MTX AND INFECTIOUS RISK IN RA

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Agenda

- Screening tests
- General risk of infections (serious and not serious)
- Peri-operative management
- Relevant viral infections
- Vaccines

Systematic review of 2008-2012 literature and update of recommendations for the use of methotrexate in rheumatic diseases, with a focus on rheumatoid arthritis

Reumatismo, 2013; 65 (5): 207-218

Table I - 2012 recommendations for the use of methotrexate in rheumatoid arthritis and in other rheumatic diseases.

Recommendation (level of evidence; strength of the recommendation)	Changes in comparison with the 2010 version
1. The work-up for RA patients who are MTX candidates should include the following tests: liver function tests; serum albumin; blood cell counts; serum creatinine; hepatitis B and C serology; chest X-ray. MTX treatment should not be introduced during pregnancy or in the presence of hepatic cirrhosis, severe renal function impairment; alcohol abuse; bone marrow depression; or active hepatitis B or C (4; C).	Partially modified
2. The therapeutic range of MTX is 7.5-25 mg/week. The optimal initial strategy is a starting dose of 12.5-15 mg/week (1b; B). In the absence of adverse events and/or subjective intolerance, in patients with early RA, close monitoring of therapeutic efficacy and therapeutic targets with rapid up-titration (5 mg/week a month) is more effective (1b; B). As MTX-related toxicity is dose-dependent, the maximum weekly dose of 25 mg (2b; B) should not be exceeded. It can be given initially by oral or parenteral route. Oral bioavailability of the drug varies, in particular at high doses (3b; B). Parenteral MTX can increase efficacy with a similar safety profile (1b; B). In patients refractory to oral MTX, switching to parenteral administration may be a useful strategy before introducing other therapies (2b; B).	Extensively modified
3. Weekly supplementation with folic acid (5-10 mg/week) should be administered to reduce the risk of adverse events/intolerance (1a; A). In most cases, it should be taken 24 hours after MTX. To date there is sufficient evidence that folic acid supplements do not nullify the clinical efficacy of MTX (1a; A).	Partially modified
rate due to hepatotoxicity is about 5%. Alcohol consumption should be avoided, because it appears to be an adjunctive risk factor for the development of hepatic fibrosis. MTX is not a significant risk factor for the development of infections, including severe infections. In patients with RA, MTX, and DMARDs in general, are associated with a greater incidence of tuberculosis reactivation (3b; B). MTX does not appear to be a risk factor for the development of neoplasms (3b; B). MTX can prolong the survival of RA patients by reducing cardiovascular mortality (2a; A).	
7. The administration of MTX (at ≤10 mg/week) can be continued in RA patients who undergo orthopaedic surgery as MTX does not affect the incidence of perioperative surgical complications whereas treatment discontinuation may increase the incidence of disease reactivation. MTX dosage reduction or treatment discontinuation may be considered for doses >10 mg per week in patients undergoing major surgery (1b; B).	Unchanged
8. MTX must be discontinued at least 3 months before conception (both in men and in women), it must be strictly forbidden during pregnancy and avoided during breastfeeding (4; C).	Unchanged
9. MTX must be considered the DMARD of first choice in RA patients both alone and in combination (with low dosage glucocorticoid and/or other DMARDs) (2b; B).	Partially modified
10. In patients that are non-responders to MTX at the maximum tolerated dosage, combination therapy can be started with DMARD or a biological agent (1b; B). Currently, addition of a biological agent should be preferred in patients with poor prognostic factors or documented radiological progression (1b; B).	Partially modified
11. Administration of MTX must be temporarily discontinued in patients who develop severe infections (any infection requiring hospitalization and/or intravenous antibiotics/antifungals and/or presenting with sepsis or is life-threatening, according to the NIH) (5; D).	Unchanged

1. The work-up for RA patients who are MTX candidates should include the following tests: liver function tests; serum albumin; blood cell counts; serum creatinine; hepatitis B and C serology; chest X-ray. MTX treatment should not be introduced during pregnancy or in the presence of hepatic cirrhosis, severe renal function impairment; alcohol abuse; bone marrow depression; or active hepatitis B or C (4; C).

Screening tests for complete serological status HBV/HCV before MTX medication

World Journal of Hepatology

World J Hepatol 2015 March 27; 7(3): 344-361

Table 2 Nomenclatures and definitions used in hepatitis B virus infection

Markers	Chronic inactive carrier	HBeAg positive CHB	HBeAg negative CHB	"Resolved hepatitis B"
HBsAg	+	+	+	-
HBeAg	-	+	-	-
Anti-HBe	+	-	+/-	+/-
Anti-HBs	+	-	+/-	+/-
Anti-HBc	+	+/-	+	+/-
ALT	-	+/-	+	-
Serum HBV-DNA	Undetectable/< 2000 IU/mL	Persistent/intermittent ↑ (> 20000 IU/mL)	Persistent/intermittent ↑ (> 2000 UI/mL)	Detectable or undetectable
Liver injury	+/-	Moderate/severe CHB	Minimal to severe CHB	-
Necroinflammation	No (> 90%)	Yes (> 90%)	No (> 90%)	No

What should we do in case of inactive carrier or resolved/OBI?

Long-term use of methotrexate does not result in hepatitis B reactivation in rheumatologic patients

Charlie Laohapand · Emvalee Arromdee · Tawesak Tanwandee

Hepatol Int (2015) 9:202–208

Study design: cross-sectional study

Population: Thai rheumatological pts (67% RA)

Intervention: long term (>24 wks) MTX therapy**

Outcome 1: prevalence of HBV seromarkers

Outcome 2: comparison HBV status between entry and previous data (if any)

***mean MTX therapy duration: 10 years*

Table 3 Prevalence of hepatitis B virus seromarkers in chronic methotrexate-treated patients ($N = 173$)

Measure	*N* (%)
HBV surface antigen (HBsAg)	
Positive	1 (0.58)
Negative	172 (99.42)
HBV surface antibody (anti-HBs)	
Positive	67 (38.73)
Negative	106 (61.27)
HBV core IgG antibody (anti-HBc IgG)	
Positive	65 (37.57)
Negative	108 (62.43)
Presence of HBV seromarker	
Any positive	77 (44.51)
Negative all seromarkers	96 (55.49)
HBV DNA viral load (HBV VL) among HBsAg and/or anti-HBc IgG positive patients ($n = 65$)	
VL <20 IU/ml	64 (98.5)
VL ≥20 IU/ml	1[a] (1.5)

[a] Patient no. 157, a 56-year-old female with HBsAg positive since previous study and anti-HBc positive, showed HBV VL of 452 IU/ml

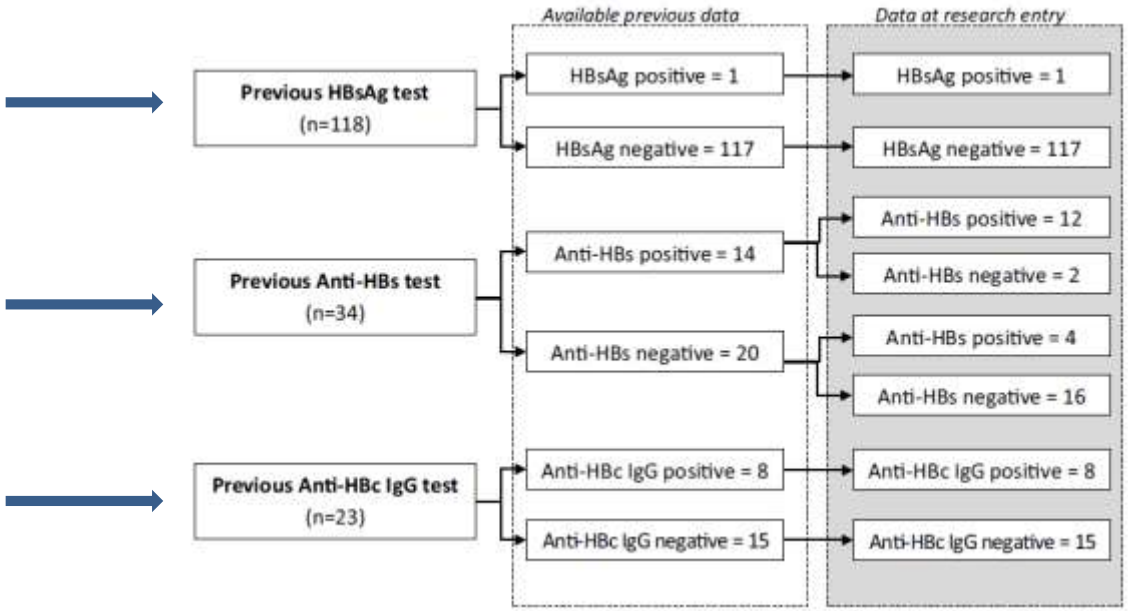
About one third of the patients had exposure to HBV (anti-HBc IgG in 37.6 % pts).

Long-term use of methotrexate does not result in hepatitis B reactivation in rheumatologic patients

Charlie Laohapand · Emvalee Arromdee · Tawesak Tanwandee

Hepatol Int (2015) 9:202–208

118 pts with research entry and baseline data, too.



- None of HbcAb+ had HBV-reactivation over 10 years of MTX treatment.
- 1 HbsAg+ received MTX with non prophylaxis with no safety concerns.

Long-term use of methotrexate does not result in hepatitis B reactivation in rheumatologic patients

Charlie Laohapand · Emvalee Arromdee · Tawesak Tanwandee

Hepatol Int (2015) 9:202–208

Measure	MTX accumulated dose in 52 weeks		
	≤500 mg ($n = 72$)	>500 mg ($n = 101$)	p value
Hematology			
Hemoglobin (g/dl)	13.73 ± 14.21	11.65 ± 1.48	**0.041**[a]
Hematocrit (%)	37.30 ± 4.40	36.23 ± 4.13	0.103[b]
WBC count ($\times 10^3/\mu l$)	6.73 ± 2.06	6.73 ± 2.31	0.822[a]
Platelet count ($\times 10^3/\mu l$)	272.32 ± 83.69	293.14 ± 65.78	**0.029**[a]
Blood chemistry			
AST (U/l)	27.93 ± 32.28	21.93 ± 8.45	0.382[a]
ALT (U/l)	19.29 ± 13.94	18.34 ± 11.12	0.803[a]
Total bilirubin (mg/dl)	0.37 ± 0.20	0.34 ± 0.17	0.268[a]
Albumin (g/dl)	[illegible]	[illegible]	0.727[a]
Globulin (g/dl)	3.60 ± 0.71	3.86 ± 2.90	0.686[a]
ALP (U/l)	82.69 ± 46.07	77.79 ± 21.45	0.611[a]
Creatinine (mg/dl)	0.91 ± 1.18	0.73 ± 0.21	0.054[a]
Immunology			
HBsAg			1.000[c]
Positive	0 (0.00)	1 (0.99)	
Negative	72 (100.00)	100 (99.01)	
Anti-HBs			0.724[d]
Positive	29 (40.28)	38 (37.62)	
Negative	43 (59.72)	63 (62.38)	
Anti-HBc IgG			0.535[d]
Positive	29 (40.28)	36 (35.64)	
Negative	43 (59.72)	65 (64.36)	

Long-termMTX in patients exposed to HBV was safe and not associated with hepatitis flare (regardless of low- vs high-cumulative dose).

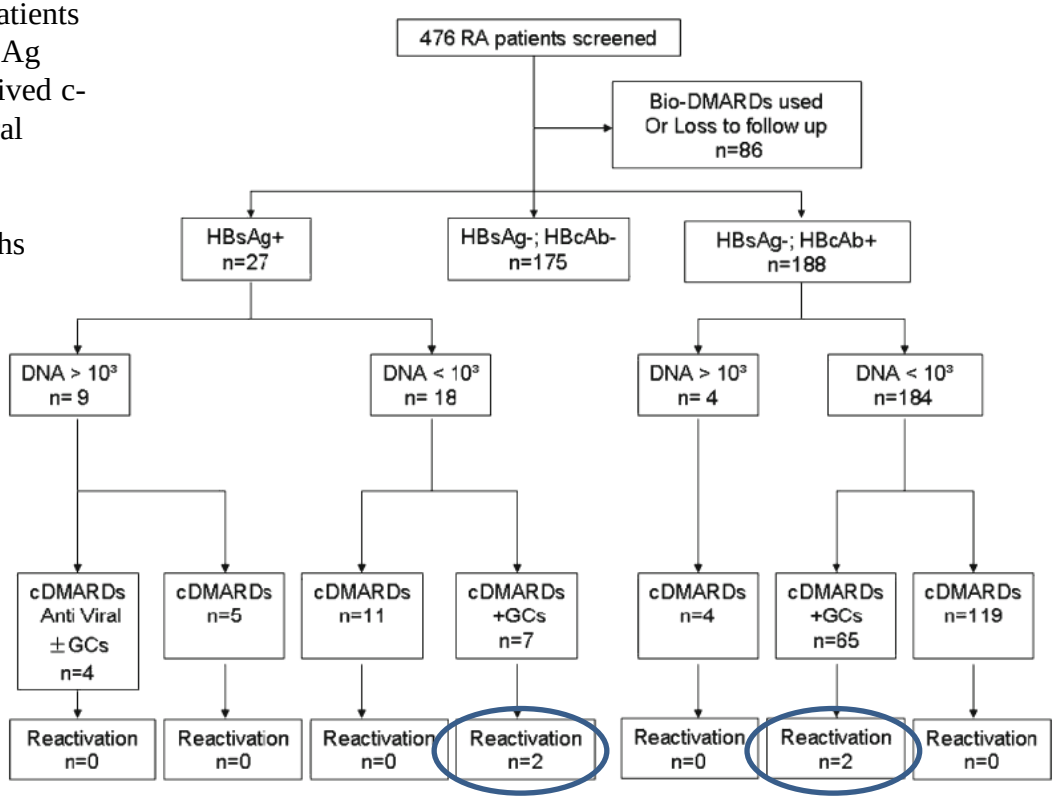
Prospective study of HBV reactivation risk in rheumatoid arthritis patients who received conventional disease-modifying antirheumatic drugs

Clin Rheumatol (2012) 31:1169–1175

Jing Tan · Jingguo Zhou · Pan Zhao · Jing Wei

Population: 211 chinese RA patients (23 HBsAg+ and 188 HBsAg negative/anti-HBc+) who received c-DMARDs without antiviral prophylaxis.

Mean follow up: 20 months



4 patients developed HBV reactivation.

Both HBsAg positive and HBsAg negative/anti-HBc positive patients have the possibility of developing HBV reactivation.

Prospective study of HBV reactivation risk in rheumatoid arthritis patients who received conventional disease-modifying antirheumatic drugs

Clin Rheumatol (2012) 31:1169–1175

Jing Tan · Jingguo Zhou · Pan Zhao · Jing Wei

Table 2 Comparison of the patients who were exposed to different potential risk factors

Potential risk factors		Reactivation	No reactivation	*P*
GCs	Used	4	69	0.0247
	Not used	0	138	
MTX	Used	3	167	0.7235
	Not used	1	40	
LEF	Used	3	145	0.7360
	Not used	1	62	
Anti-HBs	Positive	0	143	0.0169
	Negative	4	64	

Conventional DMARDs are relatively safe to HBV-infected patients with low reactivation risk (no GCs administration and anti-HB positive).

Hepatitis B Reactivation During Immunosuppressive Therapy or Cancer Chemotherapy, Management, and Prevention: A Comprehensive Review

Hepat Mon. 2016 April; 16(4):e35810.

Table 2 Immunosuppressive drug classes and corresponding risk estimates of hepatitis B virus reactivation[63,80]

Drug class	Drug	Risk estimate of HBVr for HBsAg positive	Risk estimate of HBVr for HBsAg negative/anti-HBc positive
B-cell depleting agents	Rituximab (anti-CD20)	High (30%-60%)	High (> 10%)
	Ofatumumab (anti-CD20)		
Anthracycline derivatives	Doxorubicin	High (15%-30%)	High (> 10%)
	Epirubicin		
TNF-α inhibitors	Infliximab	Moderate (1%-10%)	Moderate (1%)
	Etanercept		
	Adalimumab		
Cytokine inhibitors and integrin inhibitors	Abatacept (anti-CD80, -86)	Moderate (1%-10%)	Moderate (1%)
	Ustekinumab (anti-IL-12, -23)		
	Natalizumab (binds α4-integrin)		
	Vedolizumab [binds integrin α4β7 (LPAM-1)]		
Tyrosine kinase inhibitors	Imantinib	Moderate (1%-10%)	Moderate (1%)
	Nilotinib		
Corticosteroids	High dose, *e.g.*, prednisone ⩾ 20 mg for ⩾ 4 wk	High (> 10%)	NA
	Moderate dose, *e.g.*, prednisone < 20 mg for ⩾ 4 wk	Moderate (1%-10%)	Moderate (1%-10%)
	Low dose, *e.g.*, prednisone for < 1 wk	Low (< 1%)	Low (<< 1%)
	Intra-articular corticosteroids	Low (< 1%)	Low (<< 1%)
Traditional immunosuppression	Azathioprine	Low (< 1%)	Low (<< 1%)
	6-mercaptopurine		
	Methotrexate		

Factors to be considered:

- Viral status

- Host factors

- Underlying disease

- Concomitant therapy

…BUT….

Development of fulminant hepatitis B (precore variant mutant type) after the discontinuation of low-dose methotrexate therapy in a rheumatoid arthritis patient.

Ito S, et al.
*Clin Exp Rheumatol 20*04;22(3):375-6.

Possible risk (rare) of HBV reactivation during host immunorestitution (after MTX discontinuation)

Fulminant hepatitis in an asymptomatic chronic carrier of hepatitis B virus mutant after withdrawal of low-dose methotrexate therapy for rheumatoid arthritis.

Hagiyama H, et al.
Clin Exp Rheumatol 2004;22(3):375-6.

Disease Characteristics and Treatment Patterns in Veterans With Rheumatoid Arthritis and Concomitant Hepatitis C Infection

Arthritis Care & Research
Vol. 67, No. 4, April 2015, pp 467–474

Table 2. RA disease characteristics, disease activity, and medication use in HCV-positive and HCV-negative patients at study enrollment*

	HCV positive (n = 92)	HCV negative (n = 1,706)	*P*
Disease characteristics, no. (%)			
RF positive	71 (80)	1,264 (79)	0.8
Anti-CCP positive	46 (68)	920 (74)	0.2
Erosions	40 (54)	731 (52)	0.7
Polyarthritis	73 (90)	1,357 (91)	0.9
Nodules	28 (40)	504 (37)	0.6
Disease activity			
DAS28 score, mean ± SD	4.68 ± 1.71	4.02 ± 1.61	< 0.001
MD-HAQ score, mean ± SD	1.5 ± 0.62	0.92 ± 0.60	0.08
Pain score (range)	6 (4–8)	5 (2–7)	< 0.001
Patient global assessment (range)	45 (30–63)	43 (20–60)	0.03
Physician global assessment (range)	42 (25–60)	31 (15–51)	0.2
Tender joint count, mean ± SD	6.8 ± 0.7	5.0 ± 0.2	< 0.001
Swollen joint count (range)	6 (1–12)	3 (0–8)	< 0.001
ESR, mm/hour (range)	25 (12–38)	22 (10–38)	0.4
CRP, mg/dl (range)	0.6 (0.4–1.8)	0.4 (0.8–2)	0.3
Medication use, no. (%)			
Prednisone	41 (47)	593 (37)	0.06
Methotrexate	20 (23)	811 (51)	< 0.001
Hydroxychloroquine	29 (33)	425 (29)	0.2
Sulfasalazine	17 (20)	193 (12)	0.04
Anti-TNF	23 (27)	307 (19)	0.1

* RA = rheumatoid arthritis; HCV = hepatitis C infection; RF = rheumatoid factor; anti-CCP = anti–cyclic citrullinated peptide; DAS28 = Disease Activity Score in 28 joints; MD-HAQ = multidimensional Health Assessment Questionnaire; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; anti-TNF = anti–tumor necrosis factor.

HCV-positive patients were more likely to be treated with prednisone and anti-TNF therapies.

HCV-positive patients were less likely to receive methotrexate compared to HCV-negative patients.

Rheumatological manifestations of hepatitis C: incidence in a rheumatology and non-rheumatology setting and the effect of methotrexate and interferon

Rheumatology 2005;44:1016–1020

Legend:
A= amelioration
B= not affected
C= deterioration

TABLE 2. Clinical characteristics and response of patients treated with methotrexate (Group I)

	Patient number						
	2	4	6	7	12	14	19
Sex	F	F	F	F	F	F	F
Age (yr)	65	60	47	51	55	47	59
Arthralgia	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Arthritis	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Sicca syndrome	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Fatigue	Yes	Yes	No	No	Yes	Yes	Yes
Other signs	No	No	Episcleritis	Paraesthesias	Raynaud's	No	No
ESR/CRP	–	12/5.0	12/5.0	15/5.0	25/3.0	20/4.0	18/31
RF	Yes	No	No	No	Yes	Yes	Yes
ANA	Yes	No	No	No	No	No	No
SSA/SSB	Yes	No	No	No	No	No	No
Cryoglobulinaemia	Yes	Yes	No	No	No	No	–
CH50	Decreased	Normal	Normal	Normal	Decreased	Normal	–
Viraemia[a]	Yes	Yes	No	No	Yes	No	Yes
Elevated transaminases	Yes	Yes	No	No	Yes	No	No
Metavir score	A3, F4	A2, F2	–	A0, F0	A1, F2	–	A1, F1
Salivary gland biopsy	Positive	Positive	Normal	–	Normal	–	–
Mean dose of methotrexate (mg/week)	12.5	10	7.5	12.5	15	10	15
Effect on arthralgias	A	B	A	A	B	A	A
Effect on arthritis	A	A	A	A	B	B	A
Effect on sicca syndrome	A	A	A	A	B	A	B
Effect on viraemia	B	C	B	B	B	B	B
Effect on transaminases	B	C	B	B	B	B	B

MTX (mean dose 12.5±3.0 mg/week) had been used for an average duration of 15.2±9.9 months, mainly for severe arthritis.

Patients treated with MTX, experienced control of joint disease with no negative HCV-related outcomes.

Legend:
A= amelioration
B= not affected
C= deterioration

Rheumatological manifestations of hepatitis C: incidence in a rheumatology and non-rheumatology setting and the effect of methotrexate and interferon

Rheumatology 2005;44:1016–1020

TABLE 3. Effect of interferon treatment on the clinical manifestations and hepatic parameters of Group I patients

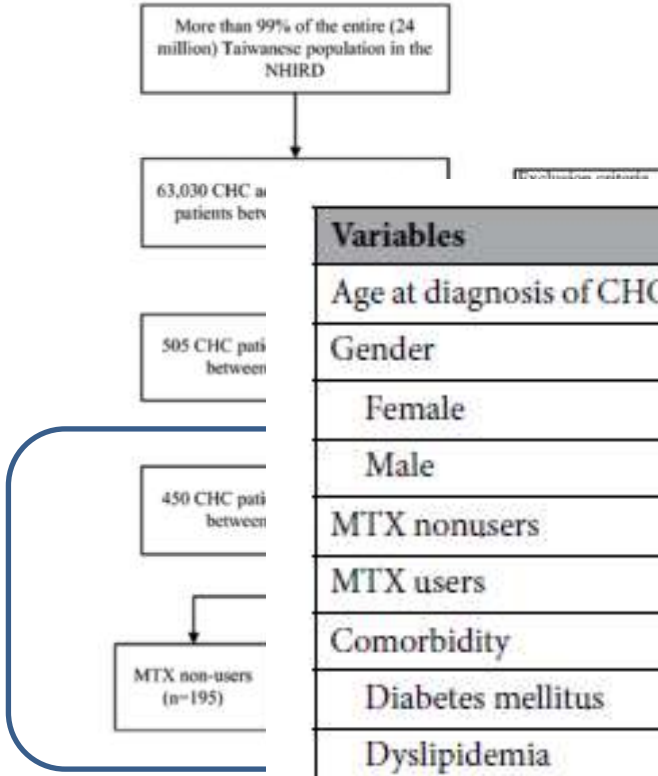
	Patient												
	2	3	4	7	8	9	11	13	14	15	16	17	18
+Ribavirin	Yes	No	No	No	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Arthralgias	C	A	C	B	C	A	B	C	C	C	B	B	–
Arthritis	–	–	C	B	C	–	B	C	–	–	–	–	–
Sicca syndrome	C	–	B	B	–	–	–	–	C	–	B	B	–
Fatigue	C	A	–	–	C	A	C	–	–	–	C	B	–
Myalgias	–	–	–	–	–	A	B	–	–	C	B	–	–
Paraesthesias	–	–	–	B	–	–	–	–	–	–	–	B	–
Viraemia	B	–	–	B	A	–	B	A	B	B	A	B	–
Transaminases	B	A	–	A	A	–	B	A	A	A	A	B	–

The effect of INF was more variable, with frequent deterioration of HCV-related symptoms

MTX might be used in HCV-infected patients with careful monitoring of LFT.

Methotrexate is not associated with increased liver cirrhosis in a population-based cohort of rheumatoid arthritis patients with chronic hepatitis C

SCIENTIFIC REPORTS | 6:33104 | DOI: 10.1038/srep33104



Variables	Adjusted HR (95% CI)
Age at diagnosis of CHC (years)	1.05 (1.03–1.08)**
Gender	
Female	1.00
Male	1.13 (0.59–2.17)
MTX nonusers	1.00
MTX users	0.33 (0.19–0.59)**
Comorbidity	
Diabetes mellitus	2.71 (1.44–5.11)*
Dyslipidemia	0.75 (0.35–1.59)
Hypertension	0.54 (0.30–0.97)*

Variables	MTX users (n = 255)	MTX nonusers (n = 195)
Age at diagnosis of CHC (years)	57.7 ± 12.7	61.0 ± 13.3
Gender		
	205 (80%)	151 (77%)
	50 (20%)	44 (23%)
	7 (3%)	0 (0%)
	46 (18%)	33 (17%)
	41 (16%)	37 (19%)
	82 (32%)	86 (44%)
	35 (14%)	5 (3%)*
	11 (4%)	3 (2%)
	152 (60%)	68 (35%)*
	205 (80%)	92 (47%)*
	163 (64%)	NA
	49 (19%)	NA
	43 (17%)	NA
	19 (8%)	36 (19%)*
	1 (0%)	3 (2%)
	6.5	5.2*

MTX doesn't significantly increase the risk of cirrhosis in CHC (chronic hepatitis C)

Adherence to current recommendations on the use of Methotrexate in Rheumatoid Arthritis in Italy: results from the MARI study

M. Manara[1], G. Bianchi[2], E. Bruschi[3], V. Azzolini[4], N. Belai Beyene [5], S. Corbanese[6], F. De Gennaro[7], L.S. Martin-Martin[8], A.B. Molica[9], M.R. Pozzi[10], N. Romeo[11], T. Rossini[12], A. Severino[13], L. Sinigaglia[1]

Clinical and Experimental Rheumatology 2016; **34**: 000-000.

Table I. Proportion of patients with rheumatoid arthritis on methotrexate treatment satisfying audit criteria derived from Italian recommendations. Values are given as number of subjects fulfilling the criteria/ number of subjects assessed (percentages).

Theme of care	Recommendation	Criteria	Attainment
Preliminary tests	The work-up for RA patients who are MTX candidates should include the following tests: liver function tests; serum albumin; blood cell counts; serum creatinine.	Patients with lab tests performed before starting MTX	1252/1336 (93.7%)
	The work-up for RA patients who are MTX candidates	Patients with hepatitis B and C serology	861/1336 (64.4%)
MTX dosage	The therapeutic range of MTX is 7.5-25 mg/week.	Patients with current MTX dosage between 7.5-25 mg/week	1283 /1314 (97.6%)
	The optimal initial strategy is a starting dose of 12.5-15 mg/week.	Patients with starting MTX dosage between 12.5-15 mg/week	298 /1044 (28.5%)
	As MTX-related toxicity is dose-dependent, the maximum weekly dose of 25 mg should not be exceeded.	Patients with current MTX dosage under 25 mg/week	1313 /1314 (99.9%)
Folic acid supplementation	Weekly supplementation with folic acid ... should be administered to reduce the risk of adverse events/intolerance	Patients supplemented with folic / folinic acid	1282/1336 (96%)
	Weekly supplementation with folic acid (5-10 mg/week) should be administered ...	Patients supplemented with folic acid at a dosage between 5-10 mg/week	789/869 (90.8%)
Monitoring	Transaminases (AST, ALT) are the most useful laboratory parameters for monitoring liver toxicity due to MTX. CBC and renal function tests should also be performed in patients receiving MTX. These tests should be performed ... every 4-12 weeks to check for hepatic, haematological or renal toxicity.	Patients with lab tests performed every 4-12 weeks	1179 /1314 (89.7%)

RA: rheumatoid arthritis; MTX: methotrexate.

The work-up for RA patients who are MTX candidates should include the following tests: ... hepatitis B and C serology. Patients with hepatitis B and C serology performed before starting MTX 861/1336 (64.4%)

Rheumatoid Arthritis, Its Treatments, and the Risk of Tuberculosis in Quebec, Canada

Arthritis & Rheumatism (Arthritis Care & Research)
Vol. 61, No. 3, March 15, 2009, pp 300–304

Table 1. Baseline characteristics of RA case patients with TB and control subjects during the year prior to the index date for the period 1980–2003*

	Case patients with TB (n = 50)	Control subjects (n = 1,500)	*P*
Age, mean ± SD years	65.6 ± 13.1	67.6 ± 14.3	0.06
Men	50.0	30.0	0.002
Diabetes	12.0	10.1	0.67
Other conditions†	2.0	1.9	0.62
Use of all DMARDs	72.0	45.6	0.0004
Methotrexate	58.0	30.3	< 0.0001
Leflunomide	6.0	0.5	0.003
Cyclosporine	6.0	0.8	0.01
Other	20.0	18.5	0.78
Current use of corticosteroids	18.0	8.1	0.03
Current use of COX-2 inhibitors	8.0	5.7	0.53
Use of NSAIDs	56.0	49.9	0.39

* Values are the percentage unless otherwise indicated. RA = rheumatoid arthritis; TB = tuberculosis; DMARDs = disease-modifying antirheumatic drugs; COX-2 = cyclooxygenase 2; NSAIDs = nonsteroidal antiinflammatory drugs.
† Other comorbid clinical conditions and risk factors are silicosis, chronic renal failure/hemodialysis, solid organ transplantation, and carcinoma.

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Table 3. Crude and adjusted rate ratios (RRs) of developing TB, according to the user type and number of prescriptions among current nonbiologic anti-RA medication users*

	Case patients with TB (n = 50)	Control subjects (n = 1,500)	Crude RR	Adjusted RR†	95% CI
New users	4	87	2.5	2.3	0.5–9.8
Long-term users	23	492	2.9	2.8	1.4–5.7
Current users	26	570	2.8	2.6	1.3–5.2
1–5 prescriptions	7	185	2.2	2.0	0.7–5.8
6–10 prescriptions	8	163	3.1	3.0	1.2–7.7
≥11 prescriptions	11	165	2.9	2.8	1.2–6.5

* 95% CI = 95% confidence interval; see Table 1 for additional definitions.
† Adjusted for age, sex, diabetes, other comorbid conditions, use of DMARDs, current use of corticosteroids, current use of COX-2 inhibitors, and use of NSAIDs.

Do we need further screening test, like latent TBC, before MTX?

Limits: not all confounding factors captured
(TBC reactivation vs de novo-infection)!

Methotrexate combined with isoniazid treatment for latent tuberculosis is well tolerated in patients with rheumatoid arthritis: experience from an urban arthritis clinic

Ann Rheum Dis 2008;**67**:462–465.

AIM: to investigate toxicity of MTX+INH in 44 RA patients

Table 1 Methotrexate–isoniazid combined treatment

Methotrexate dose (mg/week)	16.8 (SD 4.2)
Folic acid use (1 mg/day)	100%
Duration of combined treatment (months)	7.5 (3.0)
Abnormal liver function test (%)	11.3% (5/44)
⩽1.5 Upper limit of normal	6.8% (3/44)
⩽2.0 Upper limit of normal	4.5% (2/44)
>2.0 Upper limit of normal	0
Sustained liver function test elevation (>1, ⩽3 measurements)	4.5% (2/44)
Other adverse effect (%)*	2% (1/44)

*Reversible peripheral neuropathy.

Mean MTX dose (sd) = 16.8 (4.2) mg/week.

All patients received folic acid (1 mg/day).

The mean duration (sd) of INH co-treatment with MTX was 7.5 (3.0) months.

All patient received INH at dose of 300 mg/day and pyridoxine at dose of 50 mg/day.

Transient increases in LFT were seen in 11% of patients, but in no case was this more than twice the upper limit of normal values.

All abnormal LFT resolved spontaneously without intervention.

Methotrexate combined with isoniazid treatment for latent tuberculosis is well tolerated in patients with rheumatoid arthritis: experience from an urban arthritis clinic

Ann Rheum Dis 2008;**67**:462–465.

Conclusions: The use of INH for LTB was well tolerated in patients with RA on a background regimen of MTX. While the risks and benefits of all treatment must always be considered, in our experience the additive risk of INH to MTX in terms of hepatotoxicity was low. None the less it is prudent to follow LFT closely on patients taking this combination.

Systematic review of 2008-2012 literature and update of recommendations for the use of methotrexate in rheumatic diseases, with a focus on rheumatoid arthritis

Reumatismo, 2013; 65 (5): 207-218

Table I - 2012 recommendations for the use of methotrexate in rheumatic diseases.

Recommendation (level of evidence; strength of the recommendation)	Changes in comparison with the 2010 version
1. The work-up for RA patients who are MTX candidates should include the following tests: liver function tests; serum albumin; blood cell counts; serum creatinine; hepatitis B and C serology; chest X-ray. MTX treatment should not be introduced during pregnancy or in the presence of hepatic cirrhosis, severe renal function impairment; alcohol abuse; bone marrow depression; or active hepatitis B or C (4; C).	Partially modified
2. The therapeutic range of MTX is 7.5-25 mg/week. The optimal initial strategy is a starting dose of 12.5-15 mg/week (1b; B). In the absence of adverse events and/or subjective intolerance, in patients with early RA, close monitoring of therapeutic efficacy and therapeutic targets with rapid up-titration (5 mg/week a month) is more effective (1b; B). As MTX-related toxicity is dose-dependent, the maximum weekly dose of 25 mg (2b; B) should not be exceeded. It can be given initially by oral or parenteral route. Oral bioavailability of the drug varies, in particular at high doses (3b; B). Parenteral MTX can increase efficacy with a similar safety profile (1b; B). In patients refractory to oral MTX, switching to parenteral administration may be a useful strategy before introducing other therapies (2b; B).	Extensively modified
[illegible] to reduce hours after the clinical	Partially modified
ng liver to- ls receiving i-12 weeks respiratory	Unchanged
reduced or ent should ly high de- ent (2b; C).	Unchanged
6. According to its safety profile, MTX may be used for long-term therapy. Discontinuation rates due to toxicity are similar to those in patients treated with hydroxychloroquine or leflunomide, and lower than those in patients receiving gold salts or sulfasalazine (3b; B). The most frequent side effects during treatment with MTX are gastrointestinal disturbances, with constant incidence over time, and hypertransaminasemia, especially during the first 5 years. The discontinuation rate due to hepatotoxicity is about 5%. Alcohol consumption should be avoided, because it appears to be an adjunctive risk factor for the development of hepatic fibrosis. MTX is not a significant risk factor for the development of infections, including severe infections. In patients with RA, MTX, and DMARDs in general, are associated with a greater incidence of tuberculosis reactivation (3b; B). MTX does not appear to be a risk factor for the development of neoplasms (3b; B). MTX can prolong the survival of RA patients by reducing cardiovascular mortality (2a; A).	Partially modified
7. The administration of MTX (at ≤10 mg/week) can be continued in RA patients who undergo orthopaedic surgery as MTX does not affect the incidence of perioperative surgical complications whereas treatment discontinuation may increase the incidence of disease reactivation. MTX dosage reduction or treatment discontinuation may be considered for doses »10 mg per week in patients undergoing major surgery (1b; B).	Unchanged
8. MTX must be discontinued at least 3 months before conception (both in men and in women), it must be strictly forbidden during pregnancy and avoided during breastfeeding (4; C).	Unchanged
9. MTX must be considered the DMARD of first choice in RA patients both alone and in combination (with low dosage glucocorticoid and/or other DMARDs) (2b; B).	Partially modified
10. In patients that are non-responders to MTX at the maximum tolerated dosage, combination therapy can be started with DMARD or a biological agent (1b; B). Currently, addition of a biological agent should be preferred in patients with poor prognostic factors or documented radiological progression (1b; B).	Partially modified
11. Administration of MTX must be temporarily discontinued in patients who develop severe infections (any infection requiring hospitalization and/or intravenous antibiotics/antifungals and/or presenting with sepsis or is life-threatening, according to the NIH) (5; D).	Unchanged

Long-term safety of methotrexate monotherapy in patients with rheumatoid arthritis: a systematic literature research

Ann Rheum Dis 2009;**68**:1100–1104.

C Salliot,[1] D van der Heijde[2]

Table 1 Most common adverse events (AEs) attributed to methotrexate (MTX) and permanent discontinuation due to toxicity in patients with rheumatoid arthritis (RA): pooled results from 21 prospective cohorts (level of evidence 2b)[4–24]

	Patients	Mean dose of MTX (mg/week)	Mean duration of MTX (months)	Number of all AEs	Permanent discontinuation	Gastro-intestinal	Liver	Skin/hair	Central nervous system	Cytopenia	Lung
Number	3463	8.8	36.5	2524	315/3007*	1065	640	309	191	179	84 (15†)
Range	24–1155	4.6–18	27–132	22–475		10–257	0–122	0–111	0–58	0–27	0–28
%				72.9	10.5	30.8	18.5	8.9	5.5	5.2	2.4 (0.43)†

*Total number of patients in studies with data available concerning permanent discontinuation of MTX.
Gastrointestinal (GI): stomatitis, ulcer, abdominal pain, GI bleed, dyspepsia, nausea, vomiting, diarrhoea, weigh loss, appetite loss; liver toxicity: increase of aspartate aminotransferase and/or alanine aminotransferase upper limit of normal; skin/hair: ulcer, pruritis, skin rash, alopecia, skin itching, moon face, eczema; central nervous system: headache, depression, blurred vision, transient ischemic attack, stroke, vertigo, lethargy, malaise, fatigue; cytopenia: haemoglobin decreased >2 gm/dl or platelets <150 000/mm^3, white blood cells <3500/mm^3; lung: MTX pneumonitis (†), pulmonary dysfunction, cough and unspecified pulmonary adverse drug reactions.

Infections in patients with RA receiving long-term of MTX

Table 5w (online only) summarises six studies included in the analyses. Over 3 years of treatment, 8.3% of patients had serious infections, and a large majority of infections (79%) occurred during the first 2 years of treatment. According to the studies included, MTX does not seem to be associated with a higher risk for infections, in general, or serious infections, including herpes zoster and infectious complications, after total hip or knee replacements.

Association of methotrexate and tumour necrosis factor antagonists with risk of infectious outcomes including opportunistic infections in the CORRONA registry

Ann Rheum Dis. 2010 February ; 69(2): 380–386. doi:10.1136/ard.2008.089276.

Risk of infection stratified by current treatment of rheumatoid arthritis

LEF, SZS, HCQ

	MTX (n = 4206)	TNF antagonists (n = 1804)	MTX + TNF antagonists (n = 2855)	Other DMARDs (n = 1274)
Number of infections	1714	890	1514	447
Person years of follow-up	5141	2130	4031	1663
Unadjusted rate/100 person-years	33.3	41.8	37.6	26.9
Adjusted rate*/100 person-years	30.9 (29.2 to 32.7)	40.1 (37.0 to 43.4)	37.1 (34.9 to 39.3)	24.5 (21.8 to 27.5)

* Adjusted rates are per 100 person-years estimated with 95% CI in parentheses. Rates were adjusted for age, gender, race, education, duration of rheumatoid arthritis, modified Health Assessment Questionnaire, functional class, physician global, patient global, patient pain, swollen and tender joint counts, body mass index, disability status, liver disorder, lung disease, diabetes, ischaemic heart disease, alcohol use, smoking and prednisone use.

Patients treated with MTX (mean dose±sd 13,2±6,6 mg/wk) had a higher rate of infection than those treated with other non-biological DMARDs, but lower than TNFi and TNFi+MTX

Association of methotrexate and tumour necrosis factor antagonists with risk of infectious outcomes including opportunistic infections in the CORRONA registry

Ann Rheum Dis. 2010 February ; 69(2): 380–386. doi:10.1136/ard.2008.089276.

Adjusted risk of infection in patients with rheumatoid arthritis (RA)

	Adjusted IRR (95% CI)	p Value
Current RA treatments		
TNF antagonists	1.52 (1.30 to 1.78)	<0.001
MTX	1.30 (1.12 to 1.50)	<0.001
Prednisone	1.05 (0.97 to 1.15)	0.251
Other DMARDs	Reference	–
Clinical variables		
Smoking (ever)	1.52 (1.38 to 1.67)	<0.001
Chronic lung disease	1.31 (1.15 to 1.50)	<0.001
Diabetes mellitus	1.33 (1.15 to 1.52)	0.001
Tender joint count	1.01 (1.00 to 1.02)	0.009
ACR functional class	1.23 (1.12 to 1.34)	<0.001
Body mass index	1.01 (1.00 to 1.02)	0.002

MTX and TNF antagonists (prednisone>10 mg/d) were associated with increased risks of overall infections.

Prednisone and TNF antagonists (but not MTX) increased the risk of opportunistic infections.

Adjusted risk of opportunistic infection in patients with rheumatoid arthritis (RA)

	Adjusted IRR (95% CI)	p Value
Current RA treatments		
TNF antagonists	1.67 (0.95 to 2.94)	0.077
MTX	0.93 (0.54 to 1.60)	0.781
Prednisone	1.63 (1.20 to 2.21)	0.002
Other DMARDs	Reference	–
Clinical variables		
Smoking history (ever)	1.64 (1.17 to 2.29)	0.004
Physician global assessment	1.01 (1.00 to 1.02)	0.027
Diabetes mellitus	1.88 (1.19 to 2.97)	0.027

The interaction term for MTX and TNF antagonist combination therapy was not significant (p = 0.876).

Association of methotrexate and tumour necrosis factor antagonists with risk of infectious outcomes including opportunistic infections in the CORRONA registry

Ann Rheum Dis. 2010 February ; 69(2): 380–386. doi:10.1136/ard.2008.089276.

Rate of specific types of infection by treatment group

	MTX (n = 4206)	TNF antagonists (n = 1804)	MTX + TNF antagonists (n = 2855)	Other DMARDs (n = 1274)
Site of infection				
URI	660 (12.8)	303 (14.2)	522 (13.0)	148 (9.0)
Sinusitis	370 (7.2)	166 (7.8)	331 (8.2)	71 (4.3)
Urinary tract	157 (3.1)	81 (3.8)	111 (2.8)	32 (2.0)
Cellulitis	59 (1.3)	49 (2.3)	71 (1.8)	18 (1.1)
Non-pyogenic pneumonia	51 (1.0)	40 (1.9)	61 (1.5)	16 (1.0)
Pyogenic pneumonia	49 (1.0)	22 (1.0)	46 (1.1)	22 (1.3)
Bursitis	9 (0.2)	5 (0.2)	7 (0.2)	3 (0.2)
Infectious arthritis	9 (0.2)	5 (0.2)	5 (0.1)	2 (0.2)
Septicaemia	8 (0.2)	8 (0.4)	10 (0.3)	4 (0.2)
Other	342 (7.0)	211 (9.9)	350 (8.7)	131 (7.9)
Type of infectious organism				
Opportunistic	84 (1.6)	63 (3.0)	101 (2.5)	28 (1.7)
Non-opportunistic	1436 (27.9)	734 (34.5)	1245 (30.9)	378 (22.7)
All types of infection	1714 (33.3)	890 (41.8)	1514 (37.6)	447 (26.9)

***Opportunistic infections: varicella zoster, P. Carinii, active TBC*

The influence of systemic glucocorticoid therapy upon the risk of non-serious infection in older patients with rheumatoid arthritis: a nested case–control study

Ann Rheum Dis 2011;**70**:956–960.

Conclusion Glucocorticoid therapy is associated with an increased risk of NSI. The magnitude of risk increases with dose, and is higher than that seen with methotrexate, although residual confounding may exist.

Systematic review of 2008-2012 literature and update of recommendations for the use of methotrexate in rheumatic diseases, with a focus on rheumatoid arthritis

Reumatismo, 2013; 65 (5): 207-218

Table I - 2012 recommendations for the use of methotrexate in rheumatoid arthritis and in other rheumatic diseases.

Recommendation (level of evidence; strength of the recommendation)	Changes in comparison with the 2010 version
1. The work-up for RA patients who are MTX candidates should include the following tests: liver function tests; serum albumin; blood cell counts; serum creatinine; hepatitis B and C serology; chest X-ray. MTX treatment should not be introduced during pregnancy or in the presence of hepatic cirrhosis, severe renal function impairment; alcohol abuse; bone marrow depression; or active hepatitis B or C (4; C).	Partially modified
2. The therapeutic range of MTX is 7.5-25 mg/week. The optimal initial strategy is a starting dose of 12.5-15 mg/week (1b; B). In the absence of adverse events and/or subjective intolerance, in patients with early RA, close monitoring of therapeutic efficacy and therapeutic targets with rapid up-titration (5 mg/week a month) is more effective (1b; B). As MTX-related toxicity is dose-dependent, the maximum weekly dose of 25 mg (2b; B) should not be exceeded. It can be given initially by oral or parenteral route. Oral bioavailability of the drug varies, in particular at high doses (3b; B). Parenteral MTX can increase efficacy with a similar safety profile (1b; B). In patients refractory to oral MTX, switching to parenteral administration may be a useful strategy before introducing other therapies (2b; B).	Extensively modified
3. Weekly supplementation with folic acid (5-10 mg/week) should be administered to reduce the risk of adverse events/intolerance (1a; A). In most cases, it should be taken 24 hours after MTX. To date there is sufficient evidence that folic acid supplements do not nullify the clinical efficacy of MTX (1a; A).	Partially modified
4. Transaminases (AST, ALT) are the most useful laboratory parameters for monitoring liver toxicity due to MTX. CBC and renal function tests should also be performed in patients receiving MTX. These tests should be performed every 2 weeks for the first month, then every 4-12 weeks to check for hepatic, haematological or renal toxicity (1; A). Neither chest X-rays nor respiratory function tests allow prediction of the risk of MTX pneumonia (4; C).	Unchanged

11. Administration of MTX must be temporarily discontinued in patients who develop severe infections (any infection requiring hospitalization and/or intravenous antibiotics/antifungals and/or presenting with sepsis or is life-threatening, according to the NIH) (5; D).	Unchanged

ce over time, and hypertransaminasemia, especially during the first 5 years. The discontinuation rate due to hepatotoxicity is about 5%. Alcohol consumption should be avoided, because it appears to be an adjunctive risk factor for the development of hepatic fibrosis. MTX is not a significant risk factor for the development of infections, including severe infections. In patients with RA, MTX, and DMARDs in general, are associated with a greater incidence of tuberculosis reactivation (3b; B). MTX does not appear to be a risk factor for the development of neoplasms (3b; B). MTX can prolong the survival of RA patients by reducing cardiovascular mortality (2a; A).	
7. The administration of MTX (at ≤10 mg/week) can be continued in RA patients who undergo orthopaedic surgery as MTX does not affect the incidence of perioperative surgical complications whereas treatment discontinuation may increase the incidence of disease reactivation. MTX dosage reduction or treatment discontinuation may be considered for doses »10 mg per week in patients undergoing major surgery (1b; B).	Unchanged
8. MTX must be discontinued at least 3 months before conception (both in men and in women), it must be strictly forbidden during pregnancy and avoided during breastfeeding (4; C).	Unchanged
9. MTX must be considered the DMARD of first choice in RA patients both alone and in combination (with low dosage glucocorticoid and/or other DMARDs) (2b; B).	Partially modified
10. In patients that are non-responders to MTX at the maximum tolerated dosage, combination therapy can be started with DMARD or a biological agent (1b; B). Currently, addition of a biological agent should be preferred in patients with poor prognostic factors or documented radiological progression (1b; B).	Partially modified
11. Administration of MTX must be temporarily discontinued in patients who develop severe infections (any infection requiring hospitalization and/or intravenous antibiotics/antifungals and/or presenting with sepsis or is life-threatening, according to the NIH) (5; D).	Unchanged

Treatment for Rheumatoid Arthritis and the Risk of Hospitalization for Pneumonia

Associations With Prednisone, Disease-Modifying Antirheumatic Drugs, and Anti–Tumor Necrosis Factor Therapy

ARTHRITIS & RHEUMATISM
Vol. 54, No. 2, February 2006, pp 628–634

Table 1. Characteristics of the 16,788 RA patients*

Demographics	
Age, mean ± SD years	62.0 ± 13.3
Male sex	22.8
Ethnic origin	
White, not of Hispanic origin	89.7
Black, not of Hispanic origin	4.8
Asian or Pacific Islander	1.0
American Indian or Alaskan native	1.1
Hispanic	3.0
Other	0.5
Education, years	
0–8	2.6
>8–11	7.9
12	39.2
13–15	24.8
≥16	25.6
RA characteristics	
Disease duration, mean ± SD years	16.3 ± 11.3
Lifetime no. of DMARDs or biologic agents, mean ± SD	3.3 ± 2.1
HAQ (0–3), mean ± SD	1.1 ± 0.7
Semiannual direct medical costs, median dollars	7,024
Treatment	
Prednisone, all dosages	38.1
Daily dosage among prednisone users, mg	
≤5	66.9
>5–10	23.4
>10	9.8
Methotrexate	54.5
Hydroxychloroquine	17.7
Leflunomide	14.4
Sulfasalazine	5.7
Infliximab	36.9
Etanercept	12.8
Adalimumab	4.3
Comorbidity	
Smoking (ever)	54.2
Diabetes	10.1
Pulmonary disease (ever)	17.0
Myocardial infarction (ever)	8.2
Comorbidity index (0–11), mean ± SD	2.5 ± 2.0
Pneumonia-associated hospitalization	3.7
Pneumonia-associated death	0.4

AIM: to estimate the drug-related risk of hospitalization for pneumonia

Table 5. Multivariable predictors of pneumonia hospitalization*

Variable	Hazard ratio	*P*	95% CI
Treatment			
Prednisone	1.7	<0.001	1.5–2.0
Leflunomide	1.2	0.062	1.0–1.5
Infliximab	1.1	0.322	0.9–1.4
Adalimumab	1.1	0.747	0.6–1.9
Methotrexate	1.0	0.927	0.8–1.2
Hydroxychloroquine	0.9	0.481	0.7–1.2
Etanercept	0.8	0.107	0.6–1.1
Sulfasalazine	0.7	0.072	0.5–1.0
Demographics†			
Age (per 10 years)	1.3	<0.001	1.2–1.4
Sex (male = 1)	1.1	0.425	0.9–1.1
Smoking (ever)	1.1	0.161	1.0–1.3
Comorbidity			
Pulmonary disease (ever)	2.9	<0.001	2.3–3.4
Myocardial infarction (ever)	1.4	0.092	1.1–1.8
Diabetes	1.5	<0.001	1.2–1.9
RA characteristics			
HAQ (0–3)	1.5	<0.001	1.3–1.7
No. of previous DMARDs or biologic agents	1.1	0.020	1.0–1.1
Duration of RA (years)	1.0	0.687	1.0–1.0

Systematic review of 2008-2012 literature and update of recommendations for the use of methotrexate in rheumatic diseases, with a focus on rheumatoid arthritis

Reumatismo, 2013; 65 (5): 207-218

Table I - 2012 recommendations for the use of methotrexate in rheumatic diseases.

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2. The therapeutic range of MTX is 7.5-25 mg/week. The optimal initial strategy is a starting dose of 12.5-15 mg/week (1b; B). In the absence of adverse events and/or subjective intolerance, in patients with early RA, close monitoring of therapeutic efficacy and therapeutic targets with rapid up-titration (5 mg/week a month) is more effective (1b; B). As MTX-related toxicity is dose-dependent, the maximum weekly dose of 25 mg (2b; B) should not be exceeded. It can be given initially by oral or parenteral route. Oral bioavailability of the drug varies, in particular at high doses (3b; B). Parenteral MTX can increase efficacy with a similar safety profile (1b; B). In patients refractory to oral MTX, switching to parenteral administration may be a useful strategy before introducing other therapies (2b; B).	Extensively modified
3. Weekly supplementation with folic acid (5-10 mg/week) should be administered to reduce the risk of adverse events/intolerance (1a; A). In most cases, it should be taken 24 hours after MTX. To date there is sufficient evidence that folic acid supplements do not nullify the clinical efficacy of MTX (1a; A).	Partially modified
4. Transaminases (AST, ALT) are the most useful laboratory parameters for monitoring liver to-	Unchanged
7. The administration of MTX (at ≤10 mg/week) can be continued in RA patients who undergo orthopaedic surgery as MTX does not affect the incidence of perioperative surgical complications whereas treatment discontinuation may increase the incidence of disease reactivation. MTX dosage reduction or treatment discontinuation may be considered for doses ≥10 mg per week in patients undergoing major surgery (1b; B).	Unchanged
appears to be an adjunctive risk factor for the development of hepatic fibrosis. MTX is not a significant risk factor for the development of infections, including severe infections. In patients with RA, MTX, and DMARDs in general, are associated with a greater incidence of tuberculosis reactivation (3b; B). MTX does not appear to be a risk factor for the development of neoplasms (3b; B). MTX can prolong the survival of RA patients by reducing cardiovascular mortality (2a; A).	
7. The administration of MTX (at ≤10 mg/week) can be continued in RA patients who undergo orthopaedic surgery as MTX does not affect the incidence of perioperative surgical complications whereas treatment discontinuation may increase the incidence of disease reactivation. MTX dosage reduction or treatment discontinuation may be considered for doses ≥10 mg per week in patients undergoing major surgery (1b; B).	Unchanged
8. MTX must be discontinued at least 3 months before conception (both in men and in women), it must be strictly forbidden during pregnancy and avoided during breastfeeding (4; C).	Unchanged
9. MTX must be considered the DMARD of first choice in RA patients both alone and in combination (with low dosage glucocorticoid and/or other DMARDs) (2b; B).	Partially modified
10. In patients that are non-responders to MTX at the maximum tolerated dosage, combination therapy can be started with DMARD or a biological agent (1b; B). Currently, addition of a biological agent should be preferred in patients with poor prognostic factors or documented radiological progression (1b; B).	Partially modified
11. Administration of MTX must be temporarily discontinued in patients who develop severe infections (any infection requiring hospitalization and/or intravenous antibiotics/antifungals and/or presenting with sepsis or is life-threatening, according to the NIH) (5; D).	Unchanged

Methotrexate and early postoperative complications in patients with rheumatoid arthritis undergoing elective orthopaedic surgery

Ann Rheum Dis 2001;60:214–217

Table 2 Baseline features of subjects in groups A–C

	Group A	Group B	Group C
Number of subjects	88	72	228
Male	16	16	40
Mean age (years)	63	66	62
Range	(49–73)	(41–79)	(38–83)
Female	72	56	188
Mean age (years)	58	59	62
Range	(17–84)	(29–83)	(20–95)
RA disease duration			
Mean (years)	18	19	20
Range	(4–57)	(5–50)	(1–55)
Baseline articular index			
Mean	14	16.5	15
Range	0–49	0–55	0–61
HAQ*			
Mean	1.9	1.9	1.8
Range	0.4–3	0–3	0.1–3
Methotrexate			
Dose (mg)			
Median	10	7.5	
Range	2.5–25	2.5–20	
Duration			
Median	3 yr	3 yr	
Range	6 wk–10 yr	6 wk–7.5 yr	

Group A: continuing MTX

Group B: stop MTX
(2 wks before up to 2 wks after surgery)

Group C: not receiving MTX

Outcome 1: early surgical complication (infection/wound dehiscence)

Outcome 2: disease flare at 6 weeks

Table 5 Incidence of infection/complications as defined in "Methods". Results are shown as No (%)

Group	Rubor	Discharge	Systemic	Dehiscence	Complication	Total
A (88)	0 (0)	1 (1)	0 (0)	1 (1)	0 (0)	2 (2)
B (72)	4 (6)	4 (6)	0 (0)	1 (1)	2 (3)	11 (15)
C (228)	9 (4)	10 (4)	2 (1)	2 (1)	1 (0.4)	24 (10.5)

Results:

1) surgical complication/infection **in A was less frequent** than in B and C groups.

2) At 6 wks **no flares in A**, 8% and 3% in B and C, respectively.

Rheumatoid arthritis: Perioperative management of biologics and DMARDs

Seminars in Arthritis and Rheumatism 44 (2015) 627–632

Table
Perioperative medication management recommendations for drugs in use for the therapy of rheumatoid arthritis.

Medication	Pharmacologic $t_{1/2}$	Dosing interval	Pre-operative Withhold	Continue	Special considerations
Methotrexate	3–15 h, dose dependent	Weekly	None	Yes	Monitor renal function
Leflunomide	14 Days	Daily	1 Week	No	
Hydroxychloroquine	32–50 Days	Daily	None	Yes	Monitor renal function
Azathioprine	5 h	Daily	None	Yes	Monitor renal function
sulfasalazine	7–15 h dependent on acetylation rate	Daily	None	Yes	Monitor renal function
TNFα inhibitors					
Etanercept	3–5.5 Days	Weekly	2 Weeks	No	
Golimumab	7–20 Days	Monthly	6 Weeks	No	
Adalimumab	10–20 Days	2 Weeks	3 Weeks	No	
Infliximab	7–12 Days	4–8 Weeks	6 Weeks	No	
Certolizumab pegol	14 Days	4 Weeks	6 Weeks	No	
Tocilizumab	SC: 5–13 days IV: 11–13 days	SC: 1–2 weeks IV: every 4 weeks	SC 3 weeks IV 4 weeks	No	Signs of inflammation like temperature and CRP may be masked
Rituximab	18–32 Days	16–24 weeks	None	Yes	Infection risk not related to interval between dose and surgery
Abatacept	13–14 Days	SC: 1 week IV: 4 weeks	SC 2 weeks IV 4 weeks	No	

Cosider global patient's risk for specific type of surgery!

MTX AND RELEVANT VIRAL INFECTIONS

- HZV
- EBV

RA AND HZV

- The incidence of herpes zoster in health population increases from about 3/1000 person-years before 30 years of age to 8/1000 person-years after 60 years of age.

- Of the many risk factors associated with herpes zoster, the most important are older age and immunodeficiency (mainly affecting cellular immune system).

- The risk of herpes zoster is elevated in patients with chronic autoimmune or inflammatory diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and chronic inflammatory bowel disease (IBD).

- The excess risk may stem not only from the disease, but also from the drugs used to treat it.

RA AND HZV RE-ACTIVATION

Table 1
Immunomodulating drugs and herpes zoster.

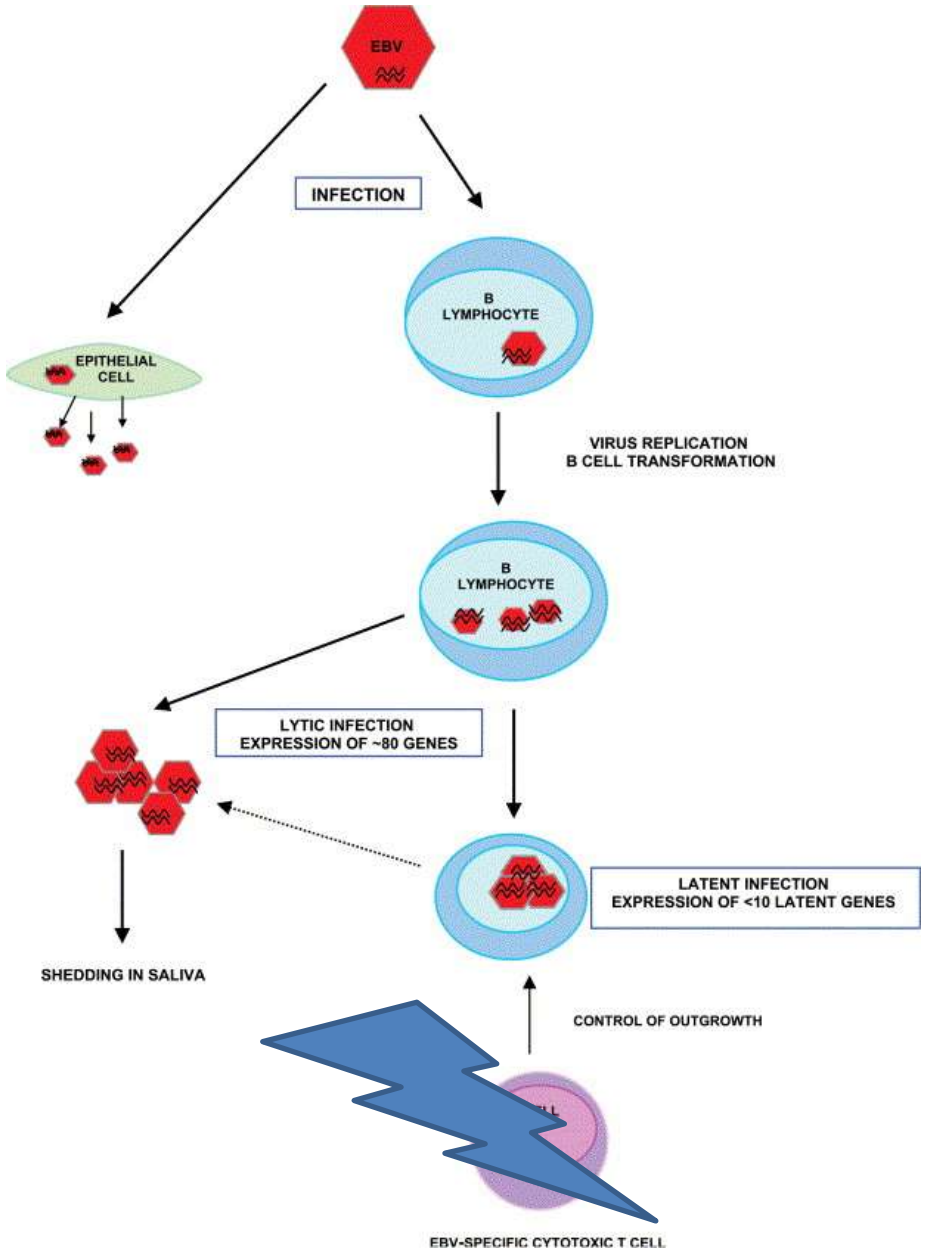
Authors	Populations	Treatments	Sample size	Design	Results	95%CI
Wolfe et al., 2006 [17]	RA	TNFαA (I, A, E)	6167	Prospective	I: HR = 1.2	(1.0–1.5)
		DMARD		Multivariate	A: HR = 0.4	(0.2–0.9)
				analysis	E: HR = 0.9	(0.7–1.2)
					MTX: HR = 1.0	(0.8–1.3)
					Leflu: HR = 1.4	(1.1–1.8)
					Aza: HR = 2.0	(1.2–3.3)
					GC: HR = 1.5	(1.2–1.8)
Smitten et al., 2007 [13]	RA	Biologics (I, E, AN)	32	Case-control	aOR = 1.54	(1.04–2.29)
		or DMARD	306		aOR = 1.37	(1.18–1.59)
		or GC	166		aOR = 2.51	(2.05–3.06)
		vs. no GC or DMARDs	877		Reference	
Strangfeld et al., 2009 [19]	RA	TNFαA (I, A, E)	3266	Prospective	aHR = 1.63	(0.97–2.74)
		vs. DMARD	1774		Reference	
McDonald et al., 2009 [22]	RA	TNFαA (I, A, E)	3661	Retrospective	I: HR = 1.32	(0.85–2.03)
					A: HR = 0.53	(0.31–0.91)
					E: HR = 0.62	(0.40–0.95)
		DMARD			MTX: HR = 1.13	(0.75–1.70)
					Leflu: HR = 0.95	(0.58–1.56)
					Aza: HR = 1.06	(0.46–2.40)
		GC			GC: HR = 1.08	(0.69–1.70)
Galloway et al., 2013 [20]	RA	TNFαA (I, A, E)	1,1881	Prospective	aHR = 1.7	(1.1–2.7)
		vs. DMARD	3673		Reference	
Veetil et al., 2013 [14]	RA	TNFαA	137	Retrospective	HR = 1.24	(0.56–2.74)
		DMARD			MTX: HR = 1.34	(0.85–2.10)
		GC			GC: HR = 1.72	(1.03–2.87)
Winthrop et al., 2013 [15]	RA, CIBD, Pso, PsA, SpA	TNFαA	33,324	Retrospective	aHR = 1.09	(0.88–1.36)
		(initiation of I, A, E)				
		vs. DMARD	25,742		Reference	
Che et al., 2014 [21]	RA	TNFαA	Equivalent to	Metaanalysis	Pooled risk ratio = 1.61	(1.16–2.23)
		vs. DMARD	163,077		Reference	
			patient-years			
Pappas et al., 2015 [7]	RA	TNFαA	4321	Retrospective	Reference	
	(CORONA registry)	vs. other biologics (rituximab, abatacept, and tocilizumab)	2170			
					aHR = 0.834	(0.51–1.37)
		vs. DMARD	1505		aHR = 1.359	(0.82–2.25)

Rheumatoid arthritis, methotrexate, and lymphoma: risk substitution, or cat and mouse with Epstein-Barr virus?

J Rheumatol 2001;28;2573-2575

MTX

- Increased risk of lymphoma in RA, due to persistent immune stimulation.
- Oncogenic role of EBV.
- Patients with RA have a defect in EBV directed suppressor T cell function.



MTX AND LYMPHOPROLIFERATIVE DISORDERS

- The WHO classification of 2001 recognized as **related to MTX-associated immunosuppression** a clinical setting of LPDs.

- In particular, ‘‘MTX-associated LPDs’’ included changes ranging from lymphoid proliferation to lymphoma, **often EBV-related**, and possibly regressing with MTX discontinuation.

- The underlying autoimmune disease was **very often RA**, but in a minority of cases it was DM or psoriasis.

- Also the **use of other immunosuppressants,** such as CyA, AZA, and CTX may lead to LPD by altering immune functions

Epstein-Barr virus, arthritis, and the development of lymphoma in arthritis patients

Margaret F.C. Callan

Curr Opin Rheumatol 16:399–405 © 2004

Table 3. Classification and Epstein-Barr virus status of lymphomas in patients with rheumatoid arthritis

Lymphoma type (WHO classification)	N = 25 Mariette *et al.* [37]	N = 35 Baecklund *et al.* [44•]	EBV+ lymphomas/ lymphomas examined for EBV N = 25 Mariette *et al.* [37]	EBV+ lymphomas/ lymphomas examined for EBV N = 30 Baecklund *et al.* [44•]
Hodgkin lymphoma	7	2	5/7	0/1
Nodular sclerosis	2	2	1/2	0/1
Mixed cellularity	4	–	3/4	–
Unclassified	1	–	1/1	–
Non-Hodgkin lymphoma	18	33	3/18	5/29
Diffuse large B cell lymphoma	12	22	2/12	4/22
Marginal zone B cell lymphoma	3	–	0/3	–
Lymphocytic B cell lymphoma	1	–	0/1	–
Follicular lymphoma	–	2	–	0/2
Lymphoplasmacytic lymphoma	–	1	–	1/1
Pleomorphic small and medium T cell lymphoma	1	–	0/1	–
Large granular lymphocyte T cell lymphoma	1	–	1/1	–
Hepatosplenic T cell lymphoma	–	1	–	–
Burkitt lymphoma	–	1	–	0/1
Unspecified high-grade B-cell lymphoma	–	2	–	0/1
Other unspecified NHL	–	4	–	0/2

EBV+ in 63%

EBV+ 18%

Globally, EBV+ in LDs among 24% RA vs 33% in general population

Determine the EBV status of the lymphoma and **halt MTX therapy in EBV positive patients**.

Consider therapy only in patients whose lymphoma progresses in spite of stopping MTX.

EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases

S van Assen,[1] N Agmon-Levin,[2] O Elkayam,[3,4] R Cervera,[5] M F Doran,[6] M Dougados,[7] P Emery,[8,9] P Geborek,[10] J P A Ioannidis,[11–14] D R W Jayne,[15] C G M Kallenberg,[16] U Müller-Ladner,[17] Y Shoenfeld,[2,4] L Stojanovich,[18] G Valesini,[19] N M Wulffraat,[20] M Bijl[12]

Ann Rheum Dis 2011;**70**:414–422.

Recommendation	Category of evidence			Strength of recommendation	Mean (SD) level of agreement by Delphi voting (VAS)
	Increased incidence of VP infection	Efficacy of vaccination	Harms of vaccination		
The vaccination status should be assessed in the initial investigation of patients with AIIRD	–			D	9.50 (0.97)
Vaccination in patients with AIIRD should ideally be administered during stable disease	–			D	8.88 (1.26)
Live attenuated vaccines should be avoided whenever possible in immunosuppressed patients with AIIRD	IV			D	9.25 (1.13)
Vaccination in patients with AIIRD can be administered during the use of DMARDs and TNFα blocking agents, but should ideally be administered before starting B cell-depleting biological therapy	II			B	9.13 (1.02)
Influenza vaccination should be strongly considered for patients with AIIRD	III	Ib	Ib	B–C	9.00 (1.10)
23-valent polysaccharide pneumococcal vaccination should be strongly considered for patients with AIIRD	III	Ib	Ib	B–C	8.19 (1.38)
Patients with AIIRD should receive tetanus toxoid vaccination in accordance with recommendations for the general population. In case of major and/or contaminated wounds in patients who received rituximab within the last 24 weeks, passive immunisation with tetanus immunoglobulin should be administered	–	II	II	B–D	9.19 (1.11)
Herpes zoster vaccination may be considered in patients with AIIRD	III	–	IV	C–D	8.00 (1.59)
HPV vaccination should be considered in selected patients with AIIRD	III	–	–	C–D	8.44 (1.41)
In hyposplenic/asplenic patients with AIIRD, influenza, pneumococcal, *Haemophilus influenzae* b and meningococcal C vaccinations are recommended	IV			D	9.50 (0.82)
Hepatitis A and/or B vaccination is only recommended in patients with AIIRD at risk	–	II*	III*	D	9.13 (0.89)
Patients with AIIRD who plan to travel are recommended to receive their vaccinations according to general rules, except for live attenuated vaccines which should be avoided whenever possible in immunosuppressed patients with AIIRD	–			D	9.25 (1.24)
BCG vaccination is not recommended in patients with AIIRD	III	–	–	D	9.38 (1.09)

2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis

ARTHRITIS & RHEUMATOLOGY
Vol. 68, No. 1, January 2016, pp 1–26

	Killed vaccines			Recombinant vaccine	Live attenuated vaccine
	Pneumococcal[1]	Influenza (intramuscular)	Hepatitis B[2]	Human Papilloma	Herpes Zoster[3]
Before initiating therapy					
DMARD monotherapy	✓	✓	✓	✓	✓
Combination DMARDs	✓	✓	✓	✓	✓
TNFi biologics	✓	✓	✓	✓	✓ *(PICO J.1)*[5]
Non-TNF biologics	✓	✓	✓	✓	✓ *(PICO J.1)*[5]
While already taking therapy					
DMARD monotherapy	✓	✓	✓	✓	✓
Combination DMARDs	✓	✓	✓	✓	✓
TNFi biologics	✓	✓	✓ **(PICO J.4, J.5)**[6]	✓	*Not recommended (PICO J.2, J.3)*[7]
Non-TNF biologics[4]	✓	✓	✓ **(PICO J.4, J.5)**[6]	✓	*Not recommended (PICO J.2, J.3)*[7]

Safety and efficacy of vaccination against hepatitis B in patients with rheumatoid arthritis

O Elkayam, M Yaron, D Caspi

Ann Rheum Dis 2002;**61**:623–625

Case-control study:

- Case group: 22 RA patients vaccinated with 3 im doses (T 0, 1, 6 months) of recombinant HBV vaccine (ENGERIX).

- Control group: 22 RA patients not receiving the vaccine.

Table 1 Demographic and clinical characteristics of patients with RA

	Study group	Control group
Women/men (%)	17 (77)/5 (23)	18 (82)/4 (18)
Age, mean (SD)	52.9 (15.4)	51 (14.3)
Mean (SD) disease duration in year (range)	11.2 (9.4)	7.6 (7)
Number of patients RF positive (%)	16 (73)	16 (73)

Table 2 Drugs used by patients and controls at vacination and after seven months. Results are shown as No (%) unless indicated otherwise

	Study group		Controls	
Drug	Week 0	After 7 months	Week 0	After 7 months
NSAIDs	10 (45)	9 (41)	12 (55)	10 (45)
Prednisone	10 (45)	10 (45)	13 (59)	12 (55)
Mean (SD) dose (mg/day)	7.5 (3.3)	7.4 (3.2)	7.4 (3.2)	7.3 (3.3)
Hydroxychloroquine	4 (18)	3 (14)	3 (14)	3 (14)
Methotrexate	17 (77)	15 (68)	10 (45)	13 (59)
Mean (SD) dose (mg/week)	11.6 (2.6)	12.3 (2.4)	14.6	14.5
Azathioprine	2 (9)	1 (5)	2 (9)	2 (9)
IM gold	5 (23)	5 (23)	2 (9)	1 (5)
Sulfasalazine	2 (9)	1 (5)	2 (9)	1 (5)

No bDMARDs!

Safety and efficacy of vaccination against hepatitis B in patients with rheumatoid arthritis

O Elkayam, M Yaron, D Caspi

Ann Rheum Dis 2002;61:623–625

RESULTS:

- Clinical disease activity: not affected

- Lab disease activity: not affected

- Humoral response to vaccine: 68% responders (HbsAb>10 UI/mL at 6 months*)

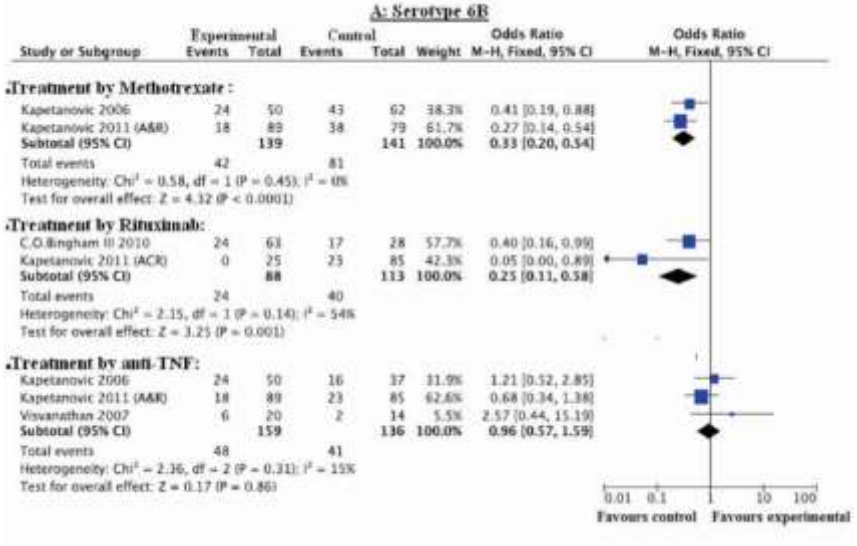
- Safety: no concerns related to vaccination

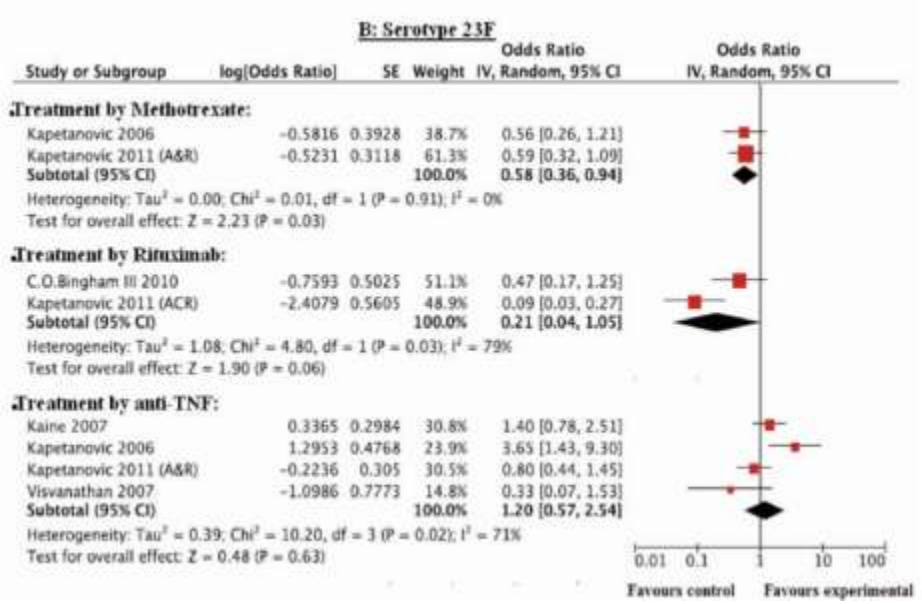
- Predictors of no response: older age

**Humoral response to hepatitis B vaccination is expected to be >85% in young healthy adults*

Effect of Methotrexate, Anti–Tumor Necrosis Factor α, and Rituximab on the Immune Response to Influenza and Pneumococcal Vaccines in Patients With Rheumatoid Arthritis: A Systematic Review and Meta-Analysis

Arthritis Care & Research
Vol. 66, No. 7, July 2014, pp 1016–1026





MTX might decreases humoral response to pneumococcal vaccination (6B and 23F serotypes).

Effect of Methotrexate, Anti–Tumor Necrosis Factor α, and Rituximab on the Immune Response to Influenza and Pneumococcal Vaccines in Patients With Rheumatoid Arthritis: A Systematic Review and Meta-Analysis

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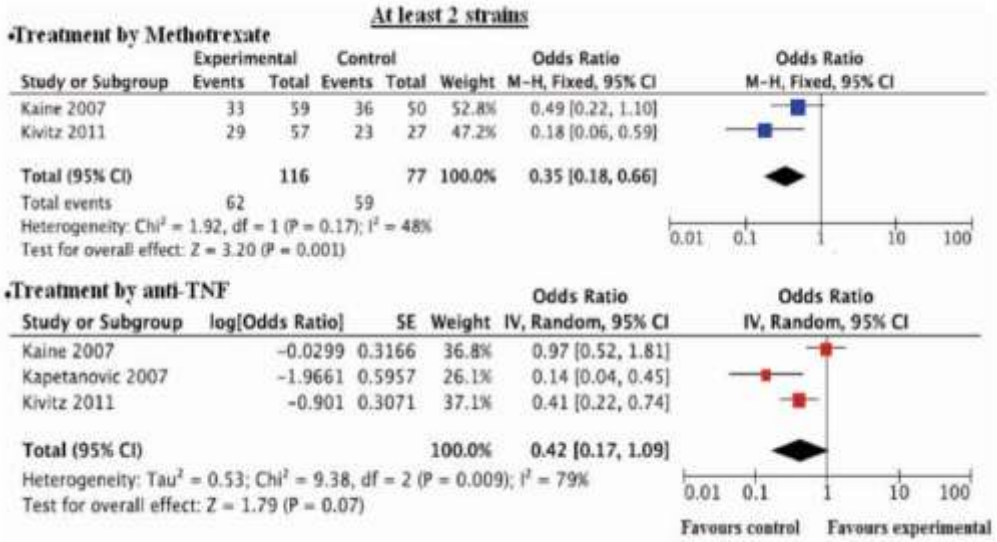

MTX might impair response to influenza vaccination.

HZV VACCINATION AND RA

- As a live attenuated vaccine is contraindicated in patients with immunodeficiencies and taking immunosuppressants (including high dose CS*).

- Along with expert opinion, vaccination may be considered 14 days before immunosuppressants introduction or 1 month after their discontinuation.

*** 20 mg/d prednisone-equivalent for more than 2 weeks*

Association Between Vaccination for Herpes Zoster and Risk of Herpes Zoster Infection Among Older Patients With Selected Immune-Mediated Diseases

JAMA. 2012;308(1):43-49

Table 1. Distribution of Person-Years of Follow-up by Herpes Zoster Vaccination Status and Patient Characteristics Among Medicare Beneficiaries

Patient Characteristics	Person-Years, No.	Vaccination Status, %	
		Vaccinated (10 868 Person-Years)	Unvaccinated (854 609 Person-Years)
Age, y			
60-69	292 723	27.7	33.9
70-79	371 315	51.0	42.8
≥80	201 439	21.3	23.3
Sex			
Women	637 704	72.3	73.7
Men	227 773	27.7	26.3
Race			
Black	65 102	1.4	7.6
White	749 442	93.9	86.5
Other	50 933	4.7	5.9
Type of immune-mediated disease			
Rheumatoid arthritis	557 751	52.2	64.6
Psoriatic arthritis	21 680	2.9	2.5
Psoriasis	161 816	26.3	18.6
Inflammatory bowel diseases	117 263	17.4	13.5
Ankylosing spondylitis	6967	1.2	0.8

TARGET POPULATION:

463.541 patients
RA, PSA, Ps, AS, IBD
Older than 60 years

AIM:

Association vaccination/infection (safety concern-window 42 days)

4% of patients received HZ vaccine: mostly white old women with RA.

633 exposed to biologics at the time of vaccination or within 42 days.

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Association Between Vaccination for Herpes Zoster and Risk of Herpes Zoster Infection Among Older Patients With Selected Immune-Mediated Diseases

JAMA. 2012;308(1):43-49

Table 2. Herpes Zoster Incidence Rate While Unvaccinated by Medication Exposure

Medications, Mutually Exclusive Groups[a]	Without Oral Glucocorticoids		With Oral Glucocorticoids		
	HZ Cases, No.	HZ IR (95% CI)	HZ Cases, No.	HZ IR (95% CI)	IR Ratio (95% CI)
Any anti-TNF[b]	741	12.6 (11.8-13.6)	627	23.0 (21.3-24.9)	1.8 (1.6-2.0)
Adalimumab	100	12.1 (9.9-14.7)	96	21.7 (17.7-26.5)	1.8 (1.4-2.4)
Etanercept	151	11.5 (9.8-13.5)	122	21.5 (18.0-25.6)	1.9 (1.5-2.4)
Infliximab	490	13.2 (12.1-14.4)	406	23.8 (21.6-26.2)	1.8 (1.6-2.1)
Other anti-TNFs	<11	15.5 (7.8-31.1)	<11	31.3 (14.1-69.6)	2.0 (0.7-5.8)
Any non-TNF biologics[b]	107	14.0 (11.6-16.9)	119	18.7 (15.6-22.3)	1.3 (1.0-1.7)
Abatacept	53	12.1 (9.2-15.8)	62	17.1 (13.3-22.0)	1.4 (1.0-2.0)
Rituximab	46	17.1 (12.6-22.4)	52	20.2 (15.4-26.5)	1.2 (0.8-1.8)
Nonbiologic DMARDs without biologics	1184	10.8 (10.2-11.4)	1179	18.6 (17.6-19.7)	1.7 (1.6-1.8)
Methotrexate[c]	744	10.2 (9.5-10.9)	766	18.3 (17.0-19.6)	1.8 (1.6-2.0)
All other non–methotrexate DMARDs[d]	440	11.9 (10.8-13.1)	413	19.2 (17.5-21.2)	1.6 (1.4-1.8)

Among unvaccinated persons, the HZ incidence rate differed by exposure to medications (lower for MTX).

Exposure to oral glucocorticoids (Y/N) was associated with a 1.2-2-fold greater risk of HZ.

The increase was significant for most medication groups.

Association Between Vaccination for Herpes Zoster and Risk of Herpes Zoster Infection Among Older Patients With Selected Immune-Mediated Diseases

JAMA. 2012;308(1):43-49

HZ <u>within 42 days</u> from vaccination:

- 0/633 patients exposed to biologics (551 to anti-TNF)

Table 3. Herpes Zoster Incidence Rate for Unvaccinated and After Vaccination[a]

	>42 Days Since Vaccination		Unvaccinated	
	HZ Cases, No.	HZ IR	HZ Cases, No.	HZ IR
Overall	138	6.7 (5.7-7.9)	9960	11.6 (11.4-11.9)
Medications, mutually exclusive groups[b]				
Biologics, regardless of concomitant DMARDs or oral glucocorticoids	14	8.5 (5.1-14.4)	1592	16.0 (15.2-16.8)
Anti-TNF therapies	12	8.5 (4.8-15.0)	1368	15.9 (15.1-16.8)
DMARDs, without biologics but regardless of oral glucocorticoids	25	7.0 (4.7-10.3)	2363	13.6 (13.1-14.2)
Oral glucocorticoids alone	21	10.3 (6.7-15.8)	2080	17.2 (16.5-17.9)

HZ <u>after 42 days</u> (over 2 years) from vaccination:

- Globally 138 cases among vaccinated
- Lower rates in vaccinated vs unvaccinated for all medication exposure (IRR= 0,58, p<0,001)

Association Between Vaccination for Herpes Zoster and Risk of Herpes Zoster Infection Among Older Patients With Selected Immune-Mediated Diseases

JAMA. 2012;308(1):43-49

• Zoster vaccine is **under-used** in patients with autoimmune diseases despite their increased risk of developing HZ.

• HZ vaccine **may not be** associated with increased risk of HZ shortly after vaccination (**re-activation of vaccine-virus**), even in patients treated with biologics (mainly anti-TNF).

• HZ vaccination is possibly associated with a **significantly reduced longer-term HZ risk** in patients with immune-mediated disease.

• Alternatives are coming!

CONCLUSIONS

- **Screening setting**

- Tests for complete HBV and HCV serology should be performed before MTX initiation.

- Close monitoring of LFT should be mandatory, even in case of MTX discontinuation.

- TBC tests could be considered case by case.

CONCLUSIONS

- **Follow up**

- MTX alone seems not to significantly increase the risk of severe and opportunistic infections (including HZ reactivation), which are substantially affected by steroids.

- In case of severe infections, MTX should be stopped.

- In peri-operative period, MTX could be continued (patient's and surgery's risk-to-benefit evaluation).

CONCLUSIONS

- **Primary prevention**

- HZV vaccination might be safe and efficacious.

- MTX might rarely be associated with lymphoproliferative disorders, often EBV-related: MTX discontinuation might result in resolution.

- Pneumococcal and flu vaccination could be adopted as preventive measure to reduce/avoid the risk of infection:

  MTX could hamper efficacious defense response.