🚨Tweetorial Alert🚨

1/
Hey #NephTwitter!
Welcome to a 🆕 #tweetorial #xtorial brought to you by @KIReports.

2/
Our author is Sai Achi @SaiAchi1 (nephrologist)
Our topic: C3 Glomerulopathy: Novel Treatment Paradigm
#MedTwitter #nephtwitter @ISNkidneycare #X

3/
There are no conflicts of interest. Please also check out #KIReportsCommunity educational #blogposts at https://www.kireportscommunity.org/. FOLLOW US at @KIReports for more expert #MedEd in #kidneydisease. #FOAMed @MedTweetorials

4/This #tweetorial/XSkytorial is based on the following articles:

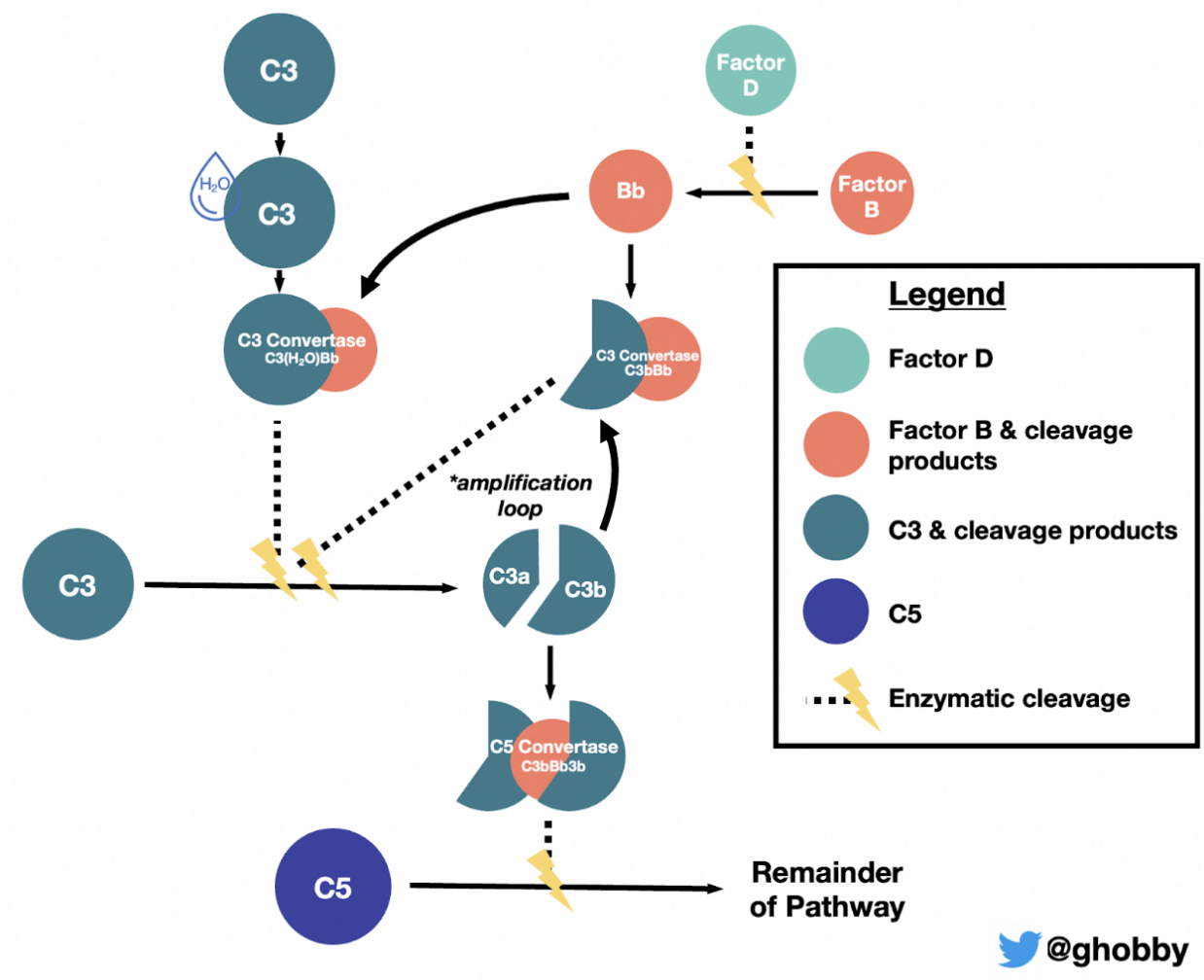
- 📃https://www.kireports.org/article/S2468-0249(23)01629-7/fulltext
- 📃https://www.kireports.org/article/S2468-0249(24)01961-2/fulltext
- 📃https://www.kireports.org/article/S2468-0249(24)01989-2/fulltext

5/ C3 glomerulopathy encompasses two disease entities: C3 glomerulonephritis (C3GN) and dense deposit disease (DDD)

5a/ C3GN is the primary focus and is defined by its complement mediated pathogenesis and histological patterns.

✔️pathogenesis is due to alternate pathway dysregulation->causing C3 fragment deposition in the glomeruli with trace or minimal immunoglobulin deposition.

5b/Here's an infographic by @ghobby detailing the alternate pathway.



5c/ C3GN can be caused by genetic factors or can be acquired (highlighted below)
https://www.kireports.org/article/S2468-0249(24)01945-4/fulltext

Table 1. Frequency of genetic and acquired abnormalities in complement proteins in patients with IC-MPGN and C3G from published cohort studies

Complement protein(s)	Reference	C3G, *n/N* (%)	C3GN, *n/N* (%)	DDD, *n/N* (%)	IC-MPGN, *n/N* (%)
Complement factor gene variant or mutation					
C3	Bomback *et al.*[19]		2/42 (4.8)	0/9 (0)	
	Ravindran *et al.*[21]	6/62 (9.7)			
	Ravindran *et al.*[20]		6/61 (9.8)		
	Garam *et al.*[39]		1/37 (2.7)	1/11 (9.1)	2/44 (4.5)[a]
	Iatropoulos *et al.*[7]		6/50 (12.0)	0/21 (0)	6/64 (9.4)[a]
	Iatropoulos *et al.*[8]		9/68 (13.2)	0/25 (0)	5/80 (6.3)[a]
CFB	Bomback *et al.*[19]		0/42 (0)	0/9 (0)	
	Ravindran *et al.*[21]	1/62 (1.6)			
	Garam *et al.*[39]		1/37 (2.7)	0/11 (0)	0/44 (0)[a]
	Iatropoulos *et al.*[7]		0/50 (0)	0/21 (0)	3/64 (4.7)[a]
	Iatropoulos *et al.*[8]		0/68 (0)	0/25 (0)	3/80 (3.8)[a]
CFH	Servais *et al.*[6]		9/56 (16.1)	5/29 (17.2)	
	Bomback *et al.*[19]		8/42 (19.0)	3/9 (33.3)	
	Ravindran *et al.*[21]	10/62 (16.1)			
	Ravindran *et al.*[20]		8/61 (13.1)	2/9 (22.2)	
	Garam *et al.*[39]		1/37 (2.7)	1/11 (9.1)	1/44 (2.3)[a]
	Iatropoulos *et al.*[7]		3/50 (6.0)	1/21 (4.8)	1/64 (1.6)[a]
	Iatropoulos *et al.*[8]		5/68 (7.4)	2/25 (8.0)	3/80 (3.8)[a]
CFHR5	Bomback *et al.*[19]		1/42 (2.4)	0/9 (0)	
	Ravindran *et al.*[21]	4/62 (6.5)			
	Ravindran *et al.*[20]		4/61 (6.6)		
CFI	Servais *et al.*[6]		4/56 (7.1)	2/29 (6.9)	
	Bomback *et al.*[19]		0/42 (0)	0/9 (0)	
	Ravindran *et al.*[21]	2/62 (3.2)			
	Ravindran *et al.*[20]		2/61 (3.3)		
	Garam *et al.*[39]		1/37 (2.7)	1/11 (9.1)	0/44 (0)[a]
	Iatropoulos *et al.*[7]		1/50 (2.0)	1/21 (4.8)	0/64 (0)[a]
	Iatropoulos *et al.*[8]		3/68 (4.4)	1/25 (4.0)	0/80 (0)[a]
MCP	Servais *et al.*[6]		2/56 (3.6)	0/29 (0)	
	Bomback *et al.*[19]		1/42 (2.4)	0/9 (0)	
	Ravindran *et al.*[21]	0/21 (0)[b]			
	Garam *et al.*[39]		4/37 (10.8)	0/11 (0)	4/44 (9.1)[a]
	Iatropoulos *et al.*[7]		0/50 (0)	0/21 (0)	1/64 (1.6)[a]
	Iatropoulos *et al.*[8]		0/68 (0)	0/25 (0)	1/80 (1.3)[a]
THBD	Garam *et al.*[39]		2/37 (5.4)	0/11 (0)	2/44 (4.5)[a]
	Iatropoulos *et al.*[7]		0/50 (0)	1/21 (4.8)	0/64 (0)[a]
	Iatropoulos *et al.*[8]		1/68 (1.5)	1/25 (4.0)	0/80 (0)[a]
Complement-associated autoantibody					
C3NeF	Servais *et al.*[6]		24/53 (45.3)	19/22 (86.4)	
	Bomback *et al.*[19]		13/42 (31.0)	1/9 (11.1)	
	Ravindran *et al.*[21]	25/61 (41.0)			
	Ravindran *et al.*[20]	30/69 (43.5)	27/59 (45.8)	3/10 (30.0)	
	Garam *et al.*[39]			5/11 (45.5)	11/44 (25.0)[a]
	Garam *et al.*[38]		7/40 (17.5)	5/12 (41.6)	15/67 (22.4)[a]
	Iatropoulos *et al.*[7]	NA/NA (54)	NA/NA (44)	NA/NA (78)	NA/NA (44)[a]
	Iatropoulos *et al.*[8]		24/62 (38.7)	18/23 (78.3)	31/77 (40.3)[a]
	Kovala *et al.*[12]	2/11 (18.2)			0/22 (0)[c]
C4NeF	Garam *et al.*[38]		7/40 (17.5)	1/12 (8.3)	9/67 (13.4)[a]
C5NeF	Ravindran *et al.*[20]		1/59 (1.7)		
Factor B	Bomback *et al.*[19]		0/42 (0)	0/9 (0)	
	Ravindran *et al.*[21]	5/60 (8.3)			
	Ravindran *et al.*[20]		5/59 (8.5)		
	Garam *et al.*[38]		3/37 (8.1)	2/12 (16.7)	2/67 (3.0)[a]
	Kovala *et al.*[12]	2/13 (15.4)			1/17 (5.9)[c]
Factor H	Bomback *et al.*[19]		3/42 (7.1)	1/9 (11.1)	
	Ravindran *et al.*[21]	3/60 (5.0)			
	Ravindran *et al.*[20]		2/59 (3.4)	1/8 (12.5)	
	Kovala *et al.*[12]	1/13 (7.7)			1/18 (5.6)[c]

C, complement; C3G, complement 3 glomerulopathy; C3GN, complement 3 glomerulonephritis; CFB, complement factor B; CFH, complement factor H; CFHR5, complement factor H related 5; CFI, complement factor I; DDD, dense deposit disease; IC-MPGN, immune complex-mediated membranoproliferative glomerulonephritis; MCP, membrane cofactor protein; NA, not available; NeF, nephritic factor; THBD, thrombomodulin.
[a]Patients with idiopathic IC-MPGN only (patients with secondary IC-MPGN were excluded from the study).
[b]Patients with C3G and monoclonal Ig only.
[c]Includes patients with primary and secondary IC-MPGN.

6/ C3GN clinical course includes hematuria, proteinuria and progressive CKD to ESKD in ~20 years from diagnosis.

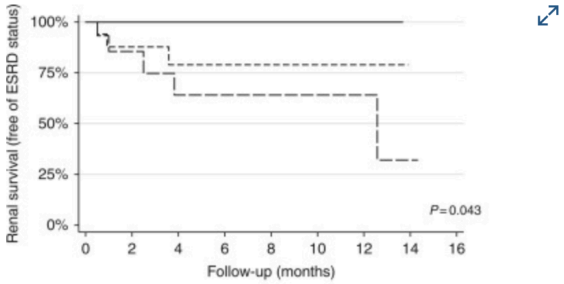
6a/ Current treatment:

✔️Supportive measures for mild disease

✔️Immunosuppression (IST): MMF+steroids for mod-severe dz (UPcr > 0.5-1 g/d)

✔️Pts on MMF+steroids had better survival rates, lower Cr rise & more remission compared to other IST

https://www.kidney-international.org/article/S0085-2538(15)60998-X/fulltext



Patients at risk according to months of follow-up

Group of treatment	0	2	4	6	8	10	12	14	16
MMF-IST	22	15	10	5	4	4	2	1	1
Other-IST	18	13	10	6	4	2	2	1	1
No IST	20	14	11	7	6	6	5	4	3

Figure viewer

Figure 1 Renal survival (defined by a status free of end-stage renal disease) in patients treated with MMF (MMF-IST), other IST (other-IST), and no IST (non-IST). ESRD, end-stage renal disease; IST, immunosuppressive treatments; MMF, mycophenolate mofetil.

7/ There are multiple agents that are being studied for C3GN

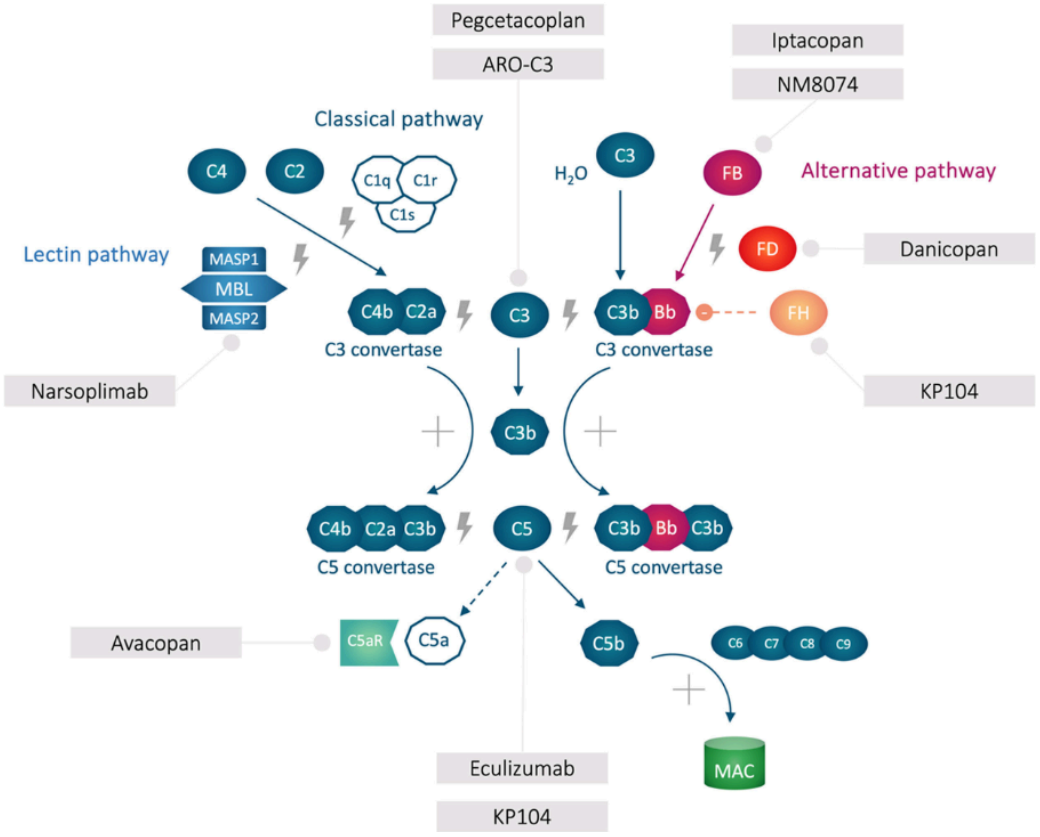
The new therapeutic agents target along the alternate complement pathway and C3 convertase which are highlighted in the table below.

Table 1. Clinical trials of complement inhibitors in C3 glomerulopathy

Target in complement cascade	Mechanism of action	Drug	Type of inhibitor	Mode of administration	Pharmaceutical company	Clinical trial phase	Identification	Status	Potential indication in kidney diseases
C3	inhibition of the binding of C3 to C3bBb and thus of the cleavage of C3	Pegcetacoplan	Pegylated peptide	s.c.	Apellis	Phase 2 ($n = 21$)	NCT03453619 (DISCOVERY)	active, not recruiting	IgAN, LN, C3G, MN, DDD
						Phase 2 ($n = 12$)	NCT04572854 (NOBLE)	recruiting	Posttransplant recurrent C3 and IC-MPGN
						Phase 3 ($n = 90$)	NCT05067127 (VALIANT)	recruiting	C3G, IC-MPGN
						Phase 3 ($n = 100$)	NCT05809531 (VALE)	not yet recruiting	C3G, IC-MPGN
	reduction of production of C3	ARO-C3	RNAi	s.c.	Arrowhead	Phase 1/2a ($n = 60$)	NCT05083364	recruiting	C3G, IgAN
Factor B	inhibition of serine protease FB and thus of the cleavage of C3 and C5	Iptacopan (LNP023)	small molecule	Oral	Novartis	Phase 2 ($n = 27$)	NCT03832114	completed	C3G (native and posttransplant)
						Phase 2 ($n = 94$)	NCT03955445	recruiting	C3G
						Phase 3 ($n = 83$)	NCT04817618 (APPEAR-C3G)	recruiting	C3G
		NM8074	mAB	i.v.	NovelMed	Phase 1b/2a ($n = 18$)	NCT05647811	not yet recruiting	C3G
Factor D	inhibition of the cleavage of FB	Danicopan (ALXN2040)	small molecule	Oral	Alexion	Phase 2 ($n = 13$)	NCT03369236	completed	C3G
						Phase 2 ($n = 22$)	NCT03459443	terminated*	C3G, IC-MPGN
						Phase 2a ($n = 6$)	NCT03124368	completed	C3G, IC-MPGN
C5	inhibition of the release of C5a and C5b, and ultimately the formation of C5b9	Eculizumab	mAB	i.v.	Alexion	Phase 1 ($n = 6$)	NCT01221181	completed	C3G
C5a receptor	inhibition of the binding of C5a to its receptor	Avacopan (CCX168)	small molecule	Oral	ChemoCentryx	Phase 2 (n=57)	NCT03301467 (ACCOLADE)	completed	C3G
C3 convertase and C5	Factor H component: inhibition of C3 convertase. C5 antibody: inhibition of release of C5a and C5b	KP104	Bifunctional biologic	i.v. and s.c.	Kira	Phase 2 ($n = 52$)	NCT05517980	not yet recruiting	C3G, IgAN
MASP-2	inhibition of the cleavage of C4 and C2	Narsoplimab (OMS721)	mAB	i.v. and s.c.	Omeros	Phase 2 ($n = 54$)	NCT02682407	completed	IgAN, LN, C3G, MN

C3G, C3 glomerulopathy; DDD, dense deposit disease; IC-MPGN, immune complex-mediated membranoproliferative glomerulonephritis; IgAN, IgA nephropathy; i.v., intravenous; LN, lupus nephritis; mAB, monoclonal antibody; MN, membranous nephropathy; RNAi, RNA interference; s.c., subcutaneous.
*Terminated because of inconclusive efficacy results. No safety findings were identified.

8/ The following is a pictorial depiction of the complement pathway and the various medications undergoing investigation, targeting the complement pathway:



9/Pegcetacoplan

⚡binds to C3->inhibits C3 convertase access, thereby blocking the cleaving of C3 in all complement pathways

9a/Trials for Pegcetacoplan are outlined in the next few tweets/skeets

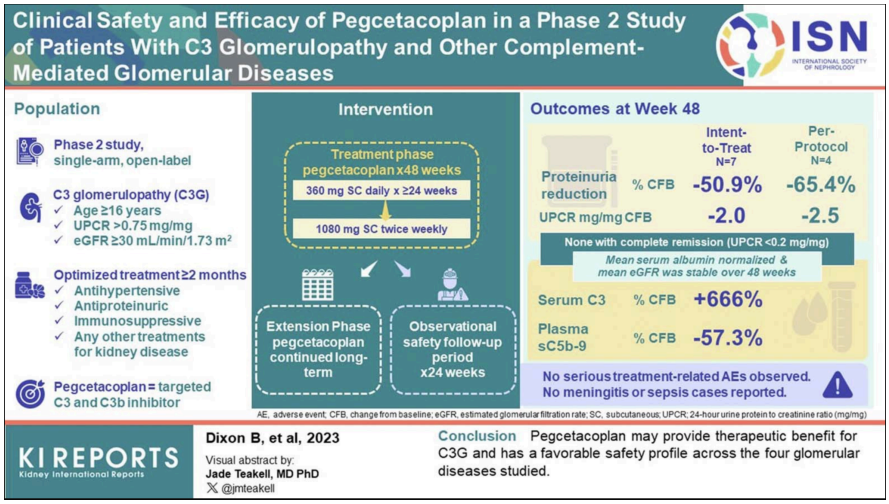
⚡(phase 3 clinical trial)- more information about the trial is found in the article: https://www.kireports.org/article/S2468-0249(23)01470-5/fulltext

9b/⚡Primary endpoint is proteinuria reduction that are highlighted in the VA by @jmteakell.

⚡seen in 50% from 3.3 mg/mg to 1.2 mg/mg

⚡complement level improved

⚡no severe adverse events

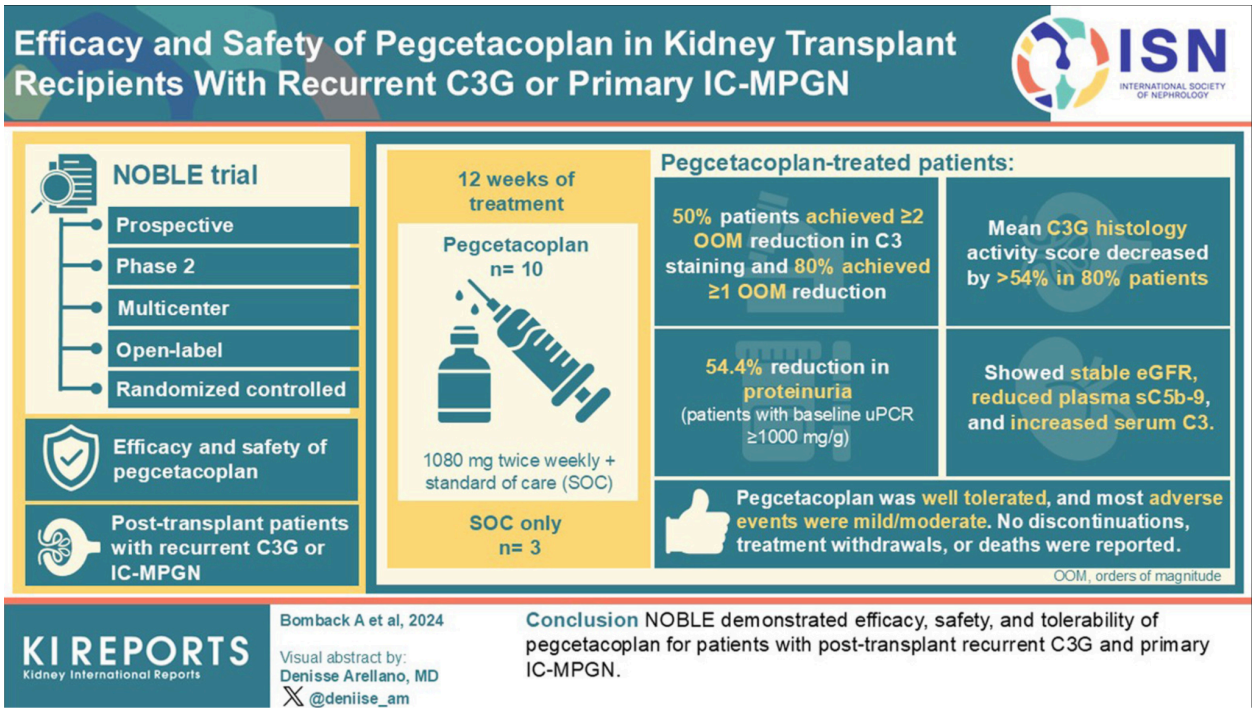


9c/NOBLE trial

https://www.kireports.org/article/S2468-0249(24)01961-2/fulltext

⚡phase 2 trial looks at efficacy and safety with posttransplant C3GN or IC-MPGN

⚡Outcomes: reduction of C3c in kidney biopsies after treatment, reduction in proteinuria, reduction in C5b-C9 and increase in serum C3 which are highlighted in the VA by @deniise_am



10/Iptacopan

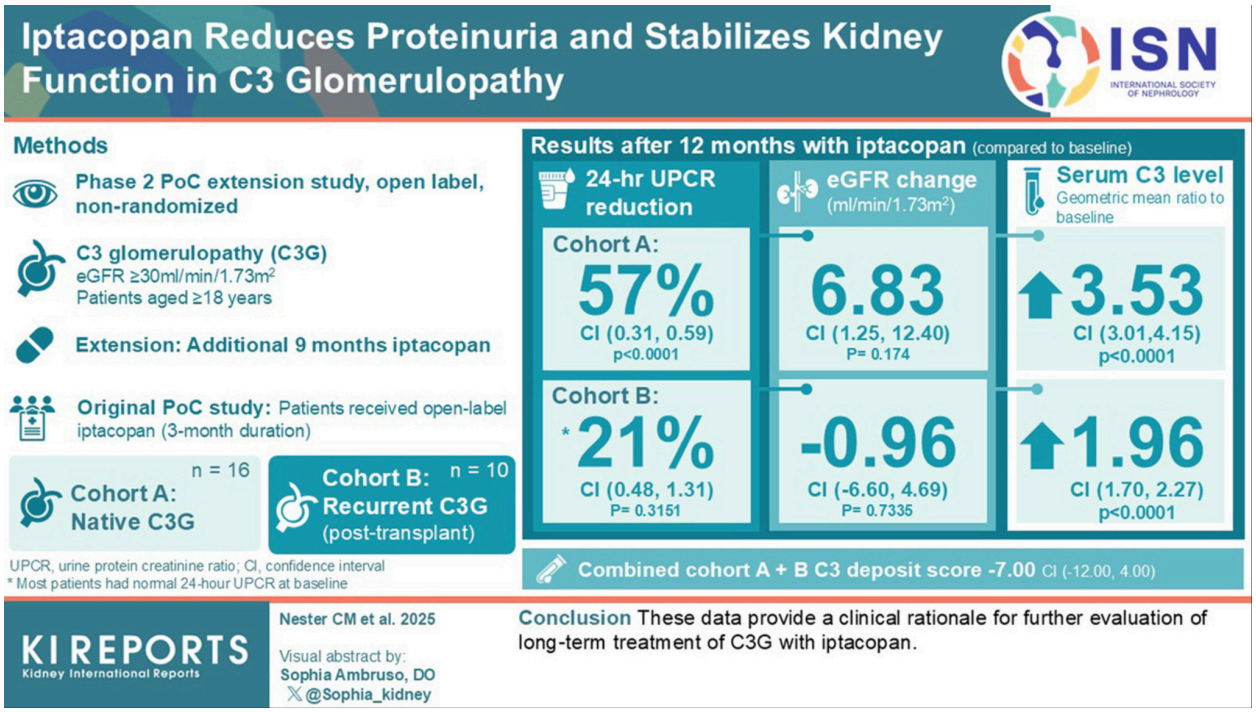
⚡oral small molecule that inhibits Factor B enzymatic activity

⚡Factor B is important factor and its breakdown product Bb has proteolytic activity on C3 convertase and C5 convertase

⚡Iptacopan suppresses both convertases therefore regulates both the upstream and downstream alternate pathway

10a/ ⚡Link to the Iptacopan study:
https://www.kireports.org/article/S2468-0249(24)01989-2/fulltext

The below VA by @sophia_kidney expands upon the key features of the study



11/Danicopan

⚡factor D inhibitor

⚡factor D catalyzes the cleavage of the Factor B and thus limits C3bBb production

⚡studies have shown that factor D inhibition allows for alternate pathway complement suppression

11a/Danicopan (cont)

2 phase 2 studies

⚡studies were discontinued because of
⚡lack of optimal systemic concentrations
⚡ lack of sustained inhibition ->limited and inconsistent clinical responses in participants.

:https://pubmed.ncbi.nlm.nih.gov/36404708/

12/Vermircopan (ALXN2050, ACH-5528) oral factor D inhibitor that is in phase 2 trials for Lupus Nephritis and IgAN but not currently for C3G

13/NM8074
⚡humanized monoclonal Ab that targetC3/C3 convertase axis by binding to the Bb and blocking the catalytic activity
⚡currently being tested in its IV formulation in a phase 1b/2a trial
Primary outcomes include change in UPCr, albuminuria, and adverse effects
⚡some trials for PNH and TMA

14/Another mechanism of action for some of the new agents is C5/C5 convertase inhibition

The terminal pathway activity plays a role in the phenotype of the C3G disease process
⚡i.e C5 nephritic factor is seen with C3NeF in those with C3G more than DDD

15/The terminal pathway axis involvement is correlated with disease severity
⚡C5b-C9 intense deposition in kidney biopsies correlates with the C3G

16/Eculizumab
⚡humanized monoclonal antibody that targets the C5 epitope
C5 epitope is involved in binding alternate pathway C5 convertase, C3bBb3b, blocks cleaving of C5 into C5a and C5b -> avoids the MAC complex formation

17/Avacopan

⚡oral small molecule which is a C5a receptor antagonist that inhibits the C5a binding to its receptor C5aR1
⚡C5a is a anaphylatoxin and increase vascular permeability, induces oxidative bursting and proinflammatory release thereby having a chemotactic effect on myeloid and lymphoid cells

18/Many trials are ongoing. Some challenges are present.

⚡identifying which patient populations would benefit from these novel therapies (ie. those who carry poor prognosis)

⚡understanding which therapy works for which patient population

⚡lack of long term safety profile data

19/

⚡Complement inhibition appears to show promising results

⚡Further trials and studies are needed to elucidate which therapies work in which situations

⚡an interdisciplinary approach that includes kidney biopsies, genetic testing, phenotypic testing, etc

20/ That was so interesting and we can't leave without testing your knowledge?

Which complement pathway is affected mainly in C3G ?

1. Lectin
2. Alternate
3. MAC

21/ The answer is Alternate Pathway. We hope this #tweetorial has increased your knowledge on C3G and the emerging therapies. Please share this #tweetorial with your followers and friends!

22/Thanks to @SaiAchi1 for authoring & @brian_rifkin, @MChanMD @sophia_kidney for great feedback! #FOAMed #nephtwitter @ISNkidneycare @KIReports