Azienda Ospedaliero Universitaria Careggi

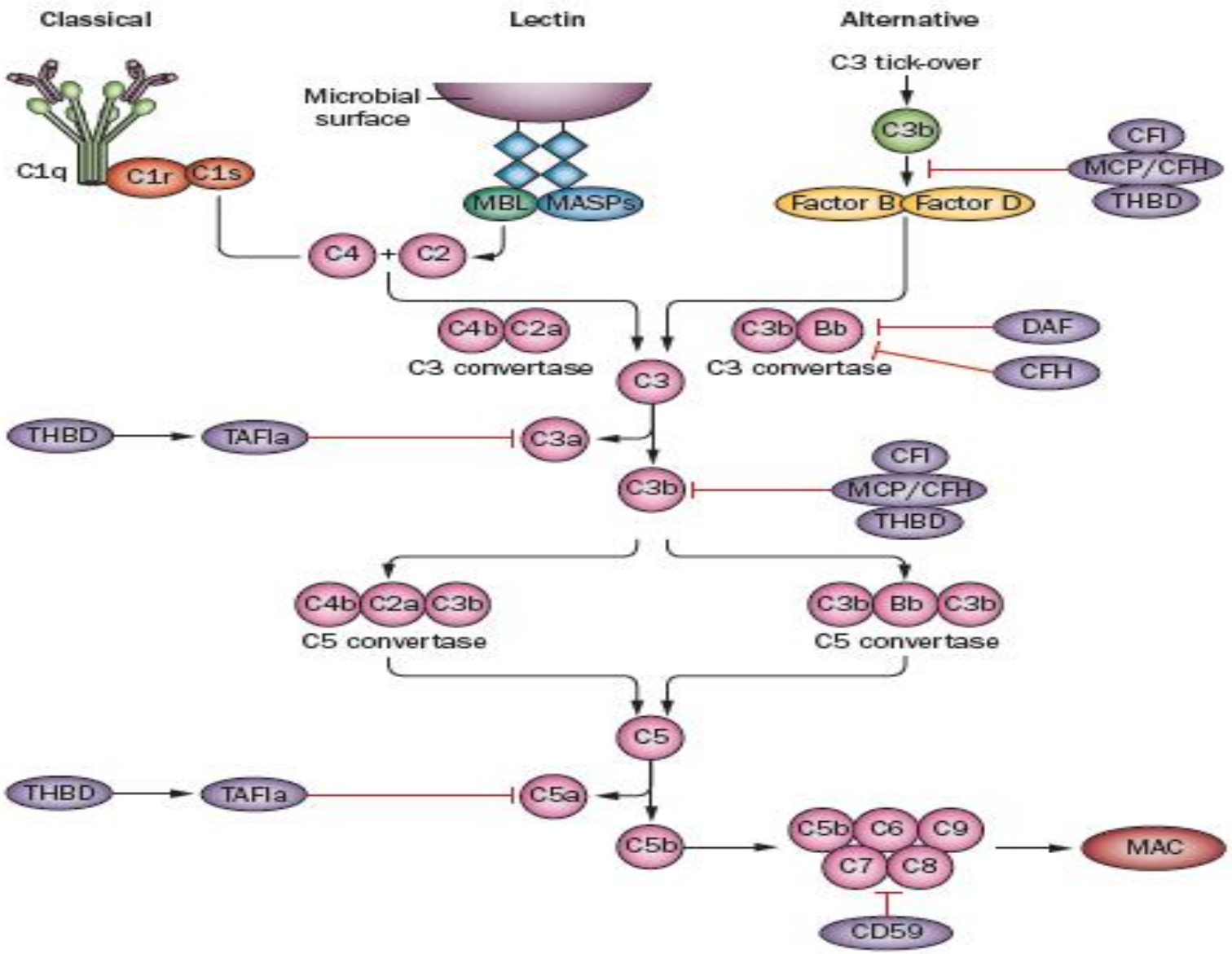
MICROANGIOPATIE TROMBOTICHE: PATOGENESI/TERAPIA

PERUGIA, 29 SETTEMBRE 2016

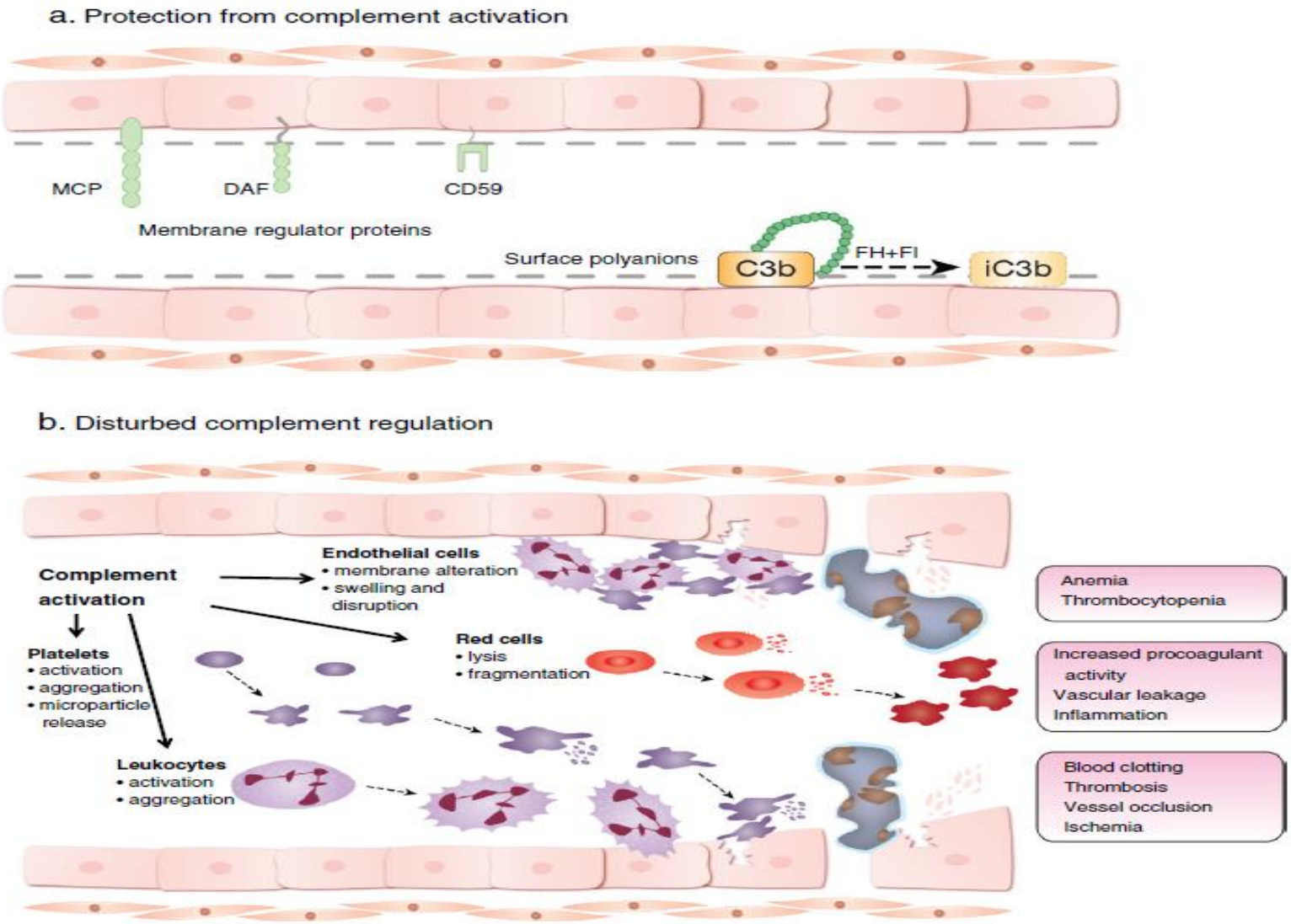
ECULIZUMAB NEL TRATTAMENTO DELLA SEU ATIPICA

Dott.ssa Giulia Antognoli
SOD Nefrologia e Dialisi
AOU Careggi Firenze

SST Servizio Sanitario della Toscana



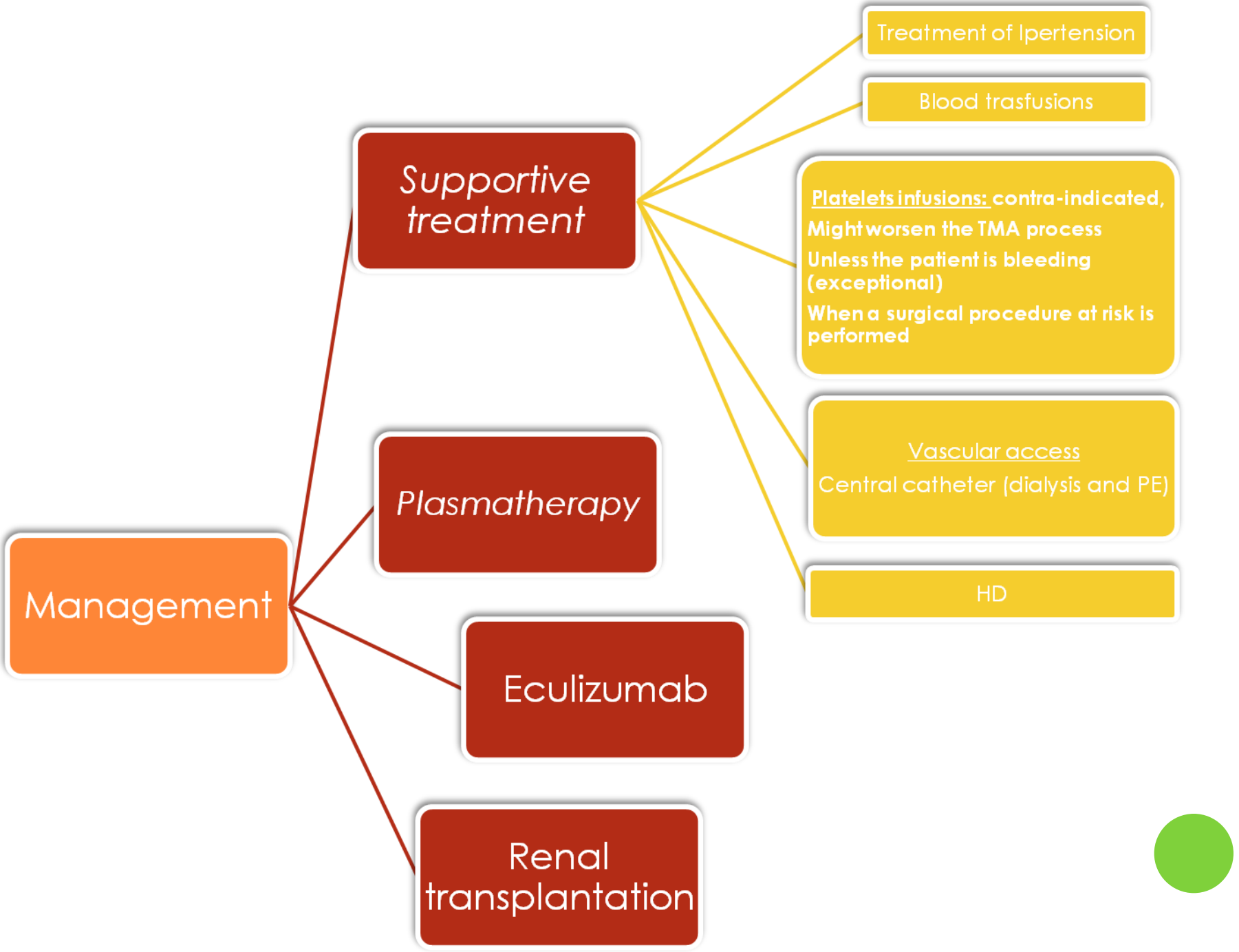
Noris M *et all. Nat Rev Nephrol. 8, 622–633 (2012)*



European Journal of Internal Medicine 24 (2013) 496–502

Triade clinica della SEUa

1. Piastrinopenia: plt < $150x10^9/mm^3$ o riduzione > 25% rispetto ai valori abituali
2. Anemia emolitica: Hb < 10 g/dl, ↓ LDH, ↑ bilirubina, ↓ aptoglobina, schistociti nel SP, Coombs neg
3. Insufficienza Renale Acuta ± oligo-anuria ± proteinuria


Management
Supportive treatment
Treatment of Ipertension
Blood trasfusions
Platelets infusions: contra-indicated,
Might worsen the TMA process
Unless the patient is bleeding (exceptional)
When a surgical procedure at risk is performed
Vascular access
Central catheter (dialysis and PE)
HD
Plasmatherapy
Eculizumab
Renal transplantation

Plasma Exchange

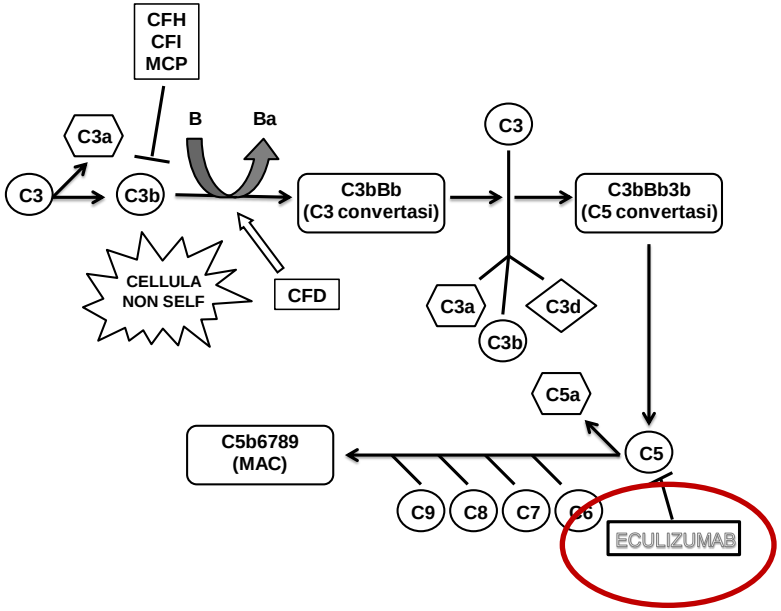
- Terapia di prima linea dal 2010 che deve essere iniziata entro 24 ore dall'esordio
- Rimozione delle forme patologiche di CFH, CFI, CFB e C3, Ab anti-CFH e altri fattori responsabili della disfunzione endoteliale e dell'iperaggregabilità piastrinica
- Sostituzione con Plasma Fresco Congelato (apporto di CFH, CFI, CFB e C3)

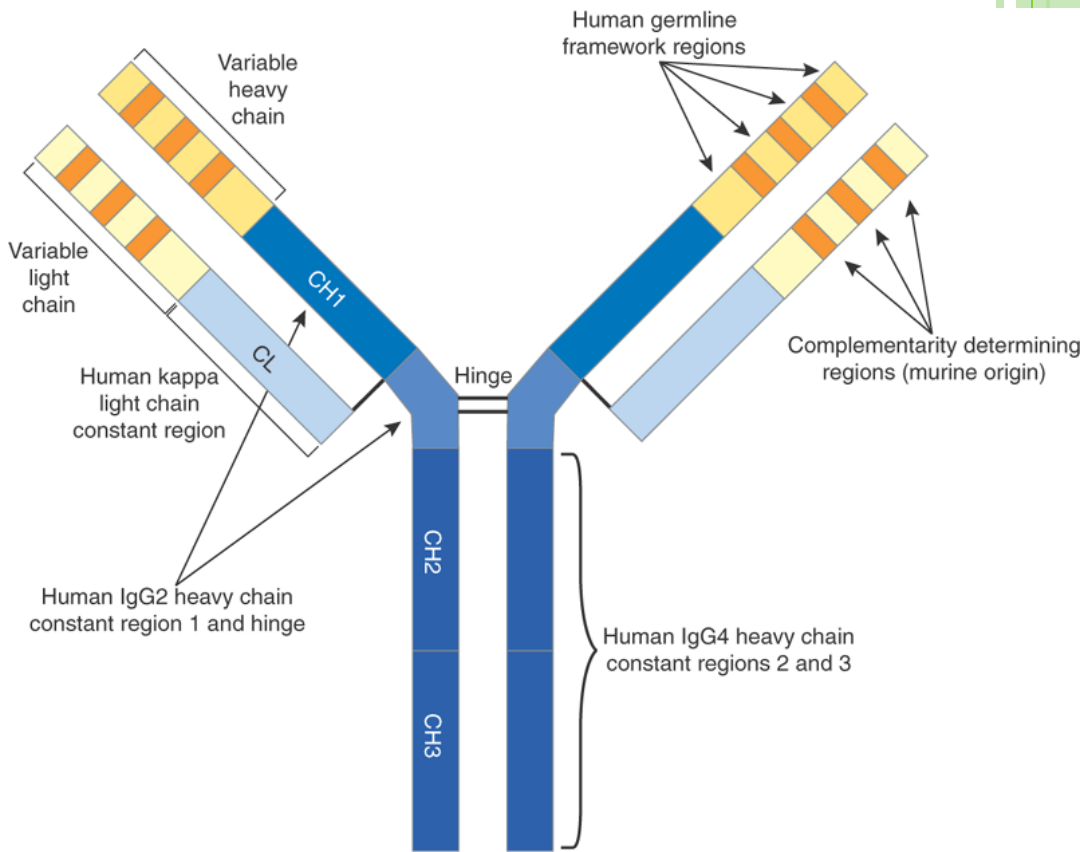
CFH mutation	·63% had a response either complete or partial ·5% Recovery ·37% evolution to death or ESRD
CFI mutation	·25% had a response ·75% progressed to death or ESRF.
MCP/CD46	·Is not a circulating protein ·Questionable
C3, CFB or THBD mutation	·The benefit of plasmatherapy is scarcely documented ·C3 mutated: 57% Response Complete / partial ; 43% Death / ESRD ·THBD-mutated: 88% Response Complete / partial ; 12 % Death / ESRD
anti-CFH antibodies	·Titre often rises after PE ·Relapses of HUS frequently occur. ·immunosuppressive treatment is recommended, (steroids and azathioprine, mycophenolate mofetil, intravenous cyclophosphamide or anti-CD20)

Plasmatherapy

Noris M et al. Clin J Am Soc Nephrol 2010, 5:1844-1859.
Clark W. Semin Dial 2012;25:214-19

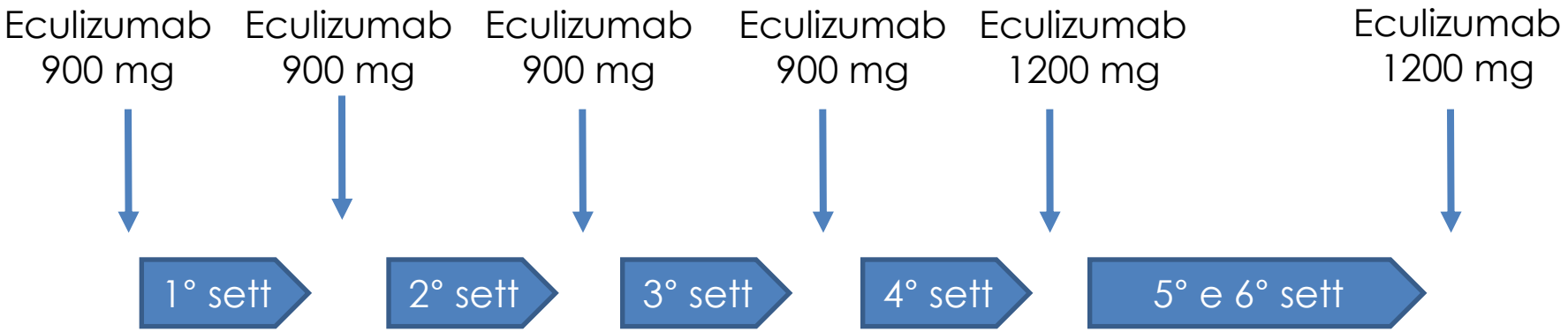
ECULIZUMAB


CFH
CFI
MCP
B
Ba
C3a
C3
C3b
C3bBb
(C3 convertasi)
C3
C3bBb3b
(C5 convertasi)
CELLULA
NON SELF
CFD
C3a
C3d
C3b
C5a
C5b6789
(MAC)
C5
C9
C8
C7
C6
ECULIZUMAB


Human germline
framework regions
Variable
heavy
chain
Variable
light
chain
CH1
CL
Hinge
Human kappa
light chain
constant region
Complementarity determining
regions (murine origin)
CH2
CH3
Human IgG2 heavy chain
constant region 1 and hinge
Human IgG4 heavy chain
constant regions 2 and 3

ECULIZUMAB

Emivita 11-12 giorni ⇨ somministrazione bisettimanale



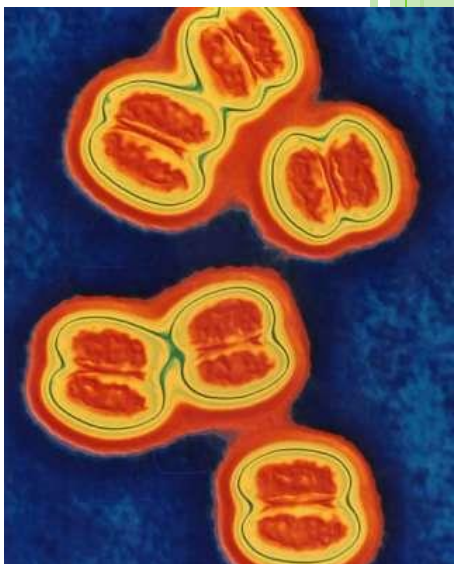
aHUS

- 50 µg/mL

Infezione da Nisseriae Meningitidis

- Il blocco della via terminale del complemento induce un aumentato rischio di infezione da Nisseriae Meningitidis
- I pazienti devono ricevere una vaccinazione per Nisseriae Meningitidis prima di iniziare terapia con Eculizumab
- Profilassi antibiotica per due settimane

MENVEO ⇨ Vaccinazione contro ceppi A, C, W, Y
BEXSERO ⇨ Vaccinazione contro ceppo B



Effetti Collaterali di Eculizumab

- Cefalea
- Mal di schiena
- Nausea
- Ipertensione arteriosa
- Infezione delle alte vie respiratorie
- Diarrea
- Vomito
- Infezione delle vie urinarie
- Leucopenia
- Anemia

ECULIZUMAB & SEUA

2009-2013

Complement Inhibitor Eculizumab in Atypical Hemolytic Uremic Syndrome

Christoph J. Mache,* Birgit Acham-Roschitz,* Veronique Frémeaux-Bacchi,† Michael Kirschfink,‡ Peter F. Zipfel,§ Siegfried Roedl,* Udo Vester,‖ and Ekkehard Ring*

*Department of Pediatrics, Medical University Graz, Graz, Austria; †Service d'Immunologie Biologique, Hôpital Européen Georges Pompidou, Assistance Publique-Hôpitaux de Paris, and Cordeliers Research Center, INSERM UMRS 872, Paris, France; and ‡Institute of Immunology, University of Heidelberg, Heidelberg, §Department of Infection, Hans Knoell Institute for Natural Products Research and Friedrich Schiller University of Jena, Jena, and ‖Clinic of Pediatric Nephrology, University of Duisburg-Essen, Essen, Germany

Eculizumab in atypical hemolytic uremic syndrome: long-term clinical course and histological findings

Sibylle Tschumi · Mathias Gugger · Barbara S. Bucher · Magdalena Riedl · Giacomo D. Simonetti

Long-term eculizumab improves clinical outcomes in atypical hemolytic uremic syndrome

Ramon Vilalta · Enrique Lara · Alvaro Madrid · Sara Chocron · Marina Muñoz · Alex Casquero · Jose Nieto

Efficacy of eculizumab in a patient with factor-H-associated atypical hemolytic uremic syndrome

Anne-Laure Lapeyraque · Véronique Frémeaux-Bacchi · Pierre Robitaille

Eculizumab in atypical haemolytic–uraemic syndrome allows cessation of plasma exchange and dialysis

Jon Jin Kim, Simon C. Waller and Christopher J. Reid

Preservation of Renal Function in Atypical Hemolytic Uremic Syndrome by Eculizumab: A Case Report

AUTHORS: Mario Giordano, MD,[a] Giuseppe Castellano, MD, PhD,[b] Giovanni Messina, MD,[a] Claretta Divella, PhD,[b] Rosa Bellantuono, MD,[a] Flora Puteo, MD,[a] Vincenzo Colella, MD,[a] Tommaso Depalo, MD,[a] and Loreto Gesualdo, MD[b]

[a]*Pediatric Nephrology and Dialysis Unit, Ospedale Pediatrico Giovanni XXIII, Bari, Italy; and* [b]*Nephrology, Dialysis and Transplantation Unit, Policlinico di Bari, University of Bari, Bari, Italy*

Early treatment with eculizumab in atypical haemolytic uraemic syndrome

Maria Garjau[1], María Azancot[1], Rosa Ramos[1], Pilar Sánchez-Corral[2], Maria Angeles Montero[3] and Daniel Serón[1]

New Treatment Options for Atypical Hemolytic Uremic Syndrome with the Complement Inhibitor Eculizumab

Özlem Köse, M.D.,[1] Lothar-Bernd Zimmerhackl, M.D., Ph.D.,[2] Therese Jungraithmayr, M.D.,[2] Christoph Mache, M.D.,[3] and Jens Nürnberger, M.D.[1]

Eculizumab as rescue therapy for atypical hemolytic uremic syndrome with normal platelet count

Eiske M. Dorresteijn · Nicole C. A. J. van de Kar · Karlien Cransberg

Eculizumab therapy in a child with hemolytic uremic syndrome and CFI mutation

F. Semsa Caycı · Nilgun Cakar · Veysel Sabri Hancer · Nermin Uncu · Banu Acar · Gokce Gur

Eculizumab therapy for atypical haemolytic uraemic syndrome due to a gain-of-function mutation of complement factor B

Rodney D. Gilbert · Darren J. Fowler · Elizabeth Angus · Stephen A. Hardy · Louise Stanley · Timothy H. Goodship

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Terminal Complement Inhibitor Eculizumab in Atypical Hemolytic–Uremic Syndrome

C.M. Legendre, C. Licht, P. Muus, L.A. Greenbaum, S. Babu, C. Bedrosian, C. Bingham, D.J. Cohen, Y. Delmas, K. Douglas, F. Eitner, T. Feldkamp, D. Fouque, R.R. Furman, O. Gaber, M. Herthelius, M. Hourmant, D. Karpman, Y. Lebranchu, C. Mariat, J. Menne, B. Moulin, J. Nürnberger, M. Ogawa, G. Remuzzi, T. Richard, R. Sberro-Soussan, B. Severino, N.S. Sheerin, A. Trivelli, L.B. Zimmerhackl,* T. Goodship, and C. Loirat

2 studi multicentrici, prospettici, open-label, di fase II

- Trial 1: 17 aHUS R a plasmaferesi o infusione di PFC
- Trial 2: 20 aHUS in tp cronica con plasmaferesi o infusione di PFC con plt stabili

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Terminal Complement Inhibitor Eculizumab in Atypical Hemolytic–Uremic Syndrome

C.M. Legendre, C. Licht, P. Muus, L.A. Greenbaum, S. Babu, C. Bedrosian, C. Bingham, D.J. Cohen, Y. Delmas, K. Douglas, F. Eitner, T. Feldkamp, D. Fouque, R.R. Furman, O. Gaber, M. Herthelius, M. Hourmant, D. Karpman, Y. Lebranchu, C. Mariat, J. Menne, B. Moulin, J. Nürnberger, M. Ogawa, G. Remuzzi, T. Richard, R. Sberro-Soussan, B. Severino, N.S. Sheerin, A. Trivelli, L.B. Zimmerhackl,* T. Goodship, and C. Loirat

2 studi multicentrici, prospettici, open-label, di fase II

- Normalizzazione plt (dopo 7 gg nel trial 1 e dopo 26 settimane del trial 2) e indici di emolisi
- Interruzione terapia con plasma
- Miglioramento fx renale
- Miglioramento Quality of life

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Terminal Complement Inhibitor Eculizumab in Atypical Hemolytic–Uremic Syndrome

C.M. Legendre, C. Licht, P. Muus, L.A. Greenbaum, S. Babu, C. Bedrosian, C. Bingham, D.J. Cohen, Y. Delmas, K. Douglas, F. Eitner, T. Feldkamp, D. Fouque, R.R. Furman, O. Gaber, M. Herthelius, M. Hourmant, D. Karpman, Y. Lebranchu, C. Mariat, J. Menne, B. Moulin, J. Nürnberger, M. Ogawa, G. Remuzzi, T. Richard, R. Sberro-Soussan, B. Severino, N.S. Sheerin, A. Trivelli, L.B. Zimmerhackl,* T. Goodship, and C. Loirat

These two clinical studies suggest that long-term eculizumab treatment is effective in patients with atypical hemolytic–uremic syndrome, with earlier intervention associated with a greater clinical benefit. The data indicate that terminal complement inhibition with eculizumab inhibits complement-mediated thrombotic microangiopathy, decreases the need for thrombotic microangiopathy–related intervention, significantly improves the platelet count and renal function across patient groups, and is associated with substantial kidney recovery and improved clinical outcomes in patients with atypical hemolytic–uremic syndrome.

N Engl J Med 2013;368:2169-81.

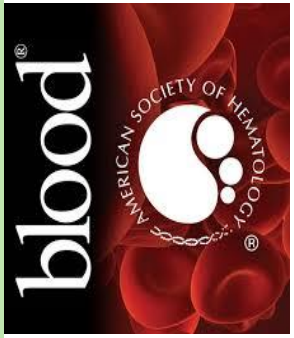
kidney INTERNATIONAL
Official journal of the International Society of Nephrology

Efficacy and safety of eculizumab in atypical hemolytic uremic syndrome from 2-year extensions of phase 2 studies

Christoph Licht[1], Larry A. Greenbaum[2], Petra Muus[3], Sunil Babu[4], Camille L. Bedrosian[5], David J. Cohen[6], Yahsou Delmas[7], Kenneth Douglas[8], Richard R. Furman[9], Osama A. Gaber[10], Timothy Goodship[11], Maria Herthelius[12], Maryvonne Hourmant[13], Christophe M. Legendre[14], Giuseppe Remuzzi[15], Neil Sheerin[16], Antonella Trivelli[17] and Chantal Loirat[18]

In conclusion, 2-year analyses of these trials demonstrated that longer-term eculizumab therapy maintained inhibition of complement activity, TMA, and improvements in hematologic parameters and renal function. Furthermore, eculizumab continued to prevent progression to end-stage renal disease in the majority of patients with aHUS.

Kidney International (2015) 87, 1061–1073



CLINICAL TRIALS AND OBSERVATIONS

Eculizumab reduces complement activation, inflammation, endothelial damage, thrombosis, and renal injury markers in aHUS

Roxanne Cofiell, Anjli Kukreja, Krystin Bedard, Yan Yan, Angela P. Mickle, Masayo Ogawa, Camille L. Bedrosian, and Susan J. Faas

Alexion Pharmaceuticals, Inc., Cheshire, CT

26-week, open-label, non randomized, single-group, multicenter, trial of eculizumab in adult patients with aHUS in which patients could continue to receive eculizumab in an extension phase

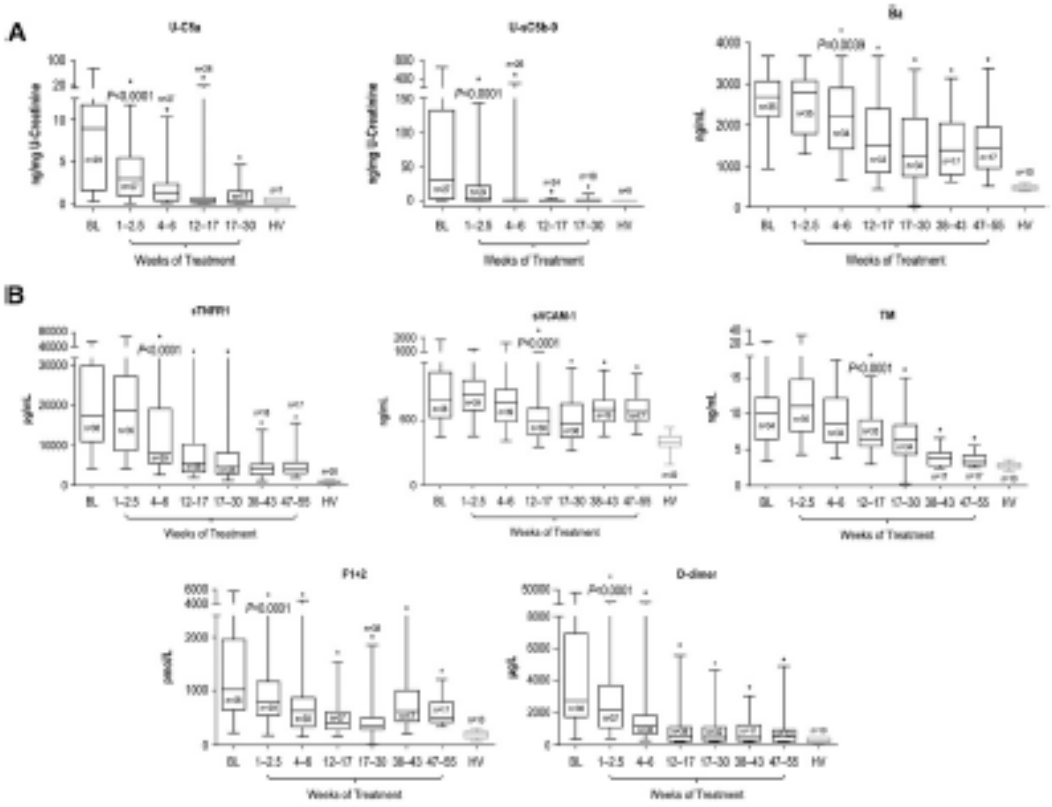
23 centers in North America and Europe

41 adult pts were treated

38 (93%) completed the initial 26-week clinical study period
21 (51%) continued treatment of 1 year during the optional extension period

Table 1. Markers of complement activation, vascular inflammation, endothelial activation and damage, coagulation, and renal injury

Disease process and biomarker	Function/association with complement
Complement activation	
AP activation	
Ba	• Alternative pathway biomarker upstream of C5[26] • Alternative pathway is stimulated by damaged endothelial cells[13] and activated platelets[61]
Terminal complement	
C5a	• Marker of C5 activation[22,23] • Proinflammatory[42] • Mediates chemotaxis, activates endothelial cells, upregulates TNF-α and VCAM-1[28,41]
Terminal complement	
sC5b-9	• Marker of C5 activation[22,23] • Mediates endothelial cell activation,[12] glomerular injury,[43] and ischemic injury leading to organ damage[44] • Stimulates von Willebrand factor multimer secretion,[45] endothelial cell prothrombinase activity,[50] and tissue factor expression[46]
Vascular inflammation/damage and coagulation	
Inflammation	
sTNFR1	• Surrogate, more stable marker for TNF-α[27] • TNF-α is pro-inflammatory; associated with vascular[49] and chronic renal inflammation and progression of renal failure[27,47,48] • TNF-α upregulated by complement activation[51]
Endothelial activation	
sVCAM-1	• Adhesion molecule released by activated endothelial cells[29] • Upregulated by TNF-α and terminal complement[29,30]
Endothelial cell damage	
Thrombomodulin	• Protective against thrombotic risk, inflammation, and complement activation when membrane-bound[52] • Released in soluble form by damaged endothelial cells[31] • TNF-α downregulates membrane form and increases release of soluble form[32]
Coagulation	
Prothrombin fragment F1+2	• Direct marker of thrombin generation[36] • Generated by cleavage of prothrombin after tissue factor–induced coagulation[10]
D-dimer	• Fibrin degradation product indicating fibrinolysis[37]
Renal	
Renal injury	
Urine cystatin-C	• Proximal tubular injury[38,53-55]
Clusterin	• Proximal tubular injury[38,58,59]
β2-microglobulin	• Proximal tubular injury[38,60]
TIMP-1	• Interstitial tubular injury[40,56]
L-FABP-1	• Deteriorating renal function[39,57]



Terminal complement inhibition with Eculizumab treatment markedly reduces inflamation and coagulation and decreases endothelial activation and damage

Cofiell R et all. Blood 21 May 2015

Notevole miglioramento outcome ematologico e renale

Costi elevati

Non noti effetti a lungo termine

Necessità di individualizzare il trattamento

Discontinuation of Eculizumab

Official Journal of the National Kidney Foundation

AJKD American Journal of Kidney Diseases

Discontinuation of Eculizumab Maintenance Treatment for Atypical Hemolytic Uremic Syndrome: A Report of 10 Cases

Gianluigi Ardissino, MD, PhD, Sara Testa, MD, Ilaria Possenti, MD, Francesca Tel, MD, Fabio Paglialonga, MD, Stefania Salardi, BS, Silvana Tedeschi, MD, Mirco Belingheri, MD, and Massimo Cugno, MD

"…3 of the 10 pts experienced relapse within 6 weeks of discontinuation, but then immediately resumed treatment and completely recovered…"

"…5 patients experienced relapse…within 6 months of the last eculizumab dose…Eleven patients remained in remission with no signs of acute disease…"

Discontinuation of Eculizumab Treatment in Atypical Hemolytic Uremic Syndrome: An Update

Gianluigi Ardissino, MD, PhD, Ilaria Possenti, MD
Francesca Tel, MD, Sara Testa, MD, Stefania Salardi, BS
Vito Ladisa, PharmD

In conclusion, we believe that in atypical hemolytic uremic syndrome, it is possible and relatively safe to discontinue eculizumab therapy. In general, we discourage discontinuation of eculizumab therapy in kidney transplant recipients with *CFH* mutations and patients with glomerular filtration rates < 20 mL/min/1.73 m^2. In patients with anti-CFH antibodies, we consider discontinuation of eculizumab therapy when antibody titer is <2.5 times the upper limit of normal. We suggest regular home urine dipstick monitoring for early identification of relapses, especially during acute illnesses and when patients feel unwell.

Discontinuation of Eculizumab

Official Journal of the National Kidney Foundation
AJKD American Journal of Kidney Diseases

Discontinuation of Eculizumab Maintenance Treatment for Atypical Hemolytic Uremic Syndrome

Jack F.M. Wetzels, MD, PhD, Nicole C.A.J. van de Kar, MD, PhD
Radbound University Medical Center, Nijmegen, the Netherlands

"…eculizumab treatment was withdrawn in 3 of our patients, 2 of whom had no signs of disease activity…Recurrent disease developed in 1 patients 3 months after eculizumab discontinuation…"

Can eculizumab be discontinued in aHUS?

Case report and review of the literature

Tuncay Sahutoglu, MD[a,*], Taner Basturk, MD[a], Tamer Sakaci, MD[a], Yener Koc, MD[a], Elbis Ahbap, MD[a], Mustafa Sevinc, MD[a], Ekrem Kara, MD[b], Cuneyt Akgol, MD[a], Feyza Bayraktar Caglayan, MD[a], Abdulkadir Unsal, MD[a], Moha

patients with MCP mutations, homozygous CFHR3/R1 deletions, anti-CFH antibodies, no identifiable mutations and CFI mutations carry a low risk, whereas CFH mutations pose a major risk of recurrence of TMA following discontinuation of eculizumab in patients with aHUS. Preinjury markers of

Table 1

Summary of aHUS cases who were treated with and discontinued eculizumab.

Study	Patient number	Age at onset of aHUS, sex	Kidney (native or transplanted)	Complement abnormality	Duration of eculizumab treatment before discontinuation (months)	Method of follow-up	TM recurrence, time, mo	Retreatment with eculizumab	Outcome (creatinine, proteinuria)
Alachkar et al, 2012[24]	1	24, F	Transplant 2nd	None	1.9	Unreported	Yes, 5	Yes	Graft loss
Cayci et al, 2012[19]	2	10,F	Native	CFI	0.75	Unreported	No, 4	No	Good (0.5 mg/dL, unreported)
Gulleroglu et al, 2013[14]	3	6, F	Native	MCP	1.25	Unreported	No, 9	No	Good (normal renal functions, unreported)
Carr et al, 2013[25]	4	20, F	Native	CFH	9	Unreported	Yes, 6	Yes	Dialysis-free (values unreported)
Pu et al, 2014[21]	5	85, F	Native	None	3	Unreported	No, 12	No	Good (normal renal functions)
Wetzels et al, 2015[22]	6	30, F	Unreported	CFH	35	Unreported	No, 17	No	Stable
	7	21, F	Unreported	CFH	4.5	Unreported	Yes, 3	Yes	Unreported
	8	43, F		CFH	4	Unreported	No, 11	No	Stable
Ardissino et al, 2015[10]	9	4.3, M	Unreported	CFH	6.7	Home-based urine dipstick test thrice weekly to detect microscopic hematuria	Yes, 1.5	Yes	Good (0.57 mg/dL, not detectable)
	10	37.7, F	Unreported	CFH+CFI+THBD	14.4		Yes, 0.9	Yes	Good (1.16mg/dL, 1.12mg/mg)
	11	52.7, M	Unreported	CFI	1.5		No, 40	No	Good (0.78 mg/dL, 0.22 mg/mg)
	12	34.8, F	Unreported	CFI	10.4		No, 28.2	No	Good (2.11 mg/dL, 1.30 mg/mg)
	13	2.6, M	Unreported	CFI	5.6		Yes, 17.3	Yes	Good (0.45mg/dL, 0.31 mg/mg)
	14	1.3, F	Unreported	CFHR3/R1 del/del	13.4		No, 23.7	No	Good (0.24mg/dL, 3.81 mg/mg)
	15	19.1, M	Unreported	Anti-CFH+	5.5		No, 31.4	No	Good (1.13mg/dL, 0.15mg/mg)
	16	5.4, F	Unreported	MCP	0.5		No, 31.2	No	Good (0.54mg/dL, 0.20mg/mg)
	17	13.3, M	Unreported	Anti-CFH+CFHR3/R1 del/del	2.6		No, 25.8	No	Good (0.8mg/dL, 0.19mg/mg)
	18	10.9, F	Unreported	CFH+CFHR3/R1 del/del+Anti-CFH	0.9		Yes, 1.2	Yes	Good (0.8mg/dL, 0.07mg/mg)
	19	44, F	Unreported	None	4.1		No, 24.7	No	Good (0.84 mg/dL, not detectable)
	20	52, F	Unreported	CFHR3/R1 del/del	8.3		No, 8.9	No	Good (2.3 mg/dL, not detectable)
	21	60, M	Unreported	None	4.5		No, 7.2	No	Good (1.1 mg/dL, not detectable)
	22	15.8, F	Unreported	Anti-CFH+CFHR3/R1 del/del	0.8		Yes, 0.7	Yes	Good (0.83 mg/dL, 0.74 mg/mg)
	23	1.7, M	Unreported	MCP	0.5		No, 0.7	No	Good (0.68 mg/dL, 0.16 mg/mg)
	24	40.8, F	Unreported	None	0.6		No, 0.4	No	Good (0.81 mg/dL, 0.33 mg/mg)

aHUS = atypical hemolytic uremic syndrome, CFI = complement factor I, CFH = complement factor H, CFHR = complement factor H-related protein, MCP = membrane cofactor protein, THBD = thrombomodulin, TMA = thrombotic microangiopathy.

Therapeutic drug monitoring of Eculizumab

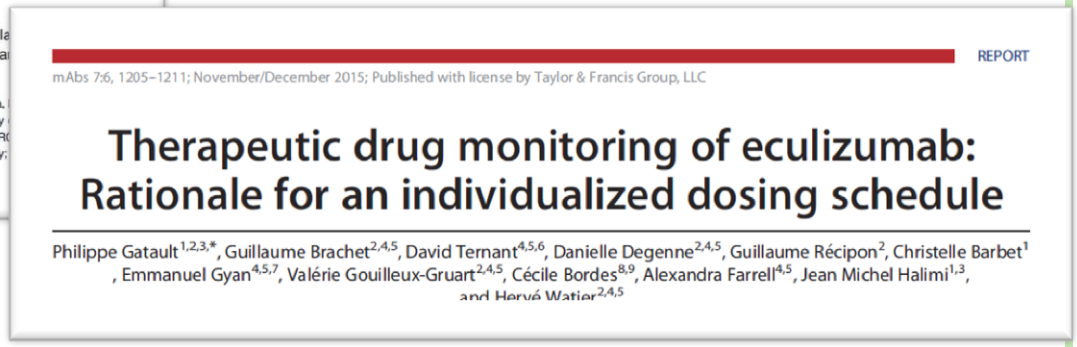
Regular Article

CLINICAL TRIALS AND OBSERVATIONS

Dynamics of complement activation in aHUS and how to monitor eculizumab therapy

Marina Noris,[1] Miriam Galbusera,[1] Sara Gastoldi,[1] Paolo Macor,[2] Federica Banterla,[1] Elena Bresin,[1] Cla
Serena Bettoni,[1] Roberta Donadelli,[1] Elisabetta Valoti,[1] Francesco Tedesco,[4] Alessandro Amore,[5] Rosa
Piero Ruggenenti,[6] Eliana Gotti,[6] and Giuseppe Remuzzi[1,6]

[1]IRCCS - Istituto di Ricerche Farmacologiche "Mario Negri," Clinical Research Center for Rare Diseases "Aldo e Cele Daccò," Ranica, "Centro Anna Maria Astori" Science and Technology Park Kilometro Rosso, Bergamo, Italy; [2]Department of Life Sciences, University Italy; [3]Tumor Immunology Unit, Human Pathology Section, Department of Health Sciences, University of Palermo, Palermo, Italy; [4]IR Auxologico Italiano, Milan, Italy; [5]Unit of Nephrology, Dialysis and Transplantation, Regina Margherita University Hospital, Turin, Italy; Nephrology and Dialysis, Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy

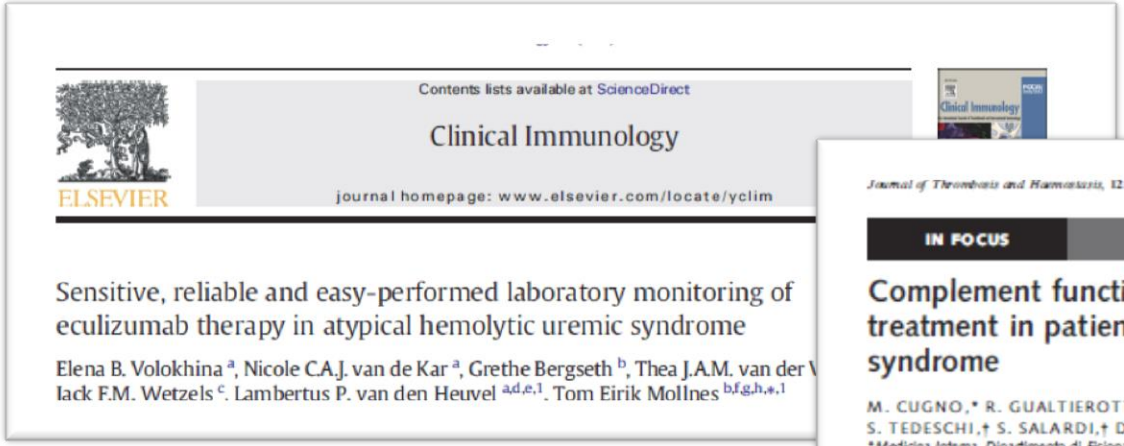


REPORT

mAbs 7:6, 1205–1211; November/December 2015; Published with license by Taylor & Francis Group, LLC

Therapeutic drug monitoring of eculizumab: Rationale for an individualized dosing schedule

Philippe Gatault[1,2,3,*], Guillaume Brachet[2,4,5], David Ternant[4,5,6], Danielle Degenne[2,4,5], Guillaume Récipon[2], Christelle Barbet[1], Emmanuel Gyan[4,5,7], Valérie Gouilleux-Gruart[2,4,5], Cécile Bordes[8,9], Alexandra Farrell[4,5], Jean Michel Halimi[1,3], and Hervé Watier[2,4,5]



Contents lists available at ScienceDirect

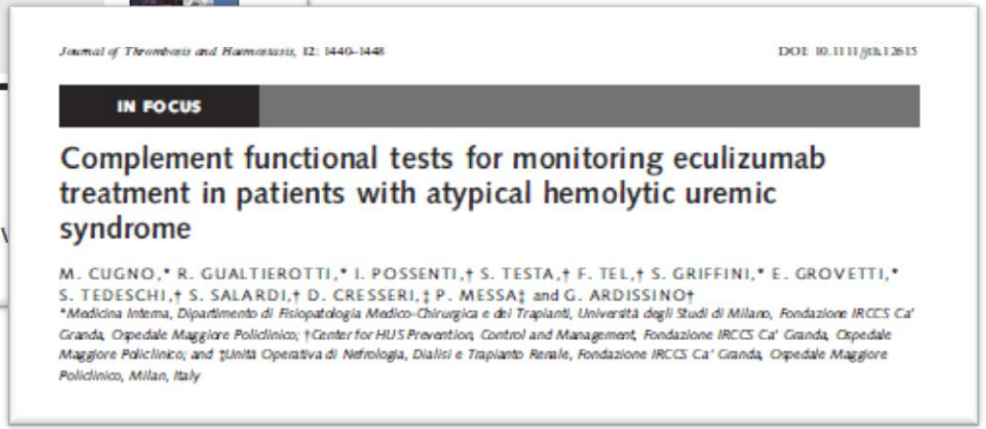
Clinical Immunology

journal homepage: www.elsevier.com/locate/yclim

ELSEVIER

Sensitive, reliable and easy-performed laboratory monitoring of eculizumab therapy in atypical hemolytic uremic syndrome

Elena B. Volokhina [a], Nicole C.A.J. van de Kar [a], Grethe Bergseth [b], Thea J.A.M. van der V
Iack F.M. Wetzels [c], Lambertus P. van den Heuvel [a,d,e,1], Tom Eirik Mollnes [b,f,g,h,*,1]



Journal of Thrombosis and Haemostasis, 12: 1440–1448 DOI: 10.1111/jth.12615

IN FOCUS

Complement functional tests for monitoring eculizumab treatment in patients with atypical hemolytic uremic syndrome

M. CUGNO,* R. GUALTIEROTTI,* I. POSSENTI,† S. TESTA,† F. TEL,† S. GRIFFINI,* E. GROVETTI,* S. TEDESCHI,† S. SALARDI,† D. CRESSERI,‡ P. MESSA‡ and G. ARDISSINO†

*Medicina Interna, Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Università degli Studi di Milano, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, †Center for HUS Prevention, Control and Management, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico; and ‡Unità Operativa di Nefrologia, Dialisi e Trapianto Renale, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milan, Italy

Dynamics of complement activation in aHUS and how to monitor eculizumab therapy

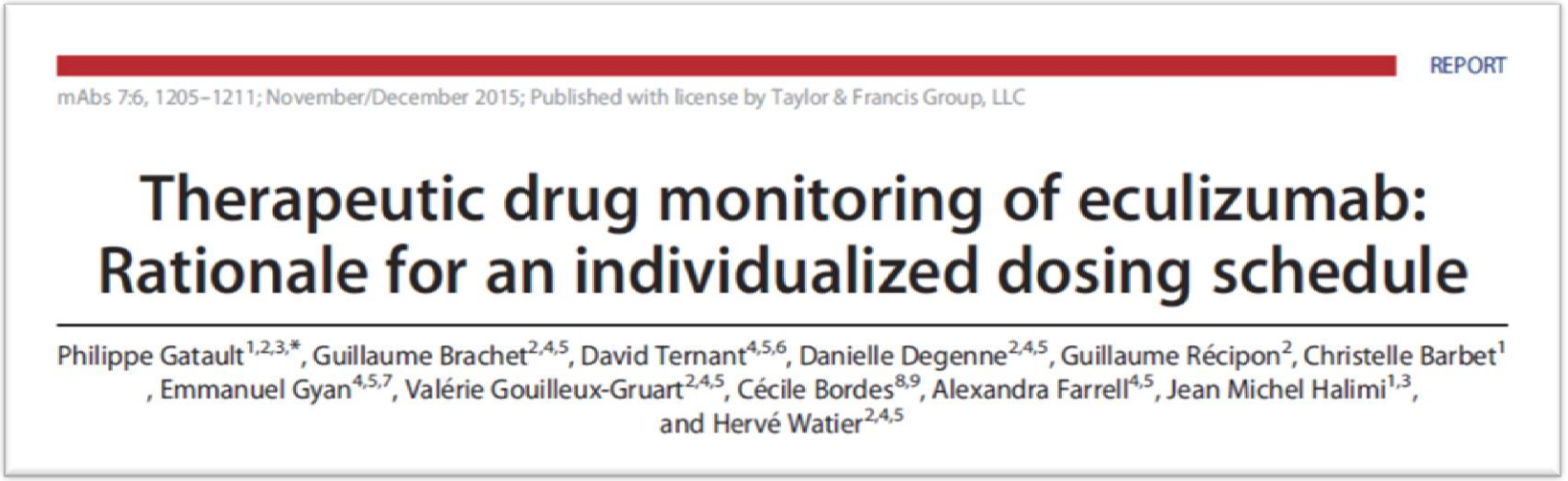
Marina Noris,[1] Miriam Galbusera,[1] Sara Gastoldi,[1] Paolo Macor,[2] Federica Banterla,[1] Elena Bresin,[1] Claudio Tripodo,[3] Serena Bettoni,[1] Roberta Donadelli,[1] Elisabetta Valoti,[1] Francesco Tedesco,[4] Alessandro Amore,[5] Rosanna Coppo,[5] Piero Ruggenenti,[6] Eliana Gotti,[6] and Giuseppe Remuzzi[1,6]

Key Points

- Endothelial-restricted complement activation occurs in aHUS, and clinical remission relies on efficient endothelial complement inhibition.
- Ex vivo serum-induced endothelial C5b-9 deposits are a sensitive tool to monitor complement activation and eculizumab effectiveness in aHUS.

"… In 8 eculizumab-treated aHUS patients, C3/sC5b-9 circulating levels did not change post eculizumab, whereas serum-induced endothelial C5b-9 deposits normalized after treatment, paralleled or even preceded remission, and guided drug dosing and timing…"

Blood 2014;124(11):1715-1726



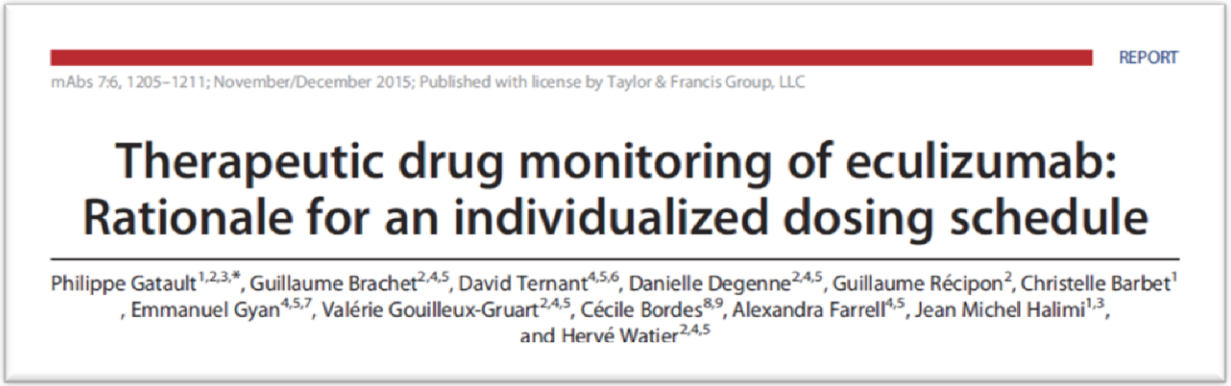
REPORT

mAbs 7:6, 1205–1211; November/December 2015; Published with license by Taylor & Francis Group, LLC

Therapeutic drug monitoring of eculizumab: Rationale for an individualized dosing schedule

Philippe Gatault[1,2,3,*], Guillaume Brachet[2,4,5], David Ternant[4,5,6], Danielle Degenne[2,4,5], Guillaume Récipon[2], Christelle Barbet[1], Emmanuel Gyan[4,5,7], Valérie Gouilleux-Gruart[2,4,5], Cécile Bordes[8,9], Alexandra Farrell[4,5], Jean Michel Halimi[1,3], and Hervé Watier[2,4,5]

- Bassa variabilità intra-individuale (coeff di variabilità ≤ 25%)
- Elevata variabilità inter-individuale (coeff di variabilità del 63%)
- Peso corporeo: maggior responsabile della variabilità



REPORT

mAbs 7:6, 1205–1211; November/December 2015; Published with license by Taylor & Francis Group, LLC

Therapeutic drug monitoring of eculizumab: Rationale for an individualized dosing schedule

Philippe Gatault[1,2,3,*], Guillaume Brachet[2,4,5], David Ternant[4,5,6], Danielle Degenne[2,4,5], Guillaume Récipon[2], Christelle Barbet[1], Emmanuel Gyan[4,5,7], Valérie Gouilleux-Gruart[2,4,5], Cécile Bordes[8,9], Alexandra Farrell[4,5], Jean Michel Halimi[1,3], and Hervé Watier[2,4,5]

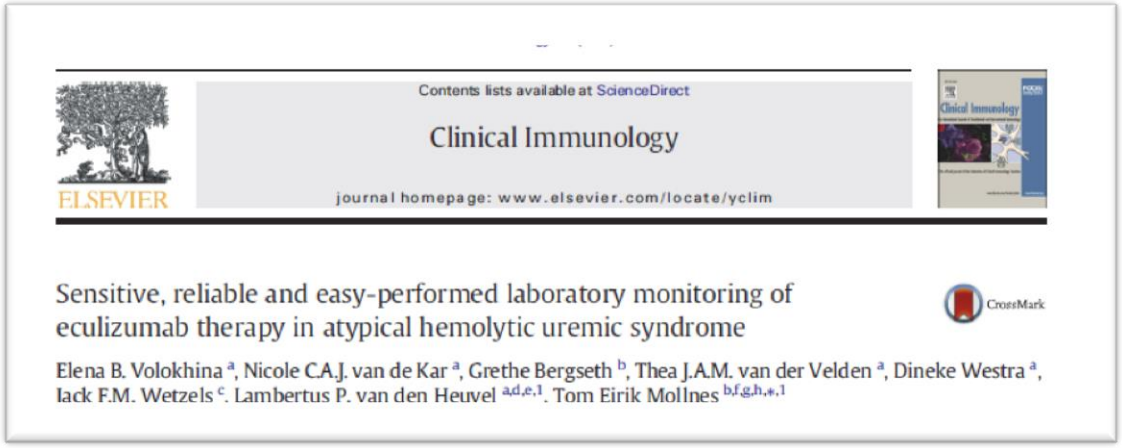
Nine adult patients who received eculizumab for aHUS or PNH

Measurement of eculizumab trough levels

Pharmacokinetic study

The following weight-based schedule could be proposed

90 to 120 kg:	• 1200 mg every 2 weeks;
70 to 90 kg:	• 1200 mg every 4 weeks;
<70 kg:	• 1200 mg every 6 weeks.



Contents lists available at ScienceDirect

Clinical Immunology

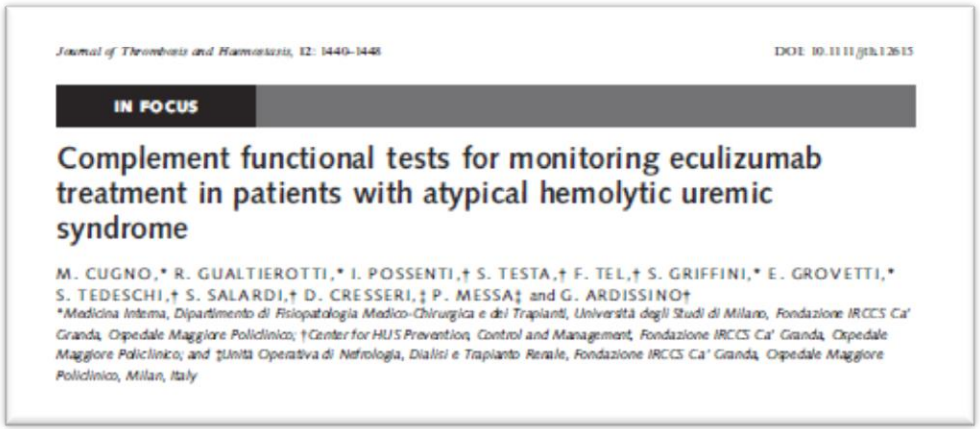
journal homepage: www.elsevier.com/locate/yclim

Sensitive, reliable and easy-performed laboratory monitoring of eculizumab therapy in atypical hemolytic uremic syndrome

Elena B. Volokhina [a], Nicole C.A.J. van de Kar [a], Grethe Bergseth [b], Thea J.A.M. van der Velden [a], Dineke Westra [a], Jack F.M. Wetzels [c], Lambertus P. van den Heuvel [a,d,e,1], Tom Eirik Mollnes [b,f,g,h,*,1]

9 patients CP -AP activity: ⇩ 3-4 weeks

18 patients CP –AP-MBL activity: ⇩ 3 weeks



Journal of Thrombosis and Haemostasis, 12: 1440–1448 DOI: 10.1111/jth.12615

IN FOCUS

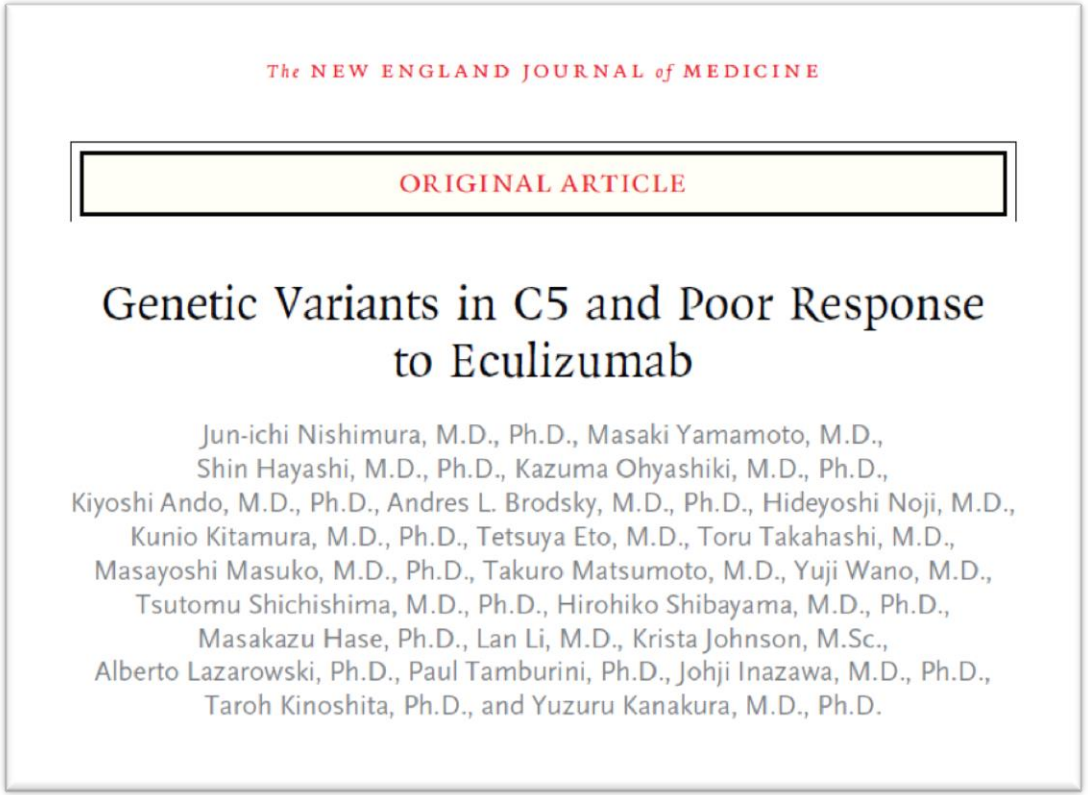
Complement functional tests for monitoring eculizumab treatment in patients with atypical hemolytic uremic syndrome

M. CUGNO,* R. GUALTIEROTTI,* I. POSSENTI,† S. TESTA,† F. TEL,† S. GRIFFINI,* E. GROVETTI,* S. TEDESCHI,† S. SALARDI,† D. CRESSERI,‡ P. MESSA‡ and G. ARDISSINO†

*Medicina Interna, Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Università degli Studi di Milano, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico; †Center for HUS Prevention, Control and Management, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico; and ‡Unità Operativa di Nefrologia, Dialisi e Trapianto Renale, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milan, Italy

Wieslab® complement system screen (Euro Diagnostica AB,Malmö, Sweden) (ELISA)

This kit detects serum complement activity through CP, LP and AP



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Genetic Variants in C5 and Poor Response to Eculizumab

Jun-ichi Nishimura, M.D., Ph.D., Masaki Yamamoto, M.D., Shin Hayashi, M.D., Ph.D., Kazuma Ohyashiki, M.D., Ph.D., Kiyoshi Ando, M.D., Ph.D., Andres L. Brodsky, M.D., Ph.D., Hideyoshi Noji, M.D., Kunio Kitamura, M.D., Ph.D., Tetsuya Eto, M.D., Toru Takahashi, M.D., Masayoshi Masuko, M.D., Ph.D., Takuro Matsumoto, M.D., Yuji Wano, M.D., Tsutomu Shichishima, M.D., Ph.D., Hirohiko Shibayama, M.D., Ph.D., Masakazu Hase, Ph.D., Lan Li, M.D., Krista Johnson, M.Sc., Alberto Lazarowski, Ph.D., Paul Tamburini, Ph.D., Johji Inazawa, M.D., Ph.D., Taroh Kinoshita, Ph.D., and Yuzuru Kanakura, M.D., Ph.D.

345 Japanese pts with PNH

11 poor response

Single missense C5 eterozygous mutation

⇩

Polimorfismo p.Arg885His

15% of patients Refractory to Eculizumab

De Vriese AS et al. JASN 2015, 26:2917-29

Trapianto di Rene

- Rischio di ricorrenza di aHUS intorno al 50%
- Rischio correlato con il tipo di mutazione genetica
- 80-90% Rischio di perdita del graft in caso di recidiva

Mutazione	% Rischio di recidiva
CFH	75-90
CFI	45-80
C3	40-70
CFB	100 ma soli 3 pz
THBD	nv
MCP	15-20
Ab anti-CFH	Correlato al titolo Ab

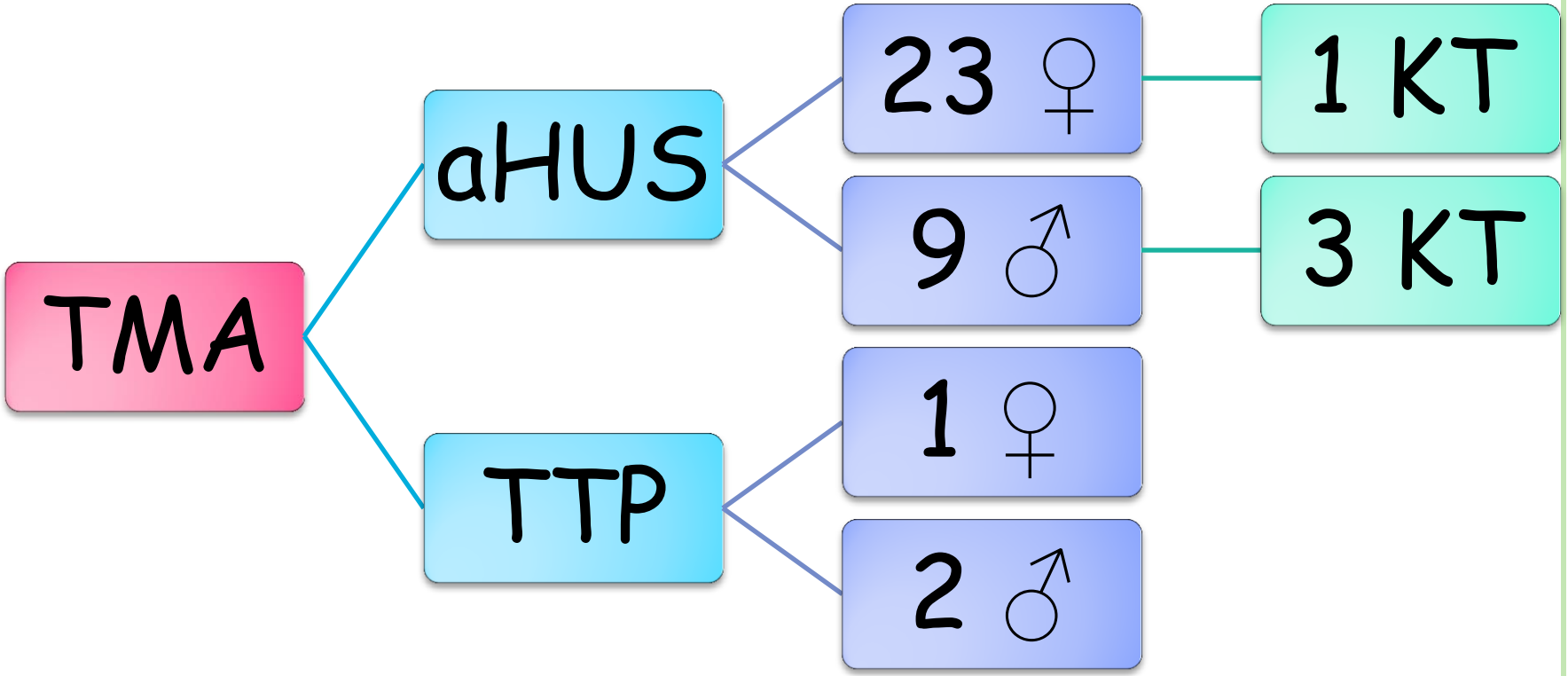
Lorait C and Frémeaux-Bacchi V OJRD 2011,6:60

Recidiva post-trapianto

- Eculizumab + efficace di PEX nel trattamento delle recidive post-trapianto
- "Plasmaferesi preventiva"

- Eculizumab un'ora prima del tpx in pazienti ad elevato rischio di recidiva

Eculuzumab & aHUS: l'esperienza di Careggi

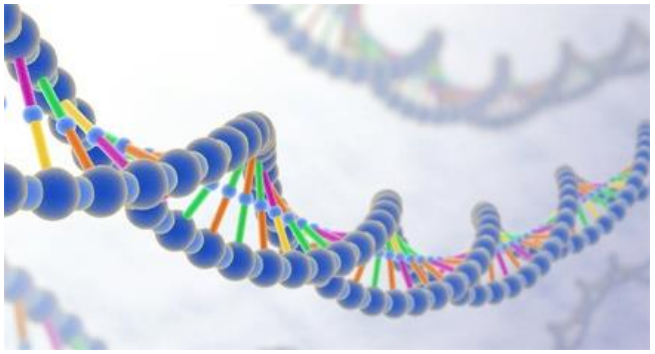


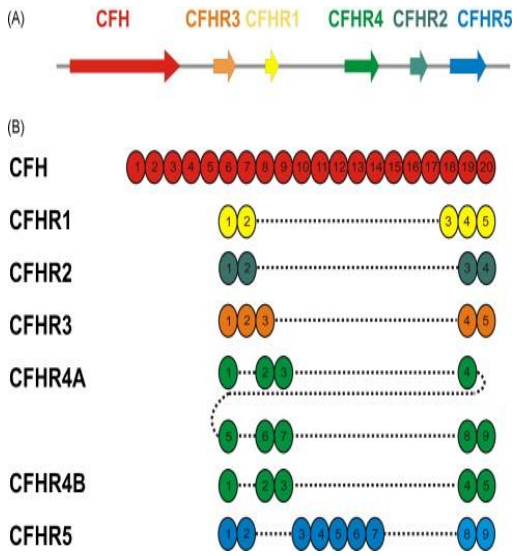
Eculuzumab & aHUS: l'esperienza di Careggi

Dal 2011

10 pazienti trattati con Eculizumab (6 ♀; 4 ♂)

- 1 recidiva post-trapianto
- 1 pz al V episodio di ricaduta di malattia
- 3 pz in terapia con IFN-beta
- 4 pz senza fattori di rischio al primo episodio di malattia
- 1 pz profilassi per trapianto di rene

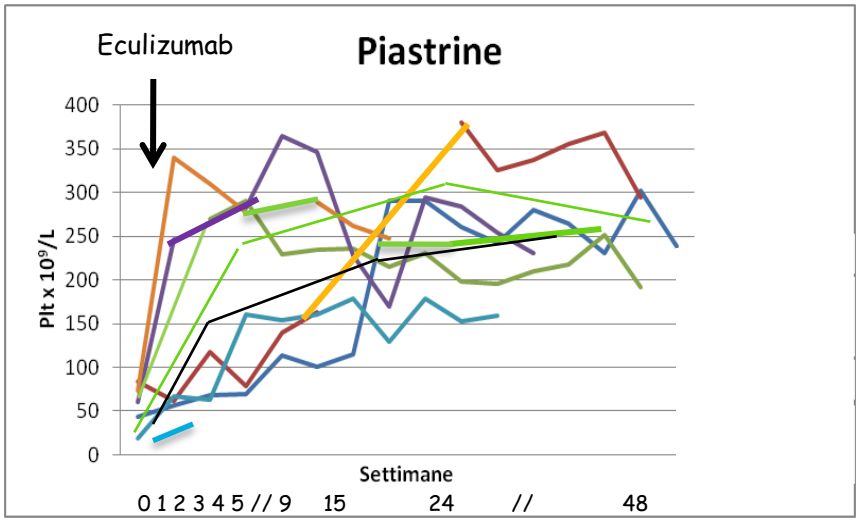




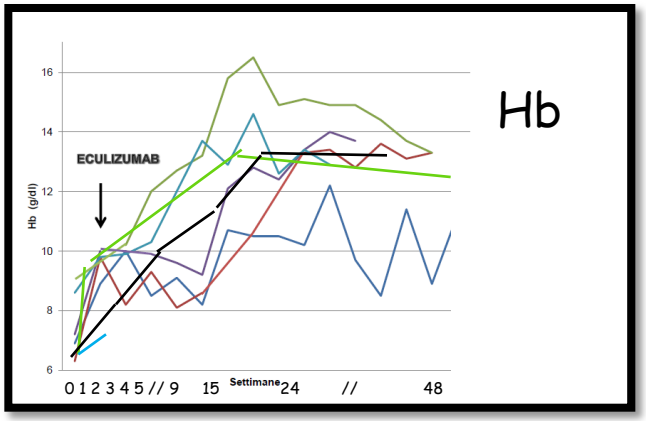
Genetica

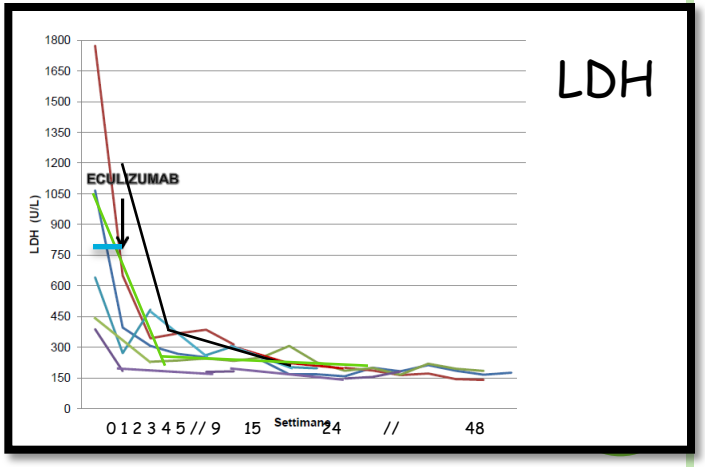
- 4 pazienti neg
- 1 pz con mutazione CFH
- 1 pz con mutazione MCP
- 1 pz con delezione in eterozigosi di CFHR3-CFHR1
- 1 pz con una mutazione in eterozigosi di MCP + delezione in eterozigosi di CFHR3-CFHR1
- 1 pz con mutazione di CFI e C3
- 1 pz con genetica in corso

Eculuzumab & aHUS: l'esperienza di Careggi



- Pt1
- Pt2
- Pt3
- Pt4
- Pt5
- Pt6
- Pt7
- Pt8
- Pt9





Eculuzumab & aHUS: l'esperienza di Careggi

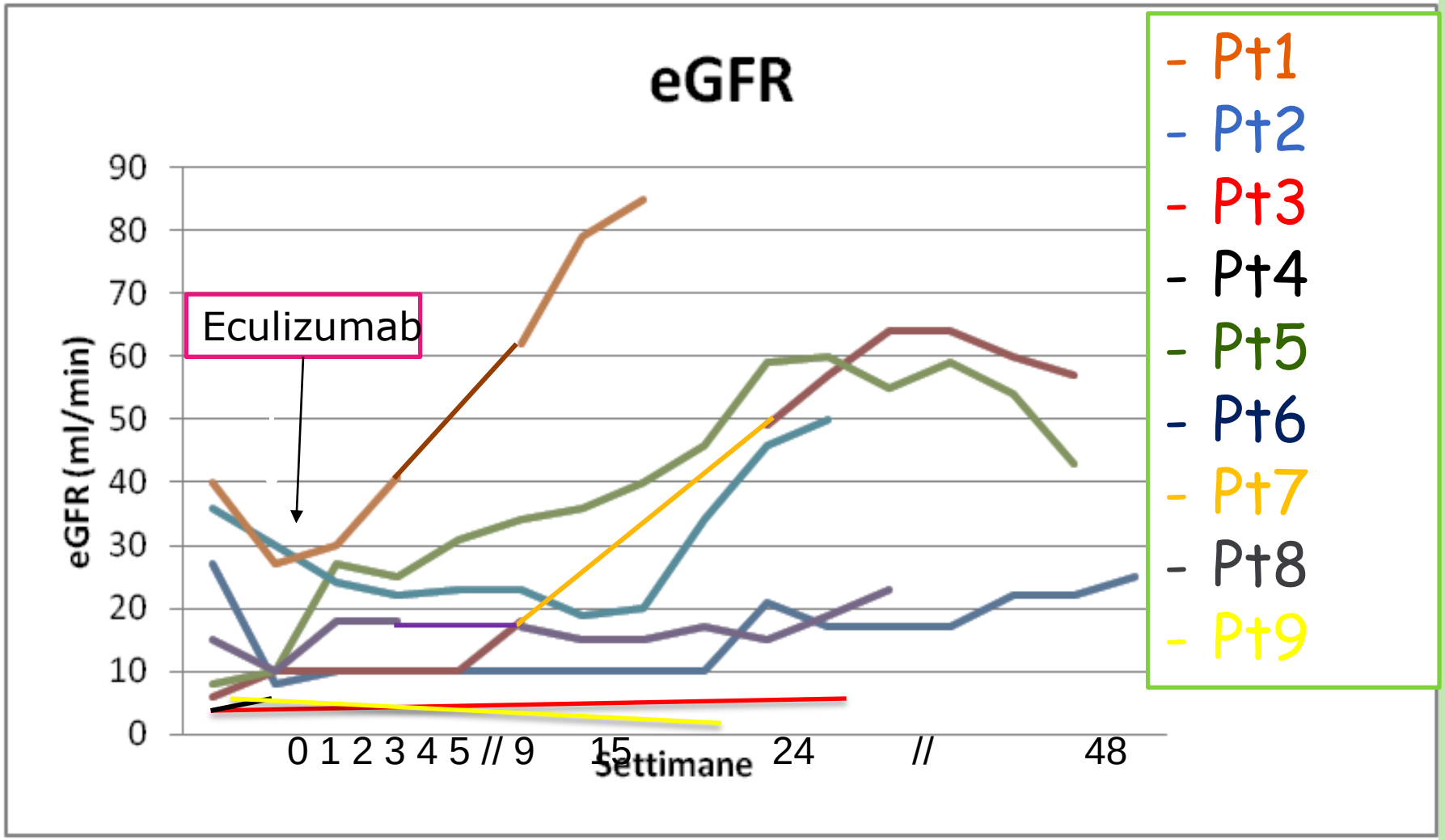


Table 4. Summary of the value of eculizumab in aHUS

Positive effects
No deaths in any trial
Few serious side effects
Stabilizes hematological abnormalities
Can improve neurological abnormalities
Stabilizes renal abnormalities
Can reverse acute renal injury
Can improve eGFR
Patients may become dialysis-independent
Effective regardless of the type of detected mutation
Effective in aHUS without detected mutation
Effective in cases with DEAP
Prevents recurrent episodes pre-transplant
Prevents post-transplant recurrence
Rescues critically ill patients before and after renal transplant
Success in plasmapheresis-resistant AMR
Can be used safely in pregnancy
Negative effects
Rare cases of meningitis
Expensive
Not universally available

Nel Futuro...

- Inibitori di C5 ⇨ molecole di piccole dimensioni con minore attività immunogena e potenziale assorbimento intestinale
- CFH ricombinante
- Ab anti-properdina
- Eculizumab long-acting
- Inibitori della C3 convertasi (Compstatin, Ab anti-C3b e CR1 solubile)

MICROANGIOPATIE TROMBOTICHE: PATOGENESI/TERAPIA

PERUGIA, 29 SETTEMBRE 2016

9.30 Apertura segreteria

I Sessione

FISIOPATOLOGIA DELLE MICROANGIOPATIE TROMBOTICHE

Moderatori: Paolo Gresele (Perugia), Raimondo De Cristofaro (Roma)

10.00 Fisiopatologia delle Microangiopatie Trombotiche
Raimondo De Cristofaro (Roma)

10.30 Le sindromi trombotiche microangiopatiche: il ruolo del laboratorio
Paolo Gresele (Perugia)

10.50 Discussione

11.00 Pausa caffè

II Sessione

PRESENTAZIONE CLINICA E DIAGNOSI DIFFERENZIALE DELLE MICROANGIOPATIE TROMBOTICHE

Moderatori: Franco Baldelli (Perugia), Brunangelo Falini (Perugia), Emidio Nunzi (Perugia)

11.30 Sindrome uremico-emolitica o emolitico uremica nel trapianto di midollo osseo
Alessandra Carotti (Perugia)

11.50 La Sindrome Emolitico Uremica (SEU) nel paziente infettivologico
Franco Baldelli (Perugia)

12.10 La Sindrome Emolitico Uremica atipica (SEUa) ed il ruolo del Nefrologo
Rachele Brugnano (Perugia)

12.30 Le Microangiopatie Trombotiche in gravidanza
Sandro Gerli (Perugia)

12.50 Discussione

13.10 Pausa pranzo

III Sessione

GESTIONE TERAPEUTICA DELLE MICROANGIOPATIE TROMBOTICHE

Moderatori: Maurizio Caniglia (Perugia), Mauro Marchesi (Perugia)

14.10 Il ruolo della PE/PI nelle Microangiopatie Trombotiche
Olivia Minelli (Perugia)

14.30 Eculizumab nel trattamento della SEUa
Giulia Antognoli (Firenze)

14.50 Casi clinici:
- Medicina emergenza-urgenza — Cristina Vedovati (Perugia)
- Oncoematologia pediatrica — Elena Mastrodicasa (Perugia)

15.10 Discussione

15.30 Consegna dei questionari ECM

SPONSOR ALEXION

SEDE
Università degli Studi di Perugia
Scuola di Medicina
Piazzale Severi, 1 - Perugia
Aula 8 Edificio B piano -2

PRESIDENTE: Paolo Gresele
Professore Ordinario Università degli Studi di Perugia

SEGRETERIA ORGANIZZATIVA
Mail: info@elleventi.it
Telefono: 338 98 58 343 - 340 82 57 297
Viale Somalia 133 00199 Roma, Italia

ACCREDITAMENTO E.C.M.
Il Corso è stato inserito nel Piano formativo 2016 per la formazione Continua in Medicina (ECM) ed ha ottenuto n. 8,5 crediti formativi

ISCRIZIONI
L'iscrizione al corso è gratuita e dovrà essere effettuata on line al seguente indirizzo:
http://www.elleventi.it/eventi/2016/perugia2016/iscrizione.php

Grazie per l'attenzione!