Nuove strategie terapeutiche nella SEU

Azienda Ospedaliero Universitaria Careggi

CONVEGNO TMA UCSC 2016
Fondazione Policlinico Universitario A. Gemelli

ROMA 19.02.2016

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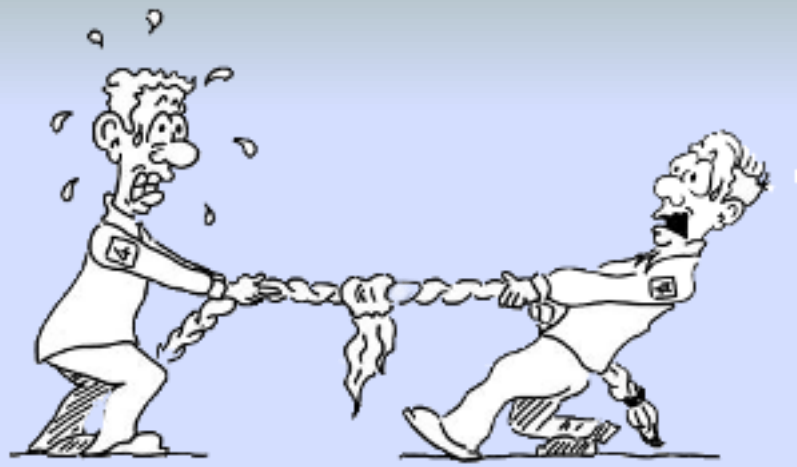
MALATTIE RARE



L'autore dichiara l'assenza di *conflitto di interessi* in relazione al contenuto della seguente presentazione

(art. 53 d.lgs. n. 165/2001 come modificato dalla legge 190/2012)

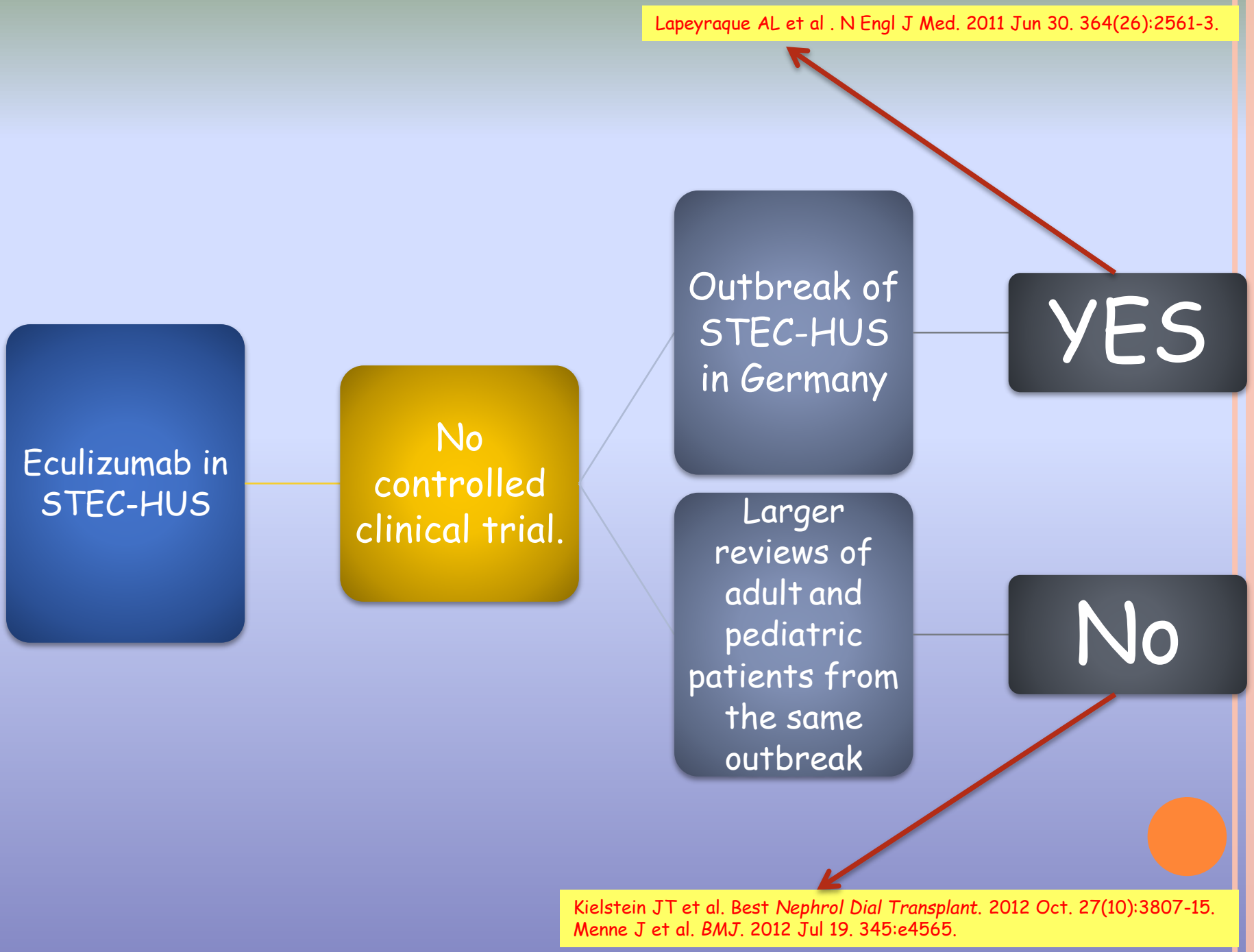
Primary Thrombotic Microangiopathy (TMA) Syndromes.

Table 1. Primary Thrombotic Microangiopathy (TMA) Syndromes.*

Name	Cause	Clinical Features	Initial Management
Hereditary disorders			
ADAMTS13 deficiency–mediated TMA (also called TTP)	Homozygous or compound heterozygous *ADAMTS13* mutations	Initial presentation is typically in children but may also be in adults; possible evidence of ischemic organ injury; acute kidney injury is uncommon; patients with heterozygous mutations are asymptomatic.	Plasma infusion
Complement-mediated TMA	Mutations in *CFH, CFI, CFB, C3, CD46*, and other complement genes causing uncontrolled activation of the alternative pathway of complement	Initial presentation is often in children but may also be in adults; acute kidney injury is common; patients with heterozygous mutations may be symptomatic.	Plasma infusion or exchange, anti-complement agent
Metabolism-mediated TMA	Homozygous mutations in *MMACHC* (encoding methylmalonic aciduria and homocystinuria type C protein)	Initial presentation is typically in children <1 year of age; also reported in one young adult with hypertension and acute kidney injury.	Vitamin B_{12}, betaine, folinic acid
Coagulation-mediated TMA	Homozygous mutations in *DGKE;* mutations in *PLG* and *THBD* also implicated	Initial presentation with acute kidney injury is typically in children <1 year of age with *DGKE* mutations; clinical features of disorders associated with other mutations have not been described.	Plasma infusion
Acquired disorders			
ADAMTS13 deficiency–mediated TMA (also called TTP)	Autoantibody inhibition of ADAMTS13 activity	Initial presentation is uncommon in children; often presents with evidence of ischemic organ injury; acute kidney injury is uncommon.	Plasma exchange, immunosuppression
Shiga toxin–mediated TMA (also called ST-HUS)	Enteric infection with a Shiga toxin–secreting strain of *Escherichia coli* or *Shigella dysenteriae*	Initial presentation is more common in young children, typically with acute kidney injury; most cases are sporadic; large outbreaks also occur.	Supportive care
Drug-mediated TMA (immune reaction)	Quinine and possibly other drugs, with multiple cells affected by drug-dependent antibodies	Initial presentation is a sudden onset of severe systemic symptoms with anuric acute kidney injury.	Removal of drug, supportive care
Drug-mediated TMA (toxic dose–related reaction)	Multiple potential mechanisms (e.g., VEGF inhibition)	Gradual onset of renal failure occurs over weeks or months.	Removal of drug, supportive care
Complement-mediated TMA	Antibody inhibition of complement factor H activity	Initial presentation is acute kidney injury in children or adults.	Plasma exchange, immunosuppression, anticomplement agent

* The primary TMA syndromes are described by evidence supporting a defined cause. Shiga toxin–mediated TMA (also called Shiga toxin–related hemolytic–uremic syndrome [ST-HUS]) occurs primarily in children and may be the most common of the nine primary TMA syndromes. Among adults, acquired thrombotic thrombocytopenic purpura (TTP) may be the most common primary TMA syndrome; acquired TTP is rare in children, in whom the incidence may be similar to that of hereditary TTP. The frequencies of TMAs that are mediated by complement, metabolism, coagulation, or drugs are unknown. The demonstration of antibodies that can neutralize the activity of complement factor H suggests that acquired TMA mediated by a deficiency in complement factor H may occur. DGKE denotes diacylglycerol kinase ε, PLG plasminogen, THBD thrombomodulin, and VEGF vascular endothelial growth factor.

George JN, Nester CM. N Engl J Med 2014;371:654-666.


Lapeyraque AL et al . N Engl J Med. 2011 Jun 30. 364(26):2561-3.
Eculizumab in STEC-HUS
No controlled clinical trial.
Outbreak of STEC-HUS in Germany
YES
Larger reviews of adult and pediatric patients from the same outbreak
No
Kielstein JT et al. Best Nephrol Dial Transplant. 2012 Oct. 27(10):3807-15.
Menne J et al. BMJ. 2012 Jul 19. 345:e4565.

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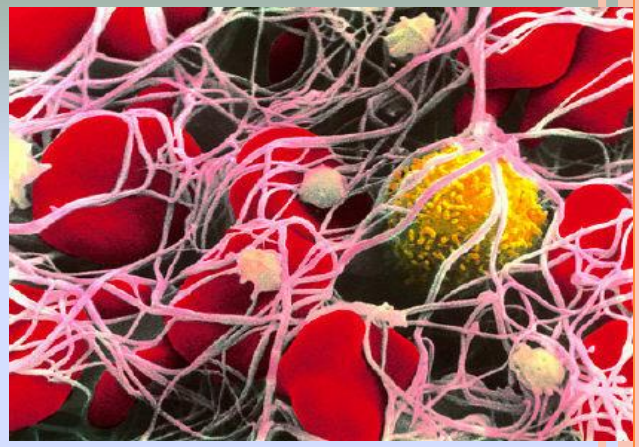
George JN, Nester CM. N Engl J Med 2014;371:654-666.

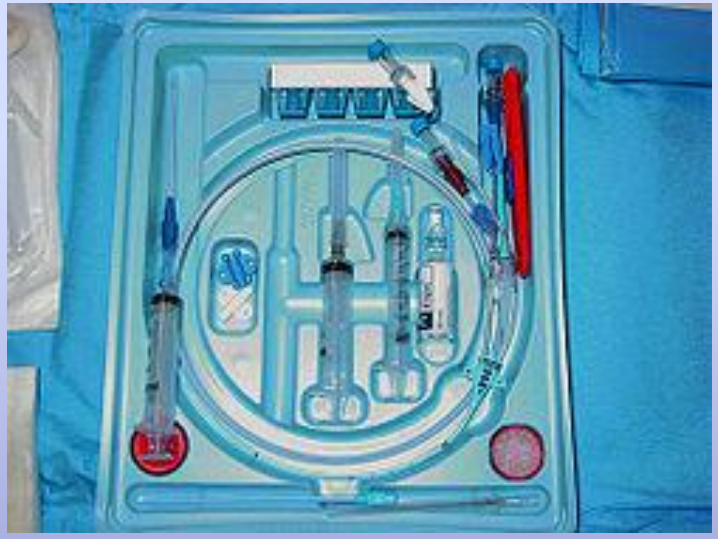
Management

Any patient suspected of having aHUS needs to be transferred to a specialized centre (Nephrology or if necessary Critical Care) where management of acute renal failure and hypertension, the various techniques of dialysis and plasma exchange (PE) are daily practice.

Platelets infusions: contra-indicated,

- ❑ **Might worsen the TMA process**
- ❑ **Unless the patient is bleeding (exceptional)**
- ❑ **When a surgical procedure at risk is performed**

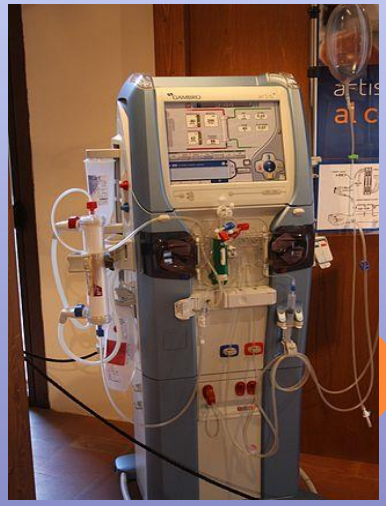




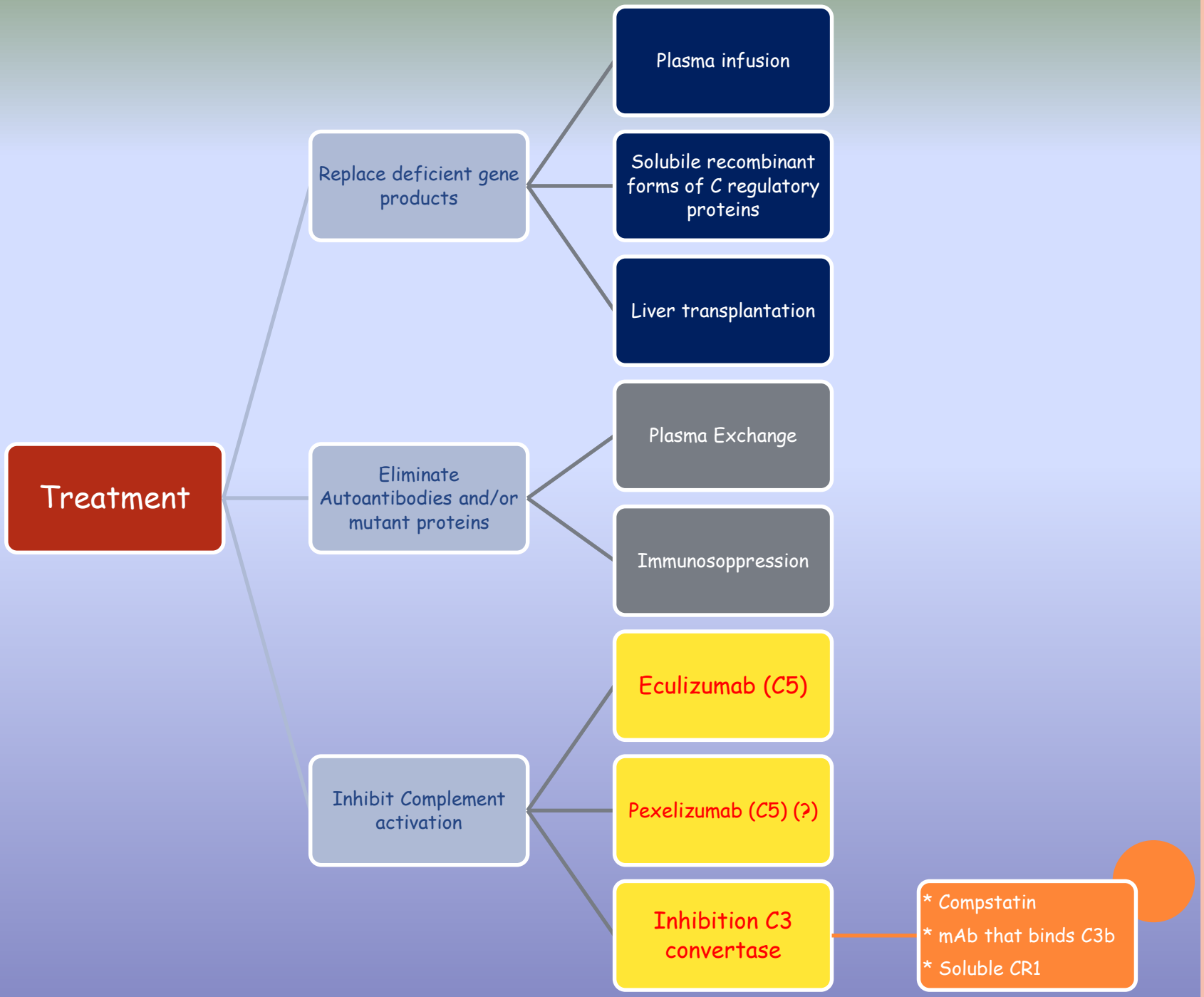
Vascular access

- ❑ Central catheter (dialysis and PE)

HD



Supportive treatment


Treatment
Replace deficient gene products
Plasma infusion
Solubile recombinant forms of C regulatory proteins
Liver transplantation
Eliminate Autoantibodies and/or mutant proteins
Plasma Exchange
Immunosoppression
Inhibit Complement activation
Eculizumab (C5)
Pexelizumab (C5) (?)
Inhibition C3 convertase
* Compstatin
* mAb that binds C3b
* Soluble CR1

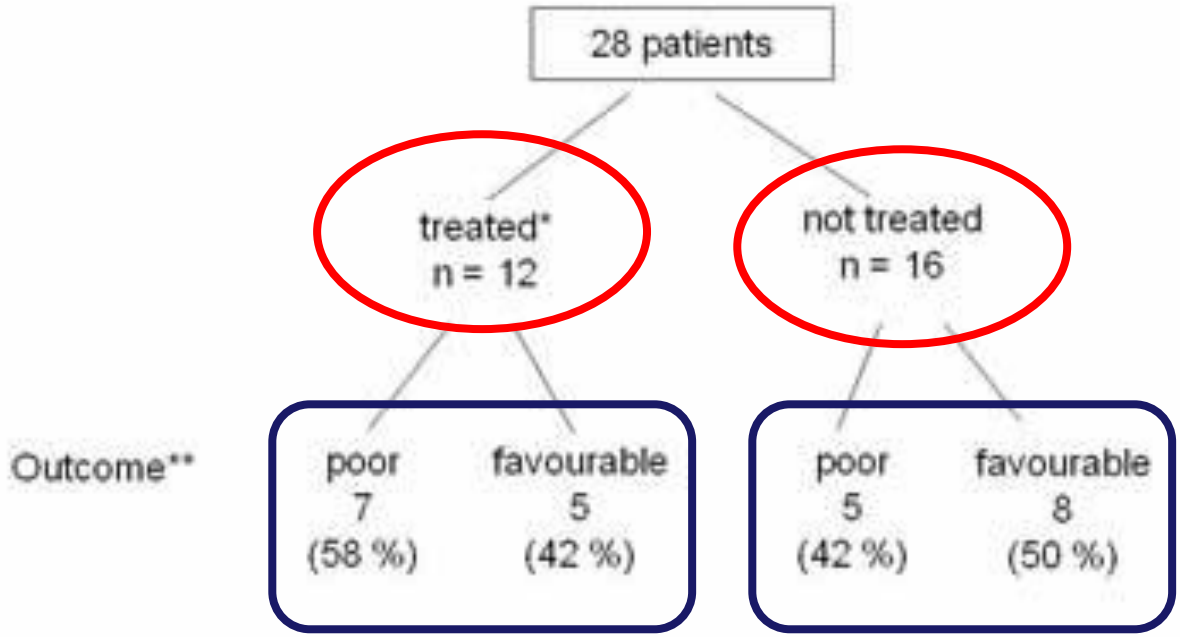
CFH mutation	·63% had a response either complete or partial ·5% Recovery ·37% evolution to death or ESRD
CFI mutation	·25% had a response ·75% progressed to death or ESRF.
MCP/CD46	·Is not a circulating protein ·Questionable
C3, CFB or THBD mutation	·The benefit of plasmatherapy is scarcely documented ·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

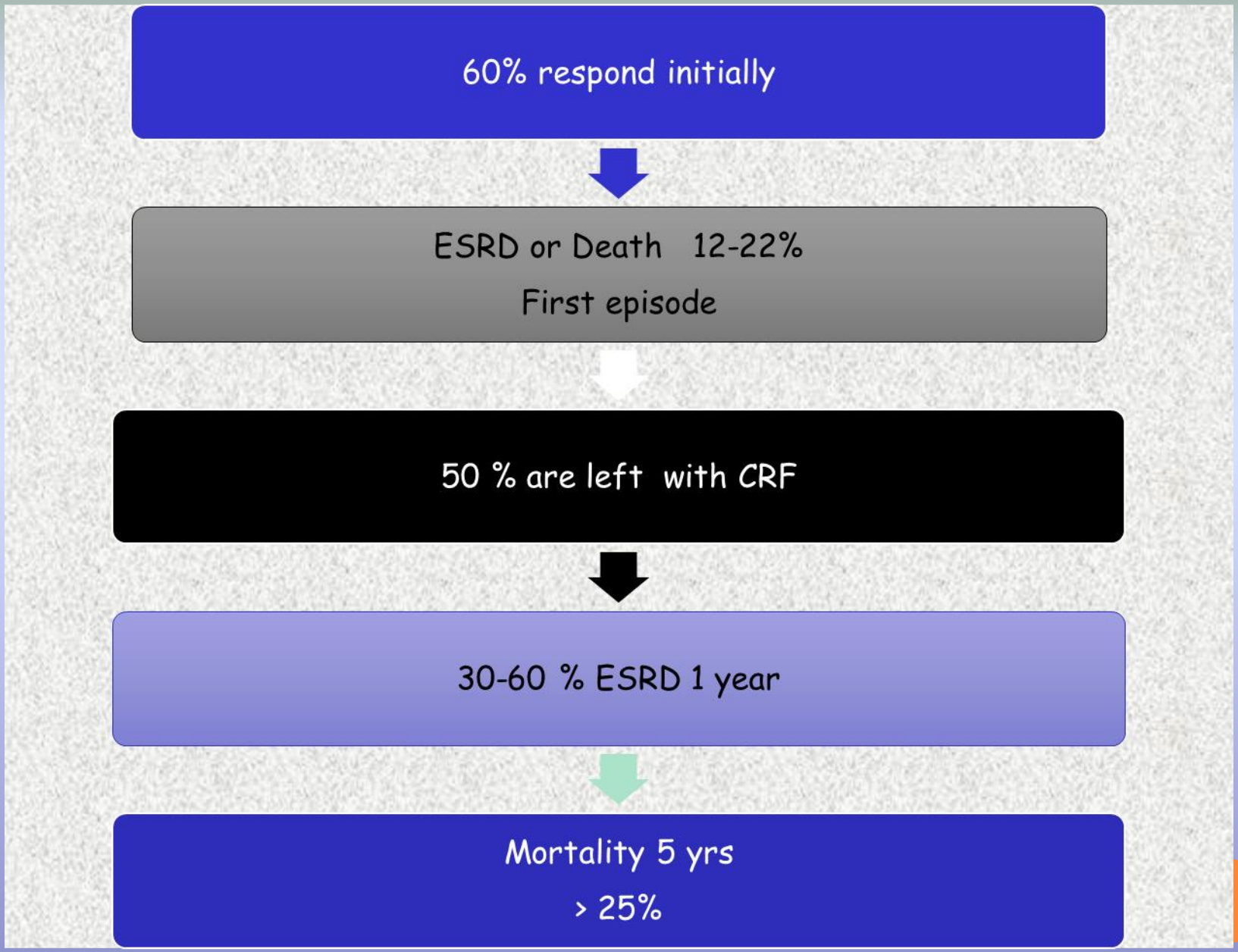
Noris M et al. Clin J Am Soc Nephrol 2010, 5:1844-1859.
Clark W. Semin Dial 2012;25:214-19

PLASMATHERAPY IN UNEXPLAINED HUS

28 patients (French pediatric cohort) without CFH, MCP, CFI, CFB, C3 mutations, and anti-CFH antibodies



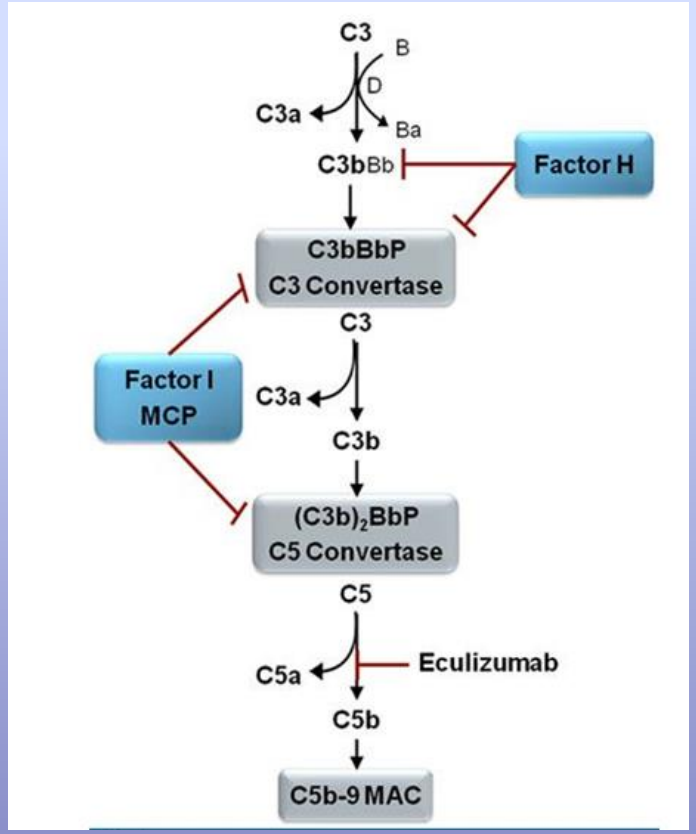
* FFP 10 ml/kg x ≥ 4 d (n = 4)
PE with FFP 30-60 ml/kg x ≥ 4 d (n = 8)
** poor : death, ESRD, CRI ; favourable : no sequelae or mild proteinuria

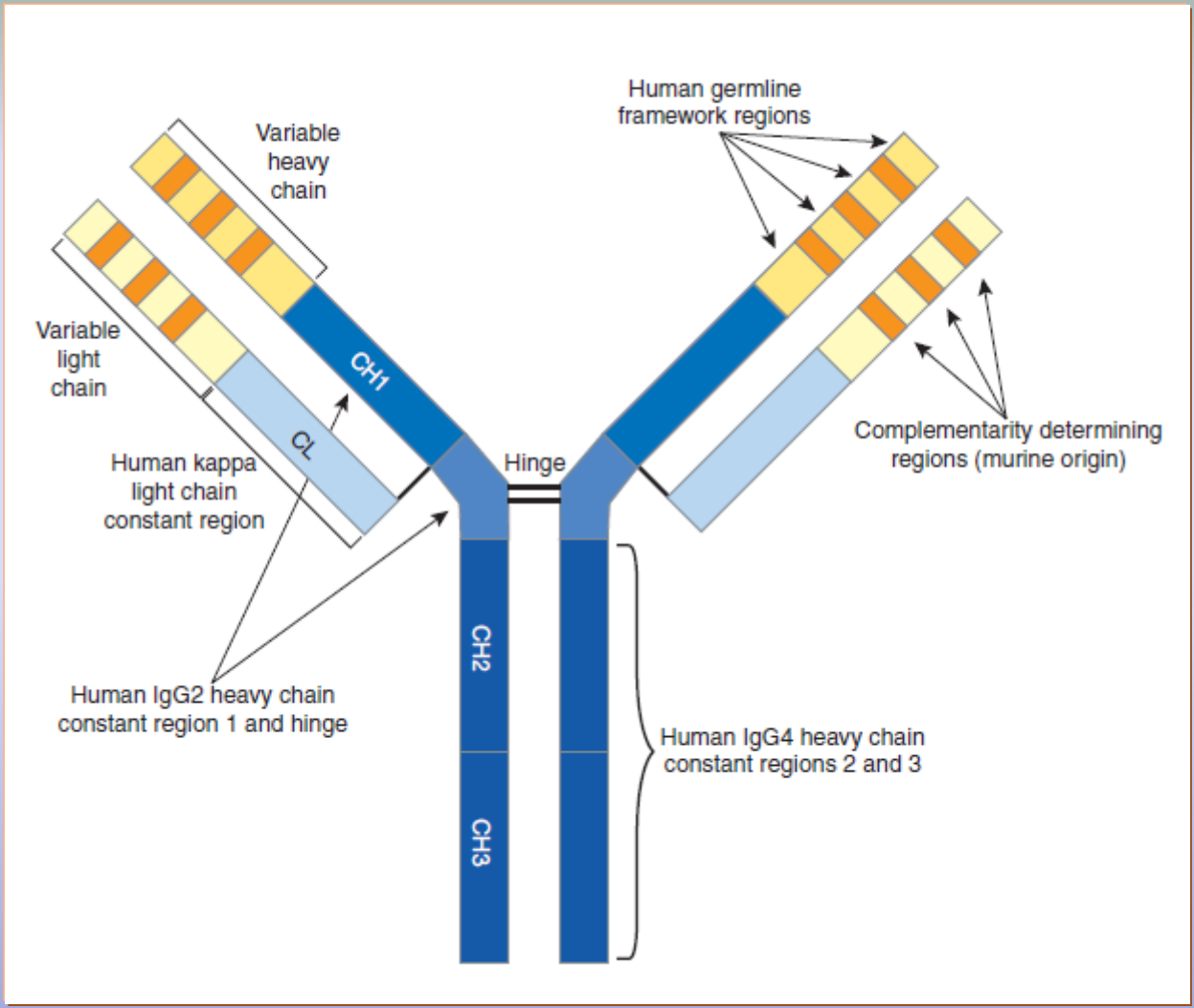


Clark W. Semin Dial 2012;25:214-19

Emerging Therapy

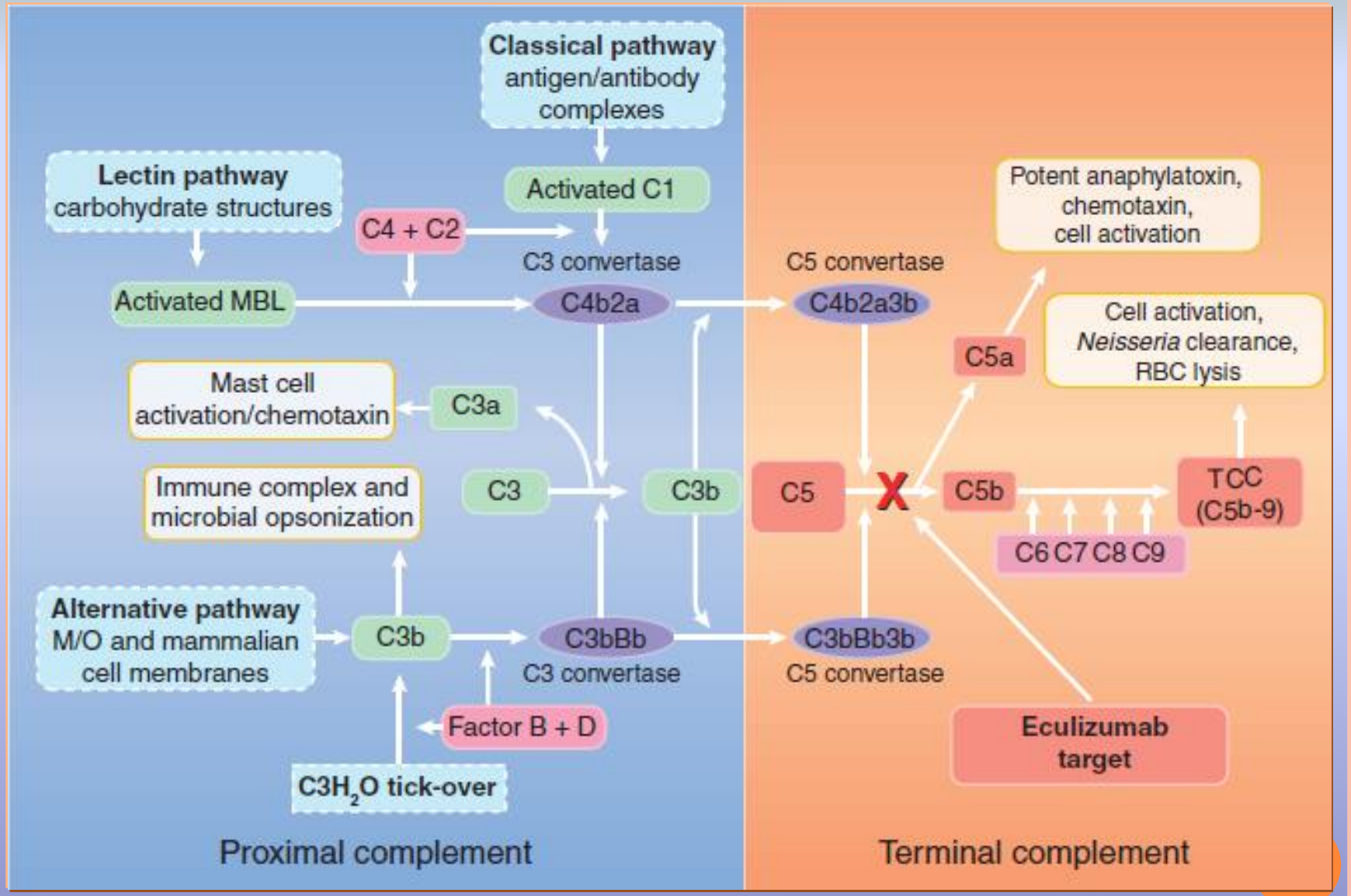
Eculizumab





Murine Myeloma Cells
IgG 2/4 k

Rother R al. Nat Biotechnol. 2007; 25:1256-1264.



Rother R al. Nat Biotechnol. 2007; 25:1256-1264.

Administration schedule
Adult

- 900 mg (intravenous over 30 minutes), weekly for 4 weeks (a total of 4 injections at weekly interval),
- Then 1200 mg for the fifth injection and then every 14 days as maintenance treatment on the long term.

These doses induce eculizumab circulating trough levels > 35 µg/mL that consistently block terminal complement activation.

> 35 µg/mL in PNH and > 50 µg/mL in aHUS

ECULIZUMAB & aHUS

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

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]

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]

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

Trial 1 = 17 pts

Progressing TMA

PLT<150.000/ml)

≥4 PE/PI sessions in the wk before screening

Evidence of hemolysis

Impaired renal function

Trial 2 = 20 pts

No PTL decrease >25% during the 8-wk observation period

≥1 PE/PI sessions every 2 wk, but ≤3 times per wk for ≥8 wk

Evidence of hemolysis

82% normal PLT

88% TMA event-free

Improvement CKD > 1 stage

90% normal PLT

80% TMA event-free

Improvement CKD > 1 stage

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

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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

BMJ Open

A systematic review of eculizumab for atypical haemolytic uraemic syndrome (aHUS)

John Rathbone,[1] Eva Kaltenthaler,[1] Anna Richards,[2] Paul Tappenden,[1] Alice Bessey,[1] Anna Cantrell[1]

2013 Nov 4;3(11):e003573. doi: 10.1136/bmjopen-2013-003573.

1398 citations
1218 excluded
189 articles examinated
176 excluded
3 examinated
2 NEJM
1 retrospective single arm study *

* Simonetti GD et al. Pediatr Nephrol 2011; 26:1663

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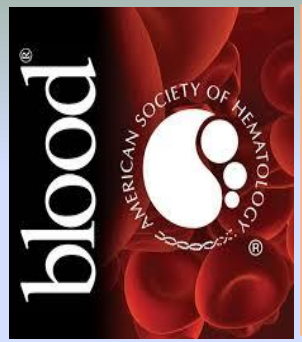
CONCLUSIONS

The results from three, small, uncontrolled studies indicate that eculizumab is clinically effective in patients with aHUS and reduces TMA activity as measured by TMA event-free status, and normalises platelet count in the majority of patients. No severe life-threatening adverse events were associated with treatment. Study extension results suggest the benefits of treatment are sustained. However, due to the study design limitations, inference of treatment effects may be confounded by the lack of a control group.

BMJ Open 2013;3:e003573.doi:10.1136/bmjopen-2013-003573



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

BLOOD, 21 MAY 2015 x VOLUME 125, NUMBER 21

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]

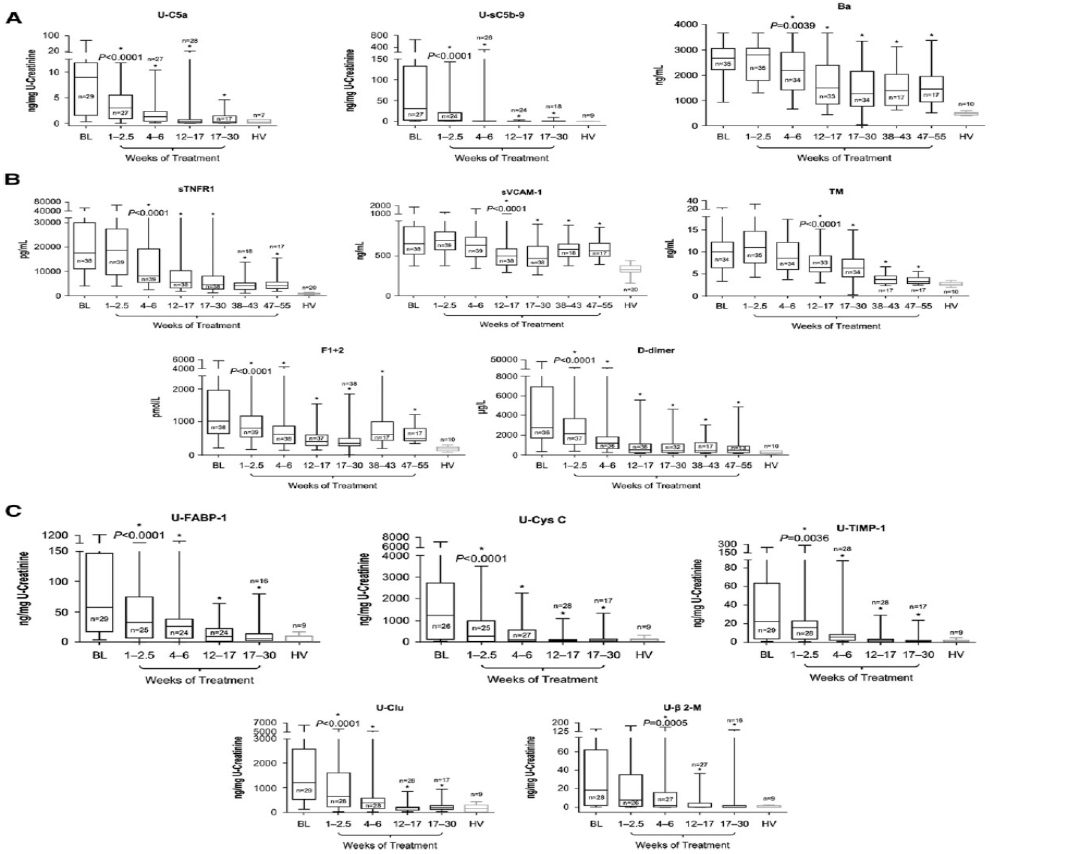
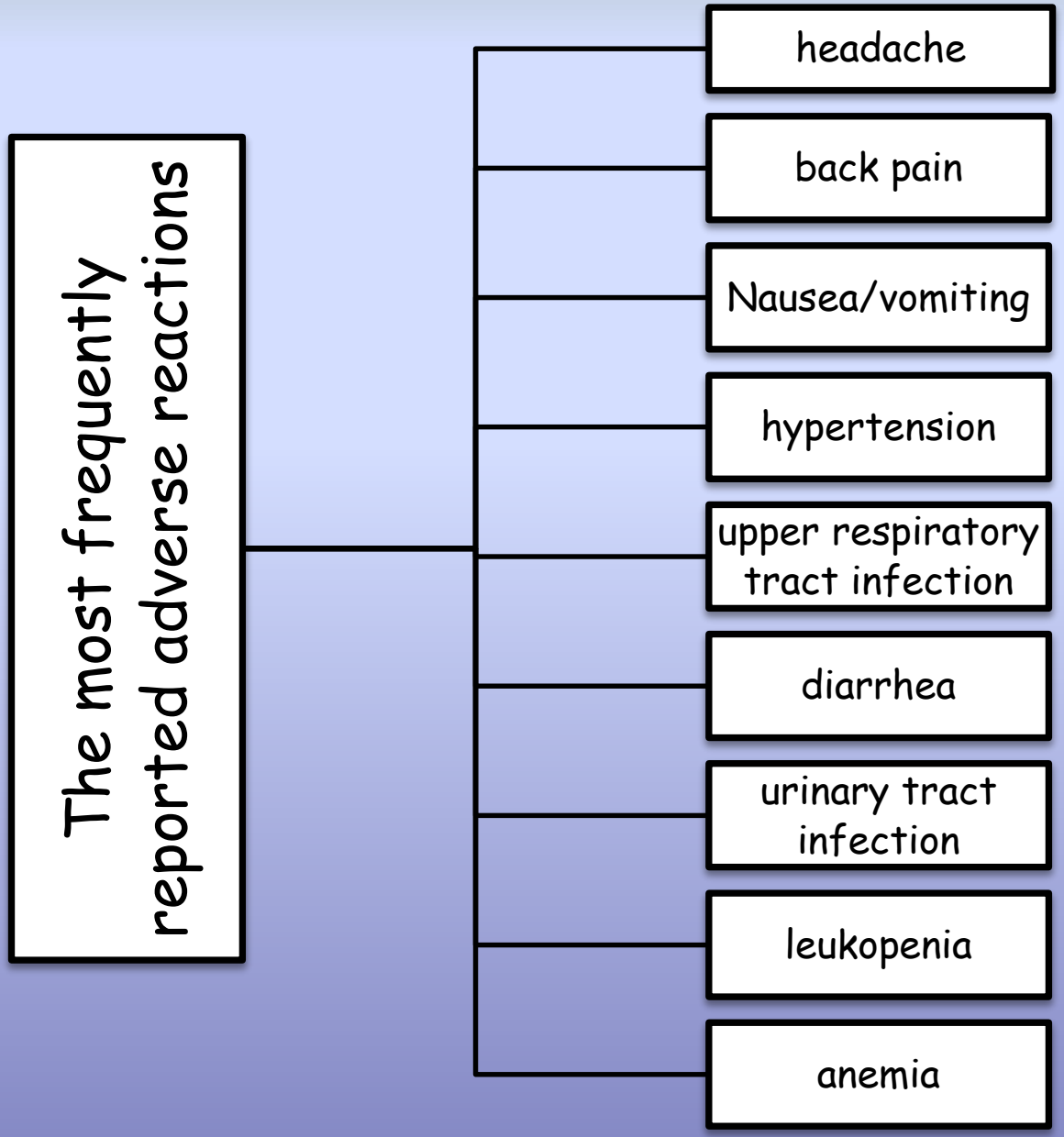


Figure 3. Biomarker levels during terminal complement blockade with eculizumab. Longitudinal decreases in median levels of biomarkers of (A) complement activation, (B) vascular inflammation/damage and coagulation, and (C) renal injury were demonstrated with eculizumab therapy in patients with aHUS compared with HV. Changes in biomarker levels with ongoing eculizumab treatment are displayed using box-whisker graphs showing median, 25th and 75th percentiles, and range. *Levels were significantly reduced compared with baseline; the *P* value of reduction at the first significant time point is shown.

Terminal complement inhibition with eculizumab treatment markedly reduces inflammation and coagulation and decreases endothelial activation and renal damage

Soliris Side Effects



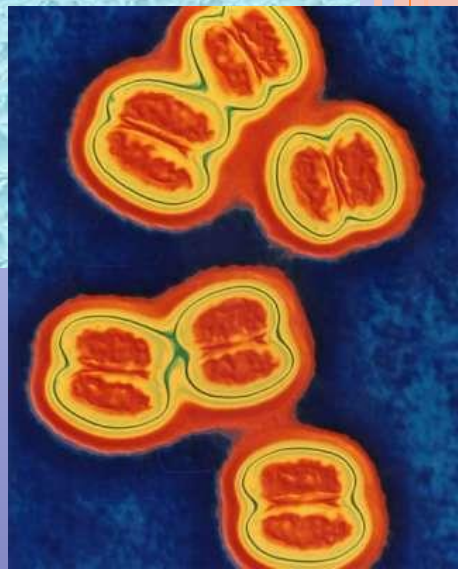
Neisseria meningitis infection

Blockade of the complement terminal pathway induces an increased risk of Neisseria meningitis infection .

Patients must receive vaccination against Neisseria meningitis before being treated with eculizumab .

Permanent antibioprophylaxis

Vaccination : A, C, Y, and W-135 strains → MENVEO
Serogroup B → BEXSERO



Discontinuation of Eculizumab?

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

Ardissino GL et al. AJKD 2014;64:633-7

3* of the 10 patients experienced relapse

Recovery with resumed treatment

*Mutations:
1) CFH; 2)CFH,CHI, THBD
3)CFHR3/R1 – anti CFH

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

5 of the 16 patients experienced relapse

Recovery with resumed treatment

Ardissino GL et al. AJKD 2015;66:172

Discontinuation of Eculizumab Maintenance Treatment for Atypical Hemolytic Uremic Syndrome

Wetzel JF van de Kar NC. AJKD 2015;65:342

1 of the 3 patients experienced relapse
CFH mutation in exons 19 or 20: more prone to recurrence

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] 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]

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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]

[1]Service de Néphrologie et Immunologie clinique; CHRU de Tours; France; [2]Laboratoire d'Immunologie; CHRU de Tours; France; [3]EA 4245; Université François-Rabelais de Tours; France; [4]UMR 7292; Université François-Rabelais de Tours; France; [5]UMR 7292 GICC; CNRS; [6]Laboratoire de Pharmacologie-Toxicologie; CHRU de Tours; France; [7]Service d'Hématologie et Thérapie Cellulaire; CHRU de Tours; France; [8]CHU de Bordeaux; France; Laboratoire d'Immunologie et d'Immunogénétique; France; [9]Université de Bordeaux; UMR 5164 CIRID; France

Clinical Immunology 160 (2015) 237–243

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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]

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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

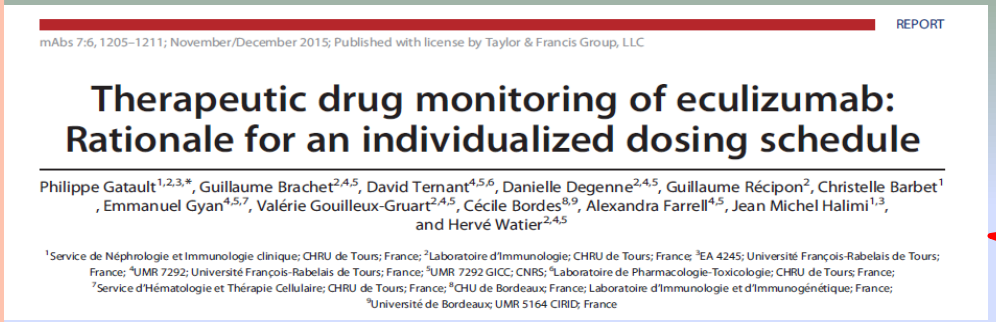
Dynamics of complement activation in aHUS and how to monitor eculizumab therapy

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]

Blood. 2014;124(11):1715-1726

"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".

- 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.



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Eculizumab concentrations > 50 µg/ml

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.

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18 pts CP –AP-MBL activity: ⇩ 3 week

9 pts CP -AP activity: ⇩ 3-4 week

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

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

COMPL 300[1] / COMPL 300 RUO[2]	ELISA kit for total functional assessment of the Complement System	96 wells break-apart
COMPL CP310[1] / COMPL CP310 RUO[2]	ELISA kit for total functional assessment of the Classical Pathway	96 wells break-apart
COMPL MP320[1] / COMPL MP320 RUO[2]	ELISA kit for total functional assessment of the Lectin Pathway (MBL)	96 wells break-apart
COMPL AP330[1] / COMPL AP330 RUO[2]	ELISA kit for total functional assessment of the Alternative Pathway	96 wells break-apart
COMPL F3 RUO[2]	ELISA kit for total functional assessment of the Lectin Pathway (Ficolin-3)	96 wells break-apart

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Genetic Variants in C5 and Poor Response to Eculizumab

N Engl J Med 2014;370:632-9.
DOI: 10.1056/NEJMoa1311084

345 Japanese pts with PNH
11 poor response
Single missense C5 eterozygous mutation.

Refractory to Eculizumab

15 %

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

Renal transplantation in aHUS
indications, risks and new issues

- The risk of post-transplant recurrence of aHUS is according to complement abnormality
- The overall risk of aHUS recurrence is 50%
- The risk of graft loss 80-90% in patients with recurrence

	Risk of recurrence %
CFH mutation	75-90
CFI mutation	45-80
C3 mutation	40-70
CFB mutations THBD mutation	100 but only 3 pts
MCP mutation	15-20
Anti-CFH antibodies	If high titer

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

New time with eculizumab?

15 reported cases for the treatment of recurrence of aHUS in renal allografts

10 cases in pre-emptive

Wong E K S et al. Mol Immunol.2013; 56(3): 199–212.

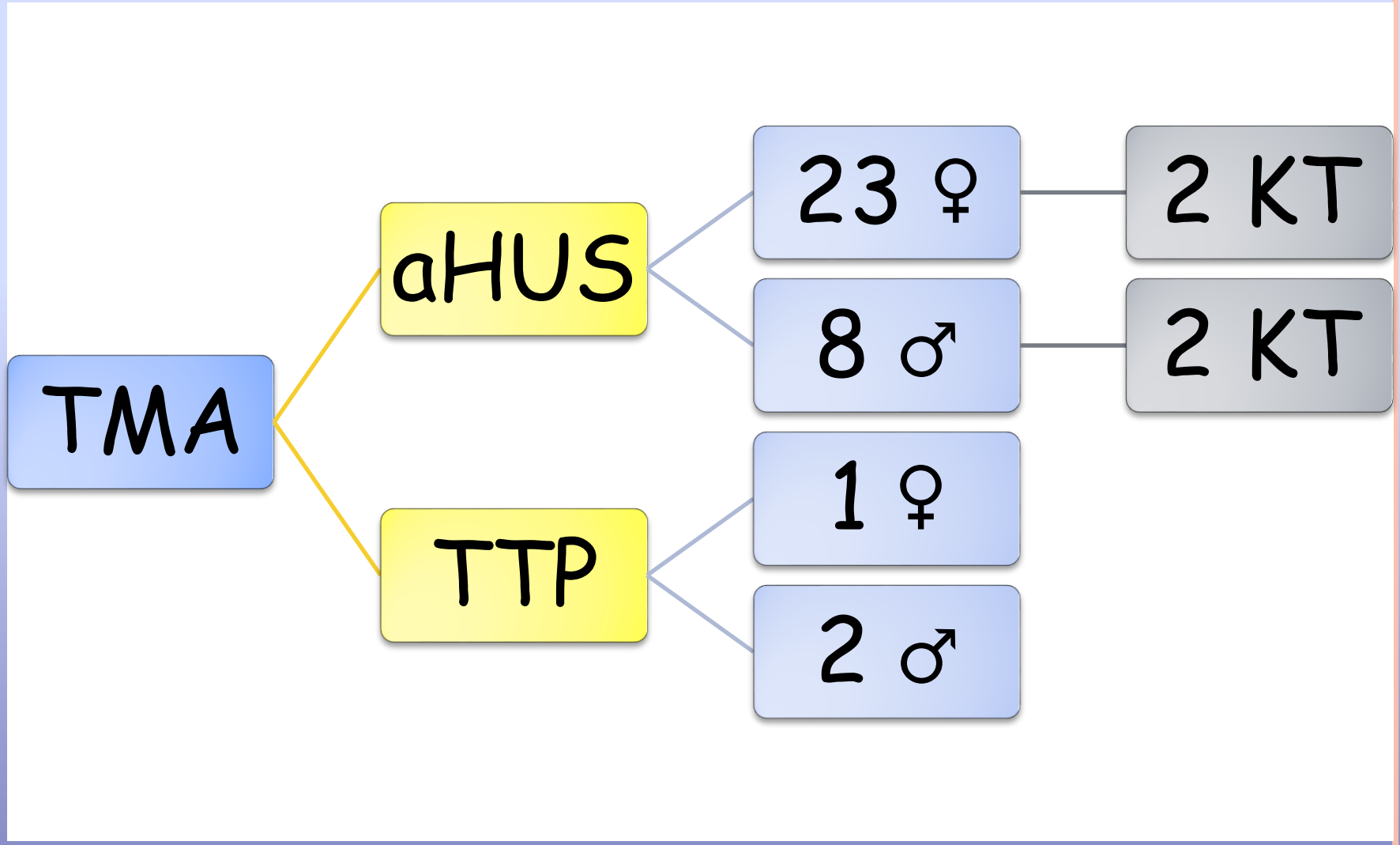
Living-related kidney donation is not recommended

- Contraindicated for patients with CFH, CFI, CFB, C3 or THBD mutation
- Questionable for patients with unexplained aHUS
- Debatable for patients with MCP mutation.

- The risk for the donor to develop HUS after kidney donation has to be taken into account.

Loirat C. Pediatr Transpl 2008

Eculizumab & aHUS: l'esperienza di Careggi

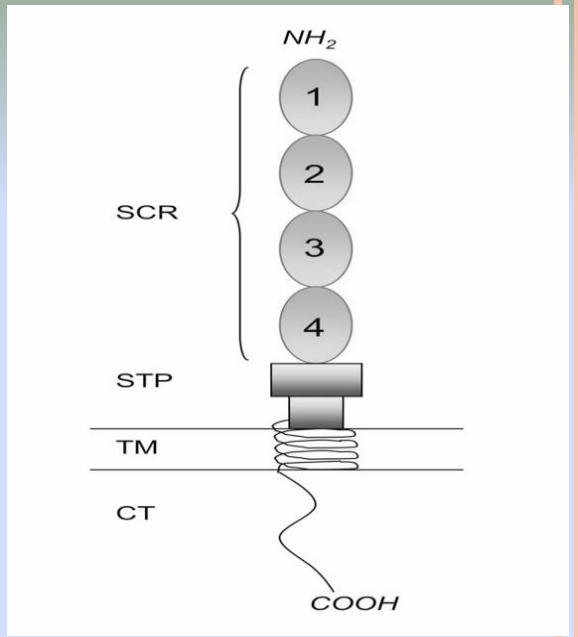


Eculizumab & aHUS: l'esperienza di Careggi

Dal 2011:

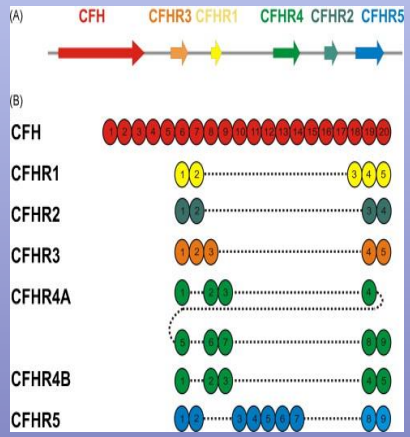
9 pazienti trattati con Eculizumab (5 ♀; 4 ♂)

- 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

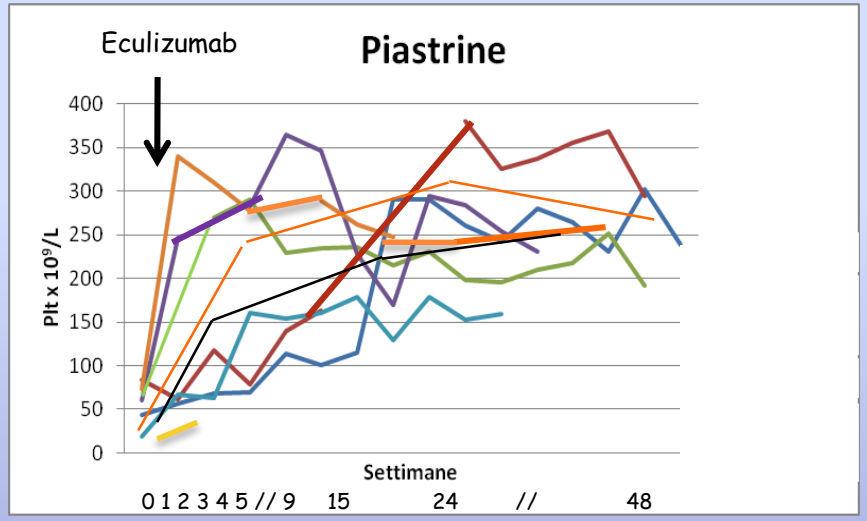


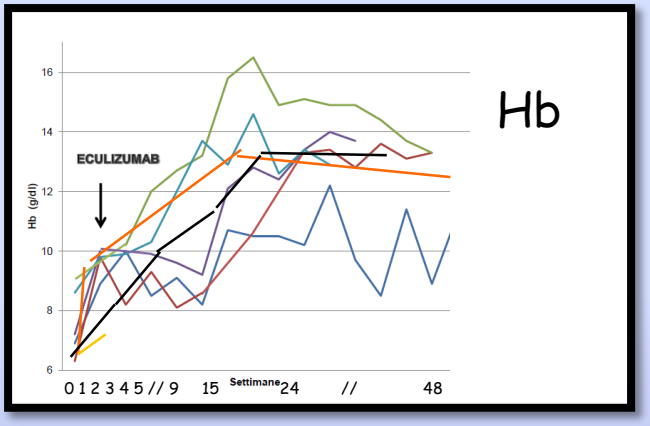
Genetica

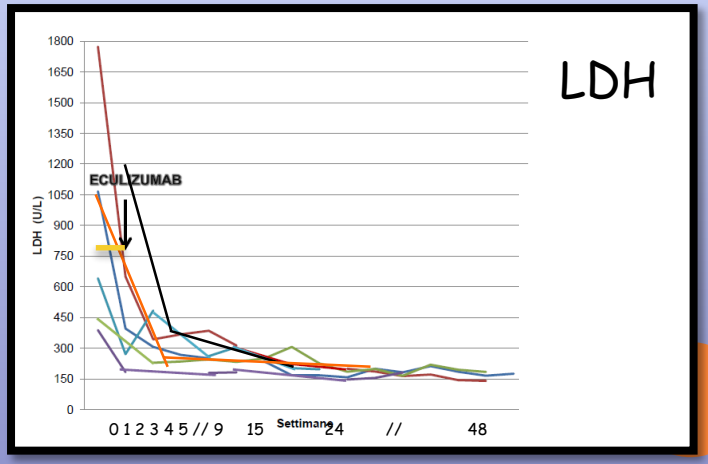
- 4 pazienti neg
- 1 pz con mutazione CFH
- 1 pz con mutazione MCP
- 1 pz con delezione in eterozigosi di CFHR3-CFHR1
- 1 pz con una mutazione in eterozigosi di MCP + delezione in eterozigosi di CFHR3-CFHR1
- 1 pz con genetica in corso



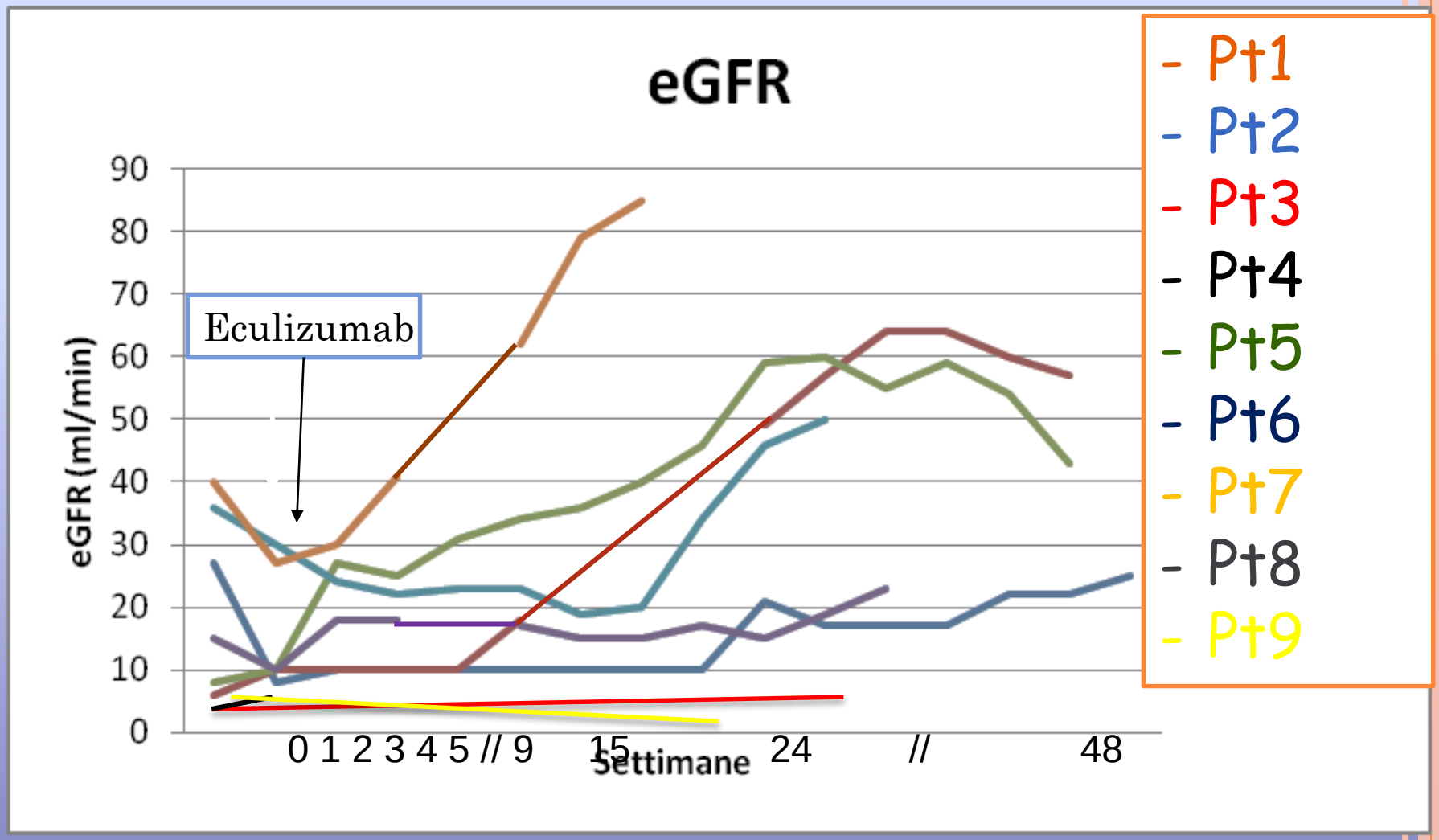
Eculizumab & aHUS: l'esperienza di Careggi







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


eGFR
eGFR (ml/min)
90
80
70
60
50
40
30
20
10
0
Eculizumab
0 1 2 3 4 5 // 9 15 24 // 48
Settimane
- Pt1
- Pt2
- Pt3
- Pt4
- Pt5
- Pt6
- Pt7
- Pt8
- Pt9

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

Grazie per la Vostra attenzione

FINE

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