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Original Article

Response of Transplant Recipients to Influenza Vaccination Based on Type of Immunosuppression: A Meta-analysis

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ABSTRACT. Influenza vaccination is widely used in transplant recipients, but there is little known about the significance and correlating factors of its effectiveness. In the current study, we reviewed the existing literature on clinical trials performed in transplant recipients on the effectiveness of influenza vaccination and to evaluate the relevance of the type of immunosuppression employed in these patients on the humoral reaction to the vaccine. A comprehensive search of the literature was performed through Pubmed and Google Scholar to find reports indicating immunogenicity of influenza vaccination in transplant patients. Finally, data from 15 published clinical trials were included in the meta-analysis. Data of 947 transplant recipients retrieved from 15 clinical trials investigating the immunogenicity of influenza vaccination were analyzed in this meta-analysis. Analysis showed significantly lower rates of sero-conversion among transplant recipients receiving mycophenolate mofetil (MMF) than other immunosuppressive agents (relative risk: 0.724; 95% confidence interval: 0.596–0.880; $P = 0.001$). No significant correlation was found with tacrolimus, sirolimus, cyclosporine and azathioprine. Different immunosuppressive agents seem to have different effects on the humoral response rate to influenza vaccination, with MMF having the most significant deleterious effect. The limited and controversial data available in the literature do not support any differential effect for other immunosuppressive agents.

Introduction

The influenza virus is one of the most prevalent human respiratory viruses that affects people of all populations, with more catastrophic consequences in immunocompromised individuals. The immunosuppression employed for management of the immune reaction against the graft and preventing rejection episodes also reduces the ability of the body to defend against infectious agents, including the influenza virus.[1] This issue becomes more critical when we consider the substantial increase

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in the number of transplant patients and their survival after the introduction of new potent immunosuppression regimes to the transplantation practice. Therefore, implementation of efforts to prevent infectious diseases in this patient population is of utmost importance.

There are guidelines published on the vaccination protocols for transplant populations by different societies;[2] however, there is no mention on the type of evidence these guidelines are based on and how effective they are. There are few studies investigating the clinical effectiveness of vaccination protocols against influenza virus with little promising evidence. For all nations in general, and for developing nations in particular, it is of high relevance to have a precise judgment on the clinical effectiveness of vaccines. Almost all studies investigating the effectiveness of influenza vaccination in transplant recipients concentrate on the correspondent humoral or cellular reactions. In the current study, we reviewed the existing literature on clinical trials performed in transplant recipients on the effectiveness of influenza vaccination, and to evaluate the relevance of the type of immunosuppression employed in these patients on the humoral response to the vaccine.

Methods

A comprehensive search of the literature was performed through Pubmed and Google Scholar to find reports indicating immunogenicity of influenza vaccination in transplant patients. All studies investigating the humoral response to influenza vaccination of any type were reviewed for analysis of the effect of immunosuppression types on the response to influenza vaccination. In studies where both influenza A and B were investigated, the data from influenza A vaccination was involved in the analysis. Moreover, wherever humoral reactions to more than one antigen were investigated, the least number of antigens were included to have the highest number of seroconversion rates in the different study groups. The other selection was the rate of antibody production. In several studies, different rates of antibody production had been analyzed. In such cases, a four-fold increase of antibody production against influenza vaccine was considered for inclusion into the meta-analysis, and others were censored. Data from the following types of immunosuppressive agents were gathered to be included into the analysis: Mycophenolate mofetil (MMF), tacrolimus, sirolimus, cyclosporine (CsA) and azathioprine.

After the initial search of the literature, 74 studies were found. Because these studies were not originally designed as case–control studies investigating the potential inconsistent effects of different immunosuppressive agents on influenza vaccination response, we had to search inside each study to find whether they had analyzed their data regarding immunosuppression types. Moreover, we tried to search their references to find similar reports that might have been lost in our initial literature search of the Pubmed and Google Scholar. Finally, data from 15 published clinical trials[3-17] were included in the meta-analysis, comprising 947 transplant recipients who received influenza vaccination.

Statistical Analyses

The software used for data analysis was Stata v. 9.0 (StataCorp. LP, 4905 Lakeway Dr, College Station, TX 77845, United States). All statistical tests were performed at the 0.05 significance level.

Results

Data of 947 transplant recipients retrieved from 15 clinical trials investigating the immunogenicity of influenza vaccination were enrolled in this meta-analysis (Table 1). A comparative analysis of the effectiveness of different immunosuppressive agents employed in transplant recipients was performed with regard to seroconversion rates. Analysis of the impact of each of the immunosuppressive agents was as follows:

MMF

Overall, eight clinical trials were included in

Table 1. Demography of the included clinical trials.

Study ID	First author	Ref.*	Year of publication	Country of origin	Participant number	Transplant type
1	Nilufer E. Broeders	3	2011	Belgium	111	Renal
2	Marta Crespo	4	2011	Spain	55	Renal
3	William R. Mulley	5	2012	Australia	131	Renal
4	O. Manuela	6	2007	Canada	60	Lung
5	Nicolas C. Issa	7	2011	USA	82	Stem cell TX
6	P.J. Mazzone	8	2001	USA	43	Lung
7	Monika Lindemann	9	2006	Germany	65	Renal
8	D. J. Versluis	10	1989	Netherlands	59	Renal
9	Ana Sanchez-Fructuoso	11	2000	Spain	49	Renal
10	John M. Dopp	12	2009	USA	66	Lung
11	Rebecca Pellett Madan	13	2008	USA	30	Liver
12	Kenneth G. C. Smith	14	1998	Australia	38	Renal
13	L. C. Willcocksa	15	2007	UK	32	Renal/liver
14	S. Candona	16	2009	France	66	Renal
15	Susanne Brakemeier	17	2012	Germany	60	Renal

*Ref: reference number; TX: transplant.

the meta-analysis. Figure 1 summarizes the data of the meta-analysis of clinical trials investigating the effects of MMF on the immunogenicity of the influenza vaccination in transplant recipients. Analysis showed significant difference between those taking MMF and other immunosuppressive agents [relative risk (RR): 0.724, 95% confidence interval (CI): 0.596–0.880, $P = 0.001$, z = 3.24; Figure 1]. The heterogeneity of the included studies was not significantly high [$P = 0.374$, heterogeneity $\chi^2 = 8.21$ (d.f. = 7) I-squared = 14.8%].

Tacrolimus

Overall, seven clinical trials were included to the meta-analysis. Figure 2 summarizes the data

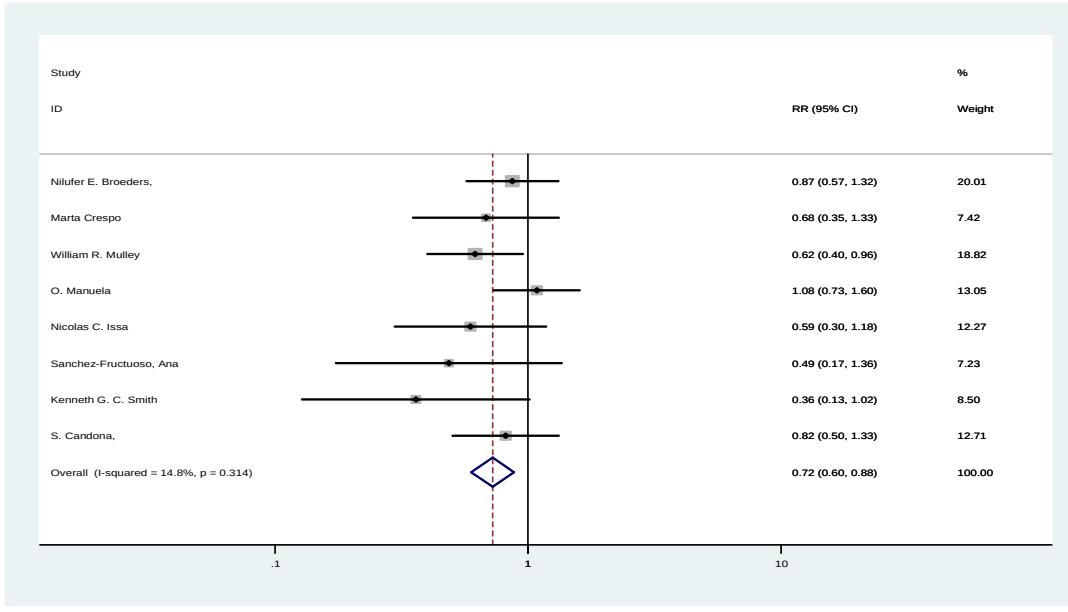

Figure 1. Forest plot of analysis of vaccine response in patients on mycophenolate mofetil versus other immunosuppressive agents.

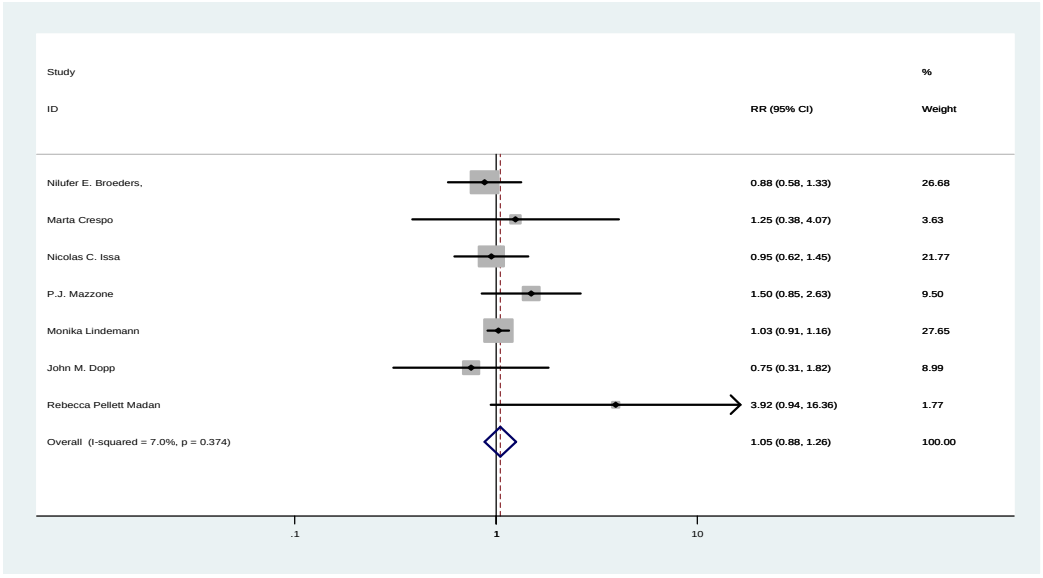

Figure 2. Forest plot of analysis of vaccine response in patients on tacrolimus versus other immunosuppressive agents.

of the analysis. The rate of seroconversion after influenza vaccination was not associated with the use of tacrolimus versus other immunosuppression types (RR: 1.048, 95% CI: 0.879–1.256; z = 0.51, *P* = 0.607). The heterogeneity of the included studies was not significantly high [*P* = 0.374, heterogeneity χ^2 = 6.45 (d.f. = 6) I-squared = 7%].

Azathioprine

Five clinical trials were included to the meta-analysis. Figure 3 summarizes the data of the analysis. The rate of seroconversion was not associated with the use of azathioprine versus

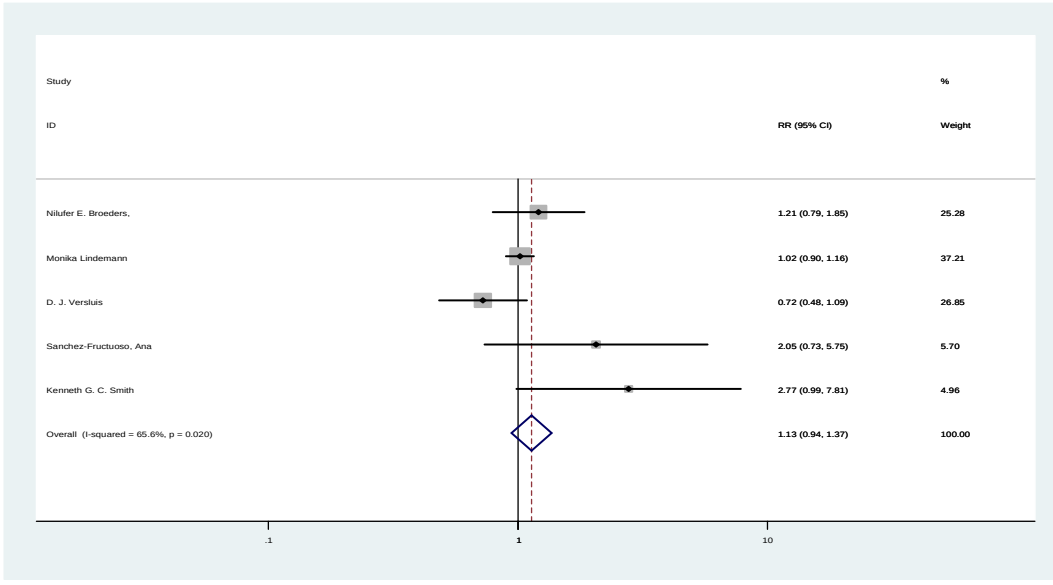

Figure 3. Forest plot of analysis of vaccine response in patients on azathioprine versus other immunosuppressive agents.

other immunosuppression types (RR: 1.134, 95% CI: 0.942–1.365; z = 1.33, *P* = 0.185). The heterogeneity of the included studies was not significantly high [*P* = 0.374, heterogeneity χ^2 = 11.63 (d.f. = 4) I-squared = 65.6%].

CsA

Only two clinical trials were included in the analysis. The seroconversion rate after influenza vaccination in transplant recipients was not related to the use of CsA versus other immunosuppression types (RR: 0.882, 95% CI: 0.543–1.433; z = 0.51, *P* = 0.613). The heterogeneity of the included studies was not significantly high [*P* = 0.186, heterogeneity χ^2 = 1.75 (d.f. = 1) I-squared = 42.7%].

Sirolimus

Three clinical trials were included in the analysis. Analysis of the seroconversion rate showed no correlation with the use of sirolimus versus other immunosuppression types (RR: 1.254, 95% CI: 0.963–1.632; z = 1.68, *P* = 0.092). The heterogeneity of the included studies was not significantly high [*P* = 0.964, heterogeneity χ^2 = 0.07 (d.f. = 2) I-squared = 0%].

Discussion

Studies investigating the potential effects of particular immunosuppressive agents on the response rates to influenza vaccination had revealed controversial findings. In the general population, vaccination has been effective in preventing influenza in up to 80% of people.[15] In early studies on transplant recipients receiving immunosuppression with prednisolone and azathioprine, no difference in antibody titers was detected compared with healthy controls after influenza vaccination,[18] while response to influenza vaccination was reportedly reduced by CsA[10] and MMF.[14]

The current study analyzed the potential effects of each of the major immunosuppressive regimens commonly employed in transplant recipients on their humoral response to influenza vaccination. Because immunosuppression is a critical aspect of transplant recipients to avoid rejection episodes and graft loss, both the cases and controls were on different immunosuppression regimens and there were no transplant recipients on placebo to compare; therefore, in each analysis, we had to compare the antibody response regarding the existence of one of the studied agents in the patients' immunosuppressive regimens. This makes interpretation of the findings complicated. For example, if immunosuppressant A had any effect on response rate over agent C, but agent B that has been used in the regimen of the control group (consisted of B and C) has similar effect; analysis would not be able to show the difference because of the overlapping effect of immunosuppressant B. Hence, the only possibility for observing a discrepancy in the vaccination response is that the assessed agent had a substantial effect over all other agents; thus, none of the agents employed in the regimens of the control groups can cover its differential effect.

Pooling data from eight clinical trials, this study showed that transplant recipients with MMF in their immunosuppression regimen had a significantly lower response rate to influenza vaccination than those on other types of immunosuppression. This corroborates reports of a number of studies reporting similar findings in their trials.[11,14,19-22] Moreover, the low rate of heterogeneity (14.8%, *P* = 0.3) strengthens this finding to be original and not of a high magnitude of a large study with controversial results.

For the other agents, however, we found no significant effect on antibody response between those who were taking any particular immunosuppressant than controls. There are controversial reports in the literature that propose some significant effect for some of these specific agents over other types. Hayney et al,[19] investigating the comparative response to influenza vaccination in 68 lung transplant recipients on calcineurin inhibitors, reported that patients whose immunosuppression regimen contained sirolimus had increased rates of seroprotection. On the other hand, Willcocks et al[15] reported a similar rate of seroprotection in the two groups, while sirolimus had been associated with reaction to a higher number of

antigens. In our analysis, although we did not find a significant effect of use of sirolimus, the *P*-value was borderline ($P = 0.09$), and because of the limited number of trials included in the analysis, there is need for further evidence to be able to assertively conclude on any potential effects of sirolimus on response rate to influenza vaccination. Mazzone et al,[15,23] found a significantly lower response rate in patients on CsA therapy than those on tacrolimus. One of the reasons why we did not find similar results is that there was no possibility to compare the effects of the agents individually. This idea gets strengthened further when we consider that Manuel et al[24] have reported that the number of immunosuppressive drugs in the regimen was a significant associate of the response rate and, in several trials, these numbers were not comparable.

This study has some limitations. First of all, the most powerful trials are those with randomization and those that have placebo groups in their trial. However, as mentioned earlier, the very high relevance of immunosuppression in the transplant population makes it impossible to use placebo groups and also very hard to manipulate immunosuppression in the two groups based on randomization. Furthermore, simultaneous use of other immunosuppression agents, which were not essentially equal even in numbers, creates another controversy in interpreting our results. The limited number of trials included in this meta-analysis is also another point of weakness. However, we believe that despite these limitations, our study has some scientific relevance. First of all, this meta-analysis corroborated previous presumptions on the indisputable effect of MMF versus other agents to reduce the response rate of influenza vaccination in transplant recipients. This finding puts physicians on alert to more precisely follow this patient population on infection prevention issues, especially for influenza vaccination. On the other hand, this study suggests data shortage on sirolimus therapy and its potential favorable effect on vaccination response. Also, there is a profound scarcity of data on the feasibility and clinical effects of influenza vaccination in transplant recipients, and future studies are very necessary in this field.

In conclusion, different immunosuppressive agents seem to have different effects on the humoral response rate to influenza vaccination, with MMF having the most significant deleterious effect. The limited and controversial data available in the literature do not support any differential effect for other immunosuppressive agents.

Conflict of interest: None declared.

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