A Systematic Review and Meta-Analysis of Anti-Rheumatic Drugs and Vaccine Immunogenicity in Rheumatoid Arthritis

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ABSTRACT

Objectives: Vaccination is a key strategy to reduce infection risk in RA patients and is advocated in internationally recognised rheumatology society guidelines. The aim was to evaluate to the impact of anti-rheumatic drugs on influenza and pneumococcal vaccine immunogenicity.

Methods: We conducted a systematic literature review and meta-analysis comparing the humoral response to influenza (pandemic and seasonal trivalent subunit vaccines) and pneumococcal (PPV23, PCV-7, PCV-13) vaccination in adult RA patients treated with anti-rheumatic drugs. Vaccine immunogenicity was assessed by seroprotection rates measured 3 to 6-weeks post immunisation. Odds ratios and 95% CIs were pooled.

Results: In total, 9 studies were included in the meta-analysis (7 studies investigating anti-rheumatic drug exposures and influenza humoral response, 2 studies investigating pneumococcal vaccine response). Methotrexate was not associated with reduced humoral response for any influenza strain. TNF inhibitor drug exposure was associated with reduced influenza B strain vaccine response compared to healthy controls (pooled OR 2.48, 95% CI 1.11 - 5.54), however H1N1 and H3N2 influenza strain responses were not adversely affected. Limited data were available to draw firm conclusions regarding pneumococcal serotype responses with methotrexate or TNF inhibitor drug exposure.

Conclusion: Vaccination should be considered in all RA patients. Anti-rheumatic drugs are safe and should not preclude immunisation against vaccine preventable disease, which should be encouraged as part of routine care. Systematic review registration number: PROSPERO 2016: CRD42016048093.

INTRODUCTION

Rheumatoid arthritis (RA) patients are at a two-fold increased risk of infection compared to healthy subjects,[1]. The is due to a multifactorial complex interaction between inherent immune dysfunction, comorbidity, disease activity and immunosuppression,[2]. Highly targeted biologic therapies (including Tumour Necrosis Factor inhibitor drugs (TNFi), Rituximab (RTX), Tocilizumab (TOC) and Abatacept (ABA)) have revolutionised RA management over the last decade, however the infection risk associated with these drugs has been a concern for clinicians and patients.

British Society of Rheumatology (BSR), European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) guidelines,[3, 4] recommend vaccination against immune preventable diseases (including influenza and pneumococcal infections). The seasonal influenza vaccine is an inactivated trivalent subunit vaccine comprised of 3 viral antigens (2 'A' strains, H1N1 and H3N2 and a single 'B' strain). The pandemic influenza vaccine (pH1N1) is also utilised when necessary. Two commercially available pneumococcal vaccines are used in clinical practice, a 23-valent polysaccharide vaccine (PPV23) and a 13-valent conjugate vaccine (PCV-13) which superseded a 7-valent conjugate vaccine (PCV-7) in 2010. In the U.K., routine vaccination schedules advise annual influenza and single PPV23 vaccination in individuals over the age of 65 or anybody with chronic comorbid illness including pulmonary, cardiac, renal or liver disease. Immunocompromised patients (of any cause) should also be offered vaccination. Historically uptake of vaccination in RA populations has been poor, particularly with regard to pneumococcal vaccination,[5]. The reasons may include a lack of awareness about the indications for vaccination amongst primary or secondary care providers, concerns pertaining to vaccine safety, efficacy or fear of worsening disease activity.

We undertook a systematic review of the literature and meta-analysis to evaluate the impact of immunosuppressive drugs commonly used in RA on humoral immune responses to influenza and pneumococcal vaccination. In addition, the impact of vaccination on disease activity and measures of health quality were evaluated.

METHODS

The study was conducted in accordance with the preferred reporting items for systematic reviews and meta-analysis guidelines,[6]. The systematic review was registered with the international prospective register of systematic reviews (registration number: PROSPERO 2016: CRD42016048093).

Search strategy and information sources

The literature was searched systematically by two investigators (S.S. and K.B.) using MEDLINE and EMBASE databases. The vaccines of interest were influenza (seasonal, pH1N1) and pneumococcal (PCV-7, PCV-13, PPV23) vaccines. The search terms were 'inflammatory arthritis' or 'rheumatoid arthritis' and 'immunisation' or 'vaccination' or 'vaccine' or 'influenza' or 'pneumovax' or 'prevenar'. The search was undertaken in October 2016 and re-run prior to the final analysis to identify further studies that could be retrieved for analysis.

Eligibility criteria and study selection

English language publications of prospective cohort studies and randomised control trials published between January 1990 and October 2016 were sought. Case reports and conference abstracts were excluded. RA patients aged over 18 years treated with anti-rheumatic drugs who had received influenza and/or pneumococcal vaccines were considered. Alternative diagnoses of inflammatory arthritis were excluded.

The primary outcome of interest was evidence of seroprotection (SP) as a surrogate measure of vaccine immunogenicity, classified by anti-rheumatic drug exposure. Seroconversion (SC) and/or seroresponse (SR) were considered if SP rates were not published or calculable from the data presented. For influenza vaccination, SP was considered as a post-vaccination antibody (Ab) titre measured by haemagglutination inhibition assay (HI) of ≥ 1:40, SR or SC a 4-fold increase in post vaccine Ab titre. For this study and in the absence of an accepted universal correlate of vaccine protection, a post-vaccination Ab titre of 1 mcg/ml was used as a marker of likely protection following pneumococcal vaccination, SR was defined as ≥2-fold increase in post-vaccine Ab titres. Studies reporting only on geometric mean titres (GMT), opsonisation index (OI) or Ab response rates were excluded. Vaccine response was assessed between 3 and 6-weeks post influenza and pneumococcal vaccination. Healthy controls (HC) or subjects not taking anti-rheumatic or immunosuppressive therapies served as the comparator groups. Secondary outcomes of interest were the effect of vaccination on disease activity and quality of life measures.

Titles and abstracts of studies retrieved using the search strategy detailed above and those from additional sources (including reference lists of selected publications) were screened independently (by two investigators, S.S. and K.B.). The full text of the potential studies for inclusion were retrieved and assessed for eligibility.

Data collection process and outcomes and quality assessment

Data were extracted independently (by S.S. and K.B.). Disagreements over study eligibility, quality (as assessed using the Newcastle-Ottawa Score (NOS) for cohort studies) or risk of bias were resolved through discussion with a third reviewer (J.G.). where necessary. Data collated included the source (main author, journal, publication date), study design, vaccination intervention, anti-rheumatic drug exposure and patient characteristics (age, disease duration, disease activity, quality of life measures where available). SP, SR and SC rates were documented or calculated from data available.

Data synthesis and statistical analysis

Analyses were performed using Review Manager software version 5.3 (Cochrane Collaboration, Oxford, U.K.). Sensitivity analyses compared vaccine response within immunosuppression class and descriptive analysis was undertaken to assess the effect of vaccine response in patients with RA by drug class. Drugs exposures studied included methotrexate (MTX), TNFi, RTX, TOC and ABA. Other disease modifying anti-rheumatic drugs (DMARDs) were not studied. Summary data rather than individual level data were aggregated for quantitative analyses. Summary estimates of response were tabulated and compared using a meta-synthesis approach with forest plots.

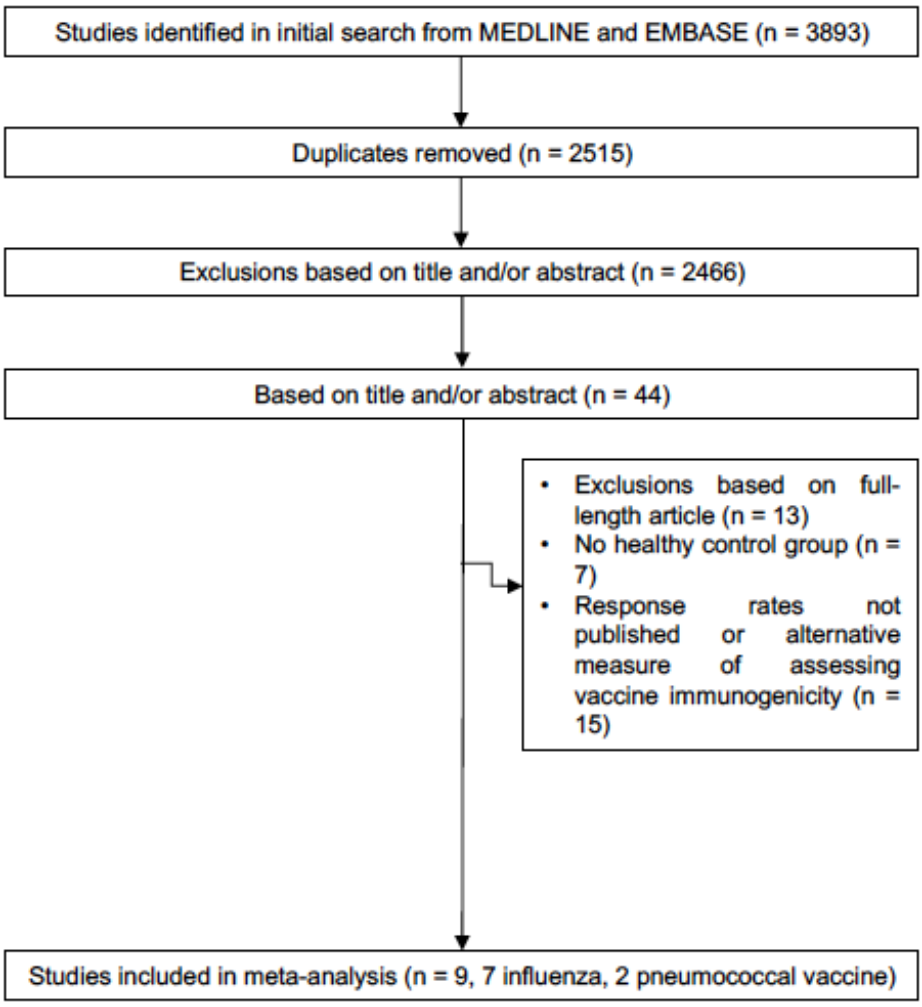
RESULTS

Literature search and study characteristics

The initial search strategy yielded 3893 articles for screening which was reduced to 44 after application of filters and screening of titles and abstracts. Nine studies were selected for inclusion (7 influenza (seasonal or pandemic) and 2 pneumococcal vaccine studies). The search strategy is detailed in Figure 1. The characteristics of studies examining influenza and pneumococcal vaccine immunogenicity are detailed in Tables 1 and 2, forest plots for the odds ratio (OR) of response rates for influenza vaccine strains and pneumococcal serotype responses separated by anti-rheumatic drug exposure (MTX or TNFi) are represented in Figures 2 and 3. It was not possible to evaluate the impact of RTX, ABA or TOC in meta-analyses either due to an absence HC or comparator groups, unpublished vaccine response rates or limited number of studies available for analysis. These studies are discussed further as part of a narrative review. Studies examining the immunogenicity of pneumococcal vaccine in the context of anti-rheumatic drug exposures have been included in a supplementary table. There was good agreement between reviewers on the quality of included studies; all included studies scored

between 5 and 7 on the NOS scale.

Figure 1: Flow chart of studies in the meta-analysis



Influenza vaccine responses

MTX and influenza vaccination response

Five studies including 787 subjects (350 RA patients, 437 controls) assessed MTX exposure and influenza vaccine humoral responses,[7-11]. Three studies assessed the response to pH1N1 influenza vaccination, these results were pooled with seasonal influenza H1N1 responses,[11-13]. MTX exposure was not associated with reduced vaccine responses to H1N1 (pooled (OR) 0.58, 95% Confidence Interval (CI) 0.21 to 1.59), H3N2 (pooled OR 0.56, 95% CI 0.06 to 5.01) or B strain (pooled OR 1.66, 95% CI 0.04 to 70.86).

TNFi and influenza vaccination response

In total, 803 subjects from 7 studies were pooled in the meta-analysis examining TNFi impact on influenza vaccine immunogenicity (304 RA patients, 499 controls),[7-13]. Three studies exclusively

examined the influence of TNFi exposure on pH1N1 influenza response, these results were combined with seasonal influenza H1N1 responses,[11-13]. No significant difference noted between SP responses for H1N1 (pooled OR 0.57, 95% CI 0.28 to 1.19) and H3N2 strains (pooled OR 0.82, 95% CI 0.25 to 2.62) in TNFi exposed patients compared to HC. However, B strain responses were reduced in TNFi exposed patients compared to HC (pooled OR 2.48, 95% CI 1.11 to 5.54].

RTX and influenza vaccine responses

Two studies have described reduced seasonal influenza vaccine responses in RTX treated patients compared to DMARD treated patients and HC [14, 15]. Arad et al. ,[14] reported that a longer interval between RTX administration and influenza vaccination was associated with an improved Ab response in contrast to Oren et al. ,[15] who found no such relationship.

ABA and influenza vaccine responses

Ribeiro et al. ,[16] reported a significantly poorer humoral response to pH1N1 vaccination in ABA treated patients compared to age matched MTX treated patients and HC. Alten et al. described preserved influenza vaccine responses in 296 ABA exposed patients pooling the results from 2 multi-centre, open-label sub-studies,[17]. In total, 49.5% of patients achieved an appropriate post-vaccine humoral response. Despite vaccine responses not being compared against a comparator group, the authors felt the vaccine responses were preserved.

TOC and influenza vaccine responses:

Iwamoto et al. ,[11] reported appropriate humoral responses to pH1N1 vaccination in TOC treated patients compared to HC. However, combination MTX+TOC compared to TOC monotherapy has been associated with a blunted vaccine response in subjects receiving pH1N1 vaccination ,[18]. Tsuru et al.,[19] reported preserved SP rates for all 3 strains of seasonal influenza vaccine in TOC exposed compared to TNFi/DMARD treated patients.

Table 1: Characteristics of the studies examining influenza vaccine immunogenicity included in the meta-analysis

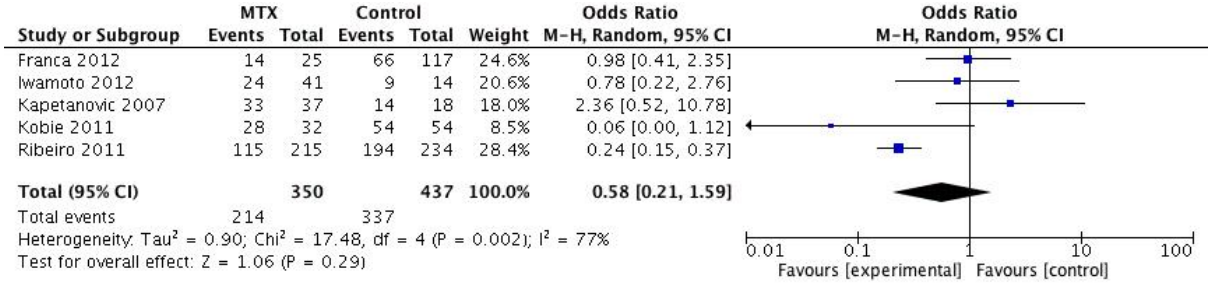
Author, Year (ref)	Number of Subjects (n)	Vaccine Intervention	Outcome	Age, years (SD)	% Women	Disease duration years (SD)	DAS28 score * (SD)	HAQ	SC % (95% CI)	SP % (95% CI)	NOS score
MTX											
Franca et al. 2012 [12]	RA MTX (25) HC (117)	Pandemic Influenza A/H1N1/2009	SP: HI >1:40 SR: >4-fold increase from baseline after 3 weeks	RA 46.5 (10.6) HC 44.3 (12.4)	RA 67 HC 79	15.6 (10.4)	-	-	RA 56.0 (36.5, 75.5) HC 74.3 (66.4, 82.3)	RA 56.0 (36.5 - 75.5) HC 78.6 (71.2 - 86.1)	7
Iwamoto et al. 2012 [11] §	RA MTX (41) HC (14)	Pandemic Influenza A1/H1N1/2009	SP: HI >1:40 SR: >4-fold increase from baseline after 3 weeks	RA median 67 (range 29-90)	RA 98 HC -	-	-	-	RA 58.5 (44.1 – 71.9) ** HC 64.3	RA 60.4 (46 – 73.6) ** HC 71.4	5
Kapetanovic et al. 2007 [7]	RA MTX (37) HC (18)	Influenza trivalent subunit vaccine, H1N1/H3N2/B	SP: HI >1:40 SR: >4-fold increase from baseline after 4-6 weeks	RA 61.3 (20.8-81.4) HC 30.3 (19.2-60.3)	RA 68 HC 74	Median 7.0 (min 0.9– max 46.9)	Pre Vaccine DAS28, low 53, med 35, high12	-	-	RA H1N1 89%, H3N2 76%, B 95%. HC H1N1 78%, H3N2 72%, B 67%	5
Kobie et al. 2011 [8]	RA MTX (70) HC (97)	Influenza trivalent subunit vaccine H1N1/H3N2/B	SP: HI >1:40 SR: >4-fold increase from baseline after 4 weeks	RA 58.4 (12.2) HC 39.8 (13.6)	RA 77 HC 63	>3years 60%, <1 year 17%	-	0.71 (0.00-2.22)	-	RA H1N1 88%, H3N2 94%, B 97% HC H1N1 100%, H3N2 100%, B 100%	5
Ribeiro et al. 2011 [13]	RA MTX (215) HC (234)	Influenza A/H1N1/2009	SP: HI >1:40 SR: >4-fold increase from baseline after 3 weeks	RA 55.8 (11.5)	RA 87 HC -	16.7 (10.4)	Pre Vaccine 3.66 (1.35) Post Vaccine 3.49 (1.36) No significant change		RA 46.3 (39.6 - 53.0) HC: 76.9 (71.0 - 82.2)	RA 53.2(46.6 - 59.9) HC 82.9 (77.5 - 87.5)	6
TNFi											
Franca et al. 2012 [12]	RA (41) (IFX/ADA 30, 11 ETA) HC (117)	Pandemic Influenza A/H1N1/2009	SP: HI >1:40 SR: >4-fold increase from baseline after 3 weeks	RA 45.1 (11.8) HC 44.3 (12.4)	RA 60 HC 79	18.4 (10.1)	-	-	RA 65.9 (51.3, 80.4) HC 74.3 (66.4, 82.3)	RA 65.9 (51.3-80.4) HC 78.6 (71.2-86.1)	7

Iwamoto et al. 2012 [11] §	RA (28) IFX 3, ETA 18, ADA 7) HC (14)	Pandemic Influenza A1/H1N1/2009	SP: HI >1:40 SR: >4-fold increase from baseline after 3 weeks	RA median 64.5 (range 29-78)	RA 100 HC -	-	-	-	RA 38.9 (23.1 – 56.5) * HC 64.3	RA 47.2 (30.4 – 64.5) * HC 71.4	5
Kapetanovic et al. 2007 [7]	RA TNFi (62) (IFX 27, ETA 35) HC (18)	Influenza trivalent subunit H1N1/H3N2/B	SP: HI >1:40 SR: >4-fold increase from baseline after 4-6 weeks	RA median 53.7 (15.1-85.3) HC 30.3 (19.2-60.3)	RA 76 HC 74	Median 20.8 (min 1.5- max 55.9)	Pre Vaccine DAS28, low 49%, medium 41%, high 10%	-	-	RA H1N1 58%, H3N2 74%, B 87% HC H1N1 78%, H3N2 72%, B 67%	5
Kobie et al. 2011 [8]	RA: TNF (61) (ETA 35, IFX 17, ADA 9) HC (97)	Influenza trivalent subunit H1N1/H3N2/B	SP: HI >1:40 SR: >4-fold increase from baseline after 4 weeks	RA 55.4 (12.3)	RA 82 HC 63	>3 years 93%, <1year 5%	-	0.71 (0.00-2.22)	-	RA H1N1 97% H3N2 94% B 97% HC H1N1 100%, H3N2 100%, B 100%	5
Kubota et al. 2007 [10]	RA TNFi (27) (ETA 11/IFX 16) HC (52)	Influenza trivalent subunit H1N1/H3N2/B	SP: HI >1:40 SR: >4-fold increase from baseline after 4-6weeks	RA 55.7 (12.6) HC 55.9 (9.82)	-	-	-	-	-	RA H1N1 44.4%, H3N2 44.4%, B 29.6%, HC H1N1 17.3%, H3N2 25%, B 9.6%	6
Ribeiro et al. 2011[13]	RA: TNF (47) (20 IFX, 16 ADA, 11 ETA) HC (234)	Pandemic Influenza A/H1N1/2009	SP: HI >1:40 SR: >4-fold increase from baseline after 3 weeks	RA 55.8 (11.5)	RA 87 HC -	16.7 (10.4)	Pre Vaccine: 3.66 (1.35) Post Vaccine: 3.49 (1.36) No significant change	-	RA: 51.0(45.0 to 57.0) HC: 76.9(71.0 to 82.2)	RA 67.4 (53.7-81.1) HC 82.9 (77.5-87.5)	6
Salemi et al 2010 [9]	RA TNFi (28) (n = unknown IFX, ADA, ETA) HC (20)	Influenza trivalent subunit H1N1/H3N2/B	SP: HI >1:40 SR: >4-fold increase from baseline after 30 days	RA 53 (3)	RA 82 HC -	-	2.47 (0.2), no significant change at 30 days	-	RA TNF H1N1 45%/H3N2 35%/B 15% HC: H1N1 50%/H3N2 60%/B 20%	RA H1N1 68%, H3N2 75%, B 50% HC H1N1 90%, H3N2 80%, B 40%	6

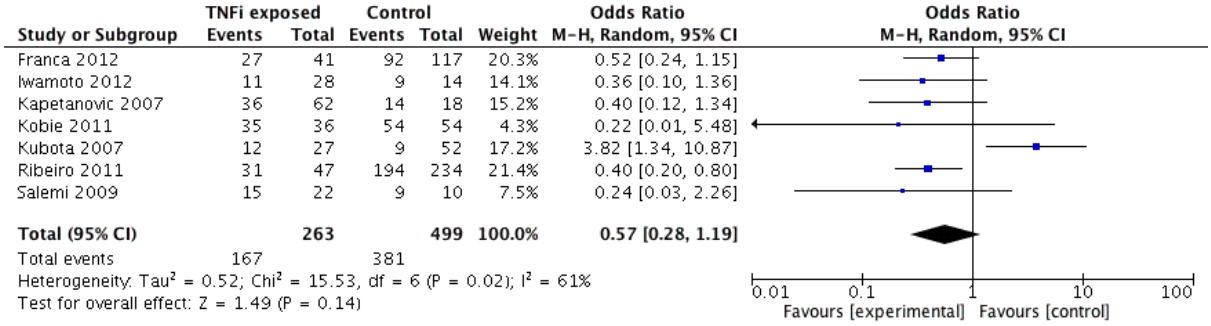
§ additional data supplied on request by the author; RA = Rheumatoid arthritis; HC = Healthy Control; TNFi = Tumour Necrosis Factor inhibitor drug; IFX = Infliximab; ADA = Adalimumab; ETA = Etanercept; MTX = Methotrexate; HI = haemagglutination inhibition assay; SP = Seroprotection; SR = Seroresponse; * DAS28 = Disease Activity Score of 28 joints, scores pre vaccination are quoted unless stated otherwise; HAQ = Health Assessment Questionnaire; 95% CI = 95% Confidence Interval; - = data not provided; Disease duration = mean disease duration unless otherwise stated; ** includes RA patients on non-biological DMARDs including non-MTX users;

Figure 2: Forest plots for the odds ratios of response rates for influenza vaccine serotypes between rheumatoid arthritis patients receiving anti-tumour necrosis factor drugs or methotrexate and healthy controls

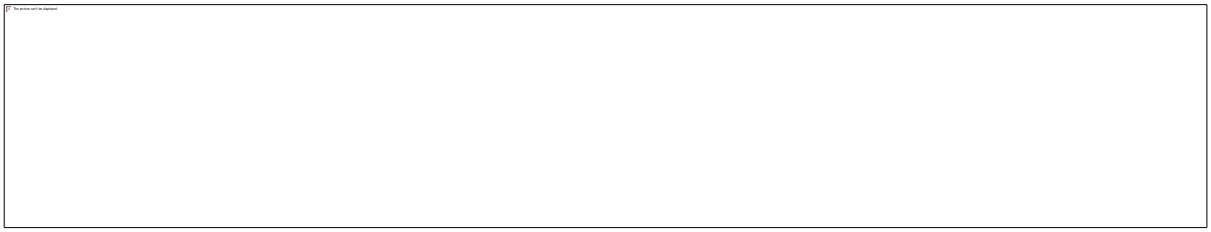
Treatment with MTX and H1N1 strain responses (including pandemic and seasonal H1N1 pooled)



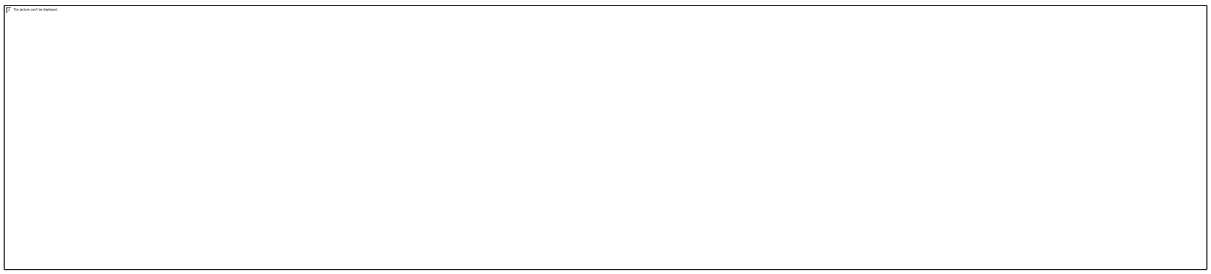
Treatment with TNFi and H1N1 strain responses (including pandemic and seasonal H1N1 pooled)



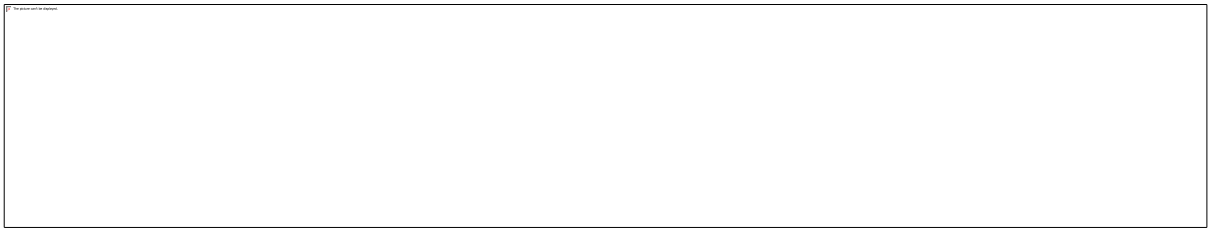
Treatment with MTX and H3N2 strain responses



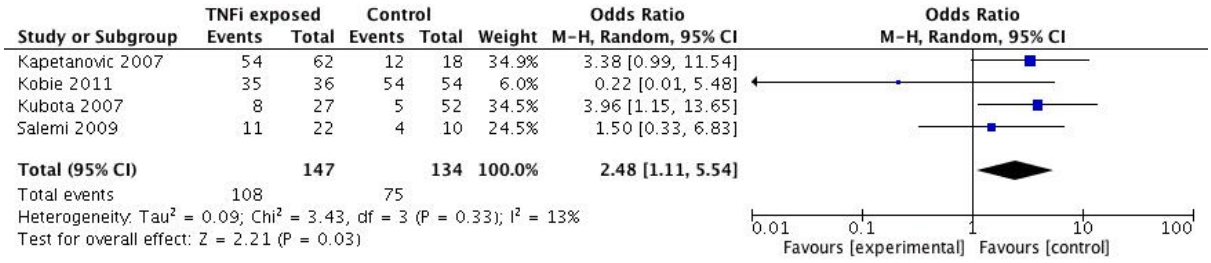
Treatment with TNFi and H3N2 strain responses



Treatment with MTX and B strain responses



Treatment with TNFi and B strain responses



95% CI = 95% Confidence Interval; M-H = Mantel-Haenszel; MTX = Methotrexate; TNFi = Tumour Necrosis Factor inhibitor Drug

Pneumococcal vaccination

MTX and pneumococcal vaccination response

Two studies reporting on 254 subjects (122 RA patients, 132 healthy controls) examining MTX exposure and 6B and 23F pneumococcal serotype responses were included in the meta-analysis,[20, 21]. From the limited data for the two serotype studies, MTX exposure had no detrimental effect on vaccine response compared to HC (pooled OR 0.28, 95% CI 0.16 to 0.49).

TNFi and pneumococcal vaccination response

Two studies reporting on 273 subjects (141 RA patients, 132 healthy controls) assessing 6B and 23F pneumococcal serotype responses with TNFi exposure,[20, 21] were included in the meta-analysis. From the limited data, TNFi exposure had no significant negative impact on vaccine response compared to HC, (pooled OR 0.97, 95% CI 0.38 to 2.47).

RTX and pneumococcal vaccine response

Comparing RA patients treated with RTX+MTX (n = 65) with MTX monotherapy (n = 28), Bingham et al. ,[22] reported that RTX exposed patients had a reduced response to vaccination for each of the 12 PPV23 serotypes tested. The proportions of RTX treated patients with a positive vaccine response (to at least 1, 2, 3, 4, 5, and 6 serotypes) was also decreased compared to MTX monotherapy.

ABA and pneumococcal vaccine response

The data on ABA exposure and humoral vaccine response are conflicting. Migita et al.,[23] found significantly decreased Ab response rates for 6B and combined 6B/23F SR rates in ABA exposed patients compared to MTX and RA control groups. In contrast, Alten et al. ,[17] described preserved SP response to PPV23 vaccination with 55.4% of ABA exposed patients achieving adequate SP response to PPV23 vaccination.

TOC and pneumococcal vaccine response

TOC monotherapy is not associated with impaired PPV23 vaccine response however combination with MTX has been reported to blunt 6B and combined 6B/23F serotype responses [19, 24, 25].

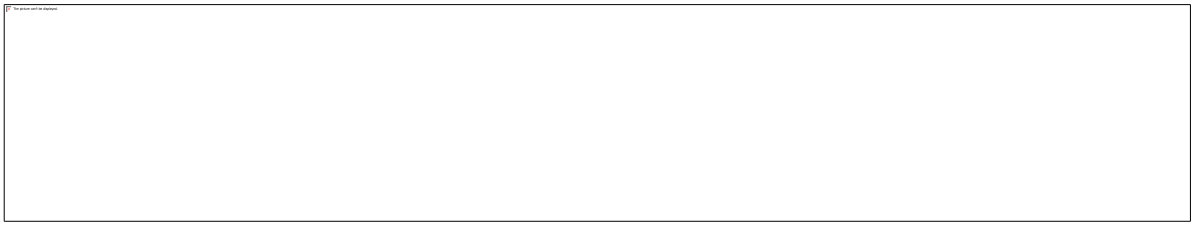
Table: Characteristics of the studies examining pneumococcal vaccine immunogenicity included in the meta-analysis

Pneumococcal Vaccination											
Author, Year (ref)	Number of Subjects (n)	Vaccine Intervention	Outcome	Age, years (SD)	% Women (SD)	Disease duration years (SD)	DAS28 score (SD)	HAQ	SC % (95% CI)	SP % (95% CI)	NOS score
MTX											
Kapetanovic et al. 2006 [20]	RA MTX (37) HC (47)	PPV-23	2-fold increase in post-vaccination titres for 6B and 23F serotypes, 4-6 weeks post vaccination	RA 61.3 (20.8-81.4) HC 30.3 (19.2-60.3)	RA:68 HC: 74	Median 7.0 (minimum 0.9 - maximum 46.9)	Pre Vaccine DAS28, low 53% medium 35%, high 12%	-	-	RA 13.5 HC 38.2	5
Kapetanovic et al. 2011 [21]	RA MTX (85) HC (86)	PCV-7	2-fold increase in post-vaccination titres for 6B and 23F serotypes, 4-6 weeks post vaccination	RA 61.5 (14) HC 51.6 (12)	RA 78.8 HC: 45	RA 11.4 (10) HC 12.7 (12)	RA 3.7 (1.2)	0.7 (0.6)	-	RA 21.2 HC 47.7	6
TNFi											
Kapetanovic et al. 2006 [20]	RA TNFi (62) (IFX 27/ETA 35) HC (47)	PPV-23	2-fold increase in post-vaccination titres for 6B and 23F serotypes, 4-6 weeks post vaccination	RA median 53.7 (15.1-85.3) HC median 30.3 (19.2-60.3)	RA: 76 HC: 74	Median 20.8 (1.5 - 55.9)	Pre Vaccine DAS28, low 49%, medium 41%, high 10%	-	-	RA 50 HC 38.2	5
Kapetanovic et al. 2011 [21]	RA TNFi (79) (TNFi not specified) HC (85)	PCV-7	2-fold increase in post-vaccination titres for 6B and 23F serotypes, 4-6 weeks post vaccination	RA 59.8 (14) HC 51.6 (12)	RA TNF: 87 HC: 45	RA 20.6 (11) HC 12.7 (12)	RA 3.9 (1.1)	1.2 (0.7)	-	RA 36.7 HC 47.7	6

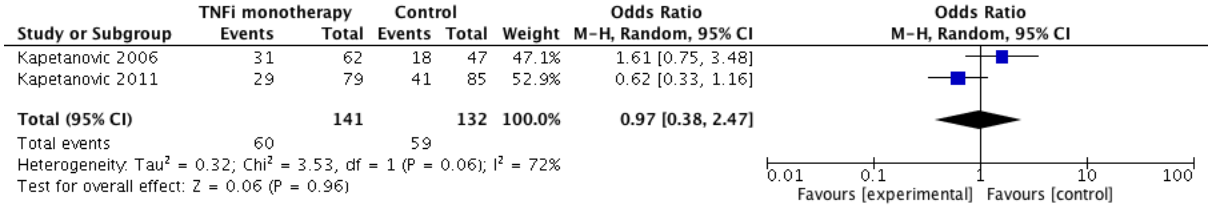
RA = Rheumatoid arthritis; HC = Healthy Control; TNFi = Tumour Necrosis Factor inhibitor drug; IFX = Infliximab; ADA = Adalimumab; ETA = Etanercept; MTX = Methotrexate; HI = haemagglutination inhibition assay; * DAS28 = Disease Activity Score of 28 joints, scores pre-vaccination are quoted unless stated otherwise; HAQ = Health Assessment Questionnaire; 95% CI = 95% Confidence Interval; - = data not provided; PPV23: Pneumococcal polysaccharide vaccine; PCV-7: Conjugate pneumococcal vaccine. Disease duration = mean disease duration unless otherwise stated; Age = mean age unless otherwise stated

Figure 3: Forest plot for the odds ratios of response rates for pneumococcal vaccine (combined 6B and 23F serotype responses) between rheumatoid arthritis patients receiving methotrexate or anti-tumour necrosis factor drugs and healthy controls

Treatment with MTX and pneumococcal 6B/23F serotype responses



Treatment with TNFi and pneumococcal 6B/23F serotype responses



95% CI = 95% Confidence Interval; M-H = Mantel-Haenszel; MTX = Methotrexate; TNFi = Tumour Necrosis Factor inhibitor

DISCUSSION

Our meta-analysis found no detrimental effect of MTX therapy on influenza or pneumococcal vaccine response, however there are reports in contrast to our findings,[26, 27]. There was an observation of diminished influenza B strain vaccine response with TNFi exposure. On further literature review, several studies not included in the meta-analysis due to their study design provide evidence that TNFi do not significantly diminish the response to pneumococcal or influenza vaccines,[26, 28-34].

Meta-analysis of pneumococcal vaccination responses with immunosuppression exposure was challenging due to the significant heterogeneity in reporting vaccine response. We included 2 studies from a single centre analysing 2 serotypes (6B and 23F), thus the generalizability of our conclusions is limited. Despite not being the most prevalent serotypes, bacterial pneumonia associated with 6B and 23F have a high mortality risk ,[35]. We accept that vaccine response may differ across individual pneumococcal vaccine serotypes. Despite achieving a satisfactory response to one serotype, it is not appropriate to assume that vaccine responses for other serotypes will be equal. Vaccine efficacy was defined as achievement of post-vaccination SP Ab titres, however subjects could achieve SP without SR or SC. SP doesn't provide information on vaccine efficacy and we acknowledge alternative methods of reporting vaccine immunogenicity and efficacy, e.g. OI or GMT rises.

Vaccine responses for PCV-7 and PPV23 responses were pooled. PCV-7 however is no longer part of the routine U.K vaccine schedule and was replaced by PCV-13. Both PCV-7 and PCV-13 include 6B and 23F serotypes. Although comparing a conjugated and polysaccharide vaccination may not be appropriate when considering long term vaccine responses, comparison of vaccine immunogenicity at 3 to 6 weeks post vaccination is similar,[36].

Although it was not possible to undertake meta-analysis of the impact of RTX on humoral responses to influenza and pneumococcal vaccination, there are consistent reports in the literature of poorer serological responses to immunisation,[15, 22, 26, 37, 38]. The timing of RTX has also been an important consideration in the assessment of vaccine immunogenicity; a greater interval between RTX administration and vaccination has been associated with an improved vaccine response,[14]. There were limited data to perform meta-analysis on TOC exposure on vaccine responses compared to healthy controls, although review of the literature suggests there no significant effect on PPV or influenza vaccine immunogenicity,[18, 24]. Comparatively, ABA has been reported to impair the responses to pH1N1 and PPV23 response,[16, 23].

EULAR guidelines recommend vaccination against influenza and pneumococcal disease should be undertaken prior to commencement of TNFi or DMARD therapy, we accept that in practice this is challenging and may be unrealistic. EULAR guidance ,[3] also advises vaccination should be undertaken in a period of disease stability however in U.K. practice, biologic drugs (often a trigger to administer vaccinations) are only considered in patients with persistent high disease activity states (DAS28 >5.1). There is limited evidence that vaccine responses are attenuated in RA in patients with high disease activity states. A key clinical decision is determining the best time to vaccination, either before immunosuppressive therapy or in a period of disease stability.

Only 2 studies included in the meta-analyses reported specifically on the effect of vaccination on disease activity however several confirm no evidence of a detrimental effect on parameters of disease activity post vaccination,[9, 13-15, 26, 32, 33, 37, 39, 40]. The safety profiles of influenza and pneumococcal vaccines are favourable; vaccination does not increase the risk of development of RA,[41].

To our knowledge, there has been 1 previous meta-analysis assessing the influence of anti-rheumatic drug therapies on influenza and pneumococcal vaccine responses,[42]. Hua and colleagues reported that MTX decreased humoral responses to pneumococcal vaccination, in contrast to our

results. This is accounted for by an alternative methodological approach to analysis and probable access to unpublished data. In Hua's meta-analysis, the definitions and characteristics of treatment exposed and control groups differed, for example when assessing the influence of MTX on pneumococcal vaccine response, the experimental group compared MTX + TNFi exposed patients to TNFi monotherapy rather than HC. We recognise that biologics are co-prescribed with DMARDs including MTX in routine clinical practice. However, by comparing drug therapies with HC groups in our analysis, we felt it would allow better assessment of the impact of drug therapy on vaccine immunogenicity, albeit to the detriment of potential number of studies and subjects that could be included in meta-analysis.

Limitations

There was a relative paucity of data examining newer biologic agents including RTX, TOC and ABA compared to TNFi drugs. We were limited by the number of studies and subjects that could be included in the meta-analysis due to considerable heterogeneity in study design and methods of reporting on vaccine response, particularly with studies on pneumococcal vaccine efficacy. Several studies reported on Ab response rates, GMT rises or OI without providing numerical data on response rates for SP, SR or SC.

Seasonal and pandemic influenza vaccination utilise strains that vary each season depending on the most virulent predicted strains. Thus, although vaccine responses were broadly categorised by A or B strain responses for the meta-analysis, there may have been variation in the immunogenicity of each vaccine between studies, and this was not possible to correct for.

In routine practice, co-prescription of MTX with a biologic is recommended to maximise efficacy and reduce drug immunogenicity. For the purposes of this analysis, efforts were made to compare TNFi monotherapy to a HC group to prevent aberrancies due to MTX exposure. Concerning influenza vaccine responses with TNFi exposure, 3 studies included patients taking TNFi with concomitant MTX,[8, 11, 12]. Exclusion of these studies increased the heterogeneity but not OR interpretation. Three of the 4 other studies included in the meta-analysis did not explicitly comment if TNFi exposed patients were taking concurrent MTX,[9, 10, 13]. In addition, the studies included different TNFi drugs. An assumption was made that any TNFi exposures had similar class effects irrespective of whether they were a monoclonal antibody or fusion receptor protein.

Adjustment for confounding factors including age and smoking status or significant comorbidity which could impact on vaccine immunogenicity was not possible. Older subjects are at higher risk of serious infection and attenuated vaccine responses to vaccination, a consequence of immunosenescence,[30, 43]. Smoking is associated with a reduced pneumococcal vaccine response in RA patients treated with MTX, however this was poorly reported in studies included,[44].

Conclusion

Vaccination is a key strategy in mitigating against infection risk in RA patients who at risk of potentially fatal infections. Our meta-analysis and systematic review suggests that MTX exposure does not diminish the humoral response to influenza or pneumococcal vaccination. TNFi therapy is associated with a reduced response to influenza B strain response, but no significant negative impact on influenza A strain or pneumococcal vaccine response. Immunosuppression should not preclude vaccination against immune preventable disease. Vaccination is safe and well tolerated and should be encouraged as part of routine clinical care. A challenge lies in increasing the awareness and uptake of vaccinations in RA patients which will require collaborative approaches between primary and secondary care.

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Supplementary Table: Studies examining pneumococcal vaccine responses with different anti-rheumatic drug exposures

Author, Year [Reference]	Subjects (n)	Vaccine	Outcome	Mean Age, years (SD)	Female n (%)	Disease duration, years (SD)	DAS28 score (SD)	HAQ score (SD)	Vaccine response	Comments
O'Dell et al. 1996 [27]	RA (40) 20 treated with MTX, 20 no MTX exposure	PPV23	Ab titres >300ng/ml or ≥ 2-fold increase compared to pre-vaccine titres Type 3, 7F, 9N and 14 serotypes	-	30 (60)	MTX group 7.5 No MTX 8.4	-	-	Adequate response in 77% of patients with no MTX exposure, 50% in group treated with MTX	Poorer response in MTX exposed patients
Kapetanovic et al. 2006 [20]	RA (149, 62 TNFi monotherapy, 50 TNFi + MTX, 37 MTX monotherapy) HC (47)	PPV23	≥ 2-fold or higher increase in 6b and 23f serotype Ab concentration, 4 to 6-weeks post vaccination	Median age: TNFi monotherapy 53.7 TNF+MTX 52.8 MTX monotherapy 61.3 HC 30.3	TNFi (76) TNFi + MTX (70) MTX (68) HC (74)	TNFi 20.8 TNFi + MTX 10.8 MTX 7.0 HC -	% of patients with Low/Intermediate/ High DAS28 at time of vaccination: TNFi: 49/41/10 TNF+MTX: 50/44/6 MTX: 53/35/12	-	% of patients with adequate vaccine response: TNFi 50%, TNFi + MTX 32%, MTX 13.5%, HC 38.2%	MTX associated with a reduced response to PPV23 vaccination, no effect of TNFi on vaccine response
Visvanathan et al. 2007 [30]	RA (70, 20 IFX 3mg/kg + MTX, 36 IFX 6mg/kg + MTX, 14 Placebo + MTX)	PPV23	≥ 2-fold increase at least 6 vaccine serotypes compared to pre-vaccine levels	Median age: IFX 3mg/kg: 52 IFX 6mg/kg 50 Placebo 50	IFX 3mg/kg: (65) IFX 6mg/kg: (66.7) Placebo (78.6)	-	-	-	>80% of patients in each group responded to 1≥ serotypes, 20-25% responded to 6≥ different serotypes	No impact of MTX exposure on vaccine responses
Kaine et al. 2007 [28]	RA (218, 109 Placebo ± MTX, 109 ADA ± MTX)	PPV23	≥ 2-fold titre increase in ≥ 3 of 5 vaccine serotypes and protective Ab titres ≥1.6 mcg/ml, 4-weeks post vaccination. Serotypes 9V, 14, 18C, 19F, and 23F	51.7 ± 11.66	Placebo 82 (75.2) ADA 84 (84.8) Overall 166 (79.8)	-	-	-	% of patients achieving a ≥ 2-fold increase in ≥ 3 of 5 pneumococcal Ab titres: ADA 37.4% Placebo 40.4%, % of patients achieving protective Ab titres >1.6mcg/ml in ≥ 3 of 5 antigens) 4 weeks post-vaccination: ADA 85.9% Placebo 81.7%	No impact of TNFi exposure on vaccine responses

Bingham et al. 2010 [22]	RA (93, RTX+MTX 65, MTX 28)	PPV23	≥2-fold increase or an increase of 1 mcg/ml from pre-vaccination level. 12 pneumococcal serotype responses assessed	RTX + MTX 49.7 (9.6) MTX 49.7 (10.5)	RTX + MTX 51 (75) MTX 25 (78)	-	RTX +MTX 6.2 (1.1) MTX -	-	Decreased responses to PPV23 RTX+MTX 57% of subjects had a 2-fold rise in Ab titre response to >1 serotype, compared with 82% of MTX monotherapy patients. Lower proportions of patients responding to each serotype in RTX+MTX group compared to MTX monotherapy	Reduced vaccine response in RTX exposed patients compared to MTX
Kapetanovic et al. 2011 [21]	RA (253, MTX 85, TNF+MTX 89, TNF 79) SpA/HC (85)	PCV-7	ARR ≥ 2, 4 to 6-weeks post-vaccination, serotypes 6b and 23f	MTX 61.5 (14) TNFi + MTX 60.1 (10) TNFi 59.8 (14) SpA/HC 51.6 (12)	MTX: 67 (78.8) TNFi + MTX 69 (77.5) TNFi 69 (87.3) SpA/HC 39 (45.3)	MTX 11.4 (10) TNFi + MTX 16.2 (12) TNFi 20.6 (11) SpA/HC 12.7 (12)	MTX 3.7 (1.2) TNFi + MTX 3.4 (1.2) TNFi 3.9 (1.1) SpA/HC 3.0 (1.1)	MTX 0.7 (0.6) TNFi + MTX 0.9 (0.7) TNFi 1.2 (0.7) SpA/HC 0.5 (0.5)	Number (%) of subjects achieving ≥ 2-fold increase in pre-vaccination Ab levels MTX 18 (21.2) TNFi + MTX 14 (15.7) TNFi 29 (36.7) SpA/HC 41 (47.7)	MTX associated with a reduced response to PCV-7, no effect of TNFi therapy on vaccine response
Mori et al. 2012 [24]	RA (190, MTX 62, TOC + MTX 54, TOC 50, Control 24)	PPV23	≥2-fold in IgG concentrations or ≥10-fold or more increase in opsonisation indices	MTX 68.3, TOC + MTX 65.1, TOC 68.3, Control 69.2	MTX 51 (82.3), TOC + MTX 50 (92.6), TOC 43 (86), Control 19 (79.2)	MTX 10.0, TOC + MTX 9.1, TOC 12.5, Control 11.3	-	-	Fold increases 6b/23f (SD) MTX 1.5 (1.1-3.0)/ 2.6 (1.4-4.1 TOC + MTX 1.6 (1.2-1.9)/ 2.9 (1.0-6.9) TOC 2.8 (1.4-4.4)/ 3.4 (1.5-6.8) Control 1.8 (1.3-3.7)/ 3.5 (1.7-5.6)	Post-vaccination Ab responses may be reduced when TOC combined with MTX.
Kapetanovic et al. 2013 [45]	RA (88, RTX ± MTX 55, ABA ± MTX 17, TOC ± MTX 16)	PCV-7	ARR ≥ 2, 4-6 weeks post-vaccination, serotypes 6b and 23f	Total cohort 60.2 (2.0)	65 (74)	16 (2.0)	4.5 (0.2)	1.3 (0.1)	ARR significantly lower in RTX group compared to MTX, control and TOC groups but not ABA group. TOC better ARR compared to RTX and ABA	RTX and ABA associated with reduced vaccine response. No detrimental effect of TOC exposure on vaccine response.
Kivitz et al. 2014 [29]	RA (207, Placebo +/- MTX 110, CZP+/- MTX 107)	PPV23	≥ 2-fold increase in ≥ 3 of 6 pneumococcal antigens at 6 weeks, serotypes: 6b, 9v, 14, 18c, 19f, 23f	Placebo 52.7 (11.1) CZP 53.1 (11.8)	Placebo (76.3) CZP (83.6)	Placebo 7.9 (8.4) CZP 7.4 (8.1)	Placebo 5.5 (0.9) CZP 5.5 (1.0)	-	Adequate response in patients with/without protective titres at baseline: Placebo 58.2%/62.5%, CZP 53.3%/54.5%	No significant effect of TNFi exposure on vaccine response.
Tsuru et al. 2014 [19]	RA (21, TOC)	PPV23	≥2-fold increase in Ab titres in at least 6 of 12 measured serotypes	54	17 (81)	9.0	-	-	100% patients achieved adequate sero-response	No comparator group in study.

Bingham et al, 2015 [25]	RA (74, TOC + MTX 50, MTX 24)	PPV23	≥2-fold increase or an increase of 1 mcg/ml from pre-vaccination level, to ≥6/12 serotypes	TOC + MTX 51.1 (8.9) MTX 51.4 (9.5)	TOC+MTX 41 (75.9) MTX 22 (81.5)	TOC+MTX 13.2 (11.5) MTX 8.4 (7.0)	-	-	Proportions of responders to ≥6 of 12 anti-pneumococcal antibody serotypes: TOC + MTX 60%, MTX 70.8%	No significant effect of TOC exposure on vaccine response, however individual serotype responses may vary.
Migita et al. 2015 [23]	RA (111, RA control 35, MTX 55, ABA 21)	PPV23	≥2-fold increase in IgG concentrations of 6b or 23f serotypes	RA control 70.5 (10.8) MTX 63.8 (11.5) ABA 59.8 (12.0)	RA control 23 (65.7) MTX 44 (80) ABA 17 (81)	RA control 11.7 (12.5) MTX 14.1 (10.9) ABA 13.5 (11.2)	RA control 2.79 (1.17) MTX 2.61 (0.98) ABA 2.48 (1.31)	-	Fold increase in GMT 6b (95%CI)/23f (95% CI) RA control 2.38 (1.41 - 5.62)/3.36(1.85 to 9.42) MTX 1.75(1.15-3.11)/ 2.00(1.27 to 5.48) ABA 1.41(0.87-3.09)/ 2.45 (1.23-7.44)	Reduced responses in ABA and MTX exposed patients compared to RA control group.
Rakoczi et al 2016.	RA (22, ETA+MTX 15, ETA 7) HC (24)	PCV-13	ARR ≥ 2, 4-weeks post-vaccination	RA 55.1 (10.4) HC 63.9 (9.8)	ETA 17 (77.3) HC 18 (75)	-	2.78 (0.62)	-	IgG levels 4 weeks post vaccination: ETA: 2.6-fold (±1.5) increase, HC 6.13-fold (± 7.3) increase.	Reduced response rate in TNFi exposed group compared to HC. No significant adverse effect of MTX + ETA combination compared to ETA monotherapy.
Alten et al. 2016 [17]	RA (125, 115 ABA + MTX, 10 ABA)	PPV23	≥2-fold increase in post-vaccination titers to ≥3 of 5 antigens and protective Ab levels of ≥1.6 mcg/mL to ≥3 of 5 antigens. Serotypes measured 9V, 14, 18C, 19F, 23F	45.7 (13.8)	107 (85.6)	-	5.0 (1.9)	1.4 (0.8)	83.9 % demonstrated protective Ab levels following PPV23 vaccination.	No comparator group in study.

LEGEND:
n: number, SD: standard deviation, DAS28: Disease Activity Score of 28 joints, HAQ: Health Assessment Questionnaire, RA: rheumatoid arthritis, HC: Healthy Controls, SpA: Spondyloarthropathy, MTX: methotrexate, TNFi: Tumour Necrosis Factor inhibitor drug, PPV23: pneumovax vaccine, PCV-7: 7 conjugate pneumococcal vaccine, PCV-13: 13 conjugate pneumococcal vaccine, Ab: antibody, ARR: antibody response ratio (i.e., ratio of post to pre-vaccination antibody levels), DMARD: Disease Modifying Anti-Rheumatic Drug, RTX: Rituximab, ABA: Abatacept, TOC: Tocilizumab, IFX: infliximab, CZP: Certolizumab pegol, ADA: Adalimumab, ETA: Etanercept

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