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Influenza Prevention in Solid Organ Transplant Recipients: An Ongoing Challenge

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Abstract

Background: Vaccination and immunosuppression are two processes that work in diametrically opposite ways creating an interesting paradox in the immunosuppressed individual. Though influenza vaccination has proven to be useful in allograft recipients the efficacy varies widely in different organ transplants withoverall lower antibody response as compared to the general population.

Methods: Systematic search for scientific literature from January 1960 till August 2015 was conducted using PubMed and Google Scholar.

Results: Single dose of adjuvant vaccine appears inadequate for optimal seroconversion and protection and needs further large scale studies. Genetic predisposition confers increased susceptibility in certain ethnic populations. Immunosuppressive agents seem to affect the innate and adaptive immune system. Co-administration of small molecule inhibitors of inflammatory cytokines appears to boost the immune system in animal models.

Conclusions: Current literature demonstrates a lower immunogenicity in post-transplant populations. The type of organ transplant and immunosuppression regimen may affect immunogenicity. Adjuvant vaccines still appear to be producing insufficient antibody response. Ongoing research (TRANSGRIPE study) will help shed light on multi dose vaccines. Further research is warranted in the development of better vaccination protocols in immunosuppressed populations especially in the setting of varying genetic susceptibilities in different ethnicities.

Keywords: Influenza; Vaccination; Solid organ transplant; Immunosuppression

Introduction

Vaccination in immunosuppressed individuals poses additional challenges as compared to their immunocompetent counterparts. Allograft recipients are known to be more susceptible to influenza infections with associated higher morbidity and mortality [1-3]. Annual influenza vaccination has proved to be useful in reducing the incidence of the flu in this patient population but the efficacy of the vaccine as determined by antibody response in these patients appears to be lower as compared to the general population [4-7]. Irrespective of the immunosuppressant regimen used the antibody response appears to be lower than corresponding controls [8-10]. This review presents a discussion of the existing literature on the use of adjuvants versus multi dose vaccination to boost the serological response and to pose the question if a combination of vaccination and chemoprophylaxis would be the answer in immune suppressed post-transplant patients in the setting of evidence for genetic susceptibilities in certain ethnicities and populations.

Methods

Systematic search for scientific literature from January 1960 till August 2015 was conducted using PubMed and Google Scholar. The data examined and analyzed was qualitative in nature hence no statistical analyses were conducted. 51 relevant papers were reviewed to assess the protection provided by current vaccination protocols and to gain insight into possible mechanisms influencing susceptibility to influenza virus infections in the solid organ transplant population.

Results

Use of adjuvants in solid organ transplants

The use of adjuvants in an attempt to boost the immune response is an important topic of investigation. In a small case control retrospective analysis of cardiac allograft recipients, adjuvant vaccination showed an association with increased rejection [10]. Recently Kumar et al. have shown in a small randomized control trial involving renal transplant patients that adjuvants were safe to use and had the same immunogenicity as the non-adjuvant vaccines but had no ability to enhance immunogenicity in this population [11]. In a prospective study on solid organ transplant recipients (kidney, liver and heart) no rejection was noted with the adjuvant vaccine, a lower median antibody titer was noted in the transplant patients and a booster dose helped with an increase in titers in the latter group of patients. Non-responsiveness was correlated with lower renal function, triple drug therapy for immunosuppression and notably treatment with mycophenolic acid [12]. Manuel et al. have shown that in solid organ transplant recipients (kidney, liver) the antibody titers were lower as compared to treated HIV and control subjects. In this study the triple drug therapy transplant patients had a lower response rate but had marginal statistical significance [13]. A prospective study by Siegrist et al. showed the weakest responses in the lung transplant patients. Age, type of organ transplant and higher serum levels of mycophenolate were independently associated with weaker serological responses. Levels of calcineurin inhibitors did not appear to influence the response to vaccination in this study [14]. The booster doses of adjuvant HINI vaccine did not confer protection in lung transplant patients secondary to poor antibody responses [14]. Interestingly, in a small prospective study of pediatric kidney and liver transplant patients adjuvant HINI vaccine conferred

adequate response with no major side effects or episodes of rejection [15]. Low seroconversion after one dose of adjuvant was demonstrated in the study by Resende et al. in a small observational study of solid organ transplant recipients [16]. Though several of these studies are small the use of a single dose of adjuvant vaccine appears questionable for adequate seroconversion and protection and needs further large scale studies (Table 1).

Multi- dose vaccine use in solid organ transplant recipients

The concept of multi-dose vaccines seems attractive in the setting of transplant recipients as the serological response for adequate coverage seems suboptimal with one dose. However multiple dosing co uld also over–stimulate the immune response leading to undesirable events such as allograft rejection. Schuurmans et al. have shown in an observational study of lung transplant patients that adverse events were not increased when H1N1 vaccine alone was administered in two doses [1]. In 4% of the study subjects there were severe adverse events that were self-limiting. 2 out of 148 of the vaccinated subjects had a flu infection but 5 out of 20 had an infection in the unvaccinated group. The calculated efficacy of the vaccine was approximately 95%. This study also noted that co-administration of two vaccines the seasonal flu and the H1N1 were well tolerated in this population. The infections noted were mild and treated in an outpatient setting. The study had its limitations due to its small size and being observational in design. However, it demonstrates the effectiveness of close follow up of patients by a dedicated team and prophylactic treatment of any flu-like symptoms in a timely fashion at the onset of any suspicious symptoms [1]. In a 61 subject prospective study by Soesman et al. liver transplant patients showed a rise in mean geometric titers after a second dose of a commercial trivalent vaccine [6]. Such a rise was not noted in the healthy controls or a group of patients with cirrhosis who had not undergone transplantation [6]. Overall the seroconversion levels were lower in the transplant population as compared to non-transplanted controls or the subjects in the cirrhosis group. In a small cohort of heart transplant patients the second booster dose did not improve the titers and on the whole the seroconversion was poorer in the post-transplant subjects [8]. It is uncertain if higher doses of antigen would elicit a better response in this population. A recent study by Felldin et al. shows a benefit in using a booster dose of vaccination to improve titers in solid organ recipients as no rejection episodes or adverse events were noted with this protocol [12]. A second dose of adjuvant vaccine did not improve the sero protection titers in transplant patients in the prospective study by Manuel et al. [13]. Siegrist et al. showed that two doses of adjuvant vaccine did not confer adequate seroprotection titers in solid organ recipients and the weakest response was found in lung transplant patients and patients treated with mycophenolate for immune suppression [14]. In such cases it appears that chemoprophylaxis would be important to provide the required protection [14]. In a study involving only renal transplant patients a booster dose improved the antibody response in 42% of the recipients [21]. Other mechanisms yet unknown and possibly differential genetic susceptibility may influence the immune response. Table 2 summarizes some of the studies using the multi dose regimen.

Route of vaccine administration

The route of vaccine administration appears to play a role in the extent of immune response mounted by immune suppressed individuals. In renal transplant patients Morelon et al. have shown with the same amount of antigen, the intradermal route tended to produce higher levels of antibodies as compared to the conventional route of administration [17]. In another randomized prospective study in immune suppressed individual's lower doses of antigens produced similar response with intradermal injections. This study involved patients with HIV infection, TNF alpha treatment and post stem cell transplantation. No solid organ transplant patients were included [18]. In a study on solid organ transplant recipients (kidney, liver, lung, heart) a high-dose intradermal vaccine showed equal immunogenicity as standard vaccine and did not cause a significant increase in donor specific HLA-antibodies which is an important aspect to consider in transplant populations [19]. In lung transplant patients no additional benefit was noted by administering a booster intradermal dose following the standard vaccine regimen suggesting that other mechanisms also participate in the control of immune response in this subgroup as lung transplant recipients consistently seem to elicit the poorest response [20]. Prophylaxis and early treatment probably may help combat the influenza challenge in this subgroup of solid organ recipients.

Chemoprophylaxis

The mainstay of influenza prevention should be adequate vaccination. The insufficient response noted with the existing vaccines in solid organ transplant patients points to adding adjunct modalities to confer protection in this vulnerable population. Prophylaxis could be used along with vaccination. However, dosing strategies in this population are less defined. Identification of risks and early treatment could be the key to attaining complete protection in addition to administration of vaccines [22]. The existing literature points to lung transplant patients as the worst responders to immunization. Therefore, a very low threshold should exist for initiation of prophylactic treatments in this sub group of solid organ recipients.

Prophylaxis with antivirals should be considered in certain high risk sub populations but it cannot be used as a universal strategy because of development of drug resistance. Kumar et al. provide a useful guidance document on the prevention, prophylaxis and treatment of the flu virus infection [23]. Transplant patients who have had exposure should be treated for 10 days from the known day of exposure. The guidelines also recommend alternatively watching for symptoms and treating at first suspicion [23]. Another aspect in prevention is to have all personnel involved in the care of transplant patients vaccinated with inactivated vaccines. The use of live vaccines should be contraindicated in close contacts and family members of patients receiving immunosuppressant therapies [23].

Development of resistance to antiviral drugs should be an important consideration in using adjunct prophylaxis. Addition of other drugs has been suggested in cardiothoracic transplant populations in the setting of drug resistance. Resistance to Oseltamivir would prompt addition of

Study	Study Design	Type of Organ Transplant	Conclusions	References
Fraund et al.	Case Control	Heart	Increased Rejection	10
Kumar et al.	Randomized Control Trial	Kidney	No change in immunogenicity	11
Fellden et al.	Prospective Study	Kidney/Liver/Heart/Lung	No rejection	12
Siegrist et al.	Prospective Study	Kidney/Lung/Liver/Heart /Pancreas	No increase in antibody titer	14
Gavalda	Prospective study (pediatric)	Liver/Kidney	Adequate immune response	15

Table 1: Use of Adjuvants in Solid OrganTransplant Recipients

Study	Study Design	Type of Organ Transplant	Conclusions	References
Schuurmans et al (2011)	Prospective Study	Lung	No increase in adverse effects noted	1
Soesman et al (2000)	Prospective Study	Liver	Two dose regimen improved immunogenicity	6
Blumberg et al (1996)	Prospective Study	Kidney/Liver/Heart/Lung	No increase in immunogenicity with 2 dose regimen	8
Siegrist et al (2012)	Prospective Study	Kidney/Lung/Liver/Heart /Pancreas	No increase in antibody titer	14
Brakemeier (2012)	Prospective study	Kidney	Marginal increase after the booster dose	21
Fellden et al (2014)	Prospective Study	Kidney/Liver/Heart/Lung	No rejection or adverse events	12
Martinez-Atienza (2014)	Randomized Control Trial	Kidney/Liver/Heart/Lung	Ongoing study	52

Table 2: Effect of Multi dose vaccination regimens

rimantadine or amantadine or use of zanamivir as monotherapy in this population [24].

Genetic Susceptibility of the Host

Genetic predisposition of the host to viral infections and its role in mounting an immune response has been sparsely studied. The genomic profile is also influenced by environmental factors in different ethnic groups. Solid organ transplant patients with genetic susceptibility suffer an added challenge in that their immune systems are chronically suppressed.

Murine models have proven to be useful in studying the pathogenesis of influenza viruses [25]. Many mammalian genes including Mx1, Stat1, Pkr, Ifnar1, and Ncr1 genes have been found to be important in defining host defense against influenza [26-29].

In murine models susceptibility assessment led to the observation that an exaggerated innate immune response by the host can lead to very detrimental outcomes [30]. In the genetically susceptible mice the LD50 was almost a 1000 fold lower than their genetically robust counterparts [30]. The susceptible mice showed a higher inflammatory response and an increased viral load suggesting a genetic predisposition of the host to infectivity [30].

In the human system mutations in the CD55 gene has been shown to influence severity of the disease [31]. CD55 expression protects the respiratory epithelium from complement damage. Hence deletion mutations in the promoter region considerably reduced the transcriptional activity of the CD55 gene leading to more severe disease [31]. In the study by Zhou et al. single nucleotide polymorphism (SNP) rs2564978, from the promoter region was associated with severity of the H1N1 flu [31]. Ethnic variations in genotypes can predispose to susceptibility to the flu virus. Studies on the frequency of occurrence of the SNP rs2564978 T mutant showed a 54-63% frequency in Chinese populations and a 39% occurrence in Japanese subjects. On the other hand European and Western Pacific individuals had the highest frequencies of the protective C allele of the SNP rs2564978 and interestingly had lowest rates of deaths suggesting a relationship between genetic susceptibilities and severity of infection [32]. Genetic diversity via mutations in the pattern recognition receptors involved in activating the innate immune system can confer differential susceptibility on the host to viral infections. Mutations in the Toll-like receptor 3 (TLR3) - a pattern recognition receptor, is associated with influenza - associated encephalopathy in the pediatric population [33]. The adaptive phase of immunity is crucial in the host defense against spread of the influenza virus. This phase involves mounting a cellular and humoral response. In solid organ transplant recipients this stage can pose a challenge in the setting of chronic immunosuppression. The genetic basis of host susceptibility and the complex host–viral interactions which define outcomes needs further investigation.

Role of immunosuppression on vaccine effectiveness and disease outcomes

The first immunologic response to flu viruses are initiated by activation of the innate immune system [34,35]. The key players are pattern recognition receptors (PRR) that recognize unique sequences known as Pathogen-Associated Molecular Patterns (PAMP). The PRR include Toll-Like Receptors (TLR), Nucleotide-binding domain and Leucine-rich-repeat Receptors (NLR) and Retinoic acid-inducible gene-I like Receptors (RLR). Toll-like receptors are integral components of the innate immune system and are found in the cell membrane or endosome of antigen presenting cells.

It is important to recognize that the innate immune system strongly influences adaptive immunity resulting in decreased responses against a viral pathogen. The role of immunosuppression on the innate immune system is now becoming more evident through their effect on toll-like receptors (TLRs). This effect would also contribute to the lower response to vaccinations and a significant effect on vaccination outcomes in solid organ recipients secondary to chronic suppression of the adaptive immune system. In liver transplant patients the response to regular vaccination is suboptimal [5] and when treated with calcineurin inhibitors (cyclosporine A or Tacrolimus) stimulation of TLR2,TLR4,TLR7/8 in peripheral blood mononuclear cells produced lower levels of inflammatory growth factors (IL-6, IFN gamma, TNF alpha). Impaired cytokine production by natural killer cells was also noted which would influence lower rates of response to infection [36].

Existing literature points to inhibition of the innate as well as adaptive immune systems. Inhibition of mTOR (mammalian target of rapamycin) produces complex immunoregulatory effects in that it upregulates proinflammatory growth factors such as IL-12 and IL-1β and down regulates the anti-inflammatory cytokine IL-10. Additionally, mTOR influences type I IFN production as well as expression of other chemokine receptors and costimulatory molecules. mTOR inhibition in both the human cells and murine models affects the activity of toll-like receptors which impacts the innate immune system [37-41]. NK cell proliferation is decreased in mTOR inhibition suggestive of suppression of the innate immune system [42]. Influence of sirolimus on the innate immune system merits more investigations.

The role of different combinations of immune suppressants on the innate immune system is interesting. In a study on renal transplant patients it was noted that both combinations (tacrolimus/mycophenolate mofetil, cyclosporine/azathioprine) depleted both innate and adaptive immunity in the months immediately after transplant. However at 1 year post transplant, patients who received the tacrolimus/mycophenolate mofetil had a higher natural killer cell count and effector function suggesting that this combination may favor better defense against

viral infection and cancer. This area warrants further investigation to optimize immunosuppression to decrease susceptibility and increase vaccine response while maintaining adequate protection against graft rejection [43].

Co-administration of small molecule inhibitors of inflammatory cytokines

Another area of ongoing investigation is the role of co-administration of small molecule inhibitors of inflammatory cytokine receptors in enhancing vaccine response. Administration of vaccines causes an inflammatory response involving a large migration of monocytes to lymph nodes. This causes a down regulation of cellular and humoral responses and therefore a lower response in general to the vaccine itself. The two chemokines essentially regulating the recruitment of monocytes to sites of inflammation are MCP1 (CCL2) and MCP 3 (CCL7) [44]. Deletion of CCL2 or CCL7 or the CCL2 receptor (CCR2) abolishes this effect [45]. Hence the idea of using small inhibitor molecules was conceived to down regulate the monocyte recruitment [46]. A spiroperidine containing compound RS102895 was found to bind with high affinity to the B2 subunit of CCR2 [47]. RS102895 improved vaccine response in mice by reducing monocyte recruitment to lymph nodes [48]. Mice injected with CCR2 inhibitor RS102895 along with the vaccine showed increased vaccine immunity [49] suggesting such co- administration could boost the immune response by monocyte migration to lymph nodes. Investigations in the human system need to be initiated in the future.

Immune suppression and disease susceptibility

Immune suppression has been shown to affect both the innate and adaptive immune systems. Figure 1 summarizes the multiple factors that can increase susceptibility to influenza. However certain combinations of immunosuppressive drugs allow reconstitution of the innate immunity after the initial post transplant period at about a year after transplant [43]. In an immune suppressed macaque model when infected with the influenza virus (H1N1), lower levels of immune cells with higher viral loads were noted as compared to their immunocompetent counterparts suggesting increased severity of the disease in immune suppressed non-human primates [50].

In an interesting study in rats treated with Cyclosporine/azathioprine/prednisone versus Tacrolimus/mycophenolate/prednisone it was noted that both triple therapies decreased ciliary beating frequency, mucociliary transport velocity, and neutral mucus production with the former

combination being worse than the latter. These findings are suggestive of increased susceptibility to the disease process as a result of the anti-rejection drugs [51]. Effect of immunosuppression on the respiratory tract warrants further investigation. Figure 1 shows the possible mechanisms influencing increased susceptibility to influenza virus infections in solid organ transplant patients.

Conclusions

It appears that the current literature supports the finding that solid organ recipients mount a lower immune response to vaccines. It is also becoming evident that immunosuppressant drugs down regulate both innate and adaptive immunity at least in the early post-transplant period. Optimization of immunosuppressant drug combinations may have a positive effect as not all combinations support reconstitution of the innate immune system a year or more post transplantation. Other factors that influence susceptibility include age of the recipients and the type of organ received. Lung transplant recipients seem to have one of the poorest immunogenic responses to vaccines. Considering the challenges that the transplant patients have to face, it is imperative to seek immunization strategies and adjunct therapies to confer full protection in this population. Since none of the existing strategies (use of adjuvants/multi dose vaccination) confer total protection, a combination of approaches may be the answer especially in populations that are genetically susceptible. Co-administration of small molecule inhibitors of growth factor receptors appears to be an interesting concept that needs further validation.

Future Directions

The effectiveness of multi dose vaccination in solid organ transplant patients is currently being explored in a randomized clinical trial TRANSGRIPE 1-2 study [52]. Figure 2 briefly summarizes some of the strategies that may be used to improve vaccine response and immunity. In summary, much research is warranted in the area of protection of solid organ transplant recipients by immunizations as algorithms have to be evolved which strike a fine balance between protection from infection and prevention of graft rejection. Genetic susceptibilities need to be taken into consideration in different populations who undergo immunosuppression as this presents an additional challenge.
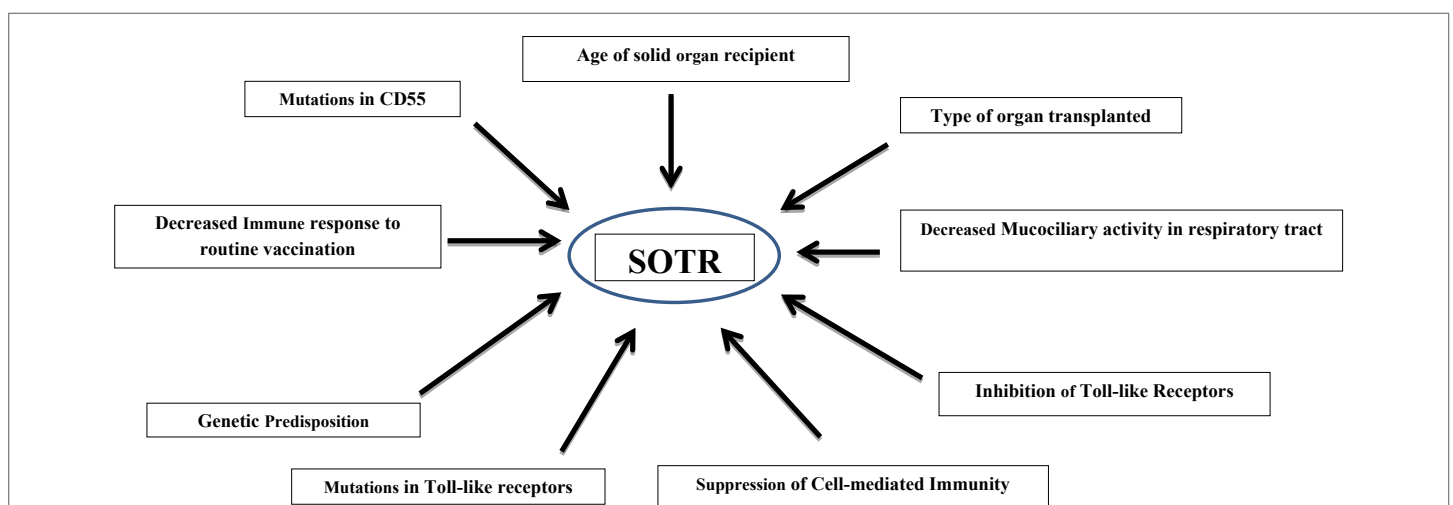
Figure 1: shows the different possible mechanisms increasing susceptibility to influenza virus infection in solid organ transplant recipients (SOTR)

Figure 2: shows strategies derived from the current literature to improve immunity
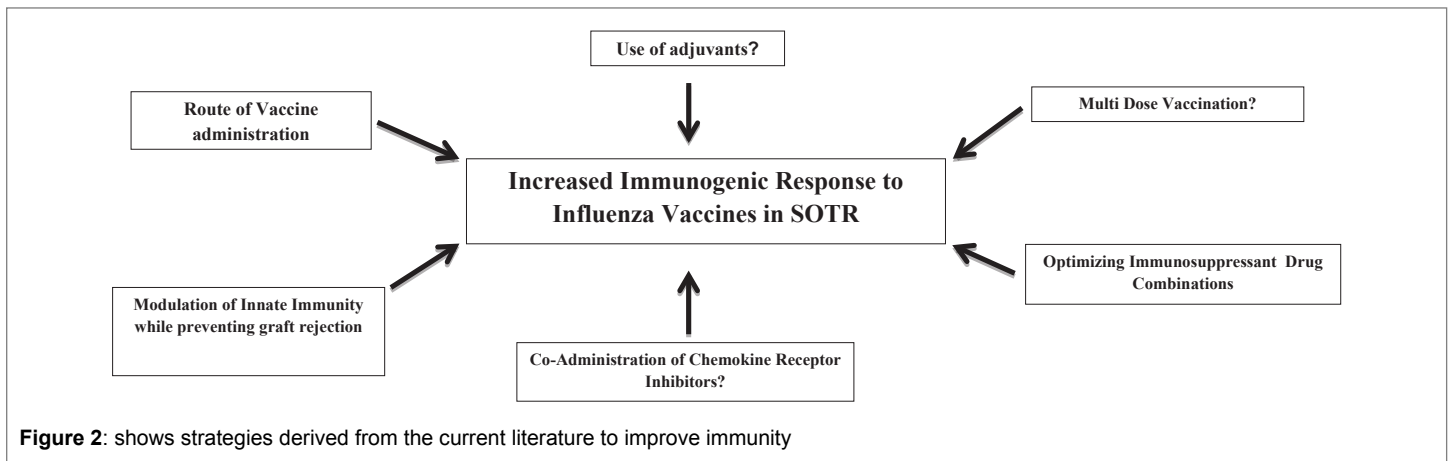
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