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A Study of Serious Adverse Event associated with the use of Antiproliferative Immunosuppressive Drugs (MMF) in organ transplanted Patients

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ABSTRACT

Organ transplantation by Mycophenolate mofetil (MMF) is crucial component for treatment of choice for patients suffering from End Stage of Organ Disease, But to prevent the patient life, after transplantation the foremost requirement is a well-defined immunosuppressive therapy. Mycophenolate mofetil (MMF) was first used in the early 1990s and it is a highly effective immunosuppressant drug used in the prophylaxis of organ rejection.27 MMF is a prodrug that is rapidly metabolized to its active metabolite mycophenolic acid. 324 cases were reported from literature sources. 296 cases were judged as serious and the remaining 28 cases were judged as non-serious. Thirty two cases were reported with a fatal outcome. A total of 324 cases consisting of 1116 ADRs. This study aims to identify and characterizing to Serious Adverse Event associated with Mycophenolate mofetil used to prevent graft rejection in solid organ transplant and graft-versus-host disease in transplant patients

1. INTRODUCTION

Due to improvements in surgical techniques and advance in medical technology used in immunosuppressant to treat Organ transplantation for patients suffering from End Stage of Organ Disease, but to prevent the patient life, after transplantation the foremost requirement is a well-defined immunosuppressive therapy. Organ transplantation initially came to the first exclusively successful kidney transplantation in 1954[1]. Number of candidate on waiting list for organ transplant regularly to increase, while number of donor's level reduced. In United States, there were 11,663 organ donors and 23,360 organ transplants from January to October 2012[2]. From2010to2011 the organ transplantation patients in United States increased by 0.2% from 54505 to 54599 but the number of organ transplantation declined by 0.7% from 17726 to 17604[3]. By various epidemiological studies it has been found that in 2004 a total of 26,539 solid organ transplantations were performed in which Kidney transplants were most common; 9,025 from cadaveric donors and 6,646 from liver donors[4].

Immunosuppressive agents: Immunosuppressive agents aims to provide minimum suppressions to immune system to prevent transplant rejection whereas avoiding or minimizing complication of immunodeficiency. It is generally achieved by depleting lymphocytes, diverting lymphocyte traffic, or locking lymphocyte response pathways. Immunosuppressant's generally have multiple actions including therapeutic effect (suppressing rejection), infection or cancer (secondary effect of immunosuppression) and toxicity to other tissues[5].

Classification of Immunosuppressive drugs: They include small molecule drugs, depleting and non-depleting protein drugs (polyclonal and monoclonal antibodies), fusion proteins, intravenous immunoglobulin, and glucocorticoids. Table 1 shows the classification of immunosuppressive agents which are generally used in solid organ transplantation[6,7].

Table.1.Classification of immunosuppressive drugs

Class	Drug name
Calcineurin inhibitors (Specific T-cell inhibitors)	Cyclosporine, Tacrolimus
mTOR inhibitors	Sirolimus,everolimus,pimecrolimus
Antiproliferative Drugs	Azathioprine, Mycophenolate mofetil (MMF), Methotrexate
Corticosteroids	Methyl prednisone, Prednisolone.
Antibodies	Muromonab CD3, Antithymocyte globulin (ATG).

Types of immunosuppressive therapies: Immunosuppressive therapies can be sub-divided into following types.

Induction Therapy: The main aim of this therapy is to provide high level of immunosuppression, as to prevent the graft from body early immune response. It consists of one of two perioperative immunosuppressive strategies:

a. The provision of highly intense level of immunosuppression either universally on the basis of patient risk factors like age, race etc.

b. The use of antibody therapy to provide enough immunosuppression is to delay the initiation of therapy with nephrotoxic calcineurin inhibitors.

The above (a) practice is generally followed in renal transplanted patients in whom newly transplanted kidney is highly susceptible to nephrotoxic injury, where in liver and heart transplanted patients the rationale of using this practice is to protect them with pre-existing renal insufficiency from further injuries[8].

Maintenance Therapy: The goal of this therapy is to provide low or moderate level of immunosuppression while saving graft from rejection. Therapy typically involves a calcineurin inhibitor, glucocorticoids and anti-proliferative drug like mycophenolate mofetil[9].

Anti-Rejection Therapy: The prime aim of this therapy is to minimize the immune response so that to prevent the graft from the injury. The therapy generally started with pulse therapy of methyl prednisolone, with or without subsequent increase in doses of ongoing immunosuppressive regimen of patient. Generally the acute rejection is reversed with three to four doses of methyl prednisolone but some cases are less responsive to this therapy so subsequently antibodies like Anti Thymocyte Globulin (ATG) or Muromonab[4].

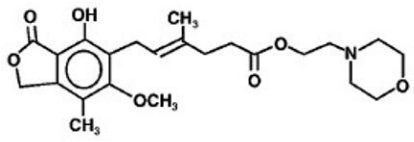

Figure.1.Chemical structure of Mycophenolate mophetil

Drug review: Mycophenolic acid (MPA), the active metabolite of mycophenolate mofetil, was first isolated from Penicillium brevicompactum in 1896 by Bartolomeo Gosio, an Italian physician and microbiologist[10].

Mycophenolate mofetil (MMF) was first used in the early 1990s.27 MMF is a prodrug that is rapidly metabolised to its active metabolite mycophenolic acid. A few years ago, mycophenolic acid also became available directly as Myfortic. MMF inhibits lymphocyte function by blocking purine biosynthesis via inhibition of the enzyme inosine monophosphate dehydrogenase[11]. In most eukaryotic cells, blocking inosine monophosphate dehydrogenase has little effect on cell division because purines can also be generated from nucleotide breakdown products, the so-called purine salvage pathway. Because B and T lymphocytes lack this pathway, MMF is a more selective antiproliferative agent than azathioprine[12,13].

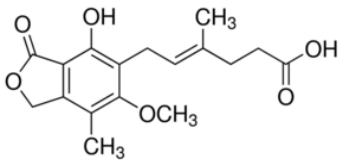

Figure.2.Chemical structure of Mycophenolic acid

2. MATERIALS AND METHODS:

(i) Individual Case Safety Reports

(ii) MedDRA

(iii) Safety Database

A Primary Search for Case Reports was carried out in PubMed. The PubMed Search used the following MeSH terms: Immunosuppressive Drugs, Mycrophenolate Mofetil, Serious Adverse Event, Pharmacovigilance, and Organ Transplant Patient. The same search was repeated using Review [Publication type] in order to yield source material for a secondary reference search.

Additional Electronic Searches using similar strategies were carried out using the Cochrane Library and Google Scholar. Case Reports were examined for Identifiable Patient, Suspected Drug, Adverse Drug Event, Seriousness, Listdness.

The Individual Case Safety Reports received from Local database and Literature search were included in the study. Adverse Reaction terminologies and the indication were coded as per Medical Dictionary for Regulatory Activities. (MedDRA Version: 19.1)

Literature case reports were included and processed based on the Good Pharmacovigilance Practices. As per Good Pharmacovigilance Practices 'If the medicinal product source or the invented name is not specified and ownership of the product cannot be excluded on the basis of the active substance, formulation or route of administration, the MAH should assume that it is one of their products the publication refers to, although the report should indicate that the specific product source and the invented name was not specified.

Method used: study of case report obtained from literature: The data from the case reports of patients

receiving Mycrofinolate mofteail were extracted from literature.

Line listing of data extracted from case reports: The Line Listing of Case Reports was prepared in Microsoft Excel including various parameters like Country, Patient Age, Gender, Product Name, Adverse Drug Reactions (lower term and preferred term), System Organ Class, Outcome of the Event etc.

Coding using MedDRA: Adverse Drug Reactions and System Organ Class were coded using MedDRA. The preferred term (PT) hierarchy of the medical dictionary for regulatory activity was used to identify serious adverse events that resulted in life –threatening experience, persistent or significant disability or birth defects, initial or prolonged hospitalization or any other important medical outcomes. Within these reports signals were evaluated for specific adverse events[14,15,16,17].

Analysis of adverse drug events/ cases: In Excel Spread Sheet using Pivot table: Using Pivot tables various tables were generated containing various parameters which aid in analysis of various parameters.

3. RESULT AND DISCUSSION

324 cases were reported from literature sources. 296 cases were judged as serious and the remaining 28 cases were judged as non-serious. Thirty two cases were reported with a fatal outcome. A total of 324 cases consisting of 1116 ADRs, 303 were serious unlisted, 503 were serious listed, 221 were non serious listed and 89 were non serious unlisted. Listedness was done as per the SmPC of Mycophenolate mofetil. The maximum numbers of ADRs were reported from the SOC "Infections and infestations" with 169 ADRs. Second highest number of ADRs was reported from the SOC "Gastroinestinal Disorders" with 118 ADRs.

Demographics profile of the patients: Male predominates over female. Of the total 324 patients, 207(64%) were males and 117(36%) were females. Highest number of patients (both males and females included) were in the age group of 52-67 years (135patients, 41.6%), followed by the age group of 42-51 years (67 patients, 20.7%), and 12-47 years (122 patients, 37.7%).

Disease profile of the patients: It was observed that most of the organ transplantation patients treated by MMF, 324 cases were reported from literature sources. 296 cases were judged as serious and the remaining 28 cases were judged as non-serious. Thirty two cases were reported with a fatal outcome.A total of 324 cases consisting of 1116 ADRs, 303 were serious unlisted, 503 were serious listed, 221 were non serious listed and 89 were non serious unlisted. Listedness was done as per the SmPC of Mycophenolate mofetil .The maximum numbers of ADRs were reported from the SOC "Infections and infestations" with 169 ADRs. Second highest number of ADRs was reported from the SOC "Gastroinestinal Disorders" with 118 ADRs.

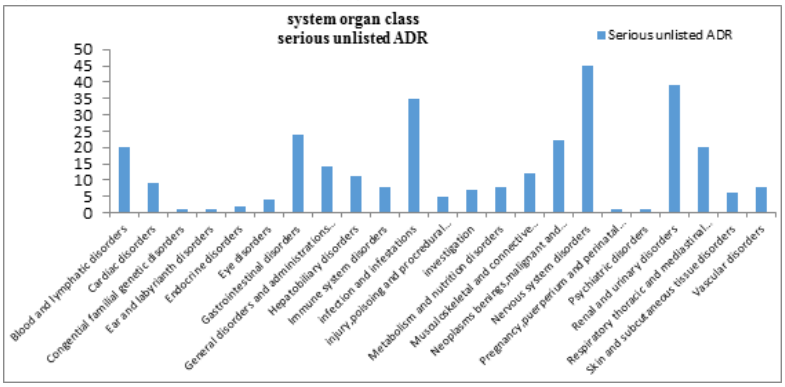

Figure.3.System organ class serious unlisted ADR

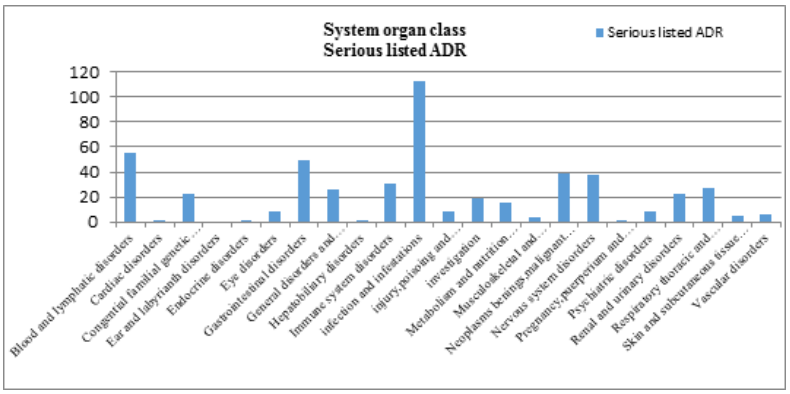

Figure.4.System organ class serious listed ADR

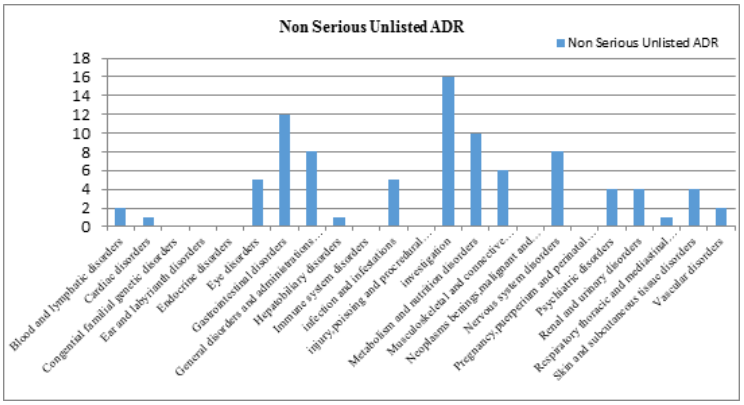

Figure.5.System organ class non-serious unlisted ADR

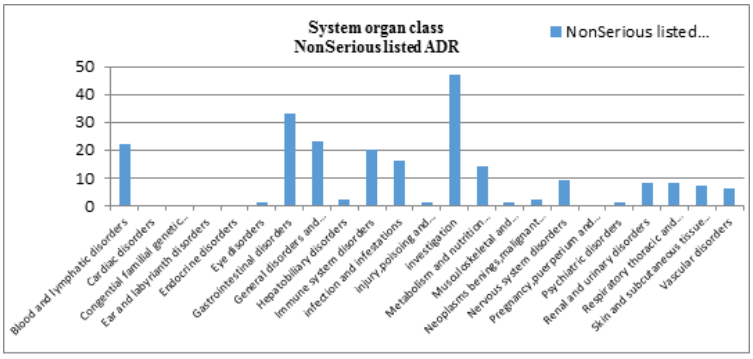

Figure.6.System organ class non-serious unlisted ADR

4. CONCLUSION

There is a high burden of solid organ transplantation disease in worldwide population that accounts for a high prevalence of morbidity and mortality. This study was conducted to evaluate the serious, Non-serious, listed, Non-serious listed and frequent adverse event (AEs)associated with Anti-proliferative Immunosuppressive Drugs (MMF)to various immunosuppressant's drug regimens. As most of the ADRs were not preventable so, this shows that its very difficult to avoid the occurrence of ADRs as most of them were Not preventable. Utilization of MMF for the prophylaxis against organ transplant rejection is associated with serious adverse events that could be fatal and life-threatening. The results highlight the importance of this public health issue and drown a attention for need improved system to overcome the risk of ADRs So special monitoring and regular follow up of organ transplant patients are required to minimize problem.

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REFERENCES

1.Patel S, Sindher S, Jariwala S, Hudes G, Chronic Urticaria With Monoclonal IgG Gammopathy:A Clinical Varient of Schnitzler Syndrome, Ann Allergy Ashthma Immunol, 109, 2012, 147-8.

2. Organ procurement and transplantation network (OPTN), united network for organ sharing (UNOS), and data as of January, 30, 2013, Rockville, MD: Department of health and human activities, Healthcare system bureau, division of transplantation, 2013. Available at http://optn.transplant.hrsa.gov.

3. Organ Procurement and Transplantation Network and Scientific Registry of Transplant Recipients (SRTR.OPTN/SRTR2011annual Data Report. Rockville Md, Department of Health and Human Services, Healthcare System Bureau, Division of Transplantation, 2012

4. Joseph TJ, Talbert LR, Yee CG, Matzke RG, Wells GB, Posey ML, Pharmacotherapy A pathophysiological approach, McGraw-Hill, 2008, 1459-1482.

5. Halloran FP, Immunosuppressive drugs for Kidney Transplantaion, N Enjl J Med, 351, 2004, 2715-29.

6. Bartlett ST, Farney AC, Jarrell BE, Philosophe B, Colonna JO, Wiland A, Keay S, Schweitzer EJ. Kidney transplantation at the University of Maryland. Clin Transpl. 1998, 177-85.

7. Tripathi KD, Essentials of medical pharmacology, Jaypee, 2007, 837-844.

8. Ponticelli C, Progression of renal damage in chronic rejection, Kidney Int Suppl, 75, 2000, 62-70.

9. Perico N, Remuzzi G, Prevention of transplant rejection: current treatment guidelines and future developments. Drugs, 54(4), 1997, 533-70.

10. Gosio B, Ricerche batteriologiche e chimiche sulle alterazioni del mais, Contributo all'etiologia della pellagra, Rivista d'Igiene e Sanità Pubblica, 7(21), 1896, 484–87.

11. Allison AC, Eugui EM, Sollinger HW, Mycophenolate mofetil (RS-61443): Mechanisms of action and effects in transplantation, Transplant Rev, 7, 1993, 129-40.

12. Eugui EM, Almquist SJ, Muller CD, Allison AC. Lymphocyte-selective cytostatic and immunosuppressive effects of mycophenolic acid in vitro: Role of deoxyguanosine nucleotide depletion. Scand J Immunol, 33, 1991, 161-73.

13. Platz KP, Sollinger HW, Hullett DA, Eckhoff DE, Eugui EM, Allison AC.RS-61443, a new, potent immunosuppressive agent, Transplantation, 51, 1991, 27-31.

14. US food and drug administration (FDA).code of federal regulatiobn of health and human services,foodanddrugadministration;2012.availavlefrom:www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=312.32.

15. Vision for MedDRA, Meddra.org. 2017 [cited 7 March 2017]. Available from: http://www.meddra.org/about-meddra/vision

16. MedDRA: ICH [Internet]. Ich.org. 2017 [cited 11 March 2017]. Available from: http://www.ich.org/products/meddra.html

17. MedDRA Structure: Catalyst Clinical Services Study Module Professional Certificate in Pharmacovigilance Program.