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JOURNAL OF
THE AMERICAN
SOCIETY OF
HEMATOLOGY

VOLUME 108

NUMBER 11

16 NOVEMBER 2006

PART 1 OF 2 PARTS

American Society of
Hematology

ty-eighth annual meeting
program and abstracts

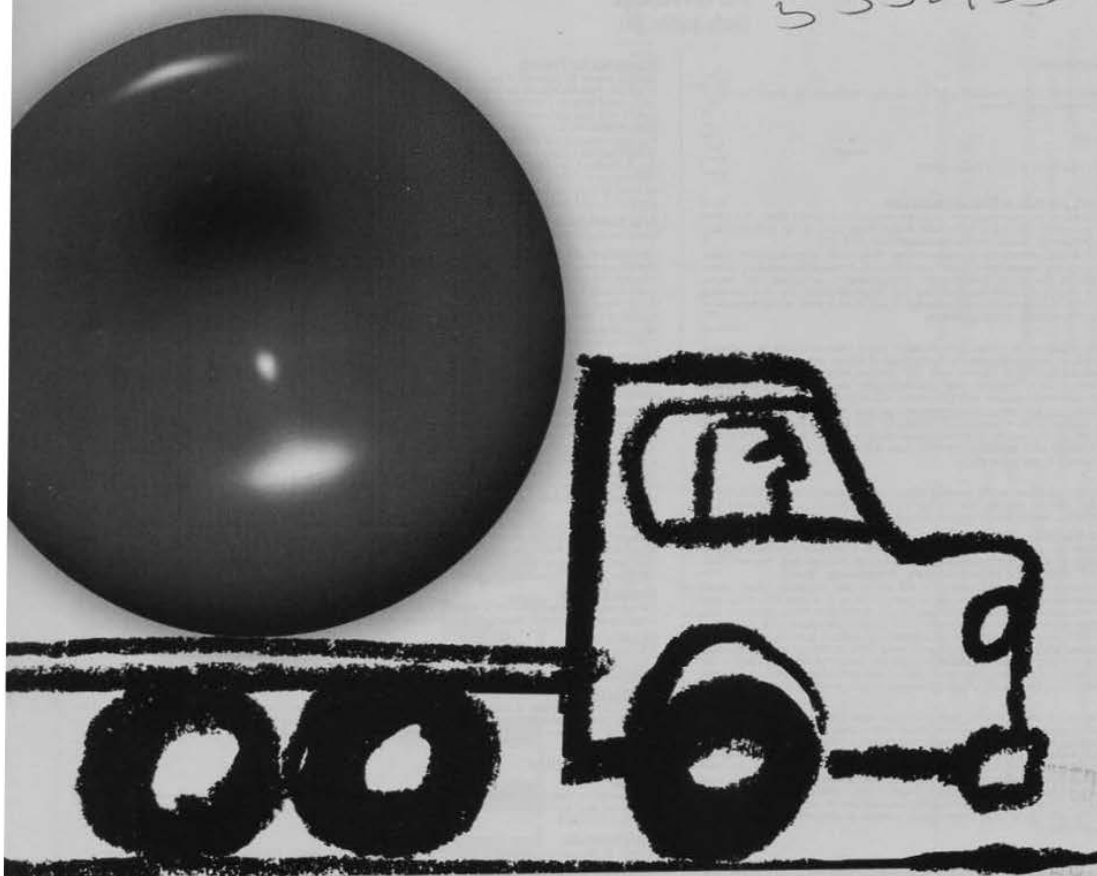
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Postmaster: Send change-of-address information to *Blood, Journal of the American Society of Hematology*, Subscription Office, 1900 M Street, NW, Suite 200, Washington, DC 20036.

Canadian regulations: Publications Mail Agreement No: 40038947. Return undeliverable Canadian addresses to: Circulation Dept. or DPGM, 4960-2 Walker Road, Windsor, ON N9A 6J3.

Manuscript submissions

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US institution, print and online: \$1,145
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International institution, online only: \$1,085

US individual: \$630
International individual: \$875*

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Price for single/back issues: \$48 (US)/\$58 (international). Single issues, both current and back, exist in limited quantities and are offered for sale subject to availability.

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Internet

Blood Home Page: www.bloodjournal.org.

ASH Home Page: www.hematology.org.

Manuscript Submission: submit.bloodjournal.org.

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Indexing & abstracting

Blood is indexed and abstracted by Index Medicus, Excerpta Medica, Current Contents/Life Sciences, Current Contents/Clinical Medicine, Science Citation Index, SCISEARCH, Automatic Subject Citation Alert, ISI/BIOMED, and BIOSIS.

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American Flamingos, Walt Disney's Animal Kingdom. Photo courtesy of Joel Sartore Getty Images.

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Results: In 2004, 479 (4.5%) of a total of 10,575 units of O-RBC were transfused due to the policy. In 2005, 689 (6.1%) of a total of 11,293 units of O-RBC were transfused due to the policy. Increase in the use of O-RBC from 2004 to 2005 was by 718 units (6.7%), while the increase in the use of group O-RBC for the policy increased disproportionately by 210 units (43.8%). Over the 2 year period, a monthly median excess of 43 units (range 24-85) of O-RBC were issued in accordance with the policy. Daily excess use of O-RBC for the policy was a median of 1 unit (range 0-19). There were 291 days when no policy-related O-RBC were used, and only 3 days when more than 10 units were used. The interval between a 1st and 2nd (confirmatory) typing, when achieved, occurred within 24 hours for 15.4% of patients, but was a median of 23 days, and ranged from minutes to 21.5 years. Confirmatory re-typing activity within less than 72h of the 1st occurred in a minority of 28%, possibly reflecting nonessential repetition and/or deliberate action to release patients from policy-related O-RBC restrictions. Patients who were protracted users of Group O policy blood (no confirmatory type and/or repeatedly indeterminate typing) were neonates (310 units [26.5%]) and recipients of ABO-incompatible hematopoietic stem cell transplants (76 units [6.5%]). The blood bank identified misdrawn blood through typing discrepancies in 6 patients over 2 years. Transfusion occurred uneventfully in 3 of these 6, as the misdraw was made apparent by comparison with prior typings on file in 2, and patient knowledge of correct type in 1. The misdrawn specimen was the 1st one in 2 of 6. Of the 3 who were not transfused, the misdraw suggested a type that would have led in all to the transfusion of clinically incompatible blood, had the knowledge of prior type, and the policy, both been absent. ABO-incompatible red cell transfusion errors did not occur, although this was a greater function of luck than the policy in the interval.

Conclusions: A policy instituted to prevent ABO-incompatible transfusion errors, by providing O-RBC to those with unconfirmed blood types, appeared to be both feasible, and potentially mistransfusion-preventative, at a high-volume tertiary-care teaching hospital.

Disclosure: No relevant conflicts of interest to declare.

Bone Marrow Failure

Abstract# 971

Poster Board #-Session: 99-I

Safety and Efficacy of the Terminal Complement Inhibitor Eculizumab in Patients with Paroxysmal Nocturnal Hemoglobinuria: Interim Shepherd Phase III Clinical Study. Neal S. Young,¹ Elisabetta Antonioli*,² Bruno Rotoli,³ Hubert Schrezenmeier*,⁴ Jörg Schubert*,⁵ Alvaro Urbano-Ispizua*,⁶ Luke Coyle,⁷ Carlos de Castro,⁸ Chieh-Lin Fu,⁹ Jaroslaw P. Maciejewski,¹⁰ Christopher F. Mojcik*,¹¹ Russell P. Rother*,¹¹ Peter Hillmen.¹² ¹NHLBI, NIH, Bethesda, MD, USA; ²Azienda Ospedaliera Univ. Careggi, Firenze, Italy; ³Università degli Studi di Napoli, Naples, Italy; ⁴Institut für Klinische Transfusionsmedizin und Immunogenetik, Helmholtzstr., Germany; ⁵Saarland Univ. Med. School, Homburg/Saar, Germany; ⁶Hospital Clinic i Provincial, Barcelona, Spain; ⁷Royal North Shore Hospital, St Leonards, Australia; ⁸Duke Univ. Medical Center, Durham, NC, USA; ⁹Cleveland Clinic Florida, Weston, FL, USA; ¹⁰The Cleveland Clinic Foundation, Cleveland, OH, USA; ¹¹Alexion Pharmaceuticals, Inc, Cheshire, CT, USA; ¹²Haematology, Leeds General Infirmary, Leeds, United Kingdom.

In paroxysmal nocturnal hemoglobinuria (PNH), lack of the GPI-anchored terminal complement inhibitor CD59 from blood cells renders erythrocytes susceptible to chronic hemolysis resulting in anemia, fatigue, thrombosis, poor quality of life (QoL), and a dependency on transfusions. Eculizumab, a terminal complement inhibitor, reduced intravascular hemolysis and transfusion requirements in transfusion dependent patients with normal or near-normal platelet counts in a randomized placebo-controlled trial (TRIUMPH). SHEPHERD, an open-label, non-placebo controlled 52-week phase III clinical study, is underway to evaluate the safety and efficacy of eculizumab in a broader PNH population including patients with significant thrombocytopenia and/or lower transfusion requirements. Eculizumab was dosed as follows: 600 mg IV every 7 days x 4; 900 mg 7 days later; and then 900 mg every 14±2 days. Eculizumab was administered to 97 patients at 33 international sites. In a pre-specified 6-month interim analysis, the most frequent adverse events were headache (50%), nasopharyngitis (23%), and nausea (16%); most were mild to moderate in severity. No infections or serious adverse events were reported as "probably" or "definitely" related to drug. Intravascular hemolysis, the central clinical manifestation in PNH and the primary surrogate efficacy endpoint of the trial, was significantly reduced in eculizumab patients as assessed by change in lactate dehydrogenase (LDH) area under the curve ($p < 0.001$). LDH levels decreased from a median of 2,051 U/L at baseline to 270 U/L at 26 weeks ($p < 0.001$; normal range 103-223 U/L). Control of intravascular hemolysis resulted in an improvement in anemia as transfusion requirements decreased from a median of 4.0 PRBC units/patient pre-treatment to 0.0 during treatment ($p < 0.001$), approximately 50% of the patients were rendered transfusion independent ($p < 0.001$), and hemoglobin levels increased ($p < 0.001$). Fatigue, as measured by both the FACIT-Fatigue and EORTC QLQ-C30 instruments, was significantly improved with eculizumab treatment as compared to baseline ($p < 0.001$ for each). Other EORTC-QLQ-C30 patient reported outcomes demonstrating improvement included global health status ($p < 0.001$), all 5 patient functioning subscales ($p < 0.001$) and 7 of 9 symptom/single item subscales ($p \leq 0.03$). These results demonstrate that the beneficial effects of eculizumab in PNH are applicable to a much broader patient population than previously studied and further underscore that eculizumab treatment markedly reduces intravascular hemolysis, thereby providing clinical benefit to treated patients. The trial will complete in September 2006 and the final results from this 52-week study will be presented.

Disclosure: There is no label for eculizumab as it is an investigational drug.; Drs Mojcik and Rother are employees of Alexion Pharmaceuticals, Inc.; Drs Hillmen, Schubert and Maciejewski have served as consultants for Alexion Pharmaceuticals, Inc.; Drs Mojcik and Rother have equity ownership in Alexion Pharmaceuticals, Inc.; Dr Hillmen has received grant support from Alexion Pharmaceuticals, Inc. Dr Young reports that Alexion made an unrestricted donation to the NHLBI in support of this research.; Drs Hillmen and Schubert have received lecture fees from Alexion Pharmaceuticals, Inc.; Drs Rotoli, Schubert, Urbano, Fu and Maciejewski have served on Advisory Committees for Alexion Pharmaceuticals, Inc.

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Poster Board #-Session: 100-I

Blockade of Intravascular Hemolysis in PNH with the Terminal Complement Inhibitor Eculizumab Unmasks Low-Level Hemolysis Potentially Occurring through C3 Opsonization. Anita Hill*,¹ Russell P. Rother*,² Antonio M. Risitano,³ Duncan S. Cole*,⁴ Matthew J. Cullen*,¹ Stephen J. Richards,⁵ Carmine Selleri,¹ Patrizia Ricci*,³ Bruno Rotoli,³ Lucio Luzzatto,³ Peter Hillmen.¹ ¹Department of Haematology, Leeds General Infirmary, Leeds, United Kingdom; ²Dept of Research, Alexion Pharmaceuticals, Inc, Cheshire, CT, USA; ³Division of Hematology, Federico II University of Naples, Naples, Italy; ⁴Dept Medical Biochemistry and Immunology, University Hospital of Wales, Cardiff, United Kingdom.

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired hemolytic anemia characterized by intravascular hemolysis, often resulting in the need for red blood cell (RBC) transfusions. PNH RBCs lack two complement regulatory molecules – CD59, a terminal complement inhibitor, and CD55, a C3 convertase inhibitor. Eculizumab, a humanized monoclonal antibody that inhibits terminal complement by binding to C5, effectively controls intravascular hemolysis as determined by a dramatic reduction in lactate dehydrogenase (LDH) to levels in or just above the normal range. Control of intravascular hemolysis in these patients led to a reduction in, or cessation of, RBC transfusions. During eculizumab treatment, a majority of patients demonstrate evidence of residual, low-level hemolysis; LDH levels remain slightly elevated, haptoglobin levels are low or undetectable, and bilirubin levels are above normal. We hypothesized that this low-level residual hemolysis may be due to clearance of PNH RBCs through a C3b-mediated mechanism. Therefore we investigated C3 deposition on RBC in PNH patients before and on eculizumab. A direct antiglobulin test (DAT) using monoclonal anti-C3d was positive in 29 out of 39 PNH patients on eculizumab. Of these 29 DAT-positive patients, who were all receiving transfusions, 25 had DAT testing prior to eculizumab therapy and only one of these was positive. DAT was negative in all of 8 normal volunteers. By two-color flow cytometric analysis with anti-CD59 and anti-C3, the majority of patients on eculizumab demonstrated three distinct RBC populations: (i) CD59+/C3- (normal RBCs); (ii) CD59-/C3- (PNH RBCs without C3 coating); and (iii) CD59-/C3+ (PNH RBCs coated by C3). No CD59-/C3+ RBCs were observed. Of 21 DAT positive eculizumab treated patients tested, the median proportion of total RBCs that were C3b positive was 17.6%. 18 of 29 [62%] eculizumab patients with a positive DAT received at least one transfusion during eculizumab therapy compared with 1 of 10 [10%] for DAT negative patients ($p = 0.01$), although even patients who did not become transfusion independent during eculizumab treatment showed a marked reduction in transfusion requirement. The median hemoglobin value for the 29 DAT positive eculizumab patients was 9.8 g/dL compared with 11.3 g/dL in the 10 DAT negative eculizumab patients ($p = 0.08$). No apparent relationship between LDH and DAT positivity was observed. It is proposed that resolution of intravascular hemolysis in PNH patients on eculizumab results in deposition of C3b on the surface of PNH RBCs which may explain, at least in part, the residual low level hemolysis occurring in some patients. This appears to be a previously undescribed mechanism of RBC clearance in PNH, most likely obscured by the rapidity of intravascular hemolysis in the absence of eculizumab therapy. Despite the low-level residual hemolysis, patients continue to receive significant benefit from eculizumab treatment.

Disclosure: RPR is an employee of Alexion Pharmaceuticals, Inc.; PH and SJR serve as consultants to Alexion Pharmaceuticals, Inc.; RPR has equity ownership in Alexion Pharmaceuticals, Inc.; PH receives grant support from Alexion Pharmaceuticals, Inc.; AH, SJR, LL and PH receive lecture fees from Alexion Pharmaceuticals, Inc.; AH, BR and LL have served on an Advisory Committee for Alexion Pharmaceuticals, Inc.

Abstract# 973

Poster Board #-Session: 101-I

Paroxysmal Nocturnal Hemoglobinuria (PNH): Long-Term Epidemiological Study. Régis Peffault de Latour*,¹ Jean Y. Mary*,² Celia Salanoubat*,³ Louis Terriou*,⁴ Gabriel Etienne*,⁵ Mohamad Mohty*,⁶ Sophie Roth*,⁷ Sophie de Guibert*,⁸ Jean Y. Cahn*,⁹ Gerard Socie*,¹ (Intr. by Gerard Socie) ¹Hematologie-Greffe, Hôpital Saint Louis, Paris, France; ²Unité INSERM U717, Hôpital Saint Louis, Paris, France; ³Service d'Hématologie Clinique, Hôpital Hotel Dieu, Paris, France; ⁴Service des Maladies du Sang, Hôpital Claude Huriez, Lille, France; ⁵Service de Médecine Interne, Groupe Hospitalier Sud, Bordeaux, France; ⁶Unité de Transplantation et de Thérapie Cellulaire, Institut Paoli Calmettes, Marseille, France; ⁷Service de Médecine Interne, Hôpital Archet, Nice, France; ⁸Service d'Hématologie Clinique, Centre Hospitalier Pontchaillou, Rennes, France; ⁹Service d'Onco-Hématologie, Hôpital Michallon, Grenoble, France.

PNH is a rare acquired disorder. We aimed to analyze a large cohort of patients on the long term to better determine prognostic factors. We already reported the analysis on 220 patients in 1996 (Socie *et al*, Lancet). Data were updated and we collected additional data on 247 patients (total of 467 patients, 252 female), diagnosed from 1950 to 2005 from 58 centers. The date of diagnosis was based on flow cytometry analysis if there was no prior positive Ham's test. The age at diagnosis was 34 years (± 17.3). The median follow-up time was 6.8 years (± 0.5). Kaplan-Meier 10-year survival estimate was 76.3% (± 2.6). Sixty seven (14.6%) patients developed pancytopenia during follow-up [10-year cumulative incidence