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Research Article

Descriptive Study of Drug Induced Liver Injury in Kidney Transplant Patients

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ABSTRACT

Drug induced Liver injury (DILI) is one of the most common complications after renal transplantation.

That's why, we conducted a study wich aims to identify and describe cases of DILI that occurred after kidney transplantation at the University Hospital-establishment-Oran (UHEO).

It is a retrospective study (June 2010 to March 2017), based on renal transplant recepients (RTRs) records archived at the kidney transplant unit of the nephrology department of UHEO.

First, we have collected DILI characteristics required for the causality assessment by two methods: the naranjo et al method and the CIOMS scale.

Our study found that 23% of renal transplant recipients developped suspected DILI. The concerned patients were predominantly young men (age ≤ 32 ans). Suspected DILIs were mainly cytolytic (57%), which is comparable to the study of Hajime Takikawa et al. (55%).

According to the CIOMS method, causality was possible in 57% of cases.

The incriminated drugs were immunosuppressants, diuretiques, antimicrobials and painkillers, and they were described as hepatotoxic according to livertox database.

Moreover, DILIs were managed principally by dose reduction, momentary drug cessation or switch to another drug. Prophylactic application of Bicyclol was reported as a protective factor against DILIs at an early stage after renal transplantation. Fortunately, all DILI cases evolution in RTRs was favourable.

Close monitoring, especially therapeutic drug monitoring, should prevent severe DILIs. Also, a performant pharmacovigilance system would allow an early identification of the offending drug for a better prognosis.

Keywords: DILI; Pharmacovigilance; Kidney transplant recepients

INTRODUCTION

After kidney transplantation, Kidney transplant receipients can develop acute liver injuries from multiple causes [1,2]. Its incidence is 20%-60% [2,3].

They often occur between two weeks and three months after kidney transplantation and are mainly drug induced [3].

Moreover, DILI a has serious impact on patients' life expectancy and life quality [3].

Therefore, we conducted a study aiming to identify and describe cases of drug hepatotoxicity that occurred in RTRs at the UHEO.

METHODS AND MATERIALS

Our study was retrospective (June 2010 to March 2017), based on RTRs records archived at the kidney transplant unit of nephrology department of UHEO.

The main inclusion criterion was the manifestation of acute hepatotoxicity after kidney transplantation contemporaneously

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with drug intake, when non-drug origin could not explain the lesion.

We have excluded any patient with an underlying condition that can explain liver damage.

To collect data, we have designed a sheet adapted to DILI characteristics necessary to assess causality.

This sheet is then analyzed:

- Analysis of drug interactions, [4,5]

- Liver injury study (chronology, contributing factors, pathogenic mechanism, non-drug origins)

- Assessing causality using a non-specific method (the Naranjo et al. method) and a DILI-specific method (the CIOMS scale) [6,7].

RESULTS

Among a total of 31 RTRs at the UHEO between June 2010 and March 2017, we found 7 cases of acute drug hepatitis (ADH) and 11 cases of asymptomatic impairment (liver transaminases rate < 2 N).

Our study showed that the age of patients who have developed liver injury ranges from 25 to 32 years.71.4% of ADH cases had an age between 20 and 29.

The gender ratio between men and women was 0.4, in favor of men Figure 1.

Cytolytic injuries were the most common (57%). Cholestatic impairments, on the other hand, were the rarest (14%).

The causality assessment with the CIOMS method was only possible for cases with liver transaminases (AST/ALT) rate > 2N.

According to the CIOMS scale, causality was « possible » in 57% of cases, unlikely in 29% and excluded in 14% of cases.

The most reported drugs were immunosuppressants in 29%. Other classes were also incriminated such as painkillers, diuretics and antimicrobials Figure 2.

According to the Naranjo et al. Method, causality was probable in 57% of cases and possible in 43%.

The agreement between the results of the two methods was estimated with the weighted kappa parameter [8-10]. (weighted kappa =0.152). The strength of agreement is considered to be poor.

Moreover, DILIs were managed principally by dose reduction, momentary drug cessation or switch. The evolution was favorable for all DILI cases.

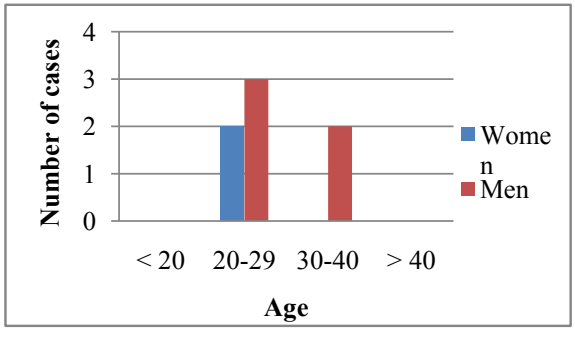

Figure 1: Cases repartition according to sex and age.

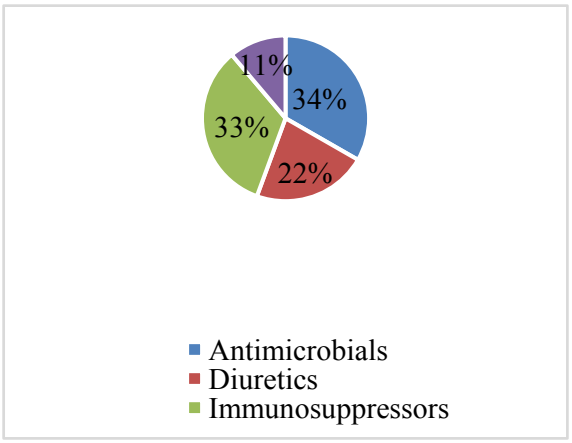

Figure 2: Incriminated drugs according to the CIOMS scale.

DISCUSSION

First, our study found that 23% of renal transplant recipients developed acute liver damage in the post-transplant period. This frequency would be higher (58%) taking into account asymptomatic impairments.

RTRs who have developed DILI were predominantly young men.

This can be explained by the greater number of male transplants recipients in comparison with female sex, As well as the rarity of kidney transplant among elderly subjects since they are offered dialysis [11,12].

Among DILI cases, cytolytic impairments were predominant (57%), which iscomparable to the study of Hajime Takikawa et al. (55%) [13].

The drugs incriminated by the CIOMS scale were described as hepatotoxic according to the livertox database, [14] especially immunosuppressants (cyclosporine >30% of patients) [15].

Comparison of the results of the two CAMs demonstrated a poor agreement, a similar strength of agreement was reported by García-Cortés M et al.2008 (kappa=0.15) [16]. We have noticed that naranjo et al method overestimates the causality grading compared to the specific method which is considered as the reference method [7] and should be used by our clinicians systematically when suspecting DILI.

Prophylactic application of Bicyclol was reported as a protective factor against drug induced liver injuries [17-19] particulary at an early stage after renal transplantation [3].

DILI can lead to liver transplantation or death in 11.7-15% of cases of idiosyncratic drug reactions [1]. Fortunately, the evolution was favorable for all DILI cases identified during our study.

CONCLUSION

Therapeutic protocols in RTRs are probably the cause of frequent and severe liver damage.

Close monitoring, particularly therapeutic drug monitoring would prevent or reduce DILI cases severity.

Moreover, a powerful pharmacovigilance system allows early identification of the offending drug for a better prognosis.

Clinicians sensibilization to report these cases is essential to secure drug use after renal transplantation.

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