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MANEJO DE LA TOXICIDAD DE LOS NUEVOS TRATAMIENTOS EN

TUMORES UROLÓGICOS

Valencia, 23 de abril de 2024

Organizado por: GUARD CONSORTIUM

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Manejo práctico de la TOXICIDAD RENAL

Xoana Barros

Nefróloga

Fundació Puigvert, Barcelona

Organizado por: GUARD CONSORTIUM

MANEJO TOXICIDADES RENALES

- **PREVENCIÓN**
- evaluación función renal previa al tto
- identificación de factores de riesgo
- **MONITORIZACIÓN DURANTE EL TRATAMIENTO**
- pruebas regulares de función renal
- alerta temprana de cambios en la función renal
- **INTERVENCIÓN ÁGIL**
- suspensión o ajuste de dosis
- manejo sintomático y de apoyo

Colaboración interdisciplinaria

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Hay daño farmacológico

Glomérulo

Daño podoci
inhib m-T

Glom

Túbulo e intersticio

contraste,
AINEs,
a B,

Vasos

Radiaci

Gemcitab

Mitomicina-C

anti-VEGF, ITKs

ICP

quinolonas)

por ICP

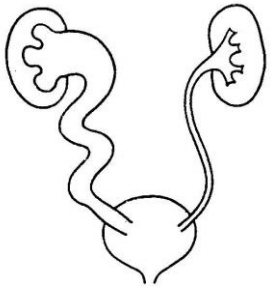
Sdme de lisis tumoral

medidas de PA
analitica
estudio orina
eco

PRERRENAL

PA y Na orina

POSTRENAL



eco

PARENQUIMATOSO

Ratio Prot/Cr y Alb/Cr y sedimento orina

CONSIDERACIONES ESPECÍFICAS

- **INMUNOTERAPIA en concreto ICP**
- Manejo interdisciplinar ágil
- Pautas de corticoides

- **TERAPIAS DIRIGIDAS**
- antiVEGF / iTK: control de la HTA y de la proteinuria
- Inh RFGF: manejo hiperfosfatemia

- **PSEUDO-AKI**

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Nefritis intersticial aguda por ICP

- Tiempo de instauración entre 6 y 21 semanas (mediana 14 semanas)
- Síntomas inespecíficos (poliuria, astenia)
- En algunos casos HTA, hematuria, edemas

PCR sérica
Ratio Retinol BP/Cr orina
IL9 urinario
TNF urinario
PET

- En laboratorio: ocasionalmente eosinofilia, piuria
  poco frecuente
- No existen marcadores ni pruebas de imagen
- Factores de riesgo: uso IBPs y AINEs, ERC previa, quinolonas, irAES extrarrenales.
- Debemos biopsiar si es que no hay un alto riesgo de complicaciones
- Si sospechamos NIA debemos iniciar prednisona cuanto antes

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Fracaso renal agudo por ICP

Grade 1 Creatinine 1.5 x baseline or >1.5 x UNL*	**Grade 2** Creatinine >1.5-3 x basal o >1.5 x UNL	**Grade 3** Creatinine >3 x basal o >3-6 x UNL	**Grade 4** Creatinine >6 x UNL
Check hydration status, medication, urinalysis and culture if symptoms Protein/creatinine ratio If obstruction is suspected Renal ultrasound / or vascular Doppleri	Check hydration status, medication, urinalysis and culture if symptoms Protein/creatinine ratio If obstruction is suspected Renal ultrasound / or vascular Doppler. If hematuria GN study according to the Nephrologist opinion Advise patient to report oliguria	Same as grade 1-2	Same as grade 1-2
Continue CPI Repeat weekly creatinine If worsening, follow grade 2 indications	Suspend CPI; Hydration and check creatinine in 48-72h. If it does not improve agree with Nephrology on the need for biopsy. If attributed to IrAE **: steroids (oral prednisolone 0.5-1 mg/kg) and creatinine/48h. If back to G1/ baseline resume CPI (if with steroids only when prednisolone < 10mg) If not attributed to IrAE continue CPI.	Suspend ICP. Monitor fluid balance.Repeat creatinine /24 h Immediate consensus with Nephrology on renal biopsy. If worsening Methylprednisolone IV 1-2 mg/kg	Same as grade 3 Admission to hospital with Nephrology (dialysis)

Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: ASCO Guideline Update

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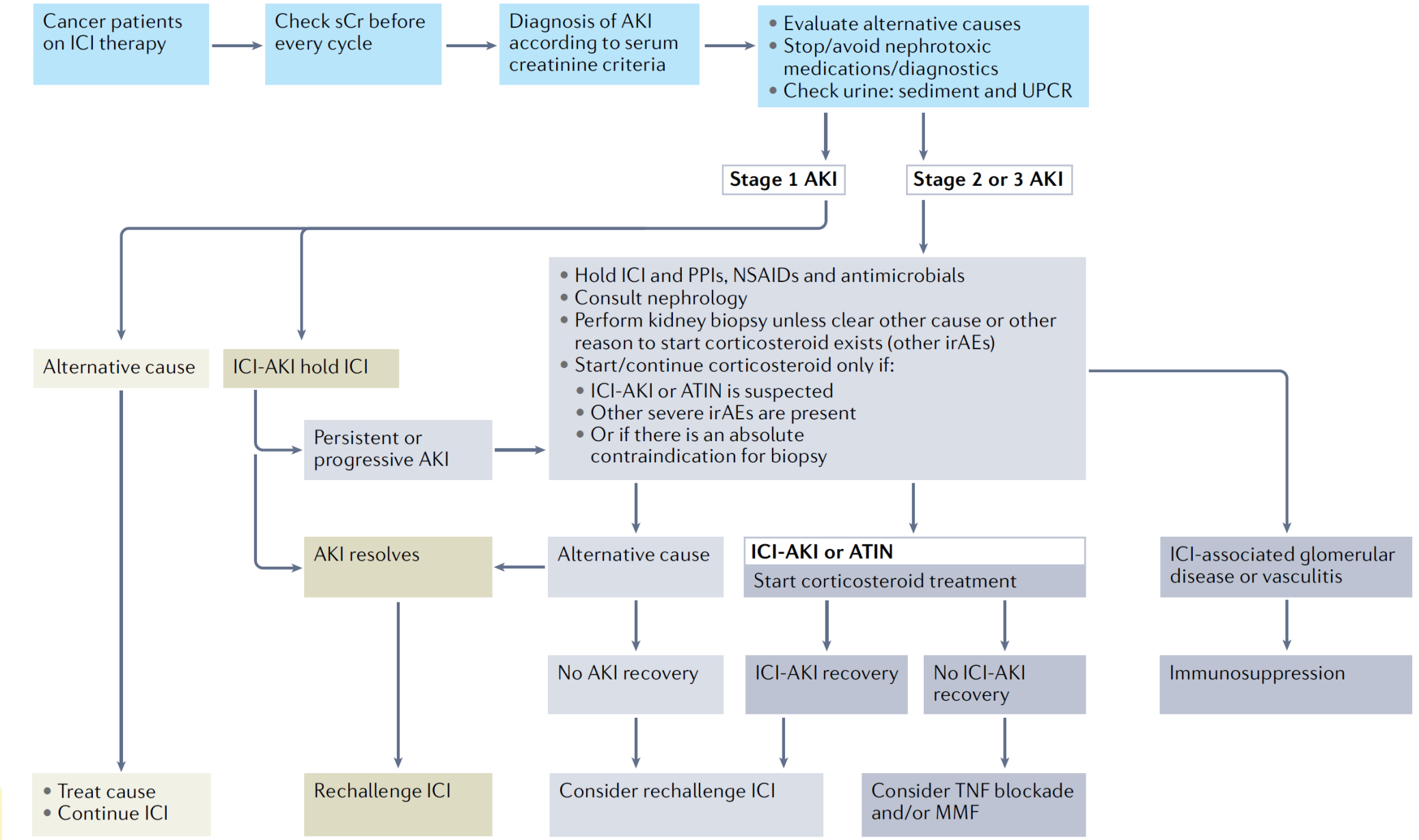
ASCO

Journal of Clinical Oncology

ASCO Guideline Update . J Clin Oncol 2021



Sprangers Nature Reviews 2022; 18: 794

NEFROLOGIA. 2023;43(5):622–635

nefrología
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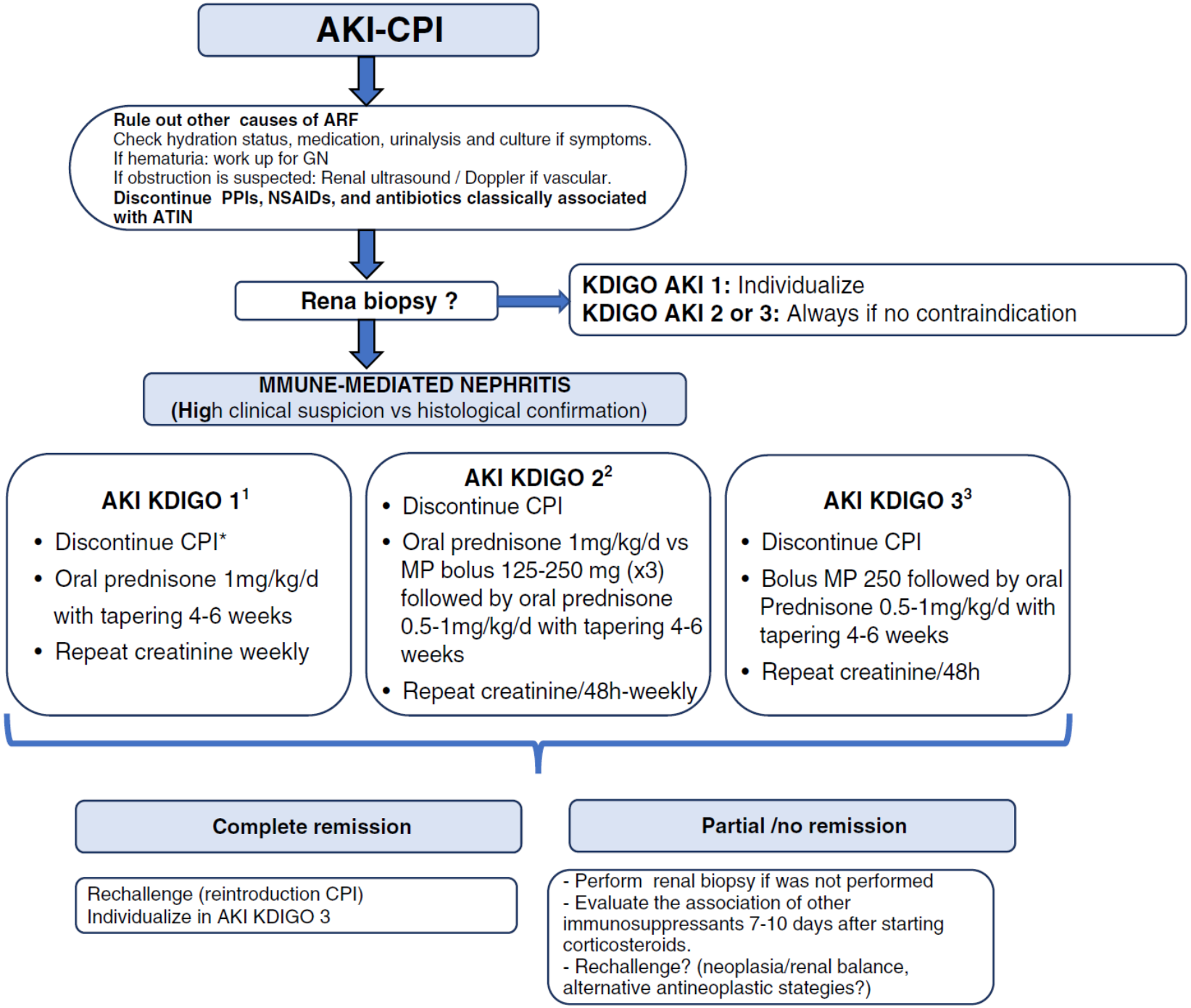
www.revistanefrologia.com

Special article

Adverse renal effects of *check-point* inhibitors (ICI) in cancer patients: Recommendations of the Onco-nephrology Working Group of the Spanish Society of Nephrology

Fabiola Alonso[a,*], *Ángel L.M. Martín de Francisco*[b], *Pilar Auñón*[c], *Clara García-Carro*[d], *Patricia García*[e], *Eduardo Gutiérrez*[c], *Manuel Mcía*[e], *Luis F. Quintana*[f], *Borja Quiroga*[g], *María José Soler*[h], *Isidro Torregrosa*[i], *Onconephrology Group of the Spanish Society of Nephrology*



Alonso F et al.
Nefrologia 2023; 43 (5): 622

3 bolus de 250mg

Semana 1: 30 mg/d
Semana 2: 25 mg/d
Semana 3: 20 mg/d
Semana 4: 15mg/d
Semana 5: 10 mg/d
Semana 6: 5 mg/d

3 bolus de 250mg

Semana 1: 30 mg/d
Semana 2: 20 mg/d
Semana 3: 10 mg/d
Semana 4: 5mg/d

Reduzco corticoides si en la semana 2 la función renal no ha mejorado?

Diferentes vidas medias de ICP pueden jugar un papel para decidir ritmo pauta descendente de corticoides?

Reintroducir ICP

Table 5 – Resuming CPI after AKI-CPI: recurrence of AKI.

	n ICP-IRA	n resumed	% with IS at the time of resumption	Recurrence AKI-CPI
Isik et al.[34]	37	16	81%	3 (19%)
Cortazar et al.[33]	138	31	39%	7 (23%)
Dolladille et al.[32]	276	78	NA	4 (5%)
Hultin et al.[36]	23	5	60%	0%
Espi et al.[37]	13	5	20%	20%
Gupta et al.[10]	429	121	49%	17%

AKI-CPI: acute renal failure associated with *check-point* inhibitors.

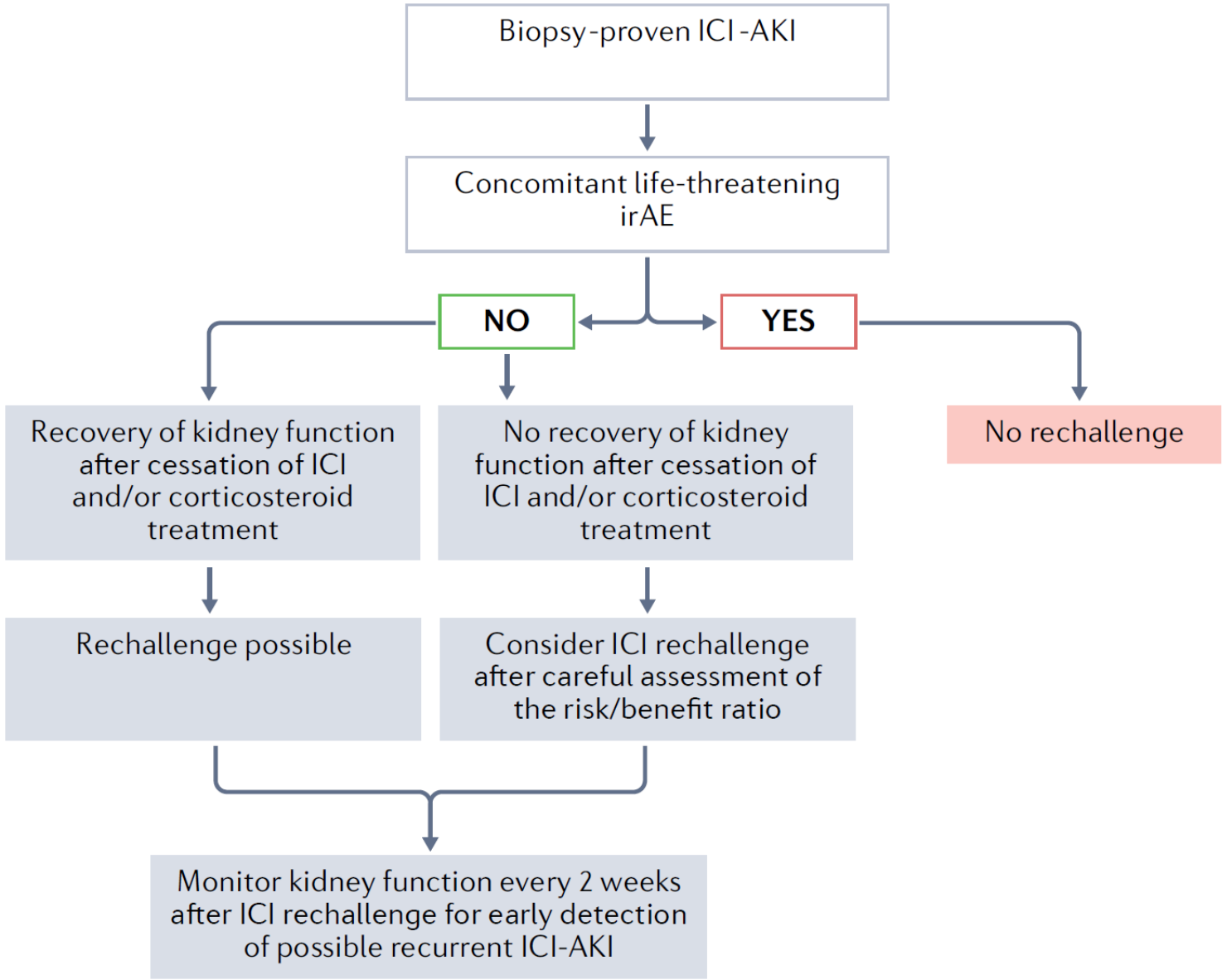
No reiniciar/individualizar si irAE grado 3

Reiniciar cuando se ha alcanzado recuperación total o parcial de función renal

Pocos datos acerca de si es necesario asociar prednisona si se decide reiniciar tratamiento

Alonso F et al. Nefrologia 2023; 43 (5): 622

Reintroducir ICP



Sprangers Nature Reviews 2022; 18:794

ICP en trasplante renal

Table 6 – Clinical characteristics of AKI associated with CPI treatment.

	Non-transplant patients	Transplant patients
Frequency	2–3%	30–40%
Time period from CPI to AKI	14 weeks	24 days
Renal histology	Cellular infiltration T/B/eos ATIN	Cellular infiltration T/B Cellular and humoral rejection
Response to Steroids	Favorable (50% recovery)	Refractory
Dialysis	5–10%	60–70%
Risk Factors	CKD; PPI; dual CPI therapy	i-mTOR and triple IS therapy (lower risk)

eos, eosinophils; CKD, chronic kidney disease; AKI, acute renal failure; PPI, proton pump inhibitors; AKI, acute renal failure; ATIN, acute tubulointerstitial nephritis; CPI, *check-point* inhibitors.

Mantener inmunosupresión
Cambio a mTOR en algunos casos (bajo riesgo inmunológico, baja proteinuria)
Aumentar prednisona a 10mg/d?

Alonso F et al. Nefrologia 2023; 43 (5): 622

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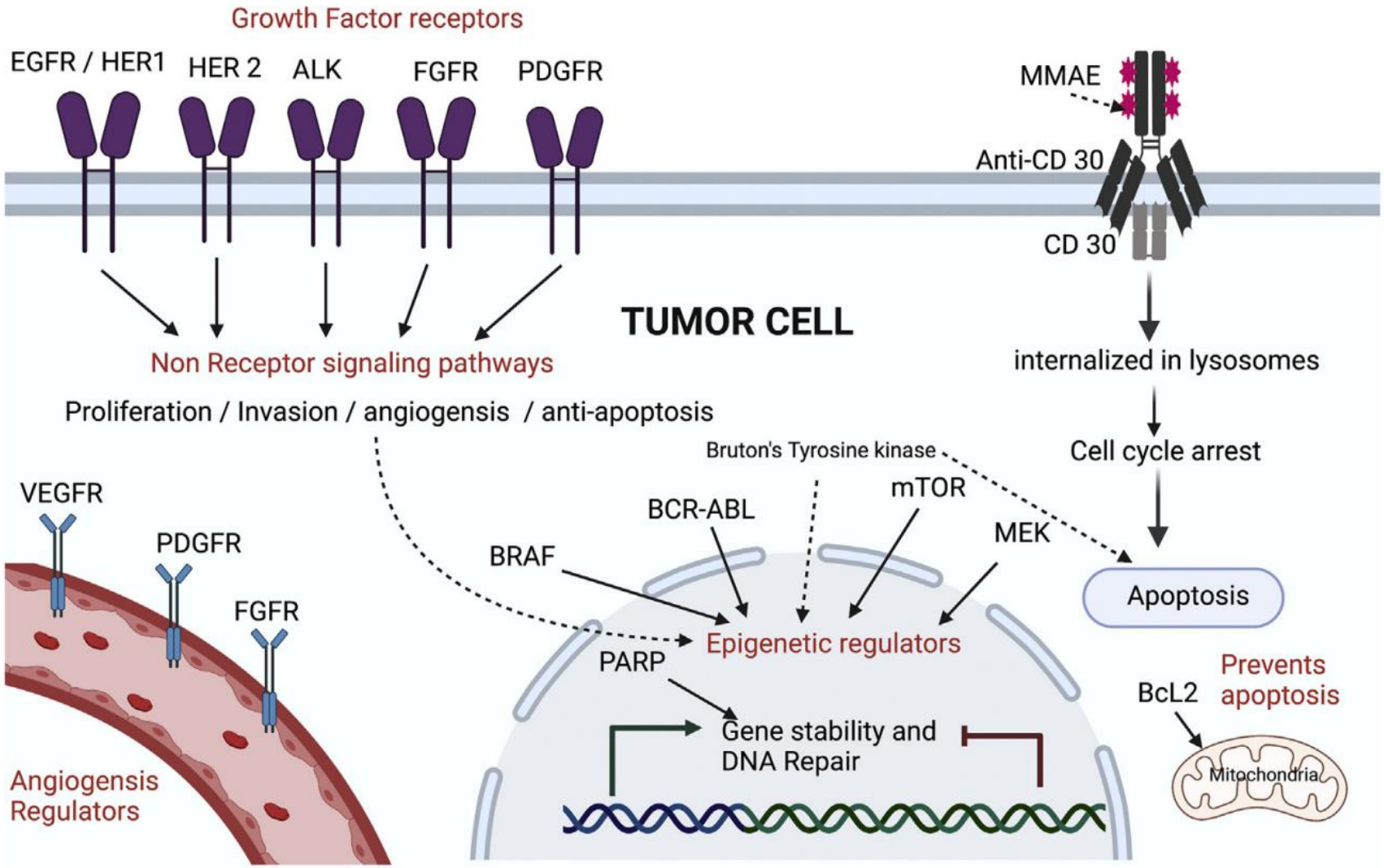
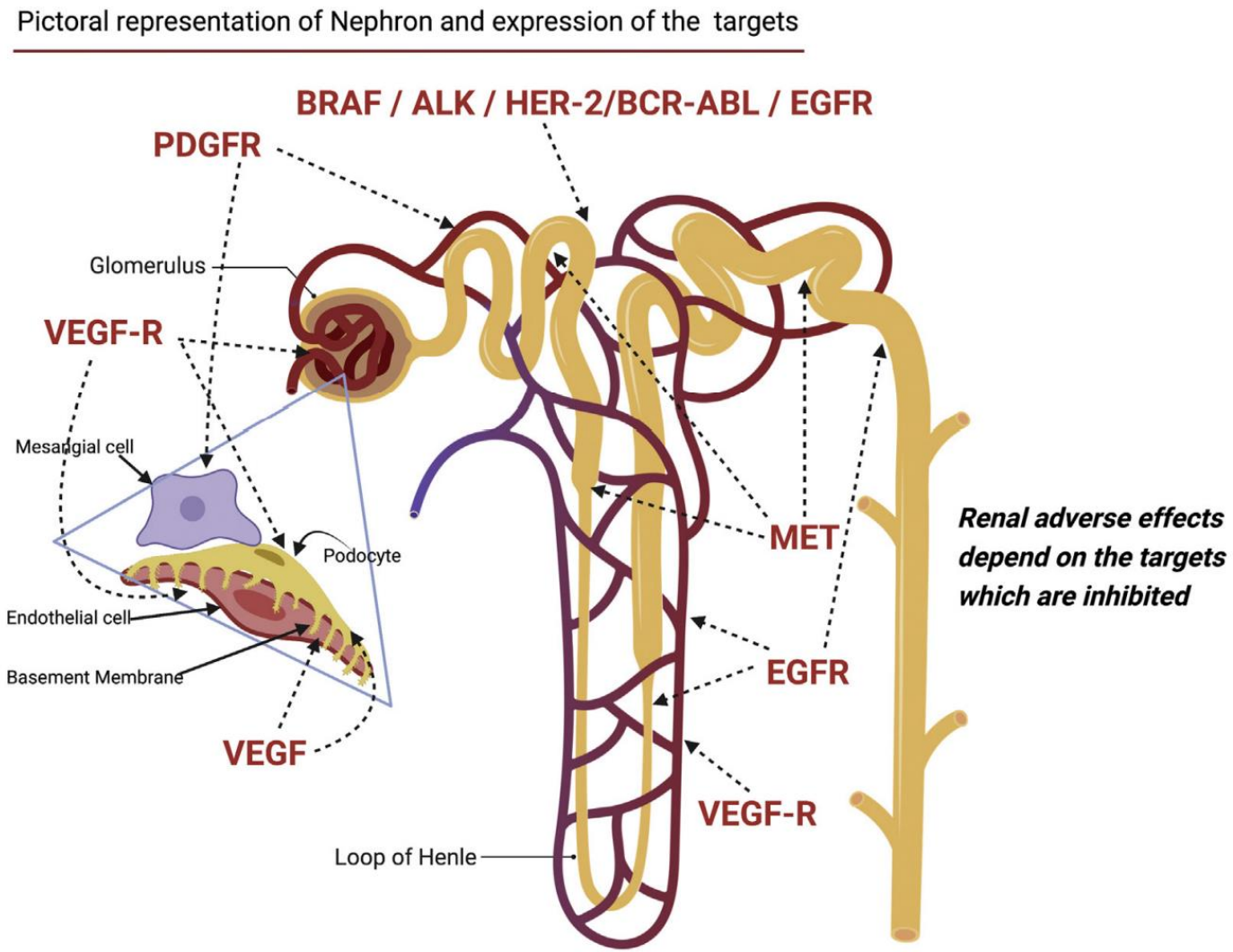
TERAPIAS DIRIGIDAS



Adv Chronic Kidney Dis 2021; 28(5): 415

TERAPIAS DIRIGIDAS



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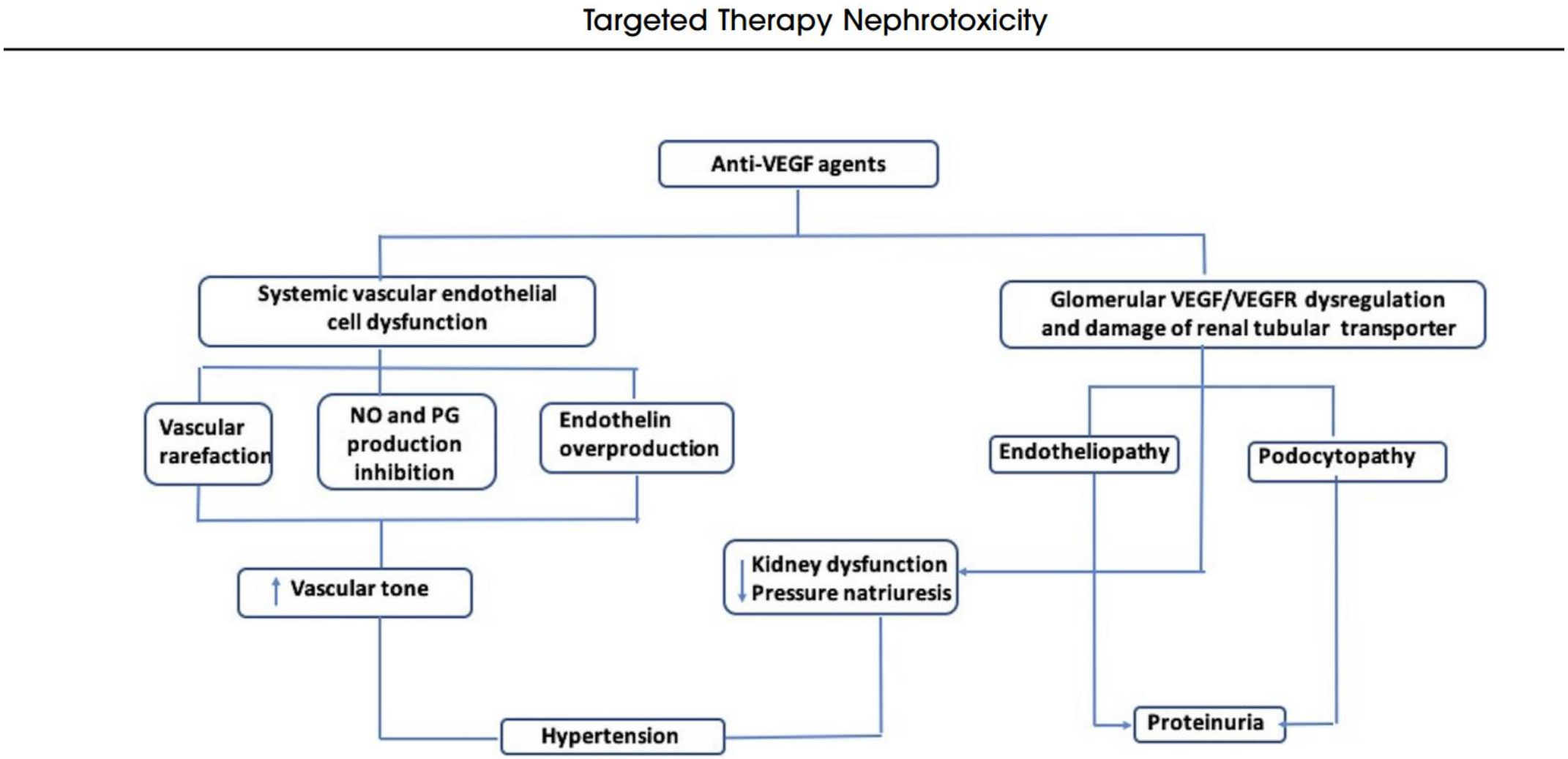
ANTIVEGF: HTA y proteinuria



Adv Chronic Kidney Dis 2021; 28(5): 415

ANTIVEGF/iTK: control HTA y proteinuria

- **Si proteinuria antes de iniciar antiVEFG**
- Tto IECAs o ARA2 al menos 2 sem antes de iniciar antiVEFG
- Valorar estudio mediante biopsia renal en algunos casos

- **Si proteinuria/HTA tras inicio tratamiento**:
- Si proteinuria no nefrótica y/o HTA <180/110:
  - mantener y tratar HTA con IECAS o ARA2 (o calcioantagonistas y betabloqueantes si no proteinuria)
  - Evitar calcioantagonistas no dihidropiridinicos (verapamilo y diltiazem) junto con iTK (porque aumentan niveles de iTK)
  - Ojo diuréticos en pacientes con baja ingesta, vómitos o diarrea dado el riesgo de FRA prerrenal
- Si proteinuria nefrótica: plantear Bx renal

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Rashidi et al. CJASN 2023; 18: 121

Anti VEGF/iTK Cuando biopsia renal?

- **Plantear biopsia renal si** proteinuria > 3g/g y/o deterioro fc renal

En contra: nefrectomías previas, trombocitopenia, dificultad control de PA, no sabemos si nos cambiará el plan

A favor**:** nos podemos encontrar otras cosas

  - MAT
  - GN mebranosa paraneolásica

- **Parar tratamiento si**:
  - MAT
  - Complicaciones de la HTA (edema agudo de pulmón, encefalopatía posterior reversible)
  - Síndrome nefrótico
- **Reintroducir tratamiento si** es la única alternativa terapéutica, con monitorización

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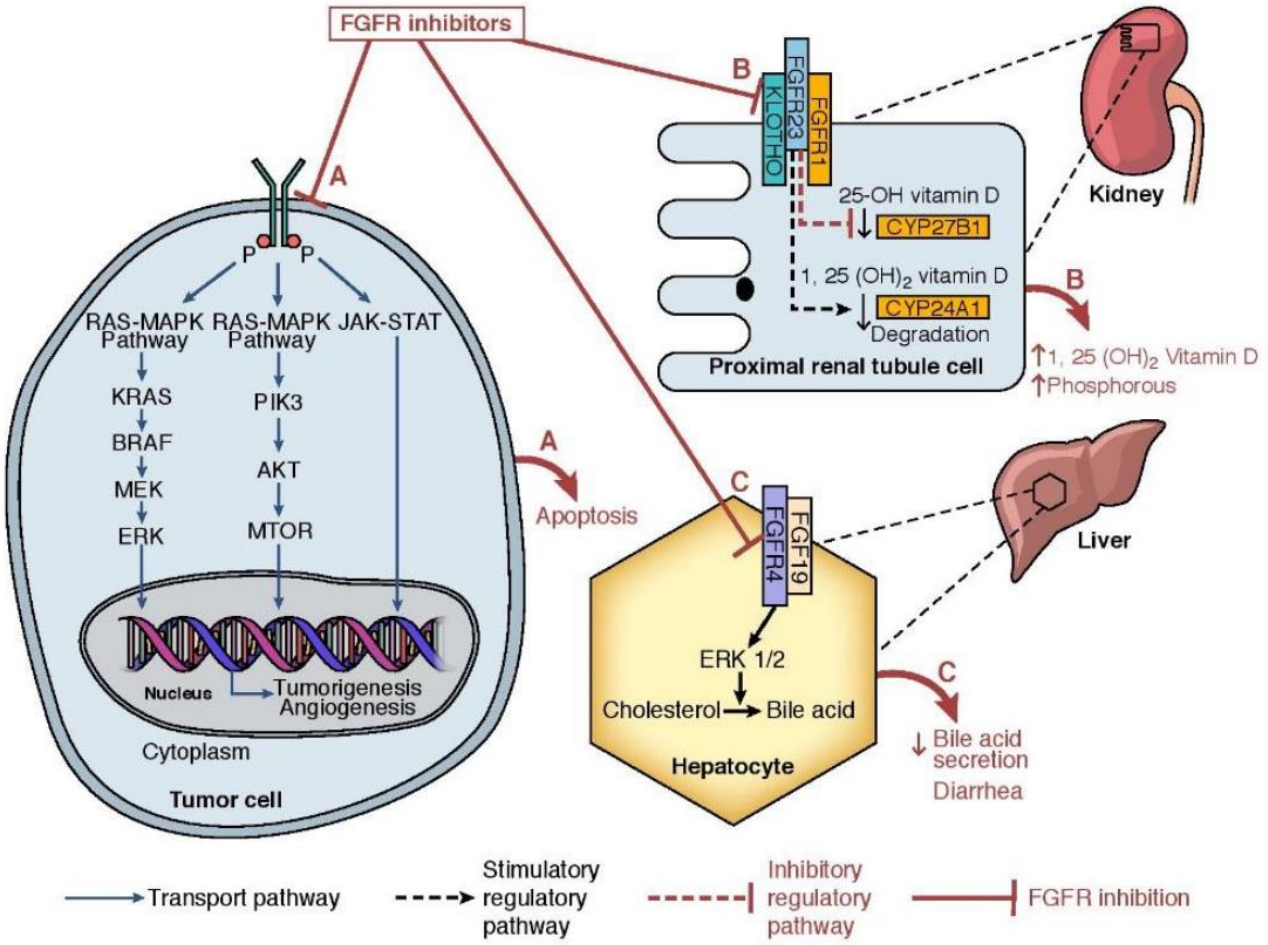
Rashidi et al. CJASN 2023; 18: 121

Inhibidores de FGFR



FGF23 → ↓ fosfaturia y déf vitD ↑

↑ **fosfato**

Kommalapati A et al, Cancers 2021; 13: 2968

Phosphorous Levels	Grade	Intervention *
Sharp rise in phosphorous levels by 25% at the first check; 3.5–5.5 mg/dL	Grade 1	– Reinforce on low-phosphate diet
5.5–6.9 mg/dL	Grade 2	– No dose adjustments for FGFR inhibitor – Consider starting phosphate binder at a lowest possible dose and re-check phosphorous levels in 1 week – Dose escalation of phosphate binder or addition of phosphaturic agent, acetazolamide should be considered if phosphorous levels remain elevated after 7 days of initial intervention
7–9.9 mg/dL	Grade 3	– Maximum recommended dose of phosphate binder in combination with phosphaturic agent, acetazolamide 250 mg twice or thrice a day. – Recheck levels in 2 weeks; if still ≥7 mg/dL; consider dose interruption of FGFR inhibitor for 2 weeks – Consider restarting FGFR inhibitor at usual dose and if phosphorous levels recurs at ≥7 mg/dL, consider first- or second-dose reduction when phosphorous levels reach <7 mg/dL.
≥10mg/dL	Grade 4	– Hold FGFR inhibitor (dose interruption) – Start the patient on maximum recommended dose of phosphate binder in combination with phosphaturic agent, acetazolamide 250 mg twice or thrice a day. – Reassess phosphorous levels every 2 weeks – Consider first- or second-dose reduction when phosphorous levels reach <7 mg/dL. – Consider permanent discontinuation of FGFR inhibitor if phosphorus level >10 mg/dL after two dose reductions

Kommalapati A et al, Cancers 2021; 13: 2968

Inhibidores de FGFR: manejo hiperfosfatemia

Drug	Initial Dose	Max. Recommended Dose
Calcium carbonate	500 mg (chewable) or 600 mg (elemental) tablets 3 times/day	500 mg (chewable) or 600 mg (elemental) tablets 3 times/day
Lanthanum carbonate	500–750 mg three times/day	1000 mg three times/day with meals (taken immediately after meals)
Sevelamer hydrochloride; Sevelamer carbonate	800 mg three times/day	2400 mg three times/day (also available at 1600 mg three times/day) (to be taken in between meals)
Sucroferric oxyhydroxide	500 mg three times/day with meals	2 g per day
Acetazolamide	250 mg once a day	250 mg twice or three times/day *

Kommalapati A et al, Cancers 2021; 13: 2968

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Pseudo AKI

Table 1. Summary of Targeted Cancer Therapies Known to Cause an Asymptomatic Rise in Serum Creatinine Levels Through Inhibition of Active Tubular Secretion.

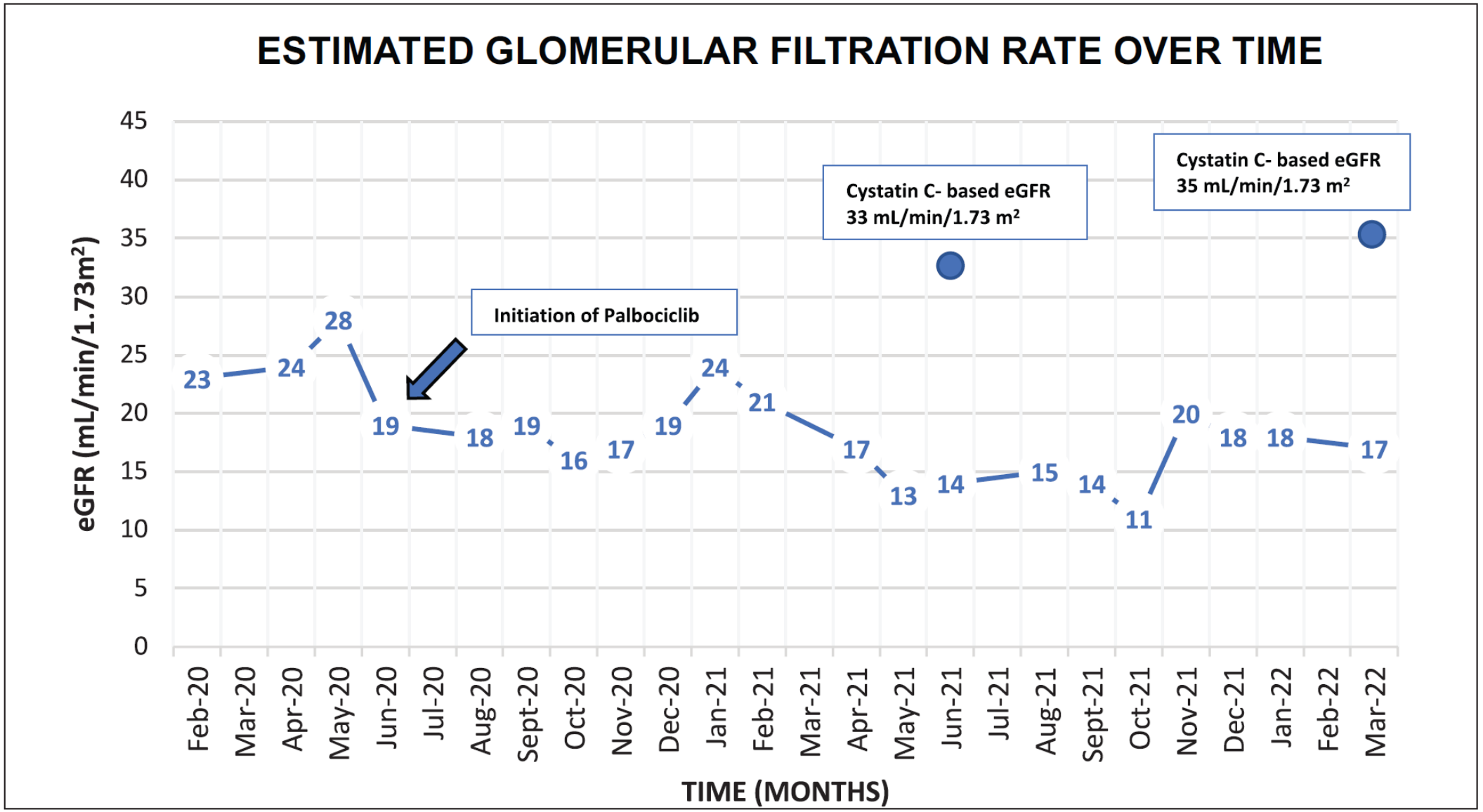
Classes of targeted cancer therapies	Examples	Target cancers
CDK 4/6 inhibitors	Palbociclib, ribociclib, abemaciclib	Metastatic HR-positive and HER2-negative breast cancer
PARP inhibitors	Olaparib, niraparib, rucaparib	Ovarian cancer (BRCA1/2 +), metastatic breast cancer (BRCA1/2 +), endometrial cancer
Tyrosine kinase inhibitors		
1. ALK inhibitors	1. Crizotinib, alectinib, ceritinib	1. NSCLC
2. BCR-ABL inhibitors	2. Imatinib	2. CML, ALL, and GIST.
3. EGFR inhibitors	3. Gefitinib	3. Metastatic NSCLC
4. VEGFR inhibitors	4. Pazopanib, sunitinib, sorafenib	4. RCC, soft tissue sarcomas, GIST, HCC, and thyroid cancer
5. HER2 inhibitors	5. Tucatinib	5. Advanced or metastatic HER2-positive breast cancer
MET inhibitors	Capmatinib	NSCLC

Mach T et al Can J Kidney Health Dis 2022: 9

Targeted agent	Main oncology indication	Incidence of increased SCr level	True AKI	(Potential) pseudo-AKI mechanism
ALK inhibitors	ALK-positive NSCLC (3%–7%)		Acute tubular necrosis [3, 15]	Based on [11–13] and PC:
			Acute tubulointerstitial	
Crizotinib		23%	nephritis [3, 19]	OCT2/MATE1/MATE2k
Alectinib		26%	Renal arteriolar vacuolization	Not expected/no interaction
Ceritinib		33%–58%	[3, 16]	OCT2
Brigatinib		2%	MCD [17, 18]	MATE1/MATE2k
Ensartinib		19%	Crescentic GN [19]	ND
Entrectinib		13%–15%		MATE1
Lorlatinib		ND		MATE1
MET inhibitors	NSCLC with *MET14ex* (3%–4%)		No reports	Based on PC:
Capmatinib	or *MET* gene amplification	19%		MATE1/MATE2k
Tepotinib	(1%–6%)	24%		OCT2/MATE1/MATE2k
CDK4/6 inhibitor	HR-positive, HER2-negative		Acute tubular necrosis [32]	Based on [24, 31] and PC:
Abemaciclib	metastatic breast cancer	11%–40%	Acute tubulointerstitial nephritis [32]	OCT2/MATE1/MATE2k
Palbociclib		12.5%		OCT2
Ribociclib		22%–28%		OCT2/MATE1
PARP inhibitors	Breast, ovarian, fallopian tube,		No reports	Based on [37] and PC:
Olaparib	primary peritoneum,	11%		OCT2/MATE1/MATE2k
Rucaparib	pancreatic and prostate	ND		OCT2/MATE1/MATE2k
Niraparib	cancers with *BRCA1/2* or other *HRR* gene pathogenic variants, markers of HRD or previous response to platinum	ND		MATE1/MATE2k
BRAF inhibitors	BRAF V600E mutated		Acute tubular necrosis [1, 2, 4]	Based on [14] and PC:
Vemurafenib	metastatic melanoma	27.9%	Acute tubulointerstitial	MATE1 (weakly)
Dabrafenib	(40%–50%), metastatic	0%–24%	nephritis	OCT2 (minimal), MATE1 (weakly)
Encorafenib	colorectal cancer (8%–12%), metastatic papillary thyroid cancer (>50%)	ND	Fanconi's syndrome [1, 2, 4]	OCT2/MATE1 (weakly)
BCR-ABL inhibitors	Ph-chromosome/BCR-ABL		Acute tubular necrosis [2]	Based on [12, 41, 42] and PC:
Imatinib	mutated CML (>90%),	7%–44.4%	Tumour lysis syndrome [2]	OCT2/OCT3/MATE1/MATE2k
Dasatinib	gastrointestinal stromal	0%–8%	Fanconi's syndrome [2]	OCT2/MATE1/MATE2k
Nilotinib	tumour	Uncommon	Pigment nephropathy due to	OCT3
Ponatinib		1%–7%	rhabdomyolysis [2]	MATE1
Bosutinib		6%–13%	Thrombotic micro-angiopathy (dasatinib) [2]	OCT2/MATE1
HER2 inhibitors	HER2 overexpressing or		No reports	Based on [43] and PC:
Tucatinib	amplification breast cancer,	13.7%		OCT2/MATE1
Lapatinib	gastric cancer, colorectal	ND		Poor inhibitor of OCTs/MATEs
Neratinib	cancer	ND		ND

Vanhoutte. Clin Kidney J 2023: 16 (4): 603

Pseudo AKI



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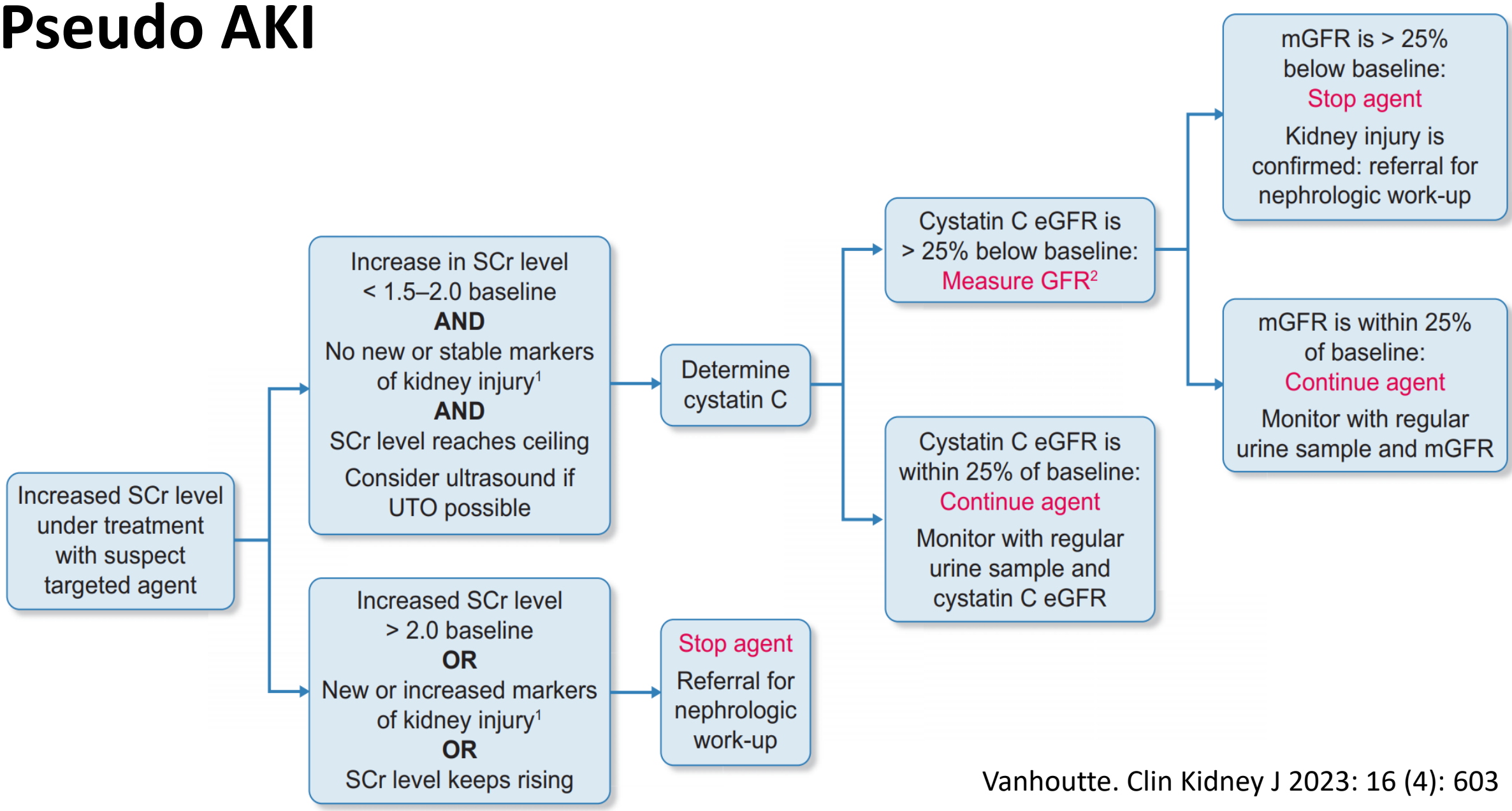
Pseudo AKI



Vanhoutte. Clin Kidney J 2023: 16 (4): 603

CONCLUSIONES

- Las toxicidades renales son una preocupación significativa en el tratamiento del cáncer urológico con terapias emergentes
- El monitoreo regular y el manejo proactivo son esenciales para minimizar el riesgo de daño renal
- La colaboración multidisciplinaria garantiza un enfoque completo y efectivo en el manejo de estas complicaciones
- Contacto rápido y ágil con nefrología para el diagnóstico y se debe continuar durante el manejo terapéutico individualizando pautas y planteando posibilidad reinicio de tratamiento

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Artículo especial

Consulta monográfica de onconefrología. Justificación y puesta en marcha

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Alonso F et al. Nefrologia 2021; 41 (2): 154


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