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PHARMACOLOGICAL THERAPEUTIC MONITORING OF MYCOPHENOLATE MOFETIL (MMF) IN AUTOIMMUNE DISEASES AT EHU OF ORAN-ALGERIA : CONTRIBUTION OF PHARMACEUTICAL INTERVENTIONS

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ABSTRACT

Introduction : Mycophenolate mofetil (MMF) is an immunosuppressant indicated for organ transplantation and other autoimmune diseases. The pharmacological therapeutic monitoring (PTM) of the MMF based on the measurement of the area under the curve (AUC) is justified. **Objective :** The objective of our study was to evaluate the contribution of pharmaceutical interventions emitted during MMF PTM of patients with autoimmune diseases in the pharmacovigilance service of the EHU of Oran-Algeria. **Material and Methods :** This is a retrospective descriptive study of 5 years, dealing with patients treated by MMF for all autoimmune diseases in pharmacovigilance service of the EHU of Oran-Algeria. In total, 60 patients were monitored. The average age of the study population was 29.81 years with a female predominance of 56.66% (sex ratio 0.7). **Result and Discussion :** In our study lupus nephropathy represents the most common pathology with a rate of 51.67%, followed by nephrotic syndrome with 41.67%. 106 AUC were measured, 37.74% were below 30 mg.h / l, 49.06% were between 30 and 60 mg.h / l and 13.20% of the AUC were above 60 mg / h. / l. The signs of intolerance observed were : 60.42% of the disturbances of the hemogram, 16.67% of the various infections, 12.5% of the cutaneous affections and 10.41% of the digestive disorders. Various pharmaceutical opinions have been issued to manage this drug iatrogenic. **Conclusion :** The results of our study show that PTM has a major interest in predicting of response to MMF in autoimmune diseases. The application of MMF PTM in routine clinical practice should be generalized to adjust the dosage of MMF to improve the efficacy and reduce the adverse effects of this drug.

Keywords: Mycophenolate Mofetil, Pharmacological therapeutic monitoring, Autoimmune disease, Pharmaceutical intervention.

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INTRODUCTION

Mycophenolate mofetil (MMF) is the ester of mycophenolic acid (MPA). MPA is a reversible inhibitory antimetabolite of inosine monophosphate dehydrogenase (IMPDH), which disrupts de novo synthesis of purine nucleotides. [1], [2] This leads to a cytostatic effect of B and T lymphocytes (helper and cytotoxic), the proliferation of which is blocked at the late stage. It has immunosuppressive properties used in organ transplantation and other autoimmune diseases.[3] MMF presents all the pharmacokinetic characteristics that make pharmacological therapeutic monitoring (PTM) necessary. Indeed, it has a narrow therapeutic margin, associated with a large inter- and intra-individual variability of pharmacokinetic parameters. [4] There are few clinical studies on the efficacy and safety of patients with autoimmune disease for which MMF therapy is initiated.[5] Efficacy and side effects are most often correlated with the patient's exposure to the drug. This exposure can be assessed by measuring the area under the curve (AUC) of blood concentrations according to time. [6] The objective of our study was to evaluate the contribution of pharmaceutical interventions emitted during MMF PTM in patients with autoimmune diseases in the pharmacovigilance service of the EHU of Oran-Algeria.

MATERIALS AND METHODS

This is a retrospective descriptive study of 5 years, from 26/12/2012 to 19/05/2017, concerning files of the patients treated

by MMF for all autoimmune diseases in pharmacovigilance service of the EHU of Oran Algeria. The blood sample is taken on a tube with anticoagulant (heparin or EDTA). It is accompanied by a monitoring sheet of the MMF as given in Figure 01.

Figure 01: MMF monitoring sheet.

The PTM is done in collaboration with the service of Pharmacology-Toxicology CHU Limoges-France. It is based on the measurement of AUC0-12h of MPA by Bayesian estimation using a limited sampling strategy (three samples over three hours). The sampling specifications were presented in Table 1. The MMF assay is performed on plasma using an enzyme immunoassay method (EMIT ; Enzyme Multiplied Immunoassay Technique) on viva-E.

Table 01: Specific hours of sampling.

Pathology	Sampling time
Lupus	C40 min, C2(h), C3(h)
Nephrotic syndrome and others	C20 min, C1(h), C3(h)

RESULTS

60 patients were included in this study, with a female predominance of 56.66% (sex ratio 0.7) as shown in Figure 02.

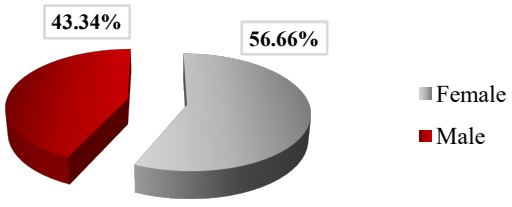

Figure 02: Distribution of the population by sex.

The distribution of patients by age group shows that the group with the highest rate is that of 20 to 50 years (48.33%), followed by the age group of 0 to 19 years with 35% and the age range greater than 50 represents 16.67%. The average age of the population was 29.85 ± 13.85 years as seen in Figure 03.

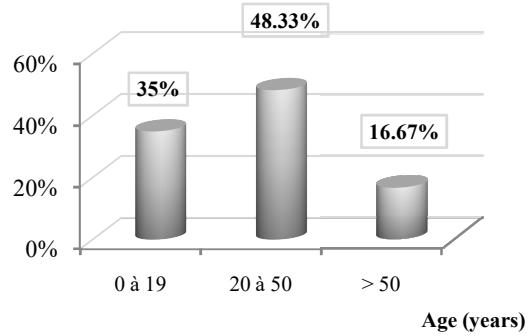

Figure 03: Distribution of the population by age group.

The distribution of the population by weight shows that 71.67% of patients weigh between 40 and 77kg. The average weight of the population was 59.48 ±15.98 kg as observed in Figure 04.

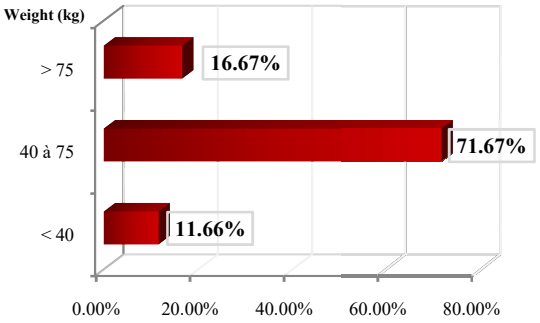

Figure 04: Distribution of the population by weight.

Lupus nephropathy represents the most common autoimmune pathology with 51.67%, followed by nephrotic syndrome with a rate of 41.67% as presented in Figure 05.

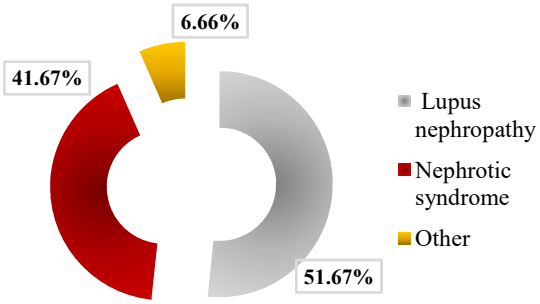

Figure 05: Distribution of patients according to the type of pathology treated.

The reason for the measurement of the MMF's AUC was : 58.5% for a control, 18.9% for a risk of toxicity and occurrence of adverse effects, 13.1% for suspicions of inefficiency and 9.5% for reasons of modification of dosage as presented in Figure 06.

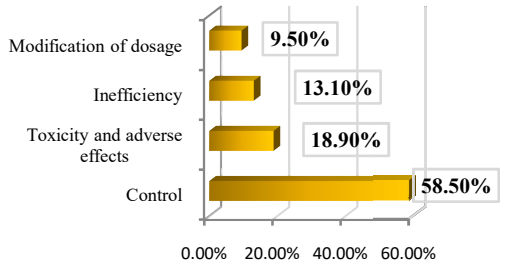

Figure 06: Reasons for the measurement of the MMF's AUC.

106 AUC were measured, 37.74% of the values were below 30 mg.h / l, 49.06% were between 30 and 60 mg.h / l (29.25% between 30 and 45 mg.h / l and 19.48% between 45 and 60 mg.h / l) and 13.20% of the AUC were greater than 60mg.h / l as seen in **Figure 07.**

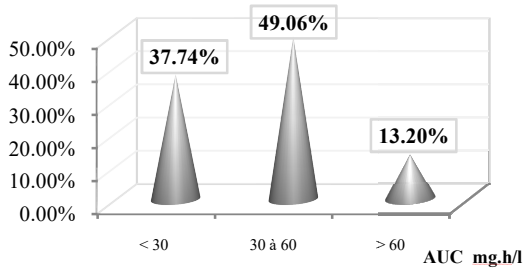

Figure 07: Distribution of MMF AUCs values relative to the therapeutic range in all patients.

Of the 24 patients who did more than one MMF test in our service; 49 AUCs were measured. The results showed that 67.35% of the AUC were included in the therapeutic range after pharmaceutical intervention, ie 22.45% of the AUCs were lower than the normal values, this is due to the non observance of the patients and to the appearance of the undesirable effects notably digestive and cutaneous in therapeutic doses and finally 10.20% of the AUCs were higher than the therapeutic values, these patients are stable and balanced with these values as shown in Figure 08.

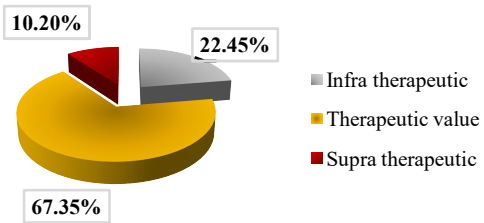

Figure 08: Values of AUCs measured after pharmaceutical intervention.

The occurrence of adverse events was associated with an infra-therapeutic AUC in 43.75%, 35.42% at an AUC within the therapeutic range and 20.83% at a supra-therapeutic AUC. This suggests that the undesirable effects of MMF appear indifferently in patients under-dosed, balanced and over-dosed as presented in Figure 09.

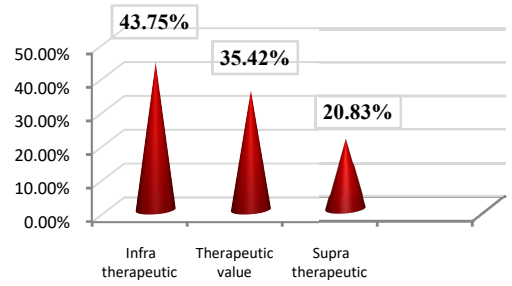

Figure 09: Exposure relationship to MMF and adverse effects.

The signs of intolerance observed in patients treated with MMF were: 60.42% of the disturbances of the hemogram, 16.67% of the various infections, 12.5% of the cutaneous affections and 10.41% were digestive disorders as presented in Figure 10.

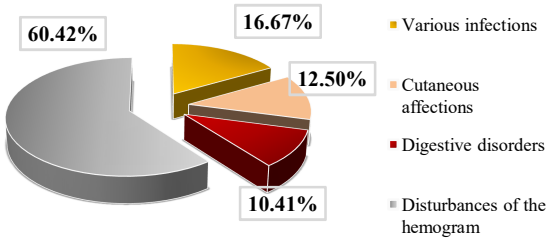

Figure 10: Nature of undesirable effects under MMF.

The disturbances of the hemogram observed were: 89.66% of the anemias and 10.34% of the leucopenia and presented in Figure 11.

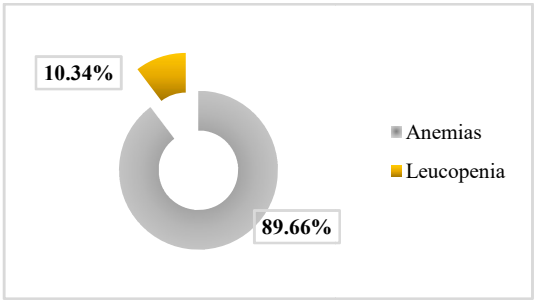

Figure 11 : Disturbances of the hemogram.

DISCUSSION

Based on our results, MMF's AUC measurement revealed that 37.74% of values were below therapeutic values and may be ineffective and 13.20% of values exceeded therapeutic values and exposes patients to toxic risks of MMF, hence the interest of our study. Several studies in adult or pediatric patients with an

autoimmune disease for which MMF therapy has been initiated have shown, at a minimum, that a MMF PTM based on the measurement of AUC is justified and this global exposure index is very likely to correlate with the expression of the disease. [6] It has been shown that MMF PTM both reduce the risk of treatment failure and improve tolerance of the drug. [7]

Our results showed that 67.35% of AUCs were included in the therapeutic range after pharmaceutical intervention. MMF dose adjustment based on AUC, pharmacokinetic modeling and Bayesian estimation, significantly reduced inter and intra-individual variability in MPA exposure and thus minimized under- and over-exposure. which was in the order of 22.45% and 10.20% respectively. According to the results of our study, the undesirable effects of MMF appear indifferently in patients under-dosed (43.75%), balanced (35.42%) and over-dosed (20.83%). There is no evidence of a relationship between the residual concentration or AUC of MPA and the occurrence of adverse effects. [1], [2], [6] According to our results, hematological disorders ranked first among the signs of intolerance observed in patients treated with MMF: 60.42% of all the undesirable effects observed. Areas under the MPA curve are predictive of serious hematologic adverse events. [7] Some adverse effects, particularly gastrointestinal side effects, may be reduced by dose fractionation or meal administration (which decreases the maximum concentration (Cmax) by approximately 40% without modifying the MMF AUC).

CONCLUSION

PTM has a major interest in predicting the response to MMF in autoimmune diseases. The application of MMF PTM in routine clinical practice should be generalized to adjust the dosage to improve the efficacy and reduce the adverse effects of this drug.
In the same way as the plasma assay, the identification of the factors involved in the pharmacokinetic variability of MMF such as renal insufficiency, hepatic insufficiency and hypo-albuminemia and also the genetic factors that control expression levels MMF metabolism enzymes, is part of individualization and therapeutic optimization. Studies correlating pharmacokinetics with efficacy and aiming at optimizing specific treatments adapted to the population in question should be implemented. [5]

CONFLICT OF INTEREST

The author declares that he has no competing interests.

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