



## Vaccination in Autoimmune Rheumatic Diseases (AIRD)

Infections are the major cause of morbidity and mortality in patients with Autoimmune Rheumatic Diseases. Immune response in these patients is impaired and the “immunosuppressive” medications used to treat them add fuel to the fire. Infections are the biggest threat in the management of rheumatic conditions. Influenza, invasive pneumococcal infection, herpes zoster and hepatitis B are the major vaccine preventable infections seen in our patients.

Vaccination in rheumatic disease and its studies present with a unique set of challenges. Vaccination leads to immune response to particular antigen; however, non-specific response in this situation might lead to flare of the autoimmune disease. Ideally, studies on efficacy should use clinical endpoints to test the role of vaccines in rheumatic diseases to establish its clinical benefits. Such studies with clinical endpoints are logistically demanding and require a large sample size. Hence, most of the current studies use laboratory parameters (serologic titres of antibodies or T cell reactivity against antigen) to establish the efficacy of the vaccines. However, laboratory surrogates lack correlation with the clinical endpoints of reducing infection. Studies related to vaccination need to be interpreted with this consideration in mind.

In this write-up we will focus on the evidence of efficacy of various vaccines in rheumatic diseases and end with the current recommendations pertaining to vaccination.

### Influenza virus

Influenza vaccine currently available in the market include inactivated and live attenuated. Trivalent and tetravalent vaccines containing three and four strains are available; however, the most commonly used is the **trivalent inactivated vaccine**. Multiple studies including a prospective<sup>1</sup>, and a retrospective large registry based Taiwanese study<sup>2</sup> with clinical endpoints suggest reduction in pneumonitis, bronchitis, hospitalization in Rheumatoid arthritis and SLE patients vaccinated with influenza vaccine as compared to unvaccinated patients. In SLE, the serological response to the influenza subunit varied among different studies. Few studies show mild reduction in sero-protection while the others did not show any difference in seroconversion between vaccinated and unvaccinated patients.<sup>3,4</sup> Serologic evidence of protection in Systemic Sclerosis<sup>5</sup>, Granulomatosis with polyangiitis<sup>6</sup> and Sjögren’s syndrome<sup>7</sup> have been observed after influenza vaccination. Significant body of evidence exists to suggest efficacy of Influenza vaccination with concomitant use of glucocorticoids, csDMARDs and antiTNF therapy and tocilizumab. In one study, the arm on combination therapy with methotrexate and anti-TNF had lower titres of antibodies to influenza as compared to methotrexate alone, however, multiple other studies have shown good response with combination therapy as well.<sup>8</sup> Studies with rituximab in RA however have documented significant lower seroconversion rates.<sup>9</sup> None of the studies have raised concerns regarding the safety or flare of underlying autoimmune disease.

Antigenic Drift and Shift leads to changing immunogenicity of the Influenza strains each year. Depending on the strains in circulation in a particular demographic area, the manufacturers “update” their vaccine to include the recent strains. This should be kept in mind while administering vaccine to patients. The best time to vaccinate with yearly shot is **before the onset of monsoon<sup>10</sup> (April-May)** since influenza infection is particularly more common in monsoon and winter.

Thus, current body of evidence suggest influenza vaccines are well tolerated but underutilized in rheumatic diseases patients and are generally immunogenic even with immunosuppressants with the exception of rituximab. Vaccines should ideally be administered before B cell-depleting biological

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therapy [BCDT] is started or, when patients are on such a treatment already, **at least 6 months after the start but 4 weeks before the next course**. The European League Against Rheumatism (EULAR) recommend yearly vaccination with influenza of all patients with rheumatic diseases<sup>11</sup>.

### Streptococcus pneumoniae

Currently two forms of pneumococcal vaccines are available. PPSV23 is derived from polysaccharide capsule while PCV13 is a conjugated vaccine with diphtheria carrier protein. PPSV23 response is T cell independent while PCV13 is T cell dependent. **The immunological response is robust in PCV13 compared to PPSV23**. Hence, boosters are required in PPSV23 while a single dose is sufficient in PCV13. Majority of the available literature has used PPSV23 in rheumatic diseases. Another reason for heterogeneity among the available data is lack of generally accepted serologic protection criteria for immunologic response to Pneumococcal vaccine.

In RA, good body of evidence exists to suggest adequate serologic response to pneumococcal vaccination independent of the DMARD used and disease activity<sup>12</sup>. However, newer studies have documented mildly reduced seroconversion with methotrexate-antiTNF combination and severely impaired humoral response with BCDT.<sup>13,14</sup> Recent studies of PPSV23 in SLE suggest reduced immunogenicity as compared to healthy controls.<sup>15</sup> Efficacy of pneumococcal vaccine is also established in Systemic sclerosis<sup>16</sup> and Psoriatic arthritis.<sup>17</sup>

Center for Disease Control (CDC) recommends PCV-13 followed by PPSV-23 at least 8 weeks later for general population. For those who have already received PPSV-23, PCV-13 should be given at least 1 year later with an additional PPSV-23 booster given as usual 5 years from the first<sup>18</sup>

EULAR Guidelines strongly recommend pneumococcal vaccination in all patients with rheumatic diseases<sup>11</sup>.

Table 1: Immunogenicity of various vaccines in the presence of various immunosuppressants in RA and SLE

	Methotrexate	TNFi	Rituximab	Abatacept	Tofacitinib	Tocilizumab
<b>RA</b>						
Influenza	±	+	↓↓	↓	+	+
Pneumococcal	+*	+*	↓↓	↓	↓	+
<b>SLE</b>						
Influenza	+	+	↓↓	↓	NA	NA
Pneumococcal	±	+	↓↓	NA	NA	NA

\* combination – reduced immunogenicity; ± Doubtful; ↓ Reduced; + Intact immunogenicity; NA, Not available; TNFi, TNF inhibitor

### Hepatitis B

Studies in RA, SLE, Ankylosing Spondylitis, Behcet's disease suggest immunogenicity of the Hepatitis B vaccination irrespective of disease activity, steroid or DMARD use. However, the amount of the data is insufficient to draw meaningful conclusions. EULAR guidelines recommend Hepatitis B vaccination for the patients at risk including intravenous drug abuse, multiple sex partners in the previous 6 months or health care personnel<sup>11</sup>. Hepatitis B vaccination is a part of universal immunization programme in India.

### Herpes Zoster

Herpes zoster infection risk is increased in Rheumatic diseases. Special concerns regarding Herpes Zoster are being raised in view of increased risk in patients of RA receiving tofacitinib. **As HZV is a live attenuated vaccine, its use in immunosuppressed patients is controversial.** However, evidence is accumulating from larger registry based studies suggesting its safety in immunosuppressed patients with rheumatic diseases<sup>19</sup>. American Advisory Committee on Immunization Practices (ACIP) recommends using HZV in general population  $\geq 50$  years, persons anticipating immunosuppressant (at least two weeks prior to administration of immunosuppressive agent), in persons taking low-dose immunosuppressive therapy (e.g.,  $<20$  mg/day of prednisone or equivalent or using inhaled or topical steroids)<sup>20</sup>. Temporary discontinuation of immunosuppressive medication before vaccination with live attenuated vaccines might also be considered, but there are no studies to support this strategy.

Live vaccination should be avoided in following scenarios

- 1) **Steroids** - steroid more than 10 mg for two weeks or more
- 2) **DMARDs** - Cyclosporine  $>2.5$  mg/kg per day, Sulfasalazine  $>40$  mg/kg per day or 2 g/day, Azathioprine  $>3$  mg/kg, Cyclophosphamide  $>2.0$  mg/kg per day, Leflunomide  $>0.5$  mg/kg per day
- 3) **Biologic** except B cell depletion therapy (BCDT) - Avoid anti TNF for four weeks
- 4) **BCDT** - Avoid after BCDT for 6 months and can be given 4 weeks prior to BCDT initiation

Vaccine coverage in an outpatient rheumatology clinic in Germany were 18% and 25% for pneumococcal and influenza respectively.<sup>21</sup> Another telephone based survey reported reasons for failure to receive pneumococcal and influenza vaccine were lack of doctor recommendations (55%), safety or efficacy concern (21%) and lack of motivation (19%)<sup>22</sup>. Simple interventions shown to be useful in increasing coverage include: presentation to rheumatology providers, creation of immunization algorithm, placing reminders on clinic forms, stocking the vaccine in clinic, establishing protocols for vaccination at admission.

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To summarize, Box 2 shows the EULAR recommendations for the vaccination of individuals with AIRD. Recently, updates of these guidelines were presented in EULAR Meeting, Amsterdam, 2018. It is under

- Vaccination status should be assessed in the initial work-up of patients
- Vaccine should ideally be administered to patients with an AIRD during stable disease
- Live attenuated vaccines should be avoided whenever possible.
- Vaccine can be administered to patients being treated with DMARDs and TNF inhibitors, but vaccine should be administered before starting B-cell-depleting biologic therapy
- Influenza vaccination should be strongly considered
- PPV23 should be considered
- Patients with an AIRD should have TT vaccination in accordance with the recommendations for the general population; in case of major or contaminated wounds in patients who received rituximab within 24 weeks, tetanus immunoglobulin instead of TT vaccine should be administered
- Herpes zoster vaccination “can” be considered
- For hyposplenic or asplenic patients, influenza, pneumococcal and H. influenzae type b and meningococcal C vaccinations are recommended
- Hepatitis A and hepatitis B vaccination are only recommended for patients with an AIRD who are ‘at risk’ (i.e., intravenous drug abuse, multiple sex partners in the previous 6 months, or health care personnel)
- Patients who plan to travel are recommended to have vaccinations according to general rules, except for live-attenuated vaccines, which should be avoided whenever possible by immunosuppressed patients
- BCG vaccination is not recommended

the process of publication. Newer recommendations include: immunocompetent household members of patients with AIRD should be encouraged to receive vaccines according to national guidelines with the exception of oral poliomyelitis vaccine and live attenuated vaccine should be avoided for the first 6 months in newborn whose mother received biologics in second half of pregnancy.

### bDMARDs and Vaccination

- Ideally, vaccination should be given (live or killed) four weeks before starting B cell depletion therapy. However, partial efficacy has been noted when given at least two weeks before Rituximab.
- Killed vaccine can be given during treatment with anti TNF, tocilizumab.
- JAK inhibitor predispose to Herpes Zoster reactivation. Herpes Zoster vaccine should be given at least two weeks before starting JAK inhibitor.
- Live attenuated vaccines should be avoided whenever possible.

Table 2 summarises immunogenicity of vaccines in various CTDs, disease flare and recommendations.

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Vaccine/CTD	RA		SLE		SSc		Vasculitis		Seroconversion rates			Recommendation <sup>#</sup>
	Immunogenicity	Disease flare	Immunogenicity	Disease flare	Immunogenicity	Disease flare	Immunogenicity	Disease flare	csDMARDs	TNFi	RTX	
Influenza	E	No	Mixed	No	E	No	E	No	Same	Same/Reduction*	Reduced	Yes
Pneumococcal	E	No	Reduced	No	E	No	E	No		Mild reduction*	Reduction	Yes
Hepatitis B**	E	No	E	No	No data				Same	Variable		At Risk
HPV	No data											Should be considered less than 25 year
Tetanus	E	No	E	No	No data				Same	Same	No data	In accordance with general population
Haemophilus and meningococcal	No data											Asplenic or hyposplenic patients
Live vaccine <sup>§</sup>	Lack of data											To be avoided (details see text)

Table2: Efficacy of Vaccine in autoimmune rheumatic disease \*with methotrexate; \*\*more data needed; #see text for B cell depletion therapy; <sup>§</sup>BCG vaccine, oral poliomyelitis vaccine, oral typhoid fever vaccine and yellow fever vaccine csDMARDs, Conventional DMARDs; bDMARDs, biologics; E, Effective; RTX, Rituximab

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