Anti-lymphocyte Globulin Therapy in Aplastic Anaemia - A University Hospital Experience

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Summary
Antilymphocyte globulin (ALG) was given every other day for 5 doses with platelet transfusions immediately following ALG administration in 6 patients with aplastic anaemia. Four patients responded and 3 durable remissions were achieved. One patient relapsed and further treatment with anti-thymocyte globulin and cyclosporin also failed. One patient died of Flavobacterium septicaemia 6 days after completion of ALG. Our data suggests that using an alternate day regimen, a response rate similar to a daily regimen can be obtained.

Key Words: Aplastic anaemia, Alternate day anti-lymphocyte globulin, Flavibacterium septicaemia, Antithymocyte globulin, Cyclosporin

Introduction
Aplastic anaemia is an uncommon problem in Malaysia. Only 3-4 cases are seen in the University Hospital annually.

In its mild form, no treatment may be needed at all. When symptomatic anaemia, bleeding and infections occur, corticosteroids, androgens and anti-lymphocyte globulin (ALG) /anti-thymocyte globulin may be used.

In severe aplastic anaemia, the treatment of choice is allogeneic bone marrow transplantation (BMT). This is only possible if there is a compatible donor. In Malaysia, BMT is only beginning and therefore this option may not be feasible in all patients. In this situation, ALG therapy may produce good results and would be cheaper, easier and faster. The major drawbacks are continued persistence of mild aplasia and the risk of progression to leukaemia, paroxysmal nocturnal haemoglobinuria and myelodysplasia.

In this paper, we describe our experience with ALG for severe aplastic anaemia in the University Hospital.

Patients and methods
In 1993, six patients (aged 13-36 years) were given ALG using an alternate day protocol. These patients were considered to have severe aplastic anaemia based on accepted criteria (Patient 1, 2, 3) or if they had required extensive blood transfusion support and had either serious haemorrhages or infections (Patient 4, 5, 6).

ALG (Lymphoglobulin from Rhone-Poulenc Rorer) was given at a dose of 15 mg/kg/dose infusion over 6 hours on alternate days for 5 doses, after a test dose was given subcutaneously. If a reaction occurred, the infusion was slowed to be completed over 24 hours.

Promethazine 50 mg iv and hydrocortisone 200 mg iv were given just prior to every ALG administration. Prednisolone 2 mg/kg/day was given for 2 weeks and
then tailed to 1 mg/kg/day for another 1 week before
tailing off. Prophylactic ranitidine 150 mg twice a day
and co-trimoxazole 960 mg twice per week were used.

Six units of platelet concentrate were given
prophylactically prior to the first ALG administration
in all patients. Subsequently, immediately after
completion of each ALG infusion, another 6 units of
platelets were given prophylactically to prevent
haemorrhage. All blood products were given through
leucocyte filters. Venous access was secured via a central
venous catheter inserted in the cubital vein.

Results

Of the 6 patients, 3 had sustained responses to ALG
and are transfusion-free. Mean time to transfusion
independence was 50 days. The increase in cell counts
is shown in Table I.

Patient 4 responded to ALG but the response was not
sustained. Seven months after ALG therapy, he was
again transfusion dependent. Further treatment with
cyclosporin and anti-thymocyte globulin was
unsuccessful.

Patient 5 did not show any response at all and was
still transfusion dependent after 6 months. He had
been previously treated with steroids and androgens
without any response and had been diagnosed for 1
year prior to ALG therapy.

Patient 6 died of Flavobacterium septicaemia despite
appropriate antibiotics 6 days after completion of ALG.
He had had several febrile episodes prior to ALG
therapy which had required prolonged antibiotic therapy.

Adverse reactions were seen in 3 patients. Fever with
chills and rigors were observed. One patient developed
an anaphylactic reaction with swelling of the face and
upper part of his trunk. He responded to increased
intravenous hydrocortisone and promethazine, together
with prolongation of the infusion to 24 hours.

Discussion

Using androgens or high dose methylprednisolone to
treat aplastic anaemia, a response rate of 10-30% is
possible. Using anti-lymphocyte globulin or anti-
thymocyte globulin, with or without cyclosporin, a 40-
60 % response rate has been reported. Up to
80% long term remissions can be achieved using
BMT.

In Malaysia, the option of BMT is limited and most
patients have been frequently transfused before a firm
diagnosis is made. This would affect the outcome of
transplantation. Preparation of the patient and the
waiting list may result in a transplant being done
months after diagnosis.

ALG appears to be an alternative and it can be
administered readily soon after a diagnosis of aplastic
anaemia is established.

An alternate day protocol has produced comparable
results to other larger series using a daily
administration protocol. An alternate day
protocol has several advantages. If a reaction occurs,
the infusion can easily be prolonged to 24 hours and
still allow the patient to rest till the following
infusion. Prophylactic platelet transfusions are easier
to arrange in a setting where transfusion resources
are limited.

A shorter duration of illness appears to be associated
with more durable responses. The patient who did not
respond at all had been ill for more than 1 year. This
observation is consistent with that of published
series.

Adverse reactions were manageable and all patients
were able to complete the protocol. The use of
prophylactic prednisolone, hydrocortisone and
promethazine has made its administration safer.
Bleeding did not occur in any patient. Prophylactic
platelet transfusions were used to prevent bleeding that
might have resulted from worsening thrombocytopenia
during ALG infusion. Leucocyte filters were used to
minimise sensitisation and platelet refractoriness.

ALG therapy is an immunosuppressive therapy and
predisposes the patient to infections. In aplastic
anaemia, infection is a major problem. Using ALG
increases the risk of infection, especially when
combined with high dose steroids.
<table>
<thead>
<tr>
<th>Patient Number</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
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<tr>
<td>Age (yrs)</td>
<td>15</td>
<td>35</td>
<td>16</td>
<td>14</td>
<td>13</td>
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<tr>
<td>Sex</td>
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<td>Chinese</td>
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<td>Chinese</td>
<td>Malay</td>
<td>Malay</td>
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<tr>
<td>Duration of illness prior to ALG</td>
<td>5 weeks</td>
<td>3 weeks</td>
<td>30 weeks</td>
<td>30 weeks</td>
<td>70 weeks</td>
<td>8 weeks</td>
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<tr>
<td>Number of transfusions prior to ALG</td>
<td>6 pack cells</td>
<td>3 pack cells</td>
<td>3 pack cells</td>
<td>&gt;5 pack cells</td>
<td>&gt;15 pack cells</td>
<td>10 pack cell concentrates</td>
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<td>Yes</td>
<td>Yes</td>
<td>No</td>
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<td>Yes</td>
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<tr>
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<td>No</td>
<td>No</td>
<td>Yes</td>
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<td>Total platelet concentrates used during ALG therapy</td>
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<td>21</td>
<td>25</td>
<td>19</td>
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<td>16</td>
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<td>Days post ALG</td>
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<td>45</td>
<td>70</td>
<td>60</td>
<td>90</td>
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<td>123</td>
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<td>6.0</td>
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<tr>
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<td>2.0</td>
<td>1.5</td>
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<tr>
<td>Outcome</td>
<td>Responded</td>
<td>Responded</td>
<td>Responded</td>
<td>Response not sustained</td>
<td>No</td>
<td>Died during therapy</td>
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<tr>
<td>Duration of follow up</td>
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<td>13 months</td>
<td>14 months</td>
<td>18 months</td>
<td>20 months</td>
<td>NA</td>
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</tbody>
</table>

* reticulocyte index in %;  
# Haemoglobin in g/l;  
" cell counts in $\times 10^9$/l.  
NA = not available or not applicable.
Recent reports have indicated a possibility of developing clonal haematological disorders long after anti-lymphocyte globulin therapy i.e. the development of myelodysplastic syndrome, paroxysmal nocturnal haemoglobinuria and acute myeloid leukaemia. Other authors did not make this observation in their patients over long term follow-up. ALG should be reserved for symptomatic or severe aplastic anaemia patients, when BMT is not feasible.

**Conclusion**

ALG therapy is a safe option and yields good results and similar response to a daily protocol is observed using an alternate day protocol and prophylactic filtered platelet transfusions.

**References**