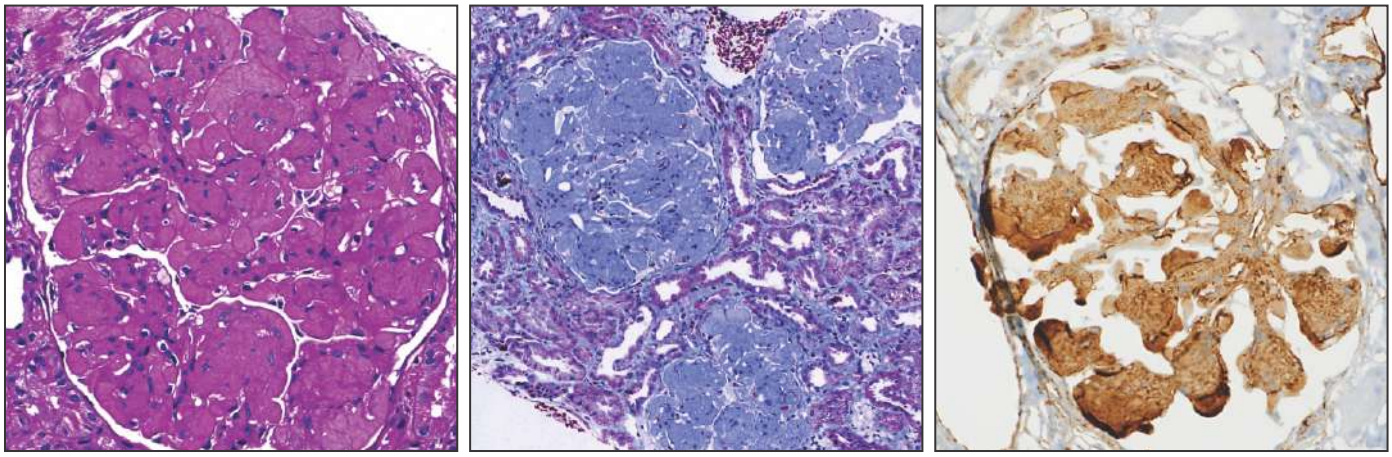
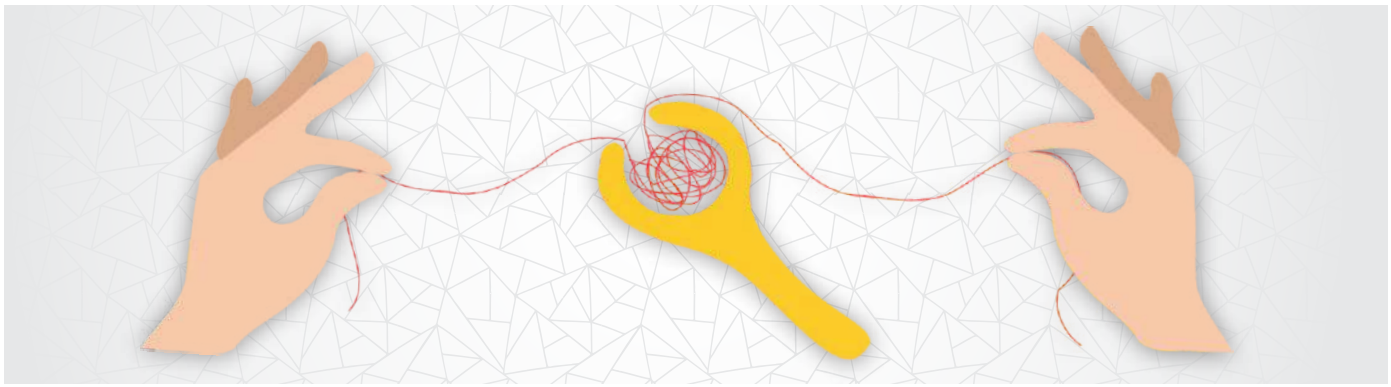
KIDNEY KOLUMNS

Freely filtered from the ISN





Dear Readers,

We present yet another edition of Kidney Kolumns..this time focussing on the recent advances in glomerulonephritis therapeutics.Glomerulonephritis is probably the only subspeciality of nephrology which is having definite advances in diagnostics as well as therapeutics.As new data and trials come in we have made a small attempt to keep our readers abreast of the advances in this field.

Happy reading folks!!!

Regards

Editors - in-Chief

Inside

KIDNEY KOLUMNS

COVER IMAGES : A Case of Fibronectin Glomerulopathy

Image 1 (Left) : **PAS Stain (40X) – Positive,** Glomerulus appearing markedly enlarged with lobular accentuation. Deposition of pink amorphous substance in the mesangium and peripheral capillary walls.

Image 2 (Center) : **Masson Trichrome Stain (20x)- Positive,** Tubules show protein reabsorption granules. The interstitium shows collections of foamy macrophages. Blood vessels show medial sclerosis. 5-10% of tubulointerstitium show chronic parenchymal damage on MT stain

Image 3 (Right) : **Fibronectin (20x)- Positive**

Image Credits Image 1, 2 & 3 - **Dr Vineeta Batra,** Director, Professor, Dept of Pathology, GB Pant Hospital

Hon. Secretary's Message

Dear Members,
Greetings from the secretariat!
The Indian Society of Nephrology is growing and making its stride felt nationally and internationally. The newsletter of Indian SN is the mouthpiece of society and it not only provides information about activities of Indian SN but also updates about recent advances and important clinical issues in Nephrology. I again congratulate this young, vibrant and hardworking editorial team for doing this fantastic job.
I will take this opportunity to highlight some of the important activities done in last quarter and update you about plans by Indian SN:

1. **The partnership with European Renal Association**: The Indian SN signed an agreement with ERA where members of Indian SN would get a discounted membership at 500 INR only and they would get all 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 all members of Indian SN to take this discounted membership of ERA. You can write an email to me at drshyambansal@isn-india.org

2. **World Congress of Nephrology**- As you might be getting messages from the secretariat regarding WCN 2025 to be held in India from 6th-9th February in Yashobhoomi convention centre Dwarka. **The members of Indian SN will get special discounted rates to register for WCN.** I would request everyone to become a member of Indian SN if you are not. The abstract submission will start in June and early bird registration will start somewhere in September 2024. Since the ISNCON will not be held this year, Indian Nephrologists should participate in WCN 2025 and make it a grand success and a memorable one. The online membership of Indian SN is available at www.isn-india.org. If you are not getting messages from the secretariat despite being a member, kindly check your spam mail or mail to me

3. **Meeting with Niti Aayog**- The Indian SN was recently invited by Niti Aayog to discuss the implementation and acceptance of Ayushman Bharat by the Nephrology community. The delegation of Indian SN discussed and handed over suggestions to Niti Aayog on the issues faced by Nephrologists. We conveyed to Niti Aayog that the quality of dialysis is not uniform under the PM-JAY scheme and there is no supervision of many dialysis units run by technicians and dialysis provider companies. The ISN demanded that no dialysis unit should be run without nephrologists in India as there are enough nephrologists to cover dialysis and approximately 400 new nephrologists are trained every year in India. We also handed over a list of procedures including tunneled hemodialysis catheter, AVF, and plasmapheresis to be included under Nephrology.

4. The ISN conducted a **Webinar on Hot Topics in Glomerulonephritis** in collaboration with the International Society of Glomerular Diseases on 10th May 2024. The webinar was attended by more than 500 delegates across the world and was greatly appreciated. The meeting faculty had a mix of Indian and International experts in Glomerular diseases including Dr Carla Nester from University of Iowa USA, Dr Kenar Jhaveri from Hofstra/Northwell USA, Dr Koyal Jain from North Carolina USA, Dr Shikha Wadhwani from North Western University Chicago USA, Dr Suceena Alexander from CMC Vellore, Dr Aman Sharma from PGI Chandigarh and Dr Shyam Bansal from Medanta- Medicity, Gurgaon.

Hot Topics in Glomerulonephritis: Online Symposium from the Indian Society of Nephrology and ISGD

5. **Meeting with National Health Authority**: The ISN was invited and had a meeting with NHA regarding the implementation of the Ayushman Bharat Digital mission (ABDM), which is the initiative by the Government of India to create a digital record of every Indian. The government is working hard towards making it possible by collaborating with various hospitals, clinics, institutes and societies, so all records can be kept in digital form. The ISN urged the NHA to come out with data on hospitalization and mortality especially in the context of dialysis to know the outcomes and give suggestions to make this data useful. We have circulated a message by ABDM for a pilot project for Nephrologists and some of our colleagues have already shown their interest in the same. Those who are interested and didn't receive an e-mail can write to me.

Dr Shyam Bihari Bansal
Hon. Secretary Indian Society of Nephrology

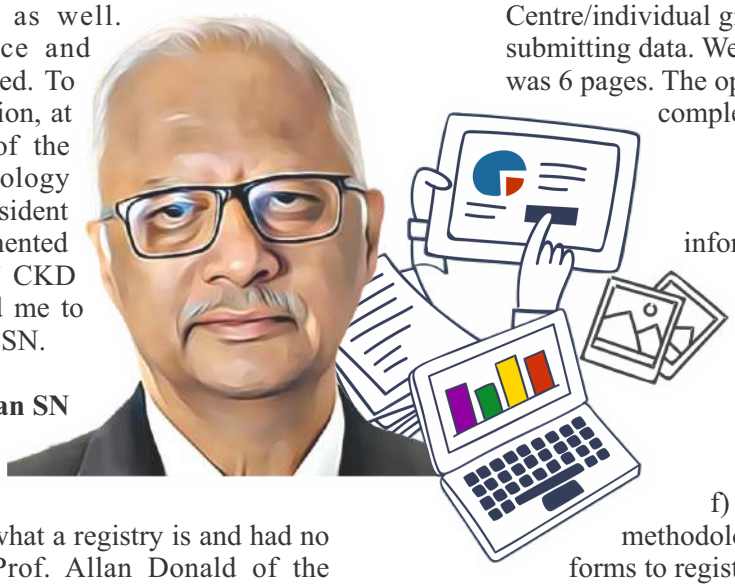
WISE VOICES

My experience of CKD registry of the Indian Society of Nephrology

Dr. Mohan M. Rajapurkar

Background :

It is well known that doctors are burdened with clinical work to the exclusion of research & teaching! The Indian physician has been arguably proud of their clinical ability especially during conferences when foreign visitors asked about lack of data from India. Also, there used to be discussions/heated debates about the type of diseases and cause of these diseases in different sectors of health providers. However, no one knew the details. The clinical experience was in the head of the famous doctors and was not retrievable and anybody's guess could be correct. This was the case for Chronic Kidney Disease (CKD) as well. Widely varying incidence and prevalence was being quoted. To partially remedy this situation, at the Varanasi conference of the Indian Society of Nephrology (Indian SN), the then President Prof. Ashok Kirpalani lamented that there was a lack of CKD registry in India. He asked me to start a registry for the Indian SN.



The CKD registry of Indian SN 2005 to 2010:

I accepted, but realized soon that I had no idea of what a registry is and had no expertise. I approached Prof. Allan Donald of the USRDS and the EDTA registry seeking help. Unfortunately, there was no response to my queries. Then someone advised me to ask the Turkish registry. They welcomed me to their office and described the process in Turkey. I realized that we cannot copy their example, but will have to decide on our own method of collecting data. The steps we took were :

a) Formation of a core group of the registry. We wanted to include representatives from all regions of India, all sectors of health – private, public and not for profit – and well-known opinion leaders of nephrology. I invited first meeting of this Core Group to decide on the following:

b) Concept of our registry. We decided to get data of incident CKD patients in a specified form from any member of the Indian SN willing to register with the registry.

c) The aims and objectives were decided as follows:

1. Establish prevalence and pattern of diseases causing CKD
2. Prevalent referral patterns of CKD
3. Demographic and socioeconomic information
4. Proportion of CKD Vs getting RRT
5. Risk factor analysis
6. Provide information platform for advocacy, prevention/treatment proposals and improvement opportunities

d) Designing a form for registering a Centre/individual giving data and a form for submitting data. We started with a form which was 6 pages. The opinion was no one will fill it completely. Finally, after discussion, we settled on a one and half page form including essentials of the information.

e) There was discussion on developing guidelines to decide the response for each question/column to be filled.

f) Decided on methodologies for getting the filled forms to registry. The nephrologist could submit data online via website (www.ckdregistry.org). They could also submit by email or use paper forms and send by courier.

g) We made a website and software exclusively for this registry.

h) Decided on the data analysis and reports to be given to Indian SN and the sponsors Janssen Cilag India, J & J who gave unrestricted research grant to Indian SN

Constant monthly reminders were generated by the software & sent by the members. Friends started to avoid me during conferences because I will remind them of their promised data. Initially we used to pay INR 5000 per centre. In later years, we started giving INR 50 per form. This was the incentive to the clerk/typist /resident

who filled these forms.

We were given an opportunity at the annual conference of Indian SN to present the data collected as a special session of the registry.

There were several limitations :

i) Most important being getting complete and correct data from all centres on time
ii) We did not achieve our initial aims & objectives
iii) We were able to produce only one original article from this data. There was no 'carrot or stick' available to us for use, in getting data from centres.
iv) All data captured was at a single time point at first diagnosis.

We wanted to continue to gather follow up data of the cohort from the registry. However, after 2010, the registry was taken over from me. There was no further progress after that till date.

Since last few years others have made a lot of effort to make different registries; to name a few i) Community acquired AKI registry by Prof. Narayan Prasad (1st paper published) ii) Registry on glomerular diseases by prof. Suceena Alexander and iii) CKD registry of the Indian Society of Pediatric Nephrology.

My hope is that providing data will be compulsory for all by law, only then we will be able to compile larger and better data for research on diseases affecting our community and be able to make informed and adequate strategies for tackling them in India systematically.

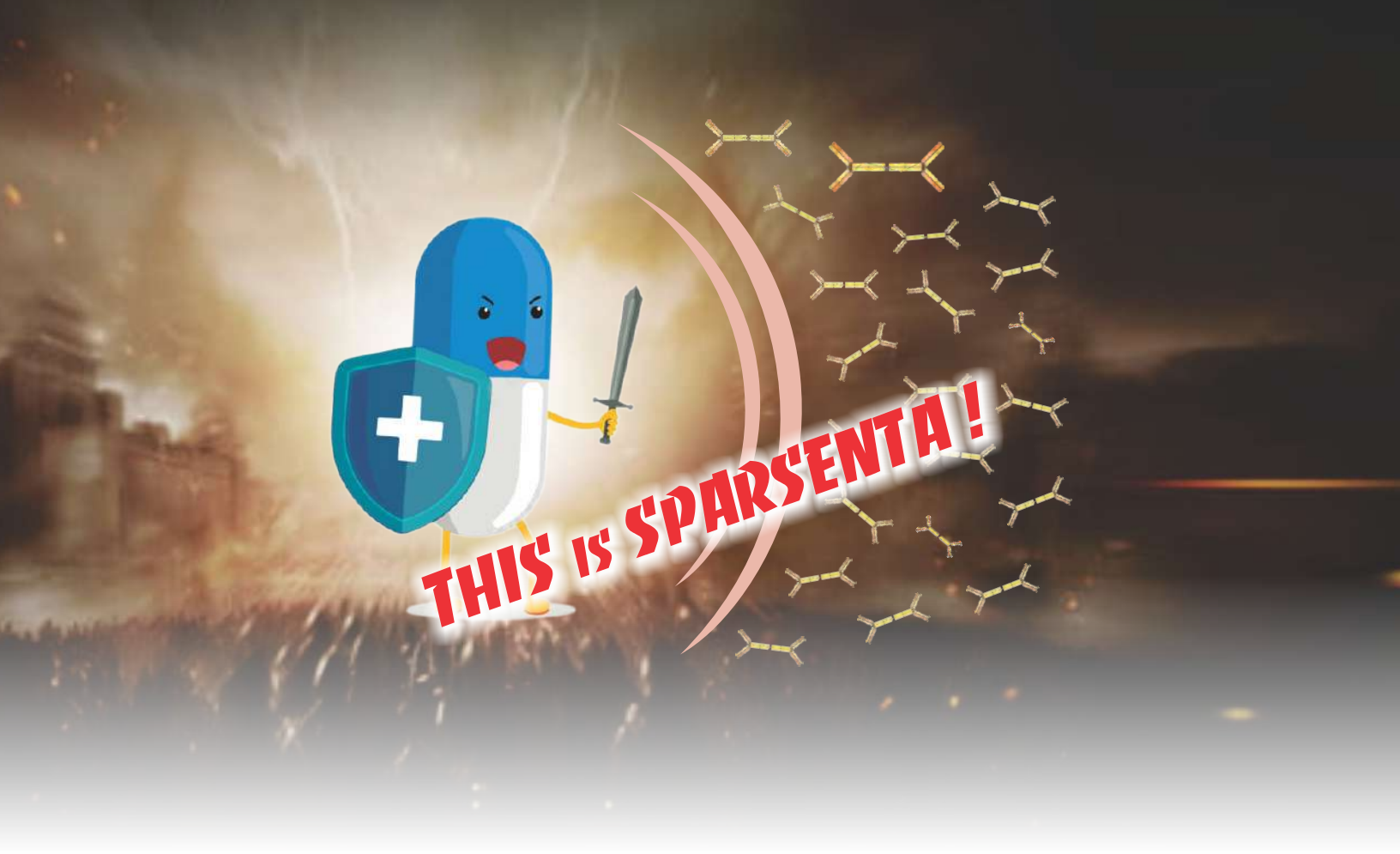
Sparsentan in IgA nephropathy – Has it maximized non-immunosuppressive PROTECTion ??

IgA nephropathy is one of the most common primary glomerular diseases in India and worldwide. Recent insights into the epidemiology of IgA nephropathy in the Indian scenario have been provided by the GRACE IgAN study (Alexander et al) where nearly 2 /3rd of the patients had a GFR < 60 ml /min at presentation and a median proteinuria of 2.1 grams. Nearly 40% of the cohort had rapid progression, as defined by KDIGO criteria of GFR loss of >5ml /min per 1.73m2 / year. Rapid progression was associated with higher proteinuria at baseline. Thompson et al, in their review, stress the fact that proteinuria reduction is a surrogate marker to assess drug efficacy in trials of IgA nephropathy due to its close association with renal injury and disease progression.

The rationale for Sparsentan in IgA: Both endothelin - 1 and Angiotensin -II contribute to the propagation of renal injury in IgA nephropathy through multiple effects like vasoconstriction, podocyte injury, inflammation and fibrosis. Sparsentan is a non-immunosuppressive, dual endothelin and angiotensin II receptor antagonist with high selectivity for the ETA receptor and angiotensin II subtype 1 receptor (AT1 receptor). With initial evidence of efficacy for the dual blockade (ETA and AT1) from animal studies and with the positive results from the phase 2 DUET study (sparsentan versus irbesartan in focal segmental glomerulosclerosis), sparsentan is the new “kid on the block” for proteinuric kidney diseases.

PROTECT Trial – The study : In this phase III trial, patients with biopsy-confirmed IgAN and ongoing proteinuria > 1.0 g/day, despite at least 12 weeks of optimal supportive care, were randomized to receive either sparsentan at 400 mg daily or irbesartan at 300 mg daily. The trial's prespecified interim analysis at 36 weeks indicated a more substantial reduction in proteinuria in the sparsentan group, with a 49.8% decrease compared to a 15.1% decrease in the irbesartan group. Notably, this reduction occurred independently of any blood pressure-lowering effects. Both treatment groups exhibited similar profiles in terms of side effects. Following these promising results, sparsentan received accelerated FDA approval for the treatment of IgAN in February 2023. Further evidence supporting the drug's efficacy came from a two-year follow-up study, which showed that proteinuria was 40% lower in the sparsentan group compared to the irbesartan group at 110 weeks. Additionally, the rate of eGFR decline was slower in the sparsentan group (−2.7 mL/min/1.73 m^2) than in the irbesartan group (−3.8 mL/min/1.73 m^2), without any significant differences in adverse events between the groups. The combination of SGLT2 inhibitors and sparsentan is already being explored in the open-label extensionof the PROTECT trial.

Where do we fit in Sparsentan in the current IgA armamentarium?



Despite advancements in the understanding of the pathophysiology of IgA nephropathy and potential therapeutic targets and multiple clinical trials, its surprising to know that sparsentan is the first USFDA-approved treatment for IgA nephropathy. The KDIGO 2021 guidelines still stress maximizing supportive care with RAS blockade and blood pressure control along with lifestyle measures. In patients who do not achieve proteinuric remission of <1g per day despite optimised RAS blockade, sparsentan could be an ideal replacement for RAS therapy with SGLT2 inhibitors as add-on therapy

Beyond IgA – PROTECTion for all glomerular diseases?

The anti-proteinuric effects of sparsentan may be extrapolated to other glomerular diseases since the pathophysiology of the progression of glomerular diseases remains similar once the injury is triggered. In the DUPLEX trial by Rheault et al , the largest trial investigating FSGS to date, a significant difference in complete remission was seen between sparsentan and irbesartan groups at 108 weeks though there was no difference in the eGFR slopes. There is also an ongoing clinical trial in the paediatric population (ClinicalTrials.gov Identifier: NCT05003986) which is looking into the efficacy of sparsentan across 5 different glomerular diseases Focal Segmental Glomerulosclerosis, Minimal Change Disease, IgA Nephropathy, IgA Vasculitis and Alport Syndrome.

Author :

Dr Srinivas Vinayak Shenoy MD (Internal Medicine) , DM(Nephrology)
Associate Professor
Department of Nephrology
Kasturba Medical College , Manipal
MAHE , Manipal , 576104
Karnataka

KDIGO 2024 Clinical Practice Guideline for management of Lupus Nephritis

Indications for renal biopsy

- 24 hr proteinuria ≥500 mg/day
- Active urine sediment – acanthocytes ≥5%, RBC or WBC casts
- ↓eGFR with no other cause

General management

Stop smoking

Optimise body weight
Manage dyslipidemia
Avoid ↑Na^+ diet

Renoprotection with RAASi, SGLT2i

Vaccination

HCQ for all patients with LN

Bones – Calcium, Vit D supplements

Limit UV exposure, use sunscreen

GnRH agonists
Sperm/oocyte cryopreservation
Contraception

Evaluate for malignancies (age-specific)
Cumulative Cyp dose <36g

Class I/II LN

Low level proteinuria
- IS if extrarenal +

Nephrotic syndrome
- R/o lupus podocytopathy → Rx as MCD with low dose GC + IS

Class V LN

Prevent complications
BP control, RAASi

Low level proteinuria
- IS if extrarenal +

Nephrotic range proteinuria
- IS with GC + MPAA/ Cyp / CNI/ Rituximab/ Azathioprine

Unsatisfactory response to Rx

Verify adherence to Rx

Check adequate drug dosing
Test levels of MPAA

Re-biopsy – to detect chronicity, TMA, etc

Switch to alternate regimen if persistent active disease

❖Add Rituximab
❖Extend IV pulse Cyp
❖Clinical trial enrolment

Class III/IV LN ± V

Initial therapy

IV MP pulses + GC + 1 of:
- ➢MPAA
- ➢Low dose IV Cyp
- ➢Belimumab + MPAA or low dose IV Cyp
- ➢MPAA + CNI (when eGFR > 45 ml/min/1.73m^2)

Maintenance therapy:
- ➢Durations ≥36 months
- ➢Low dose GC → discontinue if complete clinical renal response ≥12 months
- ➢Maintenance agents:
  - ❖ MPAA for maintenance
  - ❖ Azathioprine if MPAA not tolerated or pregnancy considered
  - ❖ Triple Rx with Belimumab / CNI → continue as maintenance
  - ❖ Mizoribine / Leflunomide if MPAA / Azathioprine cannot be used

Steroid dosing:
- ✓ Lower doses equally effective
- ✓ Fewer short and long-term toxicities
- ✓ Prednisolone 0.5-0.6 mg/kg/d (week 0) → 5mg/d (week 11-12) → <2.5 mg/d (week 25)

DRUG	INDICATIONS
IV Cyp	Difficulty in oral adherence
Oral MPAA	High risk of infertility
CNI	• Relatively preserved GFR • Nephrotic range proteinuria due to podocyte injury • Intolerance to MPAA • Unfit for IV Cyp
Belimumab	• Repeated kidney flares • High risk for kidney failure due to CKD
Rituximab	• Persistent disease activity • Inadequate response to initial standard of care Rx

LN with TMA

Check: ADAMTS13 activity, ADAMTS13 Ab, APLA;
if PLASMIC score > 5 → prophylactic PLEX

LABS	DIAGNOSIS	Rx
↓ADAMTS13	SLE associated TTP	PLEX + GC + Ritux ± Caplacizumab
Normal ADAMTS13 and APLA +ve	Antiphospholipid syndrome nephropathy	Anticoagulants ± PLEX
Normal ADAMTS13 and APLA -ve	Other TMA	Consider eculizumab

Abbr.: IS Immunosuppression, GC Glucocorticoids, Cyp Cyclophosphamide, MPAA Mycophenolic acid analogues

REFERENCE: Kidney Disease: Improving Global Outcomes (KDIGO) Lupus Nephritis Work Group. KDIGO 2024 Clinical Practice Guideline for the management of LUPUS NEPHRITIS. Kidney Int. 2024 Jan;105(1S):S1-S69. doi: 10.1016/j.kint.2023.09.002.

Visual Abstract by Dr. Ambily K (@drambilyk)

Low-dose Versus High-dose Cyclophosphamide in Class III/IV Lupus Nephritis

Higher incidences and more severe lupus nephritis are reported in patients of Asian origin. Studies such as Euro-Lupus Nephritis trial (ELNT) and other Asian studies have indicated that ethnicity has an impact on incidence, severity and treatment outcome of Lupus Nephritis (LN).

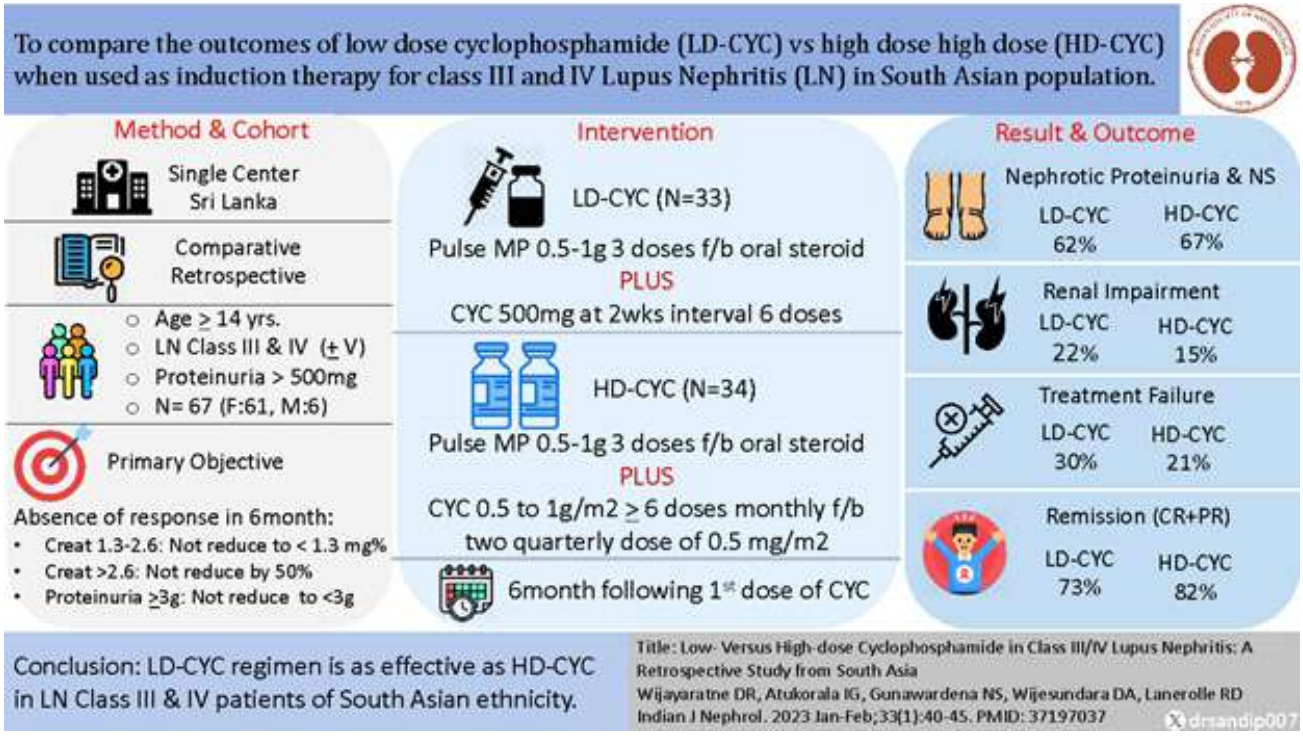
Combination of steroids and cyclophosphamide (CYC) is considered as a gold-standard in the treatment for LN. However, in Asian patients, efficacy of low-dose cyclophosphamide (LD-CYC) compared to high-dose cyclophosphamide (HD-CYC) is yet not well established.

Wijayaratne DR et al has conducted a single-center retrospective study in Sri Lankan patients with biopsy-proven class III or IV lupus nephritis. Patients were divided in two groups; High-dose Cyclophosphamide (HD-CYC) group received ≥6 doses of 0.5–1 g/m2 cyclophosphamide (CYC) followed by quarterly doses and Low-dose cyclophosphamide (LD-CYC) group received six doses of 500 mg CYC at two-weekly intervals. In this study, LD-CYC and HD-CYC induction are comparable in patients with class III and IV lupus nephritis. Treatment failure (21% vs. 10%) and complete or partial remission (82% vs. 73%) was reported to be not significantly different in HD-CYC and LD-CYC ($P > 0.05$) groups, respectively. Adverse event rates were similar.

Euro-Lupus Nephritis trial (ELNT) enrolled white Caucasians, showed no difference in the rates of renal remission, treatment failure, or severe flares and adverse effects in HD-CYC and LD-CYC ($P > 0.05$) groups.

A recent systematic review by Ming T et al from China suggests that both HD-CYC and LD-CYC regimens have similar efficacy outcomes. However, studies reported by Castro-Santana LE et al in Puerto Ricans and by Mehra S et al in the Indian population reported poorer renal outcomes in patients treated with LD-CYC group.

In the first phase of ACCESS study, the placebo arm received a treatment course based on the ELNT which comprised six doses of LD-CYC followed by azathioprine. The treatment group received abatacept in addition to the above. Forty percent of the sample was African-American and 39% was Hispanic/Mestizo and, therefore, very different ethnically from the ELNT study population. Even in their ethnically diverse sample, the ELNT protocol appeared to have similar, if not superior, outcomes to HD-CYC and MMF-based regimens.



Mehra et al suggested that HD-CYC may be a more efficacious treatment approach among Indian patients. The Indian cohort of patients had less clinically severe LN and they defined complete remission (CR) as proteinuria <0.5 g/24 hr. HD-CYC group received a median dose of 6 g cyclophosphamide (IQR 5.4–6.3 g), which was higher than that offered in Wijayaratne DR et al where they receiver 4.5 g of cyclophosphamide (IQR 4.5-7.75). In the Wijayaratne DR et al cohort of patients the overall response rates appeared to be higher than Mehra et al patient cohort with no between-group difference. This may partly be due to the more generous definition of CR by Wijayaratne DR et al (CR defined as proteinuria <1 g/d).

In conclusion, while the Sri Lankan study suggested that proliferative lupus nephritis patients in their cohort, low dose cyclophosphamide (LD-CYC) is as effective as high dose cyclophosphamide (HD-CYC), this conclusions runs counter to the study published by Mehra et al in an Indian cohort. Hence it is important to conduct multicentric, prospective studies to better understand our patient cohorts and their management.

Dr Sukant Kishore Das
Senior Nephrology Consultant and Transplant Physician
Manipal Hospital, Bhubaneswar

Pediatric membranous nephropathy in an Indian cohort : spotlight on an uncommon disease

Membranous nephropathy (MN) is a histological pattern of injury characterized by the thickening of glomerular capillary walls due to immune complex deposition. It is one of the most common causes of nephrotic syndrome (NS) in adults, with 70-80% of cases being idiopathic (IMN). In contrast, pediatric MN is rare, comprising 1-7% of pediatric nephrotic syndrome cases, usually seen in adolescents and often due to secondary factors (SMN), such as systemic lupus erythematosus (SLE), hepatitis B or C infection, or certain medications. Notably, children under 12 years with steroid-sensitive NS are not routinely biopsied, leading to an underestimation of MN prevalence in this age group.

Clinical presentation of MN varies widely, with a common feature being nephrotic range proteinuria, though it may manifest gradually and not as floridly as in minimal change disease. Children may also present with hematuria and hypertension but renal function is usually preserved. Thromboembolic complications, a significant concern in adults with MN, are less frequent in children.

Recent discovery of novel autoantigens has led to the reclassification of some cases which previously considered idiopathic. The major podocyte antigen identified in adults is M-type phospholipase A2 receptor (PLA2R), while in children, the target antigen varies with age and exposure. For instance, neonates may present with the congenital neutral endopeptidase (NEP) form, cationic bovine serum albumin (cBSA)-related MN has been seen in infants and young children and semaphorin 3B-associated MN (SEMA3B) has also been reported in very young patients from North American series, while PLA2R associated MN is predominantly observed in adolescent age group. However, a recent Indian pediatric MN cohort of ninety patients, observed PLA2R and EXT 1/2 antigen predominance, though < 10% of this cohort was < 10 years of age. In adults, other antigens identified are thrombospondin type 1 domain-containing 7A (THSD7A), Exostosin 1/exostosin 2 (EXT1/EXT2), Neural cell adhesion molecule 1 (NCAM1), & NELL-1. Tissue staining for these antigens is recommended whenever possible.

Here we review a 15- year retrospective study by Deepthi et al analysing the 43 children below 16 years with membranous nephropathy, assessing clinical profiles, outcomes, and PLA2R IHC prevalence in kidney biopsies from a tertiary care centre in South India. The authors correlated the prevalence of PLA2R positivity in kidney biopsy with the clinical severity and longterm outcome. Out of the 43 cases of MN, 18 were IMN (42%) and 25 were SMN (58%). Out of 18 IMN cases, PLA2R-IHC was performed on 14 kidney biopsies of which 7 were PLA2R positive. The incidence of MN increased with progressing age group (70% cases in 11-15 years vs 7% in 1-5 years) and majority presented as late-onset and steroid resistant NS . In children less than 10 years of age, SMN was significantly more than IMN. Lupus nephritis was the most common cause of SMN.

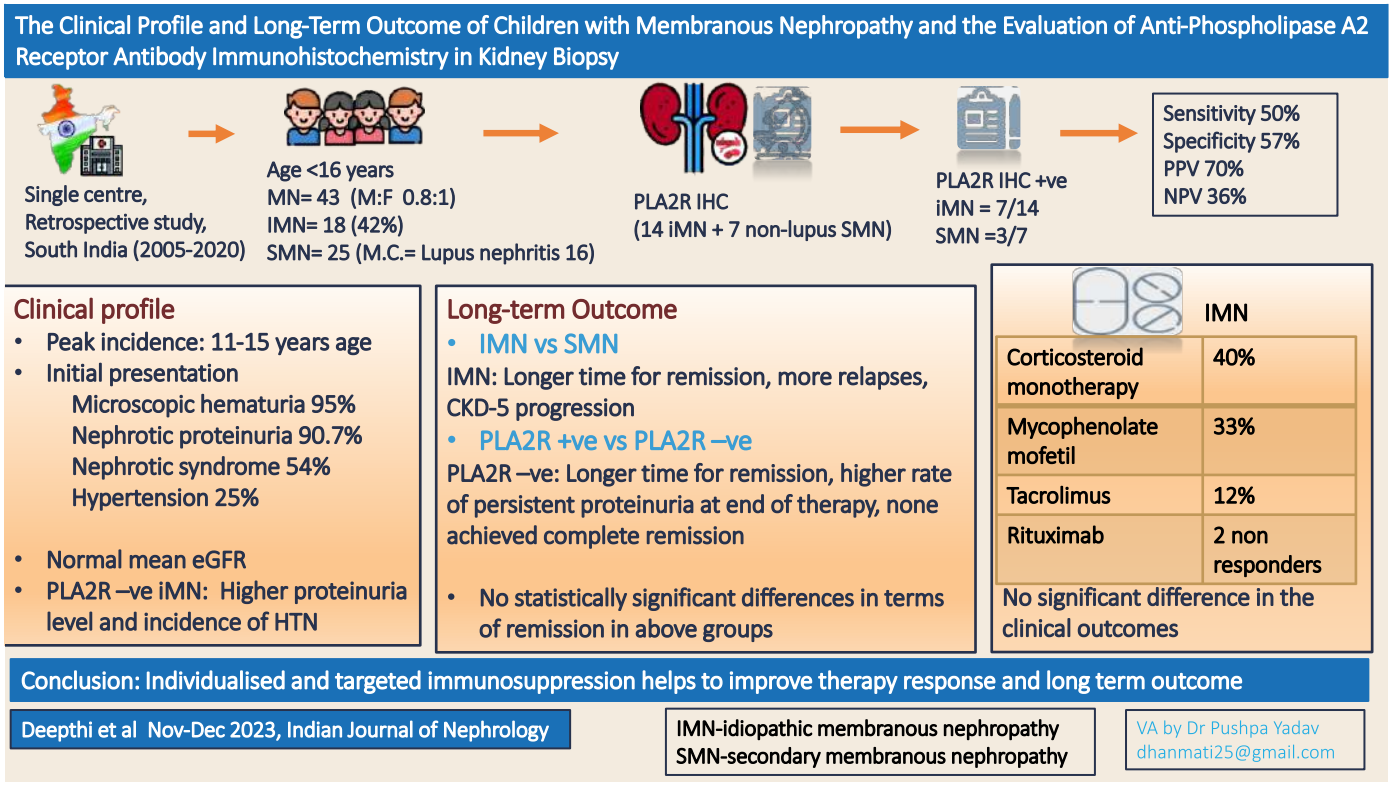
PLA2 R negative IMN children were noted to have more severe clinical presentation at the onset with higher degree of proteinuria and hypertension.

Treatment for pediatric MN is tailored based on clinical condition, age, and subtype. Addressing secondary causes often induces remission. Children with significant proteinuria usually receive conservative treatment with ACE inhibitors or angiotensin-receptor blockers. Glucocorticoid therapy may be initiated, particularly in steroid-sensitive cases, albeit with limited evidence. Cyclophosphamide, while effective, is limited due to adverse effects. Second-line agents like calcineurin inhibitors or rituximab are added as needed. Tacrolimus, combined with glucocorticoids, is effective and safer, typically administered for 6-12 months. In a recent trial, rituximab showed better remission continuation compared to cyclosporine. Glucocorticoids were most common in idiopathic MN, while mycophenolate mofetil prevailed in secondary MN. Glucocorticoid monotherapy was used in a third of cases. Despite variations, no significant differences in outcomes were observed between different immunosuppressive agents.

Children have relatively benign prognosis compared to adults, however 20% may progress to end stage kidney disease. Monitoring anti-PLA2R antibodies helps guide treatment and predict remission. The response rates for idiopathic MN remained high at various follow-up points in this study. PLA2R-negative children took longer to achieve partial remission (5.7 ± 6.3 months vs 2 ± 3.3 months) than PLA2R-positive ones, with none reaching complete remission. No significant difference in long-term remission was found between the groups. Secondary MN had shorter time to remission and lower relapse rates. However, idiopathic MN cases faced more persistent proteinuria, relapses, and progression to end-stage kidney disease after therapy.

To conclude, this study published in the IJN, provides a descriptive analysis of a sizeable Indian pediatric MN cohort and informs readers regarding their biopsy and management characteristics.

Dr Pushpa Yadav[@], Dr Jyoti Singhal[#]
[@]*FNB trainee in Pediatric Nephrology*
[#]*Consultant Pediatric Nephrology*
Pediatric Nephrology Service, Renal Unit, KEM Hospital, Pune



ApoE as a marker of Dense Deposit Disease : Illuminating the darkness

A commentary on: –Benjamin Madden, Raman Deep Singh, Mark Haas et. al. Apolipoprotein E is enriched in dense deposits and is a marker for dense deposit disease in C3 glomerulopathy. Kidney International (2024) 105, 10771087

BACKGROUND :

C3 glomerulopathy (C3GP) is an uncommon condition of alternative complement pathway dysfunction, characterized by variable clinical & light microscopic features, and unifying immunofluorescence finding of exclusive/dominant glomerular C3 staining in renal biopsies. Ultrastructural examination however differentiates two forms of C3GP as Dense Deposit Disease (DDD) which is characterized by intensely osmiophilic/ electron dense "ribbon like" or "sausage shaped" deposits along the glomerular basement membranes, mesangial areas & often tubular basement membranes, and C3 glomerulonephritis (C3GN) which reveals conventional density deposits in glomeruli.

Though DDD was recognized and reported as early as 1962 by Berger & Galle at Necker Hospital in Paris the reason for dense appearance of deposits has remained elusive. Earlier studies using laser capture dissection of glomeruli followed by mass spectroscopy confirmed the presence of alternative & terminal complement pathway components in DDD however these could not explain the extremely osmiophilic nature of these deposits.

COMMENTARY:

In this important study, Madden et al utilized the same technique of Laser Capture Microdissection followed by Mass Spectroscopy and demonstrated 9-fold abundance of Apolipoprotein E (Apo E) in deposits of DDD (12 cases) compared to the control population (12 time-zero renal allograft biopsies) and cases with C3GN (12 biopsies). Both confocal microscopy and conventional immunohistochemistry (IHC) were then performed to localize the Apo E deposits in glomeruli and tubular basement membranes, correlating with the dense deposits of DDD.

A unique strength of this study lies in use of a separate blinded validation cohort of 31 cases of C3GP (16 cases of C3GN and 15 cases of DDD) from a separate institution where Apo E IHC was performed without prior knowledge of diagnosis of C3GN or DDD. This approach enabled correct diagnosis (confirmed by Electron Microscopy) in 12/15 cases of DDD (positive predictive value of 80.6%) and 13/16 cases of C3GN (negative predictive value of 81.3%).

The present study proves with reasonable conviction that in an appropriate context, Apo E IHC may serve as a relatively specific test for diagnosis of DDD and limit the use of Electron Microscopy in many cases, providing a useful diagnostic tool to centres not having access to EM. Although the utility of EM in final diagnosis will remain in cases with equivocal results, a confident diagnosis of DDD will be possible in substantial number of cases with Apo E IHC only.

Some burning questions however remain to be answered:

a. The source of Apo E in the deposits is unclear, considering that significant amount of Apo E is not produced in kidney.
b. While DDD is associated with dysfunctional alternative complement pathway functions, there is no substantial evidence linking Apo E to complement pathway. This warrants further studies into the yet unexplored association between these.
c. The reason why Apo E abundance in imparts an unusually dense appearance to the deposits is unclear, although this might be linked to the well-known lipid binding properties of Apo E.
d. The study suggests binding of Apo E to abundant heparin sulfate proteoglycans in glomerular & tubular basement membranes via the N terminus binding domain, however the selectivity and abundance of this process in DDD remains to be answered.

This study has solved a long-standing mystery surrounding DDD and will surely pave way for further research aimed at finding the remaining pieces of the DDD puzzle. A correct stating point to understand the pathophysiology for DDD has likely been found, and we should soon witness evolution of tailored therapies for this complex and clinically challenging disease!

By
Dr Alok Sharma
Director- Renal Pathology and Electron Microscopy
Dr Lal Path Labs

KDIGO 2024 ANCA VASCULITIS GUIDELINES UPDATE

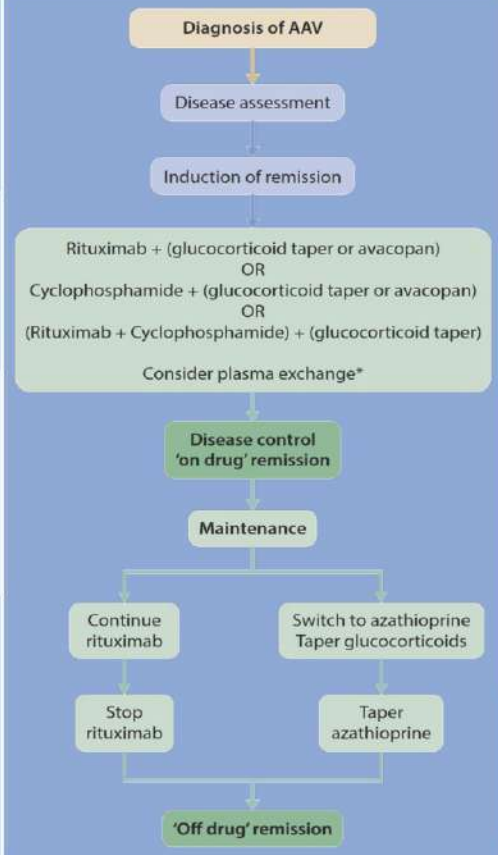
1. DIAGNOSIS

In clinical presentation compatible with small vessel vasculitis + MPO / PR3 ANCA positive serology, initiation of immunosuppressive therapy should not be delayed while waiting for a kidney biopsy to be performed or reported, especially in rapidly deteriorating patients

2. RELAPSES

Predictors of future relapses:
- Persistence of ANCA positivity
- Increase in ANCA levels
- Change in ANCA from negative to positive

3. TREATMENT



Consider discontinuation of immunosuppression after 3 months in those who remain on dialysis and who do not have any extrarenal manifestations of disease.

CHOICE OF INDUCTION THERAPY

RITUXIMAB	CYCLOPHOSPHAMIDE
• Children and adolescents • Pre-menopausal ♀ and ♂ concerned about their fertility • Frail older adults • Glucocorticoid-sparing especially important • Relapsing disease • PR3–ANCA disease	• Rituximab difficult to access • Severe GN (SCr >4 mg/dl [354 µmol/l])* ***A combination of 2 intravenous pulses of cyclophosphamide with rituximab can be considered.***

RECOMMENDED STEROID DOSE

	'Reduced-corticosteroid dose' in PEXIVAS trial		
Week	<50 kg	50–75 kg	>75 kg
1	50	60	75
2	25	30	40
3–4	20	25	30
5–6	15	20	25
7–8	12.5	15	20
9–10	10	12.5	15
11–12	7.5	10	12.5
13–14	6	7.5	10
15–16	5	5	7.5
17–18	5	5	7.5
19–20	5	5	5
21–22	5	5	5
23–52	5	5	5
>52	Investigators' local practice		

ROLE OF AVACOPAN:
- An alternative to glucocorticoids
- Patients with ↑ risk of glucocorticoid toxicity
- Patients with ↓ GFR

PLASMAPHERESIS:
- SCr >3.4 mg/dl (>300 mmol/l)
- Requiring dialysis
- Rapidly increasing SCr
- Diffuse alveolar hemorrhage +hypoxemia
- Overlap with antiGBM disease

MAINTENANCE THERAPY
- **Optimal duration : 18 months - 4 years after induction of remission**

RITUXIMAB PREFERRED
- Relapsing disease
- PR3–ANCA disease
- Frail older adults
- Glucocorticoid-sparing especially important
- Azathioprine allergy

AZATHIOPRINE PREFERRED
- Low baseline IgG (<300 mg/dl)
- Limited availability of rituximab

- Consider MMF / methotrexate for maintenance therapy in patients intolerant of azathioprine
- Methotrexate : not to be used if GFR <60 ml/min per 1.73 m2.

4. SPECIAL SITUATIONS:

- **Refractory disease**: ↑ Glucocorticoids, add rituximab if cyclophosphamide induction had been used previously, or vice versa. Plasma exchange can be considered.
- Diffuse alveolar bleeding with hypoxemia: Consider plasma exchange + glucocorticoids + cyclophosphamide or rituximab

5. TRANSPLANTATION:

- ✓ Delay transplantation until patients are in complete clinical remission for ‡6 months
- ✓ The persistence of ANCA should not delay transplantation.

REFERENCE: KDIGO 2024 CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF ANTINEUTROPHIL CYTOPLASMIC ANTIBODY (ANCA)–ASSOCIATED VASCULITIS

Infographic by Subashri (@happiedoc) Urvashi (m @melgreux)

Budesonide in IgA : An option for interim Relief till we find better alternatives

IgA Nephropathy is a significant cause of end-stage kidney disease (ESKD) with 30-45% of patients progressing to ESKD within 20-25 years after diagnosis. Due to its largely benign nature early on, it is usually detected at later stages where we do not have much to offer for its treatment. In recent years, the pathophysiology of this disease has been narrowed down to production of Galactose deficient IgA multimers due to defective signalling in the Peyer's patches.

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). This preparation of budesonide, due to high first pass hepatic metabolism, theoretically reduces the risk of systemic steroid side effects.

NefIgArd Trial tested the efficacy and safety of Nefecon in a randomised control fashion in which the trial eligible patients (White adults aged ≥18 years with primary IgA nephropathy, estimated GFR 35−90 mL/min per 1·73 m², and urine protein– creatinine ratio ≥0·8 g/g or proteinuria ≥1 g/24 h) despite optimised renin-angiotensin system blockade) received a dose of 16mg/day oral capsules or placebo to be given daily for a period of 9 months. This was followed by a 15 month follow up period off the study drug. The primary endpoint was a time weighted average of eGFR over 2 years. The results showed a statistically significant and sustained effect of the drug in delaying the decline of GFR (-7.52ml/min/1.73m2 in Placebo vs only -2.47 ml/min/1.73m2 in treatment group) over 2 years. The eGFR benefit accrued by the end of 9 months of treatment with Nefecon was maintained during the 15 months of observational follow-up. Also, a durable reduction in UPCR was seen from baseline by 40·3% in the Nefecon group, compared with a 1·0% increase in the placebo group at the end of the study with a maximum difference of 49.7% in proteinuria between 2 groups seen at the end of 12 months. The above data suggests a disease- modifying effect of Nefecon in patients with IgA nephropathy.

Safety data of Nefecon suggested that common adverse events were of mild severity and reversible in nature. These included peripheral oedema (31 [17%] of 182 patients *vs* placebo, seven [4%] of 182 patients), hypertension (22 [12%] *vs* six [3%]), muscle spasms (22 [12%] *vs* seven [4%] patients), acne (20 [11%] *vs* two [1%]), and headache (19 [10%] *vs* 14 [8%]). Treatment group did not have any significant difference in new onset diabetes and HbA1c variations and no difference in fractures. Incidence of infections during treatment was similar between the two groups (63 [35%] of 182 patients the Nefecon group and 57 [31%] of 182 in the placebo group). 2 patients died in the Nefecon group, one from COVID-19 Infection (other co-morbidcConditions were also present) and one from cerebral haemorrhage. Neither death was related to the study treatment. No treatment-emergent adverse events leading to death were reported in the placebo group.

Based on the results of this trial Nefecon has been approved for treatment of IgA Nephropathy. This drug presently is not available in India. 2 Indian studies which reported use of budesonide in IgA nephropathy patients reported proteinuria reduction and GFR improvement in patients. These studies used different doses of Budesonide which although were targeted release, were not specific to distal ileum (used for Crohn's Disease).

The long term data of these patients will be eagerly awaited to determine whether the drug will stand the test of time. Meanwhile new drugs like Sparsentan and APRIL and BLys inhibitors are also offering promising results with lesser side effects and are touted as good steroid sparing alternatives. Until then, we will have to depend on steroids and supportive care for care of our patients with IgA Nephropathy.

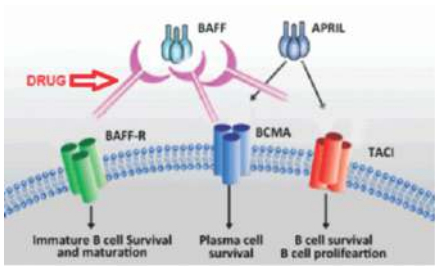
Dr. Aniketh Prabhakar,
Consultant nephrologist, Mysore, India

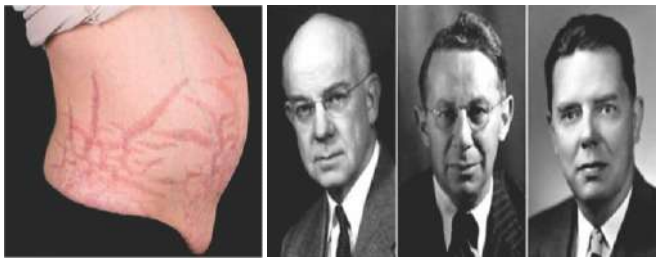
TEST your THERAPEUTICS

Vineet Behera

Question 1.

The famous American singer and actress was suffering from a serious glomerular disorder which led to major problems, and ultimately she had to undergo kidney transplant in 2017. Several oral and injectable treatment options have been tried for this potentially life-threatening glomerular disorder, all with mixed benefit and potential side effects. This new therapeutic agent with the mechanism of action as shown in the figure, has good promising results and is given as fortnightly injections for two years. Identify the therapeutic agent and the glomerular disease.



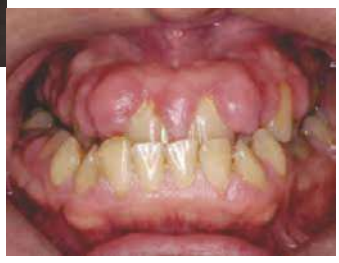


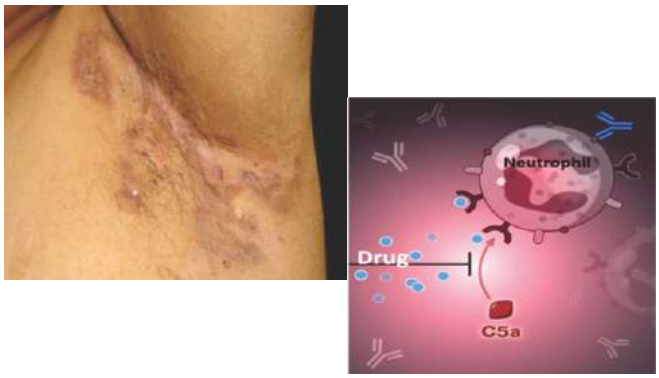
Question 2.

This therapeutic agent is an available option used in the treatment of several primary glomerular conditions, and has shown fair response in refractory primary membranous nephropathy (not responding to steroids, CYC, CNIs) and steroid resistant FSGS. It is used as subcutaneous injectable therapy and is associated with cutaneous side effects (as shown in the Figure) and hirsutism. Interestingly, the scientists shown in the figure were awarded the Nobel prize in Medicine in 1950, for their work revolving around the abovementioned drug. Identify the therapeutic agent.

Question 3.

This therapeutic agent is isolated from a unique ascomycetes fungus which has a parasitic sexual stage in a type of beetles, while its therapeutic benefits are derived from asexual mold stage in soil. It has wide applications in autoimmune conditions like rheumatoid arthritis, psoriasis, neurological conditions, and in several glomerulonephritis like podocytopathies, lupus nephritis. Long term use of this drug may be associated with side effects as shown in the figure. A semisynthetic similar molecule was recently developed, which has lesser side effects and is gradually finding application in glomerular diseases. Identify the drugs.



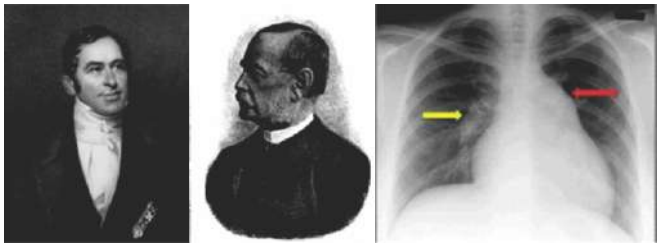


Question 4.

The therapeutic drug is effective in refractory cases of an autoimmune chronic skin disorder characterised by multiple recurrent abscesses and scarring, as shown in the figure. It was initially developed for use in a serious potentially life threatening systemic disease, but is also being used in glomerulonephritis like C3 glomerulopathy, IgA nephropathy and SLE. The drug is administered orally and the action is mediated by inhibiting the action of neutrophils as shown in figure. Identify the drug and the primary use.

Question 5.

A common systemic disease is named after the above two physicians who first described a patient suffering from the disease, and who first described the condition as an entity in the 18th century. The disease may also manifest in the kidney as a well known glomerular disease. During the recent years, a group of drugs primarily used for a pulmonary condition (as shown in the chest xray), was found to have a benefit in the glomerular condition, by reducing proteinuria. Identify the drug and the glomerular disease.



Answers

1. Belimumab in Lupus Nephritis

Belimumab is a recombinant, human monoclonal antibody directed against the cytokine BlyS (B-cell activating factor- BAFF), targeting CD20-positive B cells. It is the first targeted biological for the treatment of SLE. It is administered in a dose of 10mg/kg fortnightly (3 doses) followed by monthly doses for 2 years. Based on the BLISS-LN trial and other studies, it was shown that belimumab plus standard therapy was more effective, and had a favourable safety in patients with lupus nephritis (LN). The KDIGO 2024 guidelines recommends its use as a treatment option for initial and maintenance combination therapy for Class III or IV lupus nephritis.

Senena Gomez developed LN in 2015 and underwent kidney transplant in June 2017 at the age of 24 years.

2. Acthar Gel (ACTH injection)

ACTH Injections (Acthar Gel) is a naturally sourced mixture of adrenocorticotropic hormone analogs, that stimulates the adrenal cortex to produce steroids, without any feedback inhibition. It is used in inflammatory conditions like multiple sclerosis, rheumatoid arthritis, or inflammatory myopathy. It has shown moderate benefit in refractory glomerular diseases like membranous nephropathy, FSGS, and partial benefit in IgA nephropathy or minimal change disease. It is administered at a dose of 40 IU SC twice a week for 6 months. It is associated with side effects like fluid retention, hypertension, hyperglycemia or cutaneous side effects like striae, capillary fragility, pigmentation or hirsutism.

Incidentally, Edward Kendall, Tadeusz Reichstein, and Philip Hench were jointly awarded the Nobel Prize for Medicine in 1950 for their work on adrenal hormones which further paved the way for the use of steroids (and ACTH), which is the cornerstone of therapy in autoimmune and inflammatory conditions.

3. Cyclosporin and Voclosporin

Cyclosporin is a calcineurin inhibitor immunosuppressant and has a key role to play in glomerulonephritis like minimal change disease, FSGS, membranous nephropathy, lupus nephritis, and others. It is originally extracted from a fungi Tolypocladium inflatum from Norweigan soil in 1969, and was detected to have strong immunosuppressant properties that was used to prevent rejection in organ transplantation. It is associated with side effects like nephrotoxicity, hypertension, tremors, neurotoxicity, dyslipidemia, hyperglycemia, hypertrichosis, gum hypertrophy, and risk of infections.

Voclosporin is a cyclosporine A analog with a modification of the functional group on the amino acid 1 residue, which has more potent calcineurin inhibition but less side effects. The AURORA1 and AURORA 2 trials have shown the efficacy and safety of voclosporin in lupus nephritis.

4. Avacopan in ANCA Vasculitis

Avacopan is a complement 5a receptor (C5aR) antagonist that inhibits the interaction between C5aR and the anaphylatoxin C5a, thus blocking the action of neutrophils in the complement pathway. It is recommended for use in adults with severe active granulomatosis with polyangiitis or microscopic polyangiitis, in combination with standard therapy like steroids or cyclophosphamide. It is administered orally at a dose of 30mg once to twice a day. It also has a role in refractory cases of hidradenitis suppurativa, which is non-responsive to the standard lines of therapy.

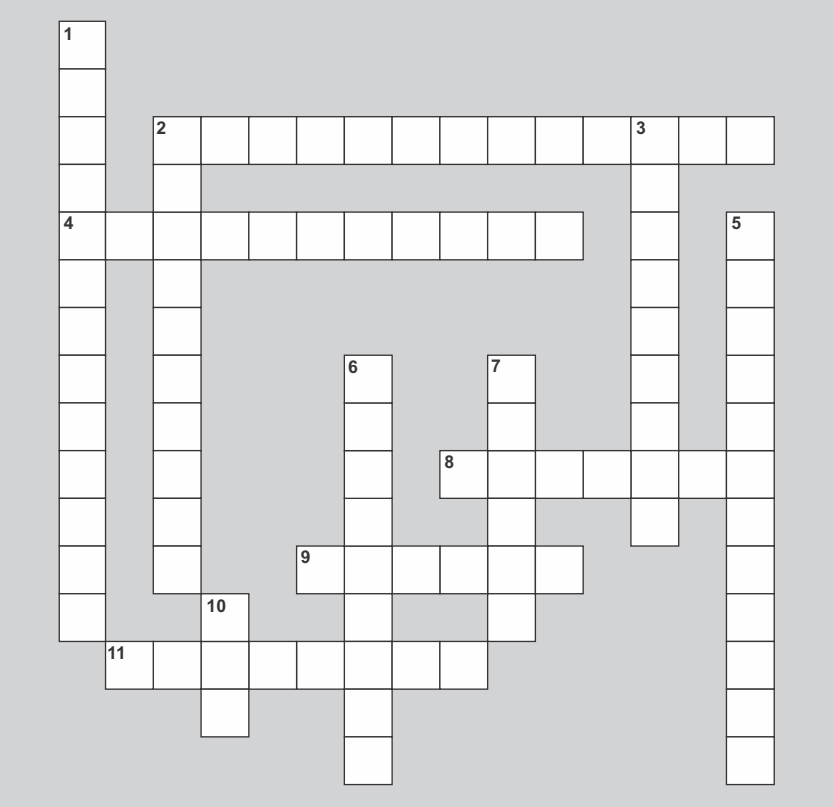
5. Selective endothelin receptor antagonist in IgA Nephropathy

IgA Vasculitis is a systemic inflammatory vasculitis also known as Henoch Schonlein purpura, named after Johann Schönlein who first described the condition as an entity in 1837, and Eduard Heinrich Henoch who reported the first case of a patient with colic, bloody diarrhea, painful joints, and a rash in 1868. It is linked to a primary glomerulonephritic disorder, IgA nephropathy.

Endothelin receptor (ER) antagonists were primarily used in the treatment of pulmonary hypertension. But selective ER antagonists with additional angiotensin receptor blocking properties (known as dual endothelin A/angiotensin 2 receptor antagonists, DEARA) have shown to reduce proteinuria and retard the disease progression in IgA nephropathy. DEARA agents like Sparsentan (PROTECT and SPARTAN trials) and Atrasentan (ALIGN, AFFINITY, and ASSIST trials) have shown benefit in IgA nephropathy.

Glomerular Games

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



Please follow the link to access the crossword

Across

2) This acute phase reactant is a natural competitive inhibitor of MPO and is a cause for ANCA negativity.(13)
4) This bisphosphonate is associated with FSGS(11)
8) Drug trial in IgAN that has a name which means its keeps the kidney away from harm(7)
9) Trial of "dual" endothelin angiotensin receptor blockade in FSGS(6)
11) Syndrome characterised by glomerulonephritis, giant platelets, granulocyte inclusion bodies, cataract, and sensorineural deafness(8)

Down

1) A humanized IgG2 monoclonal antibody that binds to and neutralizes APRIL, in trial for the treatment of IgA Nephropathy(13)
2) An RNA interference drug in Phase 2 trial which suppresses hepatic synthesis of complement C5 and reduces proteinuria in adult IgAN.(10)
3) The name for electron microscopic finding in a genetically inherited kidney disease which also involves the knees!(4,5)
5) Type II anti- CD 20 agent used in refractory membranous nephropathy(12)
6) The first case of anti-glomerular basement membrane disease was described following this infection(9)
7) Classification used in AAV to categorize glomerular lesions(6)
10) This drug causes phospholipidosis which presents with proteinuria and ultrastructurally resembles Fabry's disease.(3)

Answers to the Crossword are available on page 23

Residents' Corner

Atypical Anti-gbm Disease with Mpo-associated Vasculitis- A Rarest Of The Rare Entity

With an incidence of 0.5–1 per million population, Anti glomerular basement membrane (GBM) antibody glomerulonephritis is a rare glomerular disease. Though the immunoassays for anti-GBM antibodies are positive in around 90% of the patients, they may be absent in up to 10% of patients. In such patients, the diagnosis can be established only by kidney biopsy which shows linear IgG deposits along the GBM. Atypical anti-glomerular basement membrane (anti-GBM) disease is characterized by linear immunoglobulin G (IgG) deposition along the GBM in the absence of circulating IgG anti-GBM antibodies. Whereas the classic anti-GBM disease is more aggressive in nature, the atypical one tends milder usually. Double positivity for anti-GBM and ANCA can also be found and around 47% of patients with seropositive anti-GBM disease were also positive for ANCA and 5-14% of patients with AAV were tested positive for anti-GBM antibody also.

We present one such case which is even more intriguing as it presented with nephrotic range proteinuria and mild AKI despite diffuse crescentric GN on renal biopsy.

CASE DETAILS

A thirty-three-year-old married female with no previous comorbidities presented with bipedal swelling associated with foamy urine from the last 2 months. She also had a history of cough without sputum and fever without chills or evening rise 2 months earlier which subsided within a week with some OTC medications. She reported reddish discolouration of urine a few times in these 2 months. Her symptoms were not associated with oliguria, dysuria, blood-tinged sputum, oral ulcers, photosensitivity, rash, or joint pain. She had no children and no abortions.

On examination, her vitals showed normal pulse rate, BP and Oxygen saturation. Pallor and bipedal pitting edema up to the knees were present. Normal vesicular breath sounds were present in all lung fields except in the bilateral infra-axillary and infrascapular area where the sounds were diminished.

Her baseline investigations revealed the following - Hemoglobin-10.0g/dl, total counts 9000/cu mm platelets 1.6L/cu mm, urea 38 mg/dl, creatinine 1.43 mg/dl, albumin 2.32g/dl, sodium 143 mmol/L and potassium 4.2 mmol/L. Immunological profile was done which revealed C3 158, C4 65.3, ANA(Hep2)-Negative, Anti PLA2R(ELISA)-negative, ANCA- pANCA positive, MPO-106 and PR3- negative. Urine examination showed albumin 2+, occult blood 2+ and 6-7 RBCs and 9.8 g/day proteinuria.

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

A chest x-ray revealed bilateral pleural effusion. On Ultrasonography, both the kidneys were of normal size with slightly raised cortical echogenicity and corticomedullary differentiation was maintained. 2-D echocardiography was normal.

With high titre MPO positivity but Nephrotic syndrome presentation and mild azotemia, she underwent a renal biopsy which revealed the following - **Light Microscopy**- 8 Glomeruli, one segmentally sclerosed with Adhesion formation, rest 7 show mild mesangial matrix and focal mesangial hypercellularity. A total of 5 glomerulus shows fibrocellular crescents. Capillary loops were open, and GBM was fragmented at the site of crescent formation. Preserved tubules show acute tubular injury. Vessels- arteriosclerosis noted. Multifocal lymphocytic infiltration was pointed out in the scarred Interstitium. IF/TA 10 %

Immunofluorescence - 12 Glomeruli, IgG 2+ linear positivity along the capillary wall, IgA negative, IgM Segmental mesangial entrapment in 3 glomeruli, C3c negative, C1q Negative, Kappa trace linear positivity along the capillary wall, Lambda-Negative

Her creatinine peaked at 2.35 mg/dl and treatment was started with IV pulse methylprednisolone 500mg once daily for 3 doses followed by the oral steroid. She was declared atypical anti-GBM with ANCA and started on PLEX.

5 sessions of PLEX were given and but planned Rituximab injections could not be given due to local infection in the lower limbs and was deferred till the resolution of the infection. Her creatinine continued declining. She was discharged with oral steroids and antibiotics and is due for an injection rituximab.

Though the double-positive disease is found, the overlap of atypical anti-GBM with MPO/PR3 positivity is extremely rare to find and to date, there are few case reports available in the literature of such a rare case.

A major cause of non-detection of anti-GBM antibodies in serum is the trapping of these antibodies in kidneys or lungs though other causes are also described. The tests available for detection are ELISA-based and do not guarantee 100% sensitivity and specificity so may be more advanced tests can increase the chances of detection of these antibodies. Due to the very rare occurrence of such a scenario, there are no clear guidelines to treat such patients.

Despite the presence of more than 50% of crescents in this biopsy the course of our patient was not so stormy. As is the case in double positive patients, this patient was also treated with Plasma exchange and high-dose steroids and positive response of pulse steroids and PLEX in such a patient proves that treating such a patient on the lines of anti-GBM is fruitful. As the peak serum creatinine was 2.35 and it also started to come down after starting the immunosuppression, a decision to go with cyclophosphamide was withheld and rituximab was planned.

The patient will be followed up further in our institute and will be monitored for long-term outcomes of the disease. With this case, the understanding of such presentations will enhance for the clinicians.

Dr Gopambuj Singh Rathod,
Dr. Pallavi Mahato,
Dr. Aakash Roy, Dr. Debroop Sengupta
IPGME&R and SSKMH, Kolkata

Renal artery stenosis with coronary artery disease and a flash run from edema : A case report

Background:

Renal artery stenosis is defined as the narrowing of the lumen of one or both the renal arteries. Significant stenosis >/= 60% on invasion/non-invasive methods with symptoms warrants further intervention. The most common causes identified are atherosclerosis and fibromuscular dysplasia. Atherosclerotic CAD is a very common presentation in Asian as well as Western populations. Maximum visits to the emergency room in CAD are due to heart failure as per recent data. Previous studies demonstrated that 39% of atherosclerotic CAD patients have RAS through non-invasive and invasive evaluation. RAS in CAD patients with recurrent pulmonary edema is not an unusual finding in previous studies.

CASE:

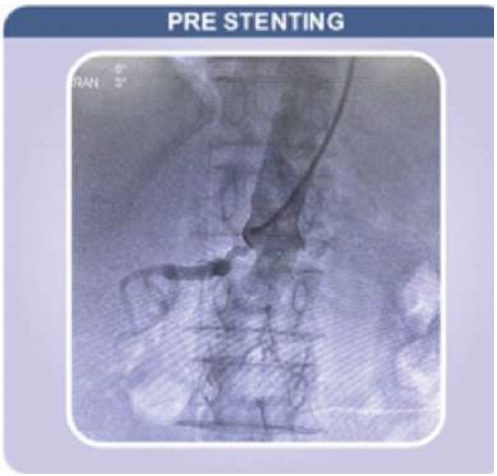
Mrs.X,74 years old female was admitted to our hospital because of acute onset dyspnoea on rest. The patient was labelled as a solitary functioning kidney with CKD for 10 years due to an atrophic right kidney on USG scan and had a baseline creatinine ranging from 1.6 to 1.8. On presentation, she also had accelerated HTN and was managed with IV nitro-glycerine. Through cardiac evaluation was done for the patient. 2D ECHO for the patient showed anterior and inferior wall hypokinesia with an ejection fraction of 35%. CAG was done and the patient was found to have critical LAD blockade (>90%) Immediate drug-eluting stent was placed in LAD and hemodynamic stability was ensured. She was sent home on dual anti-platelets and diuretics. The patient continued to have recurrent hospital admissions in view of dyspnoea in the following year. She was then evaluated for renal artery stenosis in view of disproportionate bilateral kidney size and was found to have B/L renal artery stenosis with left renal artery > 95% blockade. Immediate PTRA with drug-eluting stent (Herculink Elite 6X 18 mm) via RFA was done in the left renal artery. The patient became asymptomatic and had no emergency visits for dyspnoea in the following year. She continues to be on antiplatelets and diuretics and was also started on ACE inhibitors and tolerated well with recent creatinine of 1.6

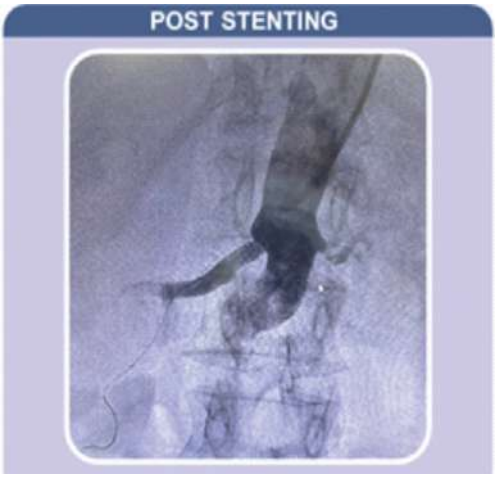
Interpretation:

Significant relief in dyspnoea was seen in the symptoms of the patient after PTRA and stenting was done for RAS.

Discussion:

RAS remains a major area of evaluation in secondary HTN. With most common cause of RAS in the Asian population is atherosclerosis. It still largely remains underdiagnosed. However, no significant HTN control or improvement in renal parameters with the intervention was noticed in previously done studies. RAS evaluation in CAD patients with multiple emergency visits in view of pulmonary edema may be included in the preliminary investigation panel. Concomitant stenting in coronaries and renal arteries in case of significant renal artery stenosis remains a less explored territory and needs further research work.

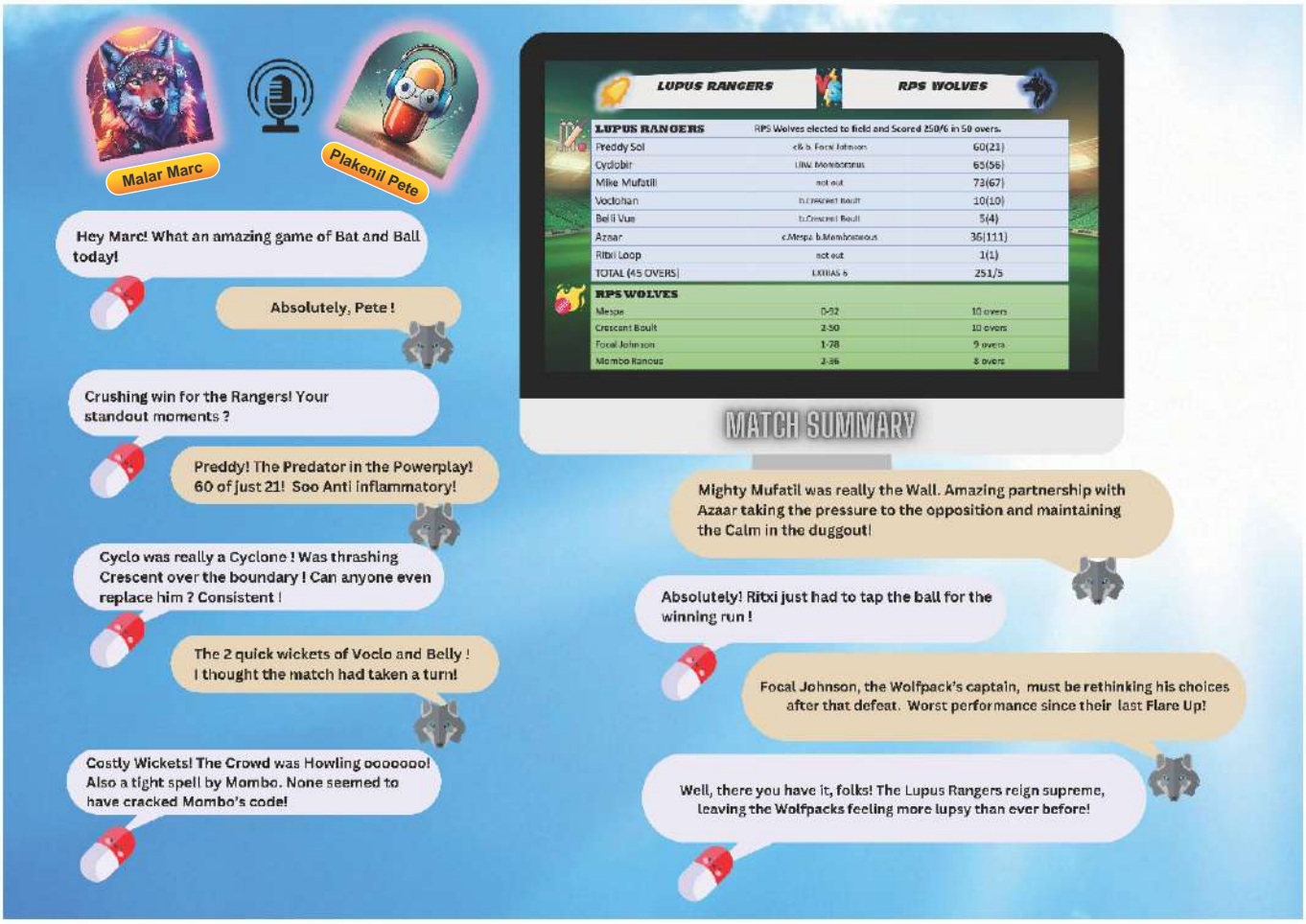




Dr. Neha Pandey, Dr. L.K. Jha, Dr. Yasir Rizvi, Dr. Pranav Tyagi, Dr. Rita, Dr. Aditya, Dr. Urvashi
DNSH, New Delhi

Stay Tooned !

A LUPSIDED ENCOUNTER



by Dr Anand Chellappan

The views and opinions expressed in this cartoon are those of the creator and not that of his/her employer. The content is fictional and any resemblance to actual persons or events is purely coincidental.

Graphic image of Malar Marc & Plakenil Pete created with the assistance of Adobe Firefly

ISN CROSSWORD ANSWERS

ACROSS

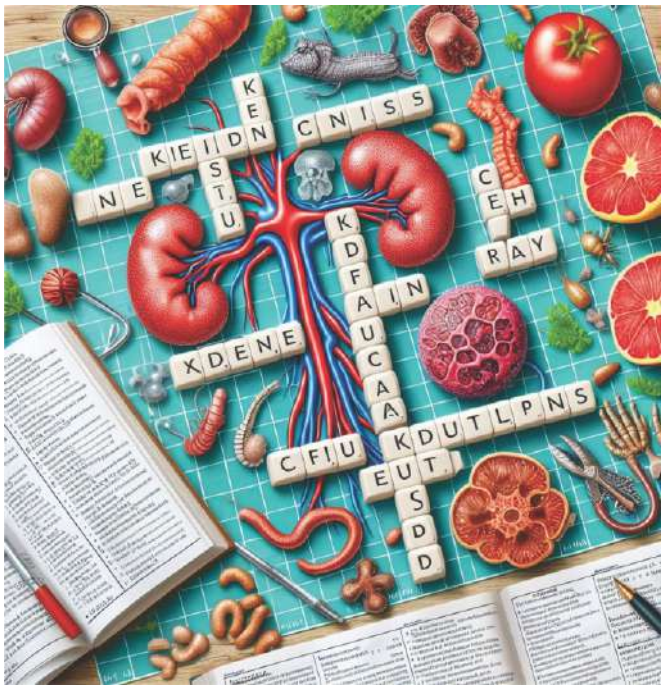
2) CERULOPLASMIN. It binds to specific epitopes of MPO and hence ANCA IgG are unable to bind to auto antigen MPO.

4) PAMIDRONATE. It is associated with collapsing FSGS and MCD.

8) PROTECT **-** This was a randomised controlled trial comparing sparsentan with irbesartan in IgAN. Primary outcome was proteinuria change from 0 to 36 weeks which was significantly higher in the sparsentan arm. Moreover, there was also a significant preservation of kidney function as assessed by chronic eGFR slope in the sparsentan arm.

9) DUPLEX **-** This RCT of irbesartan vs sparsentan use in FSGS (without secondary cause) saw a significant proteinuria reduction at 36 weeks with sparsentan but no significant difference in the primary endpoint using eGFR slope at 108 weeks

11) FECHTNER SYNDROME As a *MYH9* disorder, Fechtner syndrome is characterized by nephritis, giant platelets, granulocyte inclusion bodies (Döhle-like bodies), cataract, and sensorineural deafness



DOWN

1) SIBEPRENLIMAB A proliferation-inducing ligand (APRIL) is implicated in the pathogenesis of IgA nephropathy. Sibeprenlimab is a humanized IgG2 monoclonal antibody that binds to and neutralizes APRIL. This is a phase 2, multicenter, double-blind, randomized, placebo-controlled, parallel-group trial, we randomly assigned adults with biopsy-confirmed IgA nephropathy who were at high risk for disease progression, despite having received standard-care treatment, in a 1:1:1:1 ratio to receive intravenous sibeprenlimab at a dose of 2, 4, or 8 mg per kilogram of body weight or placebo once monthly for 12 months.

2) CEMDISIRAN. Investigational RNA interference therapeutic. Finding of RCT indicates that it resulted in reduction of proteinuria at week 32 and was well-tolerated.

3) MOTH EATEN**-** Nail patella syndrome is an Autosomal dominant inherited disorder due to mutation in LMX1B gene. Patients present with renal, skeletal and nail dystrophic changes. Renal involvement may be of variable severity with proteiinuria, which may present at any age. LM may show secondary FSGS. EM shows focal or diffuse GBM thickening with areas of electron lucent areas with type III collagen bundles.

5) OBINITUZUMAB is a novel humanized and glycoengineered type II anti-CD20 monoclonal antibody that has superior *in vitro* B-cell cytotoxicity compared with rituximab. It has been successfully used in refractory membranous nephropathy

6) INFLUENZA Ernest Goodpasture, an American pathologist, was credited with the first description of the syndrome in his 1919 paper describing a fatal case of GN and lung hemorrhage that was, at the time, attributed to an atypic influenza infection

7) BERDEN: The classification system is composed of four categories. The focal category contains biopsies wherein ≥50% of glomeruli are not yet affected by the disease. In the crescentic category, more than half of the glomeruli have cellular crescents. The mixed category involves biopsies in which a combination of normal, crescentic, and sclerotic glomeruli are present, all occurring in <50% of glomeruli. Forming the sclerotic category are biopsies characterized by ≥50% globally sclerotic glomeruli

10) HCQ. HCQ induced phospholipidosis, though rare, must be considered as one of the differentials in a person with persistent proteinuria and on EM, shows foot process effacement with multiple podocytes showing myelin like inclusion bodies in cytoplasm.

Graphic image created with the assistance of Microsoft AI