A UK single-centre survey of red cell antibodies in adult patients undergoing liver transplantation

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Background and Objectives Red cell antibodies may complicate blood provision and liver transplantation outcome. The aim of this survey was to document red cell antibodies in adults undergoing liver transplantation and make recommendations for clinical practice.

Materials and Methods We completed a 10-year retrospective review of adults undergoing liver transplant, in a single UK centre using 4- to 6-weekly red cell antibody screening.

Results Seven hundred and thirty seven patients were reviewed: 58 (7.9%) had antibodies. In 50 (6.8%) patients, the antibodies were clinically significant, and the commonest were Rhesus (49.5%) and Kell (11%). 33 patients had a single antibody, and the rest had multiple antibodies (range 2–5). Two-thirds of patients (38) had antibodies at presentation; 22% of these developed additional antibodies while on the waiting list or postoperatively.

Conclusion Consideration should be given to the proactive use of Rh- and K-typed blood in end-stage liver disease in order to reduce alloimmunization. In addition, regular antibody screening would enable staff to identify those with atypical antibodies and plan their transfusion support.

Key words: antibodies, liver transplant, transfusion.

Introduction

Liver transplantation is a life-saving procedure in patients with end-stage liver disease. A total of 764 liver transplants were carried out in the United Kingdom during 2011/2012 [1]. The procedure places considerable demands on both clinicians and clinical laboratory services especially the transfusion section. Transfusion support may be required at any time during the patient journey for both planned and emergency procedures. Emergencies in chronic liver disease such as gastrointestinal bleeds may require urgent massive transfusion. Each red cell transfusion places the patient at the potential risk of developing red cell antibodies. Red cell antibodies are relatively common in liver transplant patients before surgery [2–6]. Other sources of antibodies in these patients include pregnancy and the transplanted organ itself, including the donor red cells.

The presence of antibodies complicates the provision of compatible blood which may be required urgently. In extreme cases, where compatible blood cannot be provided at the time of transplant, the organ may be reallocated. In addition, the presence of red cell antibodies has been shown to be associated with poor outcome and survival [3] irrespective of any haemolytic transfusion reactions. In the UK, all potential transplant patients are screened for red cell antibodies during the initial evaluation for transplant. However, the care of such patients may be shared by a number of healthcare providers before being referred to a transplant centre. Currently, there is no nationally agreed policy for the pretransplant transfusion management of patients with chronic liver disease who may require transplantation in the future or once listed, that is, accepted for transplant. The aim of this survey was to document the...
prevalence and specificity of red cell antibodies in adult patients undergoing liver transplantation and to make recommendations for clinical practice.

Methods

Survey design

One UK centre was identified that had an established policy of screening for antibodies at 4- to 6-weekly intervals following listing. We identified all adults who had undergone liver transplantation, after being on the waiting list for 1 month or more, during a 10-year period between 2000 and 2010. Patients were identified from the liver unit database using appropriate search strategies. The list was then cross-referenced electronically with the antibody archive of the laboratory information management system (LIMS), in order to identify all patients with recorded red cell antibodies. The antibody was classed as significant if it reacted at 37°C by IAT and/or had the ability to promote accelerated destruction of red cells bearing the relevant antigen. The first appearance of the antibody was noted and was assigned to one of 3 periods: listing, that is, at the time of listing for transplant, while on the waiting list and post-transplant. The survey was registered with the Trust Clinical Audit Department (Reg no. CA4-03064-10).

Blood sampling

Patients were tested according to standard unit guidelines. An EDTA sample was taken for transfusion studies at presentation to the centre, at listing and at 4- to 6-weekly intervals while on the waiting list until the time of transplant. Samples were taken for transfusion testing following surgery and then post-discharge at 3-monthly intervals or when clinically indicated.

Transfusion testing

Transfusion studies included ABO and RhD typing, a direct antiglobulin test (DAT) and a red cell antibody screen. Red cell antibody screening and identification were performed by the hospital blood bank using a variety of methods including column agglutination technology (Ortho and Diamed) and more recently solid-phase technology (Capture RS, Galileo). Selected cases were referred for further identification to a serology reference service (NHS Blood and Transplant).

Transfusion support during transplant

Red cell concentrates (RCCs) were issued following transfusion testing. All units were leucodepleted. Electronic issue was used for patients with ABO-identical transplants without antibodies. Patients with antibodies or those undergoing ABO non-identical transplant were serologically cross-matched with ABO- and RhD-compatible red cells selected as antigen negative for significant antibodies. Kell negative units were chosen for all women under the age of 60 unless they were known to be Kell positive. The maximum surgical blood order schedule for liver transplant in 2010 was 6 units of RCCs, 10 units of fresh-frozen plasma (FFP) and 2 adult therapeutic doses (ATDs) of platelets.

Immunosuppression regime

The standard immunosuppression regime was triple therapy using a combination of tacrolimus, azathioprine and prednisolone. Other immunosuppressive agents used were MMF and cyclosporine.

Results

Prevalence of antibodies

Seven hundred and thirty seven adult patients fulfilled the study criteria. Of these, 58 (7.9%) had red cell antibodies reported at some time. Fifty patients (6.8%) had antibodies that were considered clinically significant [7]. The demographics of this alloimmunized group were as follows: male 26 and female 32, with an ethnic mix of 5 Asians, 1 Afro-Caribbean, the rest Euro-Caucasoid. Thirty-two of the 737 patients (4.3%) had antibodies (excluding non-specific) at the time of listing. A further 11 (1.5%) developed antibodies while on the waiting list and 10 (1.4%) during the postoperative period. The mean interval for significant post-transplant antibody development was 28 days (range 8–98 days). An overview of antibody development during the three periods is shown in Table 1.

Antibody specificities

A total of 91 antibodies with different specificities were recorded. The specificity of these antibodies is summarized.

Table 1 Red cell antibodies in adult patients undergoing liver transplant

<table>
<thead>
<tr>
<th>Period of antibody development</th>
<th>Number of patients with antibodies (excluding non-specific)</th>
<th>Number of patients with clinically significant antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>At the time of listing</td>
<td>32</td>
<td>31</td>
</tr>
<tr>
<td>On the waiting list</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Post-transplant</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Total</td>
<td>53</td>
<td>50</td>
</tr>
</tbody>
</table>

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in Tables 2 and 3. Thirty-three patients had a single antibody and 25 had multiple antibodies, with a range of 2–5 antibodies per patient. Fifteen antibodies were considered non-significant. These included 10 characterized as non-specific or autoantibodies and a further 5 considered not clinically significant. The commonest antibody specificities were of the Rh system (49.5%) followed by Kell (11%).

Red cell use
The median number of RCCs received per transplant was 4 units, with a range of 0 to 31. The median RCC use was 4.0 units (range 0–19) in patients who had developed single antibodies prior to the transplant and 3.0 units (range 0–15) in patients who had developed multiple antibodies. The median RCC use was 2.5 units (range 1–31) in patients who developed single de novo antibodies post-transplant and 5.0 units (range 2–10) in patients who developed multiple de novo antibodies.

Discussion
This is the first UK published study of red cell antibody prevalence in adults undergoing liver transplant in the UK. Eight per cent of adult patients undergoing liver transplant in a single centre had red cell antibodies; the antibodies were likely to be clinically significant in 6.8% of patients. This contrasts with the general patient population in which the prevalence of antibodies is estimated at 2–3% [8]. However, our results are similar to the previously quoted UK figure of approximately 8% following transfusion during surgery [8]. In our survey, all antibodies were detected before transplant and no organs were reallocated. The commonest antibodies were anti-Rh and K. Most were present at the time of listing, but de novo antibodies developed post-listing and post-transplant. These findings are slightly lower than those reported in other studies outside of the UK, in which the prevalence of antibodies in patients undergoing liver transplant ranged from 6–23% [5, 6]. The prevalence of antibodies in studies varies according to reporting methods including the period of study, that is, whether the postoperative period is included and whether all antibodies including positive DATs are reported. However, the prevalence of antibodies may be different due to real variables such as clinical practice, immunosuppression regime, transfusion support, patient age or ethnic heterogeneity.

The incidence of alloimmunization in this group of patients has generally reduced since the early 1990s. One of the earliest studies from Blomqvist in Sweden [9] found that 33% of patients had a positive DAT or antibodies, with only 50% detected immediately before transplant. The paper provided guidance for transfusion support at the time of transplant. Ramsey et al., [5] reviewed the records of 496 adults and 286 children undergoing 1000 consecutive transplants in Pittsburgh. They showed that 22% of adult and 14% of paediatric patients had RCC antibodies. The percentage of significant antibodies was 13.7% for adults and 6.3% for children. The commonest significant antibodies were anti-K, Rh and Jk*. Fifty-eight patients in that series had significant antibodies that were previously unrecorded leading to the use of partially typed red cells. Au et al., [2] described the antibody prevalence in 200 Chinese patients. The retrospective study showed that 8.8% of patients were immunized and highlighted that the spectrum of alloantibodies in Chinese patients was different from those previously reported. Their series of 200 liver transplants showed that 5 of 17 alloimmunized patients had anti-M and that antibodies were associated with an increased incidence of transfusion and higher post-transplant bilirubin. Antibodies were present in all but one patient 6 months post-transplant. More recently, Sharitmadar et al. [6] from Miami reviewed alloantibodies in 2000 consecutive adults receiving liver and other visceral transplants. 5.75% had clinically significant RCC antibodies before transplant and 0.06% developed de novo antibodies post-transplant. These figures are similar to our own, but our post-transplant figures were slightly higher at 1.2%. Our study and those of others [6, 9] demonstrate that alloimmunization occurs post-transplant despite immunosuppressive regimes. More recently, Luzo et al. [4] have reviewed their own experience in Sao Paulo. The incidence of alloimmunization was 23%, noted as higher than other centres. They proposed that this was due to
ethnic heterogeneity. Ethnicity is pertinent. In all but the Chinese studies, including our own, most antibodies that developed were within the Rh and K systems. This is consistent with studies of antibody development in northern European transfusion-dependent patients [8,10].

The limitation of this survey is that it is retrospective and that the data may be incomplete. Both databases have been well established for more than the 10-year period and are managed by database managers. However, they do not include the details of any pretransplant transfusion support provided by other hospitals or the patients’ obstetric history. We acknowledge that antibody production may be due to changes in clinical practice, including exposure to red cells. In this single UK centre, perioperative transfusion requirements have decreased, and the mean red cell use per primary adult liver graft is now approximately 4–5 units. The reduced requirement for RCC is due to the successful multidisciplinary approach to blood conservation [11]. However, the range of RCC units used for the procedures covered by this survey was 0–31 units, which demonstrates the importance of being able to provide suitable donor units. Our cohort is representative of patients with end-stage liver disease in the UK and therefore should inform UK practice. The findings from our study should be applicable to other north European centres; however, a local survey of antibody specificities is advised.

**Conclusions**

Transfusion plays an important role in the supportive care of liver transplant patients before, during and after surgery. Red cell antibodies are relatively common, and two-thirds of antibodies are anti-Rh and K, which could be prevented. Before transplant, patients are often transfused for bleeding due to the complications of portal hypertension, which may be compounded by the coagulopathy of liver disease. There are currently seven centres in the UK undertaking adult transplantation. However, management, including transfusion support, may take place within the context of shared care, that is, at a local hospital rather than at the transplant centre. It is therefore appropriate that there are agreed protocols and that a full transfusion history is available to the transplant centre. Current national transfusion guidelines recommend the proactive use of Rh-matched and K-selected RCC for transfusion-dependent patients with sickle cell disease [12]. In contrast, patients with end-stage liver disease who are not traditionally considered transfusion dependent receive random units. The proactive use of Rh- and K-typed units may prevent some of these patients from being immunized. We propose that patients with significant liver disease who are at high risk of bleeding, and those who are potential candidates for transplant, should be typed and receive selected RCC at the earliest opportunity. However, we recognize that not all patients develop antibodies and that patient selection may be difficult. In addition, not all phenotypes are readily available and the selection of RCCs must not impede the delivery of timely transfusion support. We also suggest that patients with a history of transfusion or pregnancy should be regularly screened for red cell antibodies especially once listed for transplant. These changes in transfusion policy would reduce alloimmunization in patients with chronic liver disease and allow the blood bank staff to ensure that they had access to typed units especially at the time of transplant.

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References


