IgA NEPHROPATHY

What’s new in pathogenesis & treatment?

John Feehally
IgA NEPHROPATHY

A single ‘disease’?
IgA1 deposition
In the glomerular mesangium
IgA1 deposition
In the glomerular mesangium

Variable pathological patterns
IgA1 deposition
In the glomerular mesangium

Variable pathological patterns

Variable clinical presentations
Geographical variations in the prevalence of IgA nephropathy
INCIDENCE OF IgA NEPHROPATHY & USE OF RENAL BIOPSY

McQuarrie E et al NDT 2009; 24: 1524
Percentage of patients with primary glomerular disease

Geographical variations in the prevalence of IgA nephropathy
IgA1 deposition
In the glomerular mesangium

Variable pathological patterns

Variable clinical presentations

Variable transplant recurrence
No proof that IgAN is a single ‘disease’

No proof that IgAN is the same ‘disease’ in all parts of the world
No proof that IgAN is a single disease

No proof that IgAN is the same disease in all parts of the world

Do not expect a single pathogenic mechanism to lead to mesangial IgA deposition and injury
Increase in circulating gd-IgA1
Galactose-deficient IgA1

Autoantibodies against gd-IgA1

Mesangial gd-IgA1 deposition

Mesangial cell proliferation & activation

Tubulo-interstitial injury
PATHOGENESIS OF IgA NEPHROPATHY

- Increase in circulating gd-IgA1
  - Galactose-deficient IgA1

- Immune complexes
  - Autoantibodies against gd-IgA1

- Mesangial gd-IgA1 deposition

- Mesangial cell proliferation & activation

- Tubulo-interstitial injury
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- Immune complexes
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Immune complexes

Genetic influences
PATHOGENESIS OF IgA NEPHROPATHY

Increase in circulating gd-IgA1
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Autoantibodies against gd-IgA1

Mesangial gd-IgA1 deposition

Mesangial cell proliferation & activation

Tubulo-interstitial injury

Immune complexes

Therapeutic opportunities
PATHOGENESIS OF IgA NEPHROPATHY

Why?

Increase in circulating gd-IgA1
Galactose-deficient IgA1

Autoantibodies against gd-IgA1

Mesangial gd-IgA1 deposition

Mesangial cell proliferation & activation

Tubulo-interstitial injury

Genetic influences

Immune complexes
$IgA_1$

$IgA_2$
Changes in IgA1 O-glycosylation in IgAN
Changes in IgA1 O-glycosylation in IgAN

Altered O-glycosylation of IgA1 in IgA nephropathy

Serum IgA1 AND Mesangial IgA1

Measured by lectin-binding ELISA
GALACTOSE-DEFICIENT SERUM IgA IN IgA NEPHROPATHY

HA lectin-binding ELISA

Novak J et al. KI 2007; 71: 1148
GALACTOSE-DEFICIENT SERUM IgA IN IgA NEPHROPATHY

HA lectin-binding ELISA

Novak J et al. KI 2007; 71: 1148
Altered IgA1 O-glycoforms are not found in all patients with IgAN.

IgA1 glycosylation is stable over time.

Altered IgA1 O-glycosylation is heritable.

Altered IgA1 O-glycosylation is necessary but not sufficient – ‘2 hits’.
O-GLYCOSYLATION

Serine or Threonine

N-acetylgalactosamine (GalNAc)

Galactose (Gal)

Sialic acid
**O-GLYCOSYLATION**

CORE1-β1-3-GALACTOSYLTRANSFERASE
C1GalT1
+ Cosmc
[chaperone protein]

N-acetylgalactosamine (GalNAc) → Galactose (Gal) → Sialic acid

Serine or Threonine
O-GLYCOSYLATION

CORE1-β1,3-GALACTOSYLTRANSFERASE
C1GalT1
+
Cosmc
[chaperone protein]

N-acetylβ-D-galactosaminidase
GalNAc

Galactose
Gal

Sialic acid

Serine or Threonine

GalNAc specific
α2,6-SIALYLTRANSFERASE

Sialic acid
O-GLYCOSYLATION

Serine or Threonine

N-acetylgalactosamine

GalNAc specific

α2-6-SIALYLTRANSFERASE

CORE1-β1-3-GALACTOSYLTRANSFERASE
C1GalT1
+ Cosmc

Multiple conflicting

functional and genetic data

.... in PBMCs or peripheral blood B cells

Sialic acid
IgA Nephropathy

- **MUCOSAL**
  - ↓ pIgA1

- **SYSTEMIC**
  - ↑ pIgA1

- **BLOOD**
  - plgA1

- Kidney

- Bone
Increase in circulating activated T cells carrying the $\alpha 4\beta 1$ systemic homing receptor

Batra A et al. NDT 2007; 22: 2540
MECHANISTIC STUDIES OF IgA1 O-GLYCOSYLATION IN IgA NEPHROPATHY

GENE EXPRESSION
- C1GalT1
- Cosmc

FUNCTIONAL ASSAY
- $\beta,1-3$ galactosyltransferase

IgA1 O-glycosylation
- Abnormal in serum & mesangium
MECHANISTIC STUDIES OF IgA1 O-GLYCOSYLATION IN IgA NEPHROPATHY

GENE EXPRESSION

C1GalT1
Cosmc
NORMAL

FUNCTIONAL ASSAY

β,1-3 galactosyltransferase
NORMAL

IgA1 O-glycosylation

Abnormal in serum & mesangium

Bone marrow

Smith AC et al.
KI 2008; 73: 1128
O-GLYCOSYLATION OF SERUM IgA1 ANTIBODIES

Smith AC et al. JASN 2006; 17: 3520-8
PATHOGENESIS OF IgA NEPHROPATHY

A disordered mucosa-marrow axis?

A shift of production of ‘mucosal type’ IgA1 from mucosa to marrow
PATHOGENESIS OF IgA NEPHROPATHY

- Increase in circulating gd-IgA1
- Galactose-deficient IgA1
  - Autoantibodies against gd-IgA1
  - Mesangial gd-IgA1 deposition
  - Mesangial cell proliferation & activation
  - Tubulo-interstitial injury

Genetic influences

Immune complexes
Geographical variations in the prevalence of IgA nephropathy

Canadian kindred
2q36

Kentucky kindred
6q22-23

North Italian kindred
4q26-31
17q12-22

IGAN1
GENETICS OF IgA NEPHROPATHY

GENOME-WIDE ASSOCIATION STUDIES

Areas of the genome identified by SNPs which are associated with IgAN

Does **not** define the genes involved
GWAS IN IgA NEPHROPATHY

Feehally et al. 2010
Europeans
n = 431

Gharavi et al. 2011
Han Chinese
n = 1,194

Yu et al. 2012
Han Chinese
n = 1,434

$p = 10^{-5}$
GWAS & META-ANALYSIS IN IgA NEPHROPATHY

Includes the three previously published cohorts

<table>
<thead>
<tr>
<th></th>
<th>Discovery Cohort</th>
<th>Discovery Cohort</th>
<th>Replication Cohort</th>
<th>Replication Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IgAN</td>
<td>Controls</td>
<td>IgAN</td>
<td>Controls</td>
</tr>
<tr>
<td>Europeans</td>
<td>1,553</td>
<td>3,050</td>
<td>2,420</td>
<td>1,780</td>
</tr>
<tr>
<td>East Asians</td>
<td>1,194</td>
<td>902</td>
<td>2,491</td>
<td>7,222</td>
</tr>
<tr>
<td>TOTAL</td>
<td>2,747</td>
<td>3,952</td>
<td>4,911</td>
<td>9,002</td>
</tr>
</tbody>
</table>

Kiryluk K et al. Nature Genetics 2014 e-pub
GWAS & META-ANALYSIS IN IgA NEPHROPATHY

9 previous reported signals confirmed – 6 new associations

Antigen recognition & processing - HLA

Complement

Risk of inflammatory bowel disease

Maintenance of intestinal epithelial barrier and response to mucosal pathogens

Overlap with susceptibility loci for autoimmune diseases

Kiryluk K et al. Nature Genetics 2014 e-pub
9 previous reported signals confirmed – 6 new associations

There were no associations with any regions of the genome known to code for molecules involved in IgA glycosylation

Overlap with regions known to code for immune diseases

Kiryluk K et al. Nature Genetics 2014 e-pub
GWAS & META-ANALYSIS IN IgA NEPHROPATHY

9 previous reported signals confirmed – 6 new associations

These 15 loci explain only........

6.2% of IgAN disease risk in European-ancestry cohorts

7.6% of IgAN disease risk in Chinese cohorts

No GWAS in African ancestry – reduced IgAN risk

Kiryluk K et al. Nature Genetics 2014 e-pub
IgA Nephropathy

Han Chinese
n = 1,434

Yu XQ et al. Nat Genet 2012; 44: 178

Membranous Nephropathy

Europeans
n = 556

IgA Nephropathy

Han Chinese
n = 1,434

Yu X-Q et al. Nat Genet 2012; 44: 178

Membranous Nephropathy

Europeans
n = 556

No proof that IgAN is a single ‘disease’

No proof that IgAN is the same ‘disease’ in all parts of the world
UPDATE ON CLINICAL MANAGEMENT OF IgA NEPHROPATHY

Defining IgAN

Predicting prognosis

Management of slowly progressive IgAN
GALACTOSE-DEFICIENT SERUM IgA IN IgA NEPHROPATHY

HA lectin-binding ELISA

Novak J et al. KI 2007; 71: 1148
GALACTOSE-DEFICIENT SERUM IgA IN IgA NEPHROPATHY

HA lectin-binding ELISA

- Sensitivity 76%
- Specificity 94%
- Positive predictive value 89%
- Negative predictive value 79%

Novak J et al. KI 2007; 71: 1148
PROGNOSIS OF IgA NEPHROPATHY IN SPAIN

Rodicio 1982
PROGNOSIS OF IgA NEPHROPATHY IN CHINA

1155 cases - mean age at diagnosis 34 yrs – mean follow up 5.4 yrs

Presentation:

- Visible haematuria 30%
- Oedema 24%
- Asymptomatic 31%

Le WB et al. NDT 2012; 27: 1479
IgA NEPHROPATHY IN INDIA

CMC Vellore 1994-2003

Cumulative probability of renal survival

Follow up (months)

Symptom (n) 478 233 129 78 40 23 8 5 2

Biopsy (n) 478 157 80 43 24 13 5 2 0

50%
LONG TERM OUTCOMES OF IgA NEPHROPATHY PRESENTING WITH MINIMAL OR NO PROTEINURIA

141 Caucasians - proteinuria < 0.4g/d – mean eGFR 111 ml/min

Mean follow up 108 months

<table>
<thead>
<tr>
<th></th>
<th>38%</th>
<th>44%</th>
<th>13%</th>
<th>5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLINICAL REMISSION</td>
<td>Normal urinalysis</td>
<td>Persistent haematuria</td>
<td>Uprot 0.5-1g/d</td>
<td>Uprot &gt;1g/d</td>
</tr>
<tr>
<td></td>
<td>median 48 months</td>
<td>Uprot &lt; 0.5g/d</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Gutierrez E et al. JASN 2012; 23: 1753
VALIGA: VALIDATION OF THE OXFORD CLASSIFICATION OF IgA NEPHROPATHY

1147 patients from 13 European countries
All degrees of clinical severity - median follow up 4.7 years

Predictive value of time-average proteinuria

Coppo R et al. KI 2014; 86: 828
REMISSION OF PROTEINURIA IMPROVES PROGNOSIS IN IgA NEPHROPATHY

Time-average proteinuria
1 - < 1g/24h
2 – 1-2 g/24h
3 – 2-3g/24h
4 - >3g/24h

Reich H et al. JASN 2007; 18: 3177
A CLINICO-PATHOLOGICAL CLASSIFICATION
FOR IgA NEPHROPATHY

Does pathology add prognostic information

.. to clinical data at time of biopsy ?

.. to clinical data during follow up ?
<table>
<thead>
<tr>
<th>Pathological Feature</th>
<th>Score Range</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesangial hypercellularity - in &gt; or &lt;50% of glomeruli</td>
<td></td>
<td>M0 or M1</td>
</tr>
<tr>
<td>Endocapillary hypercellularity – present/absent</td>
<td></td>
<td>E0 or E1</td>
</tr>
<tr>
<td>Segmental sclerosis/adhesions – present/absent</td>
<td></td>
<td>S0 or S1</td>
</tr>
<tr>
<td>Tubular atrophy/interstitial fibrosis – 0-25%, 26-50%, &gt;50%</td>
<td></td>
<td>T0 or T1 or T2</td>
</tr>
</tbody>
</table>

Recommend biopsy reports include score, e.g. M1,E0,S1,T1
DEVELOPING AND IMPROVING
THE OXFORD CLASSIFICATION OF IgA NEPHROPATHY

Never intended to be ‘the finished product’

Integrate newer retrospective cohorts

Develop prospective studies

Improving the classification

Regular consensus meetings
As done for Banff Classification
First in Oxford in June 014
Can we develop a consensus risk score for predicting individual prognosis in IgA nephropathy?

**CLINICAL**
- Proteinuria
- Hypertension

**PATHOLOGY**
- IgA glycosylation?

**Other?**
CLINICAL PRACTICE GUIDELINE FOR GLOMERULONEPHRITIS

Evidence-based consensus treatment guidelines
Including treatment of IgA nephropathy

Co-chairs:
Dan Cattran (Canada)
John Feehally (UK)
UPDATE ON CLINICAL MANAGEMENT OF IgA NEPHROPATHY

Management of slowly progressive IgAN

BP control & RAS blockade
- Corticosteroids
- Mycophenolate

Newer therapeutic approaches
TREATMENT OF IgA NEPHROPATHY

“Should I treat this patient?”

“Should I treat this patient with an immunosuppressive regimen with a significant adverse event profile?”
TREATMENT RECOMMENDATIONS FOR IgA NEPHROPATHY

Target Blood Pressure

Proteinuria < 1g/24hr  130/80

Proteinuria > 1g/24hr  125/75

RAS Blockade

Proteinuria > 1g/24hr  125/75

Combination therapy?
META-ANALYSIS OF COMBINATION ACEi & ARB IN PROTEINURIC IgA NEPHROPATHY

6 RCTs – 109 patients – follow up 2-12 months

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Mean difference IV, Random, 95% CI</th>
<th>Mean difference IV, Random, 95% CI</th>
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<tr>
<td>ACEI + ARB vs ACEI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kim2003</td>
<td>3.1 ± 0.3</td>
<td>4.2 ± 0.3</td>
<td>-0.11 [-1.29, -0.91]</td>
<td></td>
</tr>
<tr>
<td>Russo2001</td>
<td>0.72 ± 0.14</td>
<td>0.98 ± 0.14</td>
<td>-0.26 [-0.38, -0.14]</td>
<td></td>
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<tr>
<td>Song2003</td>
<td>3.5 ± 0.3</td>
<td>4.0 ± 0.2</td>
<td>-0.50 [-0.69, -0.31]</td>
<td></td>
</tr>
<tr>
<td>Tsukasa2007</td>
<td>0.8 ± 0.2</td>
<td>1.3 ± 0.3</td>
<td>-0.50 [-0.75, -0.25]</td>
<td></td>
</tr>
<tr>
<td>Yoshio 2006</td>
<td>0.22 ± 0.12</td>
<td>0.46 ± 0.24</td>
<td>-0.24 [-0.38, -0.10]</td>
<td></td>
</tr>
<tr>
<td>Yoshio 2004</td>
<td>0.28 ± 0.2</td>
<td>0.44 ± 0.31</td>
<td>-0.16 [-0.39, 0.07]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>75</td>
<td>75</td>
<td>61.3%</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau^2 = 0.10; Chi^2 = 67.61, df = 5 (P < 0.00001); I^2 = 93%
Test for overall effect: Z = 3.40 (P = 0.0007)

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<td>Tsukasa2007</td>
<td>0.8 ± 0.2</td>
<td>1.5 ± 0.4</td>
<td>-0.70 [-1.01, -0.39]</td>
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<tr>
<td>Yoshio 2006</td>
<td>0.22 ± 0.2</td>
<td>0.53 ± 0.33</td>
<td>-0.28 [-0.47, -0.09]</td>
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<tr>
<td>Yoshio 2004</td>
<td>0.28 ± 0.2</td>
<td>0.55 ± 0.38</td>
<td>-0.27 [-0.53, -0.01]</td>
<td></td>
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<tr>
<td>Subtotal (95% CI)</td>
<td>42</td>
<td>44</td>
<td>38.7%</td>
<td></td>
</tr>
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</table>

Heterogeneity: Tau^2 = 0.01; Chi^2 = 6.30, df = 3 (P = 0.10); I^2 = 52%
Test for overall effect: Z = 4.53 (P < 0.00001)

Total (95% CI) 117 119 100.00% -0.42 [-0.59, -0.26]
Test for overall effect: Z = 4.96 (P < 0.00001)

No effect on:
- GFR
- BP
- Serum K

TREATMENT RECOMMENDATIONS FOR IgA NEPHROPATHY

Target Blood Pressure

- Proteinuria < 1g/24hr: 130/80
- Proteinuria > 1g/24hr: 125/75

RAS Blockade

- Proteinuria > 1g/24hr: 125/75

Combination therapy?

SALT RESTRICTION
Recruitment-Update STOP IgAN
- Status 28.2.2011 -

**Study patients**
\( n = 356 \)

**Randomised**
\( n = 127 \)
Proteinuria > 1g/day ± hypertension

*If* BP target achieved…

*and* proteinuria still >1g/24 hr

consider corticosteroids, immunosuppressive regimens …

How good is the evidence of benefit in *these* circumstances?
UPDATE ON CLINICAL MANAGEMENT OF IgA NEPHROPATHY

Management of slowly progressive IgAN

BP control & RAS blockade

Corticosteroids

Mycophenolate

Newer therapeutic approaches
We suggest that patients with persistent proteinuria ≥1 g/d, despite 3-6 months of optimized supportive care (including ACEi or ARBs and blood pressure control), and GFR >50 ml/min, receive a 6-month course of corticosteroid therapy (2C).
CORTICOSTEROID TREATMENT FOR IgA NEPHROPATHY

Randomised controlled trial – serum creatinine < 130 µmol/L

Survival without end point - doubling of serum creatinine

Randomised controlled trial – serum creatinine < 130 µmol/L

Survival without end point - doubling of serum creatinine

BP control  good but NOT ideal

RAS blockade inconsistently used

<table>
<thead>
<tr>
<th>Country</th>
<th>Steroids</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Italy</td>
<td>1/48</td>
<td>8/49</td>
</tr>
<tr>
<td>China</td>
<td>1/30</td>
<td>7/33</td>
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Statistically significant

Lv J et al. 2009 AJKD; 53: 26  
Manno C et al. NDT 2009; 24: 3694
CORTICOSTEROIDS PLUS ACE INHIBITOR IN PROTEINURIC IgA NEPHROPATHY

<table>
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Statistically significant

But.. achieved ACE inhibitor dose rather low

Lv J et al. 2009 AJKD; 53: 26
Manno C et al. NDT 2009; 24: 3694
CORTICOSTEROIDS PLUS ACE INHIBITOR IN PROTEINURIC IgA NEPHROPATHY

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<td>1/30</td>
<td>7/33</td>
</tr>
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</table>

*Statistically significant*

_But.. neither study had a ‘run-in‘ period_

Lv J et al. 2009 AJKD; 53: 26
Manno C et al. NDT 2009; 24: 3694
### CORTICOSTEROIDS FOR IgA NEPHROPATHY

**VALIGA STUDY**

<table>
<thead>
<tr>
<th>1147 subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>55 centres in 13 European countries</td>
</tr>
<tr>
<td>97% Caucasian</td>
</tr>
</tbody>
</table>

**Propensity scoring**

- 184 – treated with RAS blockers
  - *matched with*
  - 184 – treated with RAS blockers plus corticosteroids
CORTICOSTEROIDS FOR IgA NEPHROPATHY
VALIGA STUDY

Matched by propensity scoring

Benefit of corticosteroids greater with increasing proteinuria

Tesar V et al  JASN  2014 – in press
CORTICOSTEROIDS FOR IgA NEPHROPATHY
VALIGA STUDY

Matched by propensity scoring

Benefit of corticosteroids regardless of initial renal function

Whole propensity matched cohort

Initial eGFR<50

Initial GFR>50

Tesar V et al  JASN  2014 – in press
Enteric corticosteroid preparation designed for ileo-caecal release of active compound with limited systemic effect

$n = 16$ - Ualb $> 500$mg/d - sCreatinine $< 200$µmol/l

eGFR (MDRD) rose by 8% ($p=0.003$)

Smerud HK et al. NDT 2011; 26: 3237
PILOT STUDY OF ENTERIC BUDESONIDE IN PROTEINURIC IgA NEPHROPATHY

Enteric corticosteroid preparation designed for ileo-caecal release of active compound with limited systemic effect

n = 16 - Ualb > 500mg/d - sCreatinine < 200µmol/l

eGFR (MDRD) rose by 8% (p=0.003)

RCT underway

Smerud HK et al. NDT 2011; 26: 3237
UPDATE ON CLINICAL MANAGEMENT OF IgA NEPHROPATHY

Management of slowly progressive IgAN

BP control & RAS blockade

Corticosteroids

Mycophenolate

Newer therapeutic approaches
<table>
<thead>
<tr>
<th>[number of patients]</th>
<th>Benefit</th>
<th>BP achieved</th>
<th>ACE inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>BELGIUM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maes 2004 [34]</td>
<td>None</td>
<td>125/73</td>
<td>100% salt restricted</td>
</tr>
<tr>
<td>HONG KONG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tang 2005 [40]</td>
<td>ESRD reduced</td>
<td>122/71</td>
<td>100%</td>
</tr>
</tbody>
</table>
TREATMENT RECOMMENDATIONS FOR IgA NEPHROPATHY

- The role of corticosteroids and immunosuppressives after tight BP control and maximal RAS blockade?
- The effect of ancestry on treatment responses
We are still short of evidence ..... 

What new evidence is coming soon?
# CURRENT RCTs in IgA NEPHROPATHY

<table>
<thead>
<tr>
<th>‘Name’</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>STOP-IgAN (Germany)</td>
<td>Corticosteroids +/- cyclophosphamide/azathioprine</td>
</tr>
<tr>
<td>TESTING (International)</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>NEFIGAN (Europe)</td>
<td>Enteric budesonide</td>
</tr>
<tr>
<td>(China)</td>
<td>Mycophenolate</td>
</tr>
<tr>
<td>(USA)</td>
<td>Rituximab</td>
</tr>
<tr>
<td>(Europe)</td>
<td>SYK inhibitor</td>
</tr>
</tbody>
</table>