



## Commentary

### **When treating rheumatoid arthritis be vigilant for influenza (& pneumonia): Don't ignore, don't neglect**

This is a world of microbes<sup>1</sup>. Our relationships with them are complex and unpredictable. The immune system needs to constantly wage a war to survive. The microbes constantly evolve to evade and escape. Their fury is often borne by patients with compromised immune systems. Rheumatoid arthritis (RA) is a prime example. Severe infections and coronary artery disease are leading causes of premature mortality in RA<sup>2</sup>. Respiratory tract is a prime target, and influenza viruses and pneumococci are leading microbes<sup>3,4</sup>. Anti-rheumatoid medications such as disease modifying anti-rheumatoid drugs (DMARDs) such as methotrexate (MTX), steroids and biological agents such as infliximab and rituximab add to the risk of infection. MTX is pivotal in the management of RA.

In several parts of the world including India, influenza epidemics are an annual affair and require astute vigilance for timely and effective vaccination<sup>5</sup>. Several evidence-based guidelines recommend that RA patients should be vigorously protected and vaccinated against influenza and pneumococcal infections<sup>6-8</sup>. The recommendations have been further strengthened in view of increased use of the highly targeted, powerful biologicals in RA.

The study by Jain *et al*<sup>9</sup> published in this issue is a rejoinder for the clinicians to seriously consider appropriate immunization in RA patients specifically to influenza. A single dose of inactivated seasonal trivalent [subtype A (two strains - H1N1, H3N2) and B (Yamagata strain)] influenza vaccine was administered to all participants in a three-arm open-label study; two arms were RA patients (51 each) and one arm was healthy control (45 individuals). Patients were either early RA and naive for DMARD use (DMARD naïve) or chronic RA on long-term MTX ( $\geq 15$  mg weekly). None had a prior history of influenza immunization. Immediately prior and four-week post-vaccination,

blood samples were analyzed to evaluate immune response (rise in antibody titre) and seroprotection ( $\geq 40$  units antibody titre). Based on the study data, the authors made three important conclusions - influenza vaccination was safe, MTX use did not dampen the post-vaccination immune response and that there was a need (in view of high pre-vaccination status) to review the recommendation for an annual influenza vaccination. The DMARD naive subjects were younger with more active disease and higher frequency of steroid use, and these characteristics are likely to have influenced the immune responses to vaccine. However, there was no further follow up to evaluate long-term efficacy and safety.

The world experience with influenza vaccine confirms its safety<sup>5</sup>. However, it ought to be repeatedly evaluated due to frequent change in the viral antigen characteristics. Post-2009 pandemic, H1N1 strain is invariably included in the trivalent vaccine<sup>10</sup>. Only killed inactivated intramuscular influenza vaccine is advocated for the use in RA. Although vaccination has been implicated as a non-specific trigger for a reactive form of autoimmune arthritis<sup>11</sup>, it is well known that the risk of disease flare or relapse in RA is much higher with infection rather than vaccination.

The literature does not seem to agree with the conclusion of Jain *et al*<sup>9</sup> regarding the effect of MTX on influenza vaccination uptake in RA. The authors based their study sample size on an American study which demonstrated that the antibody titre for influenza H1N1 in the DMARD (MTX)-treated patients was almost one-third of the titre in healthy subjects and about half of the titre reported in RA naive subjects for DMARD/MTX<sup>12</sup>. Surprisingly,  $>70$  per cent of individuals at baseline (pre-vaccination) showed a seroprotective titre to influenza antigens except for Yamagata strain (26%) in healthy controls<sup>9</sup>. Tandale

*et al*<sup>13</sup> demonstrated seroprotection titre (influenza) in 26.4 per cent H1N1 and 55.3 per cent H3N2 antigen in the regional Indian population. A seroprotection rate of 33 per cent (17-41%) was considered as herd immunity threshold for the Caucasian population<sup>14</sup>. Thus, the basal immune response (herd immunity) to influenza antigens in the current study is indeed high and reassuring.

Post-vaccination, the seroprotection response increased and was reported to be 94-100 per cent for all the three influenza antigens in RA patients despite MTX exposure; duration of MTX exposure was not described by the authors<sup>9</sup>. The proportionate increase was much more in the DMARD naive groups as compared to MTX use (H1N1: 39 vs. 24%; H3N2: 27 vs. 14%; Yamagata: 15 vs. 25%). The lower degree of post-vaccination seroprotection for Yamagata B strain in healthy individuals (84.4%) as compared to RA patients (94.1% DMARD naive and 100% MTX use) is difficult to understand. It is likely that the MTX effect in the current Indian study was somehow negated by the high degree of pre-vaccination antibody titre. However, negative influence of MTX on influenza vaccine uptake cannot be totally dismissed in this study<sup>9</sup>.

Though it is difficult to precisely measure seroprotection, the geometric mean titre for influenza antigens in the MTX group was lower than that of the DMARD naive group and healthy controls following vaccination. Very little data exist to endorse the safe cut-off titre for each of the three influenza antigens that confer maximum protection to RA patients. A general consensus in the world literature suggests that RA patients treated with MTX and/or anti-tumour necrosis factor (TNF) therapy achieve a satisfactory humoral response but is certainly lower than that demonstrated in healthy population<sup>12,15</sup>. MTX decreases humoral response to pneumococcal vaccination<sup>16</sup>. The immune response to both vaccines is reduced with rituximab, abatacept, but sulphasalazine, anti-TNF inhibitors and tocilizumab do not seem to have a negative effect on vaccine immunogenicity<sup>16,17</sup>.

A recent well-designed randomized study evaluated the effect of tofacitinib (TNB) (JAK inhibitor) on the success of 2011-2012 trivalent influenza and 23-valent pneumococcal polysaccharide (PPSV-23) vaccination in RA patients<sup>18</sup>. Patients were also stratified for concomitant MTX use. Primary endpoints of vaccination success were predefined and depended

on increased antibody titre to two or more of the three influenza antigens and six or more of 12 pneumococcal serotypes. In TNB naive patients, the immune response to both influenza and pneumococci vaccine was much less compared to healthy controls. Intriguingly, the immune response to both the vaccinations was much better in patients on long-term management with TNB as compared to mono- or combination therapy with MTX. The negative effect of MTX on antibody titre was more pronounced in case of pneumococcal vaccine. Amongst the influenza antigens, the lowest response was shown for B antigen. Responses to the H1N1 and H3N2 vaccine components were more robust. The authors concluded that to maximize PPSV-23 responsiveness, clinicians should vaccinate before TNB or MTX treatment. However, in case of influenza, vaccination could be undertaken yearly (as recommended) regardless of TNB and or MTX therapy<sup>18</sup>. Live attenuated pneumococcal polysaccharide vaccine 23 is considered to be less immunogenic than the inactivated protein conjugate form. Several but not all studies have shown that MTX reduces immune response to pneumococcal vaccine<sup>19,20</sup>.

Do we need to address the questions of administering influenza vaccine to our RA patients every year? The current study provides ample evidence that the basal seroprotection against influenza A antigens in Indian RA patients seems to be high and comparable to healthy individuals and demonstrated an impressive increment in antibody titres and seroprotection following vaccination. Therefore, there seems to be a case to administer influenza vaccine to RA patients irrespective of MTX exposure in high-risk categories such as elderly age and concomitant morbidity, before immunosuppressants. We need careful evaluation of the risk profile for infections. The vaccine ought to match the seasonal, variable and unpredictable behaviour of influenza.

In the study by Jain *et al*<sup>9</sup>, there was reduction in RA disease activity (disease activity score on 28 joints/DAS 28) in the DMARD naive group following influenza vaccination, implying that vaccination *per se* has a therapeutic effect in RA. Even the pre-vaccination proportion of seroprotection against influenza antigens in DMARD naive group was lower and this could be due to high disease activity. In the TNB study, disease control led to an improved response to PPV-23 but not influenza<sup>18</sup>. The beneficial association between vaccination and disease activity in RA is an exciting possibility but needs further research.

It is important to acknowledge the burden of RA in the Indian population. The adjusted prevalence of RA is 0.3 per cent; there may be over five million patients of RA in the community<sup>21</sup>. Immunization programme for such a huge burden is no mean task, but it is reassuring that Indians have a robust level of herd immunity as discussed above. The synergism between influenza virus and pneumococcus can cause severe life-threatening complications<sup>22</sup>. Thus, RA patients may need both influenza and pneumococcal vaccination.

Although there is strong evidence that adequate immune antibody titres are achieved with vaccination in RA patients, this may not translate into clinically visible protection levels. The vaccination studies typically focus on immunogenicity of the vaccine in terms of antibody titre. The protective antibody titres for healthy volunteers may not correlate with protection in RA patients. It is also not clear how long protective antibody titre exists in RA patients. We need to have prospective controlled trials to address clinical efficacy (prevention and/or reduction in infections) and safety of vaccination in RA patients.

There are a few other factors such as age, hormonal status, smoking and alcohol intake, which influence immune responses and should be considered in vaccination studies. However, Dougados *et al*<sup>23</sup> reported that age, sex and DMARD treatment did not affect the immune response to influenza vaccine. Pre-vaccination seroprotection was significantly associated with positive immune response. In countries where immunization was more frequent, the predictive factors of vaccination were older age, lower disease activity, higher educational level, use of biotherapy, absence of corticosteroid therapy and presence of comorbidities<sup>23</sup>.

Vaccination of RA patients in a clinical setting worldwide seems to be deplorably dismal and erratic. Rheumatologists and other care providers do not seem to pay adequate attention to vaccination in patients of RA beginning DMARD therapy<sup>23,24</sup>. A four-fold reduction in both admissions and case fatality rates due to respiratory infection was demonstrated in RA patients, following implementation of a successful 'rheumatologist-led' vaccination programme<sup>24</sup>.

We need a close liaison between primary and secondary care to maximize vaccination in our population, RA in particular. It is likely that all patients of RA do not require vaccination and there seems to be a favourable case arising out of a robust herd

immunity in our population as demonstrated by Jain *et al*<sup>9</sup>. However, patients with RA certainly need to be protected against influenza and pneumococcal infection. Apart from vaccination, hygiene, sanitation, good disease control, minimum use of immunosuppressants are recommended. An individual approach beginning with risk ascertainment for infections may be an attractive proposition for influenza and pneumococcal vaccination in a socioeconomically challenged setting such as ours.

**Arvind Chopra\* & Vaijayanti Lagoo Joshi**

Centre for Rheumatic Diseases,  
Hermes Elegance, 1988 Convent Street, Camp,  
Pune 411 001, Maharashtra, India

\*For correspondence:  
arvindchopra60@hotmail.com

Received January 13, 2017

## References

1. Chopra A. Bugs and we: Who is chasing whom. *Indian J Rheumatol* 2011; 6 : 1-4.
2. Chopra A. Epidemiology of rheumatoid arthritis. In: Mukherjee S, Ghosh A, editors. *Monograph on rheumatoid arthritis Indian College of Physicians*. Kolkata: Marksman Media Services, Association of Physicians of India; 2012. p. 1-9.
3. Listing J, Gerhold K, Zink A. The risk of infections associated with rheumatoid arthritis, with its comorbidity and treatment. *Rheumatology (Oxford)* 2013; 52 : 53-61.
4. Widdifield J, Bernatsky S, Paterson JM, Gunraj N, Thorne JC, Pope J, *et al*. Serious infections in a population-based cohort of 86,039 seniors with rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2013; 65 : 353-61.
5. Solomon CG. Influenza vaccination. *N Engl J Med* 2016; 375 : 1261-8.
6. Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM, *et al*. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2012; 64 : 625-39.
7. van Assen S, Agmon-Levin N, Elkayam O, Cervera R, Doran MF, Dougados M, *et al*. EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. *Ann Rheum Dis* 2011; 70 : 414-22.
8. Perry LM, Winthrop KL, Curtis JR. Vaccinations for rheumatoid arthritis. *Curr Rheumatol Rep* 2014; 16 : 431.
9. Jain VK, Bhashini N, Balajee LK, Sistla S, Parija SC, Negi VS. Effect of disease-modifying antirheumatic drug therapy on immune response to trivalent influenza vaccine in rheumatoid arthritis. *Indian J Med Res* 2017; 145 : 464-70.

10. Miller E, Hoschler K, Hardelid P, Stanford E, Andrews N, Zambon M. Incidence of 2009 pandemic influenza A H1N1 infection in England: A cross-sectional serological study. *Lancet* 2010; 375 : 1100-8.
11. Symmons DPM, Chakravarty K. Can immunisation trigger rheumatoid arthritis? *Ann Rheum Dis* 1993; 52 : 843-4.
12. Gabay C, Bel M, Combescure C, Ribi C, Meier S, Posfay-Barbe K, *et al.* Impact of synthetic and biologic disease-modifying antirheumatic drugs on antibody responses to the AS03-adjuvanted pandemic influenza vaccine: A prospective, open-label, parallel-cohort, single-center study. *Arthritis Rheum* 2011; 63 : 1486-96.
13. Tandale BV, Pawar SD, Gurav YK, Chadha MS, Koratkar SS, Shelke VN, *et al.* Seroepidemiology of pandemic influenza A (H1N1) 2009 virus infections in Pune, India. *BMC Infect Dis* 2010; 10 : 255.
14. White LF, Wallinga J, Finelli L, Reed C, Riley S, Lipsitch M, *et al.* Estimation of the reproductive number and the serial interval in early phase of the 2009 influenza A/H1N1 pandemic in the USA. *Influenza Other Respir Viruses* 2009; 3 : 267-76.
15. França IL, Ribeiro AC, Aikawa NE, Saad CG, Moraes JC, Goldstein-Schainberg C, *et al.* TNF blockers show distinct patterns of immune response to the pandemic influenza AH1N1 vaccine in inflammatory arthritis patients. *Rheumatology (Oxford)* 2012; 51 : 2091-8.
16. Hua C, Barnetche T, Combe B, Morel J. Effect of methotrexate, anti-tumor necrosis factor  $\alpha$ , and rituximab on the immune response to influenza and pneumococcal vaccines in patients with rheumatoid arthritis: A systematic review and meta-analysis. *Arthritis Care Res (Hoboken)* 2014; 66 : 1016-26.
17. Whittaker M, Galloway J, Subesinghe S. Systematic review of the effect of anti-rheumatic therapies upon vaccine immunogenicity. *Arthritis Rheum* 2014; 66 : S898-9.
18. Winthrop KL, Silverfield J, Racewicz A, Neal J, Lee EB, Hrycaj P, *et al.* The effect of tofacitinib on pneumococcal and influenza vaccine responses in rheumatoid arthritis. *Ann Rheum Dis* 2016; 75 : 687-95.
19. Gelinck LB, van der Bijl AE, Visser LG, Huizinga TW, van Hogezaand RA, Rijkers GT, *et al.* Synergistic immunosuppressive effect of anti-TNF combined with methotrexate on antibody responses to the 23 valent pneumococcal polysaccharide vaccine. *Vaccine* 2008; 26 : 3528-33.
20. Kapetanovic MC, Roseman C, Jönsson G, Truedsson L, Saxne T, Geborek P. Antibody response is reduced following vaccination with 7-valent conjugate pneumococcal vaccine in adult methotrexate-treated patients with established arthritis, but not those treated with tumor necrosis factor inhibitors. *Arthritis Rheum* 2011; 63 : 3723-32.
21. Chopra A. Disease burden of rheumatic diseases in India: COPCORD perspective. *Indian J Rheumatology* 2015; 10 : 70-7.
22. Peltola VT, Murti KG, McCullers JA. Influenza virus neuraminidase contributes to secondary bacterial pneumonia. *J Infect Dis* 2005; 192 : 249-57.
23. Dougados M, Soubrier M, Antunez A, Balint P, Balsa A, Buch MH, *et al.* Prevalence of comorbidities in rheumatoid arthritis and evaluation of their monitoring: Results of an international, cross-sectional study (COMORA). *Ann Rheum Dis* 2014; 73 : 62-8.
24. Sowden E, Mitchell WS. An audit of influenza and pneumococcal vaccination in rheumatology outpatients. *BMC Musculoskelet Disord* 2007; 8 : 58.