Liver transplant outcomes in a Canadian First Nations population

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BACKGROUND: A higher incidence of autoimmune disorders may predispose First Nations (FN) individuals to higher rates and more severe episodes of rejection, graft loss and mortality following liver transplantation for advanced liver disease.

METHODS: A retrospective review of patient outcomes in a single centre providing long-term follow-up care for FN and non-FN patients transplanted for advanced liver disease was conducted.

RESULTS: A total of 20 FN and 129 non-FN charts were available for review. FN subjects were younger at transplantation (mean [± SD] age 32.4±4.1 years versus 46.3±1.4 years; P=0.00005), less often male (35% versus 58%; P=0.05), more commonly transplanted for autoimmune hepatitis (30% versus 4.7%; P=0.006), less often from urban residences (25% versus 74%; P=0.0001) and less compliant with medical care (20% versus 80%; P=0.007). After a mean follow-up period of 11.0±1.5 years and 8.4±0.5 years in FN and non-FN subjects, respectively, the incidence and severity of rejection, graft and patient survival were similar between cohorts.

CONCLUSION: Although demographic profiles, nature of the underlying disease and compliance differed, the rates and severity of rejection, graft and patient survival were similar in FN and non-FN patients who underwent liver transplantation for advanced liver disease.

Key Words: First Nations; Graft survival; Indigenous; Liver transplantation; Patient survival; Rejection

Liver transplantation has become the treatment of choice for patients with decompensated disease (1). Although outcomes for elective transplants are excellent, acute and chronic rejection, recurrent disease and the development of various comorbidities can result in adverse outcomes.

There are conflicting data regarding whether ethnicity influences outcome following organ transplantation (2,3). In studies in which adverse outcomes have been described in indigenous or minority populations, it has been difficult to discern whether ethnicity per se or differences in socioeconomic status, proximity to the transplant centre (rural versus urban) or compliance with medical care were responsible for the findings.

Immune-mediated disorders are more common and severe in Canada’s First Nations (FN) population (4-8). This immune ‘hyper-reactivity’ may relate to a genetic predisposition in which anti-inflammatory cytokine synthesis and release is attenuated (9). The resulting increase in the pro/anti-inflammatory ratio raises concerns regarding an increased risk of rejection after organ transplantation in the FN population. Indeed, higher rejection and lower long-term survival rates have been described in Canadian Aboriginal children and adults following kidney transplantation (10,11). Whether similar findings apply to liver transplant recipients remains to be determined.

In the present study, we retrospectively documented and compared the demographic features and clinical outcomes in FN and non-FN patients who underwent liver transplantation for end-stage liver disease over a 22-year period.

METHODS

Study population

Patients were identified using a computerized search of the Section of Hepatology database for all patients seen on at least one occasion in the Adult Liver Post-Transplant Outpatient Clinic at the Health Sciences Centre (Winnipeg, Manitoba) between January 1, 1986 (establishment of the clinic), and December 31, 2009. Patients younger than 16 years of age were excluded.

Subjects were defined as FN if they were registered under the Indian Act of Canada (ie, possessed a treaty number) or, if not registered (approximately 30% of the FN population), by self-report of their ethnicity.

Episodes of rejection were defined as an acute increase in serum alkaline phosphatase levels of higher than twice the upper limit of normal, or baseline values with no alternative explanation for the increase such as concomitant bacterial/viral infections, anatomical obstructions of the biliary tract or introduction of a new/potentially hepatotoxic medication and a return to baseline serum alkaline phosphatase levels with an increase in immunosuppression. In cases failing to respond to increases in immunosuppression, liver histology was required to confirm the diagnosis.

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Patients were considered to be noncompliant if they failed to appear for scheduled outpatient clinic visits on at least two consecutive occasions.

Statistical analysis
Categorical variables were evaluated using χ² analysis. The χ² test of association was used to examine differences in demographic factors, pretransplant diagnosis, treatment regimens, etc. The Armitage test was used to examine linear trends in proportions. Continuous variables (such as laboratory test values) were assessed using the Student’s t test for differences between means or the Mann-Whitney U test for differences in medians (as appropriate). The 95% CIs for means and for significant differences were also calculated. Kaplan-Meier product-limit survival distribution and survival curves were generated to estimate rejection-free and overall survival. Rates of acute rejection were calculated per 1000 person-years of follow-up post-transplant. Statistical significance for all analyses was set at P<0.05.

Statistical analysis was performed using NCSS statistical software (NCSS & PASS, 2004, USA [www.ncss.com]).

RESULTS
A total of 149 transplant recipients were identified (20 FN and 129 non-FN). The majority of transplant procedures were performed in London, Ontario (in excess of 75% for both groups). Deceased donor liver transplants were performed in 100% of FN and 94% of non-FN subjects (P=0.25).

The demographic features of the two cohorts are summarized in Table 1. The mean (± SD) age at transplantation was significantly lower in FN than in non-FN patients (32.4±4.1 years versus 46.3±1.4 years, respectively;
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The principal results of the present study indicate that the incidence of rejection, graft and patient survival between this particular FN population and a non-FN population undergoing liver transplantation for decompensated liver disease are similar. The results also indicate that FN subjects tend to be younger, more often women, tend to reside in rural communities, are more commonly transplanted for decompensated liver disease and that FN subjects tend to be younger, more often women, tend to reside in rural communities, are more commonly transplanted for decompensated liver disease than in the non-FN group (12 of 20 [60%]).

Rejection-free and overall survival curves are provided in Figures 1 and 2, respectively. The mean rejection-free survival was 9.1±1.6 years and 7.6±0.6 years (P=0.39), and overall survival was 11.0±1.5 years and 10 years post-transplantation for advanced liver disease. The differences observed were not statistically significant.

As indicated earlier, there is much uncertainty regarding whether ethnicity is predictive of outcome following liver transplantation. In a study analyzing United Network for Organ Sharing data, Neff et al (12) described one-, three-, five- and 10-year graft and patient survival rates that were significantly lower in 2963 African Americans compared with 29,430 Caucasian and 4369 Hispanic patients (12). Similarly, Devlin et al (13) described higher rejection rates (12.6% versus 5.9%) and lower three-year survival rates (47% versus 60%) in non-Caucasian versus Caucasian European liver transplant recipients (13). Conversely, no significant differences in survival following transplantation were reported by Forde et al (14) in 927 subjects (82% white, 13% black and 5% Asian) with acute liver failure. Lee et al (15) described similar rates of graft and patient survival one, five and 10 years post-transplantation.

Noncompliance was more common in the FN group (10 of 20 [50%]) than in the non-FN group (15 of 129 [12%]) (P<0.01). It was the perceived explanation for rejection in the majority of FN subjects (eight of 10 [80%] versus nine of 45 [20%]; P=0.007).

There were six deaths (30%) in the FN and 26 (20.2%) in the non-FN cohorts over the 22-year follow-up period (P=0.318). The causes of death are listed in Table 5. Only one death in each cohort was ascribed to chronic rejection. The high percentage of unknown cause of death in FN subjects (25%) appeared to correlate with rural/remote residence. Rejection-free survival was 9.1±1.6 years for FN and non-FN subjects, respectively. The mean rejection-free survival was 9.1±1.6 years and 7.6±0.6 years (P=0.39), and overall survival was 11.0±1.5 years and 10 years post-transplantation.

The outcomes of patients transplanted for autoimmune hepatitis did not differ from those transplanted for other conditions (data not shown).

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aggressive in FN subjects, which might help to explain the younger age at diagnosis; both disorders are more common in women (16,17). Moreover, both autoimmune hepatitis and primary biliary cirrhosis in FN populations. Indeed, our group and others have described a high prevalence of autoimmune hepatitis before transplantation was not surprising and were likely related finding. The results of the present study indicate that despite different demographics, more rural residences, a higher incidence of autoimmune liver disorders and less compliance with medical care in the follow-up period, FN patients have similar rates of rejection, graft and patient survival to non-FN subjects following liver transplantation for advanced liver disease.

**CONCLUSION**

The results of the present study indicate that despite different demographics, more rural residences, a higher incidence of autoimmune liver disorders and less compliance with medical care in the follow-up period, FN patients have similar rates of rejection, graft and patient survival to non-FN subjects following liver transplantation for advanced liver disease.

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