
1. Increase mesangial cell proliferation
2. Contributes to glomerular crescent formation
3. Contributes to chronic antibody rejection of kidney allografts

**Bone Marrow**
1. Increase osteoclast differentiation
2. Increase angiogenesis
3. Increase platelet
4. Responsible for joint damage in RA

**Synovial Fibroblast**
1. Increase osteoclast differentiation
2. Increase angiogenesis
3. Increase platelet
4. Responsible for joint damage in RA
Classic Membrane Bound IL-6R Signaling

IL-6

Hepatocytes & Leukocytes

Gene Transcription

IL-6/sIL-6R Trans-signaling

IL-6

gp130

Gene Splicing Enzymatic Cleavage

All gp130+ Cells

Gene Transcription

ADAM10 ADAM17
Dendritic Cell (APC)

Naïve CD4+ T-cell

Gene Transcription

IL-6/IL-6R Trans-Presentation
Dendritic Cell (APC)

Naïve CD4+ T-cell

IL-6/IL-6R Trans-Presentation

- IL-6
- IL-6R
- IL-6/IL6R

gp130

Gene Transcription

CD4+ Tn
+IL-2

Th17 RORγt
+IL-6

Tolerance

Inflammation
Autoimmunity
Allograft Rejection

Treg FoxP3+

Inflammation
Autoimmunity
Allograft Rejection

Gene Transcription
IL-6 DRIVES B-CELL ACTIVATION AND DIFFERENTIATION TO ANTIBODY-PRODUCING PLASMA CELLS

 Jordan SC et al. Transplantation. 2017
What is the current evidence of the potential of anti-IL-6 Ab for the prevention and the treatment of AMR?
Interleukin-6, A Cytokine Critical to Mediation of Inflammation, Autoimmunity and Allograft Rejection: Therapeutic Implications of IL-6 Receptor Blockade

Stanley C. Jordan, MD,1 Jua Choi, PharmD,1 Irene Kim, MD,1 Gordon Wu, PhD,1 Mieko Toyoda, PhD,1 Bongja Shin, PhD,1 and Ashley Vo, PharmD1

Abstract: The success of kidney transplants is limited by the lack of robust improvements in long-term survival. It is now recognized that alloimmune responses are responsible for the majority of allograft failures. Development of novel therapies to decrease allosensitization is critical. The lack of new drug development in kidney transplantation necessitated repurposing drugs initially developed in oncology and autoimmunity. Among these is tocilizumab (anti-IL-6 receptor [IL-6R]) which holds promise for modulating multiple immune pathways responsible for allograft injury and loss. Interleukin-6 is a cytokine critical to proinflammatory and immune regulatory cascades. Emerging data have identified important roles for IL-6 in innate immune responses and adaptive immunity. Excessive IL-6 production is associated with activation of T-helper 17 cell and inhibition of regulatory T-cell with attendant inflammation. Plasmablast production of IL-6 is critical for initiation of T follicular helper cells and production of high-affinity IgG. Tocilizumab is the first-in-class drug developed to treat diseases mediated by IL-6. Data are emerging from animal and human studies indicating a critical role for IL-6 in mediation of cell-mediated rejection, antibody-mediated rejection, and chronic allograft vasculopathy. This suggests that anti-IL-6/IL-6R blockade could be effective in modifying T- and B-cell responses to allografts. Initial data from our group suggest anti-IL-6R therapy is of value in desensitization and prevention and treatment of antibody-mediated rejection. In addition, human trials have shown benefits in treatment of graft versus host disease in matched or mismatched stem cell transplants. Here, we explore the biology of IL-6/IL-6R interactions and the evidence for an important role of IL-6 in mediating allograft rejection.

(Transplantation 2017;101: 32–44)
Anti–Interleukin 6 Receptor Antibodies Attenuate Antibody Recall Responses in a Mouse Model of Allosensitization

Irene Kim,1 Gordon Wu,1,2 Ning-ning Chai,1 Andrew S. Klein,1 and Stanley Jordan1

Background. Interleukin (IL)-6 is a regulatory cytokine for T helper type 17 (Th17) and Treg cells and a potent stimulus for B/plasma cells. The current study evaluated the effect of IL-6 receptor (IL-6R) blockade with an anti–IL-6R monoclonal (mMR16-1) in alloantibody recall responses.

Methods. A mouse model of human leukocyte antigen (HLA) A2 sensitization was used for studies to evaluate the efficacy of anti–IL-6R on alloantibody recall responses and to examine the impact of IL-6R blockade on Th17, Treg, follicular T helper (Tfh) and plasma cells using multiparameter flow cytometry, flow antibody binding, and enzyme-linked immunospot (ELISpot) assay.

Results. Re-exposure of C57BL/6 mice to HLA A2+ skin allografts resulted in a surge of donor-specific (anti–HLA A2) immunoglobulin (Ig)G antibodies. Anti–IL-6R treatment significantly decreased but did not eliminate alloantibody responses (IgG mean fluorescence intensity, 486 ± 153 vs. control 792 ± 193, P = 0.0076). Flow cytometry analysis showed that anti–IL-6R treatment resulted in reduction of IL-21+CD4+ (Th17) cells (P = 0.006 vs. control) and CXCR5+CD4+ Tfh cells (P = 0.04), but increased foxp3+CD4+ (Treg) cells in the CD4+ population (P = 0.04 vs. control). The IgG ELISpot experiments showed a significant reduction of IgG spots in the bone marrow and the spleen cells from the anti–IL-6R–treated mice. In vitro treatment of mouse hybridoma (PA2.1) cultures with anti–IL-6R decreased IgG spot formation but had limited effect on cell proliferation.

Conclusion. The data indicate that anti–IL-6R therapy attenuates alloantibody recall responses by modulating a number of immune regulatory and effector cells, including Th17, Tfh, Treg, and importantly, the long-lived plasma cells in the bone marrow.

Keywords: Alloantibody recall response, Anti–IL-6R, B cell, ELISpot, Flow cytometry, Mice, Plasma cell, Tfh, Th17, Treg.
ANTI–IL-6R INHIBITS PLASMA CELL IgG PRODUCTION AND ANTI–HLA-A2 ANTIBODY

Anti–IL-6R Significantly Suppressed IgG+ Plasma Cells in the Bone Marrow and Spleens Demonstrated in an ELISpot Assay

Detection of Anti–HLA-A2 IgG Antibodies in Conditioned Media of BM Cell Cultures by Flow-Antibody Binding Assay

\[ a \quad P < .01, \quad b \quad P < .05. \]

ANTI-IL-6 INHIBITS CORONARY ARTERY VASCULOPATHY IN A HUMANIZED MOUSE MODEL

Endothelial Cell IL-6 Production

Pober et al J. Immunology 2012
A Phase I/II Trial of the Interleukin-6 Receptor Specific Humanized Monoclonal (Tocilizumab) + Intravenous Immunoglobulin in Difficult to Desensitize Patients

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Background. Current desensitization (DES) methods are not always effective. Thus, novel, more effective approaches are desirable. Interleukin (IL)-6 is an attractive target as it promotes B-cell differentiation to plasma cells, is important for immunoglobulin production, and induces Th17 cells. Here, we undertook a phase I/II pilot study of DES using a novel drug (anti-IL-6 receptor (IL-6R) Tocilizumab (TCZ)) + intravenous Ig (IVlg) to assess safety and limited efficacy. Methods. From July 2012 to November 2013, 10 patients unresponsive to DES with IVlg + Rituximab were treated with IVlg + TCZ. Patients received IVlg on days 0 and 30 at 2 g/kg and TCZ 8 mg/kg on day 15 then monthly for 6 months. If transplanted, patients received IVlg once and TCZ monthly for 6 months. Results. No differences in baseline characteristics were seen in patients not transplanted versus transplanted. Two patients in each group developed serious adverse events: not transplantable: pulmonary congestion with epiplecticus (likely not related) versus transplanted: infectious colitis with colonic perforation and Bell Palsy (both possibly related). Five of 10 patients were transplanted. Mean time to transplant from first DES was 25 ± 10.5 months but after TCZ was 8.1 ± 5.4 months. Six-month protocol biopsies showed no antibody-mediated rejection. Donor-specific antibody strength and number were reduced by TCZ treatment. Renal function at 12 months was 60 ± 25 mL/min. Conclusions. Tocilizumab and IVlg appear to be safe. From this pilot trial, we are cautiously optimistic that targeting the IL-6/IL-6R pathway could offer a novel alternative for difficult to desensitize patients. Larger controlled studies are essential to prove efficacy.

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Course of Immunodominant DSAs

Mean Immunodominant DSA levels for TCZ-Treated and Transplanted Patients

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

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Abbreviations: AE, adverse event; AMR, antibody-mediated rejection; cAMR, chronic active antibody-mediated rejection; DSA, donor-specific antibody; eGFR, estimated glomerular filtration rate; FDA, US Food and Drug Administration; IDSA, immunodominant donor-specific antibody; IFTA, interstitial fibrosis/tubular atrophy; IL-6R, interleukin-6 receptor; IL-6, interleukin-6; IQR, interquartile range; NSTEMI, non-ST-segment elevation myocardial infarction; PLEX, plasma exchange; SAE, severe adverse event; Th17, T follicular helper cell; TG, transplant glomerulopathy; Th17, T helper cell; Tr, Traps; Traps, TRAP.

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Tocilizumab Treatment of cAMR and TG: Treatment Protocol

75 patients with chronic active AMR ± transplant glomerulopathy (TG)

39 patients treated with IVIG + rituximab ± plasma exchange (SOC)

37 patients who failed IVIG + rituximab + plasma exchange

Treated with tocilizumab 8 mg/kg monthly for 6 to 18 months

ALLOGRAFT PHENOTYPE IN PATIENTS TREATED WITH TOCILIZUMAB FOR CHRONIC AMR

eGFR IN ADULT AND PEDIATRIC PATIENTS TREATED WITH TOCILIZUMAB FOR CHRONIC AMR

ALLOGRAFT AND PATIENT SURVIVAL IN PATIENTS TREATED WITH TOCILIZUMAB FOR CHRONIC AMR

Log-rank p<0.0001

Log-rank p=0.0485

N at Risk
TCZ 36 34 24 13 9 7 6
SOC 39 27 19 15 7 5 3

N at Risk
TCZ 38 32 24 17 8 5 3
SOC 36 34 24 13 9 7 6
First Patient Treated with Anti-IL-6 Clazakizumab for CABMR
ON GOING TRIALS USING Ani-IL-6

<table>
<thead>
<tr>
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<tr>
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<td>NCT 03380962</td>
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</table>
Anti-IL-6 : TAKE HOME MESSAGES

• Anti-IL-6 to prevent and treat chronic AMR seems promising by :
  • Inhibiting plasma cell IgG production
  • Decreasing DSA level
  • Reducing microvascular inflammation and C4d deposition
  • Maintaining a stable renal function
  • Improving graft and patient survival

• Results are limited by :
  • Absence of published randomized studies
  • Small populations
  • Limited follow-up
  • Phase II/III studies planned for Clazakizumab (anti-IL-6) in 2019
Anti-CD 38 (anti-plasma cell Therapy for Desensitization)
Figure 1. Total Class I and II DSAs, baseline vs after completion of 4 doses of daratumumab

Figure 1. Class I and II DSAs, Total (N=1)

- Total Class I DSAs: Pre Daratumumab 101300, Post Daratumumab 49200 (51% reduction)
- Total Class II DSAs: Pre Daratumumab 119500, Post Daratumumab 79700 (33% reduction)
Figure 2. Average Class I and II DSAs, baseline vs after completion of 4 doses of daratumumab

*P=0.03
Plasmablasts & Plasma Cells

Regulatory B Cells

Follicular Th Cells

Normal Control
Patient: SV

DARATUMUMAB (ANTI-CD38) FOR TREATMENT OF ABMR

B cells

Plasmablast & Plasma cells

Breg

Pre-anti-CD38 (3/1/18)

Post-anti-CD38 (3/22/18)
Patient: SV

DARATUMUMAB (ANTI-CD38) FOR TREATMENT OF ABMR

Pre-anti-CD38

CD4+ cells

Post-anti-CD38

Tfh cells

Treg cells
Renal Transplant Biopsy Prior to Daratumumab Therapy

Severe Arteritis

Severe Glomerulitis

Severe PTCitis
Biopsy Immediately Post-Daratumumab (16mg/kg X 4 doses)

Normal Glomeruli

Intense T-cell Mediated Rejection

Did We Remove Tregs??
IMMUNOBIOLOGY

Daratumumab depletes CD38+ immune regulatory cells, promotes T-cell expansion, and skews T-cell repertoire in multiple myeloma

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Key Points

- CD38-expressing immunosuppressive regulatory T and B cells and myeloid-derived suppressor cells were sensitive to daratumumab treatment.
- Cytotoxic T-cell number, activation, and clonality increased after daratumumab treatment in heavily pretreated relapsed and refractory MM.

Daratumumab targets CD38-expressing mediated mechanisms (complement-de mediated cytotoxicity, and antibody-dependent crosslinking. These mechanisms which prompted evaluation of daratumumab in patients. Peripheral blood (PB) and bone marrow (BM) samples from 2 daratumumab monotherapy and at relapse. Regulatory B cells shown to express CD38, were evaluable fcd in the myeloma setting. A nonexpressing CD38 was identified. These T cells C38-negative Tregs and were reduced CD38 expression. DaRumaumab-induced robust increases PB and BM, daratumumab induced signa, and increased memory T cells responses. patients demonstrated these broad T-cell response or better showed greater maximum effectors and helper T-cell increase responses, and significantly greater increases in T-cell clonality as measured by T-cell proliferation positively correlated with increased CD8+ T-cell counts. Depletion of CD38 cells with an increase in T-helper cells, cytotoxic T cells, T-cell functional responses, or mechanisms of action for daratumumab and deserves further exploration. (Blood 2020)

Introduction

Proteasome inhibitors (PIs) and immunomodulatory drugs (IMiDs) have improved outcomes in patients with multiple myeloma (MM).1,3 Despite these advances, prognosis for patients with relapsed MM remains poor, particularly for those who have relapsed after PI and BM treatment. New therapies with novel mechanisms of action are needed for resistant patient populations.

Myeloma is associated with immune dysfunction,2 including immune evasion through the expression of immune checkpoint ligands on plasma cells,4 elevated adenosine receptor and adenosine activity,4,5 and immune suppression through myeloid-derived suppressor cells (MDSCs) and regulatory T cell (Treg) activity.4,5 CD38 is ubiquitously expressed on MM cells,6,7 but is also present (Bregs).8,9 The cell population is disease progress cell biology may target mechanisms. In a mesoderm cell, AMI110 showed promising antitumor activity in 2 canine studies (ENGOS and SIRIUS) in patients with relapsed and refractory MM, resulting in remarkable response rates that include stringent complete responses.

Suppression of CD38+ immune regulatory cells

Enhancement of T-cell responses

Induction of clonal T-cell expansion
Breastfeeding: A Natural Process with Many Benefits for Mother & Baby

What Does This Have to do with an Immunology Lecture?
The Fc Neonatal Receptor: An Interesting Odyssey

• It has been 52 years since F.W.R. Brambell hypothesized the existence of a specific receptor in neonates responsible for transport of IgG molecules from maternal milk to infants.

• Originally described in rats, the FcRn provided a shuttle service for IgG molecules from maternal milk to the infant circulation across the gastrointestinal epithelium.

• Subsequently, the FcRn was also found to be expressed in placental villi where maternal blood pools and allows for extraction of maternal IgG -> fetal circulation beginning in the 3rd trimester.
FcRn Enhances Half-Life of Circulating IgG: Inhibition of FcRn Drastically Reduces Half-Life of Circulating IgG Molecules

Normal FcRn Function Half-Life 21 days

FcRn (-/-) Half-Life 2-3 days
High Dose IVIg Enhances Clearance of Pathogenic IgG by Saturating FcRn

Figure 1A

Figure 1C
Inhibitors of the FcRn–IgG-Fc interaction. From left to right: 1) High dose IVIg can saturate FcRn and accelerate the clearance of endogenous IgG, 2) anti-FcRn heavy chain antibodies and 3) anti-β2m light chain antibodies bind FcRn epitopes, inhibiting FcRn function and accelerating degradation of circulating IgG 4) Fc-engineered IgGs that have increased, pH-independent affinity for FcRn (Abdegs), and 5) peptides and 6) small molecules that compete with IgG for binding to FcRn. To date, anti-FcRn and synthetic peptides that block IgG-Fc/FcRn interactions are now in clinical trials. (From [17] with permission)
The FcRn inhibitor rozanolixizumab reduces human serum IgG concentration: A randomized phase 1 study

Peter Klessing,1 Rocio Lledo-Garcia,2,3 Shiklko Watanabe,3 Grant Langdon,4 Diep Tran,2 Muhammad Barli,2 Louis Christoudoulou,6 Emma Jones,7 Graham Price,4 Bryan Smith,2 Frank Brennan,3 Ian White,2 Stephen Jolles3

Pathogenic immunoglobulin G (IgG) autoantibodies characterize some human autoimmune diseases; their high concentration and long half-life are dependent on recycling by the neonatal Fc receptor (FcRn). Inhibition of FcRn is an attractive new treatment concept for IgG-mediated autoimmune diseases. Rozanolixizumab (UCB78655: CA170.01519.037 IgG4F) is an anti-human FcRn monoclonal antibody. In cynomolgus monkeys, rozanolixizumab reduced IgG (maximum 75% to 90% by about day 10), was well tolerated, and did not increase risk of infection. We also report a first-in-human, randomized, double-blind, placebo-controlled, dose-escalating study of intravenous (IV) or subcutaneous (SC) rozanolixizumab in healthy subjects (NCT02220153). The primary objective was to evaluate safety and tolerability. Secondary objectives were assessment of rozanolixizumab pharmacokinetics and pharmacodynamics, including effects on circulating IgG concentrations. Forty-nine subjects were randomized to receive rozanolixizumab (n = 36) or placebo (n = 13) across six cohorts. The first three cohorts received IV doses, and the subsequent three cohorts received SC doses, of rozanolixizumab 1, 4, or 7 mg/kg (n = 6 for each cohort; plus n = 7 or 6 for placebo, respectively). The most frequent treatment-emergent adverse event (TEAE; headache, 14 of 36 [38.9%] subjects) was dose-dependent and more prominent after IV administration. Severe TEAEs occurred in four subjects, all in the highest-dose IV group (headache n = 3 and back pain n = 1). Rozanolixizumab pharmacokinetics demonstrated nonlinear increases with dose. There were sustained dose-dependent reductions in serum IgG concentrations (IV and SC rozanolixizumab). These data provide clinical evidence for the therapeutic potential of rozanolixizumab.

INTRODUCTION
Autoimmune and allergic diseases, such as anti-glomerular base ment membrane antibody disease, immune thrombocytopenia (ITP), and myasthenia gravis (MG), hemolytic anemia, and pemphigus vulgaris, are characterized by the presence of pathogenic autoantibodies, commonly of the immunoglobulin G (IgG) isotype. A number of strategies currently in development are aimed at reducing autoantibody production (immunomodulation with corticosteroids and second-line agents such as azathioprine, cyclophosphamide, and rituximab), reducing autoantibody removal (plasma exchange, immunoadsorption, or immunomodulatory drugs of intravenous immunoglobulin (IVIG)) (2). However, these treatments can be associated with side effects, accessibility issues, patient inconvenience, and overall time and cost implications (1–4).

Therapeutic plasma exchange involves the filtration of venous blood to remove high-molecular weight components, including immunoglobulins (both pathogenic and normal), albumin and protamine-salting factors that are involved in the pathogenesis of numerous autoimmune diseases (5). Although plasma exchange offers a potentially efficacious treatment option for autoimmune disorders, it is associated with numerous disadvantages including adverse reactions, exposure to blood products, and reduction of circulating plasma concentrations of all other plasma proteins (6). A second alternative treatment option is immunosuppression, which specifically reduces IgG and no other plasma component, thus reducing the breadth of impact on the patient’s humoral immune system; however, immunosuppression is also associated with adverse reactions and the disadvantages associated with hospital-based therapy (8).

IV Ig comprises human immunoglobulin (95 to 99% IgG and varying trace amounts of IgM, IgA, IgD, and IgE) prepared from large pools of healthy donors (4). The mechanisms of action of IV Ig are multiple and may include functional blockade of Fc receptors, autoantibody neutralization, inhibition of antibody production, complement inhibition, and modulation of cytokine and cytokine antagonist production (5). Administration of immunomodulatory doses of IV Ig can reduce endogenous (including pathogenic) IgG concentrations as a result of saturation of the neonatal Fc receptor (FcRn) (9–11). Although IV Ig is generally considered to have an acceptable safety profile adren, systemic reactions are common, occurring in 20 to 50% of patients (12). In most chronic autoimmune diseases in which IV Ig is used for immunomodulation, a long-term dose (1 to 2 g/kg per cycle) may be required (13, 14). A common treatment option for many autoimmune diseases is corticosteroids, used either as stand-alone therapy or in combination with second-line immunosuppressive agents, plasma exchange, or IV Ig (1). Corticosteroids are known to modestly reduce IgG concentrations in immunoglobulin (IgG) concentrations (including IgM and IgA, but not IgG) (17). An alternative treatment option is immunosuppression, which specifically reduces IgG and no other plasma component, thus reducing the breadth of impact on the patient’s humoral immune system; however, immunosuppression is also associated with adverse reactions and the disadvantages associated with hospital-based therapy (8).

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The FCRn inhibitor rozanolizumab reduces human serum IgG concentration: A randomized phase 1 study

Peter Kiessling,1 Rocío Liedo-García,1,2 Shikiko Watanabe,3 Grant Langdon,4 Diep Tran,2 Muhammad Bari,2 Louis Christodoulou,5 Emma Jones,6 Graham Price,4 Bryan Smith,2 Frank Brennan7, Ian White,2 and Stephen Jollès5

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INTRODUCTION

Autoimmune and abuminone diseases, such as anti-glomerular base ment membrane antibody disease, immune thrombocytopenia (ITP), Goodpasture’s syndrome, systemic lupus erythematosus, and pemphigus vulgaris, are characterized by the presence of pathogenic autoantibodies, commonly of the immunoglobulin G (IgG) isotype. A number of strategies currently exist to reduce pathogenic autoantibodies; these include treatments aimed at reducing autoantibody production (immunosuppression with corticosteroids and second-line agents such as azathioprine, cyclophosphamide, mycophenolate mofetil, and B-cell depletion) or increasing autoantibody removal (plasma exchange, immunoadsorption, or immunomodulatory doses of intravenous immunoglobulin (IVIg)) (2). However, these treatments can be associated with side effects, accessibility issues, patient inconvenience, and overall time and cost implications (3–6). Therapeutic plasma exchange involves the filtration of venous blood to remove high-molecular-weight components, including immunoglobulins (both pathogenic and normal), albumin and proinflammatory factors that are involved in the pathogenesis of numerous autoimmune diseases (3). Although plasma exchange offers a potentially efficacious treatment option for autoimmune disorders, it is associated with numerous disadvantages including adverse reactions, exposure to blood products, and reduction of circulating plasma concentrations of all immunoglobulin isotypes (including IgM and IgA, not just IgG) (7). An alternative treatment option is immunosuppression, which specifically removes IgG and no other plasma component, thus reducing the burden of impact on the patient’s humoral immune system; however, immunosuppression is also associated with adverse reactions and the disadvantages associated with hospital-based therapies (8).

IVIg comprises human immunoglobulin (95 to 99% IgG) and varying trace amounts of IgM, IgA, IgD, and IgE (9, 10). The mechanisms of action of IVIg are multiple and may include functional blockade of Fc receptors, autoantibody neutralization, inhibition of autoantibody production, complement inhibition, and modulation of cytokine and cytokine receptor antagonism (5). Administration of immunomodulatory doses of IVIg can reduce endogenous (including pathogenic) IgG concentrations as a result of uptake by the neonatal Fc receptor (FcRn) (9–12). Although IVIg is generally considered to have an acceptable safety profile, adverse systemic reactions are common, occurring in 20 to 50% of patients (12). In most chronic autoimmune diseases in which IVIg is used for immunomodulation (rather than replacement doses in antibody deficiency), a long-term dosing regimen (2 to 2.5 g per cycle) may be required (13, 14).

Another common treatment option for many autoimmune diseases is corticosteroids, used either as stand-alone therapy or in combination with second-line immunosuppressive agents, plasma exchange, or IVIg. Corticosteroids are known to modestly reduce IgG concentrations in plasma (15); however, long-term steroid treatment is often limited by significant dose-dependent toxicities and lack of effect over time (6). Despite the universally accepted efficacy of corticosteroids in autoimmune conditions such as MS, the long-term adverse events (AEs) make the availability of other treatment options highly desirable (1).

IgG and albumin have half-lives of 3 to 4 weeks, the longest of any plasma proteins (16, 17). Their high concentrations (IgG, 7 to 11 g/liter in humans) and long half-lives are critically dependent on salvage and
In vivo depletion of serum IgG by an affibody molecule binding the neonatal Fc receptor

Johan Sejsing1, Shengze Yu2, Fredrik Y Frej2, Ingrida Hölden-Guthenberg2 & Torbjörn Gisslén2

Lowering the total level of Immunoglobulin G (IgG) in circulation is a promising general treatment option for many autoimmune diseases driven by pathogenic autoantibodies. The half-life of IgG in circulation is unusually long as a consequence of its interaction with the neonatal Fc receptor (FcRn), which protects it from lysosomal degradation by cells in contact with blood. Blocking the IgG-FcRn interaction prevents FcRn-mediated rescue, which may lead to increased catabolism and a lowering of the total IgG level. Here, we find that an engineered alternative scaffold protein, an affibody molecule, interacting specifically with FcRn, is able to block the IgG-FcRn interaction in vitro. The affibody molecule (Zlocin) was expressed alone or as a fusion to an albumin binding domain (ABD), to extend its half-life in circulation, in both cases with retained affinity and blocking potential. Repeated i.v. injections in mice of Zlocin and Zlocin-ABD were found to result in an up to 40% reduction of the IgG serum level after 5 days. Potential applications of Zlocin as a general treatment modality for autoimmune diseases are discussed.

Pathogenic immunoglobulin G (IgG) autoantibodies are responsible for driving pathogenesis in a number of autoimmune diseases. Compared to other serum proteins, IgG have an unusually long half-life in circulation due to interaction with the neonatal Fc receptor, which protects it from lysosomal catabolism by cells in contact with blood. In humans, the average half-life of IgG in circulation is approximately 2.5 weeks and in mice it is 6–8 days.1 However, in FcRn−/− mice the half-life of IgG in circulation is reduced to 1–2 days and the mice cannot maintain IgG homeostasis, resulting in a 70–80% reduction of the total level of IgG.

FcRn is a hetero-dimeric receptor, consisting of an α-chain and β2-microglobulin (β2m), of which it has the latter in common with the class I major histocompatibility complex. It resides predominantly in the endosomes, where it can bind IgG in the slightly acidic environment (pH 6–6.5). FcRn transports IgG into the endosomal lumen and is then sorted to the endosomes, followed by transport to the cell surface, where the cargo is released upon encountering the higher pH (~7) in the blood. This rescue mechanism is responsible for the long serum circulation half-life of IgG. With a similar mechanism but with a binding site that is separate from the IgG binding site, FcRn can rescue serum albumin from lysosomal catabolism, also leading to a long residence time in circulation.7

Convincing evidence suggests that blocking FcRn-mediated rescue of IgG can ameliorate the symptoms of different autoimmune diseases.8–10 In addition, FcRn−/− mice have been found to be protected from induction of e.g. autoimmune arthritis, which suggest that FcRn may also play an important role in the development of different autoimmune diseases.11 This was further supported by the finding that FcRn deficiency could protect animals in a model of the IgG-driven autoimmune disease epididymitis bullous acquired.12 Several strategies have been evaluated for blocking the FcRn/IgG interaction towards the goal of increasing IgG catabolism in order to treat different autoimmune diseases.13 Intravenous IgG (IVIG) is the administration of large amounts of donor-derived polyclonal IgG, and has been found to be efficient for treatment of e.g. Guillain–Barré syndrome and is used clinically.14 The mechanism of IVIG action is partly to increase catabolism of pathogenic IgG by blocking IgG-FcRn interactions by FcRn through saturation of the rescue machinery.15 However, IVIG treatment requires a large amount of protein making it expensive and is derived from a limited human donor source. ABD/ABD (antibodies that enhance IgG degradation) are IgG molecules, where the Fc part has been engineered to...
Therapeutic Approaches to Reducing Alloantibody Injury to Allografts

IL-6 + IL-21

IL-6-producing plasmablast

Plasma cell

Donor-specific antibodies

APC + Alloantigen

CD4+ T_{FH} CXCR5+ Bcl-6+

Naïve B cell

Germinal center

CTLA4Ig/Anti-CD28

CTLA4Ig/Anti-CD28

Naïve B cell

Tocilizumab

Clazakizumab

Anti-CD20

Ibrutinib

IL-6

Donor-specific antibodies

IdeS

FcRn Blockade

ABMR

Anti-Plasma Cell

Daratumumab (anti-CD38)

CTLA4Ig/Anti-CD28

Proteosome Inhibitors