Four patients with Wiskott-Aldrich syndrome received bone marrow transplants (BMT) using monoclonal antibody T cell-depleted HLA-haploidentical marrow from a family member donor. The patients did not receive a significantly larger inoculum of mature T cells than other recipients of T cell-depleted marrow transplants. All four patients achieved quick engraftment, and three of the four patients are alive and well today. The three living patients have all had a complete return of normal T-cell and B-cell function. Infectious complications in the surviving patients were minimal; however, all three experienced some degree of graft-versus-host disease (GVHD). Two of these three patients received GVHD prophylaxis. The patient not receiving GVHD prophylaxis experienced severe GVHD and had a difficult posttransplant course. The patient who did not survive was chronically ill before BMT, whereas the other patients were in relatively good health at the time of BMT. Since the majority of individuals with this disease lack a matched bone marrow donor, our results using partially matched donors suggest that a greater number of patients can be successfully treated for Wiskott-Aldrich syndrome and that outcome is related to control of GVHD and state of health before BMT. Marrow transplantation should be offered earlier in the disease course before the onset of major infectious problems.

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transplant and continued daily until the total peripheral white blood cell count was 1,000/µL (day 14). ALG (20 mg/kg) was started 1 day before the day of BMT. However, a rapid doubling of the creatinine level of approximately 200 ng/mL. Grading of GVHD was based on Seattle criteria.

Patient 1 received anti-lymphocyte globulin (ALG) and prednisone. ALG (20 mg/kg) was started 1 day before the day of transplant and continued daily until the total peripheral white blood cell count was 1,000/µL (day 14). Prednisone was given on a daily basis with doses alternating 1 mg/kg and 2 mg/kg. The prednisone dose was increased to 4 mg/kg, and cyclosporine was added when graft-versus-host disease (GVHD) worsened. Patient 2 did not receive GVHD prophylaxis and experienced severe GVHD. Therefore, patients 3 and 4 received cyclosporine intravenously as a continuous infusion (5 mg/kg) beginning on the day before BMT. However, a rapid doubling of the creatinine occurred in both patients. Therefore, cyclosporine was stopped and restarted when the creatinine returned to near baseline levels. At that time, it was given in 1-hour infusions every 12 hours, beginning at 1 mg/kg each dose with gradual increases to maintain a plasma level of approximately 200 ng/mL. Grading of GVHD was based on Seattle criteria.

RESULTS

The present status of the surviving patients is shown in Table 2. All three have normal platelet counts, have remained free of infection, and have competent T- and B-cell function as measured by standard tests. No residuae or stigmata of the primary disease are present.

Graft-Versus-Host Disease Prophylaxis

The tempo of hematologic and immunologic return to normal levels is shown in Table 3. Engraftment of donor marrow was documented by HLA A and B typing of peripheral blood lymphocytes at various intervals post-BMT. Typing was unequivocal in all cases, and there is no evidence for persistence of host lymphocytes. The platelets are of normal size. Full immunologic recovery was delayed in patient 2, who had chronic GVHD, but full T- and B-cell competence has been achieved, and he attends school.

GVHD

Clinical course of patients 1 and 3. Patients 1 and 3 experienced mild to moderate GVHD. In patient 1, the primary organ systems involved were the skin and gastrointestinal tract and cyclosporine was required to attain control. The symptoms lasted over a period of 2 months with waxing and waning. Mild chronic GVHD of the skin did ensue. Patient 3 had minimal skin lesions, but pruritus was a particularly vexing symptom. Steroids and cyclosporine were given over a period of 12 weeks. No significant hepatic or gastrointestinal involvement was seen.

Clinical course of patient 2. Patient 2 was the first WAS patient transplanted with haplomatched T cell-depleted bone
marrow at the University of Wisconsin. Steroid therapy was initiated at 2 mg/kg because of a worsening of the skin on day 24 posttransplant. At this time, there was slight elevation of serum gamma glutamyl transferase (GGT) to 172 IU. He showed gradual worsening of his GVHD despite steroids, and approximately 6 weeks posttransplant, his pulmonary status acutely worsened with the picture of adult respiratory distress syndrome. He required intubation. High dose intravenous pulses of methylprednisolone (1 gm) were given and azathioprine was started. His eyes stopped tearing and corneal ulcers developed. Local prednisone ophthalmic ointment was added to the treatment regimen.

He gradually improved and ventilatory support was stopped. His liver remained involved (maximal values: GGT 4359, aspartyl aminotransferase (AST) 554, and bilirubin 8). Approximately 14 weeks after transplant, cyclosporine was added to the regimen. His skin by now was atrophic with a prominent livedo reticularis pattern. He was discharged 119 days after transplant. At that time he had chronic GVHD with skin and liver involvement and a prominent sicca syndrome requiring artificial tears. He received cyclosporin, azathioprine, and prednisone for 12 months with return of his liver enzymes to normal and marked improvement in his skin. When last seen in September, 1988, two years after the transplant, his skin was normal and there were no contractures.

Clinical course of patient 4. Patient 4 had a stormy posttransplant course and died 37 days after transplant. Before the transplant, he had experienced repeated bouts of severe Herpes simplex infections and pneumonia. Early in the transplant course, he showed evidence of liver disease. Ten days after the transplant, his creatinine rose to 1.2 (baseline 0.6) and intravenous cyclosporine (5 mg/kg continuous infusion) was stopped. His renal failure progressively worsened and hemodialysis was required. He responded, and over a period of 1 week, his creatinine gradually returned to baseline levels. During this interval his serum bilirubin slowly increased and on the ninth posttransplant day was 2.2. At that time, his alkaline phosphatase was 168, GGT 185, and AST 255. From this time until his death, his bilirubin continued to rise and was disproportionately elevated compared with GGT and AST levels. Terminally, the total bilirubin was 29.0 (direct reading 19.7), alkaline phosphatase 1127, GGT 554, and AST 144.

He showed definite neutrophil engraftment on day 15 post-BMT (1,400 total leukocyte count), and this level was sustained until his death. Skin GVHD appeared coincident with neutrophil engraftment and consisted of a generalized maculopapular eruption without bullae formation.

He developed severe hemorrhagic gastroenteritis; a colon biopsy showed only atrophic mucosa without evidence of GVHD or cytomegalovirus infection. However, Herpes simplex type I was cultured from the biopsy and adenovirus from Table 3. Tempo of Engraftment

<table>
<thead>
<tr>
<th>Neutrophils &gt;500</th>
<th>Pt 1</th>
<th>Pt 2</th>
<th>Pt 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>for 3 consecutive days</td>
<td>15</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td>Last day of platelet transfusion</td>
<td>17</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>Total lymphocytes &gt;750</td>
<td>24</td>
<td>355–393</td>
<td>120–180</td>
</tr>
<tr>
<td>CD3 + &gt; 675/μL</td>
<td>152</td>
<td>355–393</td>
<td>120–180</td>
</tr>
<tr>
<td>CD8 + &gt; 450/μL</td>
<td>152</td>
<td>355–393</td>
<td>120–180</td>
</tr>
<tr>
<td>CD8 + &gt; 225/μL</td>
<td>152</td>
<td>668–896</td>
<td>120–180</td>
</tr>
<tr>
<td>B1 + &gt; 75/μL</td>
<td>341</td>
<td>393–411</td>
<td>120–180</td>
</tr>
<tr>
<td>Specific antibody</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgA anti-E Coli</td>
<td>ND</td>
<td>&gt;895</td>
<td>NA</td>
</tr>
<tr>
<td>IgM anti-E Coli</td>
<td>ND</td>
<td>807</td>
<td>NA</td>
</tr>
<tr>
<td>IgA anti-tetanus</td>
<td>ND</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>IgM anti-tetanus</td>
<td>ND</td>
<td>510</td>
<td>NA</td>
</tr>
<tr>
<td>IgA anti-diphertheria</td>
<td>ND</td>
<td>&gt;895</td>
<td>NA</td>
</tr>
<tr>
<td>IgM anti-diphertheria</td>
<td>ND</td>
<td>510</td>
<td>NA</td>
</tr>
</tbody>
</table>

Tempo reported as number of days after BMT for values to attain criterion shown in leftmost column; where a range is shown, the value was attained during that interval between examinations.

Abreviations: Pt, patient; ND, not determined; NA, not applicable.

**"~"** means that value was greater than value as of last day of examination shown in column.

†The value did not decrease appreciably after conditioning, remaining within normal limits. Note patient 1 was never immunized pre-BMT. Values at 18 months post-BMT were indicative of nonimmunity, and the child was scheduled to undergo a primary series of immunizations.
his stool at this time. His condition progressively deteriorated, and he died of overwhelming staphylococcal sepsis 37 days after the transplant.

Patient 4 had moderate skin GVHD. Other severe systemic disease involving the liver and kidneys, followed by fatal sepsis, make the full extent of GVHD involvement (other than the moderate skin GVHD) difficult to assess in his case.

**DISCUSSION**

Bone marrow transplantation has proven to be an effective treatment for Wiskott-Aldrich syndrome and other immunodeficiencies when a matched sibling donor is available.\(^2,4,9,10-15\)

The problems of thrombocytopenia, eczema, and recurrent infections have been eliminated after successful engraftment has been established. However, more extended evaluation is needed to determine whether successful engraftment also eliminates the risk for lymphoreticular malignancies characteristic of the disease. Due to the many complications associated with this disease, a bone marrow transplant should be done early in the disease course whenever possible, or at least before the onset of major infectious complications. In our experience with other forms of primary immunodeficiency, delay has resulted in the acquisition of a complicating infection that greatly increases the morbidity after transplant and usually results in an unsuccessful outcome.\(^4\) We believe that our experience with WAS is also consistent with this view.

In the three children who were in relatively good health at the time of transplant, the engraftment was rapid and durable in two. Patient 2, who did not receive GVHD prophylaxis, experienced chronic GVHD and therefore, a lengthy recovery. We believe that had GVHD prophylaxis been instituted, he too would have had a more benign course and rapid recovery. Patient 4, however, who had a long history of severe chronic infections and was in poor health at the time of transplant, had a stormy posttransplant course and died. He may have suffered from hyperacute GVHD.

If possible, an HLA-matched bone marrow donor is used; however, the majority of individuals will lack an HLA-identical donor. In this situation a partially matched family member or closely matched unrelated individual can be used as the donor, and the marrow is depleted of T lymphocytes to prevent or diminish the severity of GVHD.\(^16\)

Our results reveal that successful engraftment can be achieved in patients suffering from Wiskott-Aldrich syndrome who do not have an HLA-identical, mixed lymphocyte culture nonreactive sibling donor. This has been accomplished with an ablative regimen consisting of TBI (or busulfan), cytosine arabinoside, and cyclophosphamide early in the disease course, followed by the administration of T lymphocyte-depleted bone marrow.\(^5,8,16\) B-cell and T-cell reconstitution were achieved within 12 months after transplant in two patients and have been ultimately attained in the third, after achieving control of chronic GVHD. Except for patient 4, infectious complications were minimal.

These data suggest that results comparable with those of Wiskott-Aldrich patients transplanted with HLA-identical donor marrow might be attained; however, one must be particularly watchful for complications of graft-versus-host disease. We believe prophylaxis is mandatory, contrary to the usual practice for combined immune deficiency disease.\(^2,4,9,10-15\) In contrast to recipients of matched non-T-cell-depleted marrow, WAS patients will also require more pretransplant conditioning (cytosine arabinoside) and may require more posttransplant immunosuppression for GVHD control. Although the long term impact on the child of these additional therapies remains to be determined, three of four children described in this report are alive and well, having previously had a disease for which there was no other treatment yet available with a curative intent. Furthermore, early transplant in growing children may prevent delayed growth and development secondary to chronic eczema, recurrent overwhelming infections, and lymphadenopathy.

The reason for the severity of GVHD in WAS is unclear. We have examined the degree of T-cell contamination for the last 21 consecutive T cell-depleted haploidentical BMT performed at the University of Wisconsin, using the method described by Martin and Hansen.\(^7\) The degree of depletion by our protocol is of the order of 1.5 to 2 logs. After depletion, the frequency of phytohemagglutinin (PHA)-responsive T cells in the bone marrow inoculum averages 1/5 to 50,000, and no patient has received more than 1.6 x 10\(^4\) mature T cells per kilogram body weight. Kernan et al.\(^15\) suggest that 10\(^3\) clonable T cells per kilogram body weight will produce GVHD. Patients 2, 3, and 4, for whom measurements are available, received 5 x 10\(^5\), 1.2 x 10\(^4\), and 1.2 x 10\(^4\), responding T cells per kilogram body weight. One cannot directly equate the number of PHA-responsive cells as determined by us to the clonable T cell number described by Kernan et al,\(^17\) but the severity of GVHD seen in other primary immunodeficiency patients previously transplanted here suggests that our numbers are of the same order of magnitude as those in their studies. In any event, the WAS patients did not receive a significantly larger inoculum of mature T cells than other recipients of T cell-depleted BMT.

We believe that the severity of GVHD is in part determined by the degree of immunity originally present in the host, and for this reason, patients with hematologic malignancy or aplastic anemia have traditionally required GVHD prophylaxis even with matched BMT, whereas those with primary immunodeficiency do not. Other factors, such as leukemia antigen and infection are also factors involved in the severity of the clinical picture.\(^18\) When the marrow is exhaustively depleted of mature T cells (3 or more log depletion), GVHD is essentially nil, but poor engraftment and leukemia recurrence are major problems.\(^11,19,20\) We have, therefore, used a less rigorous depletion protocol. In all cases of primary immunodeficiency other than Wiskott-Aldrich syndrome, this strategy has worked well without GVHD prophylaxis.\(^4\)

Although all marrows were T cell-depleted, successful engraftment was not a problem, as has been previously recorded.\(^8,11\) This confirms our experience with this conditioning regimen, which is used in the preparation of patients with hematologic malignancy as well as immunodeficiency.\(^5,8,16\)

On the basis of these results, we believe that Wiskott-Aldrich syndrome can be effectively treated with haploiden-
cal T cell-depleted bone marrow transplants. Our data indicate that outcome is related to the control of graft-versus-host disease and the overall state of health before the transplant, and our results argue for earlier, rather than later, bone marrow transplantation therapy even in the absence of an HLA-identical donor.

REFERENCES


ACKNOWLEDGMENT

We thank Joan Smith for manuscript preparation, Tom Riley for preparation of tables and graphics for this report, and the dedicated nursing staffs at The University of Iowa and The University of Wisconsin, who provide care to the children undergoing marrow transplantation.