Anti-GBM Disease

Sheena Surindran, MD
Grand Rounds
5/24/11
History

1st described by American pathologist Ernest Goodpasture from Vanderbilt University in 1919.

The term “goodpasture’s disease” was coined in 1958 by Stanton & Tange

Pathogenicity of ab demonstrated in 1967 by injecting pt’s sera into squirrel monkey caused disease.

2 peaks 18-30 and 50-65 yrs

1 in 1 million incidence
Pathophysiology

GP antigen is the C-terminal region of the alpha 3 chain of BM collagen IV.

Presence of abs to other alpha subunits of collagen IV does not cause disease.

Type 4 collagen present in kidney, lung, choroid plexus, retina and cochlea.

*Kidney International, Vol. 64 (2003)*
Fig. 2. Type IV collagen exists as a complex supramolecular network. Three individual α3(IV) chains are interwoven to form a triple helix, known as the protomer. The NC1 domains are arranged in a head-to-head fashion to form hexamers, and binding through the 7S domains completes the network structure. Hexamers can be dissociated to form dimers and monomers of NC1 domains, allowing identification of α3(IV)NC1 as the autoantigen (redrawn with permission from [72]).
Specificity of GP autoab for NC1 type IV collagen- autoantigen

Antisera obtained from 4 patients with GP, 3 pts with other GN and 7 normal controls

Immunoblot and ELISA done against type IV collagen, alpha chain 1-5 using recombinant NC1.

THE JOURNAL OF BIOLOGICAL CHEMISTRY 1993
FIG. 3. Immunoblot analysis of affinity-purified rNC1 monomers using chain-specific and GP autoantibodies. Each panel
Goodpasture’s antibody

FIG. 4. ELISA measurement of GP autoantibody binding to each of the five rNC1 monomers of human type IV collagen.

THE JOURNAL OF BIOLOGICAL CHEMISTRY 1993
Conclusions

- These results unambiguously establish that GP antibodies are specifically targeted to the NC1 domain of the alpha 3 of human type IV collagen.
- The production of large quantities of purified ra3(IV) NC1 also circumvents the problem of isolating sufficient quantities of native human a3(IV) NC1 for diagnostic and therapeutic purposes.
Role of Treg in Anti-GBM GN

- CD4+ CD25+ Treg and CD4+ CD25- control cells isolated and separated
- 8-12wk old C57B1/6J mice used- preimmunized
- One grp received t regs other control CD4+CD25-
- After 3 days, antimouse GBM antisera injected
- Urine collected 1,7,14 days and measured for urinary albumin and Cr

J Am Soc Nephrol 16: 1360–1370, 2005
Role of Treg in Anti-GBM GN

Figure 2. Transfer of regulatory T cells (Treg) significantly reduces proteinuria. Before and after induction of anti-glomerular basement membrane (anti-GBM) glomerulonephritis (GN) proteinuria was evaluated on days −1, 1, 7 (n = 14 per group), and 14 (n = 7 per group). Urine albumin excretion (in mg) was determined and expressed per milligram of urinary creatinine to standardize for the GFR. Mice that received control CD4⁺CD25⁻ T cells (■) had significant albuminuria, whereas mice after Treg transfer (□) showed only minimal albuminuria (*P < 0.05).

J Am Soc Nephrol 16: 1360–1370, 2005
Pathological changes

J Am Soc Nephrol 16: 1360–1370, 2005
Treg effect on inflammatory cells

A

Macrophage-Score [±SEM]

day 7

day 14

B

Cells in G6Pf [±SEM]

CD4⁺ T-cells

CD8⁺ T-cells

day 7

day 14
GBM staining for antibody

J Am Soc Nephrol 16: 1360–1370, 2005
Pro-inflammatory cytokines

Figure 8. The production of TNF-α and IFN-γ from spleen cell cultures is significantly reduced upon Treg transfer. Splenocytes (2 × 10⁶) from animals that received an injection of either Treg (□) or CD4+CD25+ T cells (■) were seeded in 24-well plates and stimulated with LPS (100 ng/ml) for 16 h. TNF-α, IFN-γ, IL-10, and IL-4 were determined in supernatants by ELISA (*P < 0.05; n = 4 per group).

J Am Soc Nephrol 16: 1360–1370, 2005
Conclusions

- Transfer of T reg improved renal dysfunction
- No suppression of immunoglobulin production in B cell compartment
- Significant reduction in expression of pro-inflammatory cytokines
- This may be a possible therapeutic option to be explored.

*J Am Soc Nephrol 16: 1360–1370, 2005*
HLA association and antiGBM disease

39 pts with gbm disease, caucasians

3 groups- 1-anuric/oliguric, 2-rapidly deteriorating renal failure but non oliguric, 3-stable renal fn

Aim was to study asso of HLA DR2 and HLA B7 in GP and to see if the presence of both had a effect on disease severity

**Table 5.** Clinical presentation of patients with anti-GBM disease who inherited HLA-DR2 and were referred patients directly on presentation; the patients are categorized by whether they also inherited HLA-B7

<table>
<thead>
<tr>
<th>Patients</th>
<th>Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Oliguric</td>
</tr>
<tr>
<td>HLA-B7</td>
<td></td>
</tr>
<tr>
<td>DR2 (+), B7 (+)</td>
<td>11</td>
</tr>
<tr>
<td>DR2 (+), B7 (-)</td>
<td>1</td>
</tr>
</tbody>
</table>
HLA association and GP

**Table 1. Frequencies of HLA antigens DR2, B7 and A3 in patient and control samples**

<table>
<thead>
<tr>
<th></th>
<th>Patients %</th>
<th>Controls %</th>
<th>$\chi^2$</th>
<th>$P_c$</th>
<th>Relative risk</th>
<th>Etiological fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>DR2</td>
<td>34/38 (89.5)</td>
<td>30/157 (19.1)</td>
<td>68.7</td>
<td>$0.63 \times 10^{-8}$</td>
<td>36</td>
<td>0.86</td>
</tr>
<tr>
<td>B7</td>
<td>23/39 (59.0)</td>
<td>43/193 (22.3)</td>
<td>26.5</td>
<td>$0.23 \times 10^{-4}$</td>
<td>5</td>
<td>0.47</td>
</tr>
<tr>
<td>A3</td>
<td>17/39 (43.6)</td>
<td>57/193 (29.3)</td>
<td>2.9</td>
<td>0.53</td>
<td>1.8</td>
<td>0.22</td>
</tr>
</tbody>
</table>

Plasma creatinine and HLA

Fig. 2. Plasma creatinine at presentation of 27 DR2 positive patients with anti-GBM disease together with median and 95% nonparametric confidence limits. The patients are classified by whether or not they also inherited HLA-B7. The difference between the two groups is significant ($P < 0.02$, Wilcoxon rank sum test).
Anti-GBM antibody titers in 27 DR2 positive patients with anti-GBM disease. The results together with median and 95% nonparametric confidence intervals are classified by whether or not the patients also inherited HLA B7. The difference between the groups is not significant (Wilcoxon rank sum test).

Fig. 3. Percentage of glomeruli surrounded by crescents in patients with anti-GBM disease. The patients are classified by whether or not they inherited (□) or did not inherit (■) HLA B7 together with HLA DR2.
Diagnostic criteria

- Presence of circulating anti-GBM autoantibodies
- Histological features of severe crescentic glomerulonephritis
- Linear IgG deposits on gbm
AntiGBM antibodies assays

- Gold standard is ELISA using purified NC1 domain of type IV collagen
- PPV and NPV >95%, sensitivity –close to 100%, specificity-95%
- False positive 1% may occur in pts with other diseases with polyclonal activation or SLE
# Outcome in GP

<table>
<thead>
<tr>
<th>Table 2. Outcome of patients with Goodpasture’s disease</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Number of patients</th>
<th>1-year patient survival %</th>
<th>1-year renal survival %</th>
<th>Renal recovery if initial creatinine &gt;600 μmol/L (6.6 mg/dL) % treated patients</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnson et al [85]</td>
<td>17</td>
<td>94</td>
<td>45</td>
<td>0</td>
<td>Randomized prospective study of plasma exchange</td>
</tr>
<tr>
<td>Walker et al [86]</td>
<td>22</td>
<td>59</td>
<td>45</td>
<td>18</td>
<td>Australian single center; all plasma exchanged</td>
</tr>
<tr>
<td>Savage et al [68]</td>
<td>59</td>
<td>75</td>
<td>8.5</td>
<td>NA*</td>
<td>Data from multiple British centers; Hammersmith Hospital single center</td>
</tr>
<tr>
<td>Bouget et al [87]</td>
<td>14</td>
<td>79</td>
<td>29</td>
<td>11</td>
<td>French single center</td>
</tr>
<tr>
<td>Herody et al [88]</td>
<td>29</td>
<td>93</td>
<td>41</td>
<td>0</td>
<td>French single center; most plasma exchanged</td>
</tr>
<tr>
<td>Merkel et al [89]</td>
<td>35</td>
<td>89</td>
<td>40</td>
<td>6</td>
<td>Survival at time of analysis; all plasma exchanged</td>
</tr>
<tr>
<td>Daly et al [90]</td>
<td>40</td>
<td>—</td>
<td>20</td>
<td>0</td>
<td>All plasma exchanged</td>
</tr>
</tbody>
</table>

*NA, not available.
Plasmapheresis and GP

- Single center retrospective case series of 71 pts diagnosed with GP since 1975
- All patients treated with prednisone 1mg/kg, cyclophosphamide 2-3mg/kg and plasmapheresis
- Study end points: pt and renal outcome, antibody levels and renal histology

Ann of intern medicine, 2001
Results

Flow chart showing patients in the study and outcomes at 1 year.

85 patients with anti-GBM antibody disease

10 untreated patients
2 children (ages 4 and 9 years)
2 patients with no follow-up data available

71 patients included
All received plasma exchange, prednisolone, and cyclophosphamide

19 with creatinine concentration < 500 μmol/L
13 with creatinine concentration ≥ 500 μmol/L but no dialysis
39 were dialysis-dependent within 72 hours

19 with 1-year patient survival
18 with 1-year renal survival
11 with 1-year patient survival
9 with 1-year renal survival
26 with 1-year patient survival
2 with 1-year renal survival

Ann of intern medicine, 2001
### Table 1. Renal and Patient Survival at 1 Year, according to Initial Renal Function*

<table>
<thead>
<tr>
<th>Renal Function at Presentation</th>
<th>Patients</th>
<th>Median Creatinine Concentration</th>
<th>Median Proportion of Crescents (Range)</th>
<th>1-Year Patient Survival</th>
<th>Surviving Patients with Independent Renal Function</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>µmol/L</td>
<td>%</td>
<td></td>
<td>At 2 Months†</td>
</tr>
<tr>
<td>Creatinine concentration &lt; 500 µmol/L</td>
<td>19</td>
<td>207 (53–475)</td>
<td>28 (0–87)</td>
<td>19 (100)</td>
<td>18 (95)</td>
</tr>
<tr>
<td>Creatinine concentration ≥ 500 µmol/L</td>
<td>13</td>
<td>700 (505–955)</td>
<td>55 (38–100)</td>
<td>11 (83)</td>
<td>8 (73)</td>
</tr>
<tr>
<td>Dialysis dependent</td>
<td>39</td>
<td>NA</td>
<td>100 (62–100)</td>
<td>26 (65)</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Total</td>
<td>71</td>
<td>317 (53–955)</td>
<td>41 (0–100)</td>
<td>55 (77)</td>
<td>29 (48)</td>
</tr>
</tbody>
</table>

* NA = not available.
† Renal survival at 2 months was calculated only for patients surviving at 2 months.

*Ann of intern medicine, 2001*
# Long-term outcome

## Table 2. Long-Term Outcome in Patients with Anti–Glomerular Basement Membrane Antibody Disease

<table>
<thead>
<tr>
<th>Renal Function at Presentation</th>
<th>Patients</th>
<th>Median Follow-Up</th>
<th>5-Year Patient Survival*</th>
<th>Current Survival</th>
<th>Median Time to Death (Range)</th>
<th>Surviving Patients with Independent Renal Function</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>n (%)</td>
<td>mo</td>
<td></td>
<td>At 5 Years†</td>
</tr>
<tr>
<td>Creatinine concentration &lt; 500</td>
<td>19</td>
<td>120 (12–280)</td>
<td>16 (94)</td>
<td>16 (84)</td>
<td>267 (12–280)</td>
<td>15 (94)</td>
</tr>
<tr>
<td>µmol/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>14 (74)</td>
</tr>
<tr>
<td>Creatinine concentration ≥ 500</td>
<td>13</td>
<td>96 (1–265)</td>
<td>8 (80)</td>
<td>8 (62)</td>
<td>96 (1–120)</td>
<td>4 (50)</td>
</tr>
<tr>
<td>µmol/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9 (69)</td>
</tr>
<tr>
<td>Dialysis dependent</td>
<td>39</td>
<td>22 (0.2–289)</td>
<td>16 (44)</td>
<td>14 (36)</td>
<td>5 (0.2–237)</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Total</td>
<td>71</td>
<td>90 (0.2–289)</td>
<td>40 (63)</td>
<td>38 (54)</td>
<td>9 (0.2–280)</td>
<td>21 (53)</td>
</tr>
</tbody>
</table>

* Patient survival at 5 years was calculated only for patients with at least 5 years of follow-up.
† Renal survival at 5 years was calculated only for patients surviving at 5 years.

Ann of intern medicine, 2001
Survival curves

Figure 4. Patient (top) and renal (bottom) survival curves for all treated patients with anti-glomerular basement membrane antibody disease.
Conclusions

- Pts with Creat <5.7 – 100% survival and 95% renal survival at 1yr, 84% and 74% at 10yrs
- Pts who had creat <2.8 did not progress over 10yr period
- Pts with creat >5.7- 69% had renal survival
- Need for hd on presentation- only 5% renal recovery

*Ann of intern medicine, 2001*
Thank You