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Review Article

Internal Medicine Section

Immunization in Patients with Rheumatic Diseases: A Practical Guide for General Practitioners

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ABSTRACT

Patients with rheumatic diseases are susceptible to various infections throughout the course of the disease. The increased risk of infections can be attributed partly to the aberrant immune system and partly to the effect of immunosuppressive drugs used in the treatment of the disease. Immunization appears to be an excellent strategy to prevent infections in such patients. However, the effect of vaccines in these patients is modified due to disease per se and/or immunosuppressive drugs. Biological agents, that frequently increase the susceptibility to infections, are now being initiated earlier in the course of the disease and also for new indications. Thus, concerns regarding safety, efficacy and potential adverse effects of vaccines in these patients are more complex than in any other immunosuppressive conditions. Different patients show different amount of immunosuppression in response to disease modifying drugs. Besides, there is lack of adequately powered randomised controlled trials investigating the efficacy of a vaccine in terms of actual prevention of the disease. Pneumococcal and influenza vaccines are the most studied vaccines and they are strongly recommended in rheumatic patients. In general, live vaccines should be avoided among patients receiving high doses of immunosuppressive drugs. However, they may be given to patients receiving low dose steroids and methotrexate. Non-live vaccines may be administered as per the recommendations of national guidelines. There is necessity to increase awareness among patients and doctors towards promoting the appropriate and judicious use of vaccines in the patients with rheumatic diseases.

Keywords: Immunosuppressive drugs, Live vaccines, steroids

INTRODUCTION

Prevention of infectious diseases by immunization is considered as one of the greatest achievements in the field of public health in the last century. Initiatives like, universal immunization program have played a major role in controlling the burden of many infectious diseases. Currently, vaccines are available for more than twenty diseases. It seems imperative to promote liberal use of vaccines to control various infectious diseases. Serious adverse effects like paralysis, encephalomyelitis and demyeliniting disorders have been described with the use of various vaccines [1,2]. Thus, it is important to consider the risks involved in vaccination while expecting benefits.

Patients with rheumatic diseases (RD) are more susceptible to various infectious diseases and guidelines have been published to suggest their rationalized use in these patients. Many of these patients receive immunosuppressive drugs that raise the concerns of safety and efficacy of these vaccines especially live vaccines. Considering the fact that many patients with RD are treated by general practitioners, internists and orthopedicians in our country, there is necessity to increase the awareness about the use of vaccines in patients with RD. This article strives to give a simplified review of the basis and recent recommendations of immunization practices among the patients with RD.

Rheumatic Patients: How are they Different from General Population?

Patients with RD have increased morbidity and mortality due to infection. Studies have revealed that death from infections in patients with rheumatoid arthritis are twice more common than general population [3]. Infections have been found to be a major cause of death (up to 33%) in patients with SLE and vasculitis [4,5]. The increased susceptibility to infections can be either due to immunosuppressive drug therapy or defective immune response to infection or due to other non specific causes like poor nutrition, organ failure and frailty. Drugs like azathioprine, biological agents, cyclophosphamide, cyclosporin, leflunomide and mycophenolate cause immune suppression at any dose while corticosteroids increase the risk of infection in dose-dependent manner [6-8]. However, even very low doses (like 5 mg prednisolone daily) have been found to increase risks of infections [6,9]. Adults receiving prednisolone in doses >20 mg/day for more than one week and children receiving >2 mg/kg/day for more than one month are at significantly greater risks of acquiring infections. Besides, because of derangements in the immune system of the patients with RD, there is always a concern regarding safety and efficacy of these vaccines in these subsets of the patients.

Safety of Vaccination in Patients with RD

Reports suggest that certain vaccines are associated with exacerbation of the disease activity of RD. Hepatitis B immunization, particularly, has been found to be associated with exacerbation of RD [10,11]. However, some other studies have not found any significant increase in the disease activity of RD (RA and SLE) following pneumococcal and influenza vaccination [12,13]. Based upon the quantum of evidence available at present, no change in immunization policy is required; however, close monitoring is necessary. Patients with RD have increased risks of vaccine related infection especially when they are receiving drugs that lead to significant immunosuppression. Current recommendation is to avoid live attenuated vaccines in these patients [14]. However, studies suggest that live vaccines may be given in patients receiving low doses of corticosteroids or methotrexate [15,16]. Similarly, yellow fever vaccine has been found safe in patients being treated with biological agents like infliximab and rituximab [15,16].

Efficacy of Vaccines in Patients with RD

It is plausible to expect that lower level of immune response will be generated in response to various vaccines in patients with RD as

they are in state of immunosuppression, and hence vaccines will be less effective. Reduced level of protective response to influenza vaccine is seen in patients receiving aggressive chemotherapy for haematological malignancies [17]. There is lack of adequately powered studies to find out efficacy of vaccines in patients with RD. The extent of immunosuppression is different in different RD as well as with different Disease modifying anti rheumatic drugs (DMARDs). DMARDs such as gold and sulphasalazine are usually not considered "potent immunosuppressive", whereas methotrexate seems to result in only modest reduction in the efficacy of the vaccinations [18,19]. Patients receiving moderate to high dosage of corticosteroids show lower response to flu vaccines. Lesser immunogenicity of varicella zoster vaccine has been reported in patients receiving even lesser dosage of steroids along with other immunosuppressive drugs [15,16]. Similarly, patients receiving moderate to high dosage of methotrexate show lower immunogenicity to pneumococcal (PPV23) and varicella zoster vaccines. Studies suggest that there is lower response to pneumococcal (PPV23), hepatitis B and yellow fever vaccines in patients receiving infliximab and lower response to pneumococcal (PPV23) and influenza vaccines in patients receiving rituximab [15,16,20]. Significantly lesser response to vaccination has been found in patients receiving immunosuppressive drugs with high efficacy like high dose steroids, cyclophosphamide, azathioprine [6,8,13].

Vaccination Status in Patients with RD

Studies from developed world reveal that only 20-40% of adult patients with RD receive vaccination [21]. The prevalence of vaccination among adult patients of RD has not yet been studied in Indian subcontinents or other developing countries, which is expected to be much lower. Hence, there is need to increase the awareness among rheumatologists and patients of RD. Current recommendation is to assess immunization status in the initial workup of every patients with RD [14]. During OPD visits, each patient should be enquired about his or her actual vaccination profile and side effects in previous vaccinations. Besides, adverse events and flares of the underlying RD following prior vaccinations should be queried since these might be (relative) contraindications for certain future vaccinations. Catch-up vaccination may be considered for missed vaccinations that are recommended for the general population.

Ideal Time for Vaccination

Ideally, vaccination in patients with RD should be done only during stable disease [14]. Till date, no studies have been conducted comparing efficacy and adverse effects of vaccines between patients with stable disease and active RD. Studies involving vaccination in patients with RD have (mostly) enrolled patients with quiescent disease. Few studies that included patients with moderate or severe disease activity have failed to show increased frequency of side effects, decreased efficacy or disease flares. However, numerous case reports about potential vaccination-related disease flares exist [14,15,21]. Considering the theoretical risk of disease flare following vaccination in patients with active RD, vaccination should be administered during stable disease. Besides, whenever possible vaccination should be performed before initiation of immunosuppressive drugs.

Practice Guidelines for Immunization in Adult Patients with RD

Vaccines, like pneumococcal and influenza are commonly used in adults in the different parts of the world. These vaccines are being discussed in context to patients with RD.

Influenza Vaccine

Influenza vaccine is a killed vaccine which is routinely recommended in developed countries like Europe, America and Australia [6]. Annual influenza vaccination is recommended for elderly persons {age more than 50-60 years and patients suffering from chronic diseases (respiratory diseases, heart diseases, liver diseases and diabetes)}. It has been found that individuals who are immunised in successive years develop a higher cumulative protection than those receiving first annual dose of vaccine [22].

Exact burden of influenza is unknown among patients with RD, however there is increased risks of death from pulmonary infections as has been reported in several studies [23-25]. Vaccination has been shown to reduce admissions for and mortality from influenza/pneumonia in elderly people with RD. The vaccine has found to be efficacious in patients with RD, even when treated with DMARDs, infliximab, etanercept or adalimumab except for rituximab [14,18]. Adverse events of influenza vaccination in patients with RD seem comparable to those in healthy controls. Current guidelines strongly recommend the use of inactivated influenza vaccination (both seasonal and pandemic swine flu) for patients with RD [14].

Pneumococcal Vaccines

The pneumococcal vaccine (23-PPV) contains antigens of the 23 most common pneumococcal strains. It is effective against approximately 90% of all pneumococcal infections. It is recommended for elderly (more than 65 years of the age) and other individuals with decreased immunity like, asplenia and suffering from chronic diseases. Patients with RD are at increased risk of acquiring LRTI as compared to the general population and *pneumococcus* is one of the main causative pathogens. 23-PPV vaccination induces an adequate immune response in patients with common RD, even when treated with DMARDs. Pneumococcal immunization is considered particularly important in patients with lupus nephritis with or without complement depletion [26]. The current guidelines strongly recommend 23-valent polysaccharide pneumococcal vaccination (23-PPV) for patients with RD. Certain studies advocates re-immunisation at shorter interval (less than five years) among patients with RD [14].

Hepatitis A and/or B Vaccination

Hepatitis B reactivation has been described in patients with RD following or immediately after discontinuing treatment with immunosuppressive medication (including TNF-αblocking agents). The cause of flare of Hepatitis B could be immunosuppressive drugs, disease activity of RD or the natural course of chronic hepatitis B infection. Hepatitis A and/or B vaccination is recommended only when the risk of contracting these infections is increased; like, travel/residence in places endemic for hepatitis A and/or B, increased risk of exposure as in case of medical professionals, infected family members or close contacts [14].

Human Papilloma Virus Vaccination

Studies suggest that HPV infection is more common among patients suffering from SLE [27,28]. Moreover, it is also found that the rate of spontaneous clearance of infection is lesser in patients with SLE [29]. Because of these factors, HPV vaccination is recommended in the women with SLE until the age of 25 years. It should be noted that caution and surveillance is required as venous thromboembolic events have been reported with quadrivalent HPV vaccine, mostly in patients with associated antiphospholipid syndrome [29].

Herpes Zoster Vaccination

Herpes zoster vaccine has been advised in adults over 60 years of age to prevent shingles. Patients suffering from RA, SLE, Vasculitis and PM/DM have an increased risk of developing herpes zoster in comparison to general population. The risk of developing herpes zoster is further increased in patients with RD treated with corticosteroids, TNF αblocking agents and non-biological DMARDs, like cyclophosphamide, azathioprine and leflunomide. EULAR recommends vaccination in patients with RD who are less severely immunosuppressed [14]. The consensus is to vaccinate patients

who are being treated with short-term (less than 2 weeks) or low-to-moderate dose (less than 20 mg/day) corticosteroid therapy, sulfasalazine, leflunomide, low-dose methotrexate (≤0.4 mg/kg/week), or azathioprine (≤3.0 mg/kg/day)(15). It is not recommended in patients being treated with biologicals.

Tetanus Toxoid Vaccination

There are studies to establish the efficacy of tetanus toxoid vaccination in patients with RA and SLE including the patients who are being treated with immunosuppressive drugs (including rituximab until six months earlier). There is no data regarding efficacy of the TT vaccines among patients in which rituximab was used within six months. EULAR guidelines suggest that patients with RD should receive tetanus toxoid vaccination similar to that for the general population [14]. Passive immunisation with tetanus immunoglobulins should be administered, in case of major and/or contaminated wounds in patients who received rituximab within the last six months [14,15].

BCG Vaccination

Tuberculosis is a major problem in many part of the developing world including India. The incidence of the disease is increased in patients with RD, particularly among those who are on immunosuppressive drugs especially TNF-alfa blockers. However, BCG vaccination is not recommended in patients with RD as majority of the cases of active TB are reactivations of latent TB infections which cannot be prevented by vaccination [14]. BCG vaccination has not been found to be efficacious in preventing TB in adults.

Passive Immunisation in Patients with RD

No specific recommendations have been given in patients with RD. However, it seems imperative to offer passive immunisation to the patients as and when felt appropriate, especially among the patients who are receiving B cells depleting agents. Passive immunisation with appropriate immunoglobulin should be administered within 6 days of the exposure to varicella and/or measles or after getting contaminated wounds [15].

Recommendations for Travellers with RD

Patients with RDs should be vaccinated as per the guidelines for general population. However, live vaccines should be avoided. Patients with severe immunosuppression should avoid travelling in yellow fever endemic countries [30]. If it is mandatory to travel in endemic area or when yellow fever vaccination is mandatory, temporary discontinuation of treatment with immunosuppressive drugs is required.

Patients with Splenectomy or Hyposplenism

Many patients with RD suffer from refractory thrombocytopenia for which splenctomy might have been done. Besides, functional hyposplenism are also seen among patients with active SLE. Such patients are susceptible to infections with capsulate microorganisms. In such patients, menigiococcal C, pneumococcal, influenza and H influenza B is advised [14,30].

Immunisation in Paediatric Patients with RD [15,16]

The burden of infection in childhood is greatly reduced by intensive vaccination. Children with RD have increased risk of infections which is partly attributed to the use of immunosuppressive medications. The use of vaccines among rheumatic patients with RD has concerns like safety, immunogenicity and potential side effects. There are certain guidelines that should be followed by paediatricians while determining the suitability of a vaccine by judging risks and benefits of a particular vaccine.

Non-live vaccines are generally considered safe in paediatric patients with RD and they should be administered as per the national guidelines. Usually, these vaccines are efficacious and are capable of generating acceptable serological response even when they are being treated with mild immunosuppressive agents. Determination of pathogen-specific antibody concentration is recommended after vaccination if patient is on high dose steroids or rituximab. Rituximab has been shown to blunt the response of pneumococcus, influenza and tetanus vaccines. Tetanus immunoglobulin is advised in patients with contaminated wound in which rituximab was administered in the last six months. Besides, strain specific antibody concentrations should be determined if PPV23 vaccine is given to paediatric patients with RD on methotrexate. Menningiococcus and H influenza type B vaccine should be considered proactively in patients with low complement levels or functional asplenia.

Live vaccines should be avoided in patients with RD who are receiving high doses of DMARDs, corticosteroids or biological agents. It may be considered on individual basis if benefit of vaccination is supposed to outweigh risks involved. MMR vaccine is a live vaccine which is recommended in 2 doses for children aged more than two years. As it is a live vaccine, there are concerns of vaccine induced disease in severely immunocompromised children. However, there are reports in literature that have established the safety and efficacy of MMR vaccine among patients with RD [31]. BCG vaccine should be withheld in active Kawasaki disease for the fear of increased local inflammation [32].

CONCLUSION

Most of the recommendations made for immunisation in patients with RD are based upon consensus among experts as well as extrapolation of the results from the studies involving patients suffering from other diseases leading to decreased immunity. Extent of immunosuppression in various RDs caused by various drugs is not known. More adequately powered randomized control trials are required to address many unanswered questions. Awareness should be increased among patients and doctors for promoting the appropriate and judicious use of vaccines in these patients.

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