Outcome of Renal Transplantation in Patients with Non–Shiga Toxin–Associated Hemolytic Uremic Syndrome: Prognostic Significance of Genetic Background

Elena Bresin,* Erica Daina,* Marina Noris,* Federica Castelletti,* Rumen Stefanov,† Prudence Hill,‡ Timothy H.J. Goodship,§ and Giuseppe Remuzzi,* for the International Registry of Recurrent and Familial HUS/TTP

*Mario Negri Institute for Pharmacological Research, Clinical Research Center for Rare Diseases Aldo e Cele Daccò, Rancia, Bergamo, Italy; †Department of Social Medicine and Health Management, Medical University of Plovdiv, Plovdiv, Bulgaria; ‡Department of Anatomical Pathology, St. Vincent’s Hospital, Victoria, Australia; and §Institute of Human Genetics and Department of Nephrology, University of Newcastle upon Tyne, Newcastle, United Kingdom

More than 50% of patients with non–Shiga toxin–associated hemolytic uremic syndrome (non–Stx-HUS) progress to ESRD. Kidney transplant failure for disease recurrence is common; hence, whether renal transplantation is appropriate in this clinical setting remains a debated issue. The aim of this study was to identify possible prognostic factors for renal transplant outcome by focusing on specific genetic abnormalities associated with the disease. All articles in literature that describe renal transplant outcome in patients with ESRD secondary to non–Stx-HUS, genotyped for CFH, MCP, and IF mutations, were reviewed, and data of patients who were referred to the International Registry of Recurrent and Familial HUS/TTP and data from the Newcastle cohort were examined. This study confirmed that the overall outcome of kidney transplantation in patients with non–Stx-HUS is poor, with disease recurring in 60% of patients, 91.6% of whom developed graft failure. No clinical prognostic factor that could identify patients who were at high risk for graft failure was found. The presence of a factor H (CFH) mutation was associated with a high incidence of graft failure (77.8 versus 54.9% in patients without CFH mutation). Similar results were seen in patients with a factor I (IF) mutation. In contrast, graft outcome was favorable in all patients who carried a membrane co-factor protein (MCP) mutation. Patients with non–Stx-HUS should undergo genotyping before renal transplantation to help predict the risk for graft failure. It is debatable whether a kidney transplant should be recommended for patients with CFH or IF mutation. Reasonably, patients with an MCP mutation can undergo a kidney transplant without risk for recurrence.


Hemolytic uremic syndrome (HUS) is a rare disease with manifestations of microangiopathic hemolytic anemia, thrombocytopenia, and renal impairment. In most cases, HUS is triggered by Shiga-like toxin (Stx)-producing Escherichia coli (1) and manifests with watery or bloody diarrhea (D+ HUS). Acute renal failure occurs in 55 to 70% of cases, but renal function recovers in up to 70% in various series (1,2).

Forms of HUS not caused by Stx-producing E. coli are more rare and may be familial (i.e., more than one family member is affected by the disease, and exposure to Stx-E. coli is excluded) or may occur sporadically in a patient with no familial history. The latter may be associated with pregnancy, systemic diseases (e.g., scleroderma, lupus, antiphospholipid syndrome), or HIV infection (3) or may be triggered by certain drugs (e.g., antineoplastic, antplatelet, immunosuppressive) (4). However, in approximately half of cases, no triggering condition is found (idiopathic forms) (5,6). The clinical outcome is unfavorable, with up to 50% of patients progressing to ESRD and 25% dying during the acute phase of the disease (7). Mutations in genes encoding complement regulatory proteins have been reported both in familial and in nonfamilial cases, mainly in idiopathic forms (5,6) but also in cases of pregnancy-associated (5) and postpartum HUS (8,9), ticlopidine-induced HUS (5), and postinfectious HUS (Neisseria meningitidis) (10). The first identified genetic cause was deficiency in complement factor H (CFH) (8,11–14), a plasma glycoprotein that plays an important role in the regulation of the alternative pathway of complement (15) by controlling both spontaneous fluid phase C3 activation and its deposition on host cells. To date, 54 different CFH mutations (Figure 1, top) have been identified in 80 patients (5,6,8,9,11,12,14,16–24). In nonfamilial cases, the mutation is either inherited from a healthy parent or, more rarely (only five cases reported), has ensued de novo in the proband (6,8). The majority of CFH mutations in patients with HUS are heterozy-
gous and cause either single amino acid changes or premature translation interruption, mainly clustering in the C-terminal short consensus repeats (SCR 19 to 20). More recently, an acquired deficiency of CFH as a result of the presence of anti-CFH autoantibodies in the blood was reported in three children with nonfamilial HUS (25). Two reports from independent groups have described mutations in the gene encoding membrane co-factor protein (MCP), a transmembrane complement regulator, in affected individuals of four families (26,27). Finally, five mutations in the gene encoding factor I (IF), a serine proteinase that inhibits the formation of the alternative pathway C3 convertase (C3bBb) by inactivating cell-bound C3b through proteolytic cleavage to iC3b, have been reported in patients with non–Stx-HUS (28,29). Such defects result in impaired protection of endothelial surface against complement activation (30,31), and it is likely that they predispose to rather than directly cause the thrombotic microangiopathy. Upon exposure to an agent that activates complement, C3b is formed in higher-than-normal amounts, and its deposition on vascular endothelial cells cannot be prevented adequately because of impaired function of complement regulatory proteins (3). This results in the formation of the membrane attack complex and recruitment of inflammatory cells, all events that cause damage and retraction of endothelial cells and adhesion and aggregation of platelets (3).

In this review, we use the term non–Stx-HUS to encompass

![Diagram](image-url)
such variety of forms of HUS related to inherited and acquired complement abnormalities. However, the assignment of patients with HUS to diarrhea-associated (D+ HUS) and non-diarrhea-associated (D− HUS) subgroups is no longer valid because approximately 25% of patients with HUS caused by Stx do not have diarrhea (32).

It is generally accepted that renal transplantation is an effective and safe treatment for patients who have Stx-HUS and have progressed to ESRD. In children with Stx-HUS, the incidence of disease recurrence in the graft ranges from 0 to 10% (33,34), and graft survival at 10 yr is better than that in children who receive a transplant for other causes of ESRD (35). In contrast, disease recurrence and transplantation failure are common in patients with non–Stx-HUS (36–38), even though the incidence varies widely in the literature. Most published reports are of single cases or small case series or comprise series that do not distinguish between patients with the different forms of HUS (Stx-HUS versus non–Stx-HUS). When only reports with >10 patients who had non–Stx-HUS and underwent renal transplantation are considered (6,34,36,38–41), it emerges that more than half of patients lost the graft for HUS recurrence within the first year after transplant, despite treatment with plasma exchange and/or infusion. Cyclosporine A and FK506 administration was not associated with a higher incidence of HUS recurrence, when compared with regimens that excludes these drugs (34,38,41). Graft failure for HUS recurrence was higher in adults (60%) (34,36,38,41) than in children (20%) (34,38–40). The type of kidney donor, cadaveric or living related, did not modify the outcome (36,40,41). Overall, no clinical prognostic factors that correlate with graft outcome emerge from literature. The aim of our study was to assess whether screening for abnormalities in genes encoding complement regulatory proteins could help in predicting renal transplant outcome in patients with non–Stx-HUS.

Materials and Methods

Search Strategy

To evaluate the effect of the presence of genetic mutations in renal transplant outcome in patients with ESRD secondary to non–Stx-HUS, we performed a literature search in Medline database (National Library of Medicine, Bethesda, MD), using as search terms “hemolytic uremic syndrome” and “kidney transplantation.” From the above material, we analyzed data from patients who had been genotyped for mutations in CFH, MCP, and IF genes.

For additional unpublished data, we also contacted authors who have published genetic studies in patients with non–Stx-HUS and examined medical records of patients from the International Registry of Recurrent and Familial HUS/Thrombotic Thrombocytopenic Purpura (HUS/TTP), a network of 100 hematology and nephrology units from Europe, the United States, Canada, Argentina, Israel, Turkey, Saudi Arabia, and South Africa, established in 1996 under the coordination of the Clinical Center for Rare Diseases Aldo e Cele Daccò.

Inclusion Criteria and Data Extraction

Two reviewers (E.B. and F.C.) independently assessed all obtained titles and ordered the full text of all potential articles. The two reviewers then examined all of the texts in full and included in the study the patients who had ESRD secondary to HUS; had undergone at least one renal transplant; were described as having diarrhea-negative, atypical, familial, inherited, idiopathic, or recurrent HUS; and had been genotyped for CFH, MCP and IF. Some cases have been reported in different articles. These cases have been considered once; however, all papers that provided clinical, biochemical, and genetic data on the above patients have been quoted. No patient with S. pneumoniae–associated HUS has been included in the study, because S. pneumoniae–associated HUS is a distinctive rare disorder caused by release of bacterial neuraminidase (42). All available unpublished data on genotyped patients from the Newcastle cohort (provided by T.H.J.G.) and from the International Registry of Recurrent and Familial HUS/TTP were also included.

Details on demographic characteristics, clinical history, laboratory parameters, genetic tests, and transplant outcome from patients who were genotyped for mutations in CFH, MCP, and IF, were registered in a predesigned data extraction form. As for the outcome of renal transplantation, both definite recurrences (when both clinical and histologic features of HUS reappeared after transplantation) and possible recurrences (when only histologic features consistent with HUS were present) were considered as true recurrences.

Statistical Analyses

χ², Fisher exact test, and Kaplan-Meier analysis with log rank test statistics were applied as appropriate. The time variable was defined as the duration in months from the first transplantation until return to chronic dialysis for patients with transplantation failure (event) or the last available follow-up visit for successful transplants (nonevent). Statistical analyses were done with the SPSS software (version 11.5; SPSS, Inc., Chicago, IL).

Results

CFH, MCP, and IF Mutations and Transplant Outcome in Patients with ESRD Secondary to Non–Stx-HUS

A total of 78 patients who had non–Stx-HUS and had received a total of 100 kidney transplants were identified (Table 1). For 40 patients, detailed clinical information was reported. Sixty-seven percent of patients had at least one graft failure: In 81.5% of them, the graft loss was attributed to HUS recurrence, and in the remaining 18.5%, it was secondary to acute or chronic rejection. The percentage of graft failure for recurrence was 42.8% in children and 62.5% in adults (Fisher exact test P = 0.3176). The time between renal transplantation and graft loss for recurrence ranged from 3 d to 2 yr, with 82.6% of grafts lost within the first year. In addition, two patients manifested HUS recurrence between 3 and 5 mo after transplantation but maintained functioning renal grafts. The overall incidence of disease recurrence in these 40 patients was 60.0%, with 91.6% resulting in failure of the graft. Initial immunosuppressive therapy was specified for 25 renal transplants. Cyclosporine A and FK506 (13 of 20 grafts; 65.0%) administration was not associated with a higher incidence of HUS recurrence, when compared with regimens that excluded these drugs (two of five grafts; 40.0%; Fisher exact test P = 0.3577).

Twenty-seven had CFH mutations (CFH positive) and received a total of 36 kidney grafts. The localization and the effect of CFH mutations are shown in Figure 1. The relevant clinical data of the CFH-positive group are summarized in Table 2. Among them, 12 patients (six children, four adults, two unspecified) had familial HUS, whereas nine (four children, five
adults) had no familial history; for the remaining six patients, a family history was not available. In 16 patients, a heterozygous mutation was found, indicating an autosomal dominant transmission of the disease, whereas an autosomal recessive transmission was demonstrated in five cases, two with a homozygous mutation (and consanguineous parents) and three with compound heterozygous changes (Figure 1, bottom). For six patients (6), the type of CFH mutation was not specified. HUS

<table>
<thead>
<tr>
<th>Study (First Author, Year)</th>
<th>Patient Gender</th>
<th>Familial HUS</th>
<th>Age at HUS Onset</th>
<th>Time between HUS and Dialysis</th>
<th>CFH Mutation</th>
<th>Donor Type</th>
<th>Initial Immunosuppressive Treatment</th>
<th>TR Failure</th>
<th>Reason for Failure</th>
<th>Duration from TR until Chronic Dialysis</th>
<th>Follow-Up of Functioning Grafts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caprioli, 2001, 2003</td>
<td>M</td>
<td>Yes</td>
<td>8 mo</td>
<td>No recovery</td>
<td>Yes</td>
<td>Cadav</td>
<td>CsA, Pred, MMF</td>
<td>Yes</td>
<td>Recurrence of HUS</td>
<td>5 mo</td>
<td></td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>No</td>
<td>31 yr</td>
<td>15 yr</td>
<td>Yes</td>
<td>Cadav</td>
<td>CsA, Aza, Pred</td>
<td>Yes</td>
<td>Recurrence of HUS</td>
<td>3 mo</td>
<td></td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>Yes</td>
<td>25 yr</td>
<td>No recovery</td>
<td>Yes</td>
<td>Cadav</td>
<td>Tac, Aza, Pred</td>
<td>Yes</td>
<td>Recurrence of HUS</td>
<td>5 mo</td>
<td></td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>Yes</td>
<td>3 wk</td>
<td>No recovery</td>
<td>Yes</td>
<td>Cadav</td>
<td>Tac, MMF, Pred</td>
<td>Yes</td>
<td>Recurrence of HUS</td>
<td>1 mo</td>
<td></td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>No</td>
<td>36 yr</td>
<td>No recovery</td>
<td>Yes</td>
<td>Cadav</td>
<td>Tac, MMF, Pred</td>
<td>Yes</td>
<td>Recurrence of HUS</td>
<td>7 d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>No</td>
<td>25 yr</td>
<td>No recovery</td>
<td>No</td>
<td>Cadav</td>
<td>?</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>No</td>
<td>34 yr</td>
<td>No recovery</td>
<td>No</td>
<td>Cadav</td>
<td>Tac, Aza, Pred</td>
<td>Yes</td>
<td>Acute rejection</td>
<td>1 yr</td>
<td></td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>Yes</td>
<td>26 yr</td>
<td>?</td>
<td>No</td>
<td>TR1: Cadav</td>
<td>TR1: Aza, Pred</td>
<td>TR1: Yes</td>
<td>TR1: Chronic rejection</td>
<td>TR1: 10 yr</td>
<td></td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>No</td>
<td>30 yr</td>
<td>No</td>
<td>Yes</td>
<td>Cadav</td>
<td>CsA, Pred, MMF</td>
<td>Yes</td>
<td>Recurrence of HUS</td>
<td>3 yr</td>
<td></td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>No</td>
<td>36 yr</td>
<td>No</td>
<td>Yes</td>
<td>Cadav</td>
<td>Tac, MMF, Pred</td>
<td>Yes</td>
<td>Recurrence of HUS</td>
<td>1 mo</td>
<td></td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>No</td>
<td>26 yr</td>
<td>7 mo</td>
<td>No</td>
<td>Cadav</td>
<td>CsA, Pred, MMF</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>No</td>
<td>6 mo</td>
<td>No</td>
<td>No</td>
<td>Cadav</td>
<td>?</td>
<td>Yes</td>
<td>Recurrence of HUS</td>
<td>4 yr</td>
<td></td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>No</td>
<td>31 yr</td>
<td>No</td>
<td>Yes</td>
<td>Cadav</td>
<td>Tac, MMF, Pred</td>
<td>Yes</td>
<td>Recurrence of HUS</td>
<td>1 mo</td>
<td></td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>Yes</td>
<td>31 mo</td>
<td>No</td>
<td>No</td>
<td>TR1: Cadav</td>
<td>TR1: ?</td>
<td>TR1: Yes</td>
<td>TR1: Rejection</td>
<td>TR1: 3 mo</td>
<td>TR2: 13 yr</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>No</td>
<td>4 yr</td>
<td>4.5 yr</td>
<td>No</td>
<td>?</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>International Registry</td>
<td>F</td>
<td>Yes</td>
<td>Adulthood</td>
<td>?</td>
<td>No</td>
<td>?</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(unpublished)</td>
<td>F</td>
<td>No</td>
<td>30 yr</td>
<td>No</td>
<td>No</td>
<td>Cadav</td>
<td>Tac, MMF, Pred</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>No</td>
<td>9 yr</td>
<td>?</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Newcastle cohort</td>
<td>F</td>
<td>Yes</td>
<td>?</td>
<td>?</td>
<td>Yes</td>
<td>?</td>
<td>?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(unpublished)</td>
<td>F</td>
<td>Yes</td>
<td>?</td>
<td>?</td>
<td>Yes</td>
<td>Tac, MMF, Pred</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>Yes</td>
<td>Adulthood</td>
<td>?</td>
<td>Yes</td>
<td>Cadav</td>
<td>?</td>
<td>Yes</td>
<td>Recurrence of HUS</td>
<td>1 mo</td>
<td></td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>Yes</td>
<td>Adulthood</td>
<td>No recovery</td>
<td>Yes</td>
<td>Cadav</td>
<td>?</td>
<td>Yes</td>
<td>Recurrence of HUS</td>
<td>1 mo</td>
<td></td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>Yes</td>
<td>?</td>
<td>?</td>
<td>Yes</td>
<td>TR1: ?</td>
<td>TR1: Yes</td>
<td>TR1: Rejection</td>
<td>TR1: 3 mo</td>
<td>TR2: 13 yr</td>
<td></td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>Yes</td>
<td>Adulthood</td>
<td>?</td>
<td>Yes</td>
<td>?</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>No</td>
<td>22 yr</td>
<td>No recovery</td>
<td>Yes</td>
<td>LRD</td>
<td>Tac, MMF, Pred</td>
<td>Yes</td>
<td>Recurrence of HUS</td>
<td>52 d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>No</td>
<td>6 yr</td>
<td>No recovery</td>
<td>Yes</td>
<td>Cadav</td>
<td>CsA, ATG, Pred</td>
<td>Yes</td>
<td>Recurrence of HUS</td>
<td>4 mo</td>
<td></td>
</tr>
<tr>
<td>Richards, 2003f</td>
<td>M</td>
<td>Yes</td>
<td>27 yr</td>
<td>No recovery</td>
<td>No</td>
<td>Cadav</td>
<td>CsA, Pred</td>
<td>No</td>
<td></td>
<td>16 yr</td>
<td></td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>Yes</td>
<td>31 yr</td>
<td>No recovery</td>
<td>No</td>
<td>Cadav</td>
<td>Aza, Pred</td>
<td>No</td>
<td></td>
<td>23 yr</td>
<td></td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>Yes</td>
<td>35 yr</td>
<td>No recovery</td>
<td>No</td>
<td>Cadav</td>
<td>CsA, Aza, Pred</td>
<td>No</td>
<td></td>
<td>13 yr</td>
<td></td>
</tr>
<tr>
<td>Donne, 2002</td>
<td>F</td>
<td>Yes</td>
<td>4 mo</td>
<td>No recovery</td>
<td>Yes</td>
<td>LRD</td>
<td>CsA, Aza, Pred</td>
<td>Yes</td>
<td>Recurrence of HUS</td>
<td>7 wk</td>
<td></td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>Yes</td>
<td>30 yr</td>
<td>No recovery</td>
<td>Yes</td>
<td>Cadav</td>
<td>CsA, Aza, Pred</td>
<td>Yes</td>
<td>Recurrence of HUS</td>
<td>3 mo</td>
<td></td>
</tr>
<tr>
<td>Dragon-Durey, 2004</td>
<td>M</td>
<td>Yes</td>
<td>11 mo</td>
<td>12 mo</td>
<td>Yes</td>
<td>?</td>
<td>?</td>
<td>No</td>
<td>18 mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>No</td>
<td>6 mo</td>
<td>No recovery</td>
<td>Yes</td>
<td>?</td>
<td>?</td>
<td>No</td>
<td>10 yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>No</td>
<td>16 mo</td>
<td>No recovery</td>
<td>Yes</td>
<td>?</td>
<td>?</td>
<td>No</td>
<td>4 yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>No</td>
<td>9 mo</td>
<td>No recovery</td>
<td>Yes</td>
<td>?</td>
<td>Yes</td>
<td>Recurrence of HUS</td>
<td>25 d</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
manifested during childhood in 10 patients and during adulthood in nine (for eight patients, the age of onset was not available), with no recovery after the first episode in overall 80.0%. The mean number of transplants per patient was 1.33/0.48, with seven patients receiving two kidney grafts and one patient receiving three grafts. The type of donor was documented for 20 grafts: 90.0% were from cadaveric donors, and 10.0% were from living-related donors (Table 2). The incidence of graft failure was high; overall, 77.8% of these patients had at least one graft failure. In 15 of them, the cause of graft loss was available and in 13 (86.7%) was attributed to HUS recurrence. Similar results were obtained when the number of grafts was considered. Overall, 80.6% of graft failures occurred in these patients. For 17 grafts, the cause of failure was available and in 14 (82.3%) of them was attributed to HUS recurrence. The time between renal transplantation and graft loss for recurrence ranged from 3 d to 22 mo, with overall 12 (85.7%) grafts lost within the first year and two (14.3%) lost between 18 and 22 mo (Figure 2). One additional patient (patient 17, Table 1) manifested two episodes of HUS recurrence after transplantation but maintained a functioning graft at 6 yr of follow-up. The overall incidence of disease recurrence was 73.7% in the patients with CFH mutations. Avoidance of calcineurin inhibitors did not prevent recurrence of HUS and graft loss. The incidence of graft failure was not influenced by the type of CFH mutation (missense 70.0%, nonsense 66.7% failures; Fisher exact test $P = 1.0000$) and by the position (SCR 19 to 20: 75.0%, all of the other SCR 57.1% failures; Fisher exact test $P = 0.6169$). Likewise, the incidence of graft failure was 66.7% in patients with lower-

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|c|c|c|c|c|}
\hline
\textbf{Table 1. Continued} & \\
\hline
\textbf{Study (First Author, Year)} & \textbf{Familial HUS} & \textbf{Age at HUS Onset} & \textbf{Time between HUS and Dialysis$^b$} & \textbf{CFH Mutation} & \textbf{Donor Type} & \textbf{Initial Immunosuppressive Treatment} & \textbf{TR Failure} & \textbf{Reason for Failure} & \textbf{Follow-Up of Functioning Grafts} \\
\hline
Johnson, 2004 & 41 & M & Yes & 5 mo & 3 yr & Yes & Cadav & Aza, Pred & Yes & Recurrence of HUS & 2 mo \\
Kavanagh, 2005 & 42 & F & No & 32 yr & No recovery & No & Cadav & CsA, Pred & Yes & Recurrence of HUS & 2 mo \\
\hline
\end{tabular}
\end{table}

$^a$non–Stx-HUS, non–Shiga toxin–associated hemolytic uremic syndrome; TR1, first renal transplantation; TR2, second renal transplantation; TR3, third renal transplantation; Cadav, cadaveric graft; LRD, graft from living-related donor; LUD, graft from living-unrelated donor; CsA, cyclosporine A; Pred, prednisone; MMF, mycophenolate mofetil; Tac, tacrolimus; ATG, anti-thymoglobulin; Sir, sirolimus; Bas, basiliximab.

$^b$Irreversible loss of renal function during the acute phase = No recovery.

$^c$CFH mutation described even in Buddles et al. (18).

$^d$HUS onset after nephrectomy.

$^e$CFH mutations described in Warwicker et al. (12) and Richards et al. (14).

$^f$Family described in Warwicker (12).

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|c|c|c|c|c|c|c|c|c|}
\hline
\textbf{Table 2. Characteristics and outcome after transplantation in patients with non–Stx-HUS and mutations of factor H} & \\
\hline
\textbf{Patients} & 27 & \\
\textbf{Gender} & \\
\textit{male} & 9 & \\
\textit{female} & 11 & \\
\textit{unspecified} & 7 & \\
\textbf{Disease onset} & \\
\textit{childhood (<16 yr)} & 10 & \\
\textit{adulthood (≥16 yr)} & 9 & \\
\textit{unspecified} & 8 & \\
\textbf{Type of HUS} & \\
\textit{familial} & 12 & \\
\textit{sporadic} & 9 & \\
\textit{unspecified} & 6 & \\
\textbf{Transplanted kidneys} & 36 & \\
\textbf{Type of donor} & \\
\textit{cadaver} & 18 & \\
\textit{living related} & 2 & \\
\textit{unspecified} & 16 & \\
\textbf{Kidney failures} & \\
\textit{no. of patients} & 21 & \\
\textit{no. of grafts} & 29 & \\
\hline
\end{tabular}
\end{table}

manifested during childhood in 10 patients and during adulthood in nine (for eight patients, the age of onset was not available), with no recovery after the first episode in overall 80.0%. The mean number of transplants per patient was 1.33 ± 0.48, with seven patients receiving two kidney grafts and one patient receiving three grafts. The type of donor was documented for 20 grafts: 90.0% were from cadaveric donors, and 10.0% were from living-related donors (Table 2). The incidence of graft failure was high; overall, 77.8% of these patients had at least one graft failure. In 15 of them, the cause of graft loss was available and in 13 (86.7%) was attributed to HUS recurrence. Similar results were obtained when the number of grafts was considered. Overall, 80.6% of graft failures occurred in these patients. For 17 grafts, the cause of failure was available and in 14 (82.3%) of them was attributed to HUS recurrence. The time between renal transplantation and graft loss for recurrence ranged from 3 d to 22 mo, with overall 12 (85.7%) grafts lost within the first year and two (14.3%) lost between 18 and 22 mo (Figure 2). One additional patient (patient 17, Table 1) manifested two episodes of HUS recurrence after transplantation but maintained a functioning graft at 6 yr of follow-up. The overall incidence of disease recurrence was 73.7% in the patients with CFH mutations. Avoidance of calcineurin inhibitors did not prevent recurrence of HUS and graft loss. The incidence of graft failure was not influenced by the type of CFH mutation (missense 70.0%, nonsense 66.7% failures; Fisher exact test $P = 1.0000$) and by the position (SCR 19 to 20: 75.0%, all of the other SCR 57.1% failures; Fisher exact test $P = 0.6169$). Likewise, the incidence of graft failure was 66.7% in patients with lower-
than-normal CFH levels (CFH antigen serum levels as determined by Radial immunodiffusion or ELISA assays) and 90.9% in those with normal or high CFH levels (Fisher exact test $P = 0.2848$; Figure 1, Table 1). However, normal CFH levels do not suggest normal function, because it has been shown that most CFH mutations in patients with HUS result in a normal protein secretion but cause loss of the capability of CFH to bind C3b and endothelial cells.

The incidence of graft failure was lower in the 51 patients without CFH mutations (CFH negative; 28 of 51; 54.9%), as compared with patients with CFH mutations (CFH positive; 21 of 27; 77.8%; Fisher exact test $P = 0.0533$, $\chi^2 = 3.96$, $P = 0.0467$). In this group, graft outcome was variable, with some patients experiencing a disease recurrence within a few days after transplantation and others retaining a well-functioning graft until 10 to 20 yr posttransplantation (Table 1, Figure 2). Of interest, two patients with no familial history of the disease and no CFH mutation received a living-related renal transplant, one from a sibling and the other from the father. Both recipients (patients 30 and 32) lost the graft for HUS recurrence, 7 wk and 6 mo after transplantation, respectively (43). These data underline the risk for disease recurrence in non-Stx-HUS recipients of living-related kidney graft and suggest that living-related donors may be at risk for developing a de novo disease after kidney donation to a family member with non–Stx-HUS.

Three CFH-negative patients (patients 40, 42, and 43) had a mutation in the IF gene (Table 3). All three had no familial history of HUS and lost the kidney graft for disease recurrence. Patient 40 was hospitalized at the age of 26 yr for recurrence of HUS (confirmed by renal biopsy) after a second renal transplant. She had already lost her first kidney transplant as a result of HUS recurrence coinciding with acute rejection. Patient 42 developed ESRD after an episode of HUS, during the third trimester of her first pregnancy. She received a cadaveric renal transplant that was lost for disease recurrence after 2 mo. Patient 43 received a live related transplant from his brother at the age of 35 yr. Twenty months after transplantation, the disease recurred, as documented by renal biopsy. Despite treatment with 23 plasma exchanges, renal function continued to deteriorate and the patient returned to dialysis.

For 16 CFH-negative patients (patient 6 to 16, 24 to 26, 42, and 43), information on the results of MCP gene screening was available, with four of them having MCP mutations (Table 4). Three patients are brothers from the same family (patients 24,
25, and 26) and show an autosomal dominant transmission, whereas the fourth patient is a woman without a familial history (patient 6). HUS occurred in adulthood in all patients with ESRD as a consequence of a single episode. As shown in Table 4, kidney transplant outcome was favorable in all four patients with an MCP mutation, with none experiencing a disease recurrence in the graft. Among the three brothers, one died from hepatic failure of unknown cause after 13 yr of a functioning graft, one developed Waldenström’s macroglobulinemia, and the other remains well with a functioning graft. Patient 6 had an uneventful pregnancy 7 yr after transplantation with 9 yr of disease-free follow-up.

Discussion

Children with Stx-HUS rarely progress to ESRD, but when they do, renal transplantation results in a good prognosis with a very low recurrence rate, ranging from 0 to 10% (33,34). In contrast, >50% of patients with non-Stx-HUS—most of them are children or young adults—progress to ESRD and need renal replacement therapy. However, whether kidney transplantation is an appropriate treatment in these patients is debatable. Previous reports detailing kidney graft outcome indicate a poor prognosis with >50% of graft lost for recurrence (6,34,36,38–41).

The results of our review of published and unpublished cases genotyped for CFH, MCP, and IF confirm the overall poor outcome of renal transplantation in patients with non-Stx-HUS, with recurrence occurring in 60.0% of patients and graft failure developing in 91.6% of them despite treatment. Recurrence occurred within the first year after transplantation in 82.6% of patients. Overall 1-yr kidney graft survival in patients with non-Stx-HUS was 32% for cadaveric transplants and 50% for living donor transplants. For comparison, data reported to the UNOS Renal Transplant Registry showed that in the 1990s, the overall 1-yr graft survival rate for cadaveric kidney transplants was 87%, whereas for living donor transplants was 93% (44). Similar to previous published studies (33,34), we found that the percentage of graft failure for HUS recurrence was higher in adults. Avoidance of calcineurin inhibitors did not prevent recurrence of HUS and graft loss. No clinical prognostic factors could help to distinguish patients who were at high risk for graft failure from those who could benefit from transplantation. However, we found that screening for mutations is important as it may help to define graft prognosis. First, we examined the effect of CFH mutations. We found that the presence of a CFH mutation was associated with a poor outcome after renal transplantation. The incidence of graft failure was higher in patients with a CFH mutation than in those without.

Table 3. Outcome after renal transplantation in patients with non–Stx-HUS associated to a mutation of factor I (IF)

<table>
<thead>
<tr>
<th>Study (First Author, Year)</th>
<th>Patient</th>
<th>Gender</th>
<th>Familial HUS</th>
<th>Age at HUS Onset</th>
<th>Time between HUS and Dialysisa</th>
<th>IF Mutation</th>
<th>Effect of Mutation</th>
<th>HUS Recurrence after TR</th>
<th>Outcome after Transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fremeaux-Bacchi, 2004</td>
<td>40 F</td>
<td>No</td>
<td>26 yr</td>
<td>?</td>
<td>G1666A</td>
<td>Trp528Stop</td>
<td>Yesb</td>
<td></td>
<td>Graft failure secondary to HUS recurrence</td>
</tr>
<tr>
<td>Kavanagh, 2005</td>
<td>42 F</td>
<td>No</td>
<td>32 yr</td>
<td>No recovery</td>
<td>G463A</td>
<td>Trp127Stop</td>
<td>Yes</td>
<td></td>
<td>Graft failure secondary to HUS recurrence</td>
</tr>
<tr>
<td></td>
<td>43 M</td>
<td>No</td>
<td>33 yr</td>
<td>No recovery</td>
<td>922delC</td>
<td>Premature stop</td>
<td>Yes</td>
<td></td>
<td>Graft failure secondary to HUS recurrence</td>
</tr>
</tbody>
</table>

aIrreversible loss of renal function during the acute phase = no recovery.
bDisease recurrence and graft failure for recurrence after both the first and the second transplant.

Table 4. Outcome after renal transplantation in patients with non–Stx-HUS associated with mutation of MCP gene

<table>
<thead>
<tr>
<th>Study (First Author, Year)</th>
<th>Patient</th>
<th>Gender</th>
<th>Familial HUS</th>
<th>Age at HUS Onset</th>
<th>Time between HUS and Dialysisa</th>
<th>MCP Mutation</th>
<th>Effect of Mutation</th>
<th>HUS Recurrence after TR</th>
<th>Outcome after Transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present article</td>
<td>6 F</td>
<td>No</td>
<td>25 yr</td>
<td>No recovery</td>
<td>C218T</td>
<td>Arg25Stop</td>
<td>No</td>
<td></td>
<td>Functional graft at 9 yr</td>
</tr>
<tr>
<td>Richards, 2003</td>
<td>24 M</td>
<td>Yes</td>
<td>27 yr</td>
<td>No recovery</td>
<td>6bp del</td>
<td>Loss of 237Asp and 238Ser</td>
<td>No</td>
<td></td>
<td>Functional graft at 16 yr</td>
</tr>
<tr>
<td></td>
<td>25 M</td>
<td>Yes</td>
<td>31 yr</td>
<td>No recovery</td>
<td>6bp del</td>
<td>Loss of 237Asp and 238Ser</td>
<td>No</td>
<td></td>
<td>Functional graft at 23 yr</td>
</tr>
<tr>
<td></td>
<td>26 M</td>
<td>Yes</td>
<td>35 yr</td>
<td>No recovery</td>
<td>6bp del</td>
<td>Loss of 237Asp and 238Ser</td>
<td>No</td>
<td></td>
<td>Functional graft at 13 yr, death</td>
</tr>
</tbody>
</table>

aIrreversible loss of renal function during the acute phase = no recovery.
Interpretation of these results is facilitated by the knowledge that CFH is a plasma protein that is produced mainly by the liver. Thus, a kidney transplant will not correct the CFH genetic defect in these patients (11,12). Expression and functional studies have demonstrated that mutant CFH has a severely reduced capacity to interact with both polyanions on endothelial cells and surface-bound C3b; this results in diminished complement regulatory activity on the cell membrane (31,45). Renal transplantation is a condition of complement activation, which may be triggered by ischemia reperfusion damage, immune insult, and infectious complications (46,47). In patients who carry a CFH mutation, regulation of complement activation and C3b deposition on graft vascular endothelium is impaired as a result of the loss of polyanion-binding capacity of mutant CFH, thus predisposing to recurrence of the disease in the graft.

Simultaneous kidney and liver transplant was performed recently by our group in two young children with non–Stx-HUS and CFH mutations, with the objective of correcting the genetic defect and preventing disease recurrences (20,48). However, both patients who were treated with this procedure were complicated by premature irreversible liver failure. The reasons for this are currently under evaluation but may include increased susceptibility of the transplanted liver to ischemic or immune injury related to uncontrolled complement activation. In the first patient, humoral rejection of the liver graft manifested by the 26th day after transplantation, and in a few days, the child developed hepatic encephalopathy and coma. She underwent a second, uneventful liver transplantation (20). The second case was complicated by primary nonfunction of the liver graft followed by multiorgan failure and the patient’s death (48). Thus, despite the potential to correct the genetic defect, combined kidney and liver transplant for non–Stx-HUS associated with CFH mutations should not be performed unless a patient is at imminent risk for life-threatening complications.

Forty-five percent of patients with non–Stx-HUS and no evidence of a CFH mutation, when given a kidney transplant, lose the graft within 1 yr. Of note, two patients who had no familial history of the disease and no CFH mutation and received a living-related renal transplant experienced HUS recurrence in the allograft. Both donors developed HUS after nephrectomy. Thus, the decision to offer a living-related renal transplant to patients with non–Stx-HUS should take into account the risk for a de novo disease in the donors. Unilateral nephrectomy and renal mass reduction could cause endothelial damage, triggering the disease in the donor, if the latter is genetically predisposed by a disease-associated mutation. This hypothesis is supported by the case of one of the patients with CFH mutation in this report (patient 5), who developed the disease after nephrectomy as a result of trauma caused by a motor vehicle accident.

CFH, like IF, is synthesized by the liver; therefore, it is expected that patients with an IF mutation would have a similar outcome posttransplantation as those with a CFH mutation. Indeed, graft failures for HUS recurrence were recently reported in three patients with a heterozygous IF mutation (28,29). The remarkable exception were patients with MCP mutation. Indeed, four of these patients underwent successful transplantation, with no disease recurrence. At variance with CFH and IF, which are circulating soluble regulators, MCP is a transmembrane protein that is highly expressed in the kidney. Transplantation of a kidney that expresses normal MCP therefore should correct the defect in patients with an MCP mutation.

CFH mutations have been found in approximately 30% of patients with non–Stx-HUS. Very recent published data in two different cohorts (49) that included 75 and 77 patients, respectively, and unpublished results from our International Registry (155 patients) indicate that the frequency of MCP mutations in non–Stx-HUS ranges from 5 to 14% and that the frequency of IF mutations ranges from 4 to 10%. Thus, overall genetic screening before renal transplantation would be of help to predict graft outcome for approximately 40 to 50% of patients with non–Stx-HUS. The number of patients with CFH, MCP, and IF mutation that have been reported until now is small. Multicenter trials and registries are required to get enough numbers to characterize better the predictive value of these mutations to graft outcome. CFH, MCP, and IF genotyping requires the analysis of the whole coding region of the genes because mutations that have been found in patients with non–Stx-HUS are located in different exons. We recognize that not all transplant centers are equipped for CFH, MCP, and IF genotyping. This hurdle could be overcome by centralizing the analyses in a few referring centers with proven experience in the field.

This study has important clinical implications. We suggest that genotyping for CFH, MCP, and IF is performed in all patients who have ESRD secondary to non–Stx-HUS and are being considered for transplantation. Genetic testing should be particularly recommended before living-related donation to avoid the risk for de novo disease in the donors. It is difficult to justify renal transplantation in patients with a CFH mutation because of the high risk for graft failure, and the same applies to patients with an IF mutation. Combined liver and renal transplantation in these patients theoretically could correct the genetic abnormality and prevent disease recurrence. However, this procedure is not recommended at present because it may be complicated by fatal primary liver nonfunction. In contrast, graft outcome seems to be good in patients with MCP mutations.

Despite these recent advances, the underlying genetic abnormality, if any, remains unknown in almost half of patients with non–Stx-HUS. Alterations in other genes encoding for complement regulatory proteins could be involved in determining predisposition to the disease. However, evidence is emerging that in some patients, the disease is caused by an acquired autoimmune event that leads to the formation of anti-CFH antibodies (25). Further advances in our understanding of the molecular pathogenesis of the disease are needed to enable more accurate prediction of the risk for recurrence and allow the development of tailored therapeutic approaches.

Acknowledgments

This work was supported in part by grants from “Comitato 30 ore per la vita,” from Telethon (GPP02161) and from Associazione Ricerca Trapianto and by a grant from the Foundation for Children with
Atypical HUS along with Nando Peretti Foundation. F.C. received a fellowship in memory of Libera Dossi Grana.

We thank B.S. Kaplan, MD, A. Nicholls, MD, Y. Pirson, MD, C.L. Tieleman, MD, and M.C. Venning, MD, for providing the clinical information on the patients in the Newcastle cohort.

Members of the International Registry of Recurrent and Familial HUS/TTP

**Coordinators.** G. Remuzzi, MD, P. Ruggenenti, MD (Clinical Research Center for Rare Diseases “Aldo e Cele Daccò,” Ranica, Bergamo, and Division of Nephrology and Dialysis, “Ospedali Riuniti” Azienda Ospedaliera, Bergamo), and M. Noris, ChemPharmD (Clinical Research Center for Rare Diseases “Aldo e Cele Daccò,” Ranica, Bergamo).

**Investigators (Italy).** M. Garozzo, MD (Division of Nephrology and Dialysis, “S. Marta e S. Venera” Hospital, Acireale, Catania); M. Antonelli, MD, F. Casucci, MD, F. Cazzato, MD (Division of Nephrology, “Miulli” Hospital, Acquaviva delle Fonti, Bari); L.M. Ratsch, MD (Pediatric Clinic, “G. Salesi” Hospital, Ancona); G. Claudiani, MD (Division of Hematology, “S. Liberatore” Hospital, Atri, Teramo); W. De Simone, MD (Division of Nephrology and Dialysis, “S. Giuseppe Moscati” Hospital, Avellino); P. Dattolo, MD, F. Pizziarelli, MD (Division of Nephrology and Dialysis, “S.M. Annunziata” Hospital, Bagno a Ripoli, Firenze); R. Bellantuno, MD, T. De Palo, MD (Division of Nephrology and Dialysis, “Giovanni XXIII” Pediatric Hospital, Bari); N. Lattanzi, MD (Centro Emodialisi, Bari); M. Schiavoni, MD (Assistenza Emofили e Coagulopatiи, Ospedale Policlinico Consorziale, Bari); T. Barbui, MD (Division of Hematology, “Ospedali Riuniti” Azienda Ospedaliera, Bergamo); G. Torre, MD (Pediatric Department, “Ospedali Riuniti” Azienda Ospedaliera, Bergamo); A.M. Acquarolo, MD (II Rianimazione “Spedali Civili, Azienda Ospedaliera,” Brescia); O. Carli, MD, G. Gregorini, MD (Division of Nephrology and Dialysis, “Spedali Civili, Azienda Ospedaliera,” Brescia); G. Rossi, MD (Division of Hematology, “Spedali Civili, Azienda Ospedaliera,” Brescia); A. Cao, MD (Istituto di Clinica e Biologia dell’Età Evolutiva, Cagliari); C. Setzu, MD (Pediatric Division, “G. Brotzu” Hospital, Cagliari); A. Bonadonna, MD (Division of Nephrology and Dialysis, Presidio Ospedaliero di Camposampiero, Camposampiero, Padova); C. Cascone, MD, G. Delfino, MD (Division of Nephrology and Dialysis, “S. Giacomò” Hospital, Castelfranco Veneto, Treviso); S. Li Volti, MD, (Pediatric Department, Policlinico Hospital, Catania); C. Castellino, MD (Division of Hematology, “Azienda Ospedaliera S. Croce e Carle,” Cuneo); L. Calacoci, MD (Division of Immunohematology, “S. Giovanni di Dio” Hospital, Firenze); C. Grimaldi, MD (Division of Internal Medicine and Nephrology, “S. Giovanni di Dio” Hospital, Firenze); I. Pela, MD (Division of Nephrology, “A. Meyer” Hospital, Firenze); M. Salvadori, MD (Division of Nephrology and Dialysis, “Careggi” Hospital, Firenze); E. Capussela, MD (Division of Hematology, “Ospedali Riuniti” di Foggia); D.A. Procaccini, MD (Division of Nephrology and Dialysis, “Ospedali Riuniti” di Foggia); G.C. Barbano, MD, A. Canepa, MD, M.L. Degl’Innocenti, MD, A. Trivelli, MD (Division of Nephrology, “G. Gaslini” Pediatric Institute, Genova); I. Fontana, MD (Transplant Center, “S. Martino” Hospital, Genova); S. D’Ardia, MD (Division of Immunohematology, Ixrea Hospital, Ixrea, Torino); C. Marseglia, MD (Service of Nephrology and Dialysis, “Carlo Foma” Hospital, Manova); A. Bettinelli, MD (Pediatric Division, “S. Leopoldo Mandic” Hospital, Merate, Lecco); R. Chimenz, MD (Division of Pediatric Nephrology, “G. Martino” Hospital, Messina); G. Ardissino, MD, A. Edefonti, MD (Division of Pediatric Nephrology, Dialysis and Transplant, “De Marchi” Pediatric Clinic, Milano); A. Lattuada, BiolScid, E. Rossi, MD (Division of Hematology, “L. Sacco” Hospital, Milano); V. Rossi, MD (Division of Hematology, “Niguarda Cà Granda” Hospital, Milano); V. Toschi, MD (Trasfusional Center, “San Carlo Borromeo” Hospital, Milano); L. Gaiani, MD, M. Leonelli, MD (Division of Nephrology, Dialysis and Transplant, Policlinico Hospital, Modena); D. Belotti, BiolScid, E. Fogliani, MD (Division of Hematology and Transfusional Center, “S. Gerardo” Hospital, Monza, Milano); G. Masera, MD (Pediatric Department, “S. Gerardo” Hospital, Monza, Milano); M.R. Iannuzzi, MD (Division of Nephrology, “A. Cardarelli” Hospital, Napoli); G.B. Capasso, MD, S. Scognamiglio, MD (Chair of Nephrology, Second University of Napoli, Napoli); G. Montini, MD, L. Murer, MD (Pediatric Division, Policlinico Hospital, Padova); A. Indovina, MD, R. Marcenò, MD (Division of Hematology, “V. Cervello” Hospital, Palermo); L. Amico, MD (Division of Nephrology and Dialysis, “V. Cervello” Hospital, Palermo); E. Trabassi, MD (Division of Nephrology and Dialysis, “San Massimo” Hospital, Penne, Pescara); G. Agnelli, MD (Division of Internal Medicine, University of Perugia); R. Caprioli, MD (Division of Nephrology and Dialysis, “S. Chiara” Hospital, Pisa); E. Nesti, MD (Division of Nephrology and Dialysis, “S. Minini” Hospital, S. Minato, Pisa); G. Garozzo, MD (Trasfusional Center, “M.P. Arezzo” Hospital, Ragusa); E. Bresin, MD, E. Daina, MD, S. Gamba, Research Nurse, (Clinical Research Center for Rare Diseases “Aldo e Cele Daccò,” Ranica, Bergamo); M. Santostefano, MD (Division of Nephrology and Dialysis, “Santa Maria delle Croci” Hospital, Ravenna); G. Enia, MD, P. Finocchiaro, MD, C. Zoccali, MD (Division of Nephrology and Dialysis, “Bianchi, Melacrinio, Morelli” Hospital, Reggio Calabria); V. Trapani Lombardo, MD (Division of Hematology, “Bianchi, Melacrinio, Morelli” Hospital, Reggio Calabria); A. Amendola, MD, L. Desantisi, MD, F. Mandelli, MD, G. Meloni, MD (Department of Cellular Biotechnology and Hematology, “La Sapienza” University, Roma); A. De Feo, MD, M. Ferrannini, MD (Rome American Hospital, Roma); L. De Petris, MD, S. Rinaldi, MD, G.F. Rizzoni, MD (Division of Nephrology and Dialysis, “Bambino Gesù” Pediatric Hospital, Roma); T. Cicchetti, MD, G. Porttì, MD (Division of Nephrology and Dialysis, “N. Giannettasio” Hospital, Rossano Calabro, Cosenza); R. Paolini, MD (Medical Division, Rovigo Hospital, Rovigo); A. Pinto, MD (Division of Nephrology and Dialysis, “S.G. di Dio e Ruggi d’Aragona” Hospital, Salerno); A. Del Giudice, MD (Division of Nephrology, “Casa Sollievo delle Sofferenza” Hospital, S. Giovanni Rotondo, Foggia); P.R. Scalzulli, MD (Division of Hematology, “Casa Sollievo delle Sofferenza” Hospital, S. Giovanni Rotondo, Foggia); M. Sanna, MD (Division of Medical Pathology, Sarsari Hospital, Sassari); A. Amore, MD, G. Conti, MD, R. Coppo, MD, L. Peruzzi, MD (Division of Nephrology and Dialysis, Regina Margherita” Pediatric Hospital, Torino); A. Khaled, MD (Division of Nephrology, “S. Chiara” Hospital, Trento); M. Pennesi, MD (Division of Pediatric Nephrology, “Burlo Garofalo” Pediatric Institut, Trieste); O. Amatrua, MD (Division of Nephrology, “Fondazione Macchi” Hospital, Varese); L. Tavechia, MD (Division of Hematology, “Borgo Roma” Hospital, Verona).

**Investigators (outside Italy).** J. Ferraris, MD (Division of Nephrology, “Hospital Italiano de Buenos Aires,” Buenos Aires, Argentina); M.G. Caletti, MD, M. Adragua, MD (“Juan P. Garrahan” Hospital de Pediatría, Buenos Aires, Argentina); R. Wens, MD (Clinique de Nephrologie-Dialyse, CHU Brugmann, Bruxelles, Belgium); G. Filler, MD, K. Blyth, RN (Children’s Hospital of Eastern Ontario, Ottawa, Ontario, Canada); T. Ring, MD (Department of Nephrology, Aalborg Hospital, Aalborg, Denmark); C. Bührer, MD (Department of Neonatology, Charité Campus Virchow-Klinikum, Berlin, Germany); D. Müller, MD (Department of Pediatric Nephrology, Charité, Berlin, Germany); B. Hoppe, MD (University Children’s Hospital, Cologne, Germany); C.V. Schnakenburg, MD (Department of Pediatrics, University Children’s Hospital, Freiburg, Germany); D. Landau, MD (Division of Pediatric Nephrology, Soroka Medical Center, Beer-Sheba, Israel); I. Krause, MD (Dialysis Unit, Schneider Children’s Medical Center, Petach-Tiqva, Israel); R. Rahamimov, MD (Transplantation Department, Bellinson
References


