

Does methotrexate increase the risk of varicella or herpes zoster infection in patients with rheumatoid arthritis? A systematic literature review

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ABSTRACT

Introduction. Methotrexate (MTX) has become the foundation disease-modifying anti-rheumatic drug (DMARD) for RA. However, concern exists regarding its possible association with infectious complications including varicella zoster virus (VZV) and herpes zoster (HZ). Furthermore, no consensus exists regarding pre-MTX VZV screening or the use of VZV vaccine.

Methods. We undertook systematic literature review (SLR) investigating the relationship between the use of MTX in patients with RA and VZV and HZ infection. Additionally, the European Centre for Disease Prevention and Control, HPA, the CDC, Rheumatology societies and WHO web sites and publications were consulted.

Results. Thirty-five studies fulfilled the inclusion criteria comprising 29 observational studies and 6 case reports. The case reports and 13 observation studies considered the association between MTX and HZ. Three of the observational studies reported a positive association although in 5 cases, patients were concurrently treated with prednisolone. Five studies concluded that there was no association between HZ and MTX. Three studies comparing the infection rates of MTX with other RA therapies found that MTX did not result in higher HZ infection rates. Three studies examining the association between HZ and MTX treatment duration failed to show a link.

Conclusion. No evidence exists to support an association between MTX and VZV infection in RA patients and the data regarding the role of MTX in HZ development is conflicting. The role of pre-MTX VZV screening is controversial and, as it may delay initiation of RA treatment, we suggest against VZV screening in this context.

Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease of unknown aetiology affecting up to 1% of the world's population (1). The prognosis has improved tremendously over the last decade with appropriate use of traditional and biologic DMARDs (2, 3). Due to its efficacy, safety and tolerability, MTX has become the foundation DMARD for RA (4, 5).

Historically, a reluctance to prescribe effective doses of MTX existed due to concerns regarding its tolerability and potential association with infectious complications, including varicella zoster virus (VZV) (6). Its origin as a chemotherapeutic agent may have contributed to this belief (7). An incidence of 8% of VZV infections in leukaemia patients on maintenance MTX treatment following intensive induction chemotherapy has been seen (8). However, the sole contribution of MTX on VZV infection risk in these patients is difficult to define due to the nature of the underlying pathology, the diversity of chemotherapeutic regimens and the degree of immunosuppression. Conversely failure to prescribe adequate doses of MTX in RA patients may lead to persistent inflammation, ongoing immune dysregulation and potentially a higher likelihood of infection as a result.

It is unclear whether the relatively low doses of MTX used to treat rheumatic diseases are immunosuppressive (9). MTX has been shown to suppress pro-inflammatory cytokines, such as IFN- γ , that play an important role in the host's initial innate response to VZV (10, 11). Other proposed mechanisms of MTX activity include reduced intracellular glutathione and macrophage activity, increased apoptosis of activated T cells (12, 13), suppression of neutrophil

Table I. PICO framework.

Population	Adult RA patients receiving MTX who develop VZV or HZ infection
Intervention	N/A
Controls	Risk of VZV or HZ in healthy controls and/or RA patients not receiving MTX.
Outcome	To quantify the risk of VZV and HZ infection in order to inform the potential role of pre-MTX VZV screening and vaccination of non-immune patients.

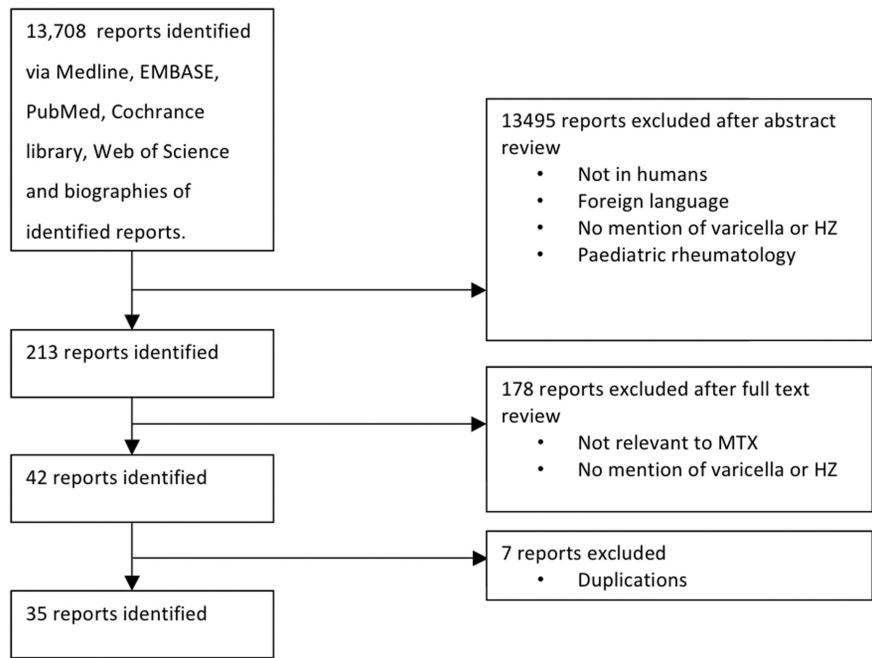


Fig. 1. PRISMA

chemotaxis and adherence, serum immunoglobulin reduction and inhibition of purine synthesis (14, 15). VZV is a human herpes virus leading to chickenpox in susceptible individuals, which may later reactivate as herpes zoster [HZ] (16). The age-adjusted annual incidence of HZ is 3.2–3.3 per 1000 person-years in population-based studies with most cases occurring in those older than 45 years (17) (18). Declining cellular immunity due to increasing age and/or immunosuppression has been implicated in causing reactivation of HZ (19). As IFN-gamma, IFN-alpha and IL-2 have been shown to be key mediators in the normal host response to VZV infection, suppression of these cytokines may potentially affect susceptibility to and severity of VZV (10). Similarly, suppression of cellular immunity is implicated in the pathogenesis of VZV dissemination and reactivation resulting in HZ (20) (21). It is notable that immune dysregulation associated with RA *per se*

confers a 2-fold risk of infection compared with age- and sex matched control subjects regardless of drug therapy (22, 23). Despite the widespread use of MTX, no clear guidelines exist regarding pre-treatment VZV screening nor is there consensus as to whether non-immune patients require vaccination. Considering that greater than 90% of adults are IgG seropositive for VZV, screening for past infection remains questionable (24, 25). We therefore undertook a SLR regarding this area utilising the PICO framework (See Table I).

Methods

The PRISMA statement was utilised to guide our search (Fig. 1). All papers investigating the relationship between the use of MTX in patients with RA and VZV and HZ infection were assessed for eligibility. The Cochrane library, PubMed, EMBASE and Web of Science databases were searched.

Four key search terms *i.e.* rheumatoid arthritis, methotrexate, varicella zoster and herpes zoster virus were searched independently, where these terms appeared in both title and abstract, using ‘explode’ option limiting to English studies from 1980 onwards, results were then combined to include studies reporting RA, MTX and VZV and RA, MTX and HZ. For second part of the search, the aforementioned key search terms were combined individually with vaccine, immunisation and guidelines. Three reviewers independently assessed each title and abstract for potential relevance to the review. The bibliographies of all included papers were also hand searched for information on any other relevant studies. Full articles were retrieved if the title and abstract did not contain sufficient information to judge fulfilment of the inclusion criteria. Papers were retrieved from 1980 onwards (when the first studies using MTX in RA were published) to May 2011 and included experimental (clinical or other controlled studies) or observational studies, case reports and case series. Manuscripts were included if they examined data on MTX given either orally, subcutaneously or intramuscularly within the normal dosing range (5–30 mg/week) for RA, provided odds/hazard ratios for any infections including VZV or HZ, and compared the risk with the general population and/or patients with RA not receiving DMARDs. Additionally, the European Centre for Disease Prevention and Control, Health Protection Agency (HPA), the Centers for Disease control (CDC), the British Society for Rheumatology (BSR) and the World Health Organisation (WHO) web sites and publications were consulted for recent papers and recommendations regarding immunocompromised patients and immunisation. Papers were not eligible for inclusion if they included:

1. patients <18 years
2. were not published in English
3. diseases other than rheumatic conditions
4. data with no clear outcomes or comparison with background population

Table II. Case studies.

Ref	Author & Year	MTX dose (mg/wk)	MTX duration (months)	Age	Presentation	Other medication	Comorbidities	Extra
(26) (see next table)	Groff <i>et al.</i> 1983	7.5 7.5	10 8		Localised VZ Generalised VZ	Prednisolone 5mg OD Prednisolone status unknown		Pt GD Pt CR
(27)	Angit <i>et al.</i> 2009	10	Diagnosed 5/12	58	Disseminated HZ: R eye lesions without conjunctival involvement and scattered generalised lesions			
(28)	Liang <i>et al.</i> 1995	10		52	Disseminated HZ following VZV +ve gastric ulcer	Cladribine, naproxen, folic acid, acetaminophen with codeine		
(29)	Lyon <i>et al.</i> 1997	10	3	84	Haemorrhagic, desquamating L. T8 thoracic HZ	0.5mg flupenthixol BD	Under review for primary hyperparathyroidism	
(30)	Golden <i>et al.</i> 1997	"low dose"		47	HZ: anterolateral L. thigh scattered skin lesions			HZ not confirmed
(31)	Ching <i>et al.</i> 1995	20	14	26	Disseminated HZ: scattered non-pruritic lesions	Hydroxychloroquine 200mg		

Results

Literature search results and trial characteristics

13,708 trials were identified with 213 abstracts being assessed for eligibility with 42 finally included. After the removal of duplicates, 35 fulfilled the inclusion criteria including six case reports (Table II) and 29 observational studies (Table III). 22 observational studies directly addressed the issue of an association between low dose MTX use and increased susceptibility to any infection including VZV or HZ infection. In addition four studies compared infection rates on MTX with other widely used RA therapies and three studies investigated infection with regard to duration of MTX therapy.

MTX and infection in RA

Nine studies considered the association of MTX with non-varicella specific infection in RA patients. Infections were defined as serious adverse events based on the International Conference on Harmonisation definitions. Eight of these concluded that the MTX therapy was not associated with increased susceptibility to infection (32–39). One study reported an increased risk for all infections, especially pneumonia, particularly in the over 65 years popula-

tion (40) however this study did not set out *a priori* to report infection risk.

MTX and VZV in RA

Only one study reported two cases VZV infection in patients taking MTX 7.5 mg/week after 10 and 8 months respectively (26). The first patient was taking 5mg prednisolone daily whereas concurrent medications were not reported in the second patient.

MTX and HZ in RA

Six case reports and 13 observation studies considered the association between MTX and HZ. Three of the observational studies reported a positive association, although in 5 cases patients were treated concurrently with prednisolone. Two studies reported a HZ infection rate of 5%; however each of the cohorts only contained 21 patients in total (41, 42). Furst *et al.* reported a similar HZ infection rate of 7% in 45 patients (43).

In a recent retrospective analysis of data from a US managed care database (n=122,272) and a UK general practice research database (n=38,621), an increased risk of HZ infection was found among all patients with RA compared with the general population (in the US, adjusted HR 1.91, 95% confidence in-

terval [95% CI] 1.80–2.03; in the UK, adjusted HR 1.65, 95% CI 1.57–1.75) (44). Increasing age, diabetes, chronic lung disease, malignancy and corticosteroid use were all identified as risk factors. Adjusting for 'traditional' DMARD use (including MTX, azathioprine, leflunomide, cyclosporine and cyclophosphamide) in both cohorts found HRs of 1.37 (1.18–1.59) and 1.27 (1.10–1.48) respectively however the contribution of individual DMARDs was not assessed.

In a further study, HZ incidence rates in RA patients receiving weekly, low-dose MTX therapy were compared with those in the general population; 14.5 cases per 1,000 patient-years among the RA patients (9 cases of HZ in 187 patients) and 1.3–4.8 cases per 1,000 patient-years in the general population (45); no cases of systemic dissemination or further episodes of HZ infection were observed in the RA patients despite 27.4 years of cumulative follow up among patients who continued on MTX. The occurrence of infection was unrelated to the duration of MTX therapy, prednisone treatment, or comorbidity with diabetes mellitus, but did appear to occur in patients with high titers of rheumatoid factor and a longer duration of RA.

Five studies concluded that there was no association between HZ and MTX (46-50). Therapy with cyclophosphamide, azathioprine, prednisone, or leflunomide was found to be a significant predictor of reactivation of HZ infection, but the treatment with MTX and biologic agents was not (46). The 12-month incidence of HZ infection in this RA population was 13.2 cases per 1,000 patient-years. Finally, one observational study reported two cases of HZ, another reported one case and two studies no cases (47-50).

MTX compared to other RA medications

Four studies considered the association between MTX with infection compared to other RA medications (51-54). Wendling *et al.* reported six cases of HZ in patients on TNF inhibitors with MTX in a retrospective review of 300 patients concluding that MTX may contribute to a higher risk of HZ when taken with anti-TNF therapy (52). However, Schneeweiss *et al.* found that biological therapy did not confer an additional risk above MTX as control. MTX was shown to have half the risk of serious bacterial infections as compared with glucocorticoids (53). Data from the German biologics register did not demonstrate a difference in the incidence of HZ infection among patients treated with TNF inhibitors compared with those treated with traditional DMARDs (54).

A retrospective cohort study comprising 20,357 RA patients, found the overall incidence of HZ to be 9.96 episodes/1000 patient years (713 episodes). RA treatments were divided among three groups according to disease severity. Fifty-four percent of patients were treated with MTX (in addition to other medications). The incidence was lowest for patients in mild disease group [receiving either hydroxychloroquine, sulfasalazine, auranofin, injectable gold, or penicillamine] (8 episodes/1000 patient-years; $p < 0.001$) but was higher for the moderate disease group [receiving methotrexate, leflunomide, azathioprine, cyclophosphamide, cyclosporine, or anakinra] (11.18/1000 patient-years, $p < 0.001$) and severe disease group [receiving TNF inhibitors] (10.60 epi-

sodes per 1000 patient-years; $p < 0.001$). Independent risk factors for HZ included older age, prednisone, medications used to treat moderate and severe RA and serious comorbidities (51). MTX was not looked at independently.

MTX duration and VZV and HZ infection

Three studies assessed the duration of MTX use and timing of infectious complications. In the study by Schnabel *et al.* only 5 cases of HZ were seen in 185 consecutive patients over 30 months (55). The authors found that the first year of MTX treatment was not associated with VZV infection (56). Boerbooms *et al.* concluded that the risk for opportunistic infection was not limited to length of treatment and van der Veen *et al.* linked a higher infection rate in MTX treated patients to disease severity rather than treatment duration (55, 57).

Guidelines

Our search did not reveal any guidelines explicitly recommending VZV screening prior to MTX treatment for adults with RA. (60-63). In contrast national guidelines do recommend VZV screening prior to MTX commencement in children with inflammatory arthritis (65-67). Similarly, the Immunisation of the Immunocompromised Child Best Practice Statement recommends that VZV antibody status should be checked prior to starting immunosuppressive treatment "if circumstances permit" (68).

Whilst the Department of Health in the UK suggests that immunisation is to protect those at most risk of serious illness, both they and the CDC state that "this is done by immunising specific individuals who are in regular or close contact with those at risk", *i.e.* not RA patients themselves (64, 69). If the VZV vaccine is to be administered, current guidelines are unclear as to whether it can be given concurrently with MTX treatment, or whether MTX treatment should be delayed.

The BSR states that live vaccines, if administered, should be given at least two weeks, and preferably four weeks, prior to immunosuppressive therapy (71) but the ACR does not specify whether

live vaccines are safe with MTX (61). EULAR suggest that live attenuated vaccines should be avoided whenever possible in immunosuppressed patients with autoimmune inflammatory rheumatic diseases (72). However, they suggest that VZV, HZ and MMR vaccines might be exceptions to the rule and may be considered in the mildly immunosuppressed.

The guidelines concerning HZ vaccination are clearer with the CDC recommending HZ vaccine for all persons aged >60 years who have no contraindications, including persons reporting a previous episode of HZ or who have chronic medical conditions (73). These guidelines are unique in that they recommend HZ vaccination of patients with inflammatory disorders who are receiving prednisone <20 mg/day, short term (<2 weeks) corticosteroids, topical or intra-articular corticosteroids, 'low dose' methotrexate (defined as <0.4 mg/kg/week), azathioprine (<3.0 mg/kg/day) or 6-mercaptopurine (<1.5 mg/kg/day).

Discussion

Our literature search failed to show a clear association between MTX use in RA and VZV infection. This concurs with data showing that long-term MTX use is not associated with an increased risk of serious infections. Evidence is conflicting regarding the increased risk of HZ infection following MTX use with the results confounded by concurrent steroid therapy, comorbidities and severity of RA. In cancer therapy, high dose MTX utilises a pharmacological mechanism that is anti-proliferative to lymphocytes resulting in an increased risk of infection (74). However, the dose threshold at which this immunosuppression is likely to occur is unknown. It is important to consider, however, that the anti-proliferative dose of MTX is much higher than that used in RA (75).

It has been proposed that immune dysregulation associated with RA itself is sufficient to increase the risk of infection, regardless of medication use (22, 35, 76-82). The excess mortality described in RA is partly attributable to infection, with reported standardised mortality rates due to infection

Table III. Observational studies.

Ref	Author and year	Conclusion	No. pts	Av age	MTX dose (mg/week)	No. of infections	VZV / HZ	HR (95% CI)	p-value	Extra
(26)	Groff <i>et al.</i> 1983	Positive association	28		2-30	7% (2 cases)	Both cases were VZV (see cases table)			
(32)	Sakai <i>et al.</i> 2011	No \uparrow in serious infection risk.	571 RA	59	Low 5.9 High 7.4	10 17		1.14 (0.50-2.60) 0.97 (0.26-3.65)	0.758 0.966	Serious infection defined by on International Conference on Harmonization
(33)	Varatharajan <i>et al.</i> 2009	No \uparrow in serious infection risk	518 RA on MTX			2 infections led to cessation of MTX	0			
(34)	Lacaille <i>et al.</i> 2008	No \uparrow in serious infection risk	27,710 RA 45% non-bio DMARD	57		Mild: 25,608 (92%) Severe: 4,941 (18%)		Rate per person-year of any infections (MTX): 1.28 (1.25-1.32)		
(35)	Doran <i>et al.</i> 2002	No association between DMARDs and \uparrow infection risk.	609 RA (21.8% MTX)		Not nec. on MTX			HR : (RA vs. non-RA): A: 1.70 (1.42-2.03) B: 1.83 (1.52-2.21) C: 1.45 (1.29-1.64)	Infection: p = 0.85 Requiring hosp: p = 0.69	A = objectively confirmed infection; B = infections requires hospitalisation; C = any documented infection
(36)	Doran <i>et al.</i> 2002	No association between MTX use and risk of infection in RA	609 RA: 21.8% received MTX at some point (1,497 total days received)	58				Infections: 0.96 (0.64-1.45) Requiring hospitalisation: 0.91 (0.57-1.45)		
(37)	Perthala <i>et al.</i> 1991	No \uparrow in infection risk due to MTX	121, 60 with MTX	55	8.2mg/wk, 63.6 months	8 on MTX had infectious complications after total joint arthroplasty	0		0.37 (8.7% MTX vs 5.5% non-MTX procedures with complications)	All infectious complications of joint replacement surgery over 6 months
(38)	Scully <i>et al.</i> 1991	No link between HZ/VZV and MTX.	124	51	9, 9	0	0			
(39)	Fehlauer <i>et al.</i> 1989	No \uparrow in infection risk due to MTX	124	51	10 \pm 2.7	6	N/A			
(40)	Bernatsky <i>et al.</i> 2007	\uparrow risk for all infections (esp>65)	23733 29.7% on MTX	62		6634				Requiring hospitalisation
(41)	Weinstein <i>et al.</i> 1985	Positive association	21		7.5-20 mean 11.1	1	1 HZ			
(42)	Steinsson <i>et al.</i> 1982	Positive association	21	51	7.5-25		1 "HZ like skin lesions"			
(43)	Furst <i>et al.</i> 1990	Positive association confounded by prednisolone	45	16-80	16.2 \pm 6.3	28 (58%)	3 HZ (7%) (doses 8.4, 17.7, 18.3 mg/wk)			All pts on prednisolone (10mg QDS)
(44)	Smitten <i>et al.</i> 2007	RA and MTX both \uparrow HZ risk	2 cohorts: A:122,272 B:38,621					RA vs non-RA: A:1.91 (1.80-2.03) B:1.65 (1.57-1.75).		

Ref	Author and year	Conclusion	No. pts	Average MTX dose (mg/week)	No. of infections	VZV / HZ	HR (95% CI)	p-value	Extra
(45)	Antonelli <i>et al.</i> 1991	No link between HZ and MTX duration. No systemic dissemination or recurrence of HZ in 27.4 years.	187	57	9 (14.5 cases per 1,000 pt-years)	All HZ			
(46)	Wolfe <i>et al.</i> 2006	No association. Overall HZ rate in RA pts was 14.7 per 1000 pt-yrs	12335 (56.7% RA)	60	341	All HZ	1.0 (0.8–1.3)	0.720	
(47)	Jeurissen <i>et al.</i> 1991	No ↑ in HZ risk	31	57	4	0			
(48)	Sany <i>et al.</i> 1991	No ↑ in serious infection risk	191	50	10.2 ± 0.2	2 HZ			
(49)	Hanrahan <i>et al.</i> 1989	No ↑ in HZ risk	128	52	5–25	1 HZ			
(50)	Szanto <i>et al.</i> 1989	No ↑ in HZ risk	41	62	8.5	0			Mean disease duration 10.3 yrs; mean treatment duration 32 months
(51)	McDonald <i>et al.</i> 2009	9.96 episodes of HZ in RA pts per 1000 pt-years.	20,357 RA 54.6%	63	713	All HZ			
(52)	Wendling <i>et al.</i> 2008	MTX combined with anti-TNF-α may contribute to ↑ risk of HZ.	300 chronic inflammatory joint disease	53	10–15 mg/week	7 (6 on MTX)			
(53)	Schneeweiss <i>et al.</i> 2007	MTX confers half the risk of serious bacterial infections cf. glucocorticoids	1900 MTX	76	580 (30.5%) 56 (3%)		Event rate per 100 pt years. 3.77 (2.64–4.90)		
(54)	Listing <i>et al.</i> 2005	No difference in HZ risk between TNF inhibitors and DMARDs.	346 infliximab (10% not on DMARD concurrently)	54	92	5 (2 severe)	3.38 (1.9–6.1) events per 100 pt yr	0.15	
(55)	Boerbooms <i>et al.</i> 1995	The risks for opportunistic infection are not limited to any period of treatment	16	59	0.48 months: 18 infections/pt year at risk x100	2 pts with HZ			Required antibiotics
(56)	Schnabel <i>et al.</i> 1996	No ↑ VZV infection risk in first year of MTX tx.	185	18.7 ± 6.9 mg/wk	5	All HZ			All 5 cases in 13 – 30 month duration
(57)	van der Veen <i>et al.</i> 1994	Higher infection rate in MTX is partly due to disease severity; not MTX therapy duration	77	5 – 15mg	3 (2 in combination with prednisone) 1 (sulfasalazine and prednisone)	3 HZ 1 HZ	1.52 (1.04 – 2.22) 1.49 (1.04 – 2.13)		Required antibiotics
(58)	Hernández-Cruz <i>et al.</i> 1998	Steroids and/or MTX were associated in 95% of infections	195	41	15	All HZ			
(59)	Weinblatt <i>et al.</i> 1988	Positive association, confounded by prednisolone	26	59	2.5–15 (13.8 mean at entry, 8.6 mean at end)	2 HZ (both on prednisolone)			

ranging from 4.2 to 14.9 (83). In immunocompromised individuals, severe disseminated VZV infection can occur upon primary infection (84) however, our search only identified two cases of VZV associated with RA and its treatment suggesting that primary VZV infection is unlikely to be increased in this patient group (26).

Our search failed to reveal any clear guidelines recommending VZV screening prior to starting MTX for adult RA patients. It is possible that screening could be based upon a self-reported history of chickenpox. Parental reports for those aged 10-14 years and self-reports for those aged over 15 were highly (>95%) predictive of seropositivity (85) although this may simply reflect the high background seropositivity (up to 98.5%) (86). Interestingly, people born or raised in tropical climates have lower seroprevalence (87, 88) questioning whether history alone could be relied upon among all populations. Alternatively, screening could be performed in those who have a greater risk of encountering VZV such as health-care workers, individuals in regular contact with children or those living in crowded conditions (89).

In the light of our findings the question remains as to whether screening for past VZV infection is required at all. The screening process is expensive, takes 10 days and in those found to be non-immune, vaccination with two doses eight weeks apart (if over the age of 13) with a post-vaccination delay of at least two (and preferably four) weeks prior to commencing MTX is recommended (71, 90). This equates with a delay of approximately 3 months which contradicts the current model of early aggressive therapy for RA (91-93). Thus delaying treatment due to VZV screening could dramatically influence the long-term course of the RA.

It could be argued that VZV testing may reveal the risk of developing HZ as well as VZV however increased levels of antibody to VZV do not confer protection against HZ or post herpetic neuralgia (94). Increased levels of antibody to VZV after the onset of HZ in fact are associated with more severe disease and a greater risk of PHN (95).

VZV vaccination appears to be effective in the general population, with a 94% seroconversion rate in adolescents and adults after two doses (96) though rates are lower in children (97, 98). Research with influenza and pneumococcal vaccinations shows that RA patients can generate sufficient immune responses, although they may be less than in the general population regardless of the use of prednisolone or DMARDs (99-101).

If a patient was to be vaccinated whilst receiving MTX data is conflicting as to its efficacy (72). The CDC states that patients vaccinated whilst on immunosuppressive therapy should be considered non-immune and should be revaccinated at least 3 months after their therapy is discontinued (102). In addition, the safety of VZV vaccination must be considered with respect to both the immune dysfunction of RA itself and potential immunosuppression if administered during MTX therapy (103-105).

An alternative to the VZ vaccine is the HZ vaccine. Most cases presumed to be second episodes of varicella in immunocompromised patients have actually been cases of disseminated HZ, sometimes occurring before or in the absence of the typical dermatomal rash (106, 107). Thus vaccination of those over 50 years has now been approved in Europe and the US (108,109). As with VZV, the HZ vaccine should be given at least two weeks (and preferably one month) prior to receiving immunosuppressive medications (110). As it is unclear whether the vaccine reduces the incidence of HZ in patients receiving MTX for RA, this delay may not be practical.

Perhaps a more pragmatic approach would be to rely on post-exposure management. This removes the difficulties associated with large screening programmes and would not hinder the current model of early aggressive therapy of RA. Vaccination within three days of exposure is >90% effective in preventing varicella and 100% effective in modifying disease severity (111, 112). If varicella infection does result, there is no evidence that vaccination increases the risk of adverse events (64). This approach would minimise the number of patients requiring vaccination and save

costs, time and the potential harm posed by unnecessary vaccination. However, as these studies have been conducted in children its efficacy in adults is unknown (64). Furthermore this paradigm relies on an acceptance that a live vaccine is safe in those treated with low-dose MTX.

Another option could be administration of VZIg following exposure to VZV or HZ, although estimations of its efficacy vary (113, 114). This approach is complicated as in the UK the Department of Health (69) maintains that serology must be tested prior to VZIg. As VZV serology takes 10 days (90) and VZIg should be administered within 96 hours of exposure, this paradigm is not possible to achieve (64). In contrast, the CDC suggests that history alone can be relied upon. We recommend circumventing the use of VZV testing as per CDC guidance and administer VZIg prophylaxis post exposure in patients who are unlikely to be immune. As most adult patients are seropositive for VZV, cases requiring VZIg prophylaxis would be uncommon and such practice should be cost effective.

A limitation of our review is that paediatric data was not included as it was deemed beyond the scope of our analysis. In addition, reporting bias may be present as clinicians are more likely to describe HZ or VZV cases in those receiving DMARD therapy. Similarly, selective reporting of HZ infections with publication bias might have led to overestimation of such complications. However, potential confounders leading to such bias have been characterised in the included studies where possible. Lastly, it was not possible to combine all the data for meta-analysis as the study populations were too diverse and the outcome measures too variable.

Conclusion

No evidence exists supporting a link between MTX and VZV infection in RA patients and data regarding the role of MTX in the development of HZ is conflicting. Studies suggesting a positive association between MTX and HZ are confounded by the presence of comorbidities and concomitant therapies. The role of pre-MTX VZV serology testing

is controversial as it may delay the institution of early aggressive therapy for RA. We suggest circumventing the use of pre-MTX VZV screening and recommend initiating MTX therapy as soon as possible if required. Future guidelines should clarify whether screening for VZV immunity prior to treatment is desirable.

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