



C3 GLOMERULOPATHY

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Disclosure of Interests

Current (In the last 1 year):

- Company A - Consultancy – Achillion
- Company B - Baxter

Past (>3 years ago):

- Company A – Consultancy - Alexion
- Company B – Investigator Funding – Celldex

Background

- Consensus on Definition
 - Outcomes-based phenotypic data not available
 - Subtleties in pathology not well understood
- Treatment data bias
 - Retrospective and case report driven
 - Publication bias
 - Target and Treatment Matching Bias

Eculizumab and C3G

Eculizumab Treatment of C3 Glomerulopathy

Author/Journal	Dz	C3Nef	Genes*/Ab	sMAC	Creatinine (mg/dl)	UP/CB(g/g)	C3	Response		Post-Biopsy			
								C	P	M	EC	S	D
<i>Bamback et al. Clin J Am Soc Nephrol. 2012;7(5):748-756</i>	DDD	Neg	CFH	1.08	2.0	0.7		D ¹	D ¹	N	D	N	D
	DDD	Pos	Neg	0.21	1.9	3.5		N	N				
	DDD - tx	Neg	Neg	-	1.2	4.5		N	N	D	D	N	D
	C3GN	Neg	Neg	0.07	1.6	2.6		D ²	D ²			I	I
	C3GN - tx	Pos	Neg	0.71	1.8	4.4		D ¹	D ¹	D	D	I	I
	C3GN - tx	Pos	MCP	0.32	1.7	0.1		D		N	N	N	N
<i>Gucken et al. Ped Nephrol. 2013; 28(10):1975-1981</i>	DDD - tx	Pos	CFH	I	1.5	2-3		D	I	I	I	I	I
<i>Radhakrishnan et al. N Engl J Med. 2012;366(12):1165-1166.</i>	MPGN	Pos	Neg	High				D	D				
<i>Garnier et al. J Am Soc Nephrol. 2011;22.</i>	MPGN	Pos	-					D	D				
<i>Le Quintrec et al. AJKD. 2014;22.</i>	DDD - tx	Neg	Neg	2200	2.2	3.5		D	D	D	D		D
<i>Dibas et al. ASN 2014</i>	C3GN	Pos			2.45	17		D	D				
<i>Besbas et al. Case Rep Nephrol. 2014;2014:201568.</i>	C3GN		CFHR5		Normal	2.0		N	N				
<i>Kema et al. Pediatr Nephrol. 2013;28(11):2227-2231.</i>	C3GN			1238	0.9	9.8			D				
<i>Berthe-Aucejo et al. Case Rep Nephrol. 2014;2014:201568.</i>	DDD	Pos	CFH		Normal	2.55		N ³	N				
<i>Sanchez-Moreno et al. Ped Nephrol. 2014</i>	DDD - tx	Pos	Neg		1.1			D	D				
<i>Ozkaya et al. Pediatr Nephrol. 2014;29(7):1283-1287.</i>	DDD	Pos	Neg			9.9		D	D				
<i>Roussel-Rouviere, et al. Pediatr Nephrol. 2014;29(6):1107-1111.</i>	DDD	Pos	Neg					D	D				
<i>Unadthay et al. ASN 2013</i>	DDD	Pos	Neg	High		5.6		D ⁴	D ⁴				

Response: D = Decreased, I = Increased, N = no response

Post-Biopsy: M = mesangial, EC = endocapillary, S = sclerosis, D = deposits, N = No change, D = decreased, I = Increased

Eculizumab and C3G

<i>McCavahan et al. Am J Transplant. 2012;12(4):1046-1051</i>	DDD - tx	Pos	Neg		4.93			D	D				
<i>Daina et al. N Engl J Med. 2012;366(12):1161-1163.</i>	DDD	Pos	SNP	High				D	D				
<i>Vivarelli et al. N Engl J Med. 2012;366(12):1163-1165.</i>	DDD	Pos	Neg					D ¹	D ¹		D	I	
<i>Le Quintrec et al. Am J Kidney Dis. 2014.</i>	C3GN	Pos	Neg	Normal	6.0	1.42		D	D	D	N	I	
<i>Le Quintrec et al. Am J Kidney Dis. 2014.</i>	C3GN	Neg	Neg	1553	4.1	1.3		D	D	D		I	N
<i>Inman et al. ASN 2014</i>	C3GN			0.36	11	6.82		D	D				
<i>Chanchlani et al. ASN 2014</i>	C3GN		Neg					D	D				
<i>Chanchlani et al. ASN 2014</i>	C3GN		MCP					D	D				
<i>Taylor et al. ASN 2013</i>	C3GN	Pos	Neg	High				N	N ⁵				
<i>Oosterveld et al. CJASN. 2015; Aug 27</i>	DDD							D	D ⁶				
	DDD							D	D				
	DDD							D	D				
	DDD							D	D				
	DDD							D	D				
<i>Berg et al. ASN. 2015; P0451</i>	C3GN				2.24	4.6		D	D				
<i>Jaberj et al. ASN. 2015; P0027</i>	C3GN				11	-		D					
<i>Nester et al. Unpublished</i>	DDD	Neg	CFH		3.9	8.7	Normal	D ¹	D ¹	D	D	N	D ⁷
	C3GN	Neg	Neg		3.5	2.7	Low	D ¹	D ¹				
	C3GN	Neg	C3		1.7	2.8	Low	N	N				
	C3GN -tx	Neg	Neg	Normal	1.7	4.4	Normal	D	D				
	12							D	D				
<i>Italian Study</i>	1							N	N				
	10							?	?				

*Complotype not routinely reported.

1. Relapsed with withdrawal of eculizumab.
2. Loss of response at 24 weeks – coincident with stop of MMF.
3. Despite advancing dose to 1800mg q week.
4. Response lost with attempt to move to q4 weeks from q2 weeks.
5. Treatment stopped at 10 doses.
6. Authors report disappearance of pyuria as a measure response.

Terminal Complement Pathway Blockade

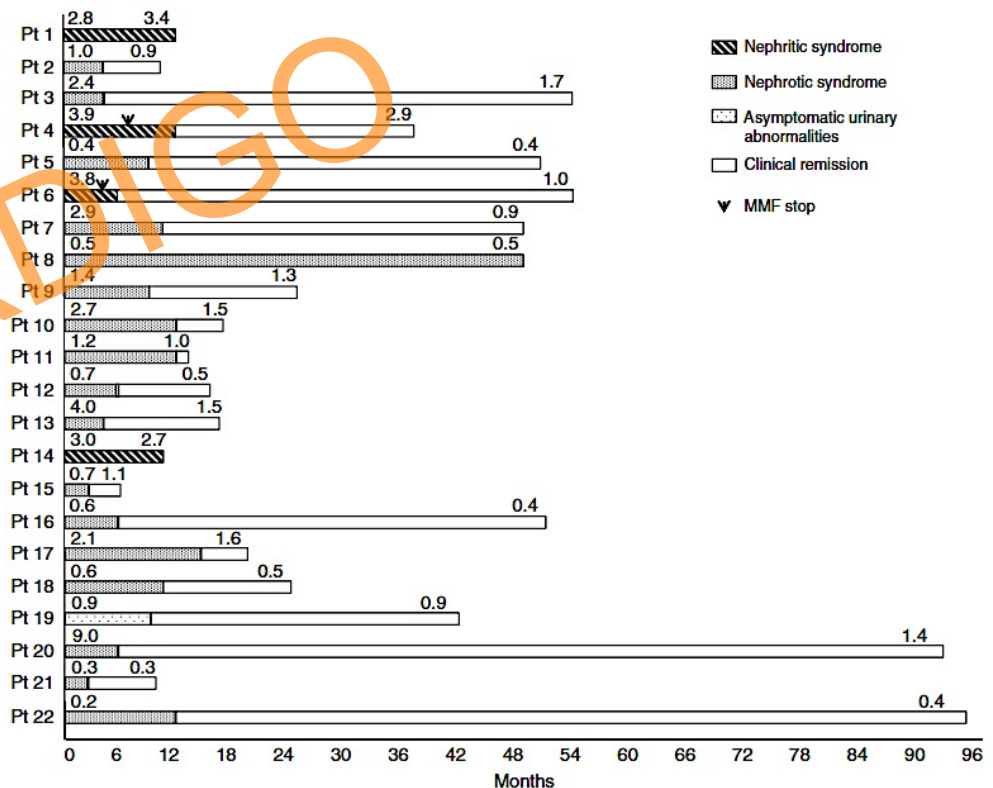
Lesson Learned:

1. Clinical response is variable
2. Clinical response does not necessarily mean histologic response
3. Relapse risk must be considered.

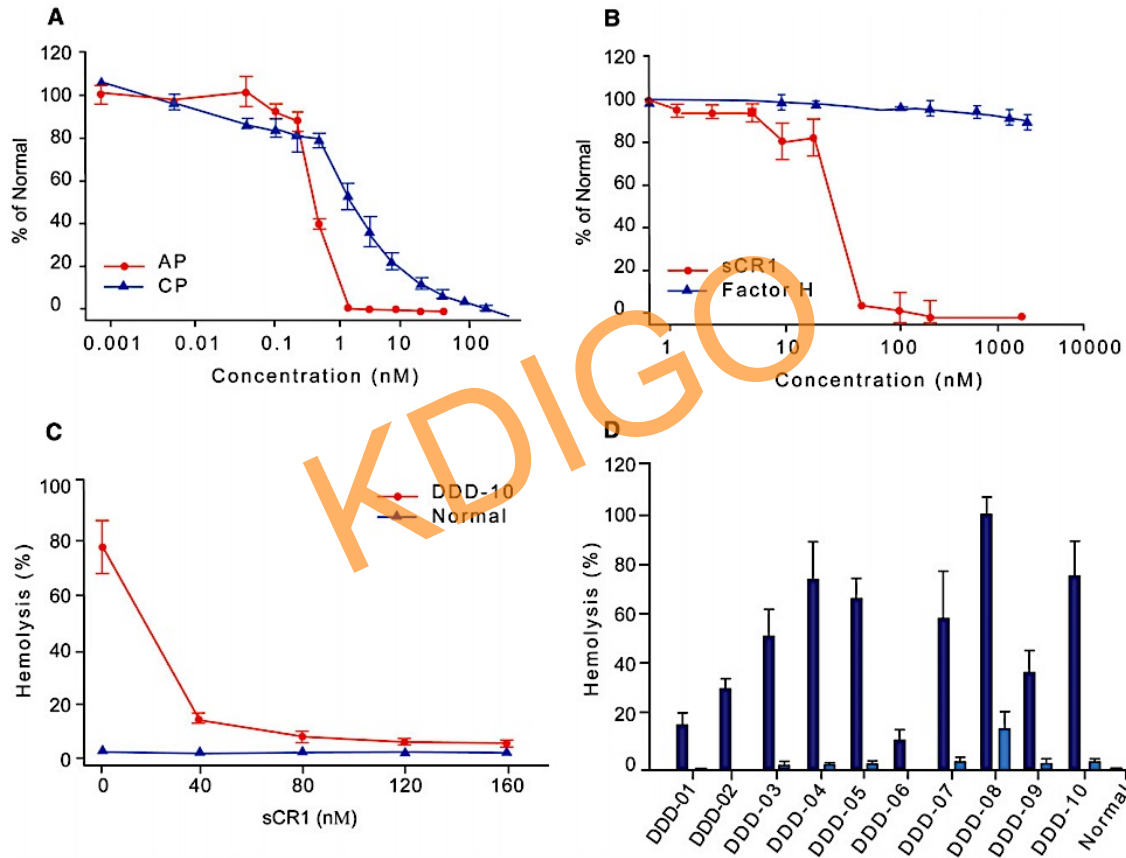
MMF and C3G

- Rabasco et al. KI 2015 July 29, Renal survival and number of patients with remission improved when MMF and steroids used.

- ASN PO0450: 58% of 24 pts with C3G responded to MMF (8CR, 6 PR) sMAC predicted success.



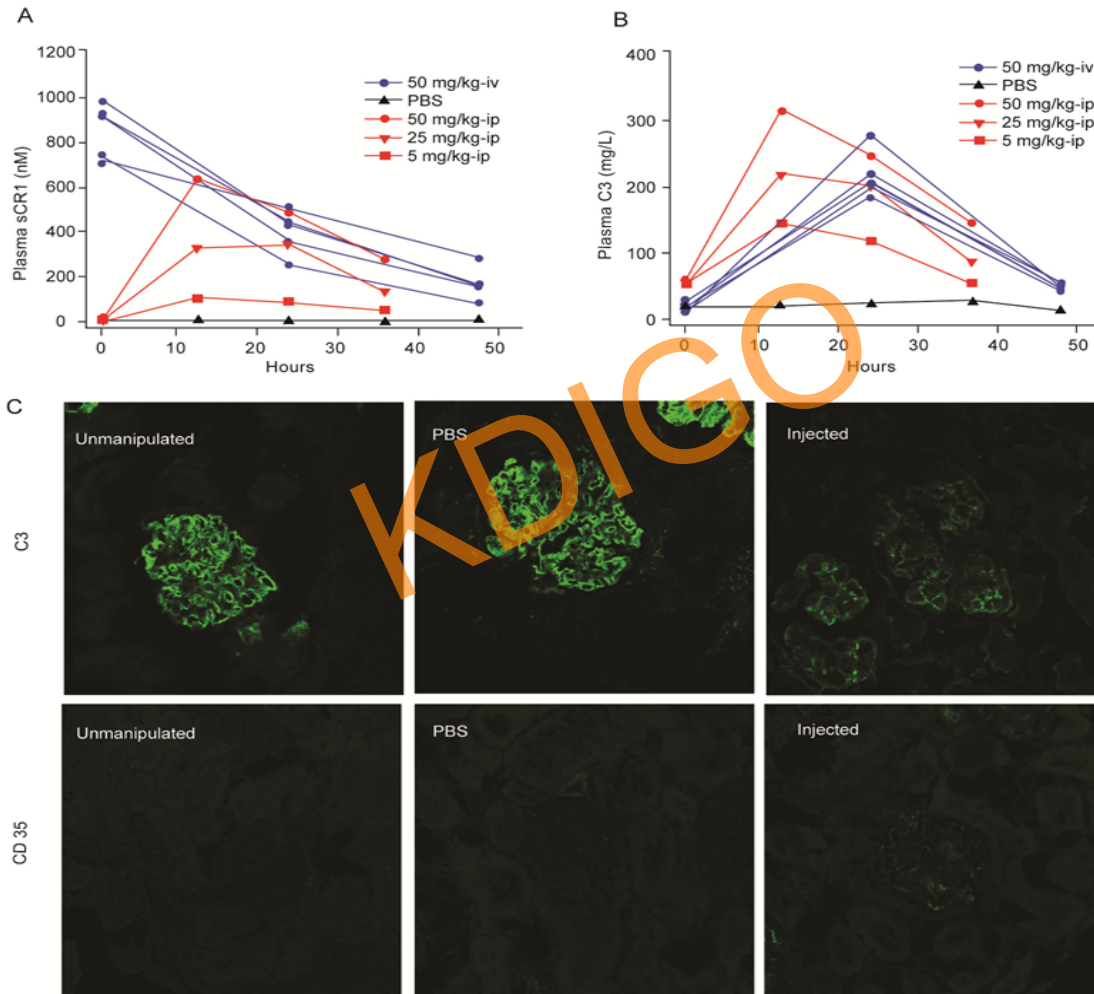
C3 Convertase Inhibitor – TP10



J Am Soc Nephrol 24: 1820–1829, 2013



C3 Convertase Inhibitor – TP10



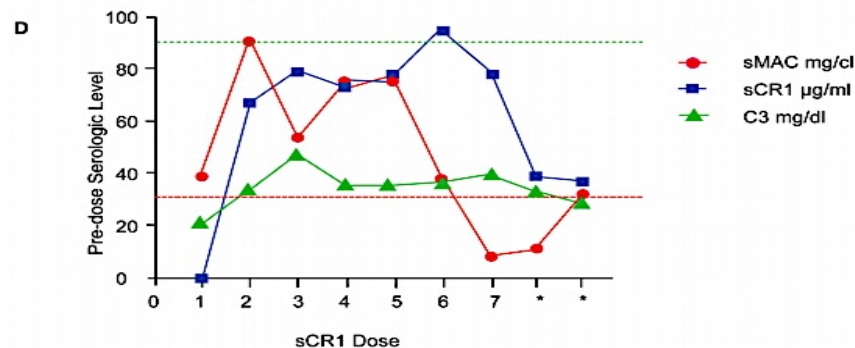
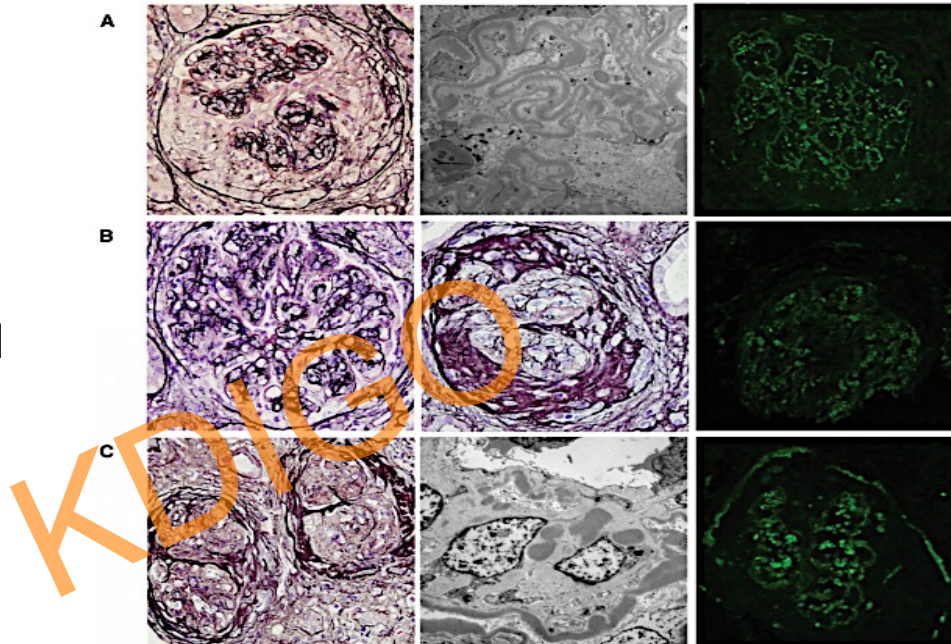
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KDIGO Controversies Conference on Complement-Mediated Kidney Diseases
November 19-21, 2015 | Barcelona, Spain

C3 Convertase Inhibitor – TP10

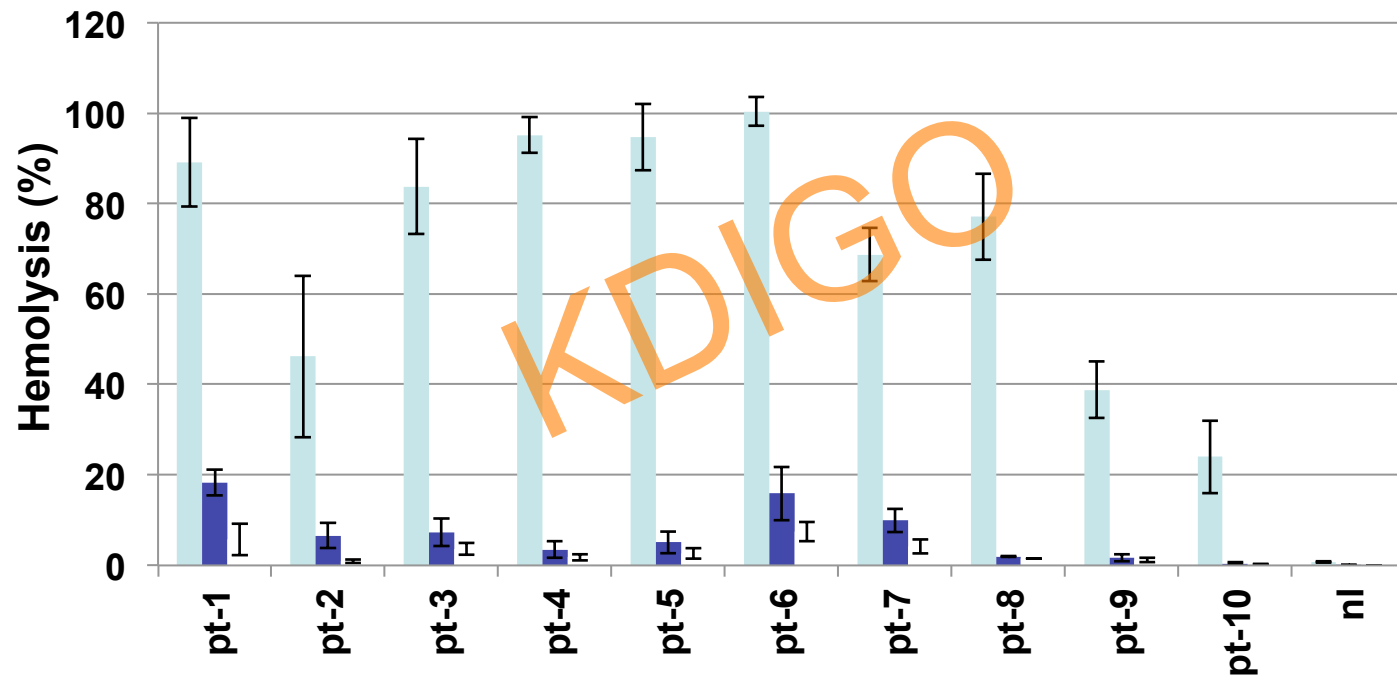
Lessons Learned:

1. TP10 was safe in a limited dose regimen.
2. TP10 effectively blocked terminal complement.
3. C3c deposits appeared to be removed from the GBM in the mouse model.
4. C3 did not recover to the normal range.



J Am Soc Nephrol 24: 1820–1829, 2013

C3 Convertase Inhibitor – CP40



Immunobiology. 2015 Aug;220(8):993-8

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C3 Convertase Inhibitor – CP40

Disease	C3GN	C3GN	C3GN	C3GN	C3GN	DDD	DDD	DDD	DDD	DDD	n/a
C3Nef	+		+				+				
C4Nef		+	+					+			
FHAA							+				
Genetic Mutation			CFH c. 3229T>C, p.Cys1077Ar g		CFB c. 608G>A, p.Arg203Gln						

Lessons Learned:

- 1) Biomarker phenotype did not limit response
- 2)

Immunobiology. 2015 Aug;220(8):993-8

- Mini-FH protein reduces glomerular C3 deposition. KI 2015, Jul 29.
- CR2-FH decreases GBM C3 deposition. JASN 2015 June 5.
- Recombinant FH restores complement regulation (Inc plasma C3 and reduce glomerular C3 deposits). ASN 2015 P0128
- CR3 deficiency enhanced severity of experimental C3G. ASN 2015 PO956
- The presence of either C5 or C3 Convertase stabilizing antibodies predicted response to anticomplement therapy. ASN 2015 PO958 and PO957

Controversies and Challenges

- Does DDD = C3GN?
 - Are there biomarkers that help us predict responders/ agent choices?
- Is there an optimal treatment for C3G?
 - Role for immunosuppression in the treatment of C3 glomerulopathy
 - How and how long should it be used? How or should eculizumab be monitored?

Controversies and Challenges

- Must we normalize the C3 in order to be successful?
- What about transplant (timing/protocol)?
 - Agent and Timing?
 - Type of donor
- How do we move forward with other agents?