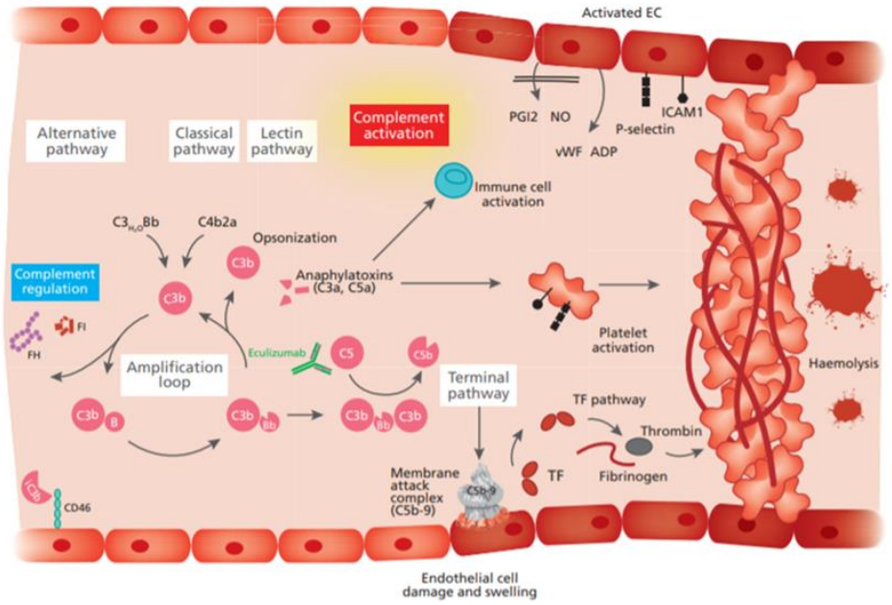
ΕΛΛΗΝΙΚΗ ΕΤΑΙΡΕΙΑ ΑΙΜΑΦΑΙΡΕΣΗΣ

15 ΠΕΡΙΦΕΡΕΙΑΚΗ ΔΙΗΜΕΡΙΔΑ ΕΛΛΗΝΙΚΗΣ ΕΤΑΙΡΕΙΑΣ ΑΙΜΑΦΑΙΡΕΣΗΣ

Η σημασία της άμεσης, πλήρους και διατηρούμενης αναστολής του τελικού συμπληρώματος



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ΓΝΘ «Παπαγεωργίου»

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Σύγκρουση συμφερόντων

- Τιμητική αμοιβή από εταιρίες
- FARAN
- GSK
- Astra Zeneca

Άνδρας, 34 ετών

- ΤΕΠ δύσπνοια, κεφαλαγία
- ΑΠ 225/125
- Οίδημα οπτικής θηλής

- Hb 7.1 PLT 110.000 LDH 910 INR 1.01
- Σχιστοκύτταρα 5%
- SCr 5.0

- **Τρέχουσα διάγνωση: Κακοήθης υπέρταση**

- Στεφανιαία Μονάδα
- Νιτρώδη εφ
- 2ΜΣΕ
- ΚΦΚ ΤΝ

Άνδρας, 34 ετών

- Διακομιδή ΓΝΘ Παπαγεωργίου
- Κρεατ 5,22
- LDH 499 Αιμοπετ 150000 Hb 9.3
- Σχιστοκ 5%

Άνδρας, 34 ετών

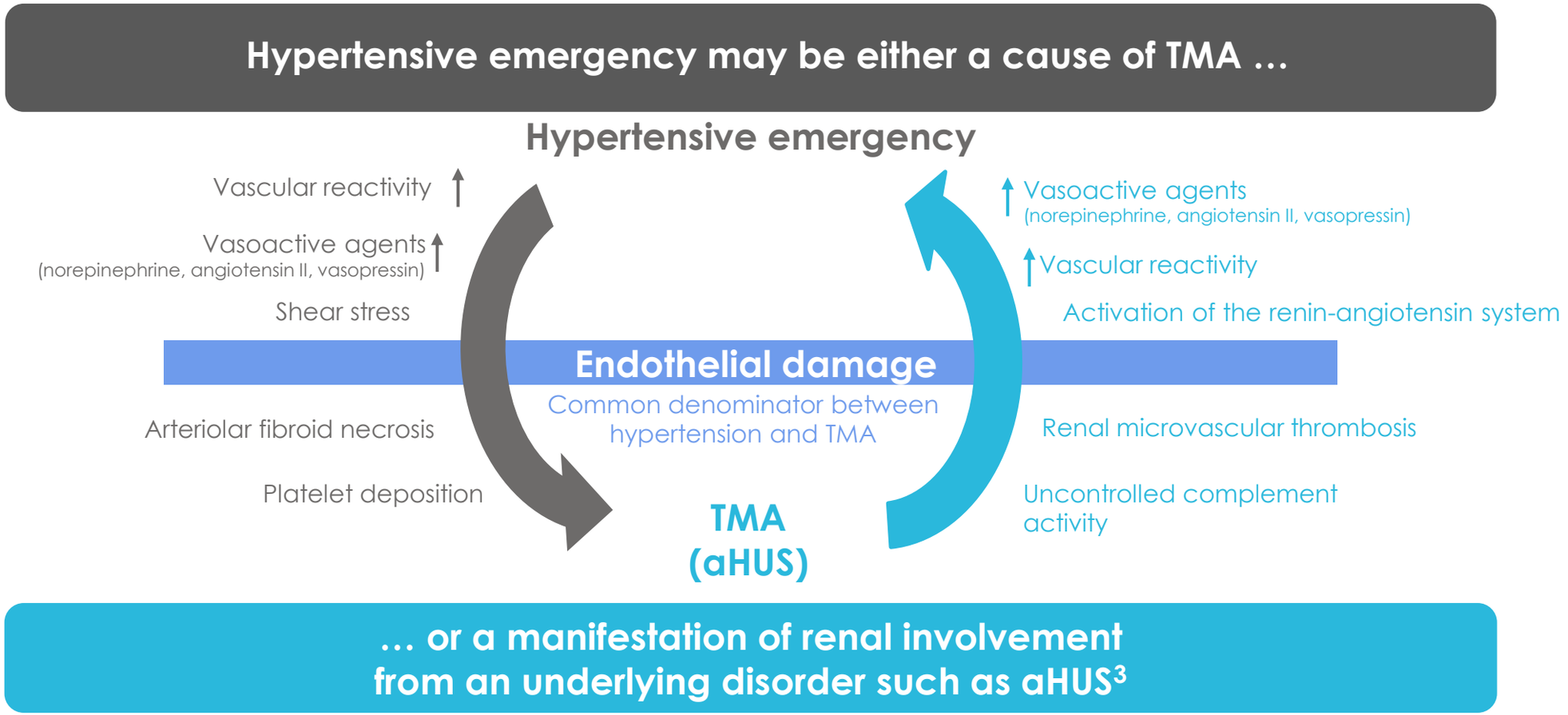
- ΠΛΗΡΗΣ ΑΝΟΣΟΛΟΓΙΚΟΣ C3 / ΙΟΛΟΓΙΚΟΣ (κφ / αρνητικός)
- ΑΝΟΣΟΚΑΘΗΛΩΣΗ ΟΡΟΥ ΟΥΡΩΝ (κφ / αρνητική)
- ADAMTS13 (75% κφ)
- ΒΙΟΨΙΑ ΝΕΦΡΟΥ (ΑΡΝΗΘΗΚΕ)

Άνδρας, 34 ετών

- Μετά από 15 ημέρες νοσηλεία
- Κρεατ 5.2 (υπό ΑΚ)
- LDH 317 PLT 210.000 Hb 9.2 (EPO 10.000x1)
- Σχιστοκύτταρα 6%
- Καλη ρύθμιση ΑΠ ΙΡΒΕΣΑΡΤΑΝΗ, ΑΜΛΟΔΙΠΙΝΗ, ΒΙΣΟΠΡΟΛΟΛΗ, ΣΠΙΡΟΝΟΛΑΚΤΟΝΗ

- **ΔΙΑΓΝΩΣΗ: ΚΑΚΟΗΘΗΣ ΥΠΕΡΤΑΣΗ ή aHUS ?**

Endothelial damage: hypertensive emergency and TMAs[1,2]



aHUS, atypical hemolytic uremic syndrome; TMA, thrombotic microangiopathy.

1. Rodriguez MA *et al. Cardiol Rev* 2010;18:102–7. **2.** Matthew RO *et al. J Am Soc Hypertens* 2016;10:352–9. **3.** Tsai HM. *Austin J Nephrol Hypertens* 2016;3:1055

Severe and malignant hypertension are common in primary atypical hemolytic uremic syndrome

Teresa Cavero[1], Emilia Arjona[2], Karina Soto[3], Fernando Caravaca-Fontán[1], Cristina Rabasco[4], Luis Bravo[5], Francisco de la Cerda[6], Nadia Martín[7], Miquel Blasco[8], Ana Ávila[9], Ana Huerta[10], Virginia Cabello[11], Ana Jarque[12], Concepción Alcázar[13], Xavier Fulladosa[14], Javier Carbayo[15], Sara Anaya[16], Carmen Cobelo[17], Natalia Ramos[18], Elena Iglesias[19], José Baltar[20], Rocío Martínez-Gallardo[21], Lourdes Pérez[22], Enrique Morales[1], Roberto González[1], Manuel Macía[12], Juliana Draibe[14], Luis Pallardó[9], Luis F. Quintana[8], Mario Espinosa[4], Xoana Barros[7], Fernando Pereira[3], Mercedes Cao[5], Juan Antonio Moreno[23], Santiago Rodríguez de Córdoba[2] and Manuel Praga[1,24]; on behalf of the Spanish Group for the Study of Glomerular Diseases (GLOSEN)

Kidney International (2019) **96,** 995–1004; https://doi.org/10.1016/j.kint.2019.05.014

The diagnosis of mHTN was based on the detection of grade 2 or grade 3 HTN accompanied by a hypertensive retinopathy grade III or IV (bilateral retinal flame-shaped hemorrhages and/or exudates or cotton wool spots with or without papilloedema

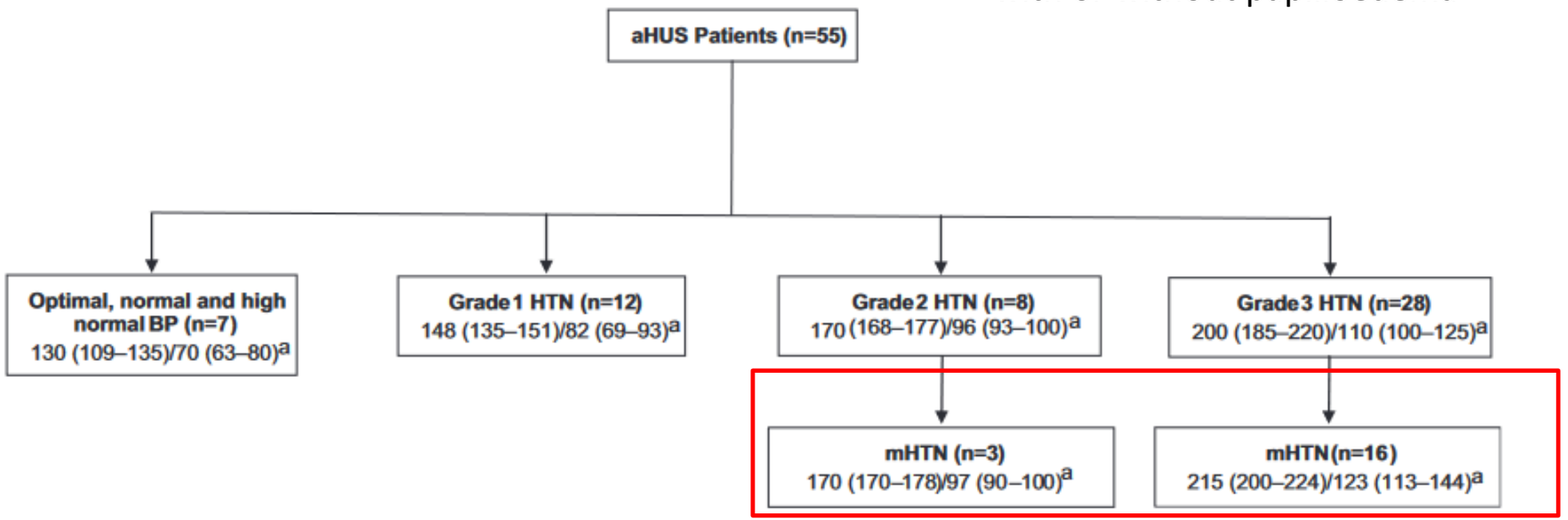


Figure 1 | Atypical hemolytic uremic syndrome (aHUS) patients classified according to the severity of blood pressure (BP) at presentation. Median [a]BP (interquartile range) are shown in mm Hg. mHTN, malignant hypertension.

Nephrol Dial Transplant (2023) 38: 1217–1226
https://doi.org/10.1093/ndt/gfac248
Advance Access publication date 24 August 2022

Thrombotic microangiopathy in patients with malignant hypertension

Teresa Cavero[1,*], Pilar Auñón[1,*], Fernando Caravaca-Fontán[1,2], Hernando Trujillo[1], Emi Arjona[3], Enrique Morales[1], Elena Guillén[4], Miquel Blasco[4], Cristina Rabasco[5], Mario Espinosa[5], Marta Blanco[6], Catuxa Rodríguez-Magariños[6], Mercedes Cao[6], Ana Ávila[7], Ana Huerta[8], Esther Rubio[8], Virginia Cabello[9], Xoana Barros[10], Elena Goicoechea de Jorge[2,11], Santiago Rodríguez de Córdoba[3] and Manuel Praga[2,12]; on behalf of the Spanish Group for the Study of Glomerular Diseases

TMA=
presence at admission of

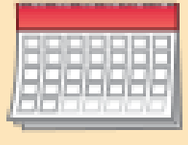
MAHA (decreased haemoglobin, elevated lactic dehydrogenase, low haptoglobin levels, evidence of schistocytes in peripheral blood smears),

low platelet count (<150 000) or a decrease in platelet count >25% with respect to baseline values)

and organ injury

8 Spanish hospitals

Patients with mHTN
n =199



2000–2020

Nephrol Dial Transplant (2023) 38: 1217–1226
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Table 2: Aetiology of HTN in patients with and without TMA.

Whole cohort ($N = 199$)
Primary HTN: 87 (43.7)
Glomerular diseases: 33 (16.6)
IgAN: 23 (11.6)
Diabetic nephropathy: 4 (2)
FSGS: 2 (1)
IC-MPGN: 1 (0.5)
aHUS: 26 (13.1)
Vasculorenal HTN: 19 (9.6)
Drug-induced HTN: 14 (7)
Illicit drugs (cocaine): 8 (4)
TKI: 3 (1.5)
CNI: 1 (0.5)
mTORi: 1 (0.5)
Gemcitabine: 1 (0.5)
Systemic diseases: 11 (5.5)
Systemic sclerosis: 4 (2)
SLE: 3 (1.5)
ANCA-associated vasculitis: 3 (1.5)
Antiphospholipid syndrome: 1 (1)
Endocrine diseases: 9 (4.5)
Primary hyperaldosteronism: 7 (3.5)
Pheochromocytoma: 2 (1)

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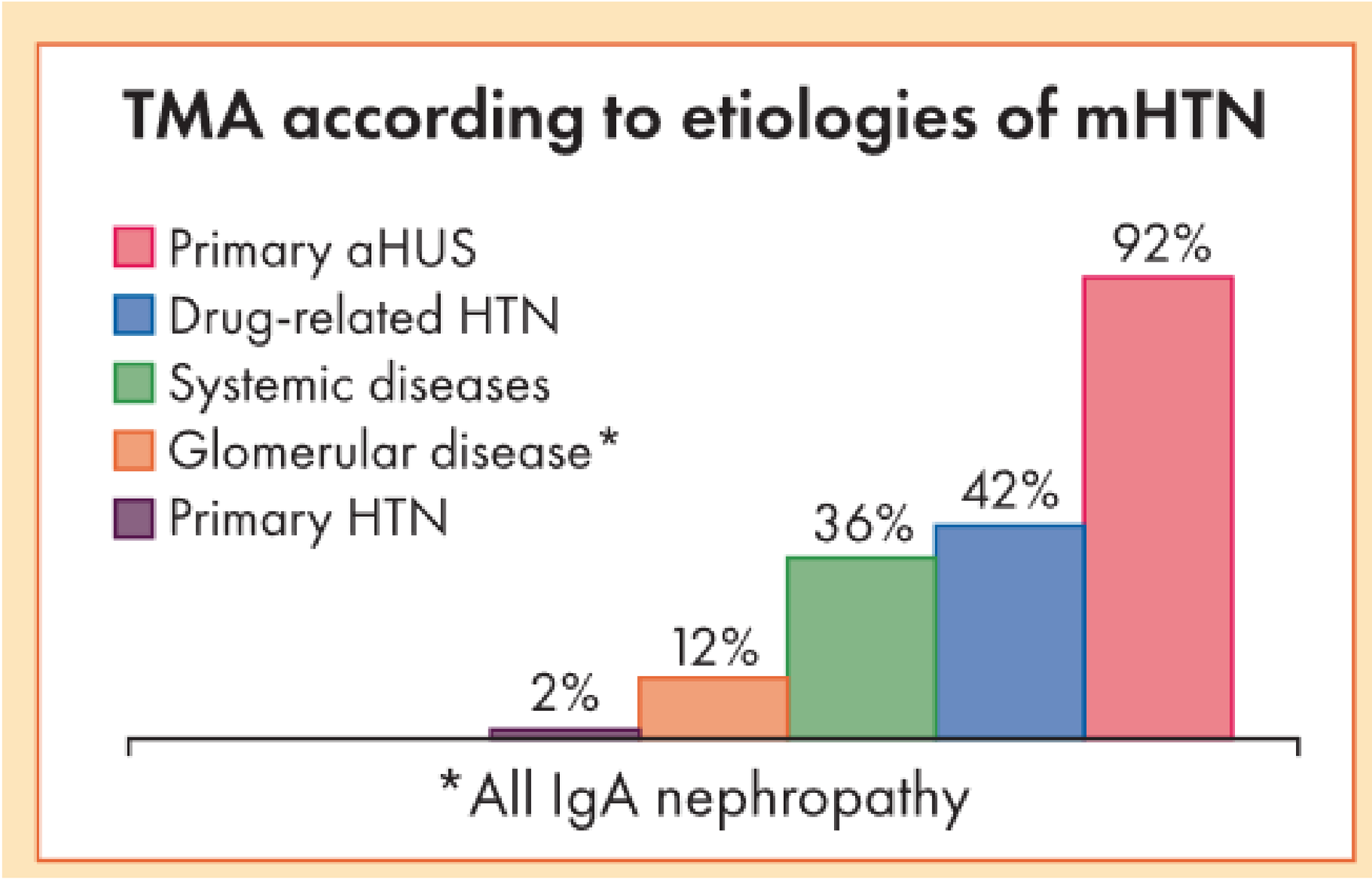
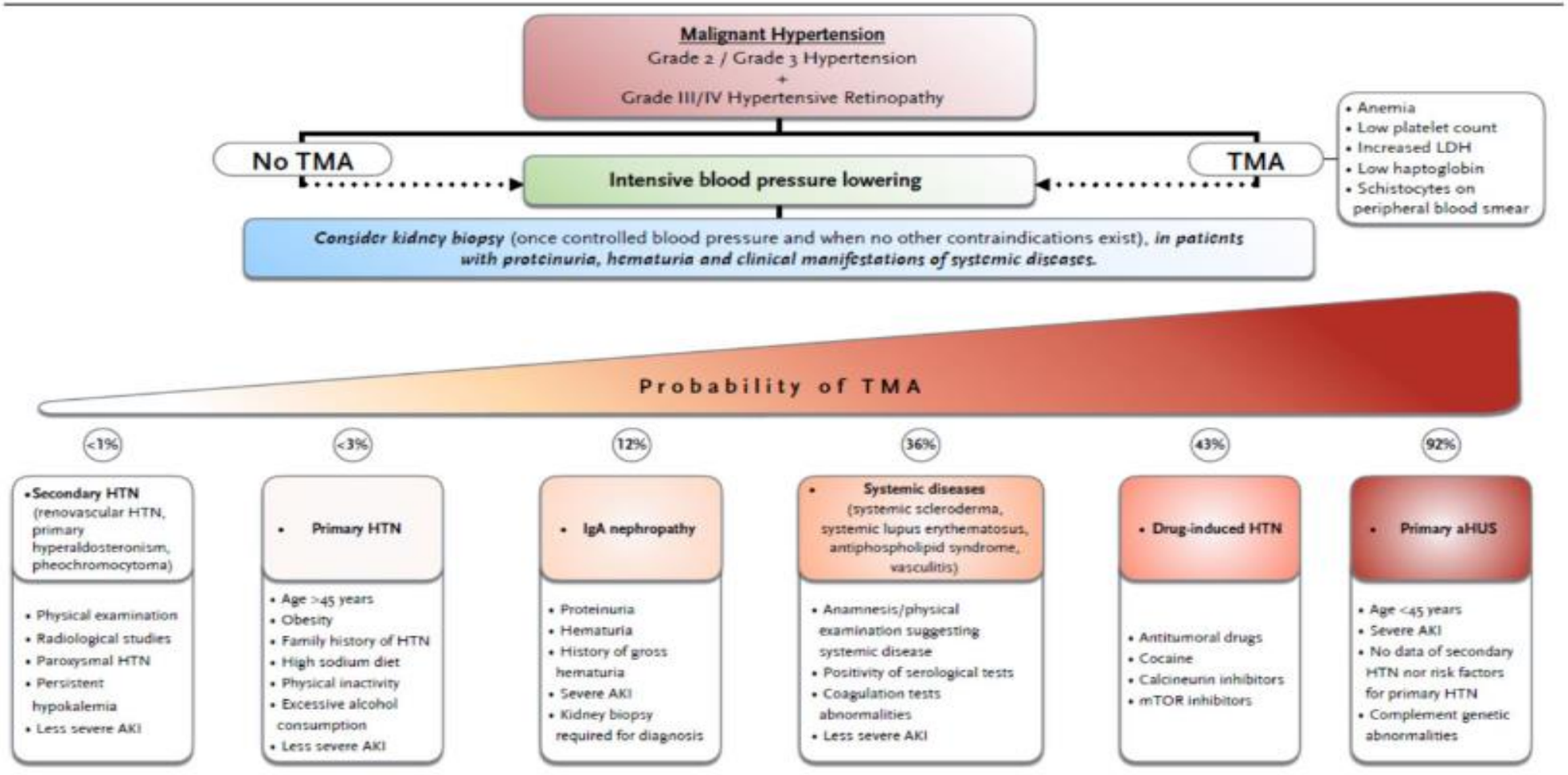
Table 2: Aetiology of HTN in patients with and without TMA.

Whole cohort ($N = 199$)	Patients with TMA ($n = 40$)
Primary HTN: 87 (43.7)	aHUS: 24 (60)
Glomerular diseases: 33 (16.6) IgAN: 23 (11.6) Diabetic nephropathy: 4 (2) FSGS: 2 (1) IC-MPGN: 1 (0.5)	Drug-induced HTN: 6 (15) TKI: 3 (7.5) Illicit drugs (cocaine): 2 (5) Gemcitabine: 1 (2.5)
aHUS: 26 (13.1)	Glomerular diseases: 4 (10) IgAN: 4 (10)
Vasculorenal HTN: 19 (9.6)	Systemic diseases: 4 (10) Systemic sclerosis: 3 (7.5) ANCA-associated vasculitis: 1 (2.5)
Drug-induced HTN: 14 (7) Illicit drugs (cocaine): 8 (4) TKI: 3 (1.5) CNI: 1 (0.5) mTORi: 1 (0.5) Gemcitabine: 1 (0.5)	Primary HTN: 2 (5)
Systemic diseases: 11 (5.5) Systemic sclerosis: 4 (2) SLE: 3 (1.5) ANCA-associated vasculitis: 3 (1.5) Antiphospholipid syndrome: 1 (1)	Vasculorenal HTN: 0 (0)
Endocrine diseases: 9 (4.5) Primary hyperaldosteronism: 7 (3.5) Pheochromocytoma: 2 (1)	Endocrine diseases: 0 (0)


TMA according to etiologies of mHTN
Primary aHUS
Drug-related HTN
Systemic diseases
Glomerular disease*
Primary HTN
92%
42%
36%
12%
2%
*All IgA nephropathy



Conclusion

The presence of TMA in patients with mHTN should guide the diagnosis towards primary aHUS, drug-related mHTN, some systemic diseases and IgA nephropathy, while it is exceptional in other causes of mHTN.

Patients with hypertension-associated thrombotic microangiopathy may present with complement abnormalities

see commentary on page 1271

Sjoerd A.M.E.G. Timmermans[1], Myrurgia A. Abdul-Hamid[2], Joris Vanderlocht[3], Jan G.M.C. Damoiseaux[4], Chris P. Reutelingsperger[5] and Pieter van Paassen[1]; for the Limburg Renal Registry

[1]Department of Nephrology and Clinical Immunology, Maastricht University Medical Centre, Maastricht, the Netherlands; [2]Department of Pathology, Maastricht University Medical Centre, Maastricht, the Netherlands; [3]Department of Transplantation Immunology, Maastricht University Medical Centre, Maastricht, the Netherlands; [4]Central Diagnostic Laboratory, Maastricht University Medical Centre, Maastricht, the Netherlands; and [5]Deptartment of Biochemistry, Cardiovascular Research Institute Maastricht, Maastricht University, Maastricht, the Netherlands

Consecutive patients with **biopsy-proven renal TMA** who presented **with severe hypertension**

Severe hypertension was defined as blood pressure levels of >180 mm Hg systolic and/or 120 mm Hg diastolic and evidence of impending or progressive target organ dysfunction secondary to hypertension

Nat Rev Nephrol . 2021 Aug;17(8):543-553

Patients with hypertension-associated thrombotic microangiopathy may present with complement abnormalities

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Table 1 | Baseline clinical features and laboratory evaluation

Patient No.	Age (yr)	Sex	BP (mm Hg)	SCr (µmol/l)	uProt (g/d)	uRBC	ESRD	Hb (mmol/l)	LDH (U/l)	MAHA[a]	Platelets ($\times 10^9$/l)[b]
1	38.4	F	184/140	1730	NA	NA	Y	5.1	1800	Y	224
2	40.3	M	205/114	1195	2.3	Y	Y	5.7	1104	Y	158
3	37.7	M	200/120	586	3.9	Y	Y	5.3	2125	Y	100
4	32.0	F	180/120	1138	NA	NA	Y	5.9	1486	Y	142
5	65.0	M	195/105	162	1.5	Y	N	7.9	271	N	98
6	41.1	F	180/120	334	0.7	Y	Y	7.5	291	N	285
7	28.5	F	224/122	1065	1.6	Y	Y	5.1	298	N	228
8	27.9	M	240/150	673	1.6	Y	Y	7.9	165	N	133
9	44.0	F	220/120	649	0.4	Y	Y	8.2	339	N	340

BP, blood pressure; ESRD, end-stage renal disease; F, female; Hb, hemoglobin; LDH, lactate dehydrogenase; M, male; MAHA, microangiopathic hemolytic anemia; N, no; NA, not applicable; SCr, serum creatinine; uProt, proteinuria; uRBC, hematuria; Y, yes.

[a]Cases with hemolytic anemia and schistocytes on peripheral blood smear were defined as MAHA.

[b]Lower limit of normal = 130 $\times 10^9$/l.

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9	44.0	F	220/120	649	0.4	Y	Y	8.2	339	N	340

BP, blood pressure; ESRD, end-stage renal disease; F, female; Hb, hemoglobin; LDH, lactate dehydrogenase; M, male; MAHA, microangiopathic hemolytic anemia; N, no; NA, not applicable; SCr, serum creatinine; uProt, proteinuria; uRBC, hematuria; Y, yes.

[a]Cases with hemolytic anemia and schistocytes on peripheral blood smear were defined as MAHA.

[b]Lower limit of normal = 130 ×10^9/l.

«Furthermore, **the absence of haematological features of TMA at referral does not rule out a diagnosis of complement-mediated aHUS**;
up to 15% of patients with acute phase aHUS have a normal platelet count and patients with aHUS **can undergo haematological remission** (either spontaneously or following plasma exchanges) **despite persistent severe impairment of kidney function.**»

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Table 2 | Complement abnormalities

Patient No.	Mutation(s)	*CFH*-H3[11]	FHAA	CP (%)[a]	AP (%)[b]	sC5b-9 (ng/ml)[c]
1	*C3*-R161W[18]	N	Negative	95	64	2800
2	*CD46*-ΔD237/S238,[15] *CFH*-Q950H[11]	Y	Negative	97	107	1000
3	*C3*-R161W[18]	Y	ND	94	97	640
4	*CFH*-C853R[16]	Y	ND	104	71	1840
5	No mutations	N	ND	99	99	1800
6	*CFI*-N151S[14]	N	ND	97	87	4200
7	*C3*-R161W,[18] Δ*CFHR1-CFHR3*[d]	N	Negative	110	62	1840
8	No mutations	Y	Negative	90	74	440
9	No mutations	N	Negative	113	110	3800

AP, functional activity of the alternative pathway; CP, functional activity of the classical pathway; FHAA, factor H autoantibodies; N, no; ND, not determined; Y, yes.
[a]Normal >75%.
[b]Normal >40%.
[c]Normal <337 ng/ml.
[d]Genetic abnormality was found in homozygosity.

sC5b-9

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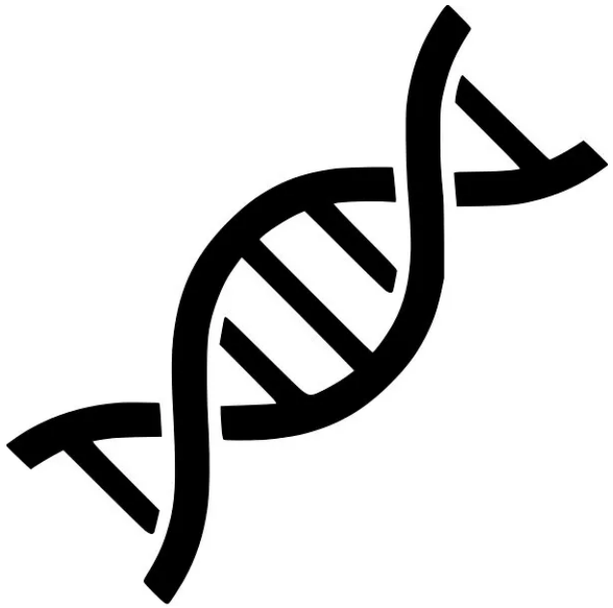
Γενετικός έλεγχος συμπληρώματος



- Σε ασθενείς με κλινική διάγνωση aHUS διαπιστώνονται γενετικές διαταραχές σε ποσοστό 30-60%
- Σε ασθενείς με κλινική διάγνωση κακοήθους υπέρτασης διαπιστώνονται γενετικές διαταραχές σε ποσοστό 37-51%

Nephrol Dial Transplant (2023) 38: 1217–1226

Άνδρας, 34 ετών

- Συνέχιση χρείας ΑΚ και ενίοτε μεταγγίσεων
- **ΔΙΑΓΝΩΣΗ: aHUS**
- Επανεισαγωγή
- ΠΑ (10, FFP) χωρίς βελτίωση νεφρικής λειτουργίας)
- Γενετικός έλεγχος
- Αίτηση χορήγησης ravulizumab
- Εμβολιασμός για μηνιγγιτιδόκοκκο

Απάντηση σε αναστολή συμπληρώματος

«Notably, patients who were treated with **eculizumab** had significantly **better renal outcomes** than those who were treated with plasmapheresis or antihypertensive treatment only, …
….favourable effect of eculizumab was evident **in both carriers and non-carriers** of complement genetic abnormalities, in agreement with the results of other studies»

Variable	Patients (n = 26)	Eculizumab (n = 7)	No eculizumab (n = 19)	p-value
Age, years[a]	38 (29 - 44)	36 (21 - 44)	38 (29 - 43)	0.63
Male sex, n(%)	16 (61.5)	4 (57.1)	12 (63.2)	1
SBP, mmHg[a]	218 (200 - 240)	230 (178 - 240)	216 (203 - 232)	1
DBP, mmHg[a]	130 (117 - 143)	120 (100 - 141)	130 (120 - 145)	0.29
Complement genetic studies, n(%)				0.57
- Pathogenic variants	7 (39)	2 (29)	5 (45)[¥]	
- VUS	3 (17)	1 (14)	2 (18)[¥]	
- No carriers	8 (44)	4 (57)	4 (36)[¥]	
Kidney recovery, n(%)	9 (34.6)	6 (85.7)	3 (15.8)	0.001
Hematological recovery, n(%)	25 (96.2)	7 (100)	18 (94.7)	0.54
Kidney failure, n(%)	16 (61.5)	1 (14.3)	15 (79)	0.003
Kidney survival at 1 year, (%)	54	86	41	0.01
Kidney survival at 3 years, (%)	34	86	11	
Kidney survival at 5 years, (%)	34	86	11	

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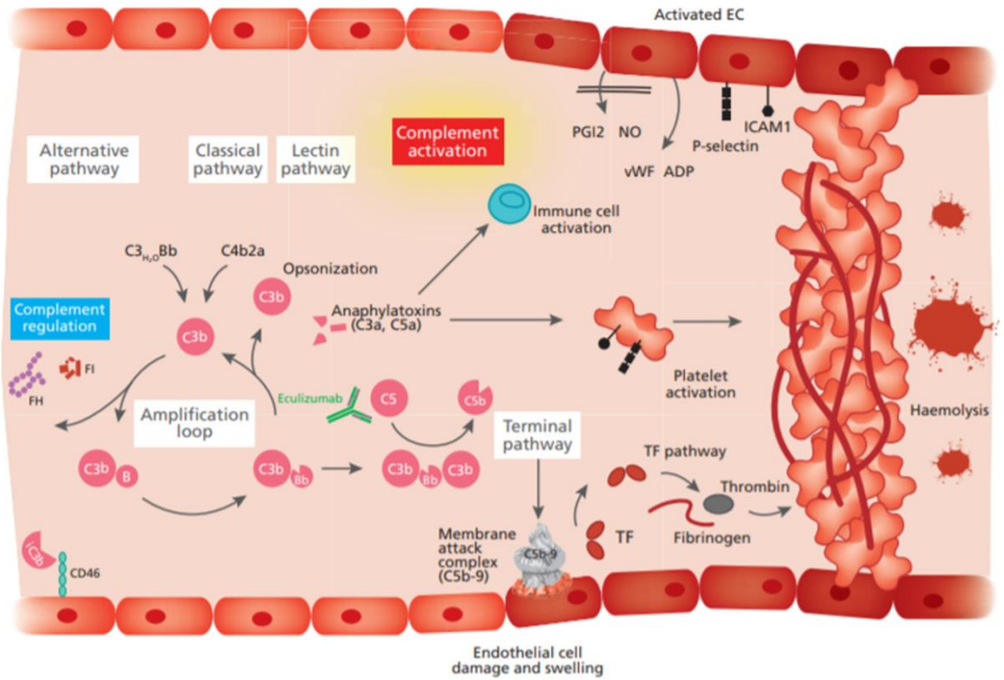
Αναστολή συμπληρώματος στο aHUS



- «the **risk of end-stage renal disease** in patients with aHUS has **decreased from 50% to 60% to ~10% to 15%.**
- This therapeutic breakthrough has, to some extent, been **dulled by the difficulty in making a reliable timely diagnosis of aHUS**
- An **accurate, rapid diagnosis with a timely treatment** have become crucial for the optimal management of patients with aHUS.»

Blood. 2023 Mar 2;141(9):984-995

Eculizumab & Ravulizumab: Εγκεκριμένες Ενδείξεις από τον EMA

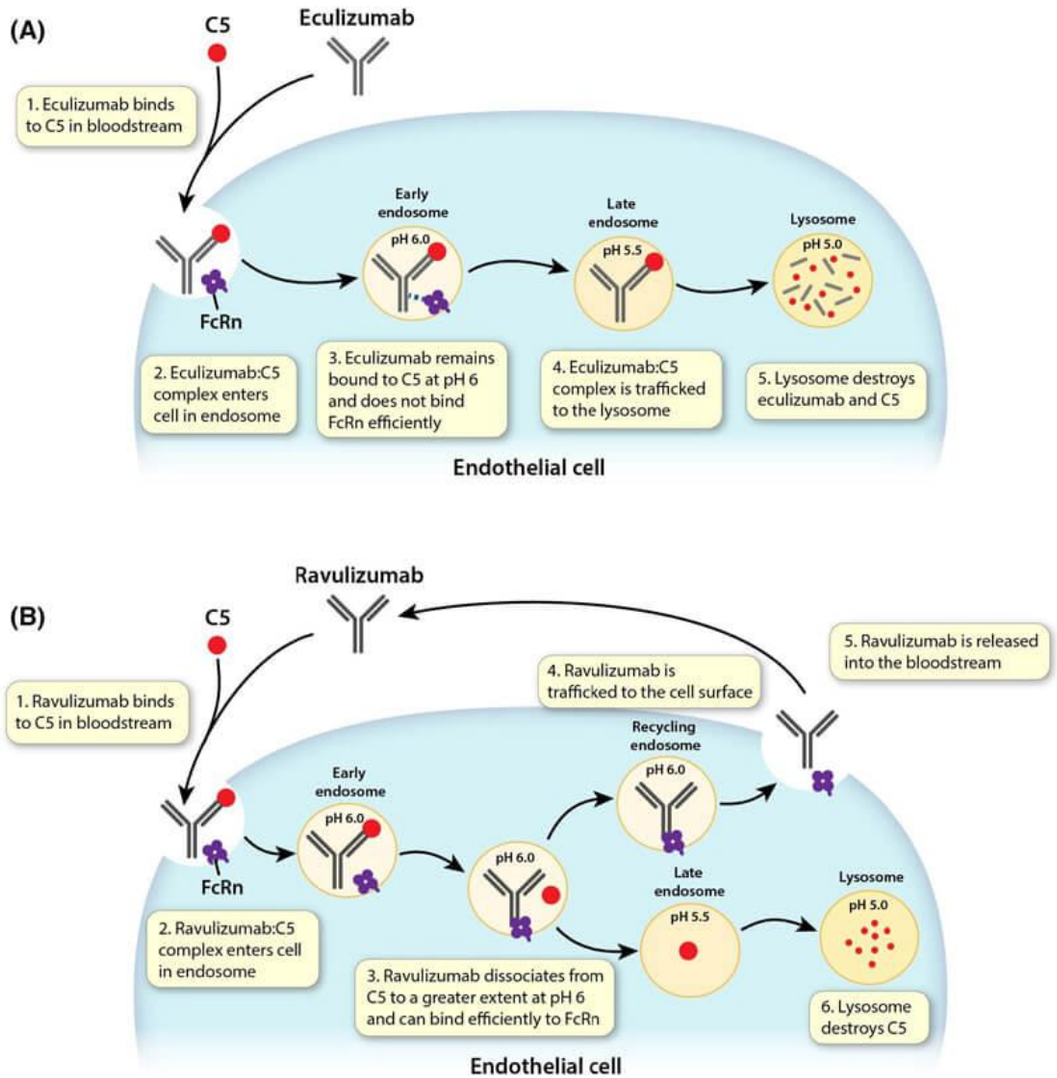
Το eculizumab ενδείκνυται για χρήση σε ενήλικες και παιδιά για τη θεραπεία:

- ***Της παροξυσμικής νυχτερινής αιμοσφαιρινουρίας (ΠΝΑ)***
  - Η απόδειξη του κλινικού οφέλους καταδεικνύεται σε ασθενείς με αιμόλυση με κλινικό(ά) σύμπτωμα(συμπτώματα) ενδεικτικό(ά) της υψηλής ενεργότητας της νόσου, ανεξάρτητα από το ιστορικό μετάγγισης
- ***Του άτυπου αιμολυτικού ουραιμικού συνδρόμου (aHUS)***
- ***Γενικευμένη μυασθένεια gravis (gMG)***
  - Το eculizumab ενδείκνυται για χρήση σε ενήλικες για τη θεραπεία της ανθεκτικής γενικευμένης μυασθένειας gravis (gMG) σε ασθενείς που είναι θετικοί για αντισώματα κατά των υποδοχέων ακετυλοχολίνης (AChR).
- ***Διαταραχές οπτικής νευρομυελίτιδας (NMOSD)***
  - Το eculizumab ενδείκνυται για χρήση σε ενήλικες για τη θεραπεία της διαταραχής του φάσματος ασθενειών της οπτικής νευρομυελίτιδας (NMOSD) σε ασθενείς που είναι θετικοί για αντισώματα κατά της ακουαπορίνης-4 (AQP4) με υποτροπιάζουσα πορεία της νόσου

Το ravulizumab ενδείκνυται για τη θεραπεία:

- ***Της παροξυσμικής νυκτερινής αιμοσφαιρινουρίας (ΠΝΑ)***
  - Το ravulizumab ενδείκνυται για τη θεραπεία ενήλικων και παιδιατρικών ασθενών με σωματικό βάρος 10 kg ή μεγαλύτερο με ΠΝΑ:
    - σε ασθενείς με αιμόλυση με κλινικό(ά) σύμπτωμα(τα) δηλωτικό(ά) υψηλής ενεργότητας της νόσου
    - σε ασθενείς που είναι κλινικά σταθεροί αφού έχουν λάβει θεραπεία με eculizumab τουλάχιστον για τους 6 προηγούμενους μήνες.
- ***Άτυπο αιμολυτικό ουραιμικό σύνδρομο (aHUS)***
  - *ενδείκνυται για τη θεραπεία ενήλικων και παιδιατρικών ασθενών με σωματικό βάρος 10 kg ή μεγαλύτερο με aHUS οι οποίοι είναι πρωτοθεραπευόμενοι με αναστολέα του συμπληρώματος ή έχουν λάβει εκουλιζουμάμπη για τουλάχιστον 3 μήνες και έχουν στοιχεία ανταπόκρισης στην εκουλιζουμάμπη.*
- ***Γενικευμένη μυασθένεια gravis (gMG)***
  - *ενδείκνυται ως προσθήκη στην τυπική αγωγή για τη θεραπεία ενήλικων ασθενών με gMG που είναι θετικοί για αντισώματα έναντι των υποδοχέων ακετυλοχολίνης (AChR).*
- ***Διαταραχή του φάσματος ασθενειών της οπτικής νευρομυελίτιδας (NMOSD)***
  - *ενδείκνυται για τη θεραπεία ενήλικων ασθενών με NMOSD που είναι θετικοί για αντισώματα κατά της ακουαπορίνης-4 (AQP4).*

1) https://www.ema.europa.eu/documents/product-information/ultomiris-epar-product-information_en.pdf
2) https://www.ema.europa.eu/documents/product-information/soliris-epar-product-information_el.pdf



J Clin Pharm Ther . 2022 Jul;47(7):1081-1087

«The long-acting C5-inhibitor ravulizumab was developed from eculizumab and was approved for treatment of aHUS in Europe in 2021.

A change in four amino acids increases the affinity of the monoclonal antibody for the neonatal Fc receptor and enhances pH dependent antibody recycling thereby extending duration of action.

Thus, with the same epitope, a similar affinity and rate **ravulizumab has a half-life period of approximately 52 days in contrast to eculizumab with 11 days** allowing for dosing intervals of 8 weeks following induction.»

BMC Nephrology (2024) 25:202

eculizumab

Στο Άτυπο Αιμολυτικό Ουραιμικό Σύνδρομο (aHUS):

Το δοσολογικό σχήμα στο aHUS για ενήλικες ασθενείς (ηλικίας ≥18 ετών) συνίσταται σε μια αρχική φάση διάρκειας 4 εβδομάδων ακολουθούμενη από μια φάση συντήρησης:

- Αρχική φάση: 900 mg ecul χορηγούμενα μέσω ενδοφλέβιας έγχυσης διάρκειας 25 – 45 λεπτών κάθε εβδομάδα για τις πρώτες 4 εβδομάδες
- Φάση συντήρησης: 1.200 mg ecul χορηγούμενα μέσω ενδοφλέβιας έγχυσης διάρκειας 25 – 45 λεπτών για την πέμπτη εβδομάδα, ακολουθούμενα από χορήγηση 1.200 mg ecul μέσω ενδοφλέβιας έγχυσης διάρκειας 25 – 45 λεπτών κάθε 14 ± 2 ημέρες (βλ. παράγραφο 5.1).

Πίνακας 1: Δοσολογικό σχήμα της ραβουλιζουμάμπης με βάση το σωματικό βάρος για ενήλικους ασθενείς με σωματικό βάρος μεγαλύτερο από ή ίσο με 40 kg

Εύρος σωματικού βάρους (kg)	Δόση έναρξης (mg)	Δόση συντήρησης (mg)*	Μεσοδιάστημα χορήγησης δόσεων
≥ 40 έως < 60	2.400	3.000	Κάθε 8 εβδομάδες
≥ 60 έως < 100	2.700	3.300	Κάθε 8 εβδομάδες
≥ 100	3.000	3.600	Κάθε 8 εβδομάδες

* Η πρώτη δόση συντήρησης χορηγείται 2 εβδομάδες μετά τη δόση έναρξης

Kidney International (2020) **97,** 1287–1296; https://doi.org/10.1016/j.kint.2020.01.035

The long-acting C5 inhibitor, Ravulizumab, is effective and safe in adult patients with atypical hemolytic uremic syndrome naïve to complement inhibitor treatment

see commentary on page 1106

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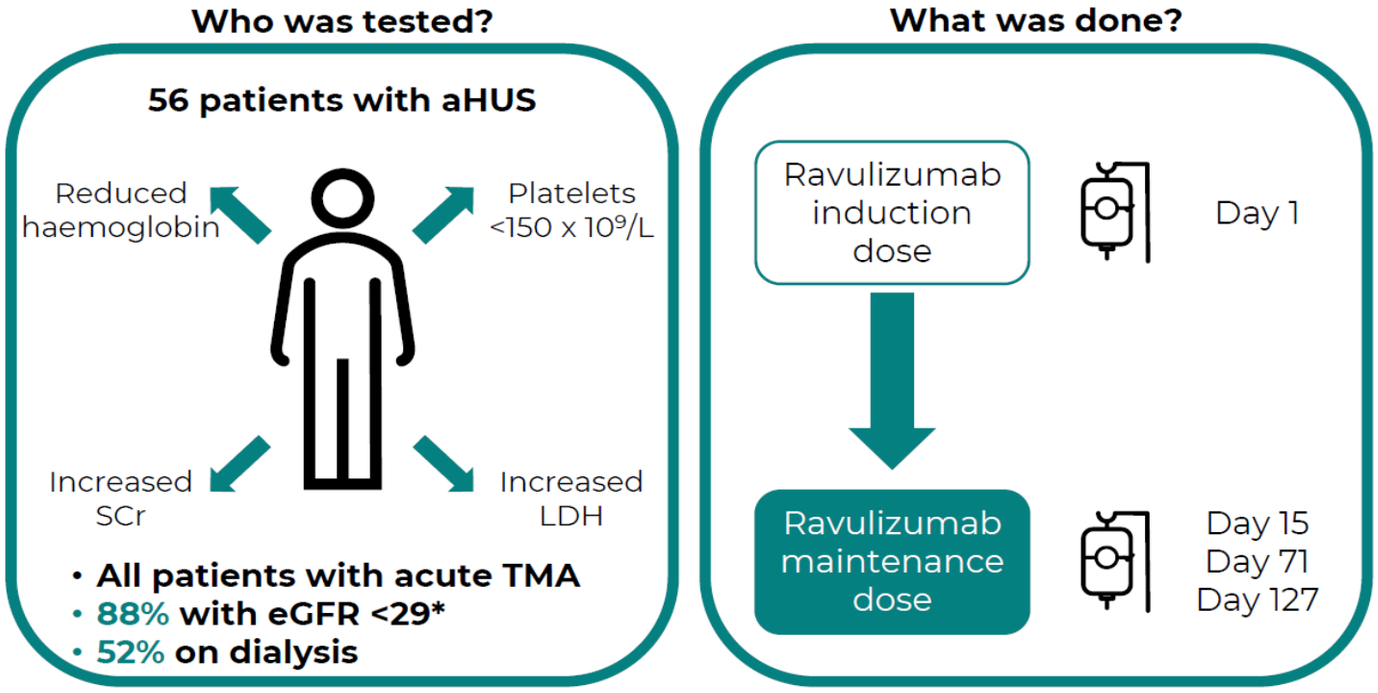
Patients with ≥1 identified pathogenic variant or autoantibody[c,d]	8 (20.5)
C3	1 (2.6)
CD46	2 (5.1)
CFB	1 (2.6)
CFH	2 (5.1)
CFH autoantibody	2 (5.1)



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48.2%(~50%) (27/56) των ενήλικων ασθενών στο κλινικό πρόγραμμα Φάσης III του ravulizumab στο aHUS έλαβαν θεραπεία ενώ βρίσκονταν στη μονάδα εντατικής θεραπείας, καταδεικνύοντας την πιθανή χρησιμότητα της θεραπείας στην οξεία φάση της νόσου

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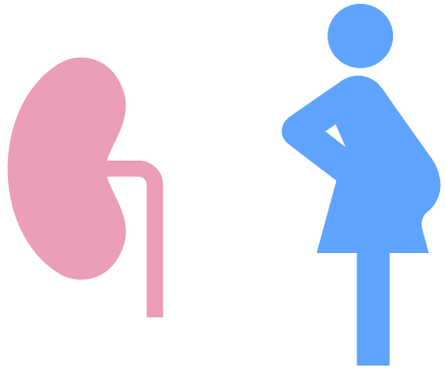

Από τους 56 ασθενείς της μελέτης, 8 (14.3%) αντιμετώπισαν επιλόχειο aHUS (επαγόμενο από trigger) και 8 (14.3%) είχαν προηγουμένως υποβληθεί σε μεταμόσχευση νεφρού

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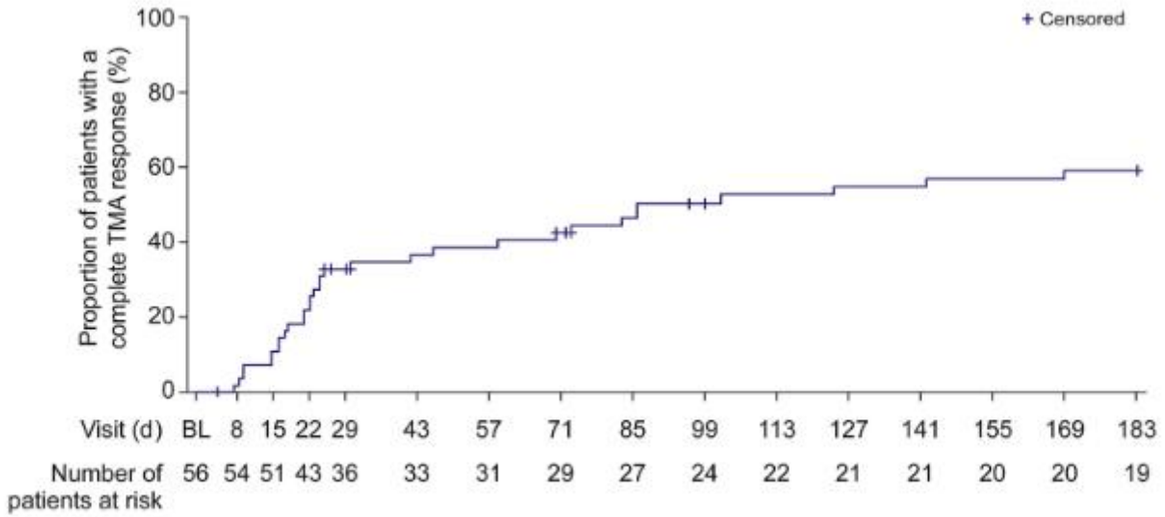
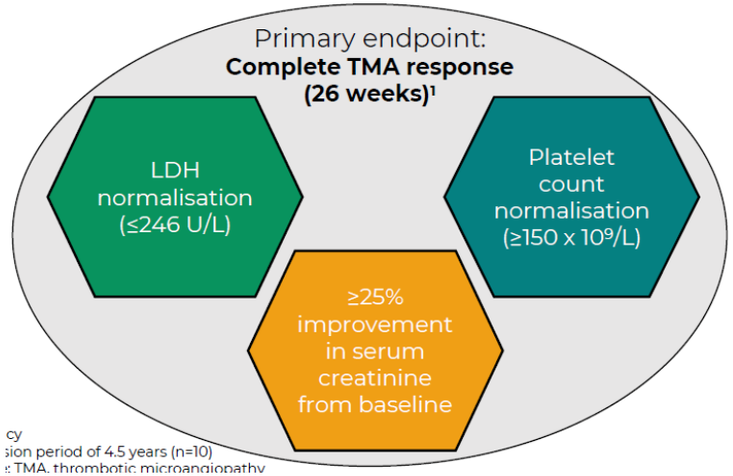


Figure 2| Kaplan-Meier graph showing time to complete thrombotic microangiopathy (TMA) response. Patients who did not have a response were censored on the day of their last study visit, or at study discontinuation. BL, baseline.



«53.6% of patients reaching the primary end point of complete TMA response»

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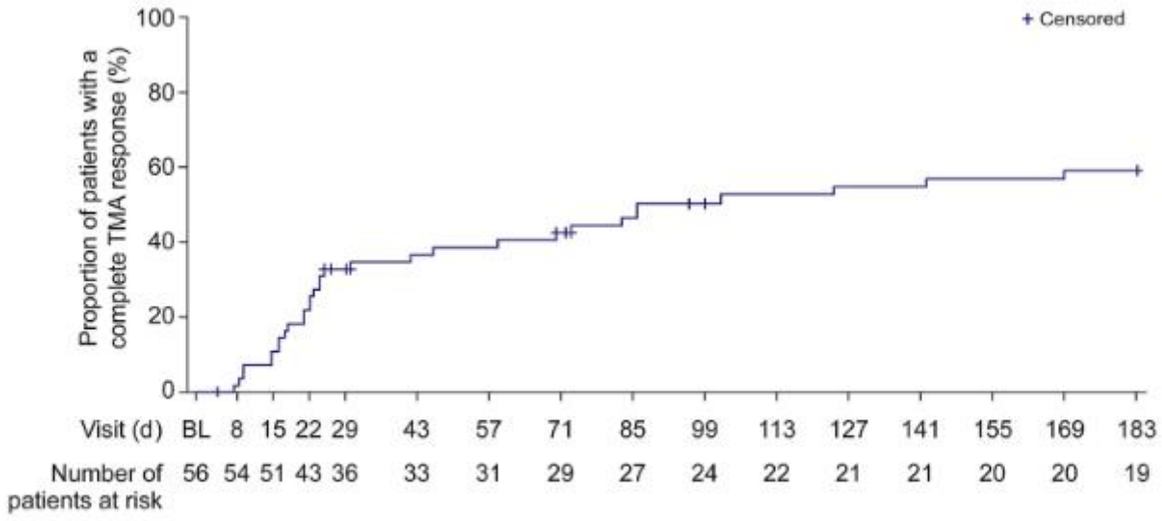

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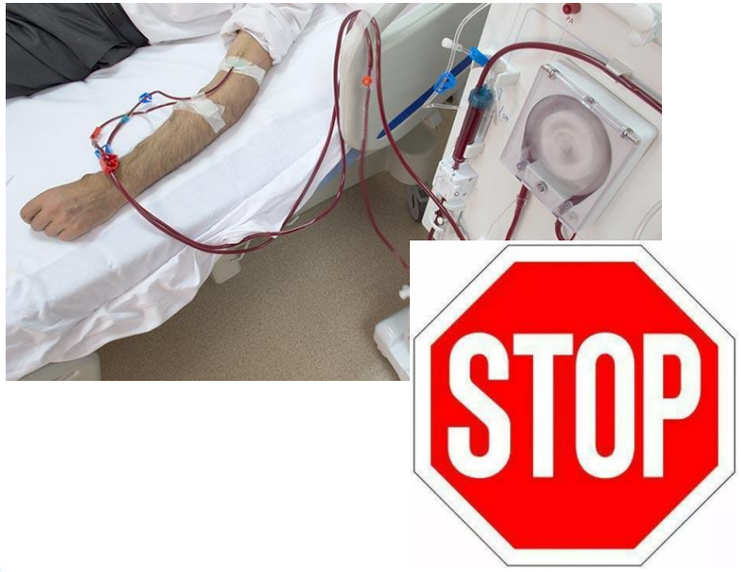

«53.6% of patients reaching the primary end point of complete TMA response»

«58.6% of the patients on dialysis at baseline came off dialysis within 6 months»

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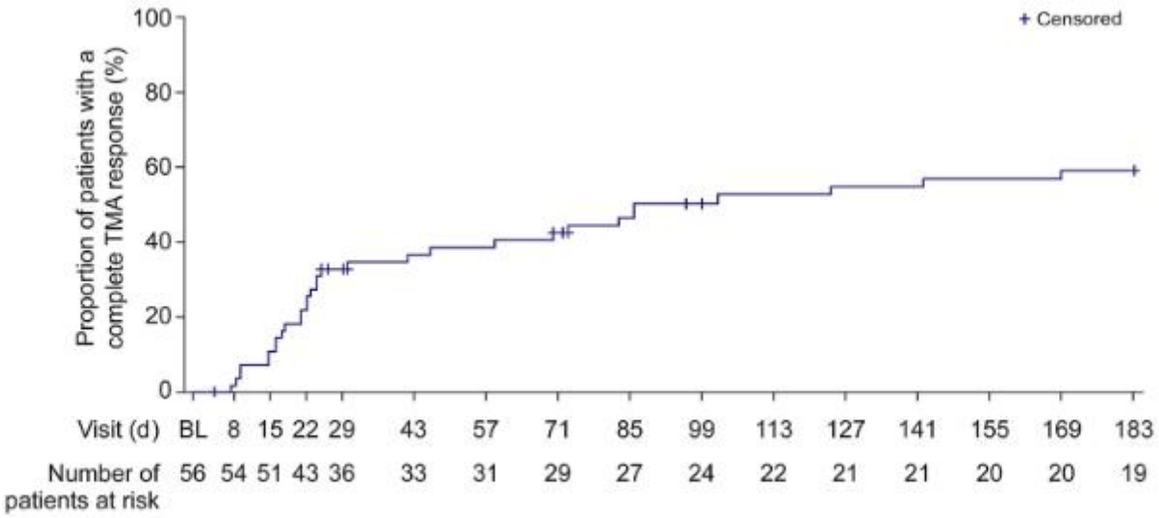

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«53.6% of patients reaching the primary end point of complete TMA response»

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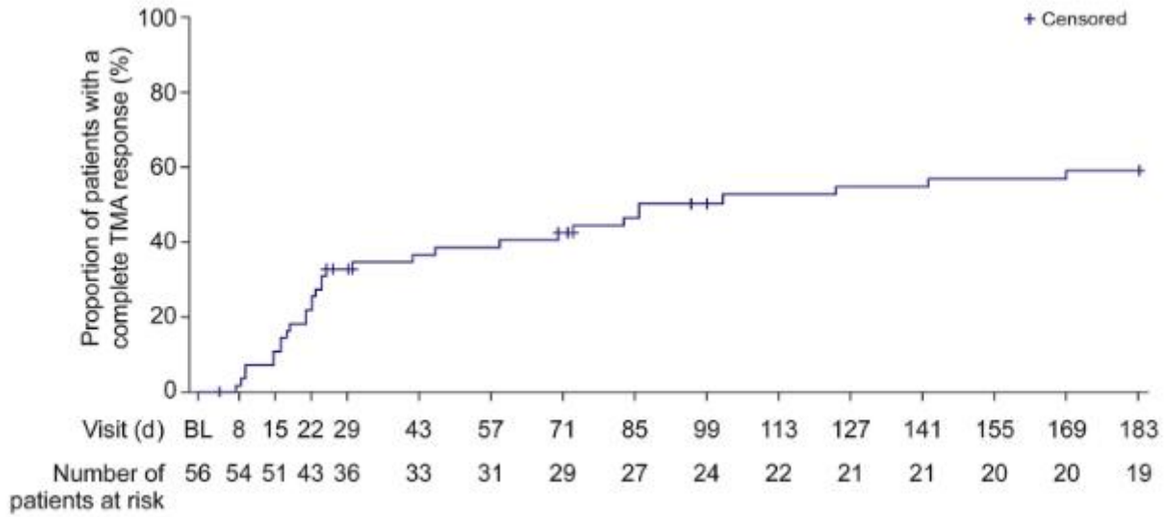

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Table 3| Summary of adverse events reported

Category	Overall (N = 58) n (%)	Events
Any AE	58 (100.0)	818
Treatment-related	20 (34.5)	58
Not treatment-related	58 (100.0)	760
Any SAE	30 (51.7)	71
Fatal TEAE	3 (5.2)	3
Fatal pretreatment SAE	1 (1.7)	1
Meningococcal infection	0 (0.0)	0
AE severity		
Grade 1	54 (93.1)	454
Grade 2	46 (79.3)	223
Grade 3	31 (53.4)	116
Grade 4	14 (24.1)	22
Grade 5	3 (5.2)	3

«53.6% of patients reaching the primary end point of complete TMA response»

«58.6% of the patients on dialysis at baseline came off dialysis within 6 months»

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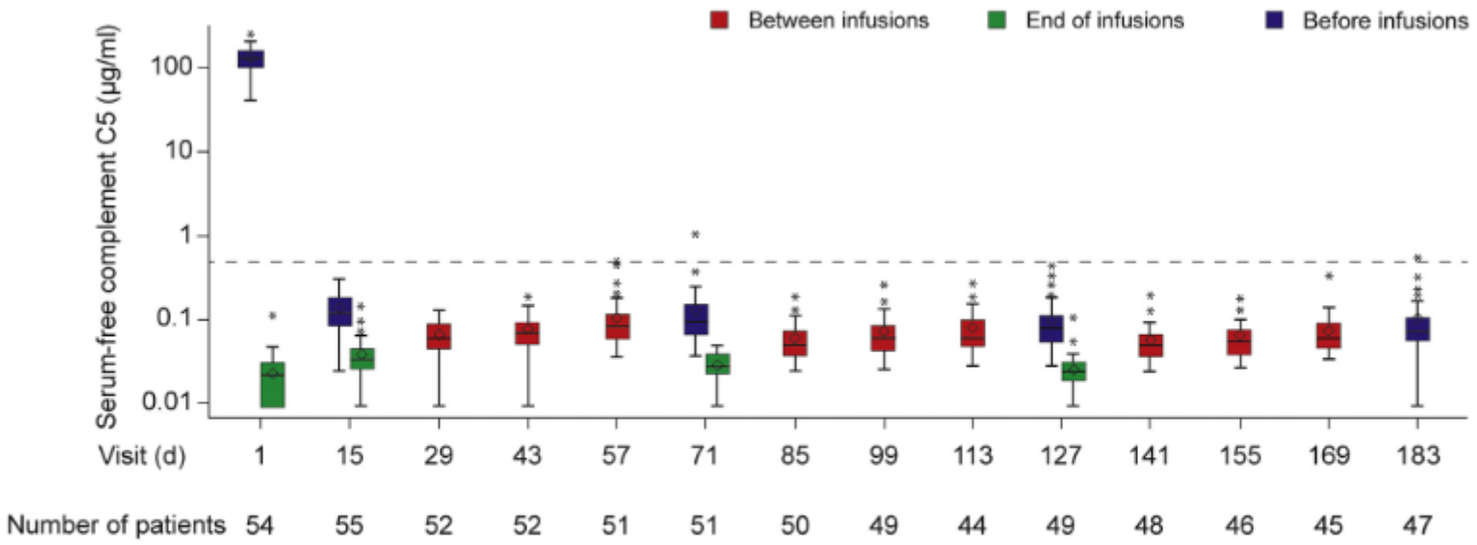

Figure 6| Pharmacodynamics of free C5 in serum concentration box plots over time (semi-log scale). Horizontal line is drawn at free C5 at 0.5 ug/ml to denote the threshold for complete terminal complement inhibition. The horizontal line in the middle of each box indicates the median, a diamond indicates the mean, and the top border and the bottom border of the boxes mark the 75th and 25th percentiles, respectively. The whiskers represent the highest and lowest values within 1.5 × the interquartile range from the lower quartile and upper quartile. Outliers are represented by an asterisk beyond the whiskers.

''Free C5 in serum results showed that ravulizumab treatment achieved immediate, complete, and sustained terminal complement inhibition as defined by free C5 in serum concentrations less than 0.5µg/ml''

Long-Term Efficacy and Safety of the Long-Acting Complement C5 Inhibitor Ravulizumab for the Treatment of Atypical Hemolytic Uremic Syndrome in Adults

Kidney Int Rep (2021) **6**, 1603–1613;

Thomas Barbour[1], Marie Scully[2], Gema Ariceta[3], Spero Cataland[4], Katherine Garlo[5], Nils Heyne[6], Yosu Luque[7], Jan Menne[8], Yoshitaka Miyakawa[9], Sung-Soo Yoon[10], David Kavanagh[11,12] and 311 Study Group Members[13]

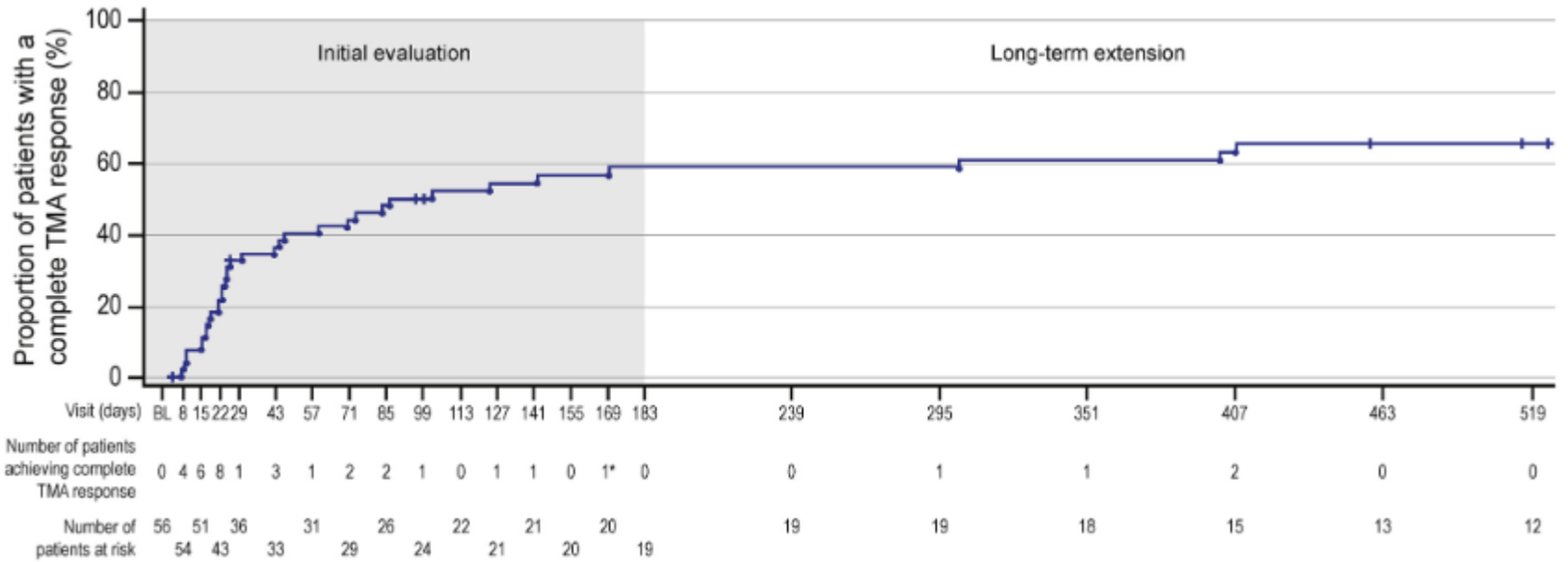

Figure 2. Kaplan–Meier graph depicting the time to complete TMA response. Patients who did not have a response were censored on the day of the last study visit or at study discontinuation. *Patient achieved initial complete TMA response measurement at day 169; however confirmatory measurement was not achieved until the extension period (day 239). BL, baseline; TMA, thrombotic microangiopathy.

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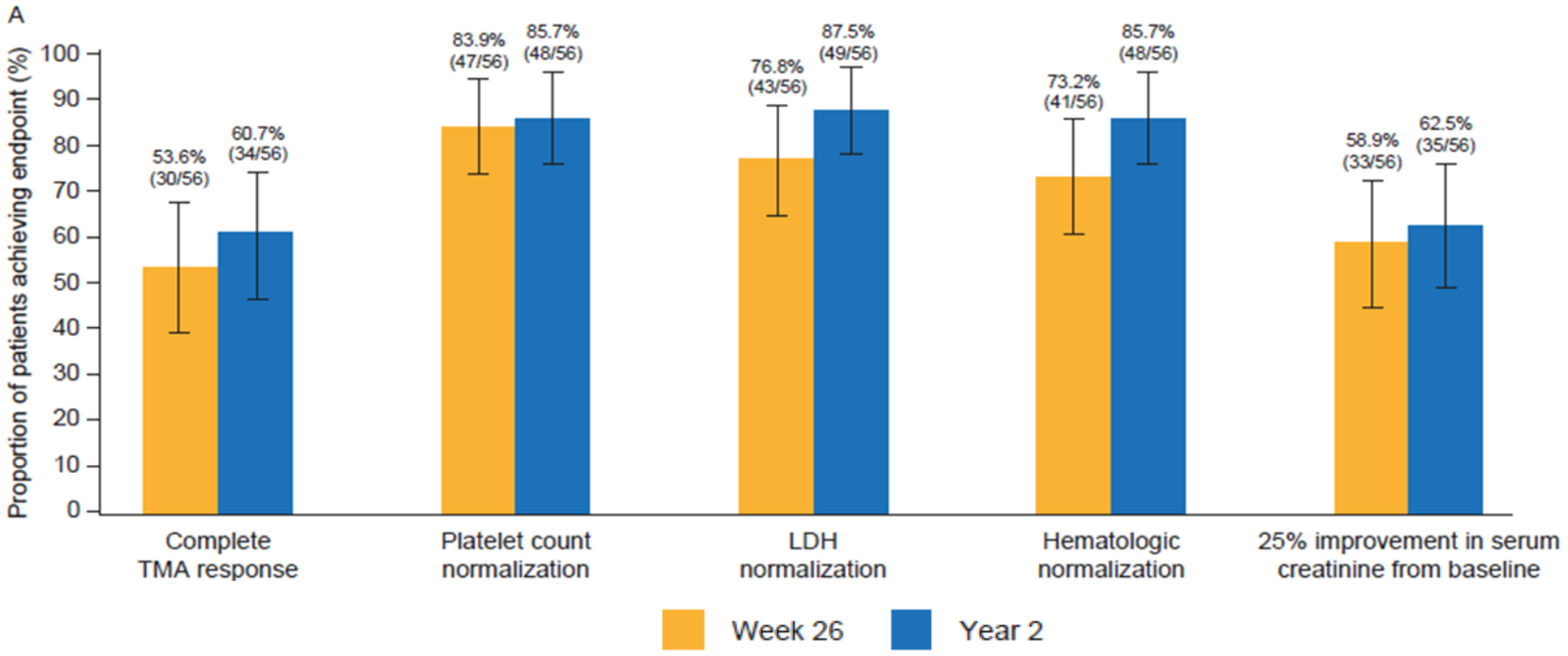

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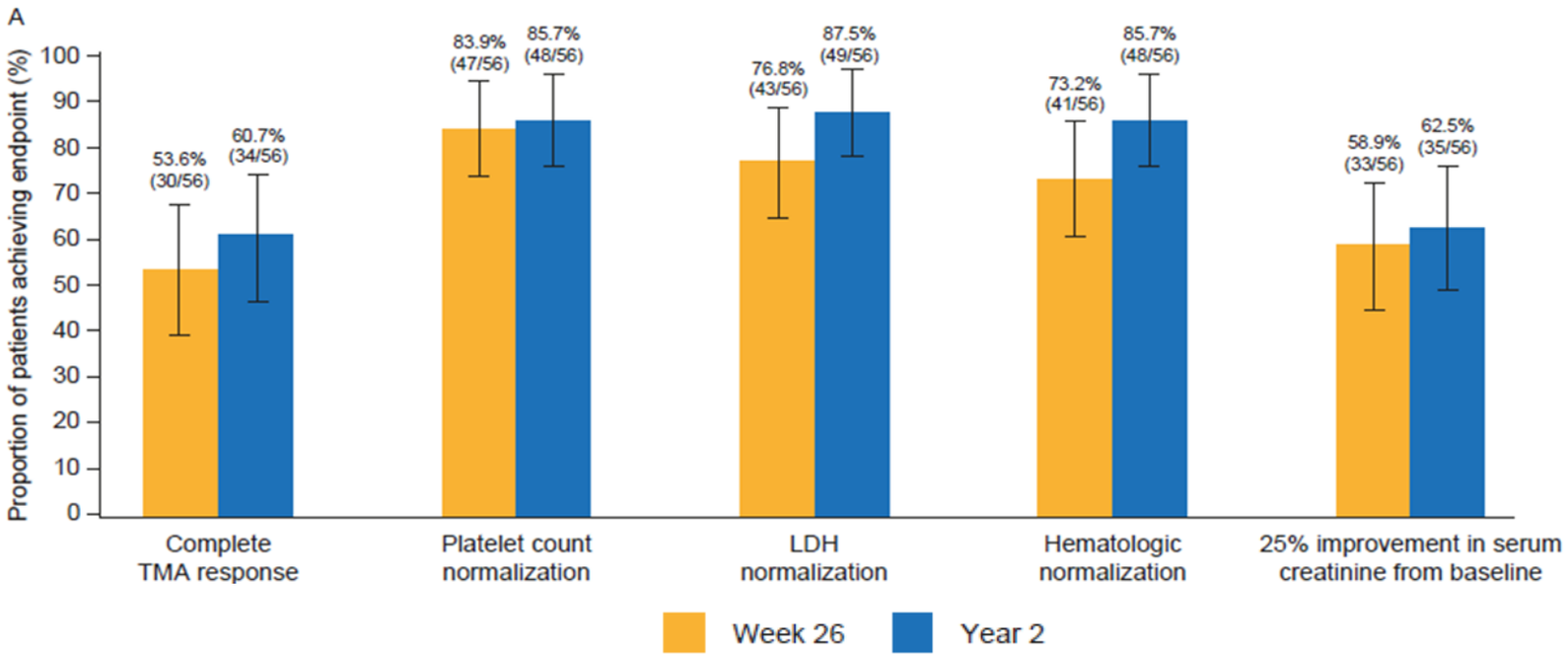


«No patient developed a meningococcal infection or died during the extension period.»

Προφίλ ασφάλειας του ravulizumab σε ενήλικες ασθενείς με aHUS

❑ Η θεραπεία με ravulizumab δεν είχε ως αποτέλεσμα κάποιες μη αναμενόμενες ανεπιθύμητες ενέργειες[1,2]

- Όλοι οι ασθενείς παρουσίασαν ≥1 ανεπιθύμητες ενέργειες[1,2]
  - Πιο συχνές: πονοκέφαλος, διάρροια και εμετός

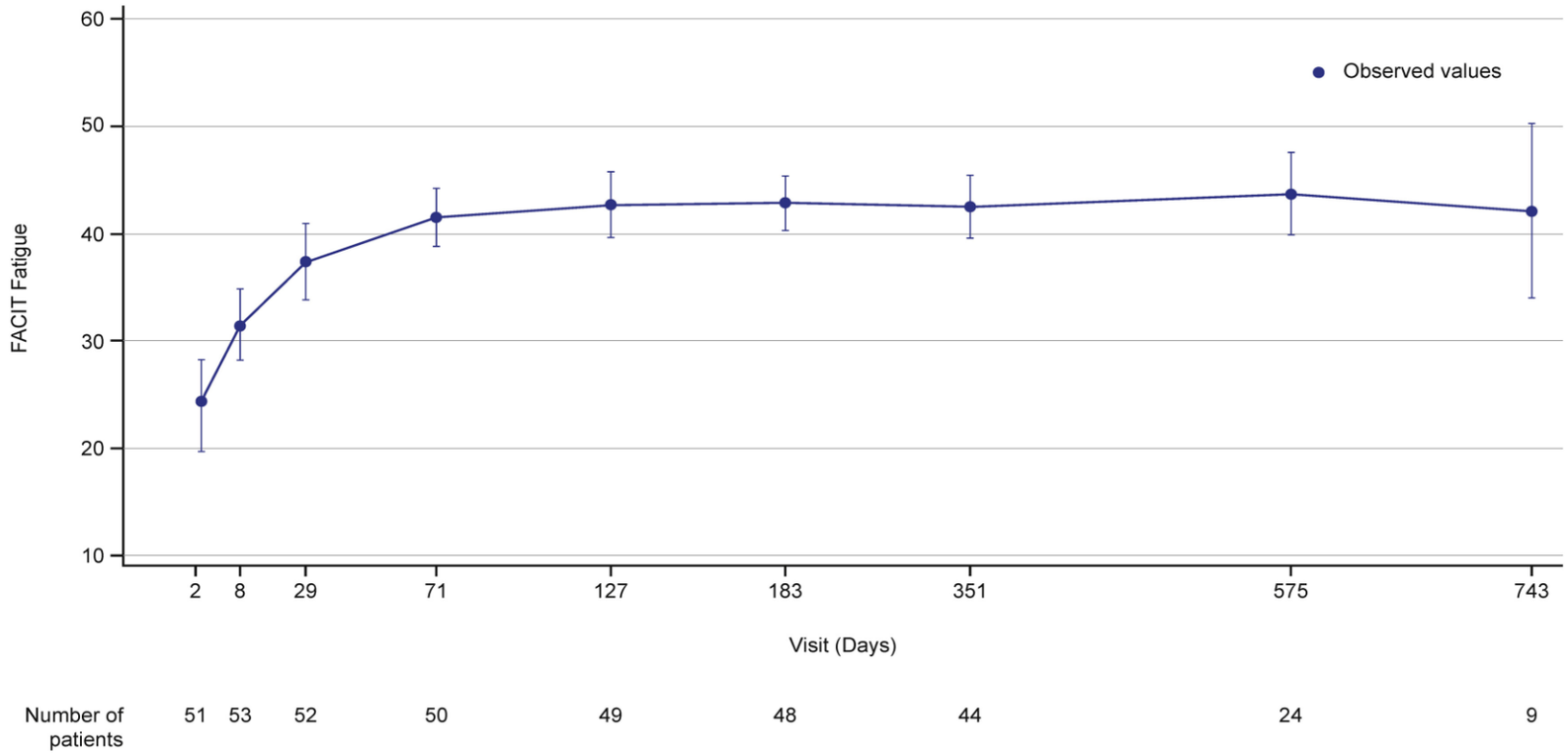
- Σοβαρές ανεπιθύμητες ενέργειες παρουσιάστηκαν σε 56.9% των ασθενών (περίοδος μελέτης επέκτασης)[2]
  - Πιο συχνές: υπέρταση, πνευμονία

✓ **Δεν παρουσιάστηκαν λοιμώξεις με Μηνιγγιτιδόκοκο κατά τη διάρκεια της μελέτης, αλλά όλοι οι ενήλικες ασθενείς θα πρέπει είτε να έχουν ολοκληρώσει τον εμβολιασμό έναντι του Μηνιγγιτιδόκοκου πριν την έναρξη της θεραπείας ή να λαμβάνουν προφυλακτική θεραπεία μέχρι και τουλάχιστον 15 μέρες μετά την ολοκλήρωση του εμβολιασμού.**

*Complete TMA response was defined as platelet count normalisation ((≥150 x 10 9 /L), LDH normalisation (≤246 U/L) and ≥25% improvement in serum creatinine from baseline
aHUS, atypical haemolytic uraemic syndrome; BL, baseline; eGFR, estimated glomerular filtration rate; LDH, lactate dehydrogenase TMA, thrombotic microangiopathy΄Gäckler A, et al. BMC Nephrol 2021;22(1):5

Δεδομένα βελτίωσης της ποιότητας ζωής ενήλικων ασθενών με aHUS οι οποίοι βρίσκονται σε θεραπεία με ravulizumab

FACIT-Fatigue score over time. Data are shown as mean (error bars, 95% confidence interval). FACIT, Functional Assessment of Chronic Illness Therapy.



Η ουσιώδης βελτίωση τόσο στις αιματολογικές όσο και στις νεφρικές παραμέτρους είχε ως αποτέλεσμα και την βελτίωση στην ποιότητα ζωής των ασθενών[1,2]

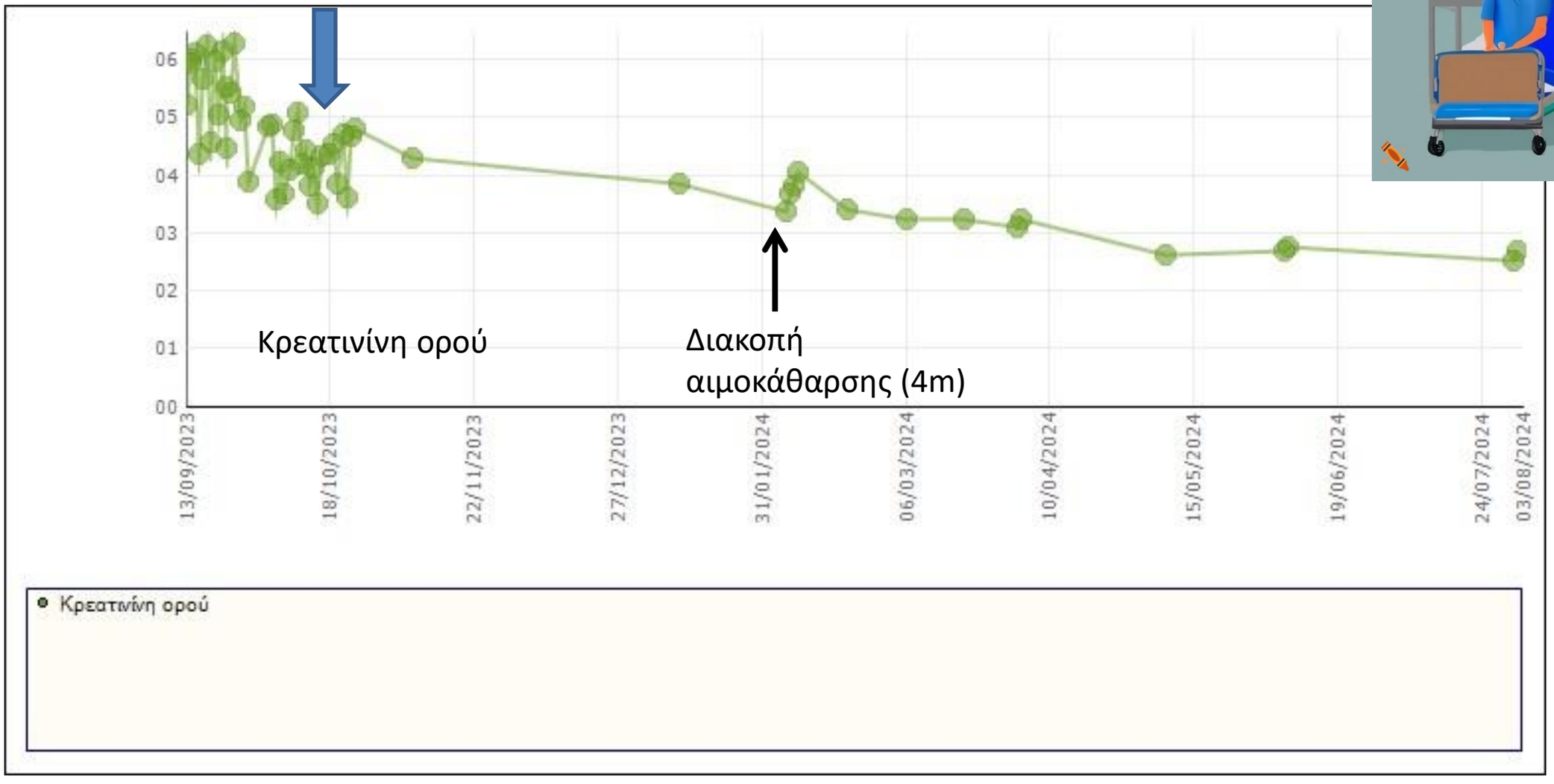
QoL: Αύξηση ≥3 βαθμών στην κλίμακα FACIT κόπωσης στο 84.1% (37/44) ασθενών (μέρα 183)[1] και διατηρήθηκε και κατά τη μελέτη επέκτασης έως την ημέρα 351[2]

aHUS, atypical haemolytic uraemic syndrome; FACIT, Functional Assessment of Chronic Illness Therapy; LTE, longterm extension; Q oL, quality of life

1. Rondeau E, et al. Kidney Int 2020;97:128796; 2. Barbour T, et al. Kidney Int Rep 2021;6:1603

Άνδρας, 34 ετών

Έναρξη ravulizumab

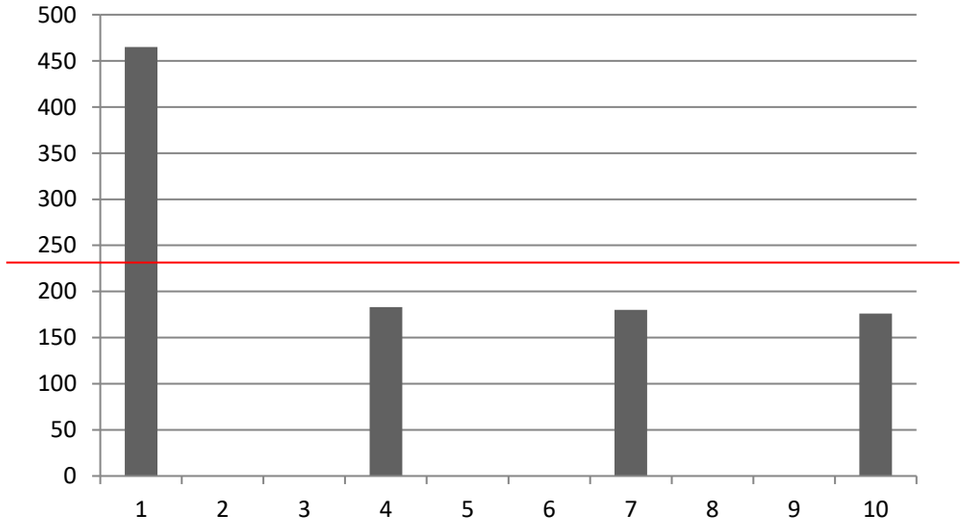


Κρεατινίνη ορού

Διακοπή αιμοκάθαρσης (4m)

Άνδρας, 34 ετών

- C5b9 (Φτ<245ng/ml) 465ng/ml
- 183
- 180
- 176 10 μήνες



- Γενετικός έλεγχος: αρνητικός

Schönfelder *et al. BMC Nephrology* (2024) 25:202
https://doi.org/10.1186/s12882-024-03638-3

BMC Nephrology

RESEARCH Open Access

Clinical efficacy and safety of switching from eculizumab to ravulizumab in adult patients with aHUS– real-world data

Kristina Schönfelder[1], Lucas Kühne[2], Lena Schulte-Kemna[3], Jessica Kaufeld[4], Hana Rohn[5], Andreas Kribben[1], Bernd Schröppel[3], Paul T. Brinkkötter[2] and Anja Gäckler[1,6*]

32 adult patients with aHUS
(including 10 kidney transplant recipients)

Patients with ≥ 1 pathogenic genetic variant % (n) 71.9 (23) 7

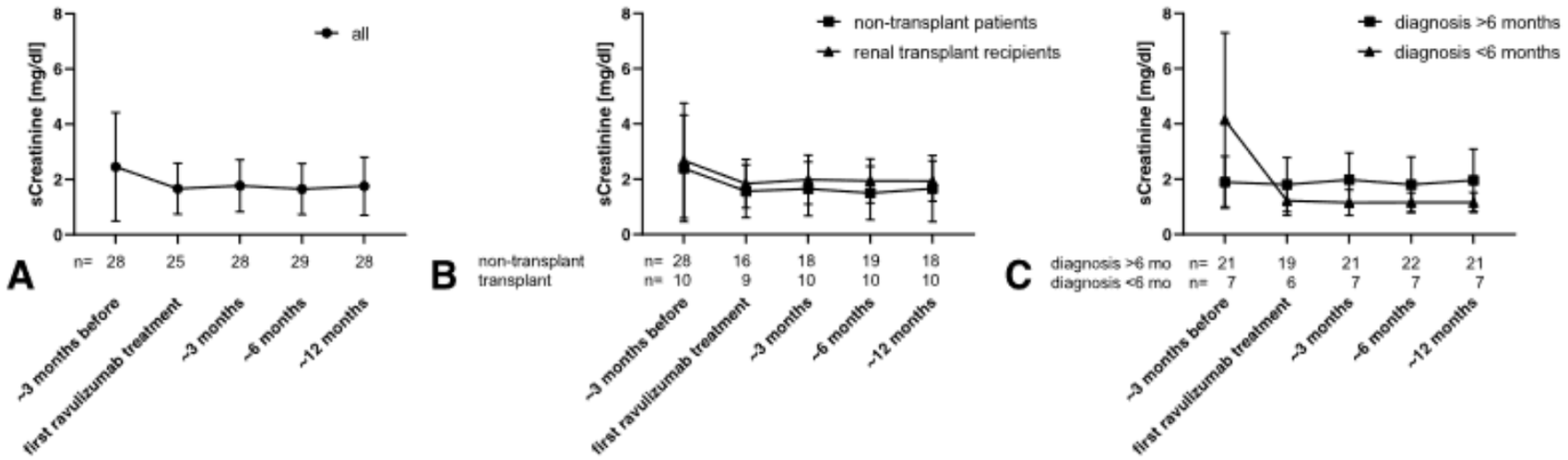


Fig. 3 Serum creatinine. Serum creatinine approx. 3 months before and up to approx. 12 months after switch from eculizumab to ravulizumab. **A** all patients; **B** non-transplanted patients and renal transplant recipients; **C** patients with diagnosis of aHUS > 6 months and < 6 months before switch of medication

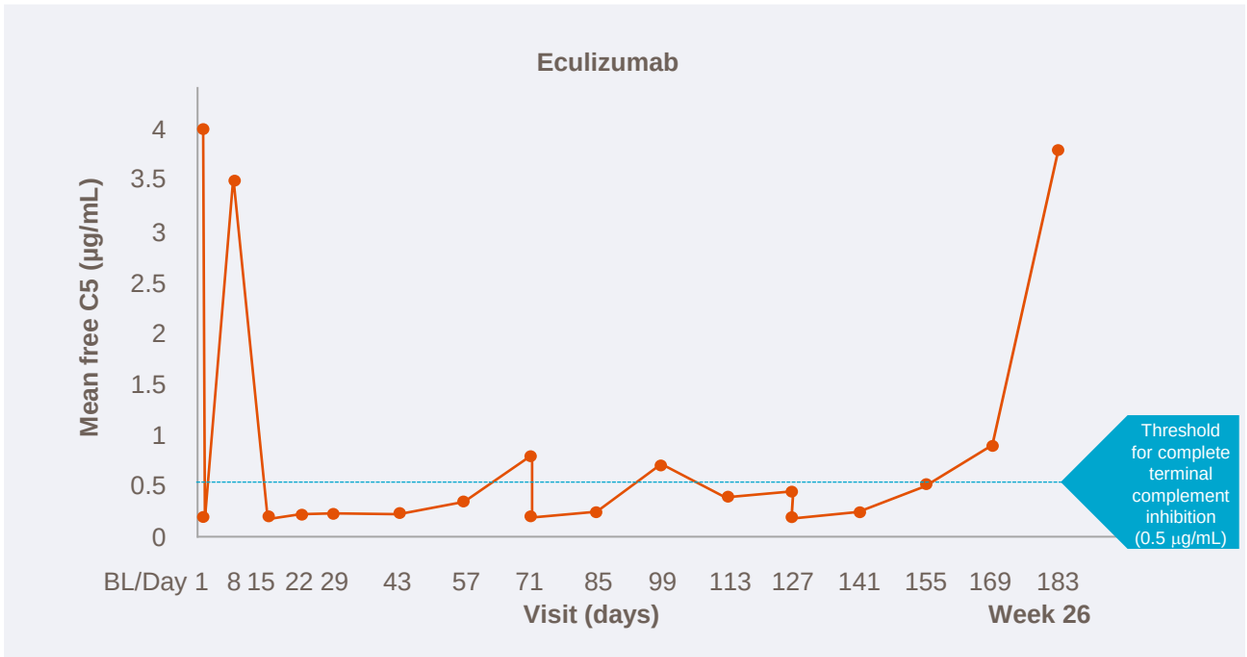
Table 2 Adverse events after switch to ravulizumab

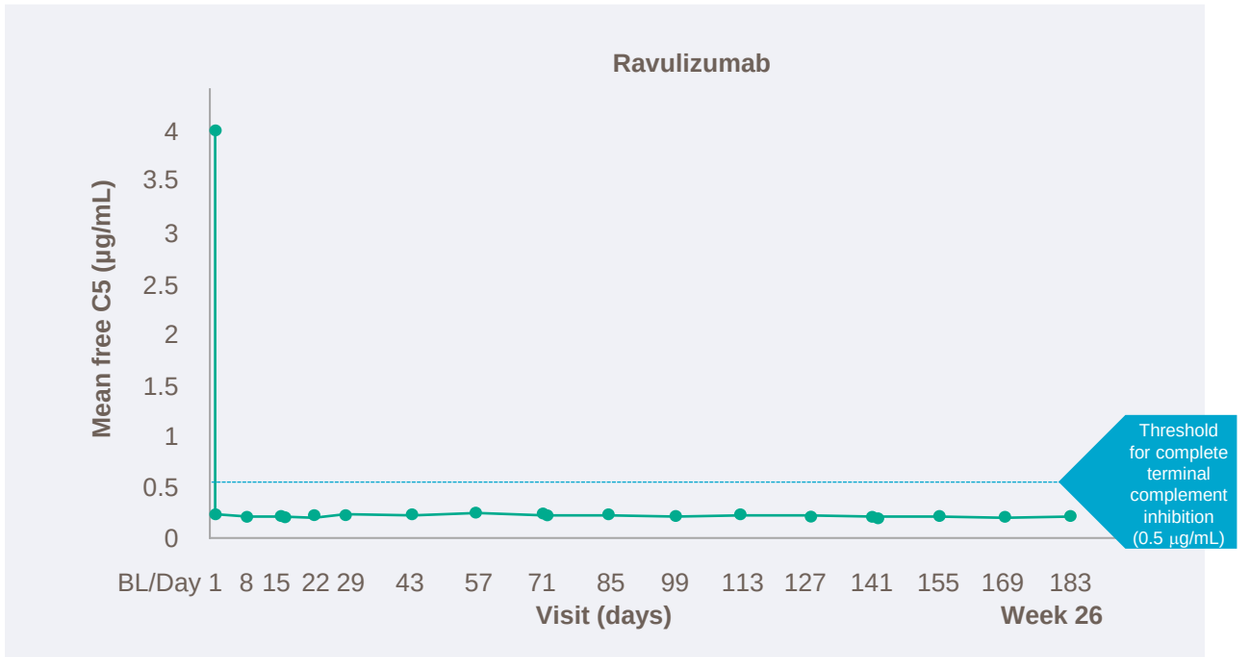
	% of adverse events	number of patients
Serious adverse event[a]		1
Adverse event		18
Upper respiratory tract infection	22.2	4
Headache/dizziness	22.2	4
Cutaneous infusion reaction	16.7	3
Transaminase elevation	5.6	1
Edema	5.6	1
Urinary tract infection	27.8	5
Meningococcal infection/death	0	0

[a] Serious adverse event was hospitalization for kidney biopsy rated as not-associated to C5 inhibitor treatment. Urinary tract infections were reported in renal transplant recipients only

Compared with eculizumab, ravulizumab is associated with immediate, complete and sustained terminal complement inhibition in patients with PNH[1–3]

Reduction in free C5 serum concentration (terminal complement)* was immediate by the end of the first ravulizumab infusion, and only inhibition with ravulizumab was sustained throughout the entire 26-week treatment period[1]





Adapted from Lee JW, et al. 2019.[1]

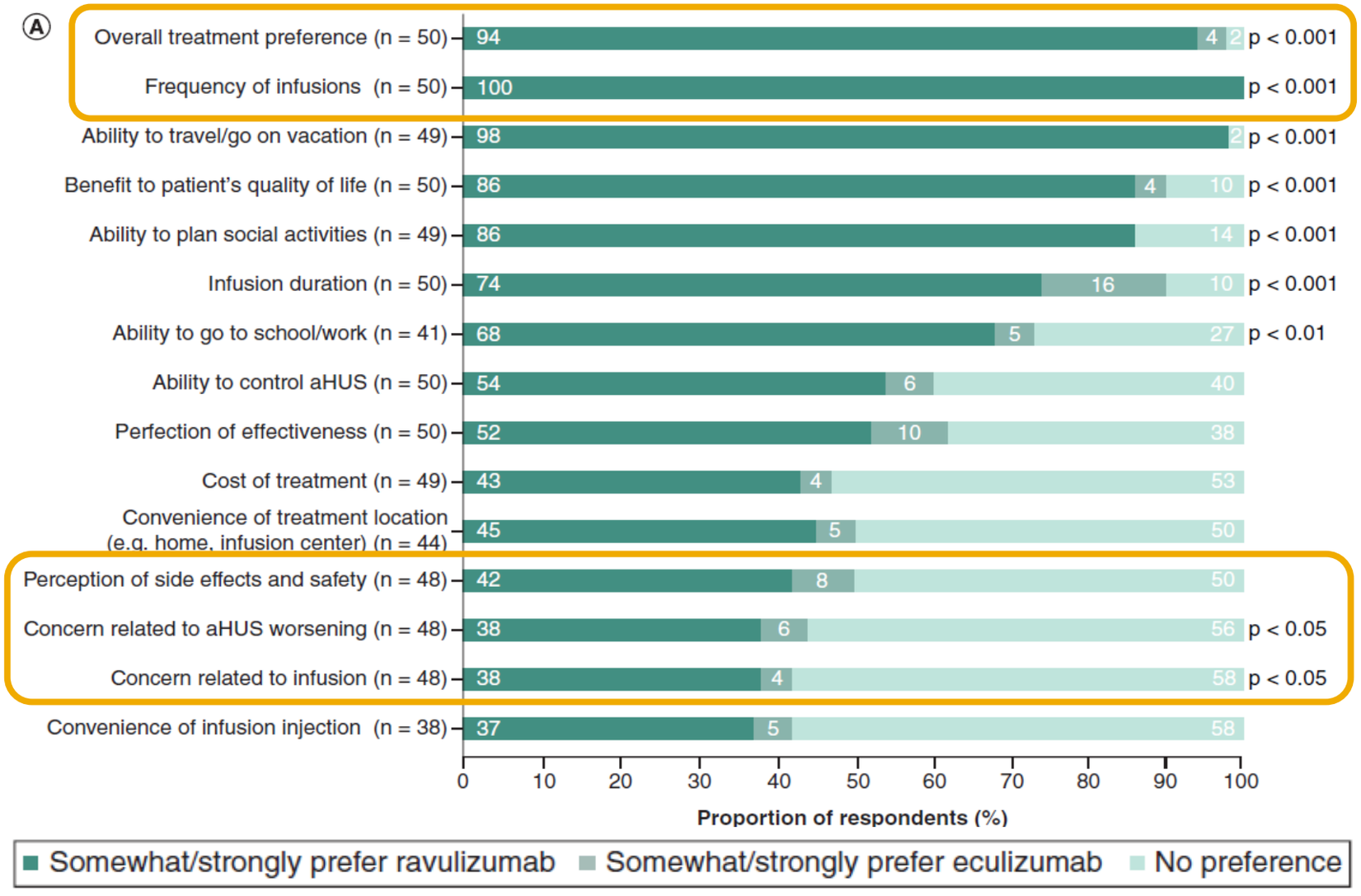
*Patients assigned to eculizumab received induction doses of 600 mg on Days 1, 8, 15 and 22, followed by maintenance dosing of 900 mg on Day 29 and every 2 weeks thereafter per the approved PNH dosing regimen.[1] This dosing regimen is lower than the recommended aHUS eculizumab dosing regimen. In aHUS, the induction dose is 900 mg, and maintenance dose is 1,200 mg[4]

†Patients assigned to eculizumab received induction doses of 900 mg followed by maintenance dosing of 1,200 mg.[3] This data does not directly compare PK/PD data from patients with PNH to patients with gMG.

aHUS, atypical haemolytic uraemic syndrome; C5, complement component 5; gMG, generalised myasthenia gravis; PNH, paroxysmal nocturnal haemoglobinuria.

1. Lee JW, et al. *Blood.* 2019;133(6):530–539; **2.** Vu T, et al. *J Neurol.* 2023;270(6):3129–3137; **3.** ECU-MG-Adult PK-PD Modeling Report Appendix 10.1.4; **4.** SOLIRIS® Summary of Product Characteristics. August 2023.

Το ravulizumab αποτελεί την θεραπεία προτίμησης των ασθενών με aHUS έναντι του eculizumab



- **Στη μελέτη προτίμησης θεραπείας το ravulizumab ήταν η θεραπεία επιλογής για τη συντριπτική πλειοψηφία των ασθενών με aHUS**
- Οι ασθενείς φαίνεται να εκτιμούν ιδιαίτερα τη βελτίωση στην ποιότητα ζωής τους λόγω του αραιότερου χρονικού διαστήματος μεταξύ των χορηγήσεων της θεραπείας
- Η προτίμηση υπέρ του ravulizumab επικράτησε υπέρ της προτιμήσεως για το eculizumab σε όλες τις ερωτήσεις ακόμα και αυτές που αφορούσαν την αποτελεσματικότητα και τις ανεπιθύμητες ενέργειες της θεραπείας

J Comp Eff Res. 2023 Sep; 12(9): e230036.

Ravulizumab was associated with lower per-patient treatment costs than eculizumab in adult and paediatric patients with aHUS in the Netherlands[1]

A cost-minimisation analysis conducted in the Netherlands indicated that ravulizumab reduces the total lifetime per-patient cost* in **adult** patients by **€2,226,479** compared with eculizumab

Adult patients

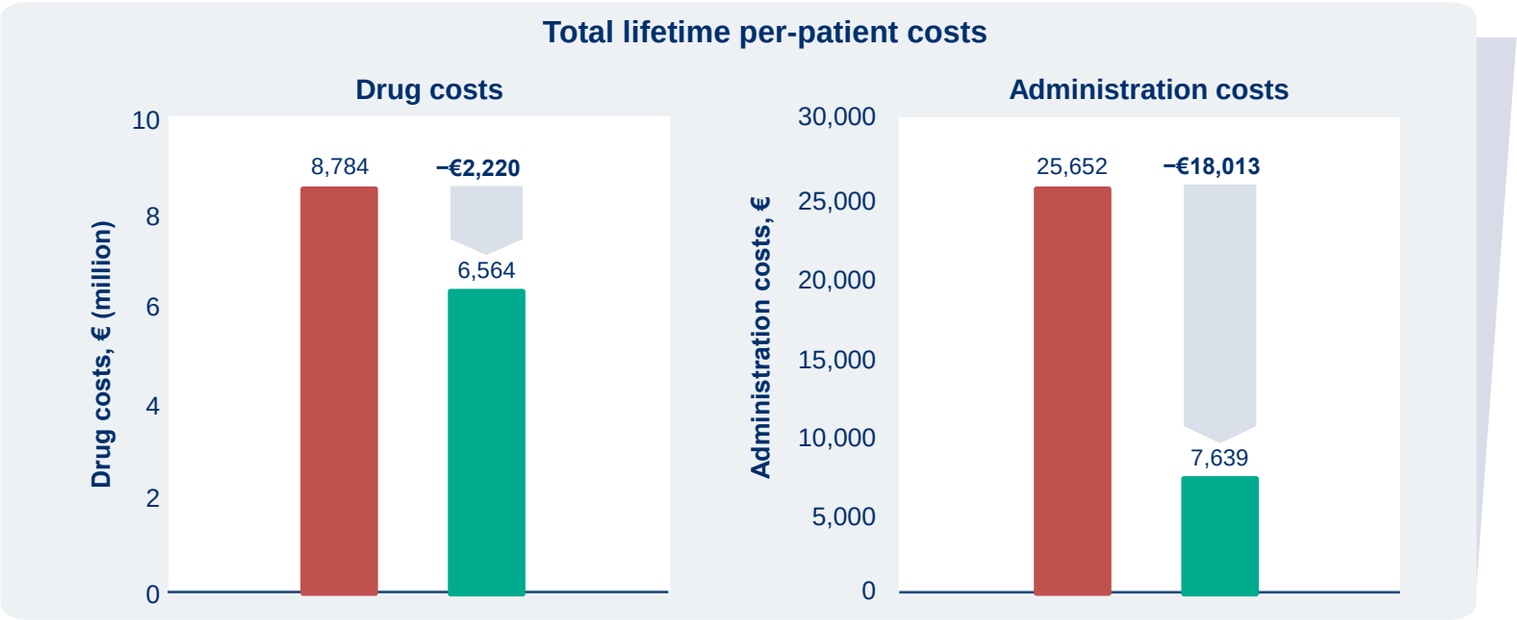


Figure adapted from Postma, et al. Poster presented at ISPOR 2022.[1]

Paediatric patients

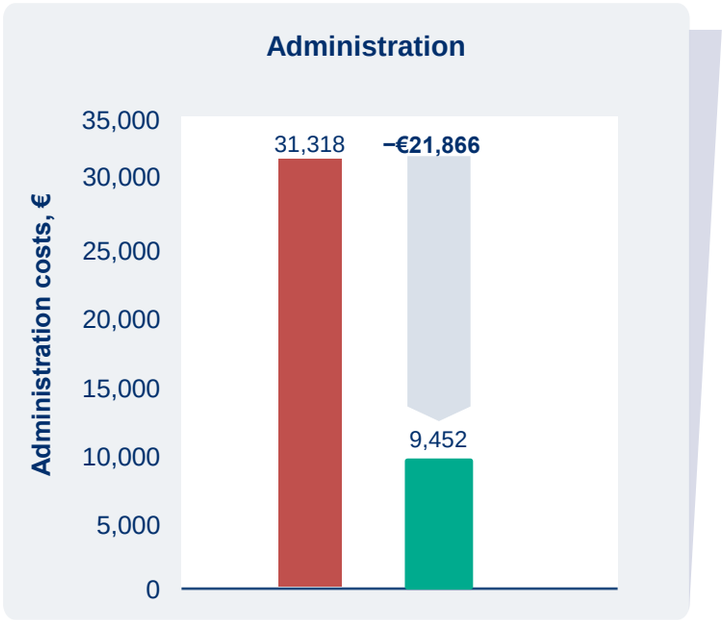


Figure adapted from Postma, et al. Poster presented at ISPOR 2022.[1]

Eculizumab Ravulizumab

This data have been presented as a poster at ISPOR 2022. Full peer-reviewed data are not yet available.
*Total lifetime per-patient costs include treatment costs (drug costs and administration costs) and societal costs (travel and informal care and productivity losses).
aHUS, atypical haemolytic uraemic syndrome.

1. Postma AJ, et al. Presented at International Society for Pharmacoeconomics and Outcomes Research; 6–9 November 2022; Vienna, Austria: Poster EE52.

Study design

ALEXION | GLOBAL HEALTH ECONOMICS AND OUTCOMES RESEARCH

Κίνδυνος υποτροπής μετά από διακοπή αγωγής

- No rare variants 5%
- Rare variants 23% - 37%

Blood. 2023 Mar 2;141(9):984-995

- relapses occur in 20–35% of patients at a median of 3 months after treatment cessation, and 90% of all relapses occur within 1 year of discontinuation

Front Med (Lausanne). 2023; 10: 1264310.

Κίνδυνος υποτροπής μετά από διακοπή αγωγής

«In patients with detected pathogenic variants, the risk of relapse after C5 blocker discontinuation ranges from

23% (carriers of CFI gene variants) to

37% (carriers of MCP gene variants) and

64% (carriers of CFH gene variants).»

Blood. 2023 Mar 2;141(9):984-995

Outcomes of a clinician-directed protocol for discontinuation of complement inhibition therapy in atypical hemolytic uremic syndrome

Blood Adv, 2021 Mar 9;5(5):1504-1512

Shruti Chaturvedi,[1] Noor Dhaliwal,[2] Sarah Hussain,[1] Kathryn Dane,[3] Harshvardhan Upreti,[2] Evan M. Braunstein,[1] Xuan Yuan,[1] C. John Sperati,[4] Alison R. Moliterno,[1] and Robert A. Brodsky[1]

[1]Division of Hematology, Johns Hopkins University School of Medicine, Baltimore, MD; [2]Maulana Azad Medical College, University of Delhi, Delhi, India; and [3]Department of Pharmacy and [4]Division of Nephrology, Johns Hopkins University School of Medicine, Baltimore, MD

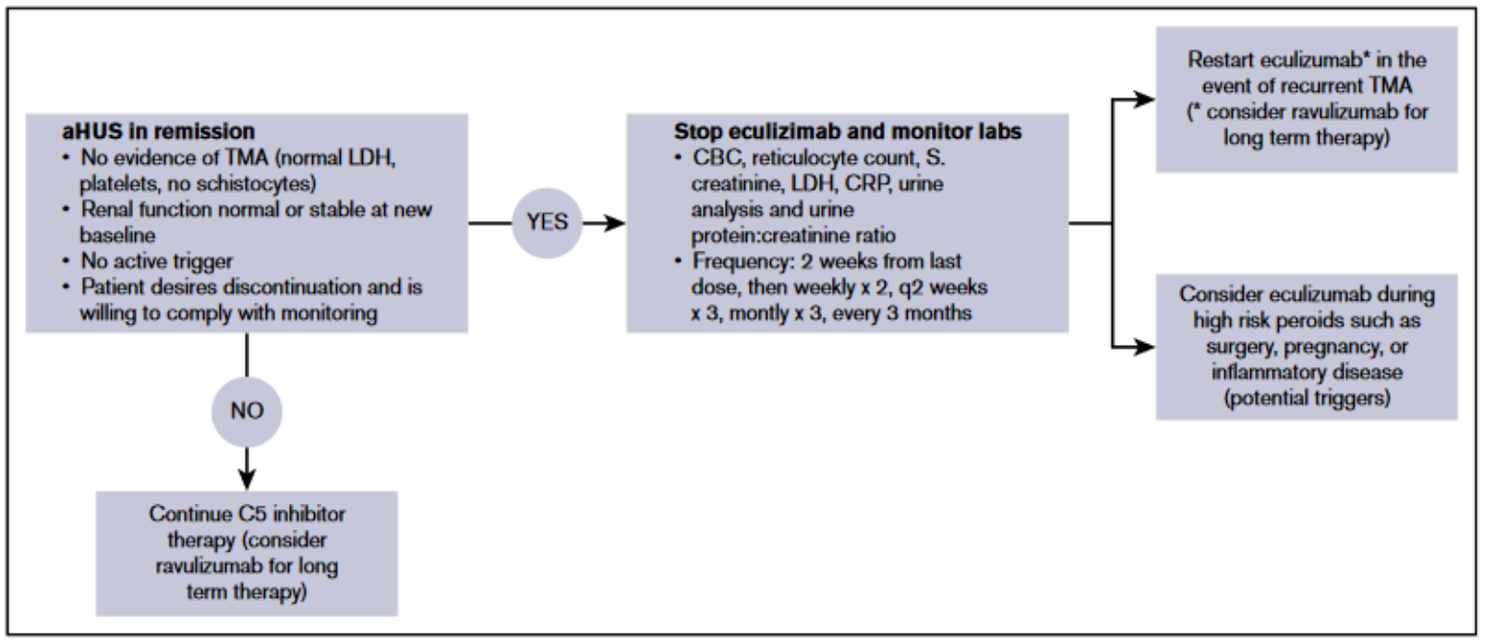


Figure 1. Protocol for eculizumab discontinuation and monitoring. All 4 of the following criteria must be met before we discontinue eculizumab: resolved TMA, renal function normal or stable at new baseline, no active trigger (in patients that had an identified trigger), and patients desire to stop therapy and agree to monitoring plan. Monitoring is conduced as outlined. Home urine dipstick monitoring may also be used as an adjunct. We restart a C5 inhibitor (eculizumab or ravulizumab) in the case of recurrent TMA, in which case therapy is continued indefinitely or possibly temporarily during high-risk periods such as pregnancy, surgery, or flare of inflammatory disease. When long-term therapy is anticipated, we suggest ravulizumab rather than eculizumab.

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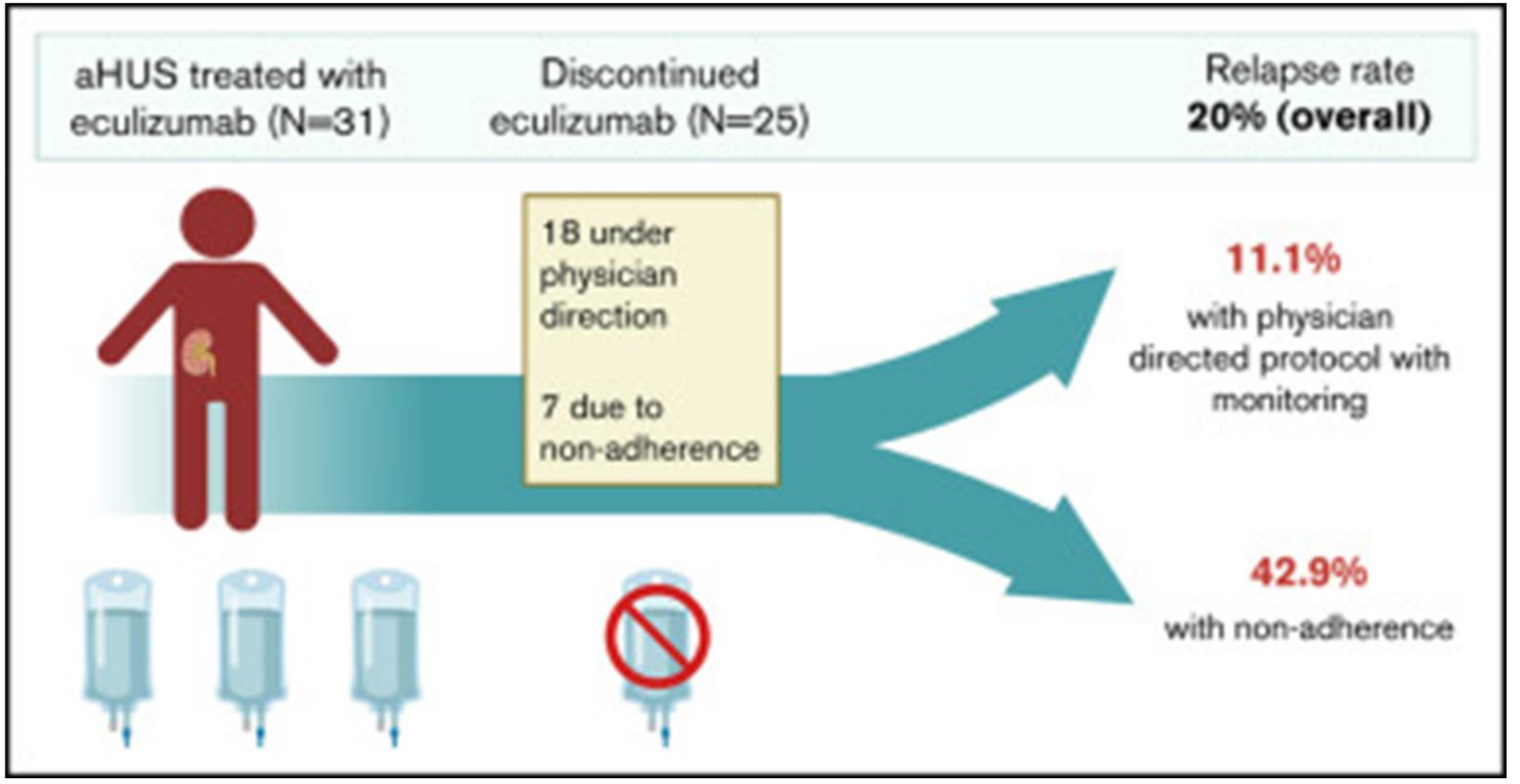
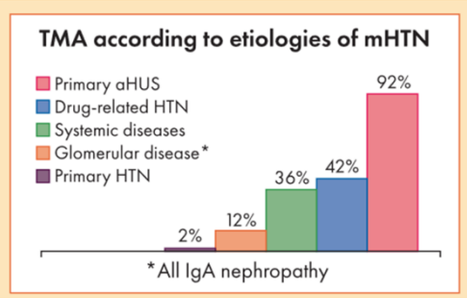


Ανακαιφαλαίωση



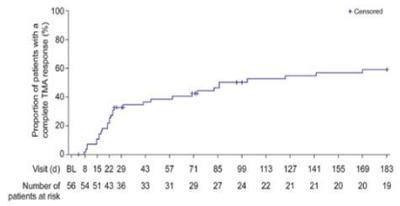


Figure 2 | Kaplan Meier graph showing time to complete thrombotic microangiopathy (TMA) response. Patients who did not have a response were censored on the day of their last study visit, or at study discontinuation. BL, baseline.

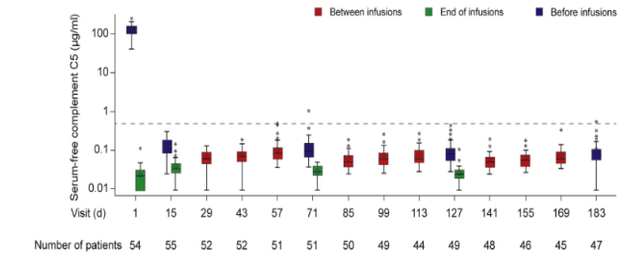


Figure 6 | Pharmacodynamics of free C5 in serum concentration box plots over time (semi-log scale). Horizontal line is drawn at free C5 at 0.5 ug/ml to denote the threshold for complete terminal complement inhibition. The horizontal line in the middle of each box indicates the median, a diamond indicates the mean, and the top border and the bottom border of the boxes mark the 75th and 25th percentiles, respectively. The whiskers represent the highest and lowest values within 1.5 × the interquartile range from the lower quartile and upper quartile. Outliers are represented by an asterisk beyond the whiskers.

- Ασθενείς με κακοήθη υπέρταση και εκδηλώσεις ΘΜΑ πιθανότατα πάσχουν από aHUS, (διαταρχή συμπληρώματος).
- Η έγκαιρη διάγνωση και αντιμετώπιση με αναστολή του συμπληρώματος αυξάνουν την πιθανότητα απάντησης στη θεραπεία.
- Το ravulizumab προσφέρει άμεση, πλήρη και παρατεταμένη αναστολή του συμπληρώματος, με δοσολογικό σχήμα φιλικότερο προς τον ασθενή, και με μικρότερη επιβάρυνση του συστήματος υγείας σε σχέση με παλαιότερες θεραπευτικές επιλογές.

Ευχαριστώ για την προσοχή σας