

# Description of cellular rejection in liver transplant patients at the Hospital Pablo Tobón Uribe 2005-2010

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## Abstract

**Introduction:** Acute cellular rejection is a complication of orthotopic liver transplantation (OLT) which occurs in between 30% and 70% of transplant patients in the first year after the procedure.

**Objective:** The objective of this study was to describe the main variables associated with cellular rejection in liver transplant patients at the Hospital Pablo Tobon Uribe in Medellín from 2005 to 2010.

**Methods:** Medical records of 248 patients who had undergone OLTs with cadaveric donor grafts were evaluated retrospectively. Patients with histological, clinical and biochemical evidence of cellular rejection were identified in accordance with universally accepted criteria.

**Results:** 44 episodes of cellular rejection in 34 patients were confirmed from among 248 liver transplantations performed in from 2005 to 2010. The incidence of rejection was 13.7%. Thirty patients (88.2%) had one episode of rejection, two (5.8%) had three episodes and two others (5.8%) had four episodes.

**Conclusions:** We describe the main features of acute cellular rejection in this series and compare them with reports in the international literature. No other reports from Colombia were found. Most cases were mild to moderate acute cellular rejection which responded well to medical management without implications for graft or patient survival.

## Keywords

Cellular rejection, orthotopic liver transplantation.

## INTRODUCTION

Liver transplantation is recognized as the optimal therapy for terminal acute and chronic hepatic illnesses. An estimated 5,000 liver transplants (orthotopic hepatic transplantation) are performed annually in the United States and Western Europe (1).

During 2011, 1,085 organ transplants were performed in Colombia. Of these, 185 were liver transplants making the liver the second most frequently transplanted organ after the kidney (2). Nowadays, hepatic transplant results are excellent due to improvements in surgical techniques, care during and after surgery, immunosuppression schemes, prophylaxis and management of infections. One year

survival rates are above 80% and five year survival rates are above 70 percent (3).

Complications occur despite these good results. The most important are vascular and biliary complications, infections, graft rejection and recurrence of illness. There are also complications associated with the treatments used in transplanted patients especially the use of immunosuppressors and broad spectrum antibiotics. The secondary and toxic effects of immunosuppressors include arterial hypertension, renal dysfunction, diabetes, ocular alterations, osteopathy, dyslipidemia, de novo neoplasia (First-line agents, including cyclosporine, increase the development of lymphoproliferative syndromes and lymphoma). All this must be taken into account when deciding upon immuno-

suppression for a transplant recipient (4). Each of these complications may interfere to one or another degree with the survival of the graft and/or the patient (3).

Cellular rejection of the hepatic graft occurs because of the intervention of the immune system which reacts to the genetic disparity between the donor and the recipient and generates a series of physiopathological conditions that cause an immune response which may advance to graft failure (5). Acute cellular rejection is the most common. It is indicated by clinical findings and biochemical changes but requires histological confirmation most of the time.

In the long run individual episodes of acute rejection have no influence upon survival of the hepatic graft or survival of the patient, but recurring events may result in permanent organ damage (5). In some cases hepatic retransplant becomes the only option to save the patient.

This study attempts to describe post-transplant cellular rejection during the first 5 years of the hepatic transplant group in a hospital in the city of Medellín. It compares those results to results reported in the world literature.

## MATERIALS AND METHODS

In the hepatic transplant program at Hospital Pablo Tobón Uribe and the Universidad de Antioquia, 269 liver transplants were performed on adults between February of 2004 and November of 2010. Of these, 15 were retransplants, all with cadaveric donors. The total number of patients at the Hospital Pablo Tobón Uribe in the city of Medellín who had hepatic orthotopic transplants from 2005 to 2010 was 248. This is a retrospective, descriptive, observational study. The sources of information are the hospital's database and the clinical histories of the patients.

### Inclusion criteria

Patients transplanted in the Hospital Pablo Tobón Uribe in the city of Medellín between 2005-2010 who showed histological, clinical or biochemical evidence of cellular rejection following surgery were included. The histology report by a pathologist had to show portal or periportal hepatitis, venulitis and/or nonsuppurative cholangitis. The severity of rejection was classified according to BANF criteria as mild, moderate and severe in accordance with inflammatory compromise. Biochemical evidence included increased levels of alkaline phosphatase, Gamma-glutamyltransferase (GGT), bilirubin, and aminotransferase. Clinical manifestations included jaundice, abdominal pain, hepatosplenomegaly and fever although these are not specific to rejection. Patients were excluded if they failed to meet these criteria.

All clinical histories and the database of the hepatic transplant group of Hospital Pablo Tobón Uribe and Universidad de Antioquia were reviewed retrospectively. Factors reviewed included social-demographic variables, tests of hepatic function and cross matched scores. In addition time of occurrence of cellular rejection, biochemical resolution time determined by normalization of hepatic function tests, and mortality rates associated with cellular rejection were also determined for our report.

Results were expressed descriptively according to existing variables in the study population. The distribution of the variables was determined by the Kolmogorov-Smirnov test. Normal distributions are presented with mean and standard deviation, but abnormal distributions are presented in terms of 25<sup>th</sup>, 50<sup>th</sup> and 75<sup>th</sup> percentiles.

## RESULTS

Between January 2005 and December 2010 (60 months), 248 liver transplants with cadaveric donors were performed in adults. The retrospective analysis found 44 episodes of cellular rejection in 34 patients for an incidence of 13.7%.

Out of the 34 patients who showed cellular rejection, 30 (88.2%) presented a single episode, while two (5.8%) presented three episodes, and two others (5.8%) presented four episodes for a total of 44 episodes among 34 affected patients (Tables 1 and 2).

**Table 1.** Behavior of cellular rejection.

Characteristic	Total	%
Age (years)	44*	12**
Gender		
Female	20	58,82
Male	14	41,18

\*Mean  
\*\*Median

**Table 2.** Episodes of rejection.

Number of patients who presented rejection		
1 episode of rejection	30	88,24
3 episodes of rejection	2	5,88
4 episodes of rejection	2	5,88

\*Mean  
\*\*Median

There were 22 cases (50%) of moderate acute cellular rejection, 10 cases (22.72%) of mild acute cellular rejection, 2 cases (4.55%) of severe acute cellular rejection, and two cases of

(4.55%) chronic cellular rejection. Eight cases (18.18%) were not possible to classify according to histological type of the rejection by means of biopsy because of counter-indications in these patients. They were classified as cases of rejection because of clinical and biochemical findings (Table 3).

**Table 3.** Histological variety.

Histopathological diagnosis	Total	%
Moderate acute cellular rejection	22	50
Mild acute cellular rejection	10	22,72
Severe cellular rejection	2	4,55
Chronic cellular rejection	2	4,55
Cellular rejection with clinical diagnosis	8	18,18

The average number of days following transplantation at which the rejection occurred was 378.18 (12.6 months) with a median of 42.5 days (1.4 months). 40 of the cases (90.9%) resolved completely, while 4 (9.1%) did not achieve resolution. One of these required a retransplant. The mortality rate associated with rejection in our study was 5.88% or 2 deaths out of 34 patients. These were both patients who did not achieve resolution. The average number of days required for biochemical resolution of cellular rejection was 30 (Table 4).

**Table 4.** Time of occurrence of rejection, time of resolution and time of biochemical resolution.

	Total	%
Time of occurrence (months)	12,6*	42,5**
Complete resolution	40	90.90
Incomplete resolution	4	9.10
Time of biochemical resolution (days)	17+	30++

\*Mean

\*\* Standard deviation

+ 25th percentile

++ 75th percentile

The average value of aspartate aminotransferase (AST) measured at the time of cellular rejection was 54.25 U/L while the average value of aspartate alanine transaminase (ALT) was 234 U/L ( $\pm 164$ ). The alkaline phosphatase (ALP) average was 257 U/L ( $\pm 184$ ) and the gamma-glutamyl transpeptidase average was 681 U/L ( $\pm 506$ ). Total bilirubin was 7.34 mg/dl ( $\pm 5.64$ ) and direct bilirubin was 2.03 mg/dl (The 75<sup>th</sup> percentile is 8.38.) The average platelet count was 142,795 ( $\pm 89,874$ ). Cross matching was negative in all patients with cellular rejection (Table 5).

## DISCUSSION

Liver transplantation has become the choice treatment for patients with terminal hepatic illness (6). Since the first

liver transplant was performed in 1963 by Thomas Starzi (7), knowledge about this procedure and its complications has increased. Cellular reaction continues to an important consideration associated with transplantation since between 30% and 70% of transplanted patients present cellular rejection within a year of the procedure. The highest incidence occurs in the first 7 to 10 days, but a great number of episodes also occur during the first and second year after transplantation (8).

**Table 5.** Biochemical profile.

Biochemical marker	Mean	SD
AST (U/L)	54,25*	218,25**
ALT (U/L)	234,48	164,08
FA (U/L)	257,68	184,16
GGT (U/L)	681,23	506,25
BT (mg/dl)	7,43	5,64
BD (mg/dl)	2,03*	8,38**
Platelets	142.795	89.874
Cross matching	34+	100++

\* 25th percentile

\*\* 75th percentile

+ Number of patients

++ Percentage

Based upon the reversibility and histologic characteristics of the inflammatory infiltrate, rejection is divided into hyper-acute (mediated by antibodies), acute (cellular) and chronic (ductopenic). Hyper-acute rejection appears a few hours after transplantation and originates as a consequence of the humoral reaction of preformed antibodies (5, 9). Acute rejection generally occurs weeks or even months after transplantation and is mediated by T cells. It is a response to recognition of allogenic determinants of the transplanted liver such as those of the major histocompatibility complex (10). Chronic rejection occurs months after transplantation. Its primary histologic characteristic is the progressive destruction of biliary ducts (6).

Risk factors identified for cellular rejection include youthful age, black race (11), transplants required as the result of auto-immune illnesses (12). transplants required as the result of hepatic failure, cold ischemia time longer than 15 hours, donors older than 30 years (7). and recipients infected with hepatitis C virus (13). Studies have shown that original illnesses also influence the incidence of rejection. The rate of rejection is lower among patients with alcoholic hepatic illness than in patients with primary biliary cirrhosis (14). Patients from rural areas have higher incidences of rejection than other patients (15). Other risk factors that have been associated with cellular rejection after transplantation include transplanted tissue containing

biochemical markers such as the modulator of mitochondrial RNA CXCL9 (16).

The 13.7% incidence of cellular rejection found in this study is lower than those reported in other studies (17). The low mortality rate of 5.88% associated with cellular rejection means that these patients have good prognoses in our institution.

The primary indication for transplantation among the patients who presented cellular rejection was cryptogenic cirrhosis. This was reported in 9 (26.47%) of the 34 patients while alcoholic cirrhosis was found in 9 patients and primary biliary cirrhosis was found in 6 patients (17.65%). These data contrast with Neuberger's report<sup>15</sup> because our study included a higher proportion of rejection among patients with alcoholic illness than in patients with primary biliary cirrhosis. In addition we observed a slight trend towards more frequent rejections among women (58%) than men. The study proportion was one woman for every 1.31 men. Base pathologies of auto-immune illnesses and cryptogenic cirrhosis were more common among women.

The mean age at rejection time was 44 years which is compatible with the risk factors previously mentioned since there is a higher rate of rejection among young adults. The low death rate among patients transplanted in the unit shows a higher percentage of success than in other studies (18), but an analytical study would be required to explain this finding. It is unlikely for acute rejections to require retransplantation while 28% to 35% of the patients who present chronic cellular rejection do not respond to treatment with high dosage of steroids and do require retransplantation. In this center, only one patient required retransplantation because of failure of rejection to resolve resulting in a lower incidence than that globally reported (19). Nevertheless, this may be due to the higher proportion of acute rejections than chronic rejections given that the latter is more closely associated with the need for retransplantation.

In conclusion, this series describes the primary characteristics of acute cellular rejection and compares them to the international literature. No other Colombian reports were found. Most cases were mild or moderate acute cellular rejections which responded well to medical management without repercussions to the survival of the graft or the patient.

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