KIDNEY KOLUMNS

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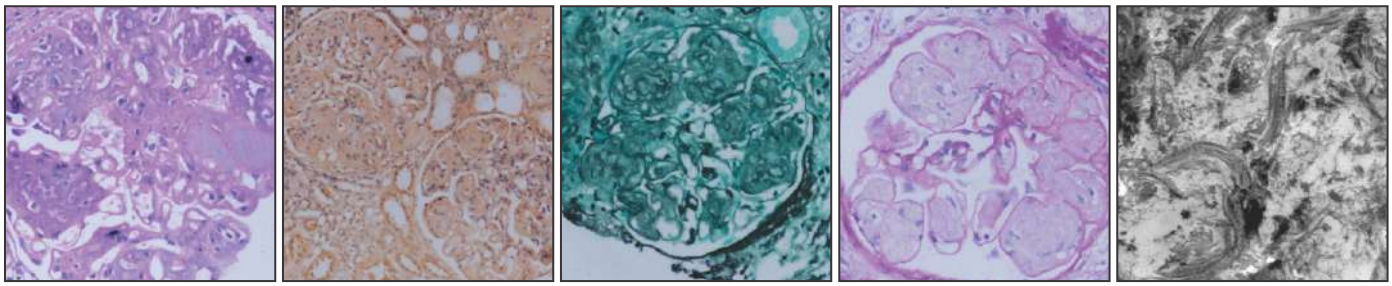

Dear Readers,

Here's wishing everyone a happy and healthy 2025. Welcome to the latest edition of Kidney Kolumns! This time we've focused on IgA nephropathy, in the news of late for a spurt in quality RCTs involving multiple new therapeutic options, a rarity in nephrology. As research progresses, we are gaining a deeper understanding of its pathophysiology, leading to innovative therapies and improved outcomes for our patients. Through this edition, we aim to provide clinicians, researchers, and students with a summary of the latest strategies and management paradigms for this complex disease. The Crossword Quad has another banger waiting for you. And though its not an outlier, the Stats explainer should have your whiskers up.

We are also thrilled to announce that preparations are in full swing for the World Congress of Nephrology 2025. This prestigious event promises to bring together leading minds from across the globe, fostering collaboration and innovation in kidney care. We look forward to seeing you there as we collectively advance the frontiers of nephrology. As always, we welcome your thoughts and feedback at education@isn-india.org. Your engagement and ideas help shape this platform into a valuable resource for the nephrology community.

Happy reading folks!!!

Regards

Editors - in-Chief

Inside

KIDNEY KOLUMNS

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COVER IMAGES : A Case of Collagenofibrotic Glomerulopathy

Light microscopy : Glomerular tufts shows marked mesangial expansion due to deposition of extracellular material which is PAS negative and weakly positive on silver methanamine. Congo Red is negative (figure 1- H&E 20x, Fig 2- Congo red 10x , Fig 3- SM20x, Fig 4- PAS20x)

Electron microscopy : Expansion of subendothelial and region with irregular bundles of fibrillary material which show a banded appearance and periodicity of 40-60 nm. Significant 50-60% foot process effacement (Figure 5)

Credits

Case Credits : Dr Sahil Arora, Interventional Nephrology Fellow , INU, Bengaluru
Photo credits : Dr Ranjit Kumar and Dr Alok Sharma, Lal Path Labs

Hon. Secretary's Message

Dear Members,

I extend a warm welcome to all joining the WCN 2025, which is happening for the first time in Delhi, India. I hope you are reading this newsletter in the Indian SN booth at WCN. Let me take this opportunity to highlight some activities of our society in the last year, particularly in the last quarter-

1. **Indian Society of Nephrology:** In the last 2 years, the Indian SN has grown tremendously. We have been able to make more than 700 new members in the previous 2 years, and our current membership has reached 2700, which is an increase of more than 30%. With this, our society has become one of the largest societies in the world of nephrology. This has been possible due to the renewed interest of Indian nephrologists to join the society due to various activities and benefits society provides. Currently, approximately 400 new nephrologists qualify in India per year. Our mission is to make every qualified nephrologist a member of society and make Indian Society one of the best in the world. If someone is not getting messages from the secretariat despite being a member, kindly check your spam mail or mail me at drshyambansal@isn-india.org.If any of your colleagues are not members yet, it is easy to register online through our website, www.isn-india.org**,** go to the registration page, and pay the amount directly online. You can deposit your money **using the account number. I am also sharing a QR code** at the end of the message.

2. **World Congress of Nephrology**- As you know, The World Congress of Nephrology 2025, co-hosted by Indian SN and ISN, is happening in Delhi from 6th-9th February in Yashobhoomi Convention Centre Dwarka. I want to thank our members for their enthusiastic participation in WCN. **According to the latest figures, approximately 50% of total registrations (1500/3000) are by Indian society members, and similarly, 50% of all abstracts (750/1500) are submitted by our members**. This time, the contribution of Indian SN in supporting WCN has been tremendous, and approximately 70% of all industry contributions are from India, which speaks excellent about the power of Indian Nephrology on the world stage.

3. **The partnership with European Renal Association**: The Indian SN has renewed its agreement with ERA where members of Indian SN would continue to get a discounted membership of 500 INR only, and they would get all the benefits of membership of ERA, including discounted registration for the ERA congress and journals of ERA- NDT and CKJ. Many members have availed of this benefit; I would request every member of Indian SN to avail of this discounted membership of ERA to keep the membership rates low.

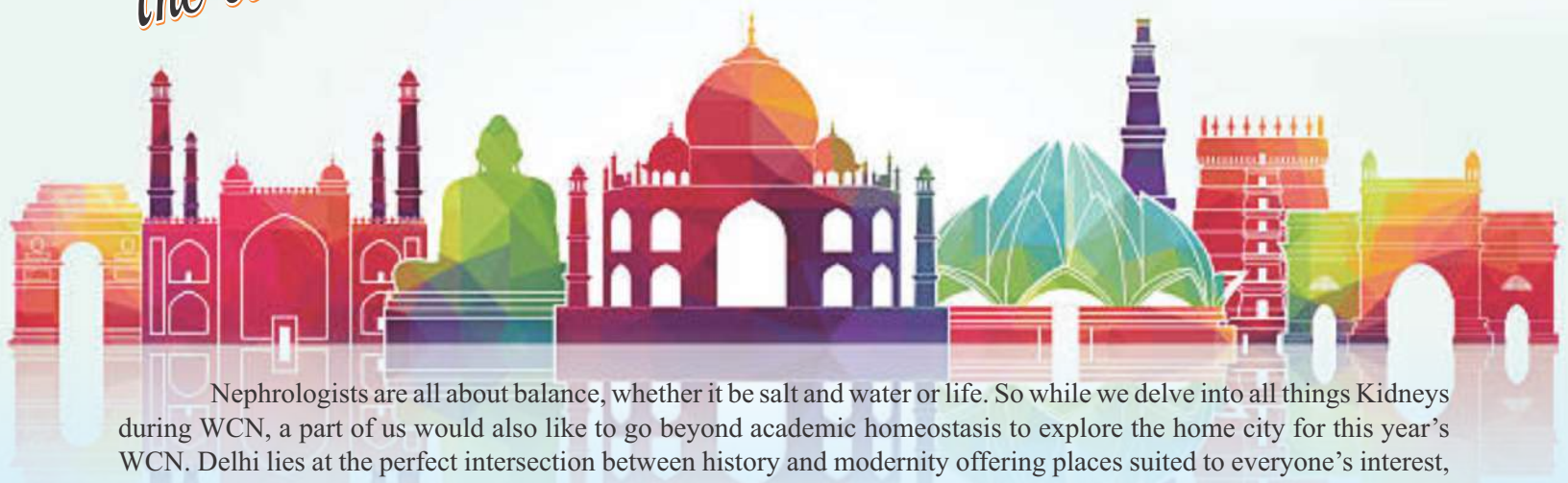
4. **Indian SN Activities**: The society is actively involved in various educational activities. Apart from Webinars, monthly Journal club and quarterly newsletter of Society `The Kidney Kolumns`, the society has started two new activities, i.e., the awaited **Clinical case discussion**, which was attended by > 350 students both times. This was done on the Indian SN webinar platform, and I thank our Scientific committee chairman, Prof N Gopalakrishnan, for initiating this activity. We invite senior teachers if they are interested in doing such classes. The second initiative was taken by our social media team, starting **Kidney Conversations,** where a series of interviews with senior members of society about their contribution and experience is well received, especially by young members.

5. **ISNCON 2025 Lucknow**: It gives me immense pleasure to announce that the **Annual Conference of the Indian Society of Nephrology (ISNCON) 2025** will be held in the historic and vibrant city of **Lucknow, Uttar Pradesh**, known for its rich cultural heritage and warm hospitality. The conference will be held under the leadership of our Dynamic organising secretary, Prof. Narayan Prasad. **The dates of the meeting shall be 18th-21st December 2025**. This year, we will have **workshops on 18th December** on **Histopathology, Critical care Nephrology, POCUS, Intervention Nephrology, Pediatric Nephrology and Transplant Immunology at SGPGI Lucknow, along with a** regular conference program. We will have renowned speakers across the globe to share their research and expertise. More details regarding registration, abstract submissions, and the scientific program will be shared soon. Please mark your calendars and stay tuned for updates.

Looking forward for your suggestions and Feedback

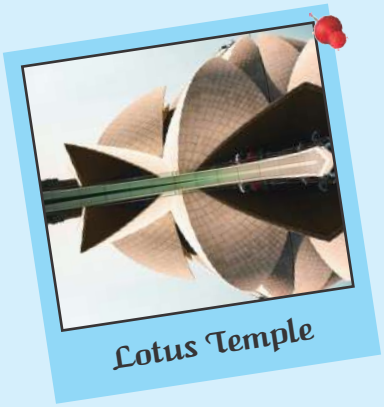
Warm regards,
Shyam B Bansal
Hon. Secretary Indian Society of Nephrology

The Ultimate Guide to Discovering Delhi During WCN25



Nephrologists are all about balance, whether it be salt and water or life. So while we delve into all things Kidneys during WCN, a part of us would also like to go beyond academic homeostasis to explore the home city for this year's WCN. Delhi lies at the perfect intersection between history and modernity offering places suited to everyone's interest, whether you're a history buff, shopaholic or a foodie. This article, a collaboration between a lifelong Delhiite and an occasional visitor from Southern India, offers a curated list of sights and haunts in this vibrant city - some are old gems but some are places you won't find on typical travel websites. And it's perfect for exploring during the limited time you have beyond the conference. (For those who don't know: t 5th February is Election Day in Delhi, so make your plans accordingly as some places might be closed that day).

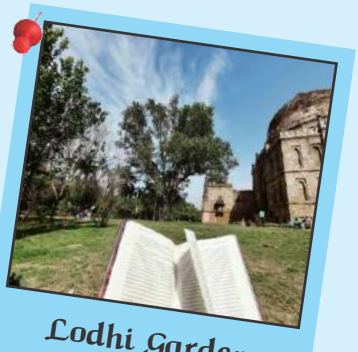
And before we dive in, let's address the smoggy cloud hovering above us. While the staunch Delhiite here claims that the reports of Delhi's poor air quality are overexaggerated, keeping masks handy for outdoor activities would be a smart move. Thankfully, early February brings us cool and pleasant weather and a light jacket should suffice - leaving plenty of room in your luggage for all the shopping.



Lotus Temple

Timeless Treasures - Must-see for the first time visitor and some hidden gems :

- **Qutub Minar -** Don't miss it at night where it's lit up to shine like a star in the sky. At 22km from the WCN venue, it's the perfect night escape
- **Lal Quila / Red Fort -** 30km from Yashobhoomi (IICC). This UNESCO world heritage site is a shining example of Mughal architecture. The sound and light show in the evening is a spectacular narration (in both English and Hindi) of the evolution of the city of Dilli
- **Humayun Tomb -** 28km from IICC. A relaxing visit to this architectural wonder should be on our sightseeing card. Bonus: Plant lovers can wander to Sundar nursery and snag some organic goodies from the shopping stalls on Sundays.



Lodhi Garden

- **Lodhi Garden -** 26km from IICC. Perfect picnic spot with instagrammable Mughal-era vibes as well as a touch of tranquility
- **Hauz Khas Village -** 24km from IICC. How do you describe a site which has modern restaurants and pubs entrenched between historical monuments, a lake, a deer park and gardens? "The National Capital of ethnic chic" seems apt.
- **Lotus Temple -** 28km from IICC. This Bahá'í House of Worship is an architectural gem which offers a calm retreat amid the bustle of the city
- **Akshardham Temple -** 35km from IICC. A massive temple for the modern times which could easily take your entire day if you get lost in deciphering its intricacies

- **Agrasen ki Bawli -** 27km from IICC. A historical stepwell that you can drop by in the middle of a shopping expedition to Connaught place
- **Jama Masjid -** 30km from IICC. One of the largest mosques in India, its stunning red sandstone and marble facade are standouts.
- **Gurudwara Bangla Sahib -** If you want some quiet time in midst of bustling Connaught place. This ivory shrine with its golden dome and tall flagpole can be seen from far. There is a holy water reservoir inside and you can sit there for some quiet thinking and some spiritual peace.Prayers inside are open for all, but head should be covered (headgear/scarf available free at entrance) and would be good to dress in modest clothing with knees and shoulders covered.
- **India Gate and Rashtrapati Bhawan -** 26km from IICC. These iconic landmarks are definitely worth a visit to take in the scale of the enormous republic of India. The Mughal gardens are open to the public only for a few months in winter (Yes, you're lucky!) as you get to experience the majestic gardens as the President of India does.
- **Sanjay Van (van = forest) -** 23km from IIC. There is always a nature lover-slash-bird watcher in any group who somehow convinces everyone to go on a nature stroll. So, if you have packed in your binoculars, then this is the spot to visit. Preferably find a local guide to cover the routes in this 443 acre green space.
- **New Delhi World Book Fair :** For all the book worms (we know there are many amongst our readers), this international book fair is on at Bharat Mandapam, Pragati Maidan from 1st-9th Feb 2025 from 11am-8 pm.


India Gate

Retail therapy - To splurge or to haggle, is the question :

This truly is the most chaotic but exciting of adventures that the city has to offer where you can flit between glitzy malls offering the best of luxury goods and then find yourself trying to find the best bargain in bustling markets. Whether you're in the mood to be rich (or pretend to be) for a day or enjoy the thrill of a hunt, here are some of the best places you can get lost in.

- Luxury lane (Warning : Could make your credit card cry!)
  - Ambience mall, Gurgaon
  - **Triple mall of Vasant Kunj -** Ambience Vasant Kunj, DLF Promenade, DLF Emporio
  - **Saket District Centre -** Select Citywalk, DLF Mall, and Shoppers Stop – three malls in one location.
  - **Worldmark Aerocity -** For a last splurge just before boarding your flight
  - **Connaught Place -** For those who find mall-shopping claustrophobic, this allows us to walk in and out of shops while taking in the city's sights and sounds. Check out the famous central park when in need of a break.
- Ethnic stuff (For the selective buyers on the lookout for something truly unique)
  - **Delhi Haat -** For handicrafts and weaves from all over India. Also head here for delectable cuisine from each state of India. Can bargain if brave enough.
  - **Emporiums on Baba Kharak Singh Marg -** bordering Connaught place, can find sarees, handlooms ,carpets, art and craft from across India at fixed prices.
  - **National Cottage Emporium at Janpath -** treasure trove of Indian handicrafts and textiles, where prices are fixed but still reasonable
  - **Dastkar Haat, Gurgaon Delhi Highway -** Handicrafts galore! A polite "Aur thoda kum?" ("a little less?") can be trialled for a bargain.


Dilli Haat

- **Greater Kailash -** For the first-time India visitors looking for ready-made blouses to pair with your sarees. You can take your pick between either the bling or understated collections.
- **Nalli's -** For the traditional South Indian sarees straight out of a movie.
- **Shahpur Jat -** For the best boutiques for trendsetters looking for Indo-western wear


Connaught place

- Shopping sprees (Pro tip: Wear your comfy shoes and be prepared to bargain)
  - **Sarojini Nagar Market -** clothes, shoes and bags at prices that seem so low that you end up emptying your wallet
  - **Janpath -** The cooler version
  - **Banjara Market -** for furniture, quirky interior decor and vintage finds
  - **Lajpat Nagar Market -** Don't forget to try Dolma Aunty momos, the most popular momos in Delhi
  - **Chandni Chowk -** whatever we say about this place, it will never be enough. Each street sells a different product from Rs 100 to Rs 10 lakh, depending on how much you want to shell out. Clothes, jewellery, spectacle frames… you name it, you get it there. Also you will find the best dry fruits and spices at Khari Baoli
  - **Majnu Ka Teela -** Tibetan market for winter clothes and awesome Tibetan food !
  - **Humayunpur -** For stylish, trendy Western wear at reasonable prices (and some mouthwatering cuisine from the north east!)

Foodie Trails :

Street Food Delights :

Take your taste buds on a wild ride through the Delhi street food scene. Warning to foreign delegates: You need an Indian GI system to truly appreciate this culinary adventure. But, if you are in for it, here are some places to try. Just be sure to pace yourself.


Kuremal Kulfi

- Parathe wali gali in Chandni Chowk
- Natraj ke dahi bhalle
- Rajinder dhaba - Tandoori chicken, Afghani Chicken
- Karim's at Chandni Chowk for everything Mughlai
- Changezi chicken at Daryaganj and Chicken Chaat from Nandlal ka Dhaba Daryaganj
- Golgappe (stalls anywhere and everywhere on the streets!)
- Kulfi from Kuremal Mohanlal Kulfi Wale. Unfortunately, the mango kulfi will not be available in winter months
- Chuski (Kaala Khatta is my personal favourite) at Lajpat Nagar Market
- Keventer's for best cold coffee and shakes in Connaught place. Hidden gem is Depaul's at Janpath for the same things + momos and snacks
- Stuffed Parathas (try chicken and keema paratha!) at dhabas near Sanjay Van


SIDECAR-the bestest pub !

Restaurant Food :

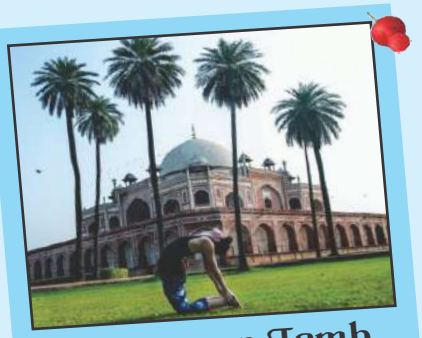
When you want to make the switch to seated dining, here are some spots.

- **Sidecar -** For those interested in some of the finest cocktails (Be it the classic cocktails or the ones with a twist, this place will blow your mind!), you must head to this amazzzzzing pub in Greater Kailash 2 (M block market). Also has delectable coffee and cuisine from across the world. Did we tell you that they are #26 on the

best 50 pubs list in the WORLD!

- **DLF Cyberhub Gurgaon -** A foodlover's dream with cuisines from world over- head here for the best cafes, pubs and restaurants
- **Worldmark Aerocity -** For Indian, visit Moti Mahal Deluxe, Dhaba Est 1986, Monsoon
- **Indian Accent and Masala library -** need prior appointment
- **Bukhara at ITC Maurya -** best for Kebabs and Mughlai
- Haldiram's/Bikanerwala for delegates interested in trying chaat and street food (but not on the streets). Don't miss RajKachori and Pav Bhaji
- **Carnatic Cafe -** for Karnataka special South Indian cuisine. Also try interesting ice cream flavours by Jatre either in same cafe or separate outlet nearby
- **Gulati's family restaurant -** for all things North Indian and yummy!

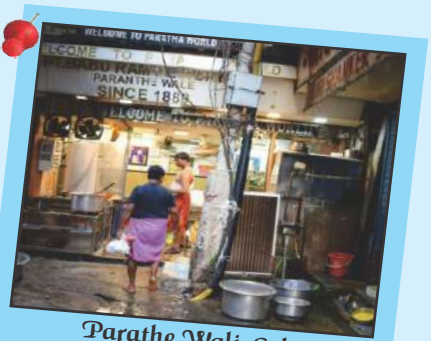
WCN isn't just a place to glomerulate around Nephrology, it is also a place to meet friends as well as future mentors and research collaborators. It also gives a chance to explore a new city in a different country each year. While our kidneys work tirelessly 24x7, our minds deserve some rest and relaxation. So, a little 'clearance' of your time to immerse yourself in the local culture may just be the answer. We have got you covered with an exhaustive list of hotspots to checkout. While just reading this list might have tired you out, we hope that you find this writeup useful enough to bookmark for this and future visits to Delhi.



Humayun Tomb

Central ridge mehrauli reserve forest and qutab minar

Jalebi Wala AtChandnChowk



Parathe Wali Gali Chandni Chowk

Sandhya Suresh & Pallavi Prasad

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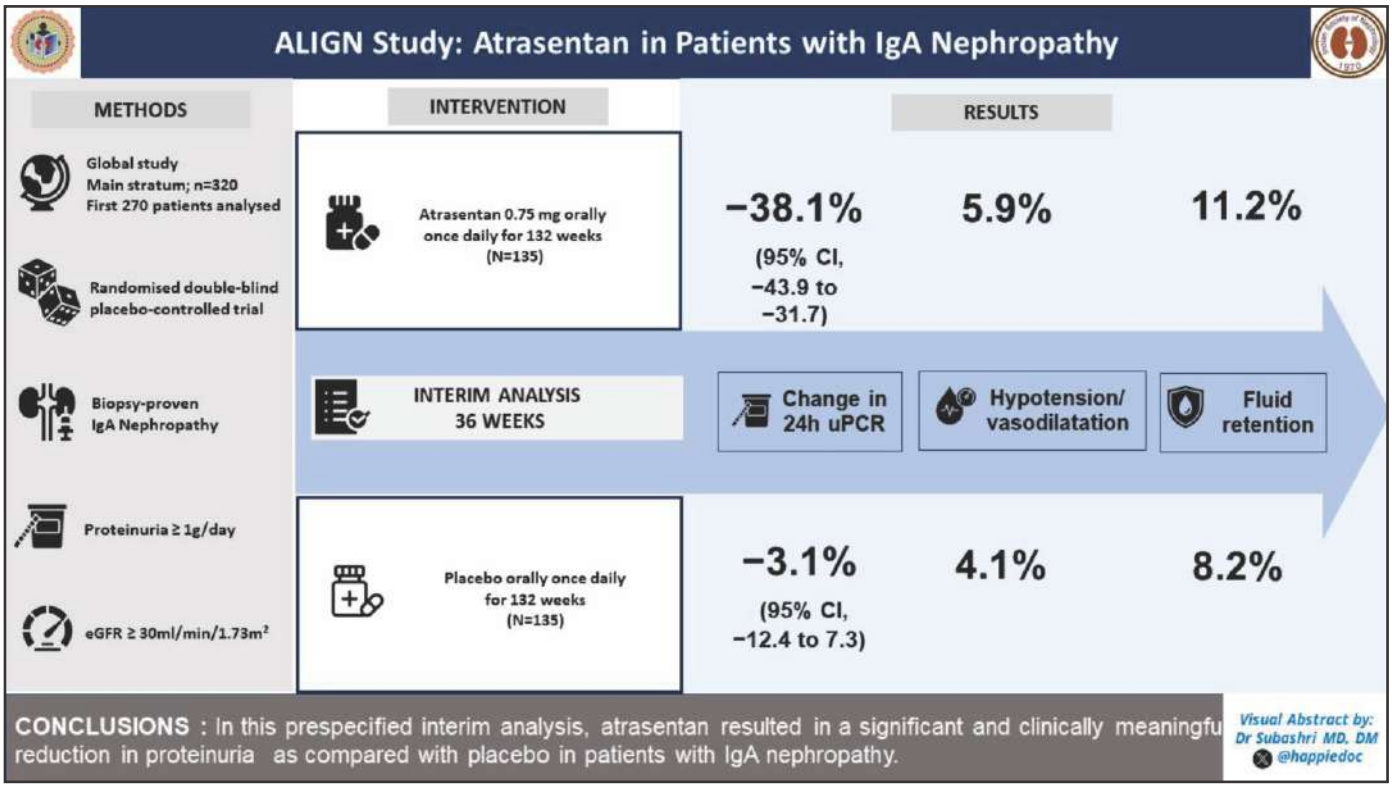
Align trial – Atrasentan for IgA nephropathy, a new kid on the block?

Role of endothelin, especially the mesangial ET-1, in the pathogenesis of IgA nephropathy is multifold, mediating podocyte dysfunction and proteinuria, tubulointerstitial injury and atrophy, mesangial cell injury, proliferation and fibrosis, efferent arteriolar constriction contributing to increased intraglomerular pressures. This has led to a search for endothelin receptor antagonists (ERA) which could potentially prevent Galactose deficient-IgA (Gd-IgA) mediated renal damage, specifically the Endothelin A receptor subtype. AFFINITY trial had already demonstrated Atresentan as an add on to optimised dose of ACE inhibitor or ARB, decreased proteinuria at 12 and 24 weeks and reduced risk of composite renal outcome of doubling serum creatinine or renal failure. Evidence for ALIGN trial also come from SONAR trial studying type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD) patients which showed 34% reduction in albuminuria and 35% reduction in composite kidney outcome.

ALIGN a multicentre (133 sites and 20 countries), randomised, double blind, placebo controlled trial included biopsy proven IgAN ≥ 18 years, who were already receiving optimised treatment with ACE inhibitor or ARB (main stratum n=340) and also patients on SGLT2 inhibitors (Exploratory SGLT2 stratum n=64), with a eGFR ≥30ml/min per 1.73m^2. Diabetic CKD and other causes of CKD, suspicion of IgA vasculitis, and rapidly progressive glomerulonephritis were excluded. The objective was to see if the addition of 0.75mg atrasentan orally to supportive care (maximum tolerated ACE inhibitor and ARB) was superior to placebo (1:1 randomization), at 132 weeks, in reducing proteinuria and eGFR decline in patients who have a proteinuria ≥ 1 gram/day.

ERA can cause acute reduction in eGFR which will not reflect true progression of CKD, and it was noted that discontinuation of therapy resulted in reverting to the original eGFR. Hence after treating for 132 weeks, analysis was done after a period of 4 week washout to know the original benefit of the drug. The major problem with ERA is fluid retention, increase in BNP, and precipitation of heart failure symptoms, as evidenced by ASCEND trial which studied Avosentan (non-selective ETA) which resulted in high mortality and early discontinuation of study. Dose finding studies of Atrasentan found a dose of 0.75mg which has maximal antiproteinuric effect which is a much lower dose that the one precipitating heart failure symptoms. SONAR trial (studied CKD and diabetes) used this dose and yet found increased edema and fluid retention in atrasentan group. Likely risk factors were older age, presence of DM, risk factors for cardiovascular disease. As patients with IgA



nephropathy were relatively younger and non-diabetic, had lesser cardiovascular risk, the incidence of heart failure is expected to be lower, as already evidenced by AFFINITY trial IgAN cohort.

ALIGN represents a cohort with a better Asian and female population compared to PROTECT (Sparsentan) and NEFIgARD (targeted release budesonide) trials. Also PROTECT studied the effect of combined Endothelin and angiotensin receptor antagonist Sparsentan which needed discontinuation of ACE inhibitor and ARBS but ALIGN studies add on the effect of atrasentan which can translate to better clinical practice as most patients are already on ACE inhibitors or ARBS. Regarding SGLT2 inhibitor use, this trial studies 64 patients, but another trial, ASSIST which is a crossover study of SGLT2 inhibitor and Atrasentan is likely to give a better picture.

In ALIGN trial, the interim analysis suggests that the geometric mean UPCR changed -36.1 percentage points in Atrasentan group compared to placebo at 36 weeks ($p<0.001$). The change in blood pressure from baseline was -3.94±11.90mmHg systolic and -4.25±8.96mmHg diastolic in atrasentan group. Change in body weight was only 0.2±2.8kg and BNP levels were 4.0±23.9 pg/mm in atrasentan group. Hence, major adverse effects were similar in atrasentan and placebo groups. Anemia, fluid retention, hypotension were reportedly more in the atrasentan group compared to placebo.

The complete results of the study are expected in the first quarter of 2026, and we shall find out if this is a promising molecule for the treatment of IgA nephropathy.

Dr Vivek K Koushik
Consultant Nephrologist,
Prashanth Hospitals,Kolathur Chennai

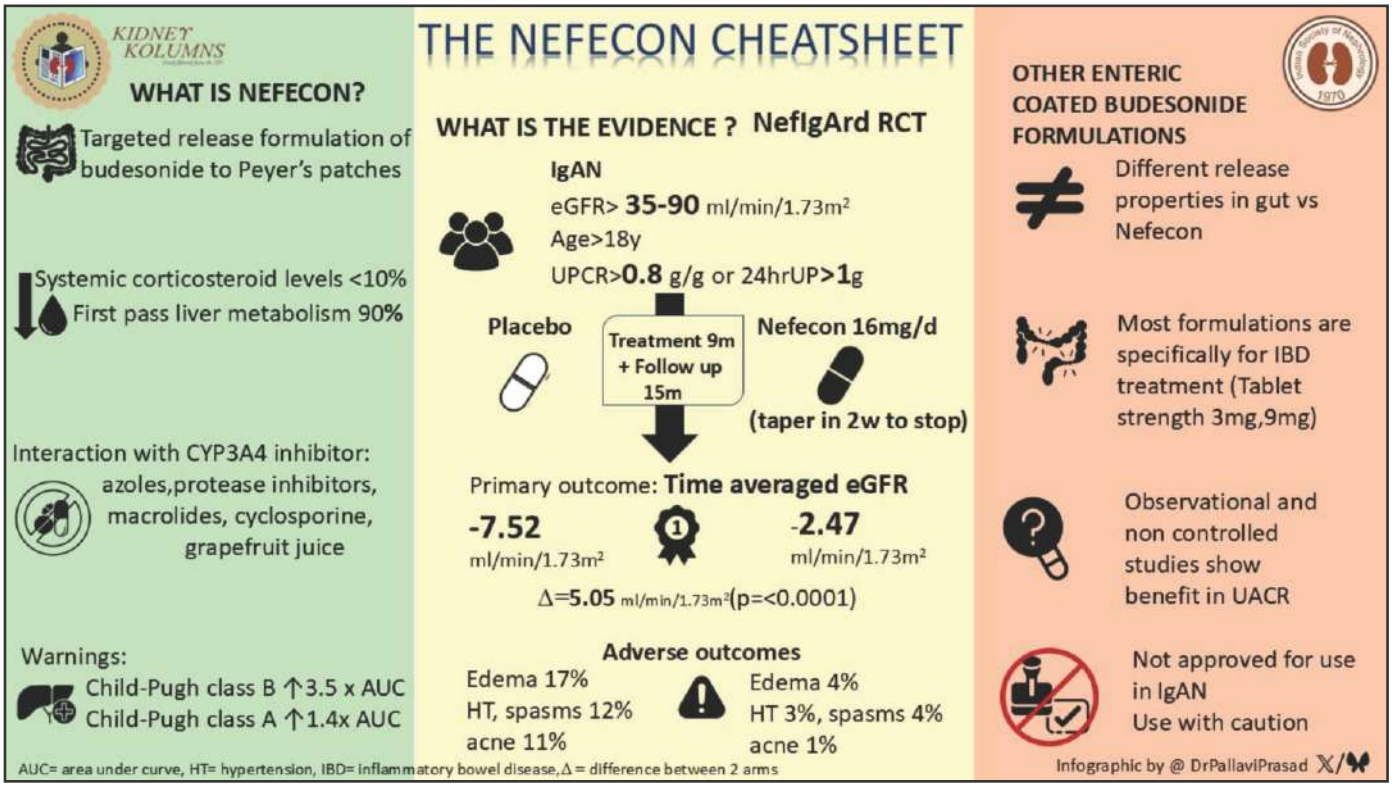
"Nefecon in IgA Nephropathy : A New Frontier in Disease Modification"

The current treatment of IgA Nephropathy focuses on RAS blockade and blood pressure control, the use of corticosteroids remains debated due to mixed results from STOP IgAN, TESTING, and low-dose TESTING trials.Nefecon, is an oral, targeted-release capsule formulation of budesonide, designed for medication release in the distal ileum for maximal exposure of the B-cell-containing Peyer's patches. Budesonide's action theoretically aligns with four major hits of IgA Nephropathy (IgAN) as it suppresses the production of abnormal galactose deficient IgA1 antibodies from the Gut associated lymphoid tissue (GALT).

NefIgArd is an important milestone in the timeline of major breakthroughs in treatment of IgA Nephropathy. This randomised double blind trial compared Nefecon 16 mg/day with matching placebo administered for 9 months followed by a 15 month observation period in patients 18 years or older with biopsy proven IgA nephropathy and persistent UPCR >0.8g/g and eGFR 35 – 90 ml/min/1.73m^2 despite optimised supportive care. Notably, these patients should not have received systemic steroids or other immunosuppressant 12 months prior to randomisation. The trial used a novel surrogate primary efficacy endpoint i.e the time weighted average eGFR over 2 years. Secondary efficacy endpoints included the time to kidney failure or eGFR reduction of 30 % and the safety endpoints included the treatment-emergent adverse events.

The time-weighted average eGFR difference was 5.05 mL/min/1.73 m² ($p<0.0001$). Proteinuria reductions were sustained, and the time to a confirmed 30% eGFR reduction or kidney failure was significantly delayed (HR 0.45). Benefits were consistent across subgroups, irrespective of baseline proteinuria levels. The most common treatment-emergent adverse events with Nefecon included peripheral edema (17%), hypertension (12%), and muscle spasms (12%), which were mostly mild and reversible. Serious infection-related events occurred in 3% of Nefecon patients and 1% of placebo patients.

Nefecon, costing approximately $150,000 for a 9-month treatment, may face limited use due to its high cost and lack of clear evidence of superior efficacy over low-dose steroids especially in LMICs. Other treatments



for IgAN, such as low-dose steroids, sparsentan, and flozins, show promise (the evidence for which was available after this study was designed) , but the best treatment sequence is still uncertain. Experts suggest using immunological therapy early for lasting remission, but whether Nefecon or low-dose steroids should be prioritized remains unclear. Flozins could complement background therapy with RAS inhibitors before steroids. The FDA has approved Nefecon, but without a head-to-head comparison, the relative benefits are unknown. Cost and access will likely dictate therapy choices. As new therapies emerge, a multitargeted approach is expected in the future. In addition, a word of caution needs to be mentioned. Controlled-release Budesonide preparations are available in India; however, it is important to note that these are not the same as the targeted-release formulation studied in clinical trials. The molecule evaluated in these trials, Nefecon, is a targeted-release preparation, and its cost may be prohibitive if launched in India. Given this, the alternative controlled-release preparations available locally warrant exploration to determine whether they provide similar benefits to those demonstrated by the original molecule. Indian studies and the clinical experience of Indian nephrologists should be thoroughly discussed to evaluate the utility of these alternatives. Furthermore, a comparative analysis against systemic corticosteroids is essential to establish their relative efficacy and safety profiles.

Dr Jeyakumar Meyyappan
Assistant Professor
Department of Nephrology
SGPGIMS, Lucknow

INSIGHTS FROM IGAN TRIALS- BEYOND TESTING

Non-immunomodulatory

PROTECT

Drug: Sparsentan (dual endothelin-angiotensin receptor antagonist)

Target: ETA and AT1 receptors

Result: UPCR reduction at 36 weeks compared to irbesartan and improved kidney function over 2 years.

Dose/Route: 400 mg orally, once daily

Duration: 36-week treatment, with up to 2-year follow-up

Status: Trial completed.

ALIGN

Drug: Atrasentan (Endothelin Receptor Antagonist)

Target: Endothelin pathway

Result: UPCR reduction

Dose/Route: 0.75 mg orally, per day.

Duration:132 weeks

Status:
Phase 3, double-blind, RCT

ENVISION

Drug: Sibeprenlimab (Anti-APRIL)

Target: APRIL pathway (reduces IgA-producing B-cells)

Result: UPCR Reduction

Dose/Route: 2/4/8 mg/kg IV monthly

Duration: 12 months

Status:
Ongoing Trial for assessment of efficacy

Immunomodulatory

NEFIGARD

Drug: Nefecon (modified-release oral budesonide)

Target: Gut-associated lymphoid tissue (GALT); immunosuppression in the gut

Result: UPCR reduction and slowed eGFR decline

Dose/Route: 16 mg orally, once daily

Duration: 9 months

Status: Drug approved.

APPLAUSE

Drug: Iptacopan (Factor B inhibitor)

Target: Alternative complement pathway (Factor B)

Result: UPCR reduction

Dose/Route: Between 200-400mg,orally per day

Duration: 6 months to 1 year with extended follow-ups)

Status: Ongoing

Immunomodulatory

CEMDISIRAN

Drug: Cemdisiran (RNAi therapeutic targeting C5)

Target: suppresses hepatic production of complement component 5 (C5)

Result: reduction of proteinuria at week 32

Dose/Route: subcutaneous cemdisiran 600 mg or placebo every 4 weeks

Duration: 36 weeks

Status: Phase 2 trial completed.

BEYOND

Drug: Zigakibart (Anti-APRIL antibody)

Target: APRIL

Result: UPCR reduction and reduction in serum levels of IGA at 52 weeks

Dose/Route: subcutaneous 600 mg zigakibart Q2W or placebo.

Duration: 104 Weeks

Status: Phase 3 Trial, ongoing,

ORIGIN

Drug: Atacicept (dual BAFF/APRIL inhibitor)

Target: BAFF and APRIL

Result:
UPCR reduction
eGFR stabilisation,
Gd-IgA1 reduction,
Good safety profile

Dose/Route: 25mg, 75mg, and 150mg weekly (75 and 150mg arms were combined for analysis)

Duration: 36 weeks

Status: Completed Phase 2b trial.

RUBY-3

Drug: Povetacicept (dual BAFF/APRIL inhibitor)

Target: BAFF and APRIL

Result: UPCR reduction, reduction in Gd-IgA1, eGFR stabilisation

Dose/Route: 80 or 240 mg administered subcutaneously once every 4 weeks

Duration: >/= 24 weeks

Status: Ongoing

MAIN

Drug: MMF

Target: IMPDH Pathway

Result: Reduced risk of disease progression

Dose/Route: initially, 1.5 g/d for 12 months, maintained at 0.75-1.0 g for at least 6 months),orally

Duration: 60 months

Status: Completed

Created by Dr. Urvashi Khan, (Twitter(X)-@Melgreux)

Sibeprenlimab - ENVISIONing a future direction in IgAN

IgA nephropathy (IgAN) is the leading cause of primary glomerulonephritis worldwide and remains a significant contributor to end-stage kidney disease (ESKD). Despite the availability of standard therapies, including ACE inhibitors, ARBs, and sodium-glucose cotransporter 2 inhibitors, the progression of IgAN to kidney failure continues to be a major challenge. In fact, approximately 30% of patients with IgAN will develop ESKD within 20 to 30 years, even with optimal care. The limited efficacy of current treatments to slow disease progression highlights the urgent need for disease-specific, safe, and effective therapies.

The pathophysiology of IgAN involves the production of galactose-deficient IgA1, which forms immune complexes that deposit in the glomeruli, triggering inflammation and progressive kidney damage. A key player in this process is APRIL (a proliferation-inducing ligand), a cytokine involved in regulating B-cell activity and IgA production. These insights into IgAN's molecular mechanisms have spurred the development of novel therapeutic agents targeting the underlying disease drivers. One such agent is Sibeprenlimab, a humanized IgG2 monoclonal antibody designed to neutralize APRIL activity and potentially reduce the formation of pathogenic immune complexes.
Recent findings from a phase 2, multicenter, double-blind, randomized, placebo-controlled trial investigating Sibeprenlimab in patients with biopsy-confirmed IgAN have provided promising results. This trial, conducted across 98 centers in 15 countries, involved 155 adults with IgAN and assessed the safety and efficacy of Sibeprenlimab at doses of 2, 4, and 8 mg/kg, administered intravenously once a month for 12 months. The primary endpoint was the change in 24-hour urinary protein-to-creatinine ratio, with secondary outcomes including clinical remission (defined as a reduction in urinary protein excretion to less than 300 mg per day), change in eGFR, and biomarkers such as galactose-deficient IgA1 and APRIL.

The results were encouraging, with a dose-dependent reduction in proteinuria observed in all Sibeprenlimab groups. The 8-mg dose demonstrated the most significant reduction, achieving a 62.0% reduction in proteinuria, compared to just 20.0% in the placebo group. Moreover, clinical remission was achieved in 26.3% of patients in the 8-mg group, significantly higher than the 2.6% in the placebo group. Secondary outcomes also demonstrated favorable results, with the sibeprenlimab-treated groups showing better preservation of eGFR compared to placebo, particularly in the 4-mg and 8-mg groups.

These findings not only highlight sibeprenlimab's potential to reduce proteinuria, a key marker of kidney damage, but also its capacity to stabilize kidney function. The preservation of eGFR in the 4-mg and 8-mg groups suggests that targeting APRIL and galactose-deficient IgA1 may help delay the progression of IgAN to kidney failure. Importantly, the safety profile of sibeprenlimab was reassuring, with no significant increase in adverse events or infections compared to placebo. The absence of significant lymphocyte depletion and the selective inhibition of APRIL, without affecting BAFF (another cytokine involved in immune responses), further suggest that sibeprenlimab may offer a safer alternative to traditional immunosuppressive therapies.

This phase 2 trial on Sibeprenlimab for IgA nephropathy shows promising results, but several limitations exist. The 12-month treatment and 5-month follow-up periods are relatively short, and the need for sustained APRIL suppression for long-term efficacy remains uncertain, as biomarkers returned toward baseline after treatment discontinuation. The sample size of 155 patients may not capture the full variability of IgA nephropathy, and larger phase 3 trials are necessary to confirm the generalizability of the results. Additionally, long-term outcomes and the role of concomitant medications require further investigation. While the safety profile is favorable, rare or long-term adverse events were not fully evaluated. Extended follow-up and additional phase 3 trials are essential to assess the drug's long-term efficacy and safety.

In conclusion, the phase 2 trial results offer a glimpse into the future of IgAN treatment, where targeted therapies like sibeprenlimab could provide significant benefits in reducing proteinuria and preserving kidney function. With its favorable safety profile and efficacy in early studies, sibeprenlimab represents a promising addition to the therapeutic arsenal for IgAN.

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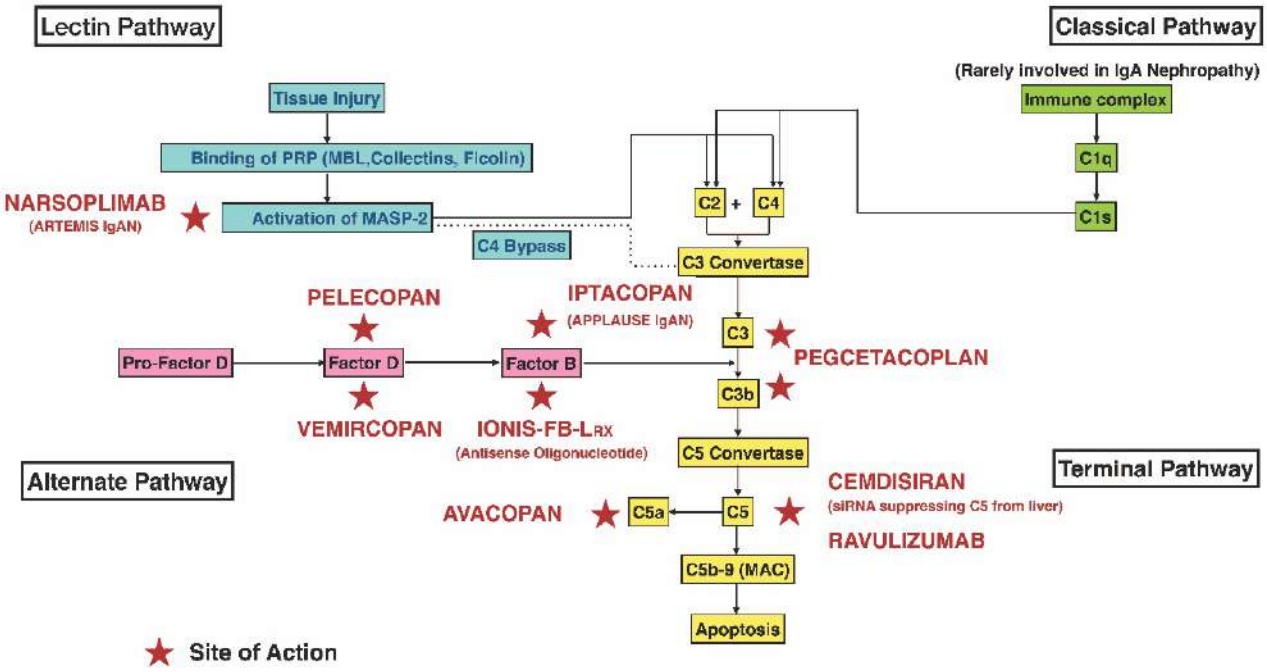
Complement Therapies in IgA Nephropathy

Complement plays an important role in the pathogenesis of Immunoglobulin A nephropathy (IgAN). Immunoglobulin A is considered incapable of activating complement. However, tissue deposition of gd-deficient IgA1-immune complexes can trigger local complement activation and facilitate glomerular inflammation. Surface-bound polymeric Ig A complexes are capable of activating complement; it has been proven that alternate complement (AP), mannose-binding lectin (MBL) pathways and terminal pathways play a significant role in the pathogenesis of Ig A nephropathy (Ig AN). The deposition of the MBL pathway and AP pathway proteins correlates well with the histological severity of Ig AN. The mainstay of therapy is the reduction of proteinuria by agents altering the glomerular dynamics. The therapeutic agents targeting glomerular inflammation are limited to corticosteroids as of now. Multiple therapeutic complement inhibitors are being tested to arrest the progression of IgAN (See Table - Complement inhibitors tested in Phase 2 /3 trials & Figure showing various sites of target in complement cascade).

The first complement inhibitor that has demonstrated favourable outcomes in Ig A nephropathy is Iptacopan; the interim results hold significant promise in expanding the physician's armamentarium. Iptacopan is an orally active agent, specifically binding complement factor B. Factor B is a cofactor for activating C3 in the alternate complement pathway. Iptacopan prevents the activation of C3 and further downstream complement activation. The trial recruited patients with biopsy-proven Ig A nephropathy (biopsy within 5 years of recruitment) with eGFR > 45 ml/min/1.73 m2 and a 24-hour urine protein creatinine ratio>1, despite optimised supportive care. Patients with eGFR 30-45 ml/min /1.73 m2 were eligible if they had a biopsy within two years, with <50% tubular atrophy and interstitial fibrosis. Eligible patients received Iptacopan 200 mg BD or placebo on a 1:1 ratio. For the main trial, 443 patients were randomly chosen from 164 sites in 34 countries. The primary endpoint was a composite that included sustained reductions in e GFR by 30% or more from baseline, e GFR< 15 ml/ ml/min/1.73 m2, shifting to dialysis, kidney transplant or death from kidney

Various Sites of Complement Blockade for the treatment of IgA Nephropathy



Infographic - Dr. Sabarinath

Trials on Complement Blockade in IgA Nephropathy

Drug	**Phase of trial /Pathway targeted**	**Mechanism**	**Recruitment criteria.**	**Results**
Narsoplimab	Phase 3- ARTEMIS IGAN MBL pathway	Human monoclonal antibody binding mannan-associated lectin-binding serine	Biopsy -proven IgAN, proteinuria >1 g/day and eGFR ≥30 mL/min/1.73 m^2	Interim analysis failed to show proteinuria reductions with Narsoplimab, hence trial stopped
Ionis FB-L_{RX}	Phase 2, single-arm, open-label Alternate pathway Phase 3- IMAGINATION STUDY - ongoing	Antisense oligonucleotide targeting complement factor B mRNA, reducing CFB production	Biopsy -proven IgAN, proteinuria >1.5 g/day and eGFR ≥40 mL/min/1.73 m^2	Geometric mean ratio reduction in proteinuria by 45%;8/10 patients had a reduction in proteinuria
Iptacopan	Phase 3 - APPLAUSE IGAN Alternate pathway	Oral complement inhibitor binding factor B	Biopsy-proven IgAN, 24 h UPCR >1 g/day and eGFR ≥30 mL/min/1.73 m^2	
Pegcetacoplan	Phase 2 - single-arm, open-label basket trial Alternate pathway	Pegylated small peptide inhibitor that binds C3 and C3b	Basket trial including complement-mediated kidney disorders - C3GN, MembranousGN, Lupus and Ig A Age >18, Protienuria >750mg/g on 24 hr collections, e GFR >30 ml/1.73m2	Ig AN cohort (n=6) –20.6 % reductions in CFB at 48 weeks in IgA N cohort
Pelecopan (**BCX9930**)	Phase 2 RENEW study Alternate pathway	Orally active small molecule binding Factor D	Basket trial including C3GN, Membranous GN, and IgA Adults >18 eGFR > 50 ml/1.73m2 >30 ml/1.73m2 with approval of the data monitoring committee Stable, maximum tolerated RASB.	Not available Drug development discontinued by 2022

Vemircopan	Phase2 double-blind placebo-controlled Alternate pathway	Orally active small molecule binding Factor D	Basket trial with lupus nephritis and IgA nephropathy	Awaited
Aro C 3	Phase 1/2a Dose-Escalating Study Alternate pathway	siRNA suppressing C3 production from the liver	Basket trial with lupus nephritis and IgA nephropathy	Recruitment completed Awaited
Ravulizumab	Phase 2: SANCTUARY study Terminal Pathway Phase 3 trial underway	Monoclonal antibody against C5	Basket trial with lupus nephritis and IgA nephropathy Proteinuria ≥1 g/d,d eGFR ≥30 ml/min per 1.73 m^2, on stable renin-angiotensin blockade	Reduction in proteinuria by 30.1% compared to placebo A trend towards e GFR stabilisation - Ravalizumab 02 ml(−2.3 to 2.7) vs -2.5 ml (−7.9 to −1.1)
Cemdisiran	Phase 2 double-blind Terminal Pathway	siRNA suppressing C5 production from the liver	18–65 years Stable, maximum or -tolerated RASB ≥3 months Urine protein ≥1 g/24 hours GFR ≥30 ml/min per 1.73 m^2	Geometric mean change in proteinuria –37.4% in cemdisiran
Avacopan	Open-label Phase 2 Terminal pathway	Selective C5a receptor blocker	UPCR >1 g/g creatinine eGF) > 60 mL/min/1.73 m2 or >45 mL/min/1.73 m2, if eGFR has not declined >10 mL/min/1.73 m2 over the previous 24 weeks.	6/7 patients who received Avacopan had reductions in proteinuria; up to 50% reductions in 3 patients

For basket trials, only recruitment criteria for Ig AN given

failure. The interim analysis focused on proteinuria in the first 250 patients who had completed 9 months with GFR data remaining blinded. Twenty patients discontinued intracompany, whereas 35 discontinued the placebo; the most common reason for discontinuation was reaching the primary composite endpoint. The median 24-hour UPCR at baseline was 1.8 (1.4-2.7) in Iptacopan and 1.9 (1.5-2.8) in the placebo group. At the end of 9 months, the Iptacopan arm showed a significant reduction in proteinuria, the adjusted geometric mean of 24 h UPCR being 0.562 in Iptacopan and 0.910 in the placebo. The proteinuria reduction was 38.3% (26-46) in the Iptacopan arm, similar to the treatment effect by Sparsentan (41%,31 -49) and higher than budesonide (27%, 13-39), a finding that is likely to translate to significant clinical benefit. Around 14 % of the Iptacopan

were on SGLT 2 blockade; the proteinuria reductions were similar. The proteinuria reduction was rapid, with effects seen as early as 2 weeks. Subgroup analysis showed similar reductions across Asia vs non-Asia, MEST-C scores, gender, proteinuria and eGFR categories. The adverse effect profile was similar, the most common being COVID-19, followed by upper respiratory infections, and no deaths were reported.

Therapies targeting the complement look like a promising future for Ig a nephropathy, the test of fire being the data on eGFR, which will be analysed later. Another pertinent question is whether complement inhibition will act as a disease modifier; leading to sustained benefits after drug withdrawal.

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Sparsentan in IgA Nephropathy : Twice the strength ; Twice the PROTECTion

IgA Nephropathy (IgAN), first recognized as a distinct entity by Berger & Hinglais (1968) is the most prevalent type of primary glomerulonephritis and a leading cause of ESRD. With 30-40% patients' progressing to ESRD, retarding the progression of IgAN remains a therapeutic challenge. The rapidly evolving therapeutic landscape for IgAN indicates lack of a single therapy of choice and possible solution lying in combination of therapies.

The Renin-Angiotensin-aldosterone pathway and the Endothelin system play an important role in the pathophysiology of IgAN, arbitrating renal injury by increasing intraglomerular pressure, inflammation, cellular proliferation and fibrosis.

Endothelin1(ET-1), the most predominant isoform, acting via ET_A receptor mediate the deleterious effects including inducing Angiotensin II (Ang II) which in addition to its own proinflammatory effects, further promotes ET-1 via positive feedback loop.

The potential benefits of endothelin receptor antagonists (ERA) have prompted trials for diverse indications like PAH, resistant hypertension, and FSGS. While trials (RADAR and SONAR with Atrasentan) showed that ERAs reduced albuminuria and CKD progression in advanced Diabetic Nephropathy, they were also associated with incidences of congestive heart failure and volume overload; ASCEND (Avosentan) had to be prematurely terminated due to a high incidence of adverse events.

Efficacy of selective ET-A antagonism in IgAN was shown using Atrasentan in AFFINITY (phase II) and ALIGN (phase III) where it showed significant reduction in proteinuria without significant severe treatment-emergent adverse events (TEAE).

Sodium and fluid retention, heart failure and hepatotoxicity remain the Achilles Heel for ERA therapy. The interaction of ET-1 and Ang II is important because while inhibiting either one reduces the other's pathophysiological effects, combined inhibition may provide greater benefits.

These trials combined maximal RAAS blockade with ERA therapy, hence the concept of dual inhibition by a single molecule emerged, leading to the development of Sparsentan, the first of dual endothelin-angiotensin receptor antagonist (DEARA).

Sparsentan was studied in FSGS in the DUET (Phase II) and DUPLEX (phase III) studies and it achieved greater reduction in proteinuria compared to irbesartan and a greater percentage of population reached the endpoint of partial remission.

Subsequent to this came PROTECT, a multicentre, randomized controlled phase 3 clinical trial comparing the efficacy of Irbesartan to Sparsentan in biopsy proven IgAN patients with eGFR > 30 ml/min/1.73m^2 and a proteinuria of > 1.0 gm/ day. Important exclusions include secondary IgAN, presence of >25% cellular crescents in biopsy. The total period of study was 270 weeks.

Primary efficacy endpoint was change in the Urinary protein-creatinine ratio (UPCR) using 24-hour collect. Secondary efficacy endpoints included chronic eGFR slope, change from baseline over time in eGFR, UPCR, UACR 24 hours protein and albumin excretion and a composite of kidney failure i.e., proportion of patients reaching a confirmed 40% reduction in eGFR from baseline, kidney failure (defined as initiation of kidney replacement therapy or sustained eGFR value of <15 mL/min per 1.73 m2), or all-cause mortality.

Total 404 patients of the 671 screened were randomized at 1:1 ratio. Analysis at 36 weeks showed UPCR reduction of 49.8% vs 15.1% in Sparsentan and Irbesartan arm respectively. This led to an accelerated regulatory approval. The benefit was sustained at week 110 (-42.8% vs -4.4% change from baseline), with Sparsentan-treated patients achieving complete remission (protein excretion <0.3 g/day) earlier and more frequently. This also translated to superiority in preservation of kidney function shown by the comparison of the chronic eGFR slope with a difference of 1.1ml/min/ 1.73m^2 per year.

Rescue immunosuppression, primarily corticosteroids, was initiated more frequently in the Irbesartan arm (8% vs. 3%). The composite of Kidney failure was reached by 9 % patients in the Sparsentan arm compared to 13 % in the Irbesartan arm.

TEAEs (Treatment-Emergent Adverse Events) were high in both the groups (Sparsentan 93% and Irbesartan 88%). TEAE frequently occurring with Sparsentan than Irbesartan were dizziness and Hypotension. However, no significant difference was seen in serious adverse effects (37% vs 35%) (AKI in 6% vs 2%) of patients. Sparsentan arm had higherbut statistically insignificant preponderance of peripheral oedema & hyperkalaemia.

Beyond primary and secondary outcomes, Sparsentan also showed benefit in exploratory analyses, with a greater proportion of patients achieving proteinuria <0.3 g/day (31% vs 11%), as achieving a proteinuria <1.0 g/day may be insufficient given the observed progressive renal failure in many IgAN patients.

The benefit was achieved despite no significant difference in between the blood pressure ranges in both arms indicating non-hemodynamic mechanisms of action.

PROTECT's representation of Asian (29%) and Caucasian (67%) populations was broad, like DAPA-CKD but unlike the geographically limited STOP IgAN trial (Germany).

The initial exclusion of SGLT2 inhibitors raises concerns about their potential interaction with the study outcomes, necessitating further analysis of the subsequent exploratory data from patients using these agents. Given that SGLT2 inhibitors are now standard of care for IgAN, further research is needed to evaluate the combined effects of ACEi/ARBs, SGLT2 inhibitors, and ERAs. Furthermore, addition of non-steroidal mineralocorticoid receptor antagonists may play a crucial role in non-immunosuppressive treatment strategies for IgAN

Despite the promising results, this study does not answer the unmet need for therapies in Advanced IgAN patients, as crescentic IgAN, eGFR< 30 ml/min/1.73m2 were excluded. Possible role of histopathological correlation and microhaematuria as an indicator of disease activity were also not evaluated.

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Clinical Associate, Kolkata Kidney Institute
Dr Pratik Das: Consultant Nephrologist,
NH-RTIICS and Kolkata Kidney Institute

BUDESONIDE CHALLENGE

To attempt this quiz online follow this link. Only one attempt per person.

Take this simple quiz to test how much do you know about the use of oral Budesonide in IgA nephropathy.

Question 1 : What is the primary mechanism of action of budesonide in IgA nephropathy?

a) Inhibition of T-cell activation
b) Suppression of the mucosal immune system
c) Inhibition of angiotensin-converting enzyme
d) Reduction of renal tubular cell apoptosis

Question 2 : Budesonide is released at what specific site in the gastrointestinal tract to exert its immunosuppressive effects in IgA nephropathy?

a) Stomach
b) Small intestine
c) Terminal ileum
d) Distal ileum

Question 3 : What is the recommended dosage of budesonide for the treatment of IgA nephropathy?

a) 3 mg once daily
b) 8-16 mg once daily
c) 12 mg twice daily
d) 18 mg once daily

Question 4 : Budesonide in IgA nephropathy is designed to be released at which pH level in the gut ?

a) pH 3-4
b) pH 5-6
c) pH 6-7
d) pH 7-8

Question 5 : What is NOT a common side effect associated with long-term use of oral budesonide in IgA nephropathy ?

a) Osteoporosis
b) Weight gain
c) Sleep disturbances
d) Gastrointestinal upset

Question 6 : What is the corticosteroid potency of oral budesonide as compared to oral prednisone ?

a) Prednisone significantly higher than budesonide
b) Prednisone marginally higher than budesonide
c) Prednisone similar patency as budesonide
d) Prednisone significantly lesser than budesonide

Question 7 : Which of the following is the most appropriate duration of budesonide therapy for treating IgA nephropathy (as per NEFIGAN trial) ?

a) 4 weeks
b) 8 weeks
c) 9 months
d) 12 months

Question 8 : Which of the following is an advantage of budesonide over traditional systemic corticosteroids in the treatment of IgA nephropathy ?

a) Higher potency
b) Lower risk of systemic side effects
c) Longer half-life
d) Stronger immunosuppression

Question 9 : Which is the trial that tested the role of oral delayed release budesonide in IgA nephropathy ?

a) PROTECT
b) ALIGN
c) NEFIGARD
d) MAIN

Question 10 : Which property of budesonide minimizes its systemic side effects ?

a) Low bioavailability
b) Long half-life
c) Minimal hepatic metabolism
d) High binding affinity to mineralocorticoid receptors

Question 11 : What is the posology of budesonide used in IgA nephropathy ?

a) Self dissolvable tablet
b) Target release formulation
c) Enteric coated tablet
d) Granules in satchet

Question 12 : Name another systemic disease where oral budesonide is commonly used with an established benefit ?

a) Rheumatoid arthritis
b) Crohn's disease
c) Myasthenia gravis
d) Psoriasis

Question 13 : What is the major difference between NEFIGAN and NEFIGARD Trial for oral budesonide in IgA nephropathy ?

a) Both similar trials, NEFIGAN done earlier
b) NEFIGAN had better study design, and pre-defined outcomes as compared to NEFIGARD
c) NEFIGAN was Phase 2b trial, while NEFIGARD was phase 3 trial
d) Both were almost similar studies, only have minor differences

Question 14 : Which is the following is not a contraindication of delayed release budesonide in IgA nephropathy ?

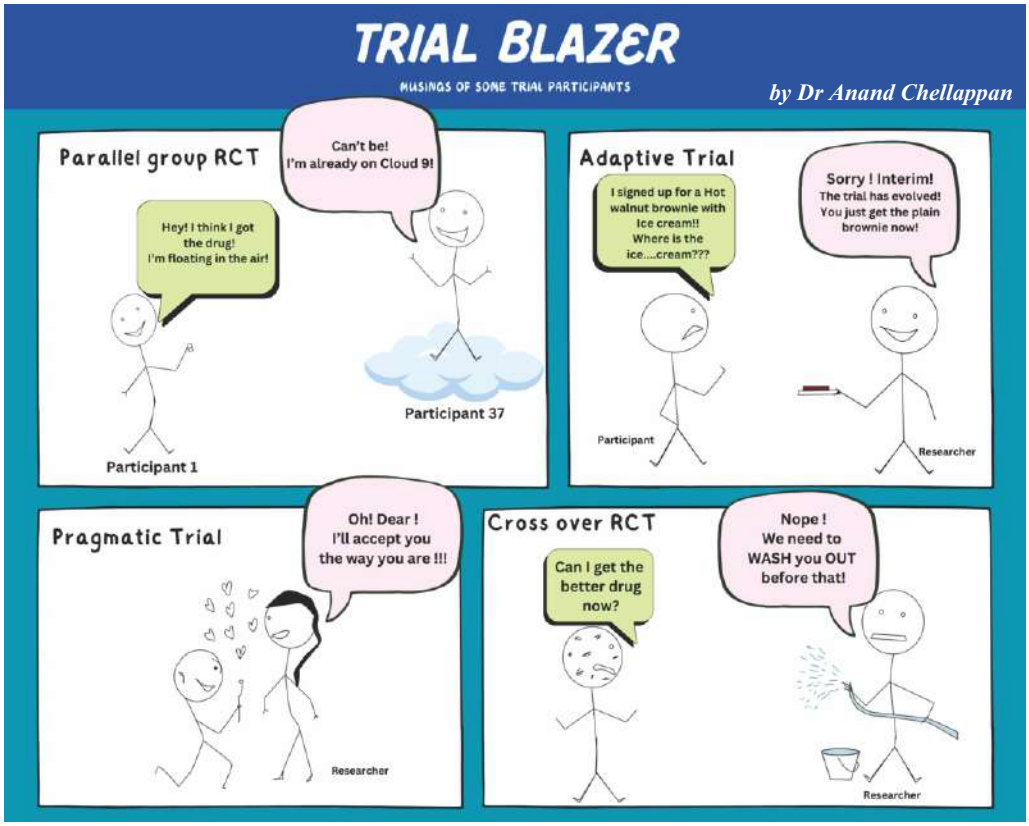
a) Chronic liver disease
b) Hypersensitivity to drug
c) Active systemic infection
d) Mild renal dysfunction

Question 15 : What is NEFECON in the NEFIGAN study of delayed release budesonide in IgA nephropathy ?

a) Nefecon is targeted-release oral capsule of budesonide
b) Nefecon is an acronym related to special pharmacology property of the drug
c) Nefecon is the name of the place where the oral budesonide was first created
d) None of these

Vineet Behera

Stay Tooned !



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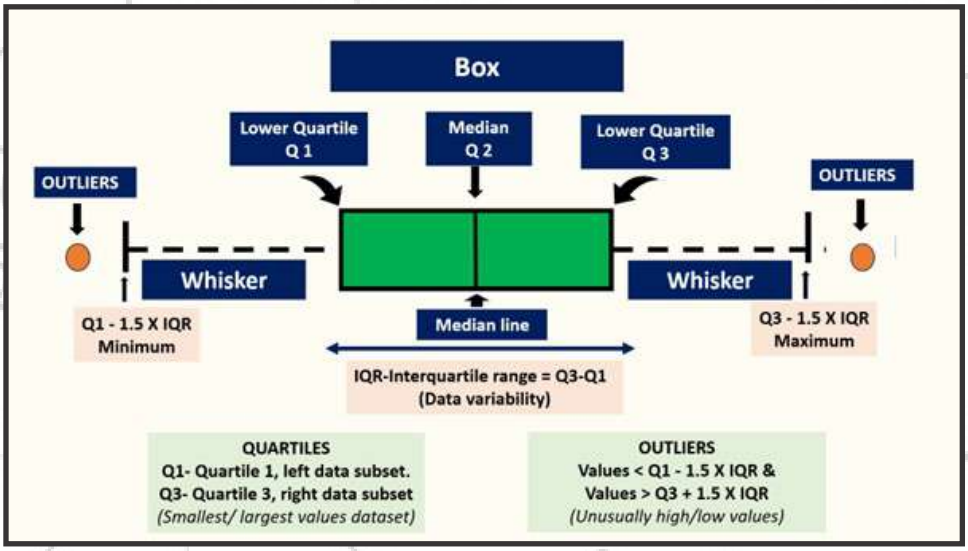
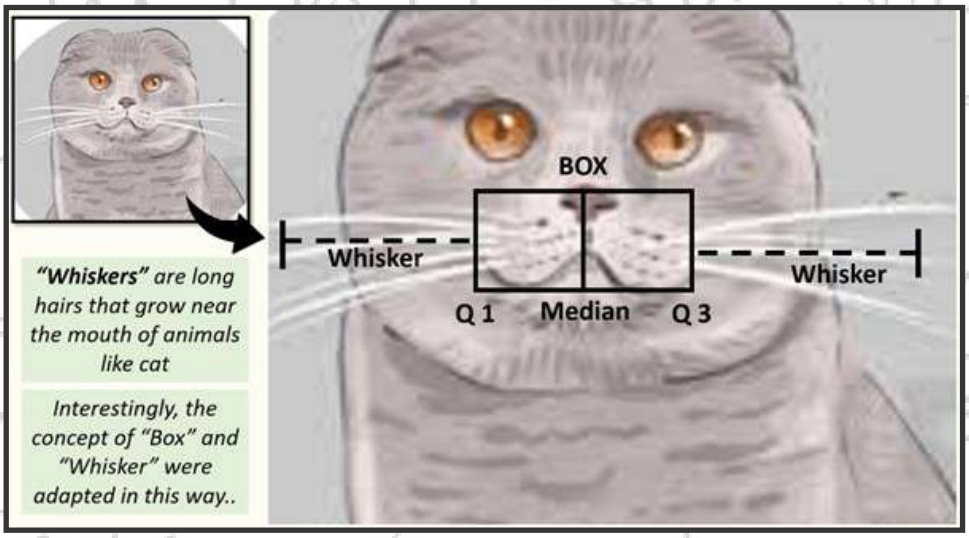
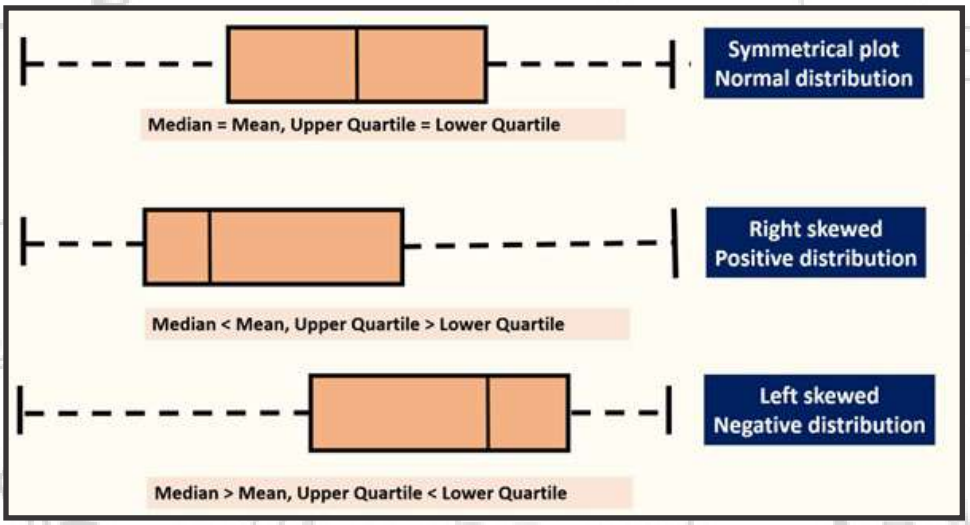
"Stats Gyaan-Box & Whisker Plot"

- Vineet Behera & Urvashi Khan



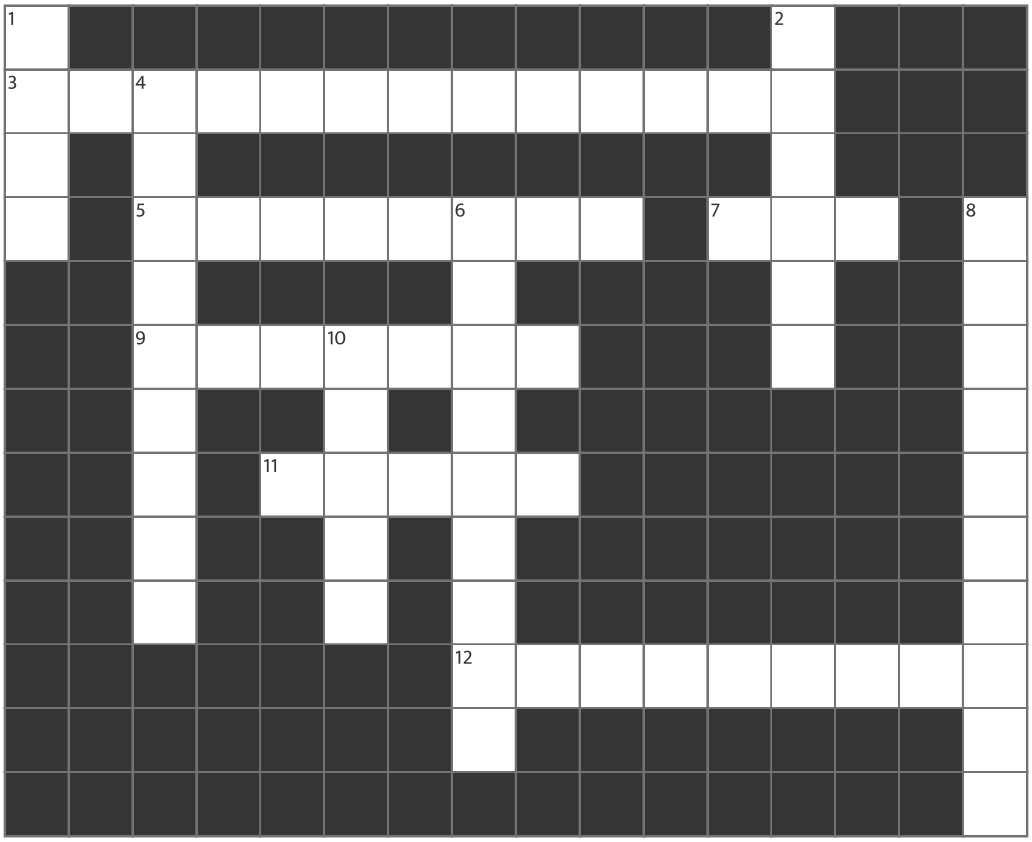




Background Image of this article is taken from internet

Mesangial Maze

By Dr Ambily K, Dr Sandhya Suresh, Dr M Subashri & Dr Pallavi Prasad



Please follow the link to access the crossword

Across

3 The MAIN trial studied the role of this drug in management of IgAN

5 The phase 2, multicenter trial in patients with IgA nephropathy, in which 12 months of treatment with sibeprenlimab resulted in a significantly greater decrease in proteinuria than placebo

7 Which subclass of immunoglobulin acts as an autoantibody targeting gd-IgA1 in the glomerular deposits of IgAN?

9 Mutation in this gene encoding for enzymeβ1,3 Gal transferase has been implicated in genetic susceptibility for IgAN

11 The first South Asian prospective cohort of IgAN patients

12 This drug is a dual anti BAFF-APRIL fusion protein

Down

1 Immunofluorescence stain used for identifying galactose deficient IgA deposits in glomeruli

2 This Parisian pathologist published the first description of IgAN in 1968

4 The International IgAN prediction tool uses all components of Oxford histological score except this

6 This drug is a potent oral selective inhibitor of factor B

8 Findings of PROTECT Trial led to the US FDA approval of this drug in the treatment of IgA Nephropathy

10 This member of TNF superfamily plays a pivotal role in B Cell differentiation into plasma cells

Answers to the Crossword & Quiz

Residents' Corner

The Storage Conundrum : From Cradle To Transplant - A Case Report

Introduction: Glycogen Storage Disorders (GSDs) are inherited metabolic conditions characterised by abnormal glycogen accumulation in various tissues due to enzyme deficiencies. Among the renal complications, focal segmental glomerulosclerosis (FSGS) is a notable consequence, leading to progressive kidney dysfunction. Cases involving complex management scenarios, such as ABO-incompatible kidney transplantation in GSD patients, are rarely reported. This case highlights a 28-year-old male with biopsy-proven FSGS secondary to GSD Type 1b undergoing an ABO-incompatible live donor kidney transplant.

Medical History: The patient, a 28-year-old male, presented with advanced uremia and fluid overload in 2023. He was initiated on maintenance hemodialysis and evaluated for kidney transplantation.

His medical history revealed abdominal distension at 9 months of age, with imaging and liver biopsy confirming GSD. Management involved nutritional therapy. At 12 years, the patient exhibited short stature and absent sexual characteristics. A kidney biopsy revealed FSGS secondary to GSD, and antiproteinuric therapy was initiated in view of sub-nephrotic range proteinuria. He was lost to follow-up and returned with end-stage renal disease (ESRD).

Diagnosis and Pre-Transplant Evaluation: Genetic studies confirmed GSD Type 1b with mutations in the glucose-6-phosphatase gene. Imaging showed no hepatocellular carcinoma (HCC) or adenomas. Lab results revealed severe proteinuria and reduced glomerular filtration rate (GFR). The patient's father, a diabetic with no end-organ damage, was identified as a suboptimal but suitable ABO-incompatible donor. Pre-transplant protocols included rituximab and plasmapheresis.

Treatment and Postoperative Management: The patient underwent transplantation on July 24. Postoperatively, he experienced hypoglycemia and lactic acidosis despite adequate hydration. Management included intravenous dextrose, insulin infusions, and frequent feeds supplemented with uncooked cornstarch—a slow-digesting carbohydrate—to prevent

Resident doctors image created with the assistance of AI from Craiyon.com

fasting hypoglycemia. These interventions stabilized metabolic derangements. The patient was discharged with stable renal function (serum creatinine: 1 mg/dL).

Discussion: GSD Type 1b results from a deficiency in glucose-6-phosphatase, leading to glycogen accumulation, hypoglycemia, and lactic acidosis. In this case, the progression to ESRD was marked by FSGS. Renal transplantation is a critical intervention for GSD-related ESRD; however, ensuring the absence of concurrent liver malignancies (hepatoma or HCC) is essential. This case underscores the importance of a multidisciplinary approach to pre-and post-transplant care. Management included nutritional strategies and metabolic monitoring, essential for preventing hypoglycemia and optimizing outcomes. ABO-incompatible transplantation adds complexity due to risks like antibody-mediated rejection. Strategies like rituximab and plasmapheresis mitigated these risks. Although the patient achieved stable renal function post-transplant, the long-term prognosis remains uncertain due to potential metabolic and immunological challenges. The importance of individualized care, including tailored dietary regimens, cannot be overstated.

Limitations: This case report is limited by a short follow-up period and lack of detailed long-term outcomes. Genetic data for familial screening and a broader literature review of similar cases could provide additional insights. Furthermore, challenges in immunosuppressive therapy adherence and potential antibody-mediated rejection remain unexplored.

Conclusion: This case highlights the successful management of a rare combination of GSD, FSGS, and ABO-incompatible kidney transplantation. It underscores the need for comprehensive pre- and post-transplant strategies and long-term monitoring to optimize patient outcomes.

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Dr. Ambily K.
Dr. Gayathri R Pillai
Dr. Hasna Haris and Dr. Dalia G
DM Residents
Pushpagiri Institute of
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Thiruvalla.

Page Kidney following renal biopsy : An avoidable complication

A 39-year-old female, a diagnosed case of Lupus nephritis, biopsied at an outside centre was referred to us post renal biopsy. Her renal biopsy was done 5 days prior to admission following which, she developed sub-acute onset left-sided flank pain, anuria and accelerated hypertension. On examination, she had pallor, grade 2 pitting oedema, the blood pressure recorded 160/100 mmHg (on 3 antihypertensive) Investigations on presentations showed, Hb -6.4 gm/dl. A CT angiogram revealed left peri-renal hematoma 11.3 cm x 8.3 cm with active extravasation and associated hemoperitoneum. CT urography revealed a large subcapsular hypodense collection around the left kidney with ill-defined hyper dense area within- likely perinephric hematoma. The collection was found to be compressing the renal parenchyma with the possibility of page kidney to be considered.

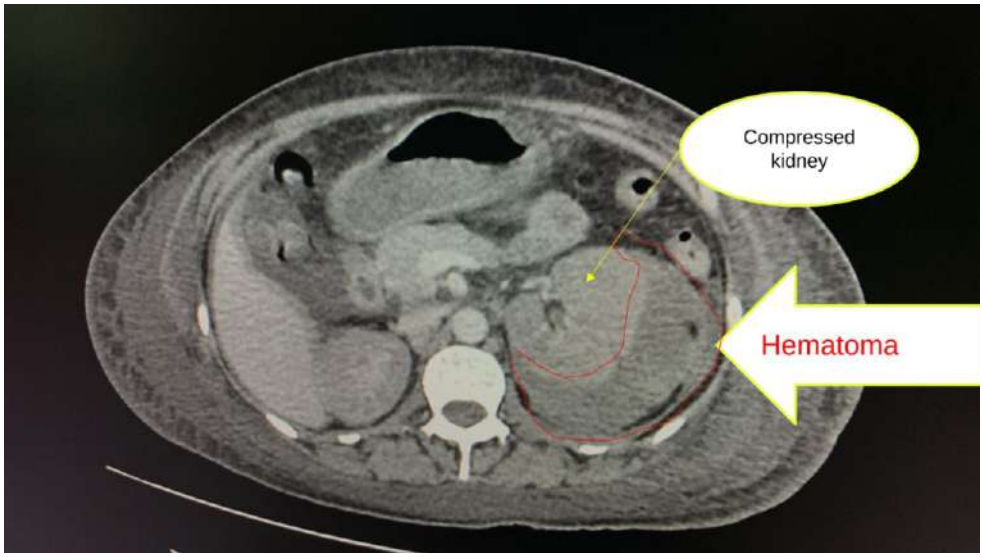
The patient required 4 units of packed red cells transfusion along with USG guided pigtail insertion done for evacuation of the collection. The pig tail catheter was removed after one week. The patient continued to be anuric and dialysis dependent. Her blood pressure remained persistently high requiring three anti-hypertensives, including RAAS inhibitors.

Page kidney or Page phenomenon results from external compression of the kidney by a chronic subcapsular hematoma. It is a rare, treatable cause of secondary hypertension mediated by activation of the renin-angiotensin-aldosterone system (RAAS). This entity was first described by Irvine Page in 1939. During animal experiments he wrapped the kidneys in cellophane, which led to an intense inflammatory response causing production of a fibrocollagenous shell that compressed the kidney causing the compression of intrarenal vessels leading to ischemia and activation of RAAS. Hypertension developed within 4 to 5 weeks and was cured by nephrectomy of the affected kidney. It may be caused by bleeding around the kidney by any of the following mechanisms: Blunt trauma - sports injuries like football, hockey, other contact sports, motor vehicle accident, violence, or fall, iatrogenic - following biopsy of native or transplant kidney, extracorporeal shockwave

lithotripsy, ureteral surgery, sympathetic nerve block, spontaneous - anticoagulation, AV malformation, tumour, vasculitis, pancreatitis, and non-bleeding causes include- lymphoceles particularly around the transplanted kidney, urinoma, retroperitoneal paraganglioma, or large simple cysts.

The mechanism of hypertension is similar to Goldblatt hypertension (Goldblatt, clamp and kidney models), hypoperfusion of the kidneys caused by clamping of renal artery leads to the release of renin and activation of RAAS leading to hypertension. In the Page kidney, external compression of the kidney by hematoma leads to decreased perfusion in intrarenal blood vessels. Microvascular ischemia ensues causing activation of RAAS leading to hypertension. If the history of flank trauma is missed and the patient presents with hypertension, it would be difficult to diagnose Page kidney because there are no unique physical findings to suggest the disease. Elevated renin activity is a marker for Page kidney but can also be seen with other conditions such as- renal artery stenosis, juxtaglomerular cell tumor, or malignant hypertension. Renal ultrasound and computed tomography are used for diagnosis. The management may include Radical nephrectomy or open surgery as the mainstays of management of classical Page kidney. Currently, conservative management is preferred and is guided towards anti-RAAS medicines, percutaneous drainage for collection (more successful, if injury is recent (<3 weeks old)). In patients with lymphangiomatosis, percutaneous drainage with the injection of sclerosing agents becomes the treatment modality of choice.

Page kidney is a readily treatable cause if evaluated promptly with high suspicion for the diagnosis. Timely intervention may lead to avoidance of the need for renal replacement therapy or other associated complications like sepsis and hypertension.



Large subcapsular hypodense collection around the left kidney with ill-defined hyper dense area within- likely perinephric hematoma.

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