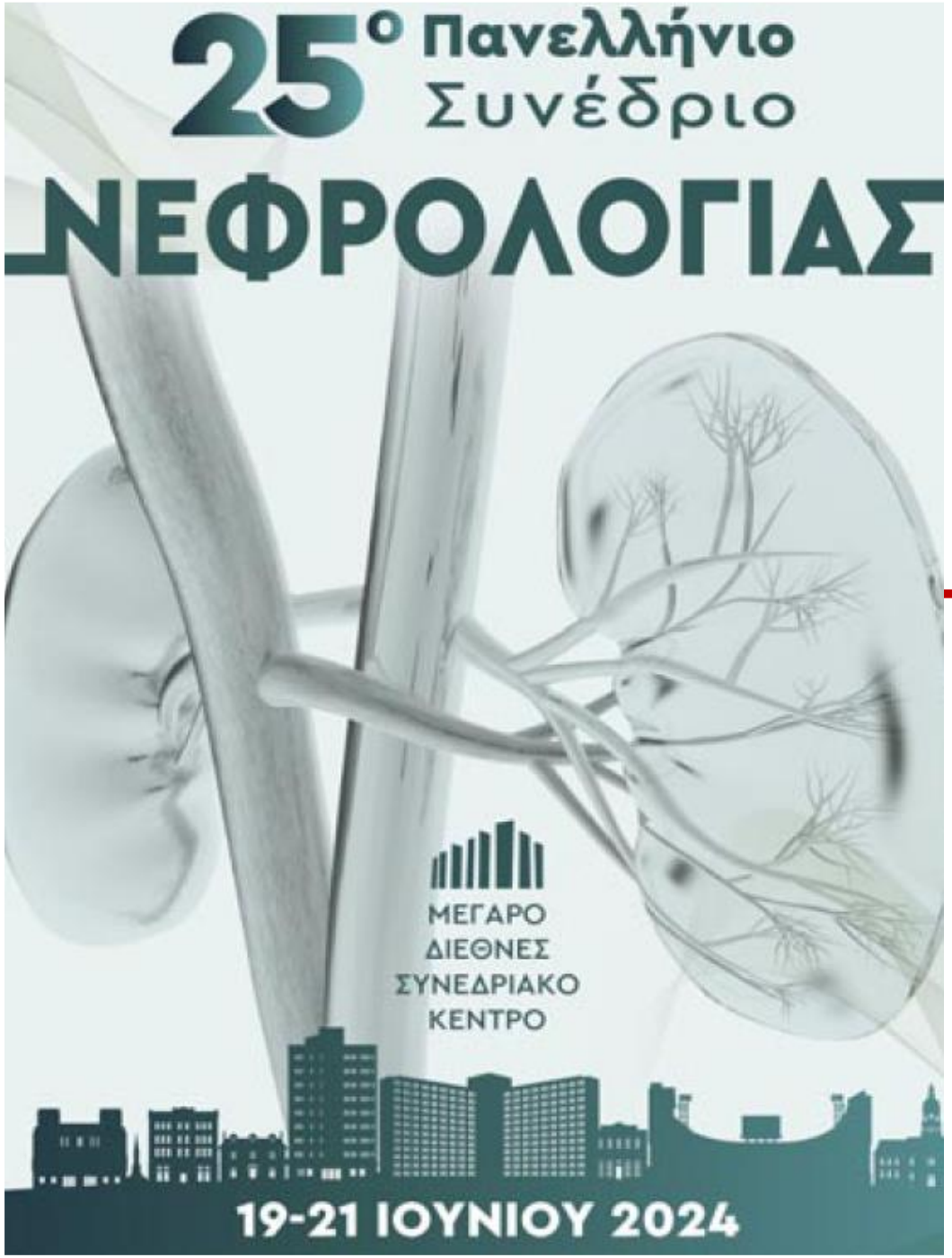


# Στοχευμένης δράσης βουδεσονίδη: Απαντήσεις και ερωτήματα από την κλινική εμπειρία

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# Ερωτήματα που προκύπτουν μετά την εφαρμογή της Targeted Released Budesonide (TRB) στη θεραπεία της IgAN

1. Υπάρχει υπεροχή της TRB έναντι των μέχρι τώρα θεραπευτικών επιλογών?

   Συντηρητική αντιμετώπιση: αMEA, sGLT2

   Στοχευμένη αντιμετώπιση: κορτικοειδή, ανοσοκατασταλτικά

2. Υπάρχει ύφεση της λευκωματουρίας? Υπάρχει βελτίωση της νεφρικής λειτουργίας?
3. Ποιοι ασθενείς είναι πιθανό να απαντήσουν?
4. Έχει επίδραση σε παθογενετικές οδούς και βιοδείκτες?
5. Πόσος χρόνος χορήγησης είναι αρκετός?
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6. **Παρενέργειες?**
7. **Πόσο συχνή είναι η υποτροπή, πότε την περιμένουμε?**

# Supportive Care in IgA Nephropathy

neph madness 2023

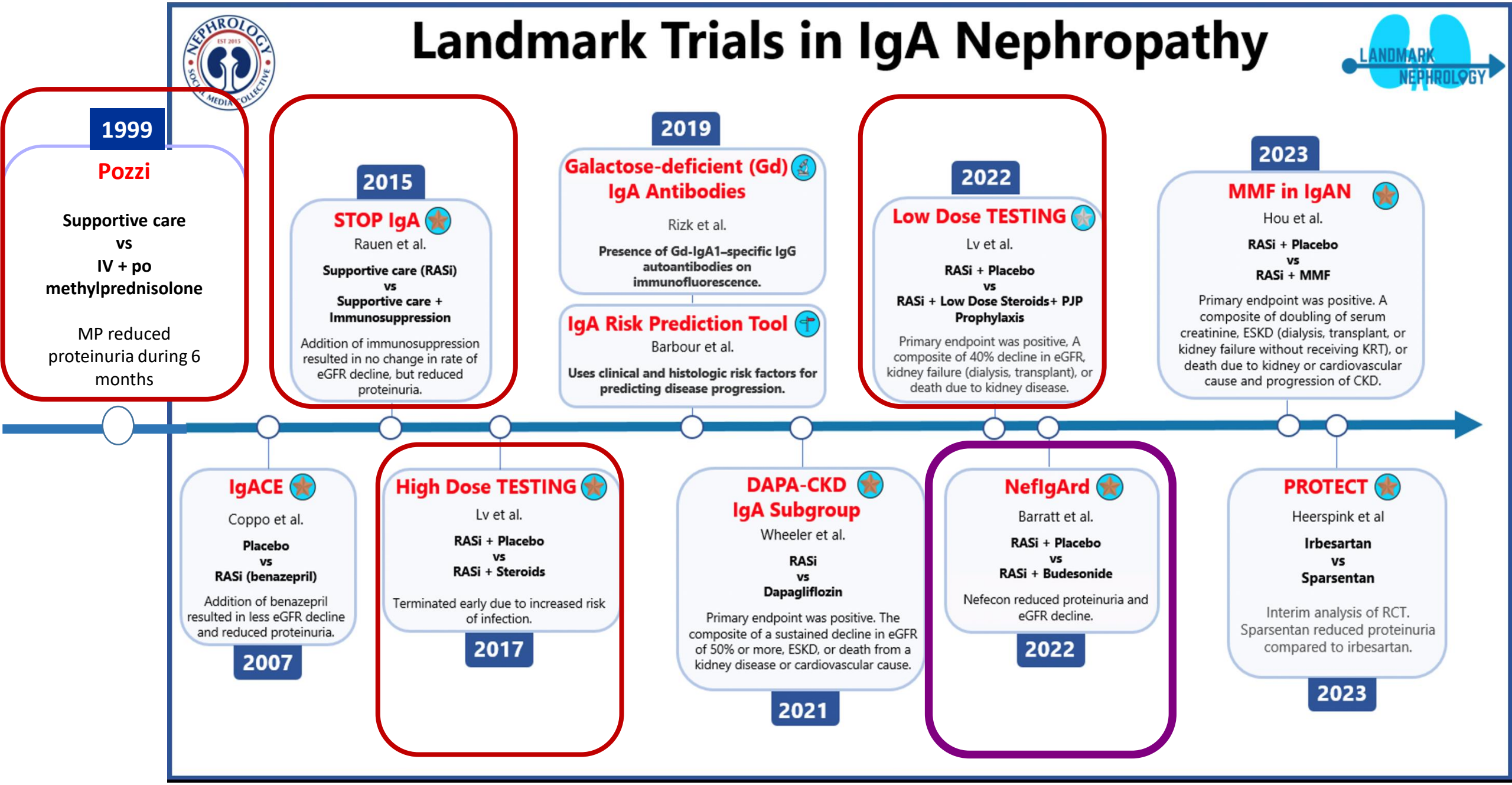
Slow kidney disease progression

| | BP reduction | RAAS Blockade ACEi & ARB | SGLT2i dapa & empa | ETAB/ARB sparsentan | Weight loss | Smoking Cessation | Dyslipidemia | Fish oil | Tonsillectomy |
|---|---|---|---|---|---|---|---|---|---|
| Goal | < 125 -130<br>< 75 - 80 | Proteinuria<br>< 1 g/d<br>or < 0.5 g/d | Albuminuria | Start for UPCR >1.5 g/g<br>Proteinuria | Proteinuria | | Proteinuria | Cardio-vascular benefits | Immuno-modulatory |
| Mechanism of Action | intraglom pressure<br>proteinuria<br>&<br>secondary glom injury | intraglom pressure<br>proteinuria | Na reabsorption in proximal convoluted tubule<br>Intraglom pressure<br>-other effects | intraglom pressure<br>proteinuria<br>Anti-inflammatory | obesity-related hyperfiltration<br>glom & segmental sclerosis | Improves general health | Proposed glomerular & mesangial protective effects | Kidney protection is not proven. Conflicting data. | Removal of source of abnormal IgA<br>circulating immune complexes & glom deposits |
| Mentions | Hypertension<br>=<br>most potent predictor of outcome | ACEi + ARB combo<br>hyperkalemia<br>No benefit | Dapaglifozin<br>Primary composite endpoint<br>eGFR decline 50%, ESKD, death from kidney or CV cause | FDA conditional approval based on proteinuria outcomes<br>*NOT PUBLISHED<br>REMS AST/ALT monitoring | Proteinuria in low calorie diet<br>*no RCTs | Cigarette smoking<br>=<br>dose-dependent predictor in IgAN progression | Proteinuria (from 800 mg/d to 500 mg/d) in statin arm<br>*Small study (n=21), short follow up | Requires high doses (3-12 g/d)<br>*do not use alone | Japanese cohort<br>hematuria reduction /clinical remission<br>*marginal improvement in proteinuria |

Best Evidence in IgAN | RCT Ongoing | IgAN specific studies backing but important therapy | Conflicting evidence

@Nephroseeker

# Landmark Trials in IgA Nephropathy



# Issues arise from treatment with Systemic Steroids

1. **Steroids reduce glomerular inflammation but do not act in the disease pathogenesis**

   no change in Gd-IgA1 circulating levels

   temporary beneficial effect – relapse of proteinuria early after withdrawal

   need to repeat steroid course

2. **Steroid toxicity (reported only in newer clinical studies)**

   infections (*Pneumocystis jirovecii*, *Nocardia* and *Cryptococcus) – need for Pneumocystis* prophylaxis

   diabetes melitus

   death due to sepsis

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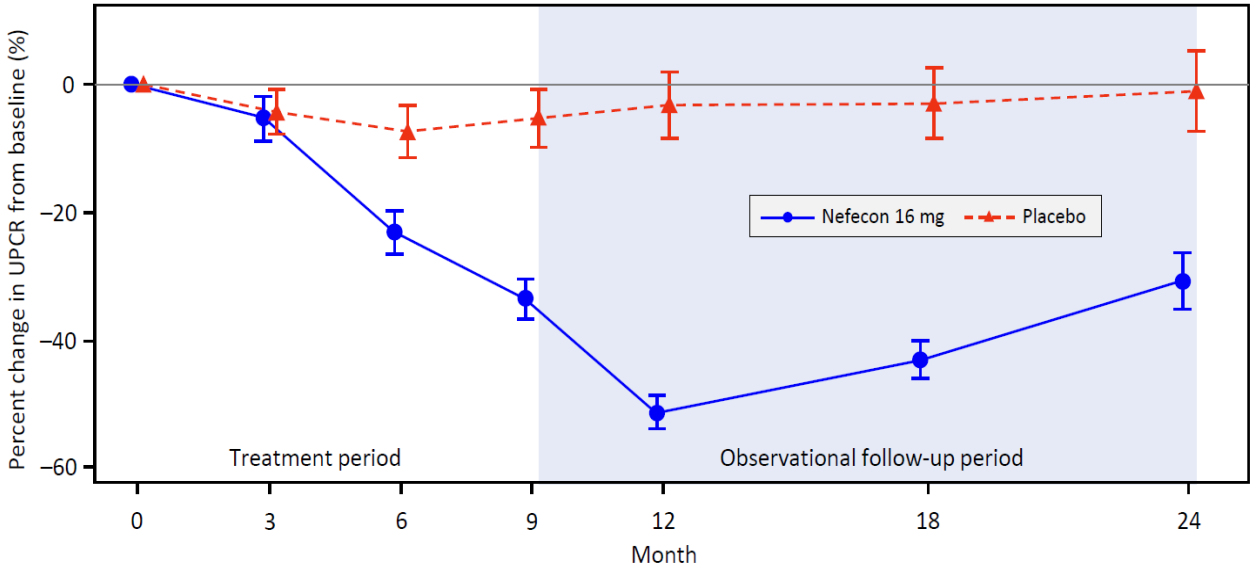


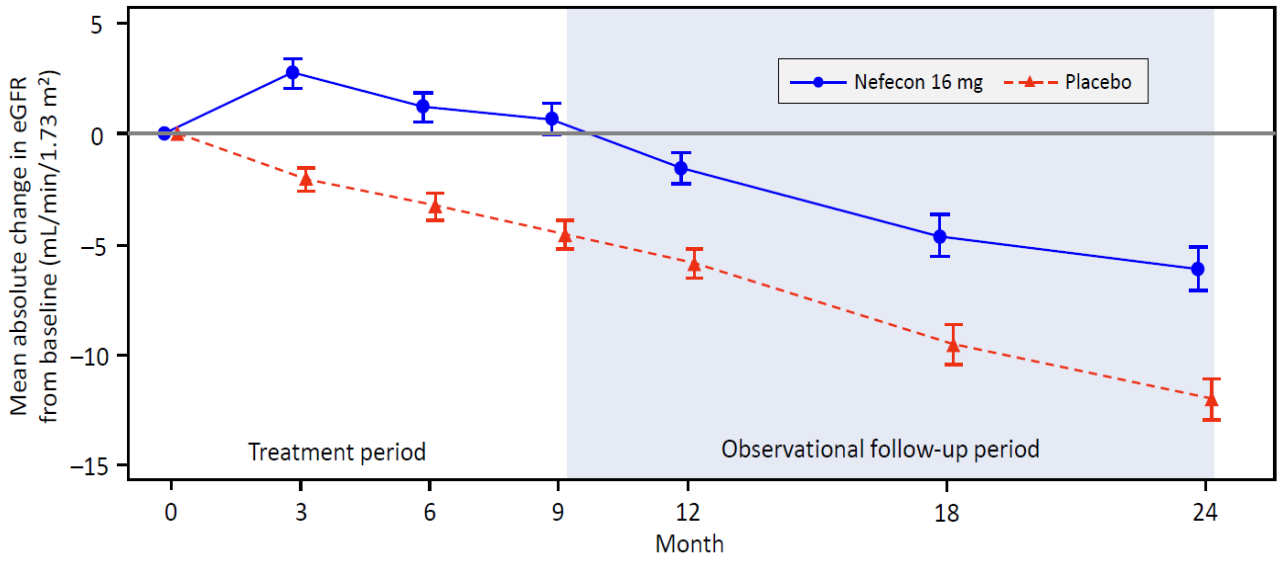

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# Factors influencing early response of IgA Nephropathy following Targeted-release budesonide (TRB) treatment. Preliminary results from a multicenter study

Christodoulos Keskinis[1,2], Eleni Moysidou[1,3], Eleni Kapsia[4], Vassilios Vaios[5], Christos Bintas[4], Maria Trivyza[6], Michalis Christodoulou[1,3], Georgios Lioulios[1,3], Stamatia Stai[1,3], Christina Nikolaidou[7], Panagiotis Pateinakis[2], Marios Papasotiriou[6], Vassilios Liakopoulos[5], Smaragdi Marinaki[4], Maria Stangou[1,3]

[1]*School of Medicine, Aristotle University of Thessaloniki (AUTH), Greece*

[2]*Department of Nephrology, Papageorgiou Hospital, Thessaloniki, Greece*

[3]*1st Department of Nephrology AUTH, Hippokration Hospital, Thessaloniki, Greece*

[4]*Department of Nephrology and Renal Transplantation, Medical School, National and Kapodistrian University of Athens, Laiko Hospital, Athens, Greece*

[5] *2nd Department of Nephrology, Medical School, Aristotle University of Thessaloniki, AHEPA Hospital, Thessaloniki, Greece.*

[6]*Department of Nephrology and Renal Transplantation, University Hospital of Patras, Greece*

[7] *Department of Pathology, Hippokration Hospital, Thessaloniki, Greece*

**Στόχος της μελέτης:** Παρακολούθηση της πορείας ασθενών με IgAN, οι οποίοι πληρούσαν τα κριτήρια και εντάχθηκαν σε αγωγή με TRB, και αξιολόγηση παραμέτρων που σχετίζονται με την απάντηση στη θεραπεία

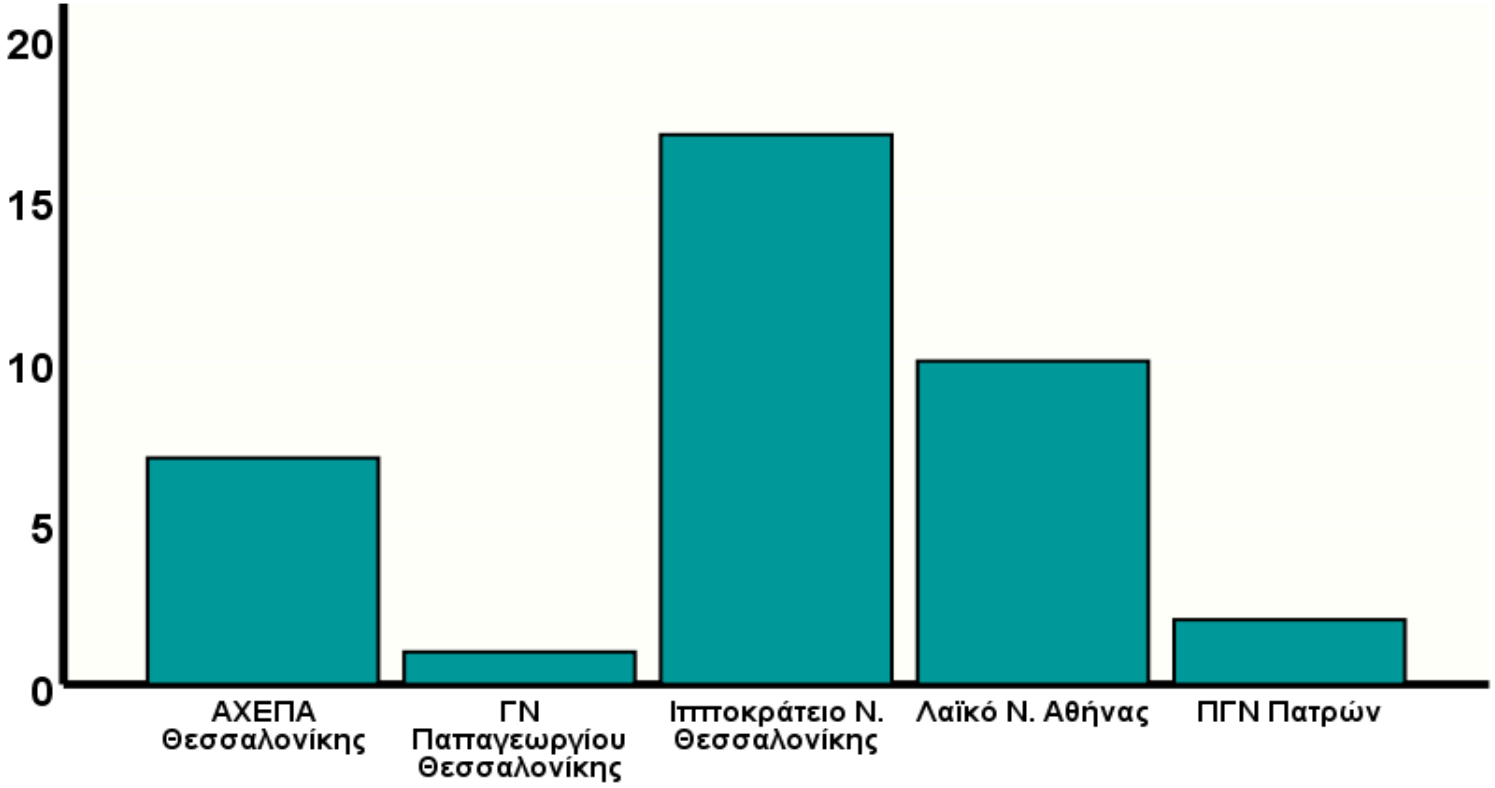
# Materials and methods

## *Inclusion criteria:*

- Age ranging from 18 to 75 years
- Caucasian race
- IgA nephropathy confirmed by kidney biopsy
- The time period since the diagnosis not more than 10 years
- eGFR>30 ml/min/1.73 $m^2$ according
- Uprot >1000mg in two consecutive r
- Treatment with maximal tolerate inhibitors (RAASi) and/or sodium-g months before joining the study
- Written consent

## *Exclusion criteria:*

- IgA vasculitis or Secondary IgA nephr
- Presence of Diabetes Mellitus
- Liver cirrhosis
- Treatment with steroids or immunos



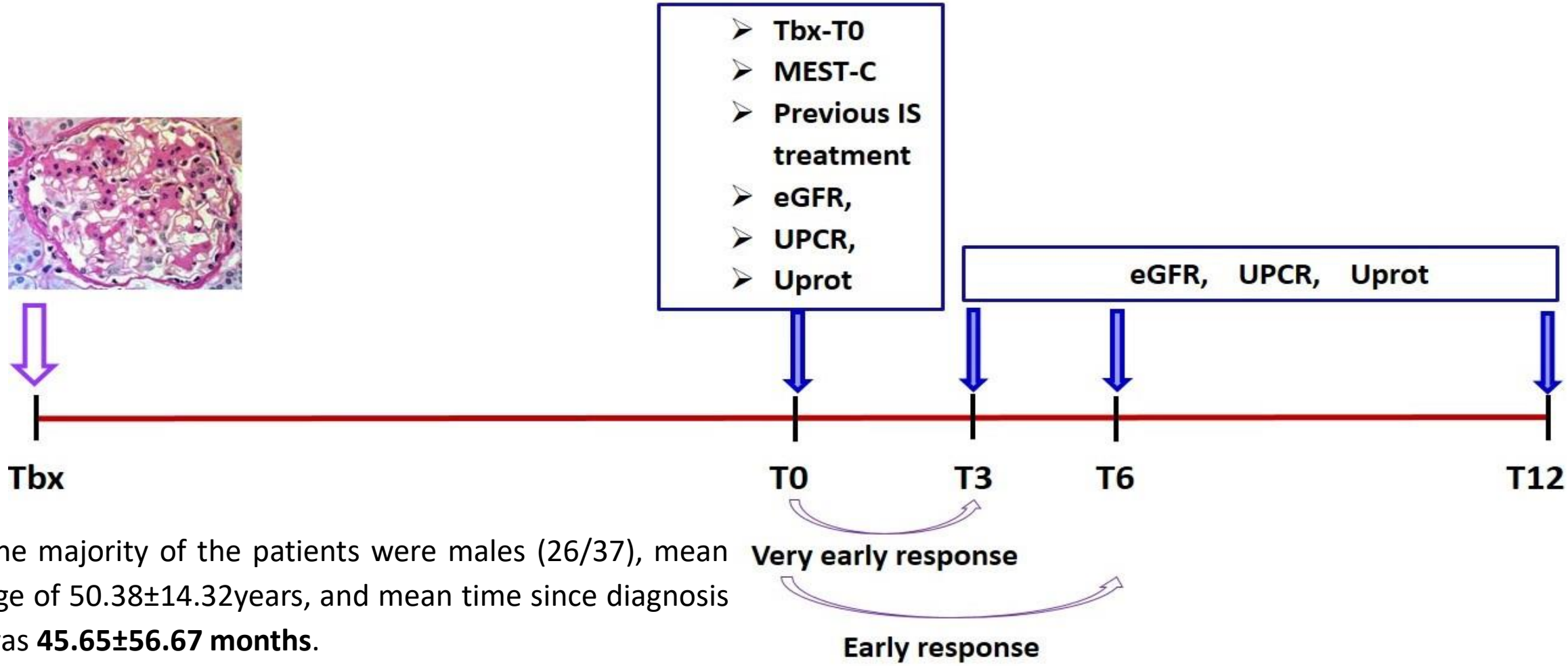
## Schedule of the study

Kidney biopsies were evaluated by one Pathologist and one Nephrologist, unaware of clinical data, and classified according to the 2016 revised Oxford classification system.[9]
Evaluation and follow up was scheduled as follows

- At time point T0: History and clinical findings
  - Time elapsed since the diagnosis of IgAN
  - Record of previous immunosuppressive treatment
- At time point T0: Histological pattern of kidney biopsy
  - Scoring kidney biopsies based on the Oxford classification system (MEST-C score)
- At time points T0, T3, T6: Laboratory findings
  - eGFR CKD-EPI, Uprot and UPCR were evaluated.

## End points

Reduction of proteinuria by ≥30%, combined with stable eGFR at T3 and T6 was regarded as very early reduction (VER) and early reduction (ER), respectively.




The majority of the patients were males (26/37), mean age of 50.38±14.32years, and mean time since diagnosis was **45.65±56.67 months**.

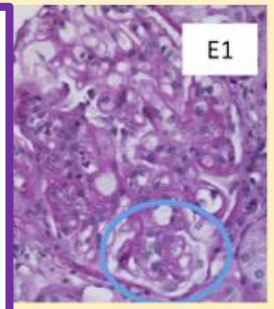
- 17/37(45.94%) systemic corticosteroids
- 2/37(5.4%) cyclophosphamide in the past.

Meanwhile, all patients were treated with RAASi, and 23(62.16%) sGLT-2 inhibitor, for at least 6 months, before starting TRB treatment.

# neph madness 2023 IgA Nephropathy: Histopathology (MEST-C)

**MEST-C classification**

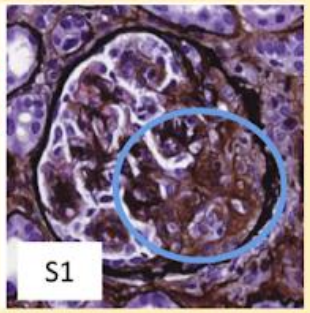
| | |
|---|---|
| M0/M1 | 5/32 |
| E0/E1 | 15/22 |
| S0/S1 | 6/31 |
| T0/T1/T2 | 9/20/8 |
| C0/C1/C2 | 25/15/0 |




lary
larity

number of cells in
apillary lumen

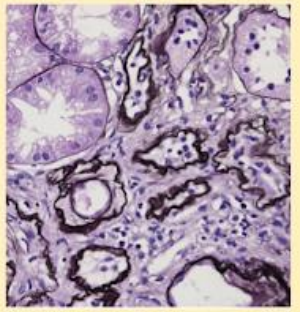
S




**Segmental glomerulosclerosis**

Adhesion or sclerosis that not involving the entire glomerulus

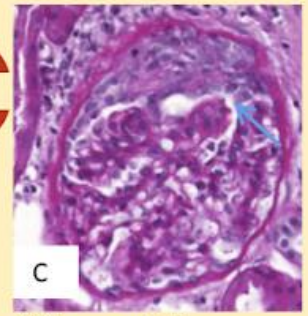
T



**Tubular atrophy/ interstitial fibrosis**

The percentage of tubular atrophy/ interstitial fibrosis of cortical area

C




**Cellular/ fibrocellular crescents**

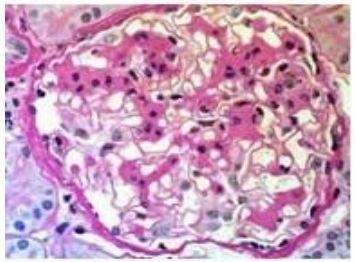
Extracapillary cell proliferation > 2 cell layers thick and <50% matrix

| | | | | |
|---|---|---|---|---|
| M0 ≤50% of glomeruli | E0 Absence | S0 Absence | T0 0-25% | C0 Absence |
| M1 >50% of glomeruli | E1 Any presence | S1 Any presence | T1 26%-50% | C1 <25% of glomeruli |
| | | | T2 >50% | C2 ≥25% of glomeruli |

Conclusion:
IgAN pathogenesis, clinical manifestations, histology, prediction tools, and treatment are reviewed, and case examples are presented to illustrate the approach to the management of patients with IgAN.

Pattrapornpisut P, Avila-Casado C, Reich HN. IgA Nephropathy: Core Curriculum 2021. Am J Kidney Dis. 2021 Sep;78(3):429-441. doi: 10.1053/j.ajkd.2021.01.024. Epub 2021 Jul 9. PMID: 34247883.

VA by @Dilushiwijay MD MRCP



- Tbx-T0
- MEST-C
- Previous IS treatment
- eGFR,
- UPCR,
- Uprot

eGFR, UPCR, Uprot

Tbx T0 T3 T6 T12

**eGFR** 61±23.42 57.29±23.52ml/min/1.73m$^2$ esponse

**Uprot** 2.81±1.88 2.83±1.6gr/24hr

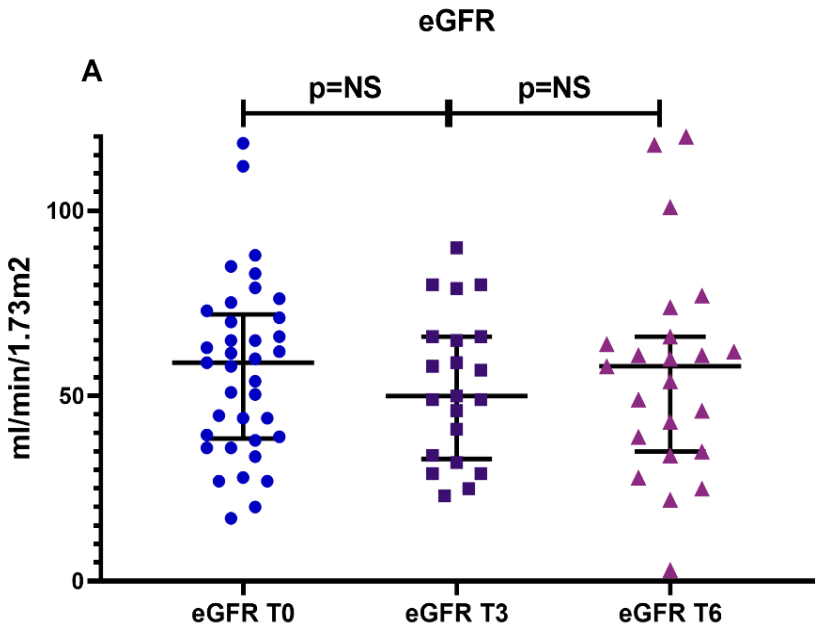
Early response

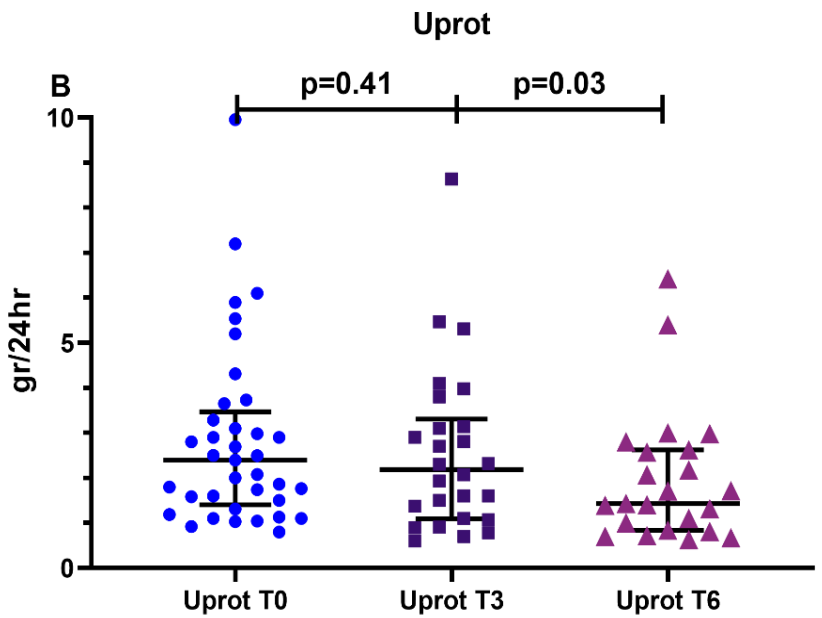
**Disease outcome before and after commencing TRB treatment**.

In the whole cohort of patients, renal function (eGFR CKD EPI) at time of diagnosis was 61±23.42ml/min/1.73m$^2$ and Uprot 2.81±1.88,

after a period of 45.69±56.67months,

eGFR was changed to 57.29±23.52ml/min/1.73m$^2$, and Uprot to 2.83±1.6gr/24hr, p=0.09 and p=0.78, respectively.




During the first 6 months of TRB treatment, and concomitant RAASi (37/37) and SGLT2i (23/37), kidney function remained stable,

| | T0 | T3 | T6 | |
|---|---|---|---|---|
| **eGFR (ml/min/1.73m²)** | 57.29±23.52 | 52.71±19.91 | 58.90±26.3 | p=0.78 |
| **Uprot(gr/24hrs** | 2.83±1.6 | 2.56±1.85gr | 1.98 ±1.47gr | p=0.009 |

| | | |
|---|---|---|
| **Change in eGFR** | from Tbx to T0, | -10.4(24.07)% |
| | from T0 to T6 | -0.33(24.85)%, p=0.096, |
| **Change in Uprot** | from Tbx to T0, | 0(88.71)% |
| | from T0 to T6 | -45.71(114.29)%, p=0.003, |

# Very Early Reduction in proteinuria (VER) after starting TRB treatment

Seventeen patients (45.94%) had a VER, as this was defined by the combination of reduction in Uprot by ≥30% and stable eGFR, after 3 months of TRB treatment.

Changes in eGFR and proteinuria levels in the 17 patients with VER, from T0 to T3

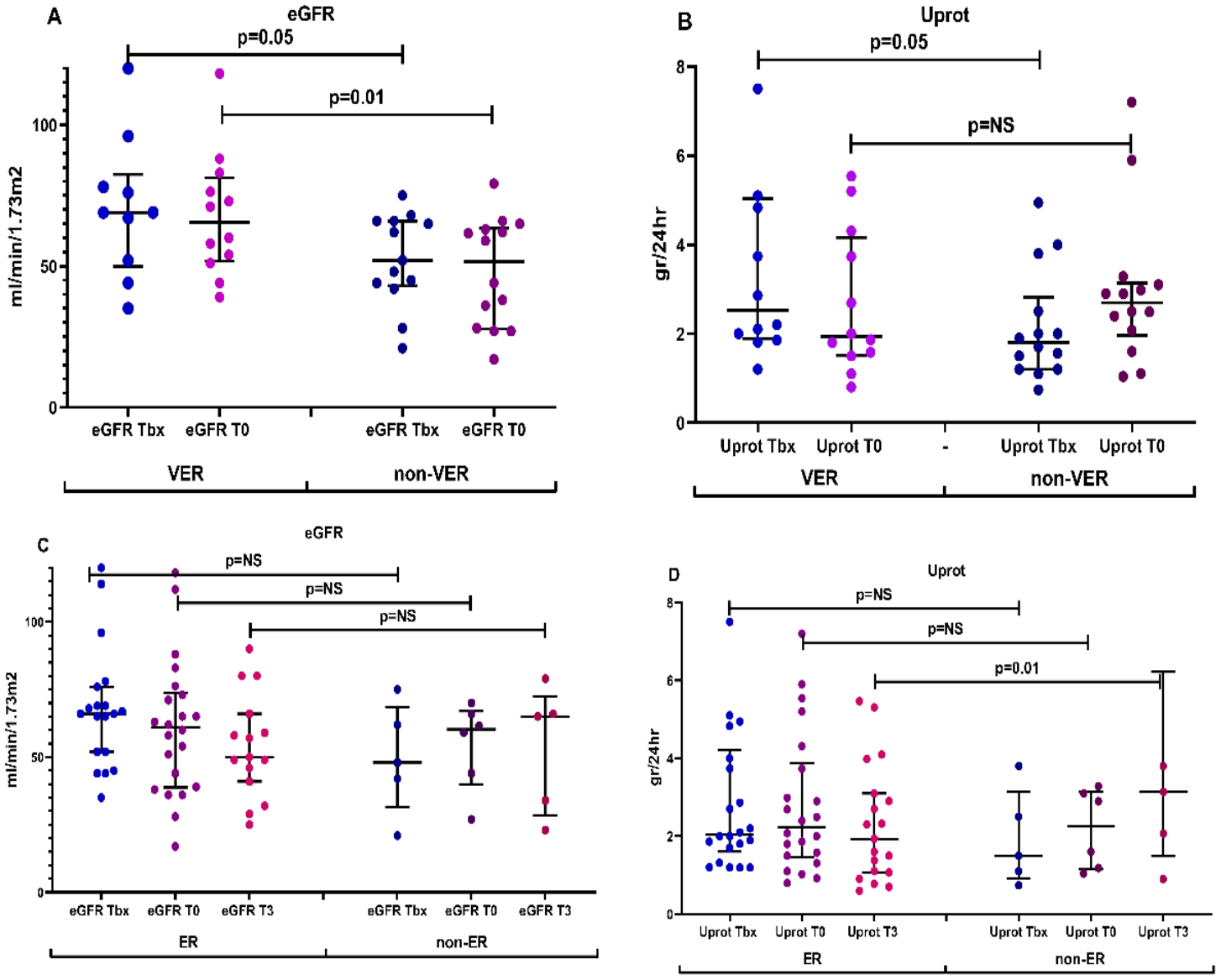
| VER | | | non-VER | | | ER | | | non-ER | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| n=17 | | | n=20 | | | n=29 | | | n=8 | | |
| eGFR (ml/min/1.73m2) | | | eGFR (ml/min/1.73m2) | | | eGFR (ml/min/1.73m2) | | | eGFR (ml/min/1.73m2) | | |
| T0 | T3 | p | T0 | T3 | p | T0 | T3 | p | T0 | T3 | p |
| 61.11±16. | 60.77±18.1 | 0.28 | 44.21±17 | 46.66±19.26 | p=0.22 | 53.07±19.8 | 54.07±19.07 | 0.61 | 51.2±16 | 53.4±23.71 | 0.7 |
| | | | | | | T3 | T6 | p | T3 | T6 | p |
| | | | | | | 54.07±19.0 | 52.21±18.34 | 0.61 | 53.4±23.71 | 46.4±18.39 | 0.16 |
| Uprot (g/24hr) | | | Uprot (g/24hr) | | | Uprot (g/24hr) | | | Uprot (g/24hr) | | |
| T0 | T3 | p | T0 | T3 | p | T0 | T3 | p | T0 | T3 | p |
| 2.67±1.61 | 1.47±0.81 | 0.002 | 2.96±1.69 | 3.49±1.98 | 0.9 | 3.06±1.79 | 2.3±1.51 | 0.014 | 2.38±1 | 3.71±2.97 | 0.26 |
| | | | | | | T3 | T6 | p | T3 | T6 | p |
| | | | | | | 2.3±1.51 | 1.58±0.82 | 0.03 | 3.71±2.97 | 3.38±2.4 | 0.62 |
| UPCR (g/g) | | | UPCR (g/g) | | | UPCR | | | UPCR | | |
| T0 | T3 | p | T0 | T3 | p | T0 | T3 | p | T0 | T3 | p |
| 2.26±0.54 | 1.37±0.45 | 0.1 | 1.89±0.2 | 2.15±0.35 | 0.61 | 1.9±0.64 | 1.94±1 | 0.37 | 2.15±0.9 | 2.2±1.2 | 0.14 |
| | | | | | | T3 | T6 | p | T3 | T6 | p |
| | | | | | | 1.94±1 | 1.73±0.89 | 0.89 | 2.2±1.2 | 2.74±1.24 | 0.12 |

# Parameters associated with VER

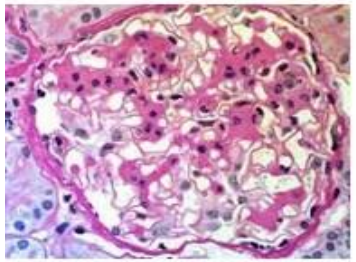
Patients with VER were closer to kidney biopsy, and were slightly younger than non-VER patients. They also had a significantly preserved renal function and higher levels of proteinuria at time of kidney biopsy (Tbx) and at T0, compared to non-VER patients. Proteinuria and UPCR levels did not have any significant difference between VER and non-VER patients at T0.

There was also no difference in the previous treatment modalities between VER and non-VER patients.

| | VER | non-VER | p |
|---|---|---|---|
| **N** | 17 | 20 | |
| **M/F** | 13/4 | 13/7 | 0.45 |
| **Age** | 45.5±13.73 | 52.36±12.95 | 0.2 |
| **Time elapsed since diagnosis (months)** | 29.41±6.96 | 65.37±17.64 | 0.05 |
| **eGFR Tbx (ml/min/1.73m2)** | 70.6±24.74 | 52.46±16.35 | 0.05 |
| **eGFR T0(ml/min/1.73m2)** | 67.96±21.98 | 48.05±19.24 | 0.01 |
| **Uprot Tbx (g/24hr)** | 3.64±2.37 | 2.15±1.24 | 0.05 |
| **Uprot T0 (g/24hr)** | 2.67±1.61 | 2.96±1.69 | 0.66 |
| **UPCR Tbx (g/g)** | 3.86±0.68 | 1.83±1.14 | 0.02 |
| **UPCR T0 (g/g)** | 2.26±0.54 | 1.89±0.2 | 0.66 |




Differences between eGFR and Uprot levels at Tbx and T0 in VER (A) and non-VER (B) patients, and eGFR and Uprot levels at Tbx, T0 and T3 in ER (C) and non-ER (D) patients



- Tbx-T0
- MEST-C
- Previous IS treatment
- eGFR,
- UPCR,
- Uprot

eGFR, UPCR, Uprot

Tbx T0 T3 T6 T12

Very early response

Early response

**Early Reduction in proteinuria (ER) after starting TRB treatment**

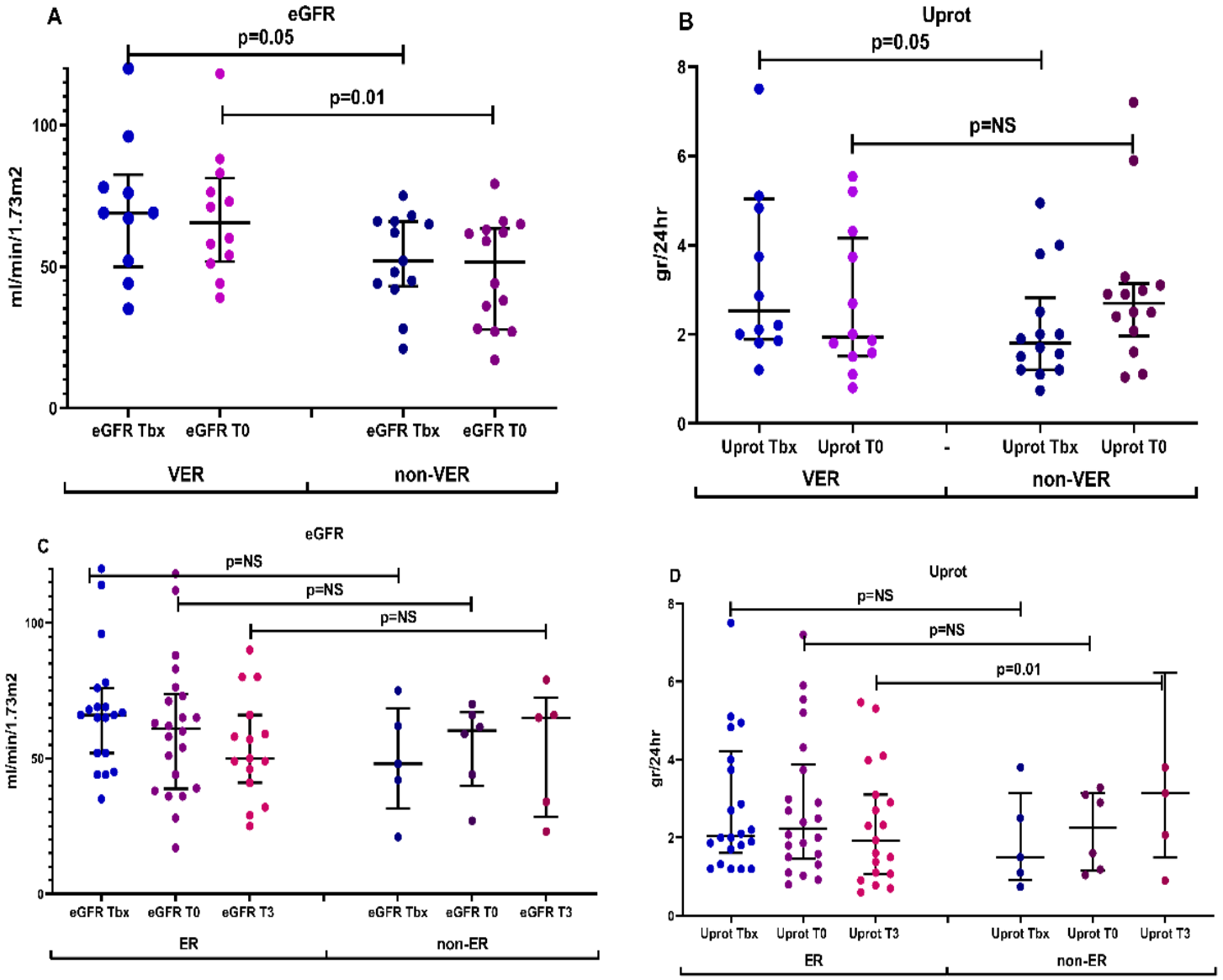
At the end of 6 months treatment, the prevalence of proteinuria reduction significantly increased, therefore, in the **17/37 patients with VER who remained in remission**,

**12 more patients were added**, increasing the number with ER to 29/37(78.3%), p=0.004.

# Parameters associated with ER

Differences in clinical and laboratory findings between patients with and without response after 6 months of TRB treatment

| | ER | non-ER | p |
|---|---|---|---|
| **N** | 29 | 8 | |
| **M/F** | 20/9 | 6/2 | |
| **Age** | 47.68±14 | 52.83±12.95 | 0.42 |
| **Time elapsed since diagnosis (months)** | 38.36±19.6 | 78.67±18.64 | 0.05 |
| **eGFR Tbx (ml/min/1.73m2)** | 67.9±22.47 | 49.6±20.47 | 0.11 |
| **eGFR T0(ml/min/1.73m2)** | 60.8±25.2 | 54.6±16.18 | 0.57 |
| **eGFR T3(ml/min/1.73m2)** | 54.06±19.06 | 53.4±23.7 | 0.95 |
| **Uprot Tbx (g/24hr)** | 2.99±2.05 | 1.9±1.2 | 0.27 |
| **Uprot T0 (g/24hr)** | 2.78±1.79 | 2.18±1.02 | 0.44 |
| **Uprot T3 (g/24hr)** | 2.07±1.02 | 3.5±1.89 | 0.01 |
| **UPCR Tbx (g/g)** | 2.39±1.44 | 1.28±0.5 | 0.48 |
| **UPCR T0 (g/g)** | 1.9±0.35 | 2.15±0.23 | 0.56 |
| **UPCR T3 (g/g)** | 2.07±1.02 | 3.53±1.89 | 0.12 |




Differences between eGFR and Uprot levels at Tbx and T0 in VER (A) and non-VER (B) patients, and eGFR and Uprot levels at Tbx, T0 and T3 in ER (C) and non-ER (D) patients

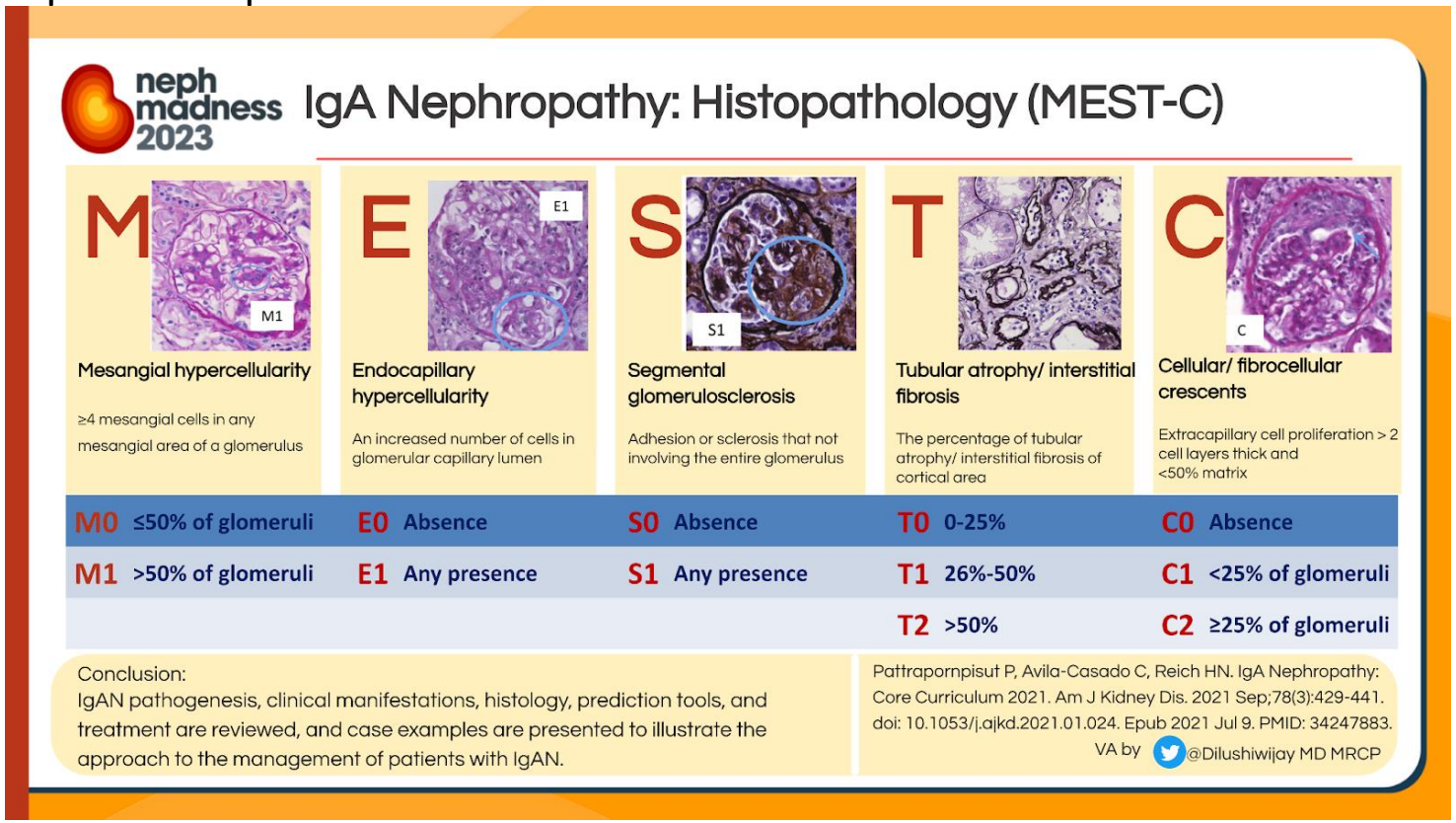
Patients with ER had better renal function at Tbx and T0, however differences were not statistically significant. The only significant difference between ER and non-ER patients was the degree of Uprot at time point T3 2.07±1.02 vs. 3.5±1.89g/24hr, p=0.01

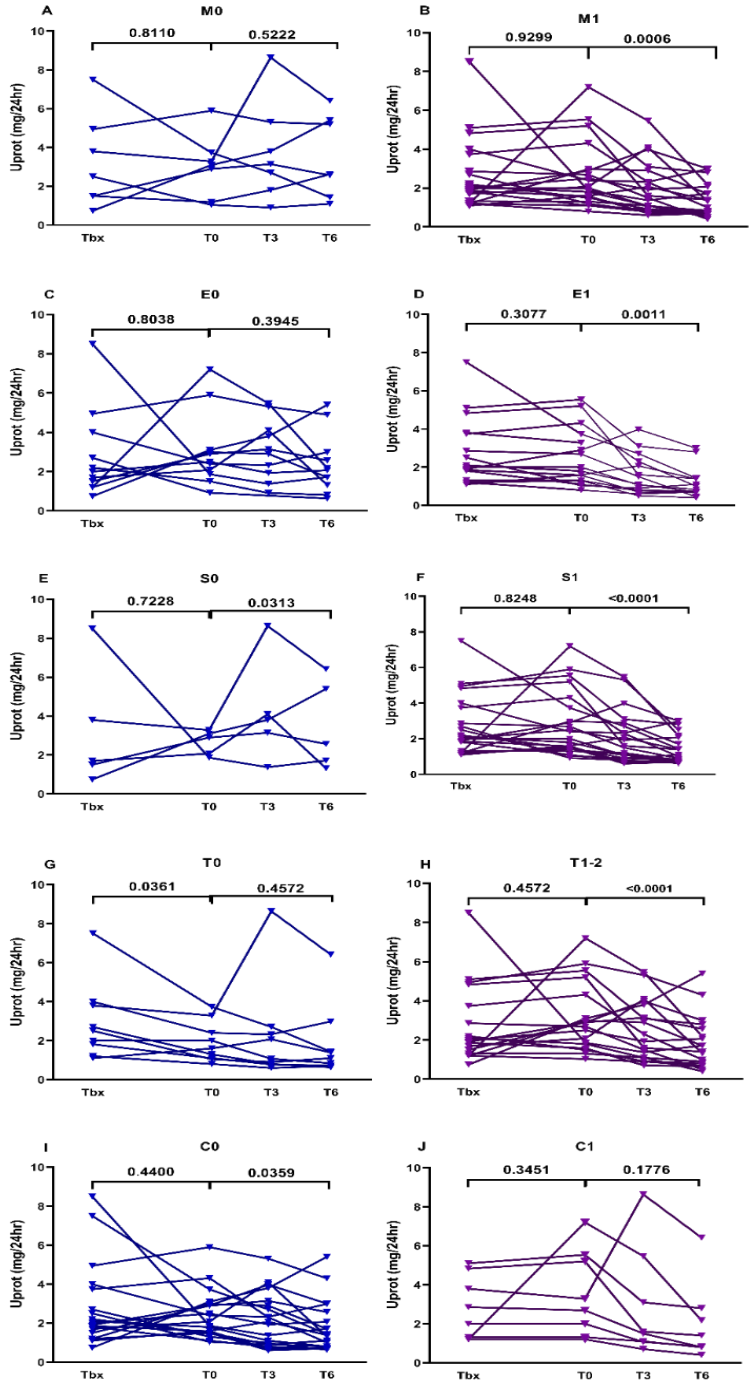
# The impact of kidney biopsy findings in reduction of proteinuria

All kidney biopsies from participated patients were classified according to MEST-C Oxford classification score. Patients who were classified as M1, E1 and S1 showed significant improvement in renal function and proteinuria, after starting TRB treatment, compared to M0, E0 and S0 patients, respectively. (Figure 3)

The presence of tubular atrophy, classified as T0, T1 and T3 and the presence of crescents, C0 and C1, did not seem to have any significant impact in response to treatment.

| **MEST-C classification** | |
|---|---|
| M0/M1 | 5/32 |
| E0/E1 | 15/22 |
| S0/S1 | 6/31 |
| T0/T1/T2 | 9/20/8 |
| C0/C1/C2 | 25/15/0 |






## The impact of kidney biopsy findings in reduction of proteinuria

Changes in Uprot from Tbx to T0 and during the 6 months of TRB treatment, different outcome in patients with M0, E0, S0, T0, C0 (A, C, E, G, I, respectively) and M1, E1, S1, T1, C1 (B, D, F, H, J, respectively). P values express significance in Uprot changes between the time interval Tbx-T0 (T-test) and changes between T0-T3-T6 (ANOVA-test)

| Models predicting Uprot at T3 | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Tested parameters** | **Enetered variables** | **R square** | **Adjusted R square** | **Std error** | **Stand Coefficients B** | **p** | **CI** | |
| M, E, S, T, C | M | 0.451 | 0.421 | 1.44 | -0.672 | <0.001 | -6.39 | -1.87 |
| | | | | | | | | |
| M, S, eGFR Tbx | M | 0.451 | 0.415 | 1.55 | -0.672 | 0.003 | -6.6 | -1.6 |
| M, S, Uprot Tbx | M | 0.451 | 0.421 | 1.44 | -0.672 | 0.001 | -6.39 | -1.88 |
| M, S, eGFR/Uprot Tbx | M | 0.451 | 0.415 | 1.55 | -0.672 | 0.003 | -6.6 | -1.61 |
| | | | | | | | | |
| M, S, eGFR T0 | M | 0.451 | 0.421 | 1.44 | -0.672 | 0.001 | -6.39 | -1.87 |
| M, S, Uprot T0 | M | 0.659 | 0.619 | 1.16 | -0.639 | 0.001 | -5.77 | -2.01 |
| | Uptor T0 | | | | 0.457 | | 0.187 | 0.89 |
| M, S, eGFR/Uprot T0 | M | 0.659 | 0.619 | 1.16 | -0.639 | <0.001 | -5.77 | -2.01 |
| | Uptor T0 | | | | 0.457 | | 0.187 | 0.89 |
| **Models predicting Uprot at T6** | | | | | | | | |
| **Tested parameters** | **Enetered variables** | **R square** | **Adjusted R square** | **Std error** | **Stand Coefficients B** | **p** | **CI** | |
| M, E, S, T, C | M | 0.756 | 0.739 | 0.841 | -0.869 | <0.001 | -5.96 | -2.96 |
| | | | | | | | | |
| M, S, eGFR Tbx | M | 0.754 | 0.736 | 0.869 | -0.868 | <0.001 | -5.71 | -2.89 |
| M, S, Uprot Tbx | M | 0.756 | 0.739 | 0.841 | -0.868 | <0.001 | -5.71 | -2.89 |
| M, S, eGFR/Uprot Tbx | M | 0.754 | 0.736 | 0.869 | -0.868 | <0.001 | -5.71 | -2.89 |
| | | | | | | | | |
| M, S, eGFR T0 | M | 0.756 | 0.739 | 0.841 | -0.869 | <0.001 | -5.96 | -2.96 |
| M, S, Uprot T0 | M | 0.756 | 0.739 | 0.841 | -0.869 | <0.001 | -5.66 | -2.96 |
| M, S, eGFR/Uprot T0 | M | 0.756 | 0.739 | 0.841 | -0.869 | <0.001 | -5.66 | -2.96 |
| | | | | | | | | |
| M, S, eGFR T3 | M | 0.771 | 0.752 | 0.855 | -0.878 | <0.001 | -5.57 | -2.73 |
| M, S, Uprot T3 | M | 0.875 | 0.855 | 0.629 | -0.578 | <0.001 | -4.19 | -1.42 |
| | Uptor T3 | | | | 0.444 | | 0.12 | 0.58 |
| M, S, eGFR/Uprot T3 | M | 0.871 | 0.848 | 0.670 | -0.599 | <0.001 | -4.33 | -1.32 |
| | Uptor T3 | | | | 0.422 | | 0.08 | 0.59 |

# Clinical Response to Intestine-targeted Steroid Therapy in Biopsy-proven Immunoglobulin A Nephropathy

Table 1. Baseline characteristics.

| |
|---|
| Me |
| Nu |
| Nu |
| Me |
| Me |
| Me |
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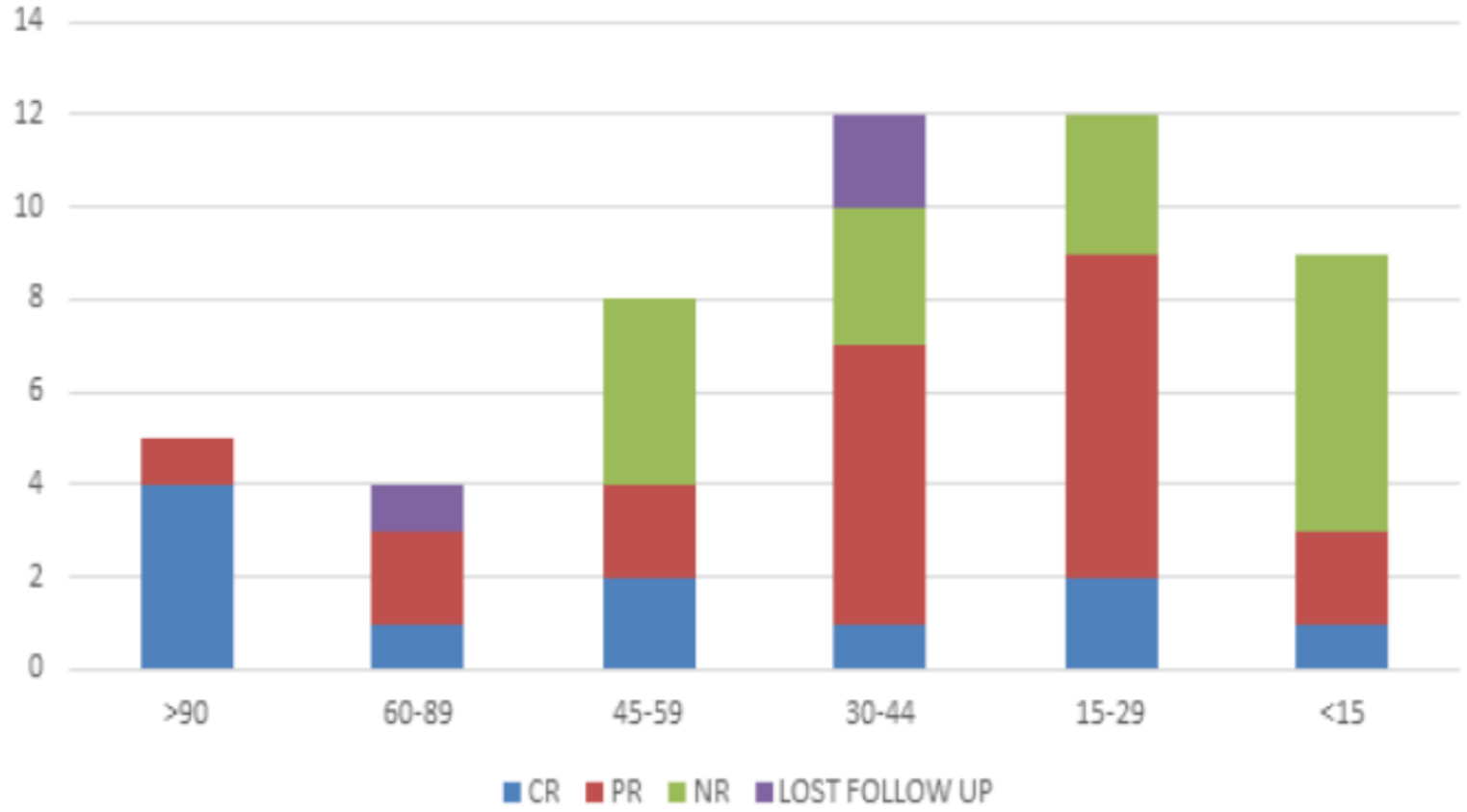



Figure 1. Comparison of clinical responses for different estimated glomerular filtration rates at presentation.

Saudi J Kidney Dis Transpl 2022;33(6):755-760

# Clinical Response to Intestine-targeted Steroid Therapy in Biopsy-proven Immunoglobulin A Nephropathy

Table 1. Baseline characteristics.

| Parameter | Value |
|---|---|
| Mean | |
| Num | |
| Num | |
| Mean | |
| Mean | |
| Mean | |
| Hype | |
| Diab | |

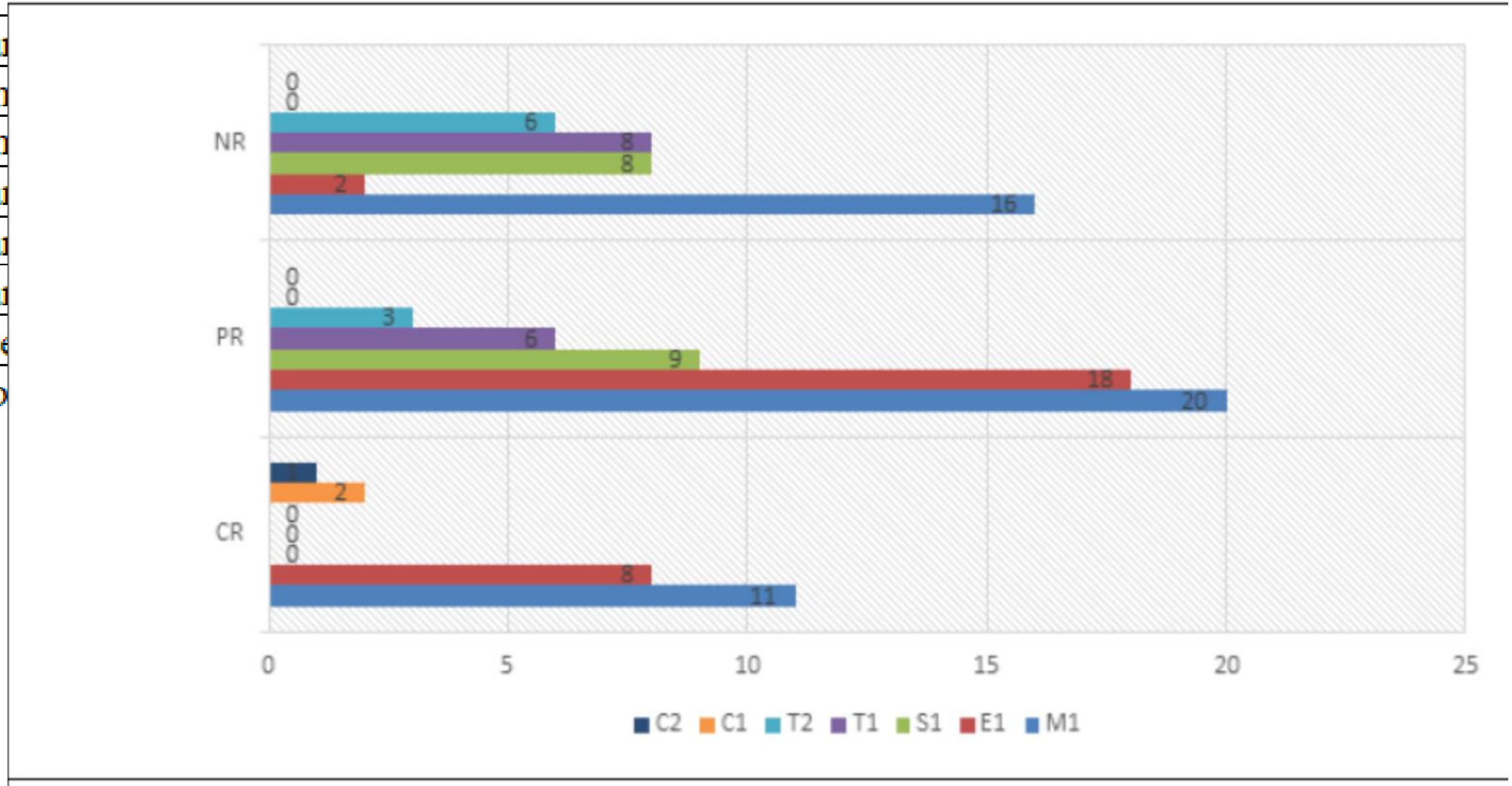
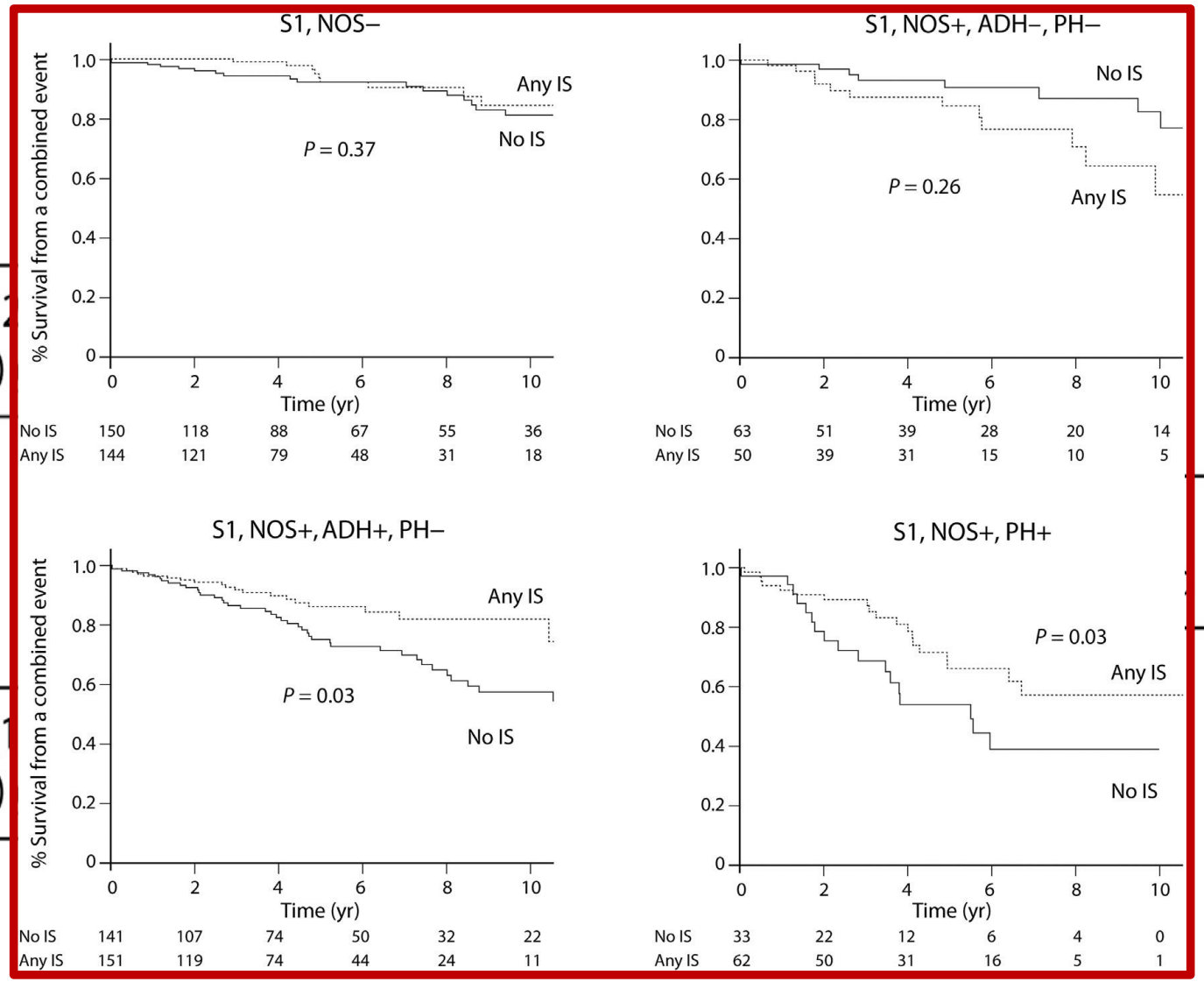


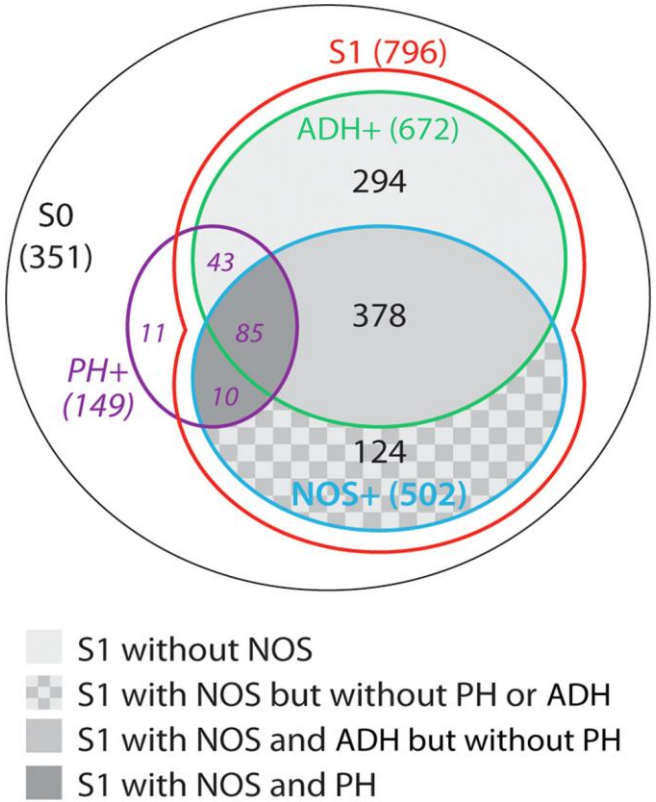

Figure 2. Comparison of clinical responses, stratified by MESTC score.

# Evidence from the large VALIGA cohort validates the subclassification of focal segmental glomerulosclerosis in IgA nephropathy

**NOS– (n = 2**
1.2 (0.5–2.3)

**ADH– (n = 1**
1.3 (0.7–2.5)




*Kidney International (2024) 105, 1279–1290*

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1. Υπάρχει υπεροχή έναντι των μέχρι τώρα θεραπευτικών επιλογών?

   Συντηρητική αντιμετώπιση: αMEA, sGLT2

   Στοχευμένη αντιμετώπιση: κορτικοειδή, ανοσοκατασταλτικά

2. Υπάρχει ύφεση της λευκωματουρίας? Υπάρχει βελτίωση της νεφρικής λειτουργίας?

3. Ποιοι ασθενείς είναι πιθανό να απαντήσουν?

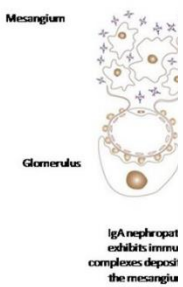
4. Έχει επίδραση σε παθογενετικές οδούς και βιοδείκτες?

5. Πόσος χρόνος χορήγησης είναι αρκετός?

6. Παρενέργειες?

7. Πόσο συχνή είναι η υποτροπή, πότε την περιμένουμε?

Title: Diagnosin

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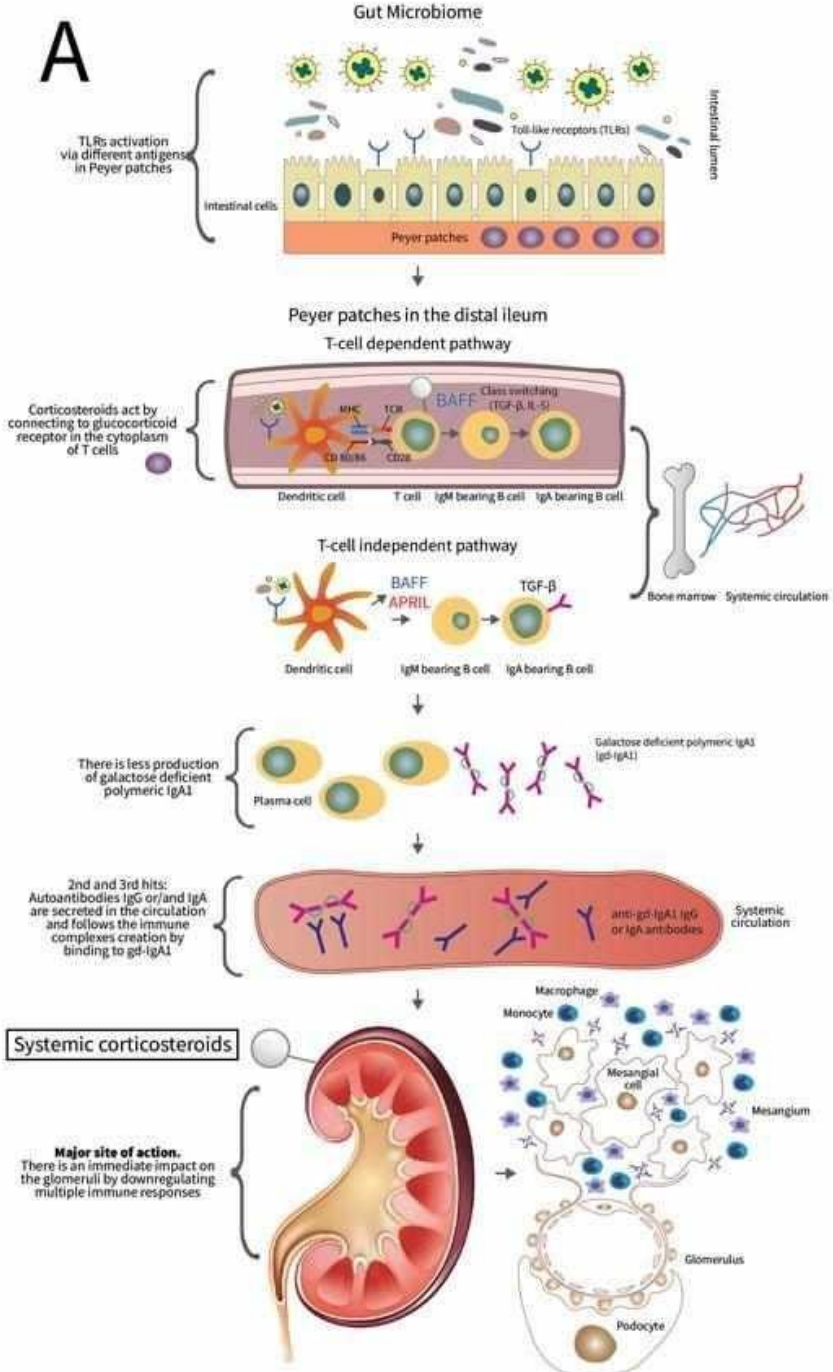
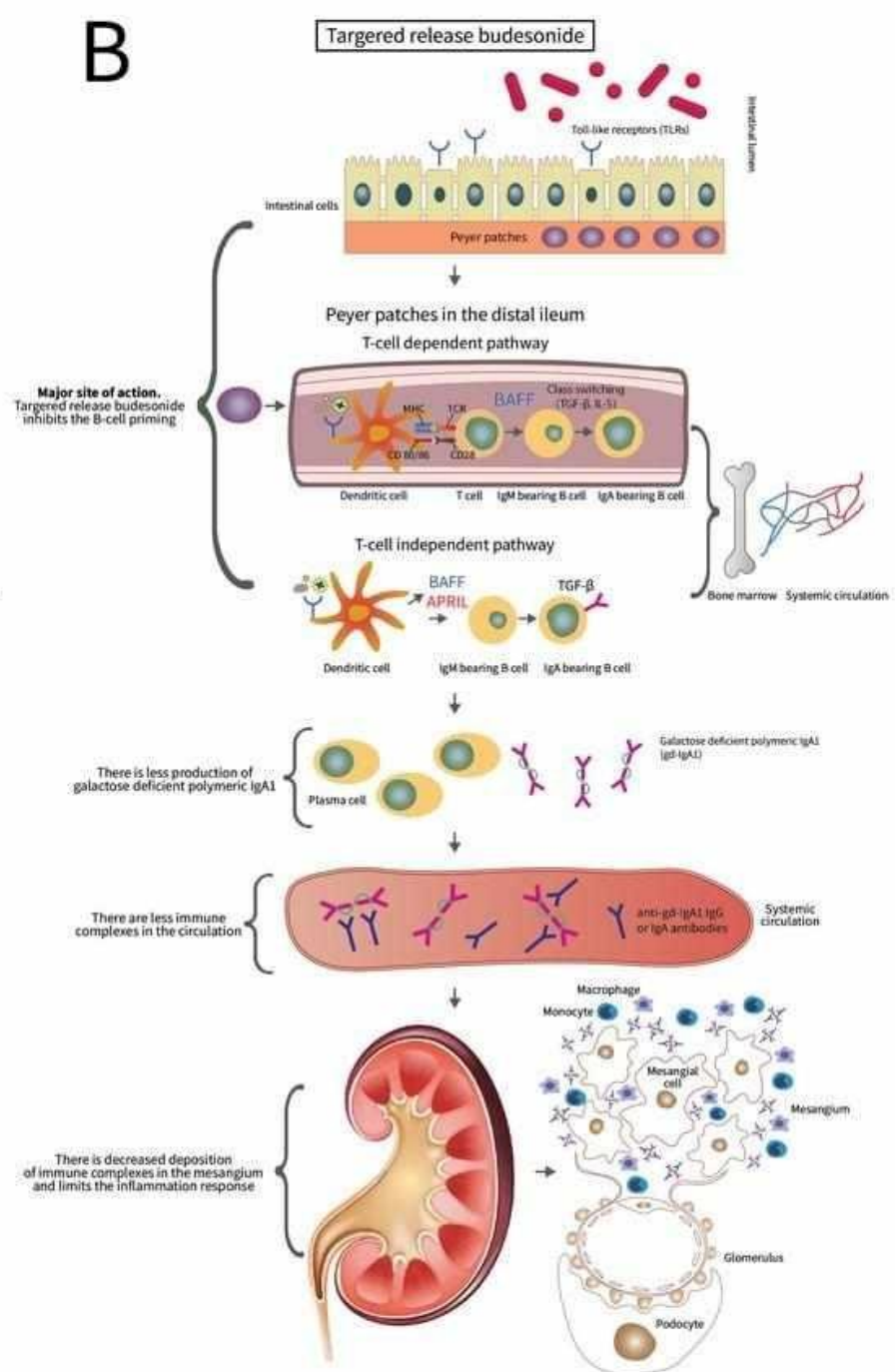
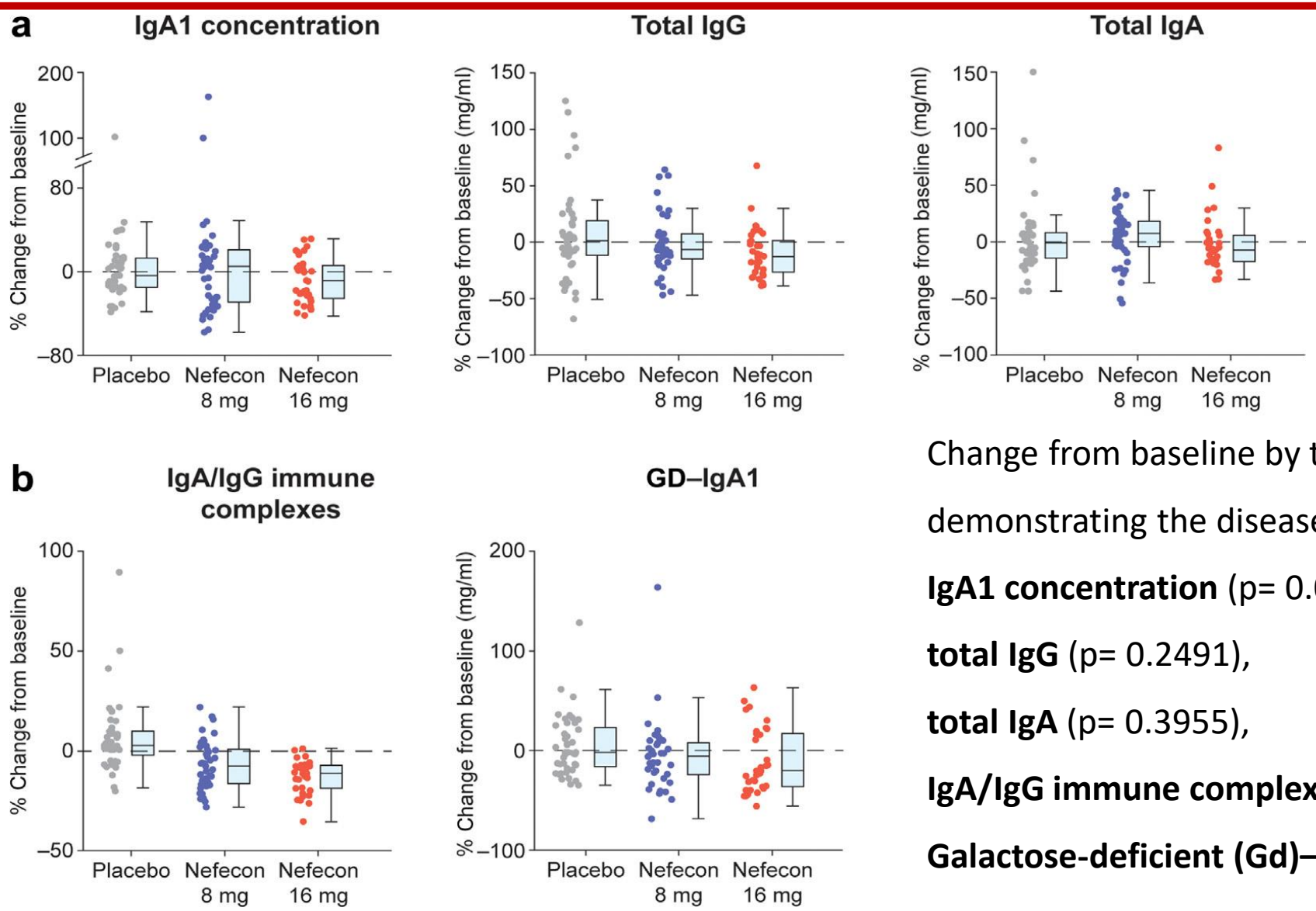


# Targeted-release budesonide modifies key pathogenic biomarkers in IgAN: insights from the NEFIGAN trial




Change from baseline by treatment group in biomarkers demonstrating the disease-modifying effect of Nefecon at 9mo

**IgA1 concentration** (p= 0.0656),

**total IgG** (p= 0.2491),

**total IgA** (p= 0.3955),

**IgA/IgG immune complexes** (p < 0.0001),

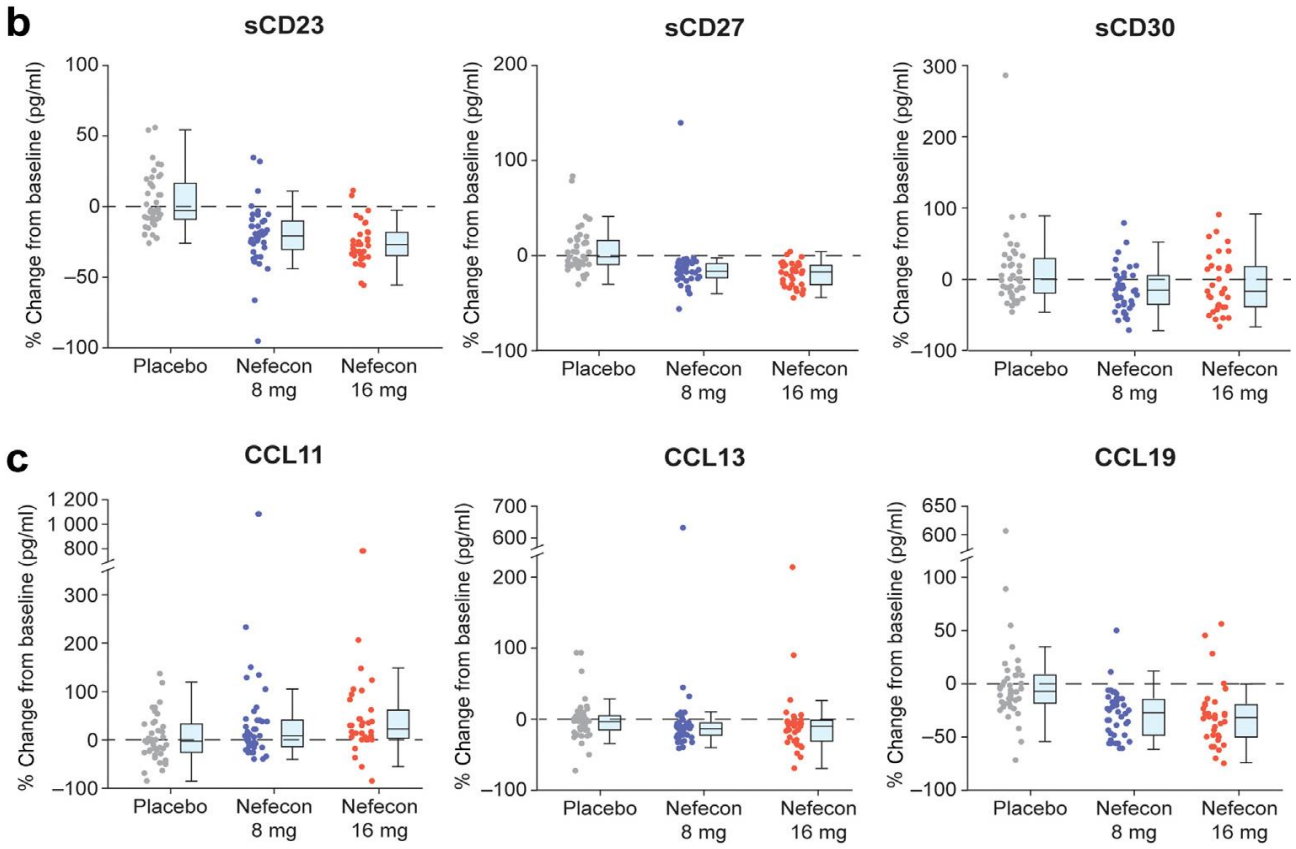
**Galactose-deficient (Gd)–IgA1** (p= 0.0163)

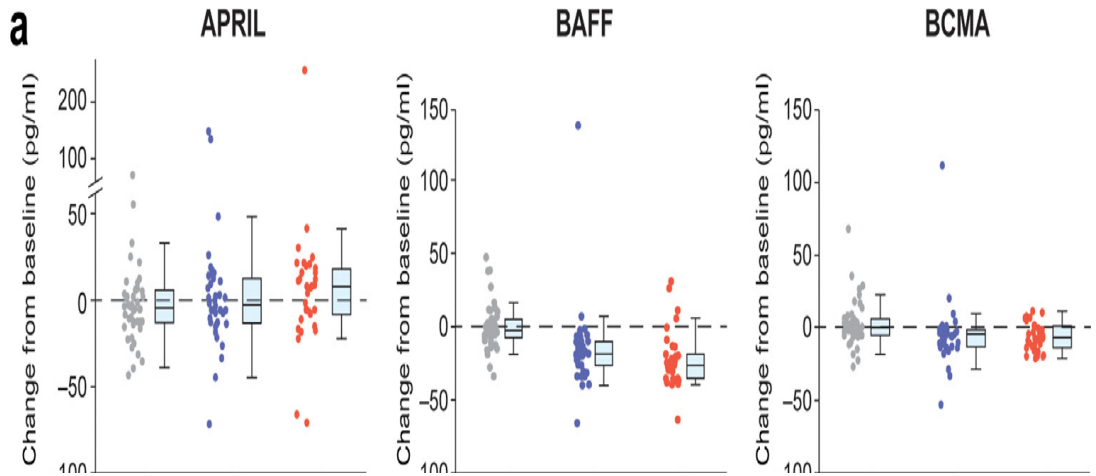
*Kidney International (2024) 105, 381–388*

# Nefecon modifies B-cell survival factors, biomarkers of lymphocyte activation, and mucosal homing

**11 biomarkers** (BAFF, TNFRSF13B, TNFRSF17, CCL11, CCL19, CCL20, CXCL5, CXCL13, sCD23/FcεRII, sCD27, and sCD30 were identified that were significantly modulated after 9 months of treatment with Nefecon 16 mg/d

and **3 biomarkers** (APRIL/TNFRSF13, CCL13, and CXCL6) were identified that required further validation

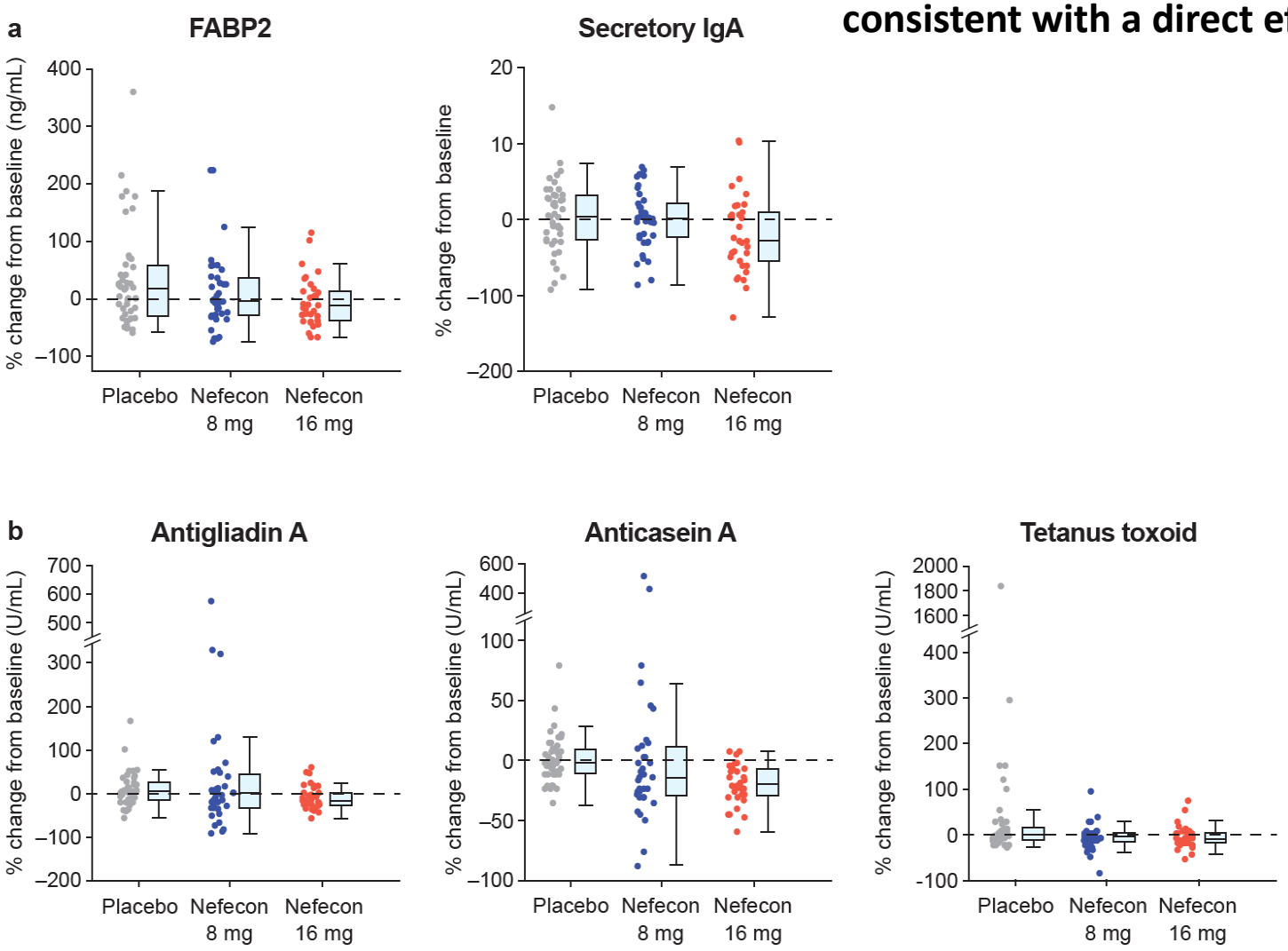



*Kidney International (2024) 105, 381–388*

# Nefecon modifies biomarkers of mucosal integrity and GALT activation

**Treatment with Nefecon 16 mg/d resulted in a reduction in FABP2, consistent with a direct effect of Nefecon on the ileal mucosal epithelium.**

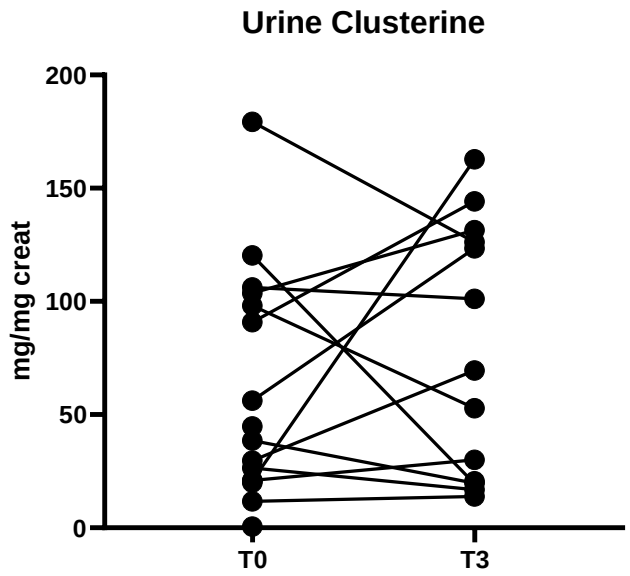


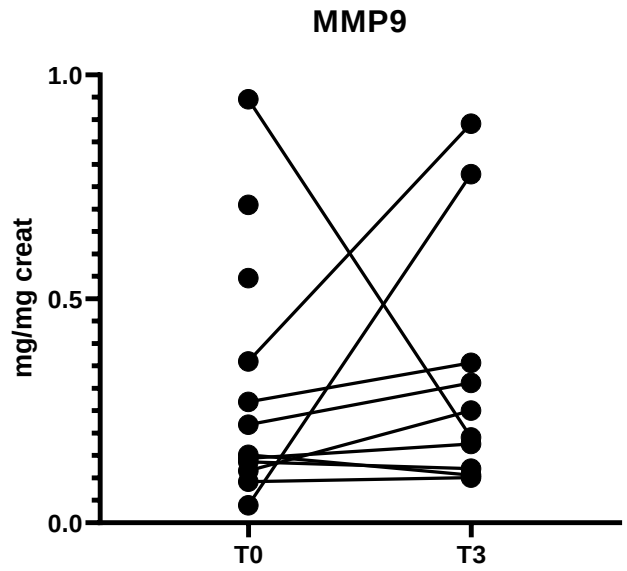

Fatty acid–binding protein 2 (FABP2) or intestinal-type FABP is expressed in epithelial cells of the mucosal layer of the small intestine tissue.

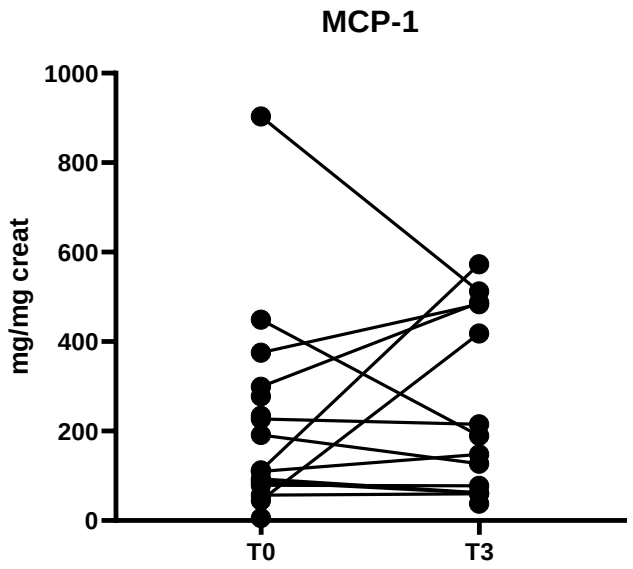
When intestinal mucosal damage occurs, FABP2 is released into the circulation, and its plasma concentration increases, allowing it to be used as a noninvasive biomarker to evaluate gut wall integrity loss and inflammation.

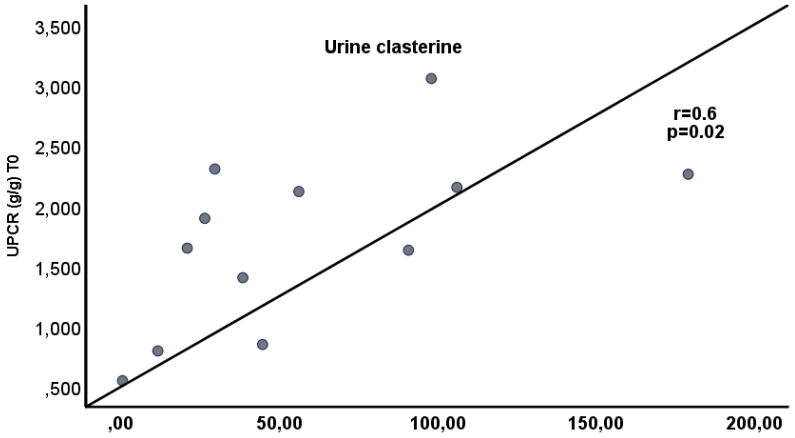
*Kidney International (2024) 105, 381–388*

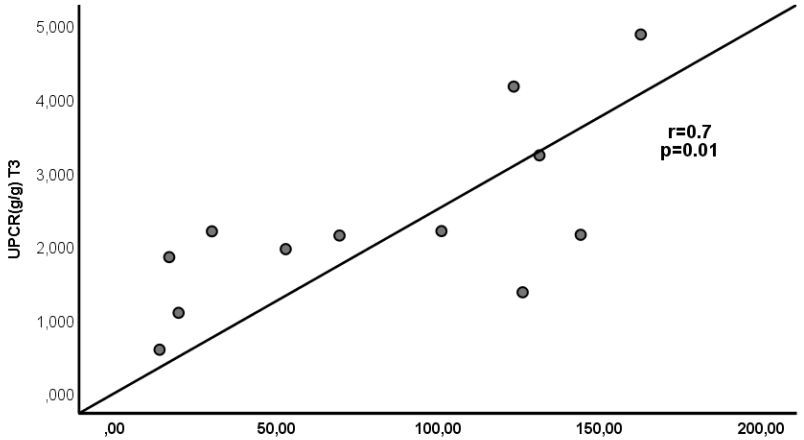
# Changes in the urine excretion of pre-inflammatory molecules during treatment

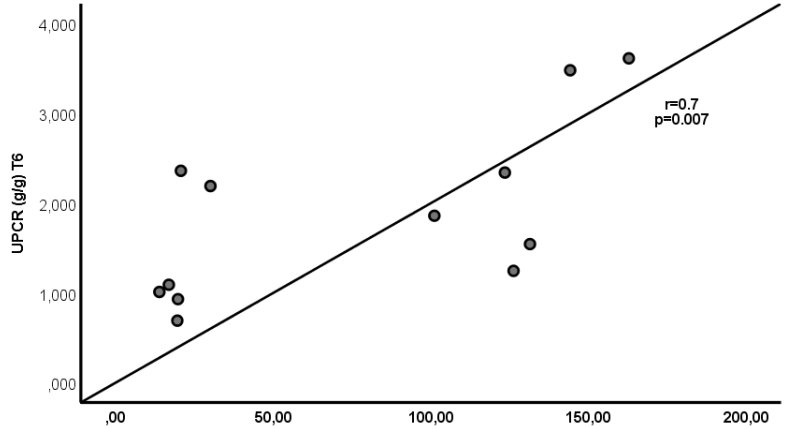


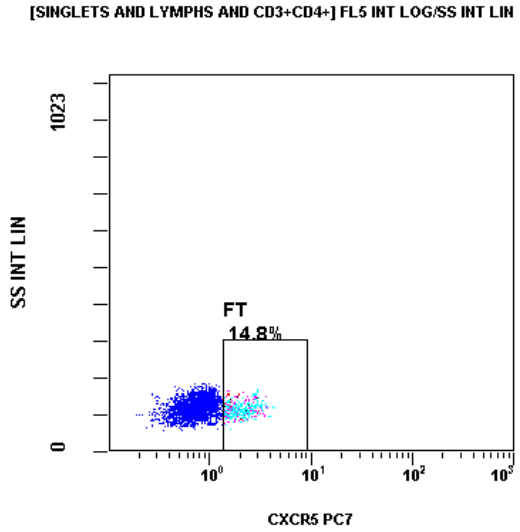



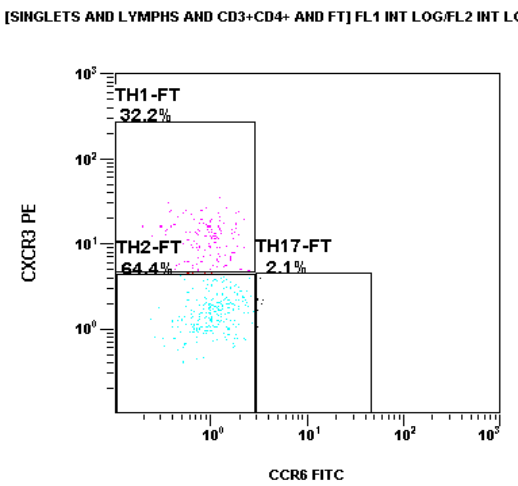
# T-follicular cells

- Ανευρίσκονται κυρίως στα δευτερογενή λεμφικά όργανα, σχηματίζοντας δομές ανοσιακής απόκρισης (germinal centers).
- Έχουν καθοριστικό ρόλο στην ειδική ανοσία υπεύθυνα για τη Β κυτταρική ενεργοποίηση και διαφοροποίηση στα βλαστικά κέντρα των λεμφοζιδίων
- Παρόμοια κύτταρα ανευρίσκονται και στο περιφερικό αίμα, συσχέτιση με ενεργότητα συστηματικών νοσημάτων, όπως ΣΕΛ και ΡΑ

**TF (cTF) (CD4+CD45RA-CXCR5+) cells,**

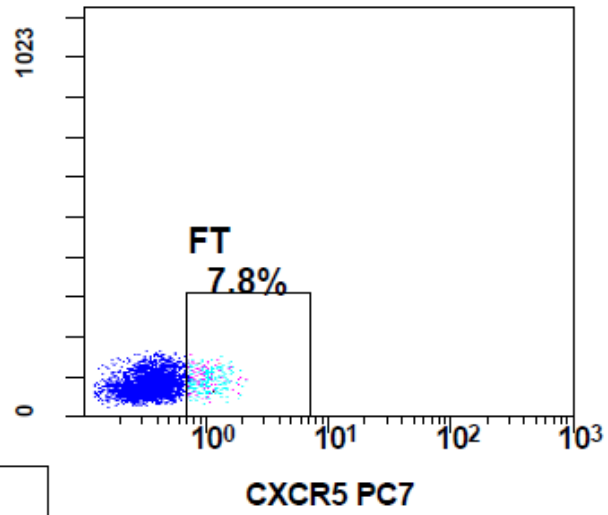
| | |
|---|---|
| cTFH1 (CD4+CD45RA-CXCR5+CXCR3+CCR6-), | cTFH17 (CD4+CD45RA-CXCR5+CXCR3-CCR6+), |
| cTFH2 (CD4+CD45RA-CXCR5+CXCR3-CCR6-) | cTF-Regulatory(cTFR) (CD4+CD45RA-CXCR5+CD127-CD25+FOXP3+) |
| | cTFH-ICOS+ (CD4+CD45RA-CXCR5+ICOS+) |

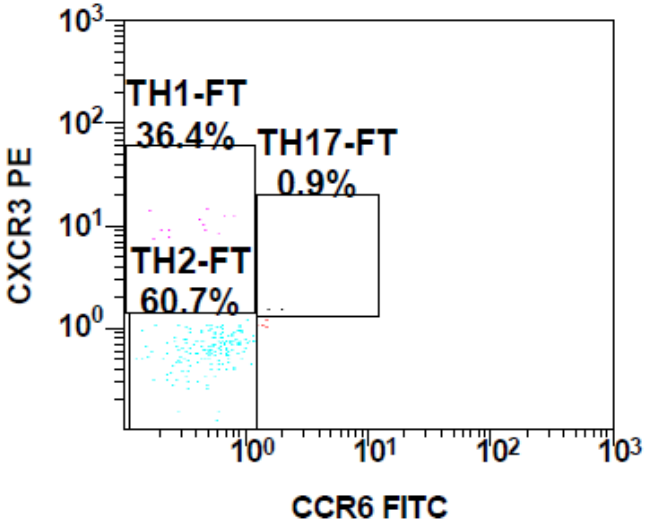


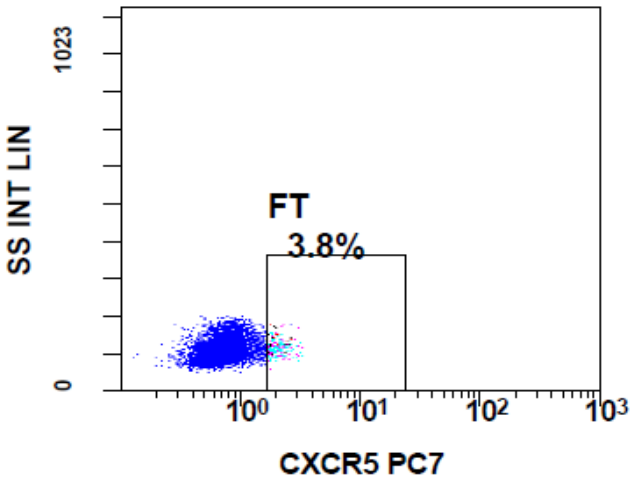



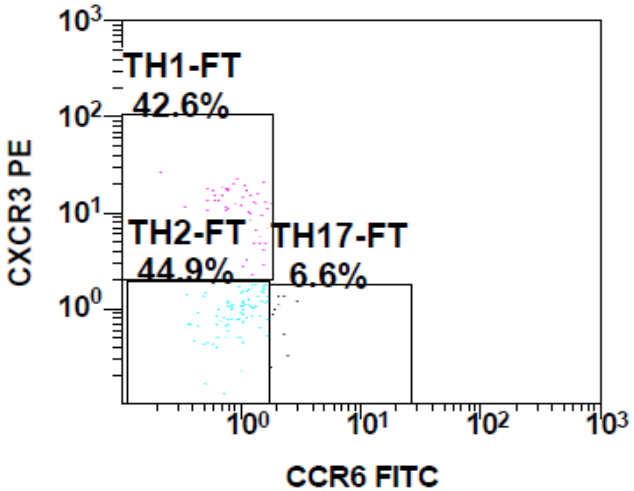

**Πριν την έναρξη αγωγής με TRB**

**3 μήνες μετά την έναρξη αγωγής με TRB**




**6 μήνες μετά την έναρξη αγωγής με TRB**

# Ερωτήματα που προκύπτουν μετά την εφαρμογή της Targeted Released Budesonide (TRB) στη θεραπεία της IgAN

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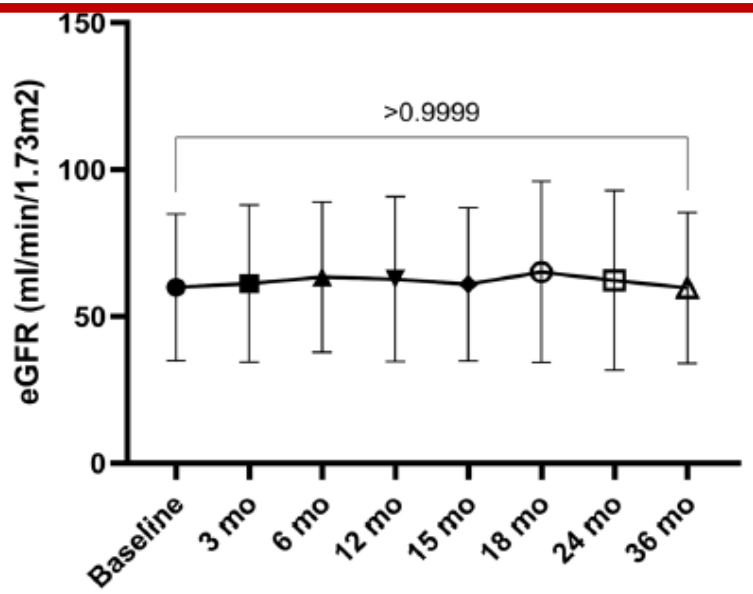
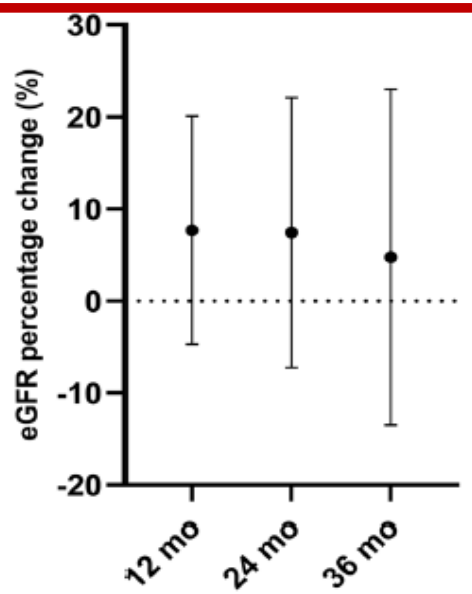
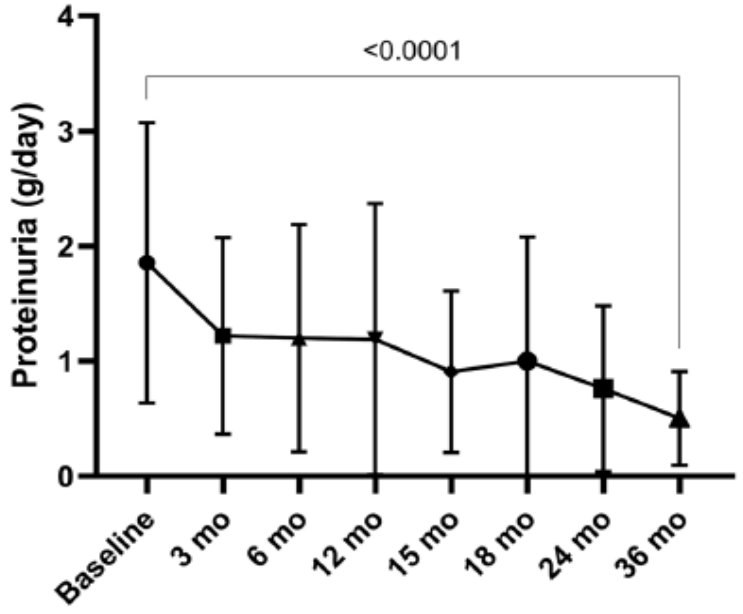
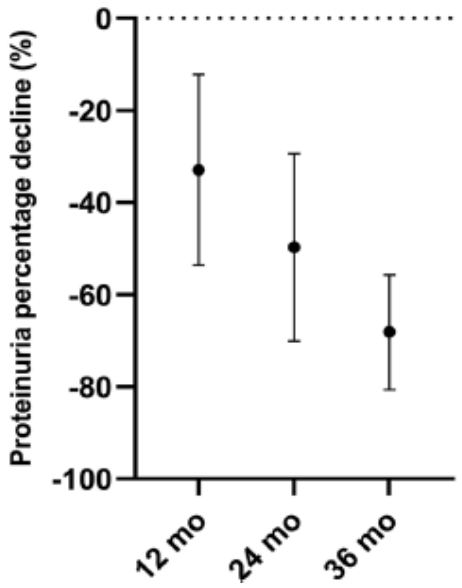
# An open-label study evaluating the safety and efficacy of budesonide in patients with IgA nephropathy at high risk of progression




## high risk of progression

Age ≥ 18 years, patients with a histological diagnosis of primary IgAN, **high risk of progression defined as**

- **persistent proteinuria over 1 g/day despite RAAS blockade or**
- **patients with proteinuria between 0.5 and 1 g/day after RAAS blockade if they had additional risk factors for progression (eGFR< 60ml/min/1.73m2, presence of proliferative lesions on kidney biopsy).**

*Scientific Reports 2023*

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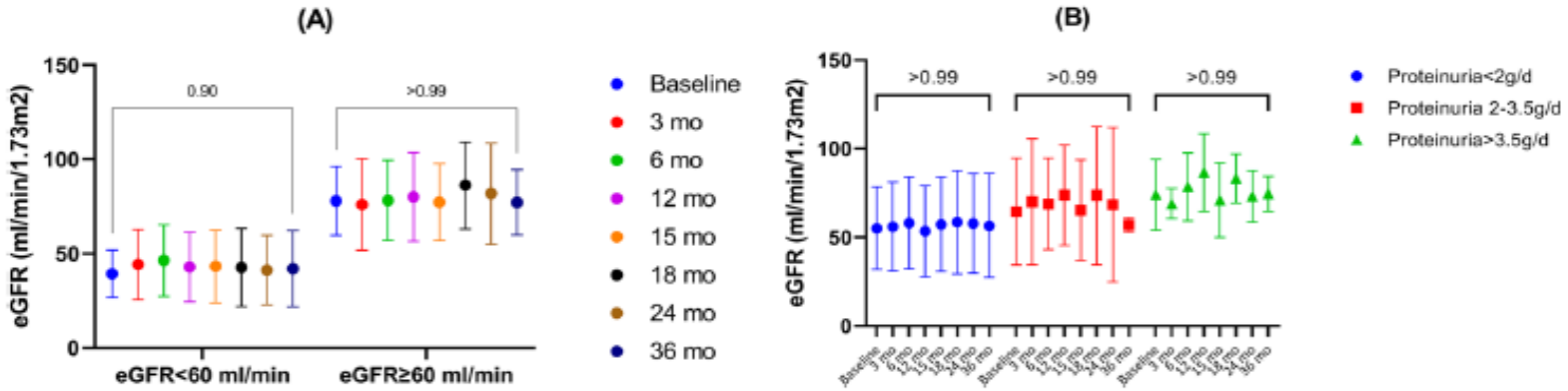
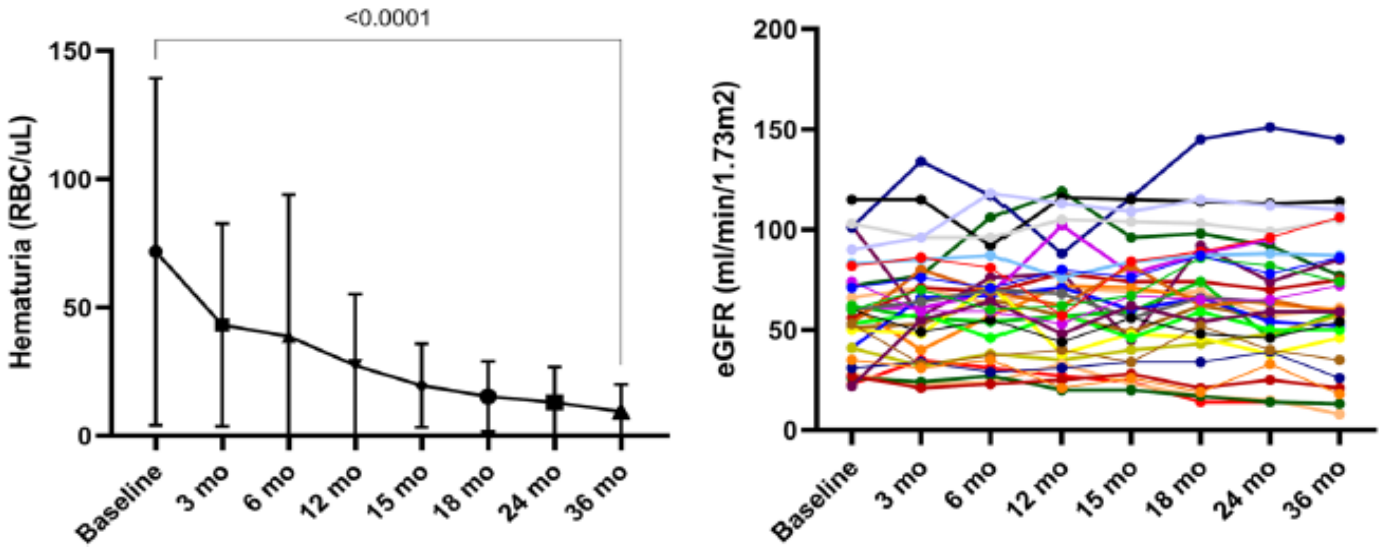



**Figure 4.** eGFR evolution. (A) According to baseline eGFR; (B) According to baseline 24-h proteinuria.




*Scientific Reports 2023*

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   Συντηρητική αντιμετώπιση: αMEA, sGLT2

   Στοχευμένη αντιμετώπιση: κορτικοειδή, ανοσοκατασταλτικά

2. Υπάρχει ύφεση της λευκωματουρίας? Υπάρχει βελτίωση της νεφρικής λειτουργίας?

3. Ποιοι ασθενείς είναι πιθανό να απαντήσουν?

4. Έχει επίδραση σε παθογενετικές οδούς και βιοδείκτες?

5. Πόσος χρόνος χορήγησης είναι αρκετός?

6. Παρενέργειες?

7. Πόσο συχνή είναι η υποτροπή, πότε την περιμένουμε?

**Adverse events**

Some adverse events were observed during the first 6 months of treatment. Three patients (8.1%) experienced non-severe infection, 1 of them caused by SARS-COV-2, one patient (2.7%), already suffered by diabetes mellitus, had glucose intolerance, 1(2.7%) showed abnormal blood pressure and 1(2.7%) female patient temporarily presented menstrual disorders. The only patient who had to gradually reduce and finally discontinue treatment, was because of severe peripheral myopathy at the 4$^{th}$ month of treatment; the patient however remained on regular follow up. All the adverse events are summarized in the following Table 5.

**Table 5.** Adverse effects presented during the first 6 months, in the 37 patients treated with TRB

| **Side Effects** | **Number of patients** | **Continue with reduced treatment dosage** | **Treatment discontinuation** |
|---|---|---|---|
| Acne | 3 | 0 | 0 |
| Infection | 3 | 0 | 0 |
| Dysregulation of diabetes mellitus | 1 | 0 | 0 |
| High blood pressure | 1 | 1 | 0 |
| Menstrual disorders | 1 | 0 | 0 |
| Myopathy | 1 | 0 | 1 |

| Adverse event | N (%) |
|---|---|
| Gastro-intestinal symptoms | 3 (9.3%) |
| Gastrointestinal bleeding | 0 (0%) |
| Respiratory tract infection | 10 (31.2%) |
| COVID-19 | 6 (18.7%) |
| Oral candidiasis | 1 (3.1%) |
| Osteoporosis | 1 (3.1%) |
| New-onset diabetes mellitus | 0 (0%) |
| Osteonecrosis | 0 (0%) |
| Worsening of hypertension | 0 (0%) |

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30 May 2024
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Committee for Medicinal Products for Human Use (CHMP)

**Summary of opinion[1] (post authorisation)**

# Kinpeygo

budesonide

On 30 May 2024, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending a change to the terms of the marketing authorisation for the medicinal product Kinpeygo. The marketing authorisation holder for this medicinal product is STADA Arzneimittel AG.

The CHMP adopted an extension to the existing indication as follows:[2]

> Kinpeygo is indicated for the treatment of **adults with** primary immunoglobulin A ~~(IgA)~~ nephropathy (IgAN) ~~in adults at risk of rapid disease progression~~ with a urine protein **excretion**~~-to-creatinine ratio (UPCR)~~ ≥1.**0**~~5~~ g/**day**~~gram~~ **(or urine protein-to-creatinine ratio ≥0.8 g/g).**

Detailed recommendations for the use of this product will be described in the updated summary of product characteristics (SmPC), which will be published in the revised European public assessment report (EPAR) and made available in all official European Union languages after a decision on this change to the marketing authorisation has been granted by the European Commission.

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# Συμπεράσματα

1. Θεραπευτική αντιμετώπιση βασισμένη σε παθογενετικές οδούς
2. Σημαντικά ποσοστά ύφεσης με βάση τους ορισμούς που εφαρμόζουμε στην καθημέρα πράξη
3. Βιοψία νεφρού: σημαντικό προγνωστικό ρόλο

   Η εκτίμηση των αλλοιώσεων στη βιοψία νεφρού με βάση το MEST-C score
4. Χωρίς υποτροπή στην πρώιμη μετα-θεραπευτική περίοδο
5. Μικρό ποσοστό ανεπιθύμητων ενεργειών

## Αναπάντητα ερωτήματα

4. Χρονικό διάστημα αγωγής σε ασθενείς υψηλού κινδύνου ή σε ανθεκτικές περιπτώσεις?
5. Μελλοντικές υποτροπές?
6. Ανάγκη βιοδεικτών περισσότερο αξιόπιστων από τη λευκωματουρία