Clinical Trials in IgA Nephropathy

Dr Frederick Tam
MBBChir PhD FRCP FHEA
Reader in Renal Medicine/Hon. Consultant Nephrologist
Outline

• Treatment of hypertension
• Blockers of angiotensin system
• Immunosuppressive treatment
  – Non-selective immunosuppression
  – Blocking SYK (Spleen Tyrosine Kinase)
Angiotensin system

Inhibitors of the angiotensin system is useful for treatment of hypertension and proteinuria in IgA Nephropathy:

• Angiotensin converting enzyme inhibitor (ACE-I)
  e.g. ramipril, perindopril, lisinopril

• Angiotensin receptor blocker (ARB)
  e.g. irbesartan, losartan
Clinical Trials of corticosteroid (1)

- Randomised control trial (RCT)
  - Corticosteroid reduced proteinuria and long term progression to end stage renal failure (Pozzi et al 1999, 2004)
  - ACE-I vs ACE-I+corticosteroid (Manno et al 2009, Lv et al 2009)
  - Limitation of older trials: angiotensin inhibitors were not optimised before adding corticosteroid
  - Concern of the side-effect of high dose steroid
Clinical Trials of corticosteroid (2)

New clinical trials

Optimised use of ACE-I and ARB, then add immunosuppressive treatment

- Supportive versus Immunosuppressive therapy of Progressive (STOP) IgAN trial
- Supportive only vs supportive + immunosuppression
  - (eGFR ≥ 60) High dose steroid for 6 months
  - (eGFR > 30, < 60) High dose steroid + cyclophosphamide/azathioprine for 3 years
- Therapeutic Evaluation of STeroids in IgA Nephropathy Global (TESTING) study
  - High dose steroid vs Placebo for 6-8 months
Mycophenolate mofetil (MMF)

• variable outcomes from controlled clinical trials
  – Belgian study (34 patients): ACE-I+MMF vs ACE-I only for 3 years, no benefit (Maes et al 2004)
  – North American study (32 patients): MMF vs placebo for 1 year (follow up at 2 year): no benefit (Frisch et al 2005)
  – Chinese study (40 patients): 6 months of MMF vs Placebo, initially improvement in proteinuria (1.4 year), improved renal survival up to 6 years follow up (Tang 2005, 2010)

• Kidney Disease Improving Global Outcomes (Kdigo) guideline: the results are too heterogenous to recommend (Kidney Int 2012)
New development

• A selective immunotherapy
Spleen tyrosine kinase (Syk)

- Intracellular tyrosine kinase
- Present in white blood cells and kidney cells
- Can be activated during immune response or inflammation
- For example, binding of an antibody to specific receptors on cell surface
Hypothesis: IgA complex activates Syk and results in kidney inflammation

Receptor for IgA1-IC

Human kidney cells

SFK

Syk

Mediators of inflammation

e.g. cytokines MCP-1, IL-6
Fostamatinib: inhibit SYK

- Fostamatinib (R788) is an oral prodrug (Provided by Rigel Pharmaceuticals & AstraZeneca)
- R406 is the active metabolite
- R406 – occupying ATP binding pocket of Syk
- Selective for Syk
- Off target effect: also inhibit Flt-3 with 5 fold less potency in cell based assays

Ref: Braselmann 2006 JPET 319:998-1008
Clinical Translation

• Does SYK increase in the pathogenesis of clinical IgA nephropathy?

• What is the evidence that patients‘ IgA will activate SYK?

• What is the consequence of blocker SYK in kidney cells?
Study of Kidney Biopsies from patients
Increase in SYK (brown staining) in IgA nephropathy

IgAN
Crescentic IgAN
Minimal change disease

Kim MJ et al J Immunol 2012;189:3751-8
Clinical Translation

• Does SYK increase in the pathogenesis of clinical IgA nephropathy?
• What is the evidence that IgA from patients will activate SYK?
• What is the consequence of blocker SYK in kidney cells?

Collaboration with Renal Unit, Leicester

• To study the potential role of SYK in IgA1 stimulated mesangial cells
Induction of activated (phosphorylated) SYK in human kidney cells by patients’ IgA

- IgA1 from patients with IgA nephropathy
- Induce expression of phospho-SYK in human kidney (mesangial) cells
Clinical Translation

• Does SYK increase in the pathogenesis of clinical IgA nephropathy?
• What is the evidence that patients‘ IgA will activate SYK?
• What is the consequence of blocker SYK in kidney cells?
Patients’ IgA stimulate production of inflammatory mediators in human kidney (mesangial) cells in culture

* $P < 0.001$

Kim MJ et al J Immunol 2012;189:3751-8
Does inhibiting SYK reduce inflammation?

- Study of human kidney cells (mesangial cells) in culture
- Stimulations with IgA purified from patients’ serum
- Inhibition with the active metabolite of SYK inhibitor (R406)
- Check the specific role of SYK further using molecular biology method (small interfering RNA, siRNA)
SYK inhibitor (R406) inhibit production of multiple inhibitors from kidney cells

**MCP-1**

![Graph showing MCP-1 production across different conditions](image-url)

Kim MJ et al J Immunol 2012;189:3751-8
SYK inhibitor inhibit production of multiple inhibitors from kidney cells

Kim MJ et al J Immunol 2012;189:3751-8
Effect of siRNA to SYK in human mesangial cells

**IL-6**

- Medium only
- IgAN-IgA1
- Control siRNA + IgAN-IgA1
- Syk siRNA + IgAN-IgA1

**IL-8**

- Medium only
- IgAN-IgA1
- Control siRNA + IgAN-IgA1
- Syk siRNA + IgAN-IgA1

**MCP-1**

- Medium only
- IgAN-IgA1
- Control siRNA + IgAN-IgA1
- Syk siRNA + IgAN-IgA1

**IP-10**

- Medium only
- IgAN-IgA1
- Control siRNA + IgAN-IgA1
- Syk siRNA + IgAN-IgA1

**RANTES**

- Medium only
- IgAN-IgA1
- Control siRNA + IgAN-IgA1
- Syk siRNA + IgAN-IgA1

**PDGF-BB**

- Medium only
- IgAN-IgA1
- Control siRNA + IgAN-IgA1
- Syk siRNA + IgAN-IgA1

* indicates statistical significance.
• Is SYK inhibitor likely to be useful in treating glomerulonephritis (GN), especially patients will have onset of symptoms and kidney damage before meeting the kidney doctors?
Is SYK inhibitor likely to be useful in treating glomerulonephritis (GN), especially patients will have onset of symptoms and kidney damage before meeting the kidney doctors?

• Research project: preclinical models of antibody mediated GN
  – It is challenging to have reproducible preclinical models of IgA nephropathy
  – We have studied two other models of experimental GN
Antibody mediated glomerulonephritis

Antibody mediated glomerulonephritis (GN)

Is fostamatinib effective in treating established GN?

- Fostamatinib was given orally twice daily
- **Groups**
  - Vehicle
  - 40 mg/kg twice daily (day 0-10)
  - 40 mg/kg twice daily (day 4-10),
    - from onset of proteinuria (day 4)
Pre-clinical development

histology of kidney

% glomeruli with crescents

vehicle    prevention (D0-D10)    treatment (D4-D10)

Fostamatinib

**p<0.01  **p<0.01
What is the effect of SYK inhibition on autoimmunity?

Experimental Autoimmune Glomerulonephritis (EAG)

• Genuine autoimmune model
• Characterised by ongoing autoantibody production
  – Recapitulates clinical diseases
  – Allows study of antibody production

McAdoo et al, J Am Soc Nephrology (accepted for publication)
Autoimmune: Treatment Study

McAdoo et al, 2014

Day 0

36

Fostamatinib 40mg/kg bd

 Preconditions development

α3

immunisation

Proteinuria

McAdoo et al, 2014
late treatment with fostamatinib reduced haematuria and proteinuria

McAdoo et al, 2014
late treatment with fostamatinib: reverse histology damage of the kidney

**

***

McAdoo et al, 2014
late treatment with fostamatinib: reduced production of autoantibody

Serum antibody

Antibody deposited in kidney

McAdoo et al, 2014
Summary (preclinical models)

- Fostamatinib is an effective treatment in established glomerulonephritis
  - Prevents and reverses histology of kidney damage
  - Inhibition of autoantibody production
  - Inhibition of inflammation
  - Reduction in proteinuria
  - Protected kidney function

Smith et al 2010, McAdoo et al, 2014
Clinical trial of SYK inhibitor in IgA nephropathy

• approved industrial funding from the drug inventor (Rigel Pharmaceuticals)
• in collaboration with Kidney Research UK
• Collaborating countries:
  Austria, Germany, Switzerland, Singapore, Taiwan, UK
Proof of Principle (Phase 2) Clinical Trial

- Recent diagnosis of IgA nephropathy by kidney biopsy and has significant proteinuria
- Initial period (3-6 months) optimise treatment of blood pressure and proteinuria with angiotensin converting enzyme inhibitor or receptor blocker
- If still has significant proteinuria, then enter randomised controlled trial with the SYK inhibitor, Fostamatinib, or placebo for 24 weeks
End points for clinical trial

• Improvement in proteinuria?
• Improvement in histology of kidney damage (kidney biopsy after 24 weeks of treatment)?
• Safety and tolerability assessment
• To ascertain what are the renal histology features predicting response to SYK inhibitor
Conclusions (selective SYK inhibition)

- Increase p-SYK in the renal biopsies of patients with IgA nephropathy
- Both pharmacological inhibition of SYK and molecular knockout of SYK reduced production of inflammatory mediators from kidney cells in culture
- SYK inhibitor was shown to be effective in reducing autoantibody production and kidney damage in preclinical models of glomerulonephritis
- Developing a proof of principle clinical trials of fostamatinib for treatment patients with IgA nephropathy
Imperial College London
- Jennifer Smith
- John McDaid
- Steve McAdoo
- Min Jeong Kim
- Gurjeet Bhangal
- Karen Yu
- Ratana Chawanasuntorapoj
- Theresa Page
- Prof. Terry Cook
- Prof. Charles Pusey

Rigel Pharmaceuticals, South San Francisco
- Esteban Masuda
- Daniel Magilavy

AstraZeneca
- Martin Braddock

University of Leicester
- Tricia Higgins
- Jonathan Barratt
- Karen Molyneux
- Prof. John Feehally

patients

Diamond Fund, Imperial College Healthcare Charity

MRC