Fortune J Rheumatol 2021; 3 (3): 11-41 *DOI: 10.26502/fjr.26880026*

Research Article

A Systematic Review of Vaccinations in Methotrexate Users

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Received: 25 June 2021; **Accepted:** 05 July 2021; **Published:** 13 July 2021

Citation: Sheryl Mascarenhas, A Systematic Review of Vaccinations in Methotrexate Users. Fortune Journal of Rheumatology 3 (2021): 11-41.

Abstract

With several COVID-19 vaccines now available, many questions regarding immunization within patients on immune modifying agents have been surfacing. One critical question is what effect methotrexate (MTX), a known inhibitor of antibody formation, may have on vaccine response during the pandemic. In particular, does holding methotrexate during the vaccination period have improved outcomes on vaccine response?

A systematic review was conducted of previous randomized controlled trials and clinical trials of vaccine studies for methotrexate use. Studies were limited to the adult population and to those with autoimmune rheumatic conditions. 29 studies were included for review. There was heterogeneity in vaccinations used including pneumococcal, influenza (H1N1, H3N2, and various B strains), tetanus toxoid, hepatitis A, and varicella zoster. Measurement of vaccine response was non-uniform among the studies. Methotrexate dosing in some studies was not reported, and in many studies was variable. 82.8% of the studies demonstrated methotrexate users were able to meet the study defined vaccine response in the majority of methotrexate users in at least 1 endpoint. Two studies examined vaccine disruption for influenza vaccines and demonstrated improved vaccine response to methotrexate users who discontinued therapy. Dosing of methotrexate was identified in 3 studies as having an impact on vaccine response.

Based off review of previous vaccine literature, a temporary hold of methotrexate in the post vaccination period may be a reasonable option to try boost the immune response to a novel vaccine.

Keywords: Methotrexate; Vaccine; Vaccination; COVID-19

1. Introduction

COVID 19 has singularly changed the world with far reaching effects on nearly all aspects of life including health, families, relationships, religious worship, travel, economies, work, and politics. In November 2020, news broke of promising results from Pfizer's COVID 19 vaccines. Soon Moderna, then later Johnson and Johnson followed suit, with others on the horizon. The news of these vaccines brought much needed hope for the world, but also many questions. One question of particular concern to rheumatologists and their patients was if the vaccine was effective in patients on medications that alter their immune system?

One of the most commonly used immune modifying agents in treating patients with autoimmune inflammatory conditions is methotrexate (MTX) [1]. According to the Centers for Disease Control and Prevention (CDC), MTX is immunosuppressive when it is administered at doses exceeding ≥0.4 mg/kg/week, whereas dosages below these levels may be considered as 'low grade' immunosuppressive [2]. MTX is a unique immune modifying agent as it has additional effects to not only treat the underlying autoimmune disease but also supplement biologic disease modifying anti-rheumatic drugs (DMARDs) by inhibiting antibody formation to these biologic agents [3]. This antibody inhibition has been further observed with MTX decreasing immunogenicity of various vaccines, including the seasonal influenza and pneumococcal vaccines [4].

In 2015 the American College of Rheumatology (ACR) released guidelines recommending vaccination in methotrexate users. These included pneumococcal, intramuscular influenza, hepatitis B (HB), human papilloma (HP), and live attenuated herpes zoster [5]. In 2019 the European League Against Rheumatism (EULAR) further supported administration of influenza, pneumococcal, tetanus toxoid, HB, hepatitis A virus (HAV), HP, vaccines to patients with autoimmune inflammatory rheumatic diseases (AIIRD) under immunosuppressive therapy, and consideration for use of herpes zoster [6]. In 2021 the American College of Rheumatology released guidelines which over the course of the pandemic have been updated. At the time of writing this article, the ACR most recently recommended for those with well controlled disease, holding MTX for 1 week after each of the 2mRNA vaccine doses; or holding for 2 weeks after single-dose COVID vaccine [7].

There have been a collection of studies evaluating immune response to various vaccines including pneumococcal, influenza, hepatitis A, and tetanus toxoid in patients on methotrexate. While none of these afore mentioned vaccines are RNA vaccines, like those being promulgated by Pfizer or Moderna, these studies offer insight into the immune response to patients on MTX and may lend additional guidance on adjustments that could be considered in managing patients on MTX.

2. Methods

The study design followed the statement on the

Preferred Reporting Items for Systematic Reviews and Meta-Analyses [8]. A search strategy was developed using PUBMED databases with the MESH search terms of Vaccine or Vaccination and methotrexate with limits of clinical trial or randomized controlled trial. Studies involving MTX use for oncologic conditions, multiple sclerosis, and inflammatory bowel disease were excluded. Studies involving non-human subjects, or the pediatric population were excluded. Studies that clustered users and non-users of methotrexate into one group were excluded. However, studies that had subgroup analyses where select treatment arms combined methotrexate users and non-users but did identify discrete use in other arms were included with only the discrete use arms. Also excluded were select study arms where authors indicated they were including previously reported data in comparison to the current trial; this was done to eliminate duplication of data in the review. Reference lists for the selected studies from the initial database search were reviewed to identify further relevant papers. Figure 1 illustrates an overview of the search protocol.

Data was extracted independently and populated in a Microsoft Excel spreadsheet. A repeat data extraction was done on the selected studies eligible from the initial database search to confirm accuracy. Variables sought from these studies included type of study, study size, study arms, patient population (e.g. rheumatoid arthritis (RA), psoriatic arthritis (PsA), mean methotrexate dose, vaccine type, method for determining antibody response, and antibody response.

Risks of bias in this systematic review included publication bias and selective reporting in studies. To limit risk of bias, the study question of whether holding methotrexate or continuing methotrexate improved vaccine response was formulated prior to the data search. All studies meeting the above criteria were included in this review, regardless of the statistical significance of the results. To further limit journal publication bias recommendations from regulatory agencies including the ACR, EULAR, and the CDC were also reviewed. Selection bias is intrinsically limited in studies of this nature as blinding and allocation concealment have no impact on the purely objective outcome measure of interest in this review, serologic antibody response. Among the studies 93.1% of them administered a standard vaccine to all participants. One study did administer a placebo vaccine to subset of patients and one study administered either a single or two dose regimens of the influenza vaccine.

Immune response to evaluate vaccine efficacy may be measured by seroprotection, seroconversion, humoral and cell mediated response, and evaluation of the quality of produced antibodies [4]. Studies in this review commonly report IgG antibody titers, often accompanied by a measure of the increase in the antibody titer after vaccination, the geometric mean fold rise (GMFR). Typically, the post vaccine measurement occurs 3-6 weeks after vaccination, corresponding to when the peak IgG vaccine antibody is reached [9].

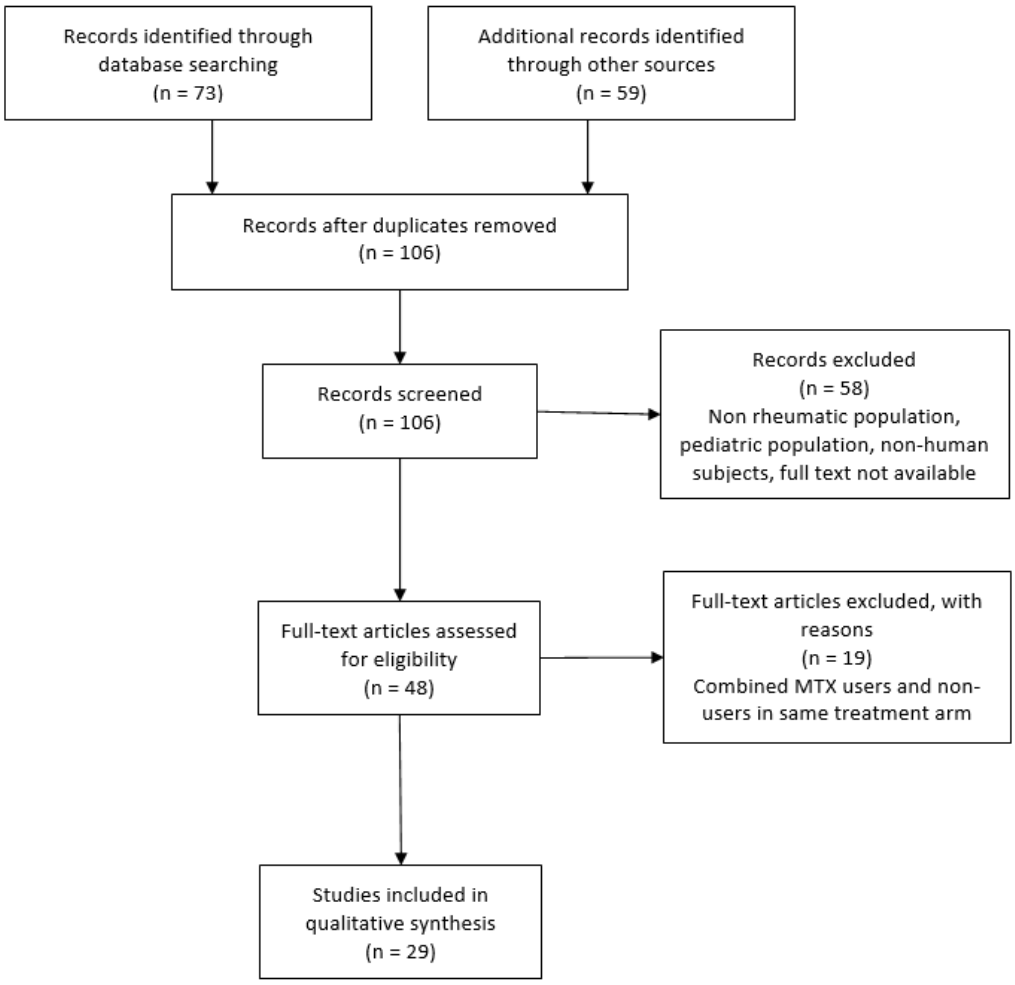

Figure. 1: Study methods.

MTX=methotrexate

3. Results

Per the protocol, 73 studies were amassed by using the study search terms on PubMed and applying limitations of clinical trials or randomized controlled trials. Studies with no human subjects, non-rheumatic disease populations, and pediatric populations were excluded. From the PubMed search 14 eligible studies were identified. The references from these publications were further reviewed for additional eligible studies. 59 studies were identified. After removing duplicates and applying the above exclusion criteria an additional 15 studies met protocol criteria to be added to the final qualitative analysis. In total 29 studies were included in the systematic review [10-38]. Supplemental Table includes the results of the data extraction from the final 29 studies.

Of note several studies included an arm that combined methotrexate users and non-users into one group. This was done when a patient was on a biologic DMARD

with or without methotrexate. Rather than excluding the entire study, where possible the heterogeneous arms were excluded only. For example, one study included both MTX users and non-users in the abatacept (ABT) group, so this study arm was excluded in the review, however the MTX and control arms were included [29]. Similarly, another study grouped MTX users and non-users within the tocilizumab (TCZ) and adalimumab (ADM) arms hence both arms were excluded; however, the study did separate out rituximab (RTX) monotherapy from RTX taken in combination with MTX and so this subset of patients were included in the review [27]. The process of trying to preserve as much applicable data for the systematic review was also applied to two additional studies [33, 35].

4. Discussion

4.1 Does methotrexate decrease vaccine responses?

An assumption of this study design was that MTX inhibits immune response to vaccinations based off existing evidence that MTX impairs humoral response to pneumococcal vaccine. In a meta-analysis from 2014 MTX decreased pneumococcal response (OR 0.33 [95% CI 0.20–0.54] for serotype 6B and OR 0.58 [95% CI 0.36–0.94] for 23F) [4]. This is further demonstrated in studies included in this review. An outlying study was early work done by Kapetanovic MC's group. This study suggested methotrexate actually seemed to improve immunogenicity for influenza vaccination, however this study did not include the mean or range doses of methotrexate for patients, a variable that may have significant effect on vaccine response as discussed later [22].

There are important practical points when reviewing these collective studies. While MTX did often result in lessened immunogenicity compared to either controls or anti-tumor necrosis factor (anti-TNF) therapies, there was generally sufficient immunity achieved for the majority of patients on MTX in at least 1 endpoint. The exceptions were demonstrated in 4 studies evaluating pneumococcal vaccine responses where 46%, 23%, 22.9%, and 18% of subjects achieved an adequate immune response to pneumococcal vaccine [12, 23, 25, 27]. The lone hepatitis A vaccine study in this review demonstrated abysmal results for methotrexate users with only 6% achieving a satisfactory immune response [36].

The practical point here is not that select studies had poor immune response, but rather that vaccinating on continuous methotrexate can still achieve an immune response in some patients. Therefore, if there are situations where a patient cannot disrupt methotrexate therapy, vaccination may still achieve reasonable immunity and be a better option than no vaccine at all. However, it lends itself to the ultimate question of this study. Does holding methotrexate around the time of vaccination improve antibody responses?

4.2 Does holding methotrexate improve vaccine response?

The most relevant data investigating this question comes out of a series of studies from Jin Kyun Park, et al. In 2017 their group conducted a multi-center trial evaluating whether holding methotrexate prior and/or after vaccination with quadrivalent seasonal influenza vaccine improved antibody responses. In this elegant study Park divided patients on MTX into 4 groups, continuing MTX, holding MTX 4 weeks pre-vaccination, holding MTX 2 weeks pre-vaccination and

2 weeks post-vaccination, and holding MTX 4 weeks post vaccination. All 4 groups mounted a satisfactory vaccine response to at least one influenza antigen, however the group which held MTX 2 weeks before and 2 weeks after the vaccination achieved greater vaccine response to at least two influenza antigens than continuous MTX users [21]. This difference was statistically significant when comparing the same groups' response to all three antigens [21].

The robustness of the antibody response for the group holding MTX 2 weeks pre- and post-vaccination compared to continuous MTX use was evidenced further when the analysis was restricted to patients who lacked seroprotection before vaccination. With this subgroup analysis, holding MTX 2 weeks before and after vaccination led to statistically significant increases with all individual antibody titers when compared to continuous MTX use [21]. This may be especially of importance when considering pandemic vaccinations where the immune system for most of the population at large would not have encountered the virus.

Park's research was the first to demonstrate that vaccine immunogenicity may be increased with vaccination occurring in the middle of a MTX discontinuation period. Additionally, the authors found that discontinuation after vaccination also achieved greater response compared to the continuous MTX users [21]. More specifically, the group that held methotrexate 4 weeks after vaccination also had significantly higher fold increases in antibody titers against H3N2 and B-Yamagata antigen and higher (though not statistically significant) increase in antibody titers against H1N1. Discontinuing MTX for 4 weeks after the vaccination was effective, although less effective than the group which discontinued 2 weeks before and 2 weeks post vaccination. This data suggests that MTX's effects on immune cells is likely immediate [21].

In 2018, Park's group investigated if a post vaccine disruption alone improved vaccine responses. In this study, subjects were randomized to either continue MTX or disrupt therapy for 2 weeks post vaccination of quadrivalent seasonal influenza. The authors found that holding MTX 2 weeks post vaccination versus continuous methotrexate had significant increases in immunogenicity to all 4 antigens (reported as % difference between holding methotrexate and continuing methotrexate (95% CI): H1N1: 11.9% (0.9% - 22.8%), p=0.033; H3N2: 16.8% (6.1%-27.4%), p=0.002; B-Yamagata: 22.7% (11.7% -33.7%), p<0.001; B-Victoria: 32.8% (21.8% -43.6%), p<0.001) [11]. Additionally, the MTX-hold group had significantly higher fold increases in their antibody titers against all four influenza antigens [11].

4.3 Does the methotrexate dose matter?

In Park's 2018 study, an analysis was performed on methotrexate dose effects. The authors reported no significant difference in vaccine response between the MTX-continue group and MTX-hold group for those who took MTX 7.5 mg or less per week [11]. However the difference was significant when comparing those on MTX 15 mg or more per week [11]. Park's study suggests that vaccine dose may have significant effect on immunogenicity. Other studies in this review noted a dose effect on methotrexate immunogenicity. While the exact dosing is not reported, Ribero AC, at al. note average/high dosing of methotrexate resulted in decreased immunogenicity [13]. Bingham CO III, et al. also found MTX dose to be a predictor of immunogenicity [16].

The outlying study however is Kaine JL, et al, where patients were divided into 4 arms, placebo, MTX, adalimumab (ADM), or ADM+MTX. The authors did a sub-analysis based on MTX dosing. They divided the MTX users into 3 dose groups which included: >0-10 mg/week, >10-15 mg/week, and > 15 mg/week. The different dose groups did not follow the patterns seen by Park; however interpretation of this study is limited due to the small sample size [26]. Additionally, this study grouped patients who were either above or below 7.5 mg into the same group. Recall the Park 2018 study noted the difference occurring with MTX dose was at or below 7.5 mg/week [11].

BAFF inhibition of immunogenicity has been implicated for the disparity among MTX users. In the 2018 Park study, among patients who continued MTX, vaccine responders had significantly lower BAFF levels than the non-responders to ≥2/4 antigens [11]. However, in patients who held methotrexate, BAFF levels did not differ significantly between vaccine responders and non-responders [11]. Further, antibody titer changes for pre and post vaccination for individual antigens H1N1, B Yamagata and B Victoria correlated inversely with serum BAFF levels in the MTX-continue group but not in the MTX-hold group ($p=0.047$, $p=0.019$, $p=0.045$, respectively) [11]. There was however no statistical significance for H3N2 ($p=0.177$) [11]. The inverse correlation between BAFF levels and antibody production seemed to be more robust in patients taking MTX>15 mg/week than those taking MTX<7.5 mg/week [11].

There appears to be some correlation with methotrexate dosing and immunogenicity. Interestingly review of the listed studies in the Supplemental Table demonstrates many do not list the methotrexate dose or that most hover around the 15 mg dose of methotrexate. This may suggest that much of the data that exists about vaccination in methotrexate users may be limited as methotrexate use has generally been considered all or none rather than dose dependent in most of the previous vaccine studies.

Further studies should be undertaken specifically evaluating the effects of methotrexate dosing on vaccine response. However, during this pandemic vaccination where time for such a study is not possible, based off the limited observations from the above studies it may be worth recommending methotrexate users on moderate to high doses more heavily consider methotrexate disruption. Potentially low dose methotrexate users may be able to continue therapy throughout the vaccination period.

4.4 Does the number of vaccine doses matter?

Talk of booster doses is already being suggested for healthy individuals, however some have already looked at boosters in methotrexate users with previous vaccines. One of the reviewed studies evaluated whether additional booster doses may be more beneficial to immunocompromised patients. This study originated in the time of a looming pandemic with influenza A (H1N1) in 2009. At that time, the outbreak led to rapid development of novel influenza vaccines that were distributed and administered globally to hundreds of millions within a few months [39]. The same questions we are asking now about improving vaccine response were being asked then in 2009. In efforts to improve vaccine responses, the medical community in Switzerland administered a novel regimen where adjuvant influenza vaccines were administered in a 2-dose schedule to

immunocompromised patients and 1 dose for healthy individuals for H1N1 [39]. Booster dosing is not a novel concept, in fact the CDC recommends consideration of an additional dose of hepatitis A vaccine in patients on anti-TNF agents and/or MTX [1].

Gabay C, et al. assessed primary and secondary vaccine responses to these novel adjuvant influenza vaccines in Switzerland between immunocompromised and healthy individuals. In Gabay's study there were 72 of 173 patients in total on MTX with the remainder on other DMARDs or immunosuppressive agents. After the first vaccine dose antibody responses were significantly lower in immunocompromised patients (GMT 146 versus 340, $p < 0.001$, seroprotection rate 74.6% versus 87%, $p < 0.001$) [39]. However, these differences became statistically insignificant after the immunocompromised group received the second vaccination when compared to the healthy controls who received 1 vaccination [39]. Key inhibitors of vaccine immunogenicity in this study included increasing age, DMARDs (except hydroxychloroquine, sulfasalazine, and tumor necrosis factor α antagonist treatment), and recent (within 3 months) B cell depletion treatment [39].

Gabay's study raises important implications for a standard 2 dose RNA vaccine. Both Moderna and Pfizer vaccines are administered as 2 dose vaccines routinely. Whether immunogenicity would be improved among immunocompromised patients with additional doses would be important to further elucidate.

5. Conclusion

A 2-week disruption of MTX as previously studied may be tenable for some well controlled patients and may possibly lead to improved immune responses to vaccinations. Given that methotrexate effects on immune cells appears to be immediate, holding methotrexate after vaccination may further improve immune response.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Supplementary Material

Study	Author	Type	MTX Arms	Vaccine	Study size	Measurement of immune response	Mean MTX dose, mg/week ± SD	Vaccine Response at 3-6 weeks	Ref
1	Winthrop KL, et al. 2017	RCT	MTX vs MTX+ TOF	Live VZV	112 Total: MTX 55, MTX+ TOF 57	GMFR for IgG and T cell response	MTX 16.9±4.3, MTX+TOF 17.1±4.7	GMFR IgG GMT (80% CI): MTX + TOF 2.11 (1.87–2.37), MTX 1.74 (1.55–1.95), Ratio of MTX+TOF/MTX: 1.21 (1.03–1.42) GMFR T cell response (80% CI): MTX+TOF 1.50 (1.31–1.70), MTX 1.29 (1.14–1.46), ratio MTX	10

								+TOF/MTX 1.21 (1.03–1.42)	
2	Park JK, et al. 2018	RCT	MTX-cont vs MTX-hold 2-week post vac	Influenza (H1N1, H3N2, B-Yamagata and B-Victoria)	316 Total: MTX-cont 156, MTX-hold 160	≥Fourfold increase of HIA titer against ≥2 of four vaccine strains	MTX-cont 13.3±3.4, MTX-hold 13.1±3.2	MTX-hold 75.5% vs MTX-cont 54.5% p<0.001 (difference 21.0%, 95% CI 10.6% to 31.7%)	11
3	Winthrop KL, et al. 2016	RCT and LTE	MTX vs MTX+TOF	Pneumococcal, Influenza (A/H1N1, A/H3N2, B)	200 Total: MTX (mono or with TOF) 112, No MTX (includes TOF mono) 88	≥Fourfold HIA titer of ≥ 2 of 3 influenza vaccine strains and ≥twofold titer increases of ≥ 6 of 12 pneumococcal serotypes	Inclusion range: ≥10 but ≤ 25	Pneumococcal, n/N (%): MTX 52/112 (46.4%) vs No MTX 61/88 (69.3%) Influenza, n/N (%): MTX 61/112 (54.4%) vs No MTX 58/88 (65.9%)	12
4	Ribeiro A, et al. 2011	CT	MTX vs No MTX	Influenza (H1N1)	340 Total: Yes MTX 215, No MTX 125	≥Fourfold increase of HIA titer, SRP (% with titer 1:40), SCR (% with ≥ fourfold increase in vac titer if prevac titer ≥ 1:10 or postvac titer≥ 1:40 if prevac	Not reported	GMFR GMT (95% CI): MTX 5.5 (4.6-6.7), No MTX 11.4 (8.4-15.4), p<0.05 SC % (95% CI): MTX 46.3 (39.6-53.0), No MTX 65.3	13

						titer <1:10.		(56.9-73.7), p<0.05 SP % (95% CI): MTX 53.2 (46.6-59.9), No MTX 71.8 (63.8-79.7), p<0.05	
5	Kapetanovic MC, et al. 2014	CT	MTX vs No MTX receiving 1 vaccine dose compared to 2 vaccine doses	Influenza (H1N1)	291 Total: 123 received 1 dose (MTX 51, No MTX 72), 168 received 2 doses (MTX 103, No MTX 65)	18 to 60-years old (>60-years-old) if ≥1 of 3 criteria is fulfilled: SPR 70% (60%); SCR 40% (30%) or GMFR) >2.5 (3). SP (postvac titers ≥400), SC (prevac titers <10 and postvac HI titers ≥40 or a ≥4-fold increase in HI titers)	Not reported	1 dose SP. n/N (%): MTX 23/51 (45.1), No MTX 53/72 (73.6) 1 dose SC, n/N (%): MTX 21/53 (45.1), No MTX 40/72 (55.6) 2 dose SP: n/N (%): MTX 58/103 (56.3), No MTX 48/65 (73.8) 2 dose SC, n/N (%): MTX 47/103 (45.6), No MTX 44/65 (67.7)	14

6	Kapetanovic MC, et al. 2006	CT	TNF vs MTX+TNF vs MTX vs healthy control (healthy)	Pneumococcal	196 Total: RA 149 (MTX +TNF 50, MTX 37, TNF 62) and healthy 47	≥Twofold increase in antibody concentration	MTX 15, range 7.5-25. MTX +TNF 15, range 5-25	Immunization response 23F, ratio (range): TNF 2.8 (0.9–68), MTX+TNF 2.0 (0.7–36), MTX 1.4 (0.3–15), healthy 2.3 (0.2–91) , p<0.05 comparing TNF vs MTX+TNF, TNF vs MTX) Immunization response 6b, ratio (range): TNF 3.4 (0.8–280), MTX+TNF 1.8 (0.9–44), MTX 1.6 (0.8–20), healthy 2.2 (0.4–75) , p<0.05 comparing TNF vs MTX+TNF, TNF vs MTX, TNF vs healthy	15

7	Bingham III CO, et al. 2009	CT	MTX vs MTX+ RTX	Tetanus toxoid, Pneumococcal, KLH, delayed type hypersensitivity with *Candida albicans*	103 Total enrolled: MTX 34, MTX+ RTX 69. Completed: MTX 28, MTX+ RTX 65	≥Fourfold rise in IgG levels and indurated response >5mm to *C. albicans*	MTX 16.4±.3, MTX+ RTX 17.2±4.2	Tetanus toxoid, n (%): MTX 11 (42.3%), MTX +RTX 25 (39.1%), −3.2 % difference (95% CI −25.7, 19.2) *C. albicans*, n (%): MTX 14 (70.0%), MTX+RTX 24 (77.4%), 7.4 % difference (95% CI−17.5, 32.3) Pneumococcal with at least 2 serotypes: MTX 82, MTX+RTX 43 GMT for KLH: MTX 1,585.5 titer units (95% CI 1,065.15-2,360.17), MTX+RTX 539.5 titer units (95% CI 461.54-630.61).	16

8	Mori S, et al. 2013	CT	TCZ vs MTX+ TCZ vs MTX vs RA Control (control)	Pneumococcal	190 Total: TCZ 50, MTX+ TCZ 54, MTX 62, control 24	≥Twofold increase in GMC IgG concentration or a ≥Tenfold increase in the OIs	MTX+TCZ 8 (6 to 8) mg, MTX 8 (6 to 8) Note range indicates 25th and 75th percentile	GMFR IgG GMC Pneumococcal 6b, µg/ml, (95% CI): TCZ 2.8 (1.4-4.4), MTX+TCZ 1.6 (1.2-1.9), MTX 1.5 (1.1-3.0), control 1.8 (1.3-3.7), p<0.05 MTX+TCZ vs TCZ GMFR IgG GMC Pneumococcal 23F, µg/ml, (95%CI): TCZ 3.4 (1.5-6.8), MTX+TCZ 2.9 (1.0-6.9), MTX 2.6 (1.4-4.1), control 3.5 (1.7-5.6) GM-OI 6b (95%CI): TCZ 12 (3.5 to 62.4), MTX+TCZ 6.8 (1.7-35.5), MTX 4.5 (1-12.5), control 8.5 (2.2-52.0), p=0.001 for TCZ vs MTX	17

								GM-OI 23F (95% CI): TCZ 18.8 (2.7-75.1), MTX+TCZ 5.0 (1- 40), MTX 7.0 (2.7-15.8), control 11.0 (3.1-30.6), p=0.001 for TCZ vs MTX	
9	Mori S, et al. 2012	CT	TCZ vs MTX+ TCZ vs MTX vs RA Control (control)	Influenza (A/H1N1, A/H3N2 and B/B1 strains)	194 Total: TCZ 62, MTX+ TCZ 49, MTX 65, RA control 18	≥Fourfold increase in HIA titers in patients whose prevac titers were ≥10	MTX+TCZ 8 (6 to 8) mg/week, MTX 8 (6 to 8) mg/week. Note range indicates IQR	GMFR GMT A/H1N1 (95% CI): TCZ 12.0 (9.8–17.7), MTX+TCZ 14.5 (7.2–21.9), MTX 12.6 (5.8–19.5), control 11.2 (3.0–19.4) GMFR GMT A/H3N2 (95% CI): TCZ 12.0 (6.6–17.3), MTX+TCZ 9.9 (5.2–14.6), MTX 9.6 (5–14.2), control 5.3 (2.7–8.0) GMFR GMT B/B1 (95% CI): TCZ 5.0 (3.3–5.7),	18

								MTX+TCZ 5.4 (2.4–8.3), MTX 3.5 (2.5–4.4), control 5.8 (3.1–8.4)	
10	Bingham CO 3rd, et al. 2015	RCT	MTX vs TCZ+ MTX	Pneumococcal and Tetanus toxoid	91 Total: MTX 31, MTX+ TCZ 60	≥Twofold or >1 mg/L increase from baseline in ≥6/12 pneumococcal antibody serotypes, ≥ Fourfold increase in tetanus toxoid antibody levels	Range for both MTX and MTX+TCZ 7.5–25	Pneumococcal responders, n (%) (95% CI): MTX 17 (70.8%) (52.6 -89.0), MTX +TCZ 30 (60.0%) (46.4-73.6) Tetanus toxoid responders, n (%) (95% CI): MTX 9 (39.1) (19.2-59.1) MTX+TCZ 21 (42.0) (28.3-55.7)	19
11	Calabrese LH, et al. 2020	post hoc analysis of RCT	TOF vs MTX+ TOF vs MTX+ ADM	Live VZV	1146 Total: 216 Vaccinated: TOF 69, MTX+ TOF 75, MTX+ ADM 72. 930	IR for Herpes Zoster	MTX+ TOF 16.0±3.8, MTX+ADM 17.1±3.6	IR for HZ for vaccinated (95% CI): TOF 1.5 (0.0–8.3), MTX+TOF 3.0 0.4–10.8), MTX+ADM 0 (0.0–5.8) IR for HZ for Non-vaccinated (95% CI):	20

					Non-Vaccinated: TOF 315, MTX+TOF 301, MTX+ADM 314			TOF 1.0 (0.2–3.0), MTX+TOF 2.2 (0.8–4.7), MTX+ADM 2.1 (0.8–4.5)	
12	Park JK, et al. 2016	RCT	MTX-cont, MTX-hold 4W pre-vac, MTX-hold 2W pre and 2 W post-vac, MTX-hold 4W post-vac	Influenza (H1N1, H3N2 and B-Yamagata)	199 Total: MTX-cont 54, MTX 4 weeks pre-44, MTX 2-week pre and post 49, MTX 4-week post 52	≥Fourfold HIA titer increase	MTX-cont 12.7±3.7, MTX 4W pre-13.3±3.4, MTX 2W pre and post 13.6±2.9, MTX 4W post 13.2±3.3	Response ≥2 antigens (%): MTX-cont 53.7, MTX 4 weeks pre-52.3, MTX 2 weeks pre and post 71.4, MTX 4 weeks post 65.4 Response ≥3 antigens (%): MTX-cont 31.5, MTX 4 weeks pre-22.7, MTX 2 weeks pre and post 51.0, MTX 4 weeks post 46.2, p=0.044 for MTX-cont vs MTX 2 weeks pre and post	21

13	Kapetanovic MC, et al. 2007	CT	TNF vs MTX+TNF vs MTX vs healthy control (healthy)	Influenza (H1N1, H3N2 and B1 or B2 Strain)	149 Total: TNF 62, MTX+TNF 50, MTX 37, healthy 18	≥Fourfold antibody titer increase, titer level ≥ 40	Not reported	Responders, n/N (%) H1N1: MTX 33/37 (89.2), MTX+TNF 26/50 (52.0), TNF 36/52 (58.1), healthy 14/18 (77.8) Responders, n/N (%) H3N2: MTX 28/37 (75.7), MTX+TNF 28/50 (56.0), TNF 46/62 (74.2), healthy 13/18 (72.2) Responders, n/N (%) B1: MTX 35/37 (94.6), MTX+TNF 42/50 (84.0), TNF 54/62 (87.1), healthy 12/18 (66.7)	22
14	Park JK, et al. 2019	CT	MTX-cont vs MTX-hold 2-week post vaccination	Influenza (H1N1, H3N2, B-Yamagata and Victoria)	316 Total: MTX-cont 156, MTX-hold 160	≥Fourfold increase in HIA titer	MTX-cont 13.3±3.4, MTX-hold 13.1±3.2	Response ≥2 antigen, n/N (%): MTX-cont 85/156 (54.5%), MTX-hold 121/160 (75.6%) Response ≥3	23

								antigen, n/N (%): MTX-cont 57/156 (36.5%), MTX-hold 99/160 (61.9%)	
15	Visvanathan S, et al. 2007	CT	INX+MTX vs MTX	Pneumococcal	70 Total: INX+MTX 56 and MTX 14	Postvac antibody levels met the threshold value used by Quest Diagnostics or ≥twofold increase in pre- to postvac antibody levels in ≥ 6 of the 12 serotypes	Dose ≥ 20: MTX 13 patients, MTX+INX 35 patients. Dose <20: MTX 1 patient, MTX+INX 21 patients	Responders receiving MTX ≥ 20 mg/week, n/N (%): MTX 3/13 (23.1%), MTX+INX 8/35 (22.9%) Responders receiving MTX < 20 mg/week, n/N (%): MTX N/A, MTX+INX 5/21 (23.8%)	24
16	Mease PJ, et al. 2004	CT	MTX vs No MTX, in patients ±ETC	Pneumococcal	184 Total: MTX 83, No MTX 101	≥Twofold increase in antibody titer	Not reported	Responders, n/N (%): MTX 19/83 (22.9%), No MTX 64/101 (63.4%), p< 0.0001	25
17	Kaine JL, et al. 2007	RCT	MTX vs No MTX	Pneumococcal and Influenza (H1N1, H3N2,	208 Total: Placebo 50, MTX 59,	≥Twofold increase in ≥ 3 of the 5 pneumococcal titers and ≥ Fourfold	Dose >0-10: MTX 16, MTX+ADM 17. Dose >10-15: MTX 21,	Pneumococcal responders, n/N (%): MTX 17/59 (28.8%), MTX+ADM	26

				and B Hong Kong)	MTX+ ADM 55, ADM 44	increase in ≥ 2 of the 3 influenza titers	MTX+ADM 19. Dose of >15: MTX 22, MTX+ADM 19	10/55 (18.2%), ADM 27/44 (61.4%), Placebo 27/50 (54.0), p < 0.001 for MTX use Influenza responders, n/N (%): MTX 33/59 (55.9%), MTX+ADM 29/55 (52.7%), ADM 22/44 (50.0%), Placebo 36/50 (72.0%)	
18	Kapetanovic MC, et al. 2013	CT	MTX+ RTX vs RTX	Pneumococcal	88 Total: RTX 29, MTX+ RTX 26. Note other arms excluded with mixed MTX users and	≥ Twofold increase in GMT	Mean dose: MTX+RTX 17.2	Post vac GMT mg/L (95% CI) 6b: RTX 0.4 (0.2-0.8), MTX+RTX 0.4 (0.2, 0.8). p not significant between RTX vs MTX+RTX Post vac GMT mg/L (95% CI) 23F: RTX 0.3 (0.2, 0.6), MTX+RTX 0.4 (0.2, 0.8) p	27

					non-users			not significant between RTX vs MTX+RTX	
19	Kapetanovic MC, et al. 2011	CT	MTX vs MTX+TNF vs TNF vs NSAID control	Pneumococcal	505 Total: 253 RA: MTX 85, MTX+TNF 89, TNF 79. 252 SpA: MTX+TNF 83, TNF 83, NSAID control 85	Antibody response ratio (ARR) ≥ 2 (ratio of post to pre vaccine antibody levels)	RA (MTX 16.4, MTX+TNF 15.7). SpA (MTX+TNF 15.8)	ARR≥2, n (%): RA patients: MTX 18 (21.2), MTX+TNF 14 (15.7), TNF 29 (36.7). For SpA patients: MTX+TNF 22.5 (26.5), TNF 42 (50.6), control 41 (47.7). OR for all users of MTX 0.41 (95% CI 0.24-0.68)	28
20	Ribeiro A, et al. 2013	CT	MTX vs healthy control (healthy)	Influenza (H1N1)	88 Total: MTX 33, healthy 55. ABT arm excluded due to mixed MTX	FI in GMT, SP (% with titers ≥1:40), SCR (% with ≥fourfold increase in vac titers if the prevac titers were ≥1:10 or titers ≥1:40 if the prevac titers were <1:10)	MTX 25, range 15-25	FI-GMT n (95% CI): MTX 8.7 (5.2-17.4), healthy 11.5 (8.0-16.7) SP. n (%): MTX 19 (58), healthy 38 (69) SC. n (%): MTX 19 (58), healthy 36 (66)	29

					users and non-users				
21	O'Dell JR, et al. 1996	CT	MTX vs RA control	Pneumoccocal	40 Total: MTX 20, No MTX 20	Antibody levels ≤ 300µg/ml prevac and ≥ 300µg/ml post vac	MTX 13	Responders (%): MTX 55, No MTX 77, p=0.03	30
22	Migata K, et al. 2015	RCT	MTX vs MTX+ GOM vs RA control	Pneumoccocal	114 Total: RA control 35, MTX 55, GOM+ MTX 24	≥Twofold increase in IgG concentrations, >tenfold increase in OI	MTX 7.8±2.37, MTX+GOM 8.33±2.55	FI 23F IgG: MTX 2.00 (1.27-5.48), MTX+GOM 1.41 (1.18-4.29), control 3.36 (1.85-9.42) FI 6b IgG: MTX 1.75 (1.15-3.11), MTX+GOM 1.23 (1.09-1.53), control 2.38 (1.41-5.62) OPA Titer 23F: MTX 3.75 (1.47-38.2), MTX+GOM 10.00 (1.33-38.49), control 6.86 (2.50-27.14) OPA Titer 6b: MTX 2.57 (1.22-	31

								22.40), MTX+GOM 6.58 (2.69-48.68), control 10.22 (1.92-79.48)	
23	Kivitz AJ, et al. 2014	RCT	MTX vs MTX+ CZP vs CZP vs placebo	Pneumococcal, Influenza (H1N1, H3N2 B/Brisbane)	Receiving pneumococcal vac: MTX 60, MTX+ CZP 63, CZP 25, placebo 28, Receiving influenza vac: MTX 57, MTX+ CZP 59, CZP 27, Placebo 26	≥Twofold titers increase in ≥ 3 of 6 pneumococcal antigens and ≥Fourfold titer increase in ≥ 2 of 3 influenza antigens	MTX 17.2±5.0, MTX+CZP 15.9±4.6	Pneumococcal response, n/N (%) (95% CI): MTX 30/60 (50) (37.3-62.7), MTX+CZP 28/63 (44.4) (32.2-56.7), Placebo 25/28 (89.3) (77.9-100.0), CZP 20/25 (80) (64.3-95.7) Influenza response, n/N (%) (95% CI): MTX 29/57 (50.9) (37.9-63.9), MTX+CZP 27/59 (45.8) (33.1–58.5), Placebo 22/26 (84.6) (70.7–98.5), CZP 19/27 (70.4) (53.1–87.6)	32

24	Kobie JJ, et al. 2011	CT	MTX vs MTX+ TNF vs RA control vs healthy control	Influenza (H1N1, H3N2, and B strains)	261 Total: MTX 70, RA control 33, healthy control 97. TNF arm excluded due to mixed MTX and non-MTX users	HIA GMT	MTX 16.5±4.0	HAI responders cumulatively over 3 years at 1 month post vac, n/N (%): H1N1: MTX 61/68 (89.7), RA control 31/36 (86.1), healthy control 90/99 (90.9%) H3N2: MTX 55/79 (69.6), RA control 32/36 (88.9), healthy control 97/99 (98.0) B strain: MTX 59/68 (86.7), RA control 35/36 (97.2), healthy control 93/99 (93.9)	33
25	Kapetanovic MC, et al. 2013	CT	RA patients: MTX, MTX+ TNF, TNF. SpA patients:	Pneumococcal	302 Total: 163 RA patients: MTX 85, MTX+ TNF 89,	Post vac GMT with antibody levels ≥1 mg/L	Not reported	Responders for both 23F and 6b: RA: MTX 67, MTX+TNF 52, TNF 58. SpA: MTX+TNF 65, TNF 78,	34

			MTX+ TNF, TNF, NSAID control		TNF 79. 139 SpA patients : MTX+ TNF 83, TNF 83, NSAID control 86			NSAID control 84 Responders for both 23F and 6b at 1.5-year follow-up: RA: MTX 40, MTX+TNF 20, TNF 32, SpA: MTX+TNF 49, TNF 60, NSAID control 70. Relative ratio at 1.5 year to 4-6week follow-up: RA: MTX 0.61, MTX+TNF 0.38, TNF 0.55. SpA MTX+TNF 0.75, TNF 0.77, NSAID control 0.84	

26	Migata K, et al. 2015	RCT	MTX vs TAC vs MTX+ TAC	Pneumoc occal	133 Total: of which 84 in MTX analysis: MTX 55, MTX+ TAC 14, TAC 29	≥Twofold increase in IgG concentrations or a> 10-fold increase in OI	MTX 7.80± 2.37, MTX+ TAC 8.29±3.22	FI IgG GMCs for 23F, n (95% CI): MTX 2.00 (1.27-5.48), TAC 7.63 (3.70-18.85), MTX+TAC 1.85 (1.14-3.82), p= 0.005 for MTX vs TAC, p < 0.0001 for MTX+TAC vs TAC GM-OI for 23F, n (95% CI): MTX 3.75 (1.47-38.32), MTX+TAC 64.38 (11.59 - 231.22), TAC 3.51 (1.00 to 8.00), p=0.048 for MTX vs MTX+TAC, p < 0.0001 for MTX+TAC vs TAC	35
27	Askling HH, et al. 2014	CT	MTX vs MTX+ TNF vs TNF	Hepatitis A	53 Total: MTX 17, MTX+ TNF 21,	anti-HAV antibodies ≥ 20 mIU/mL	15, range of 7.5-22.5	Anti-HAV ≥20 mIU/mL at month 1, %: MTX 6, MTX+TNF 5, TNF 20 Using the lower level	36

					TNF 15			of protection (anti-HAV 10 mIU/L) at 1 month: MTX 6, MTX+TNF 15, TNF 73	
28	Migata K, et al. 2015	RCT	MTX vs RA control	Pneumoccocal	111 Total: 90 in MTX analysis: MTX 55, RA control 35. ABT arm excluded due to mix of MTX users and non-users	≥Twofold increase in IgG concentrations or a> 10-fold increase in OI	MTX 7.8±2.4	FI IgG GMCs for 23F, n (95% CI): MTX 2.00 (1.27-5.48), control 3.36 (1.85- 9.42) FI IgG GMCs for 6b, n (95% CI): MTX 1.75 (1.15-3.11), control 2.38 (1.41-5.62) GM-OI 23F, n (95% CI): MTX 3.75 (1.47-38.32), control 6.86 (2.50-27.14) GM-OI 6b, n (95% CI): MTX 2.57 (1.22-22.40), control 10.22 (1.92-79.48)	37

29	Bingham CO 3rd, et al. 2015	RCT	MTX vs MTX+ TAB 120mg/ Q4W vs MTX + TAB 90mg/ Q2W	Pneumococcal, Tetanus Toxoid	69 Total: MTX 17, MTX+ TAB 120/Q4W 21, MTX+ TAB 90mg/ Q2W 30	≥Twofold increase in IgG pneumococcal, ≥fourfold increase in IgG for tetanus toxoid	Not reported	Tetanus responders, n (%): MTX 10 (58.8), MTX+TAB 120/Q4W 17 (81.0), MTX+ TAB 90/Q2W 13 (43.3) Pneumococcal responders, n (%): MTX 13 (76.5), MTX+TAB 120/Q4W 15 (71.4), MTX+TAB 90/Q2W 23 (74.2)	38

SD=Standard deviation; Ref=reference; RCT=randomized controlled trial; MTX =methotrexate; TOF=tofacitinib; VZV=varicella zoster vaccine; GMFR=geometric mean fold rise; cont=continue; HIA=haemagglutination inhibition antibody; vac=vaccination; mono=monotherapy; SCR=seroconversion rate; SPR=seroprotection rate; DMARD=disease modifying anti-rheumatic drug; SC=seroconversion; SR=seroprotection; LTE=long-term extension study; CT=clinical trial; GMT=geometric mean titer; TNF=anti-tumor necrosis factor; RTX=rituximab; KLH=keyhole limpet hemocyanin; TCZ=tocilizumab; IQR=interquartile range; GMC=geometric mean concentration; OI= opsonisation indices; GM=geometric mean; GM-OI=geometric mean opsonisation index; ADM=adalimumab; IR=incidence rate; INX=infliximab; N/A=not applicable; ETC=etanercept; NSAID=non-steroidal anti-inflammatory drug; ARR=antibody response ratio; RA=rheumatoid arthritis; FI=factor increase; ABT=abatacept; GOM=golimumab; OPA= opsonophagocytic activity; CZP=certolizumab pegol; SpA=spondyloarthropathy; TAC=tacrolimus; HAV=hepatitis A virus, Q=every; W=week, TAB=tabalumab