Method: Retrospective analysis of voriconazole trough levels in 53 pediatric patients following allogeneic HCT receiving fungal prophylaxis with oral or IV voriconazole. Ages ranged 0.5 to 20 years, median 14 years. Serum levels were measured by high-performance liquid chromatography. Samples were obtained 5 to 7 days after start or change in dose of voriconazole, 298 total levels were evaluated.

Results: The mean age of patients with levels < 0.5 mcg/ml was 6.4 years and 13 years for those with levels ≥ 0.5mcg/ml. Most patients failing to achieve adequate trough levels were ≤ 9 years of age (15/17 patients). A level of ≥ 0.5mcg/ml was achievable in a subset of these patients (8/15) when the dosage was increased from 4mg/kg/dose q 12h to doses ranging from 6mg to 11mg/kg/dose q12h. 7/15 never achieved a level ≥ 0.5mcg/ml despite doses ranging from 7 to 8.2mg/kg/dose. 2/17 patients that were ≤ 9 years of age did achieve a level ≥ 0.5mcg/ml with dosing of 4mg/kg/dose. Changing from oral to IV therapy in 3 patients with low trough levels did not improve the trough level. Multi-time point measurements were ≥ 0.5mcg/ml at 2 to 6 hours after oral / IV dose, but fell to 0.2mcg/ml by 12 hours in 3 patients tested. Of 298 voriconazole levels, 156 were ≥ 0.5 mcg/ml.

Conclusions: Unlike reports in adult patients, we found that frequent monitoring of voriconazole levels was necessary in pediatric patients less than 10 years old receiving HCT. In addition, younger pediatric HCT patients may require more frequent dosing schedules to achieve trough levels or initial dosing higher than the recommended adult dosing of 4mg/kg/dose q12h.

TREATMENT OF ADENOVIRUS (ADV) INFECTIONS RESISTANT TO CIDOFAVIR (C) WITH CMX001 (CMX) IN PEDIATRIC PATIENTS RECEIVING HCT

Morris, C.L.1, Painter, W.2, Lanier, R.2, Morris, J.D.1 1 Loma Linda University Hospital, Loma Linda, CA; 2 Chimerix Inc, Durham, NC; 3Redlands, CA

ADV infections early after HCT are fatal in up to 50% of patients. CDV is commonly used to treat ADV infection, but requires i.v. administration, has renal and marrow toxicity, and virus control is variable. CMX is an orally administered lipid conjugate of CDV with decreased toxicity and increased potency against dsDNA viruses, including ADV. We report our experience treating 4 patients with ADV infections after HCT with CMX who had developed resistance to CDV or could not tolerate CDV. All cases had GVHD prior to onset of infection. All had positive stool per (2) or culture (2) 16-60 days after HCT followed by viremia 2-11 days later. All received CDV for 2-8 weeks before switching to CMX. ADV responded to CMX in 2 patients followed by re-emergence after 6 weeks therapy. Two patients had no response to CDV, one with rising viremia during 2 weeks of treatment. Subsequent to CDV, these patients received oral CMX at 4mg/kg twice weekly. Three had undetectable viremia and negative GI stool per/cultures after 2 weeks on CMX. One patient died of multiorgan failure due to pre-existing liver-lung toxicity and GVHD after 4 doses of CMX. During treatment viremia fell from 89,000 to 19,000 copies/ml. After 4-6 weeks of undetectable ADV, 2 patients had CMX dose decreased to a 1x/week. ADV was detected within 2 weeks: 1 in stool, 1 in plasma and stool. Return to twice weekly CMX resolved infection in 1 and continues in 1 with viremia < 500 copies/ml and GI infection. Notably, repeat PK study in this patient showed < half of the expected levels of CMX in plasma. ADV typing by hexon analysis was performed on samples from plasma, stool, and biopsies. Two had subtype 31 one also with type 5 (dual infection), two had subtype 1. Sensitivity testing from ADV obtained at onset of infection (type 1) before treatment with CDV and 1 obtained after 6 weeks of treatment with CDV (type 31) showed resistance to CDV (> 100μM type 31 and 13.4 μM type 1) and CMX (both > 0.5μM). Toxicity is difficult to assess in these complex cases but no renal or marrow toxicity was attributed to CMX therapy. CMX 4mg/kg once weekly was not adequate to prevent re-emergence of ADV in our two patients with C resistant ADV. CMX can suppress, but does not appear to eradicate ADV infection in severely immune compromised patients after HCT. Outcome depends on durable pharmacologic control of both ADV infection and GVHD that permits eventual reduction in immune suppression.
possible to get a conclusively and directly interpretation to be reported on the standard CIBMTR data pattern.

**Method:** Study of a related allogeneic transplant case that we were asked to do the Comprehensive Report Form.

**Case:** Male, 53 years-old, MDS, HSCT infusion: 06/20/2009, PBSC, HLA-identical sibling, Bu + Flu, ANC recovery: 05/07/2009 and platelet recovery: 07/10/2009.

**Results:** Analyzing the chart, it’s seen that the interpretation of written clinical data to the standard official CIBMTR forms requires more than generalized information that are easily understood by the clinical staff with their real and daily involvement with them and the experience of practicing medicine. Data managers have a “virtual relationship” with patients, no personal contact with them and without scientific knowledge to interpret certain information and reports. What was concluded is that more detailed the clinical outcome in the patient records, more support of clinical staff and more acquired knowledge by data managers, greater the efficiency in reporting data with a high degree of fidelity.

**Feedback:** During the relationship’s period between our Transplant Center and CIBMTR we had a positive evolution of the way to deal with transplant data. Physician’s and data managers’ relation had global gains to our Center, working with the clinical outcome as the primary source of data to be consulted and having footing for this. The multidisciplinary team’s integration and the effort of the medical directors, gave the data managers (including database personnel and a nurse) a day-by-day know-how to read clinical data (not to interpret it, but the transcript to it CIBMTR standard) and thus, gradually, the intervention of medical staff shall not be so necessary. That is, reporting data to CIBMTR spawned to a natural evolution of our Transplant Center, of the team (physicians, data managers and nurse) and of the description and interpretation of clinical information, resulting in the reliability of data, generating a solid basis for prospective studies.

**99**

**Publication Bias in Blood and Marrow Transplantation: An Analysis of the Tandem Meeting Abstracts**

**Methods:** All abstracts presented at the 2006 CIBMTR/ASBMT Tandem Meeting were categorized based on type of study (clinical prospective or retrospective, translational, basic science, case report, or review), and whether the results were positive, negative, or not stated. An abstract was categorized as positive if it validated the authors’ hypothesis, or if it showed that a new treatment, diagnostic test, or procedure was useful. Two authors reviewed each abstract, and a third author reviewed disagreements (if present). To determine publication status, each abstract was searched in the MEDLINE database by first and last authors.

**Results:** 501 abstracts were reviewed. 217 were published, giving a publication rate of 43%. Median time from abstract presentation to full publication was 19 months (range 1 - 41 months). 52.5% of all abstracts were published in three journals - Biology of Blood and Marrow Transplantation (19.8%), Blood (17.5%), or Bone Marrow Transplantation (15.2%). The remaining 47.5% were published in 53 different journals, with no one journal having more than 3% of published abstracts. Abstracts that were positive were more likely to be published (50.1%) than those that were negative (33%) or not stated (29.7%) (p = 0.001). Clinical studies (retrospective or prospective) and translational/basic science studies were more likely to be published than case reports or primarily descriptive studies (p = 0.001). Specifically, 48.5% of clinical studies and 56.9% of basic science or translational studies were published, but only 7.1% of descriptive or case reports were published.

**Conclusion:** Publication bias does exist in the field of BMT, with positive abstracts significantly more likely to be published than negative abstracts. Full publication of negative results should be encouraged to provide a more balanced medical literature, and clinicians should be aware of the existence of publication bias.

**100**

**Optimizing the Role of Tacrolimus by Achieving and Maintaining Target Levels via a Loading Dose Followed by a Maintenance Dose at Emory Healthcare**

Ng, A., Wilton, N.M., Sarvari, M., Shab, K.S., Hatcherson, D.A. Emory Healthcare, Atlanta, GA

**Purpose:** Graft-versus-host disease (GVHD) is a common complication associated with allogeneic hematopoietic stem cell transplants (HSCT). Tacrolimus plays an integral role in GVHD prophylaxis. At Emory Healthcare, the daily intravenous dose has been 0.03 mg/kg/day based on ideal body weight. Over the last two decades, our target tacrolimus levels have gradually changed from 10 - 40 ng/mL to 6 - 12 ng/mL. However, our dosing has remained unchanged. Due to results of a prior evaluation demonstrating that the majority of our patients required dose reductions based on drug levels, we implemented a 48 hour loading dose of 0.03 mg/kg/day followed by a 0.02 mg/kg/day maintenance dose. We have now performed an evaluation to assess the impact of this tacrolimus dosing strategy compared to the previously studied cohort.

**Method:** A retrospective chart review was conducted in allogeneic HSCT patients who received intravenous tacrolimus from May 2008 to March 2009. Data collected included height, weight, tacrolimus doses on days - 2 through day + 10, and tacrolimus levels on days 0 through day + 10. This group was compared to the previously studied cohort receiving the standard 0.03 mg/kg dose as a control.

**Result:** A total of 22 patients were studied. The control group of 14 patients demonstrated an average dose adjustment of 54% (25% - 96%) on days 5, 7, and 10. The study group remained at an approximate average dose of 0.02 mg/kg/day for an average of 99% (50% - 200%) of the maintenance dose. Compared with the control group which had 100% of patients achieving levels > 12 ng/mL during days 1 through 10, the study group resulted in approximately 36% of patients with supratherapeutic levels. The control group had 50% of patients with levels < 6 ng/mL compared to 54% in the study group.

**Table 1. Clinical evolution × CIBMTR Pattern**

<table>
<thead>
<tr>
<th>Clinical Evolution</th>
<th>Evaluation Method</th>
<th>CIBMTR Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose: 192mg/dL</td>
<td>Acquired knowledge + lab report</td>
<td>Diabetes / hyperglycemia</td>
</tr>
<tr>
<td>Skin damage</td>
<td>Physician and data manager discussion + lab report + acquired knowledge</td>
<td>Acute Skin GVHD, overall maxim grade II, stage 2 (25-50% of skin surface)</td>
</tr>
<tr>
<td>Mouth / GI Chronic GVHD</td>
<td>Physician and data manager discussion + lab report + acquired knowledge</td>
<td>Chronic GVHD progressive, maximum grade: extensive, overall severity: severe</td>
</tr>
<tr>
<td>Unremarkable mouth lichen</td>
<td>Physician and data manager discussion + acquired knowledge</td>
<td>Are symptoms of chronic GVHD still present on the date of actual contact?</td>
</tr>
<tr>
<td>Pleural effusion / basilar consolidation</td>
<td>Physician and data manager discussion + acquired knowledge</td>
<td>Did the recipient develop non-infectious pulmonary abnormalities?</td>
</tr>
<tr>
<td>RSV+</td>
<td>Lab report + acquired knowledge</td>
<td>Organism: RSV, Infection site: sinuses, date of diagnosis</td>
</tr>
<tr>
<td>Moderate ascites</td>
<td>Physician and data manager discussion + lab report + acquired knowledge</td>
<td>Non-infectious liver toxicity (excluding GVHD)</td>
</tr>
</tbody>
</table>

**Pharmacy Oral**

**Optimizing the Role of Tacrolimus by Achieving and Maintaining Target Levels via a Loading Dose Followed by a Maintenance Dose at Emory Healthcare**

Ng, A., Wilton, N.M., Sarvari, M., Shab, K.S., Hatcherson, D.A. Emory Healthcare, Atlanta, GA

**Purpose:** Graft-versus-host disease (GVHD) is a common complication associated with allogeneic hematopoietic stem cell transplants (HSCT). Tacrolimus plays an integral role in GVHD prophylaxis. At Emory Healthcare, the daily intravenous dose has been 0.03 mg/kg/day based on ideal body weight. Over the last two decades, our target tacrolimus levels have gradually changed from 10 - 40 ng/mL to 6 - 12 ng/mL. However, our dosing has remained unchanged. Due to results of a prior evaluation demonstrating that the majority of our patients required dose reductions based on drug levels, we implemented a 48 hour loading dose of 0.03 mg/kg/day followed by a 0.02 mg/kg/day maintenance dose. We have now performed an evaluation to assess the impact of this tacrolimus dosing strategy compared to the previously studied cohort.

**Method:** A retrospective chart review was conducted in allogeneic HSCT patients who received intravenous tacrolimus from May 2008 to March 2009. Data collected included height, weight, tacrolimus doses on days - 2 through day + 10, and tacrolimus levels on days 0 through day + 10. This group was compared to the previously studied cohort receiving the standard 0.03 mg/kg dose as a control.

**Result:** A total of 22 patients were studied. The control group of 14 patients demonstrated an average dose adjustment of 54% (25% - 96%) on days 5, 7, and 10. The study group remained at an approximate average dose of 0.02 mg/kg/day for an average of 99% (50% - 200%) of the maintenance dose. Compared with the control group which had 100% of patients achieving levels > 12 ng/mL during days 1 through 10, the study group resulted in approximately 36% of patients with supratherapeutic levels. The control group had 50% of patients with levels < 6 ng/mL compared to 54% in the study group.