2022 EULAR Recommendations for screening and prophylaxis of chronic and opportunistic infections in adults with autoimmune inflammatory rheumatic diseases

George Fragoulis

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EULAR QoC committee Chair

Conflicts of interest

- Speaker fees/consultancies: Abbvie, Aenorasis, Amgen, Faran, Genesis, Janssen, Lilly, Novartis, Pfizer, UCB

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Sizheng Steven Zhao,[7] Delphine Sophie Courvoisier [8] Laurent Arnaud [9]
Fabiola Atzeni,[10] Georg MN Behrens,[11] Johannes WJ Bijlsma,[12] Peter Böhm,[13]
Costas A Constantinou,[14] Silvia Garcia-Diaz,[15] Meliha Crnkic Kapetanovic,[16]
Kim Lauper [7,17] Mariana Luís [18] Jacques Morel,[19] György Nagy [20,21]
Eva Poleverino,[22] Jef van Rompay,[23] Marco Sebastiani [24] Anja Strangfeld [25]
Annette de Thurah [26,27] James Galloway [3,4] Kimme L Hyrich [7,28]

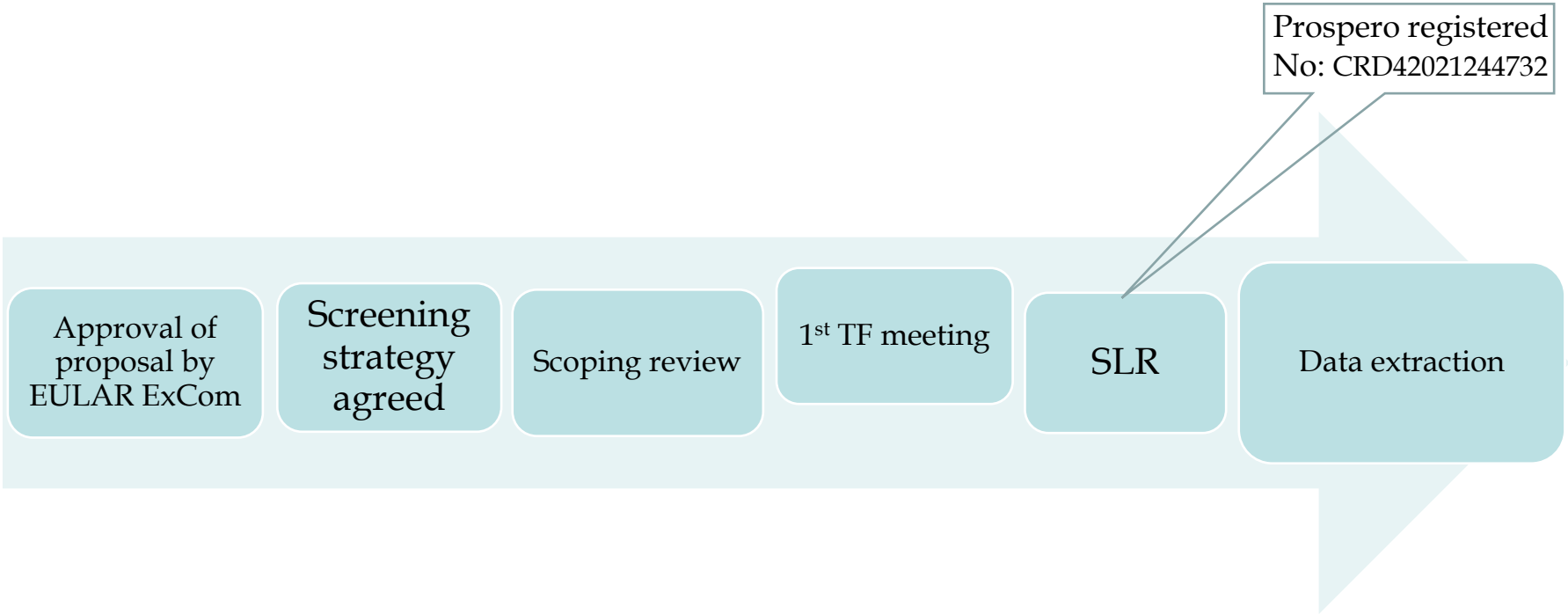
Tuberculosis in inflammatory arthritis: are biological therapies the only culprits?

*George E Fragoulis†, Costas A Constantinou†, Nikolaos V Sipsas, Kimme L Hyrich, Elena Nikiphorou

Methodology

2014 EULAR Standardized Operating Procedures

van der Heijde *et al* Ann Rheum Dis 2016,75:3-15



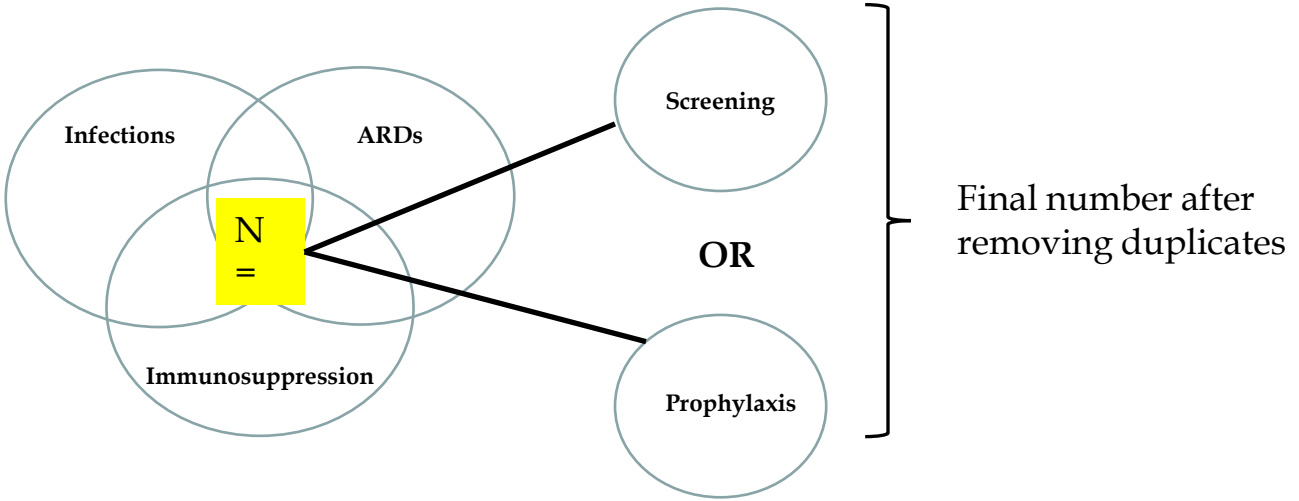
Just before the 1st meeting

- Review and discussion on the pathogens that would be included in the subsequent SLR
  - findings of the scoping review
  - as well as expert opinion of TF members

- Formulation of the research Questions
  - RQ1) Which opportunistic and chronic infections in people with ARDs **can** and **should** we screen for?
  - RQ2) What screening and prophylaxis can we use and does it work?

Screening strategy

- 1st & 2nd & 3rd & (4th OR 5th)
  - 2nd domain: ARD as a major topic



SLR

Screening strategy

1st domain (**Infections**):

Tuberculosis, hepatitis B, hepatitis C, Human immunodeficiency virus, herpes zoster, varicella zoster, HZV, VZV, pneumocystis carinii, pneumocytis jiroveci, PCP, human papilloma virus, HPV, opportunistic infections, chronic infections, Leishmaniasis, strongyloidiasis, strongyloides, histoplasmosis, histoplpasma, toxoplasmosis, toxoplasma, trypanosoma cruzi, trypanosomiasis, CMV, Cytomegalovirus, Epstein Barr virus, EBV non-tuberculous mycobacteria, west nile virus, cryptosporidiosis, nocardiosis, nocardia, actynomycosis, actinomyces, Microsporidiosis, microsporidia, Bartonellosis, bartonella, campylobacter, legionellosis, leptospirosis, leptospira, listeriosis, listeria, salmonellosis, salmonella, shigellosis, shigella, syphillis, vibrio vulnificus, aspergillosis, blastomycosis, Cocciciomycosis, candidiasis, candida, molds, Sporothrix shenkii, leprosy, BK virus, Isosporiasis, isospora, bacteria, viruses, fungi, parasites, mycoses, hepatitis E, chicken pox, shingles, Chagas, legionella, treponema, aspergillus, mycobacterium, mycobacteria, JC virus, HHV8, Wuchereria bancrofti (filariasis), Loa Loa, Onchocerca, Enterobius vermicularis (enterobiasis), ascaris (ascariasis), strongyloides (storngyloidosis), Schistosoma (Schistosomiasis), Fasciola (fascioliasis), paragonimus (paragonimiasis), Cestodes: taenia (taeniasis), echinococcus (echinococcosis), (entamoeba, endamoeba, gardia lamblia (lambliasis), cryptosporidium, leishmania, toxoplasma gondii (toxoplasmsosis), toxocara (toxocariasis), trichinella spiralis (trichinellosis), isospora (Cystoisopora belli), cyclospora (Cyclospora cayetanensis), microsporidia, Blastocystis hominis, Trichuris trichiura, hookwarms (ancylostomiasis)

SLR

Screening strategy

2nd domain (**ARDs**):

- Rheumatology, Autoimmune rheumatic diseases, rheumatic diseases, Rheumatic musculoskeletal disease, Systemic lupus erythematosus, anti-phospholipid syndrome, Sjogren's syndrome, rheumatoid arthritis, psoriatic arthritis, seronegative spondyloarthropathy, ankylosing spondylitis, Behcet's disease, ANCA-vasculitis, cryoglobulinaemic vasculitis, rheumatica polymyalgia, Takayasu arteritis, giant-cell arteritis, polyarteritis nodosa, systemic sclerosis, inflammatory myopathy, dermatomyositis, IgG4-related disease, relapsing polychondritis, autoinflammatory diseases (familial Mediterranean fever, still's disease), cutaneous limited sclerosis, limited sclerosis, cutaneous sclerosis, limited scleroderma, scleroderma

SLR

Screening strategy

3rd domain (**Immunosuppression**):

- steroids, corticosteroids, glucocorticoids, glucocorticosteroids, prednisolone, prednisone, methylprednisolone, cortisone, methotrexate, leflunomide, sulfasalazine, cyclophosphamide, mycophenolate, tofacitinib, baricitinib, JAK-inhibitors, disease modifying anti-rheumatic drugs (DMARDs), biologic DMARDs, infliximab, etanercept, adalimumab, golimumab, certolizumab, abatacept, tocilizumab, sarilumab, ustekinumab, secukinumab, ixekizumab, canakinumab, anakinra, rilonacept, rituximab, belimumab, guselkumab

SLR

Screening strategy

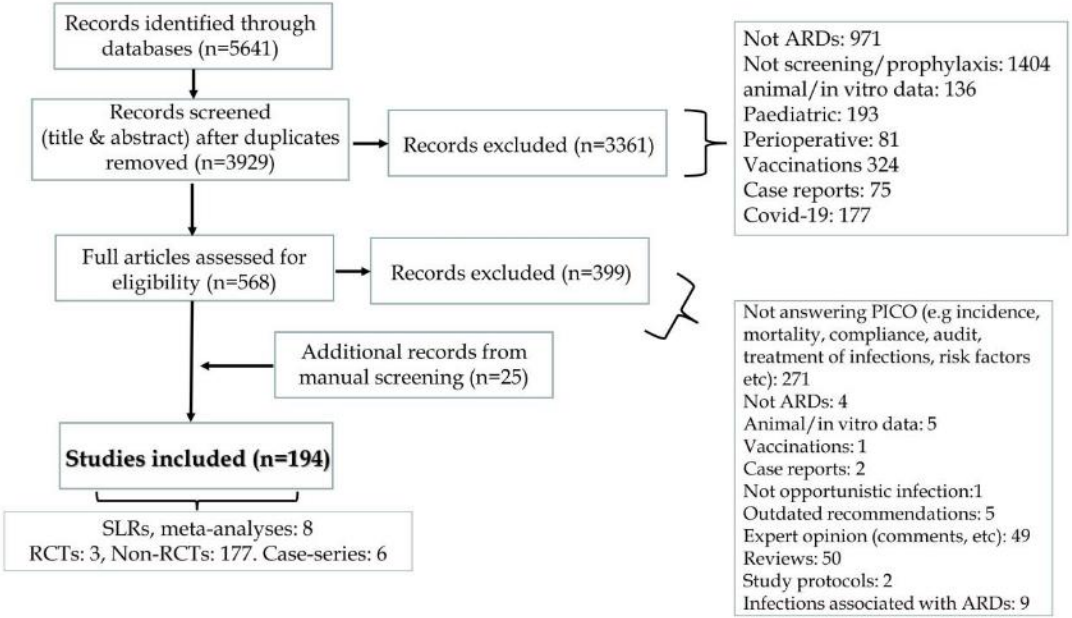
4th domain (**Screening**):

- screening, Mantoux, tuberculin skin test, quantiferon, IGRA, elispot, T Spot, chest-X-ray, HBsAg, anti-HBc, anti-HBV, HBV, HBV-DNA, anti-HCV, HCV, anti-HIV, HIV, varicella serology, anti-VZV, VZV, varicella zoster virus, chicken pox, shingles

5th domain: (**Prophylaxis**)

- prophylaxis, chemophrophylaxis, trimethoprim/sulfamethoxazole, septrim, co-trimoxazole, isoniazid, rifampin, rifampicin, rifapentine, Itraconazole, fluconazole, Azithromycin, Clarithromycin, Varicella-zoster immune globulin, entecavir, tenofovir, lamivudine, acyclovir, valaciclovir, pentamidine, valganciclovir

SLR
Flowchart



- 20% of the data extracted were validated by a second assessor.
- **Agreement ~ 98 %**

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- **Agreement ~ 97 %**

- **SLR presentation**
- **Drafting of recommendations**
  - Level of Evidence (Oxford Centre for Evidence-based medicine)
  - Grade of Recommendation (Oxford Centre for Evidence-based medicine)
- **Level of agreement** determined through anonymous online voting

Level of Evidence

Oxford Centre for Evidence-Based Medicine

Level	Therapy/prevention/aetiology/harm
1a	Systematic review with homogeneity of RCTs
1b	Individual RCT (with narrow confidence interval)
1c	All or none
2a	Systematic review with homogeneity of cohort studies
2b	Individual cohort study (including low quality RCT; e.g. <80% follow-up)
2c	'Outcomes' research; ecological studies
3a	Systematic review (with homogeneity) of case-control studies
3b	Individual case-control study
4	Case-series (and poor quality cohort and case-control studies)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

Grades of recommendation	
A	consistent level 1 studies
B	consistent level 2 or 3 studies or extrapolations from level 1 studies
C	level 4 studies or extrapolations from level 2 or 3 studies
D	level 5 evidence or troublingly inconsistent or inconclusive studies of any level

SLR

RMD Open
Rheumatic & Musculoskeletal Diseases

REVIEW

Systematic literature review informing the 2022 EULAR recommendations for screening and prophylaxis of chronic and opportunistic infections in adults with autoimmune inflammatory rheumatic diseases

George E Fragoulis [1,2] Mrinalini Dey [3,4] Sizheng Zhao,[5] Jan Schoones,[6] Delphine Courvoisier [7] James Galloway [8,9] Kimme L Hyrich,[5,10] Elena Nikiphorou [8,9]

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- 4 Overarching principles
- 8 recommendations

Drugs

Nomenclature

- TF consensus on nomenclature
  - b-ts-DMARDs: all biologic and targeted synthetic DMARDs (except Apremilast)
  - csDMARDs: methotrexate, leflunomide.
    - Sulfasalazine and hydroxychloroquine were exempted from this category, and the TF members agreed to name them specifically, if needed.
  - other immunosuppressants: cyclophosphamide, mycophenolate mofetil, azathioprine, cyclosporin, tacrolimus
  - Glucocorticoids

Isaacs et al Ann Rhem Dis 2020

Machado et al Ann Rheum Dis 2022

Overarching principles

Overarching principles	LoE	GoR	LoA mean (SD)
A. The risk of chronic and opportunistic infections should be considered and discussed with all patients with AIIRD prior to treatment with csDMARDs, tsDMARDs, bDMARDs, immunosuppressants and/or glucocorticoids and reassessed periodically.	NA	NA	9.5 (1.0)
B. Collaboration between rheumatologists and other specialists including but not limited to infectious disease doctors, gastroenterologists, hepatologists and pulmonologists is important.	NA	NA	9.6 (0.8)
C. Individual risk factors should be considered in the decision for screening and prophylaxis of chronic and opportunistic infections and reassessed periodically.	NA	NA	9.8 (0.7)
D. National guidelines and recommendations, amongst other country/region-level factors pertaining to endemic infectious diseases, should be considered.	NA	NA	9.7 (0.8)

AIIRD: autoimmune inflammatory rheumatic diseases, bDMARDs: biologic DMARDs, csDMARDs: conventional synthetic disease modifying anti-rheumatic drugs, GoR: grade of recommendation, LoA: level of agreement, LoE: level of evidence, tsDMARDs: targeted synthetic DMARDs, NA: not applicable, SD (standard deviation)

Tuberculosis

Evidence – Who to screen?

- Latent TB
  - In some countries more than the others
    - In Greece 10-15%
- People on GC or csDMARDs are at increased risk for TB
  - Endemic regions, living with people with TB, Alcohol abuse and others
  - GC
    - We do not know the exact dose but…
    - >15 mg of prednisolone (or equivalent)/day for longer periods of time (eg, >4 weeks)

Brassard et al Arthr & Rheum 2009

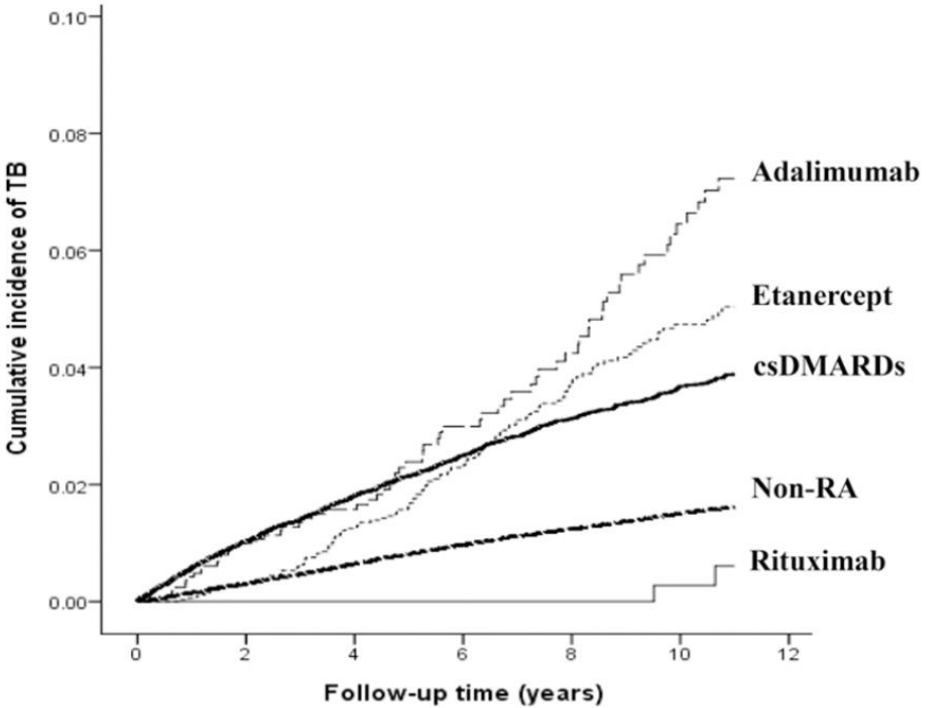
Jick et al Arthr & Rheum 2006

Brode et al Thorax 2015

Fragoulis G et al MJR 2023

Tuberculosis

Are all bDMARDs the same?



Nationwide database:
168,720 non-RA subjects
42,180 RA patients

36,162 csDMARDs-exposed, 3,577 etanercept-exposed, 1,678 adalimumab-exposed 763 rituximab-exposed patients.

Liao et al, PLoS One 2016

Treatment

Safety

- Αντι-IL-17/anti-IL-23 > TNFi
  - Tuberculosis
    - ⇩ frequency Vs TNFi (indirect comparison)

Table 6. Comparative presentation of active tuberculosis (TB) incidence rates (IR) between different biologic and targeted synthetic DMARDs.

Drug	Disease	Study type	IR§	Reference
Infliximab	RA, AS, PsA, PsO, CD, UC	LTE, RLS	52.5–2558.0	Askling *et al.*[2]; Seong *et al.*[6]; Wolfe *et al.*[8]; Dixon *et al.*[9]; Gomez-Reino *et al.*[10]; Souto *et al.*[27]; Tubach *et al.*[28]
Certolizumab	RA	LTE	474.29	Souto *et al.*[27]
Adalimumab	RA, AS, PsA, PsO, CD, UC	LTE, RLS	90.0–215.0	Dixon *et al.*[9]; Souto *et al.*[27]; Tubach *et al.*[28]
Golimumab	RA, AS, PsA	LTE	172.13	Souto *et al.*[27]
Etanercept	RA, AS, PsA, PsO	RLS, LTE	9.3–80.0	Askling *et al.*[2]; Dixon *et al.*[9]; Souto *et al.*[27]; Tubach *et al.*[28]
Apremilast	PsA, PsO	RCT, LTE, RLS	0.0	Cutolo *et al.*[35]; Edwards *et al.*[36]; Kavanaugh *et al.*[37]; Wells *et al.*[38]; Crowley *et al.*[39]; Abignano *et al.*[40]; Favalli *et al.*[41]
Tofacitinib	RA	RCT, LTE	200.0–210.0	Winthrop *et al.*[47]; Cohen *et al.*[49]
Baricitinib	RA	RCT, LTE	150.0–230.0	Smolen *et al.*[56]; Chen *et al.*[57]
Ustekinumab	PsA, PsO, CD	RCT, LTE, RLS	0.0–22.12	Ghosh *et al.*[76]; Lopez-Ferrer *et al.*[77]; Tsai *et al.*[78]; Hsiao *et al.*[79]
Secukinumab	AS, PsA, PsO	RCT, LTE	0.0–5.0	Deodhar *et al.*[95]; van de Kerkhof *et al.*[96]
Ixekizumab	PsA, PsO	RCT	0.0	Mease *et al.*[98]; Romiti *et al.*[99]

M Ward et al Arhtritis & Rheum 2019

Evangelatos G et al Ther Adv M Dis 2020

Tuberculosis

Evidence – How to screen?

- IGRA performs better than TST
  - Less affected by
    - Glucocorticoids
    - DMARDs
    - Immunosuppressants
    - BCG vaccination

Author-year/country	Patients (N)	Disease	Association with TST			RoB
			BCG	GC	csDMARDs	
Ruan *et al*[17] 2016/NA*	1940	AIIRD	Positive OR: 1.64 (95% CI 1.06 to 2.53)	Negative OR 0.45 (95% CI 0.30 to 0.69)	–	High quality
Reitblat *et al*[24] 2018/ Israel	65	RA	–	No	No	7
Agarwal *et al*[23] 2014/USA	250	RA	–	Negative (mean dose†: 6.4), (p=0.002)	No	7
Hsia *et al*[13] 2012/ multinational	2303	IA	Positive (p<0.0002 vs IGRA)	–	–	7
Klein *et al*[18] 2013/Czech	305	AIIRD	–	Negative, (p=0.0172)	Negative (combination with GC) (p=0.0003)	6
Belard *et al* [22] 2011/ Denmark	248	AIIRD‡	–	Negative (p=0.018)	–	6
Soborg *et al*[20] 2009/ Denmark	302	IA	–	Negative RR 0.4 (95% CI 0.1 to 1.0), (p=0.04)	–	6
Tamborenea *et al21 2009/Argentina*	105	RA	–	Negative (mean dose: 6 mg/day), OR 0.72 (95% CI 0.55 to 0.95), p=0.021	–	6
Vassilopoulos *et al*[15] 2008/Greece	70	AIIRD	Positive§	Negative (mean dose: 6.8 mg)¶	–	6
Arias-Guillen *et al*[26] 2018/Spain	393	IA	–	–	Positive (MTX) OR 2.15 (95% CI 1.05 to 4.44)	5
Maeda *et al*[14] 2011/ Japan	97	RA	Positive (14/19 false-positive TST)	–	–	5
Sargin *et al*[25] 2018/ Turkey	109	IA	–	No	–	4
Lee *et al*[16] 2012/South Korea	81	RA	No	–	–	4
Lee *et al*[16] 2012/South Korea	81	RA	–	No	No	4

Fragoulis et al RMDOpen 2022

Prophylaxis
Various Schemes

- INH for 6 months
  - Check for LFTs
- RIF for 4 months
  - Check for interactions
    - Especially with steroids/Upadacitinib/Tofacitinib
- RIF/INH for 3 months
- Safe to start b/tsDMARDs after 1 month of treatment

Recommendations #1-3

Tuberculosis

Recommendations	LoE	GoR	LoA mean (SD)
1. Screening for latent tuberculosis is recommended in patients prior to starting bDMARDs or tsDMARDs*. Screening should also be considered in patients with increased risk for latent tuberculosis prior to starting csDMARDs, immunosuppressants* and/or glucocorticoids (according to dose and duration).	2b 5*	B D*	9.5 (0.9)
2. Screening for latent tuberculosis should follow national and/or international guidelines and would typically include a chest X-ray* and Interferon-gamma release assay (IGRA) over tuberculin skin test (TST) where available.	2b 5*	B D*	9.5 (0.8)
3. Choice and timing of latent tuberculosis therapy should be guided by national and/or international guidelines. Special attention should be given to interactions with drugs commonly used to treat AIIRD.	5	D	9.3 (1.4)

AIIRD: autoimmune inflammatory rheumatic diseases, bDMARDs: biologic DMARDs, csDMARDs: conventional synthetic disease modifying anti-rheumatic drugs, GoR: grade of recommendation, LoA: level of agreement, LoE: level of evidence, tsDMARDs: targeted synthetic DMARDs, NA: not applicable, SD (standard deviation) *denotes separate LoE and GoR, where this is different from the rest of the statement

Hepatitis B

Evidence – HBV-status

- The risk of hepatitis B virus (HBV) reactivation (appearance/rise in HBV-DNA or conversion from HBsAg-negative to HBsAg-positive) depends on the HBV-status
- HBV carriers (HBsAg-positive)
  - Data more robust for cs/bDMARDs (20-30% reactivation)
    - Data for newer bDMARDs are limited
  - GC
    - at least 10 mg of prednisolone or equivalent for ≥4 weeks

Reddy et al Gastroenterology 2015

Sasadeusz Clin Liv Dis 2019

Zhong et al Ann Rheum Dis 2022

Hepatitis B

Evidence – How to screen?

- **anti-HBcore-positive and HBsAg-negative**
- Risk for HBV reactivation is lower
  - 1-5% for steroids, cDMARDs (scarce data)
  - 1-10% for bDMARDs (TNFi) - Possibly higher in Rituximab
    - Some experts and national societies suggest prophylaxis in RTX-tested irrespective of HBV-DNA-levels
  - Risk is more pronounced when anti-HBs are negative

Table 4 Antiviral prophylaxis and HBV reactivation in anti-HBcore-positive patients treated with b-ts-DMARDs

Author-year/country	Patients (N)	Disease	Treatment	Prophylaxis N (%)	Reactivation N (%)	RoB
Lee *et al*[18,148] 2012/South Korea*	468 patients (9 studies)	IA	TNFi	0 (0)†	8 (1.7)	Low quality
Harigai *et al*[96] 2020/Multi	215	RA	Baricitinib	0 (0)	4 (1.9)	8
Papalopoulos et al[144] 2018/Greece	212	AIIRD	bDMARDs	8 (3.8)	2 (2)	8
Lan *et al*[101] 2011/Taiwan	88	RA	TNFi	0 (0)	1/70‡ (1.4)	8
Charpin *et al*[141] 2009/France	21	IA	TNFi	0 (0)	0 (0)	8
Ahn *et al*[138] 2018/South Korea	15	RA	Tocilizumab	0 (0)	0 (0)	7
Vassilopoulos *et al*[109] 2010/Greece	19	IMID	TNFi	0 (0)	0 (0)	7
Serling-Boyd *et al*[154] 2021/USA	24	AIIRD	Tocilizumab, Tofacitinib	6 (25.0)	0 (0)	6
Wang *et al*[107] 2021/Taiwan[107]	64	RA	Tofacitinib	0 (0)	2 (3.1)	6
Kuo *et al*[150] 2020/Taiwan	64	RA	Tocilizumab	0 (0)	1 (1.6)	6
Chen et al[108] 2018/Taiwan	75	RA	Tofacitinib	0 (0)	0 (0)	6
Chen et al[98] 2017/China	41	RA	Tocilizumab	0 (0)	0 (0)	6
Gianniti et al[142] 2017/Italy	131	SpA	TNFi	0 (0)	0 (0)	6
Padovan *et al*[102] 2016/Italy	21	RA	Abatacept	4 (19.1)	0 (0)	6
Nakamura et al[145] 2016/Japan	57§	RA	bDMARDs	0 (0)	3 (5.3)	6
Biondo *et al*[139] 2014/Italy	20	IA	TNFi	0 (0)	0 (0)	6
Giardina *et al*[99] 2013/Italy	7	IA	TNFi	0 (0)	0 (0)	6
Caporalli et al[140] 2010/Italy	67	IA	TNFi	0 (0)	0 (0)	6
Zhang *et al*[155] 2013/China	41	RA	Infliximab	0 (0)	0/30 (0)	5
Ye *et al*[104] 2014/China	50	IA	TNFi	0 (0)	0 (0)	4
Chen *et al*[156] 2019/Taiwan	103	RA	Rituximab	0 (0)	9 (8.7)	8
Kuo *et al*[110] 2020/Taiwan	50	RA	Rituximab	0 (0)	4 (8)	7
Tien *et al*[149] 2017/Taiwan	44	RA	Rituximab	0 (0)	4 (9.1)	7
Varisco *et al*[151] 2016/Italy	33	RA	Rituximab	0 (0)	0 (0)¶	7
Mitroulis et al[147] 2013/Greece	12	AIIRD	Rituximab	0 (0)	0 (0)	6
Barone *et al*[152] 2021/Italy	44	AIIRD	Rituximab	0 (0)	0 (0)	5

*Meta-analysis.
†Prophylaxis was given only in 1 study with 19 patients.
‡18 patients were HBsAg-positive.
§Anti-core and/or anti-HBs (+).
¶39% became HBV-DNA (+).
AIIRD, autoimmune inflammatory rheumatic diseases; bDMARDs, biological DMARDs; HBV, hepatitis B virus; IA, inflammatory arthritis; RA, rheumatoid arthritis; RoB, risk of bias; SLE, systemic lupus erythematosus; SpA, Spondyloarthritis; TNFi, TNF-inhibitors; tsDMARDs, targeted synthetic disease modifying anti-rheumatic drugs.

Tien et al Arthr Res Ther 2018

Chen et al Ann Rheum Dis 2021

Fraenkel et al Arthr & Rheum 2021

Rheumatology, 2025, **64**, 935–942
https://doi.org/10.1093/rheumatology/keae445
Advance access publication 17 August 2024
Systematic Review and Meta Analysis

British Society for Rheumatology RHEUMATOLOGY OXFORD

Clinical science

Hepatitis B reactivation in PsA patients: an SLR and meta-analysis for IL-17, IL-23 and JAK inhibitors

Theodoros Androutsakos[1], Konstantinos Dimitriadis[2], Maria-Loukia Koutsompina[1], Konstantinos D. Vassilakis[3], Avraam Pouliakis[4], George E. Fragoulis[3,*]

- low HBVr risk of <6% in all agents
  - Higher for chronic (14.4%) vs resolved (5.1%)
  - No Difference between drugs
  - HBVr: 28% in chronic HBV who did not receive anti-viral treatment
  - For resolved hepatitis, the respective percentage was 4.7%

Rheumatology, 2023, **62**, S252–S259
https://doi.org/10.1093/rheumatology/kead243
Advance access publication 0 Month 0000
Systematic Review and Meta Analysis

British Society for Rheumatology RHEUMATOLOGY OXFORD

Clinical science

HBV reactivation in patients with rheumatoid arthritis treated with anti-interleukin-6: a systematic review and meta-analysis

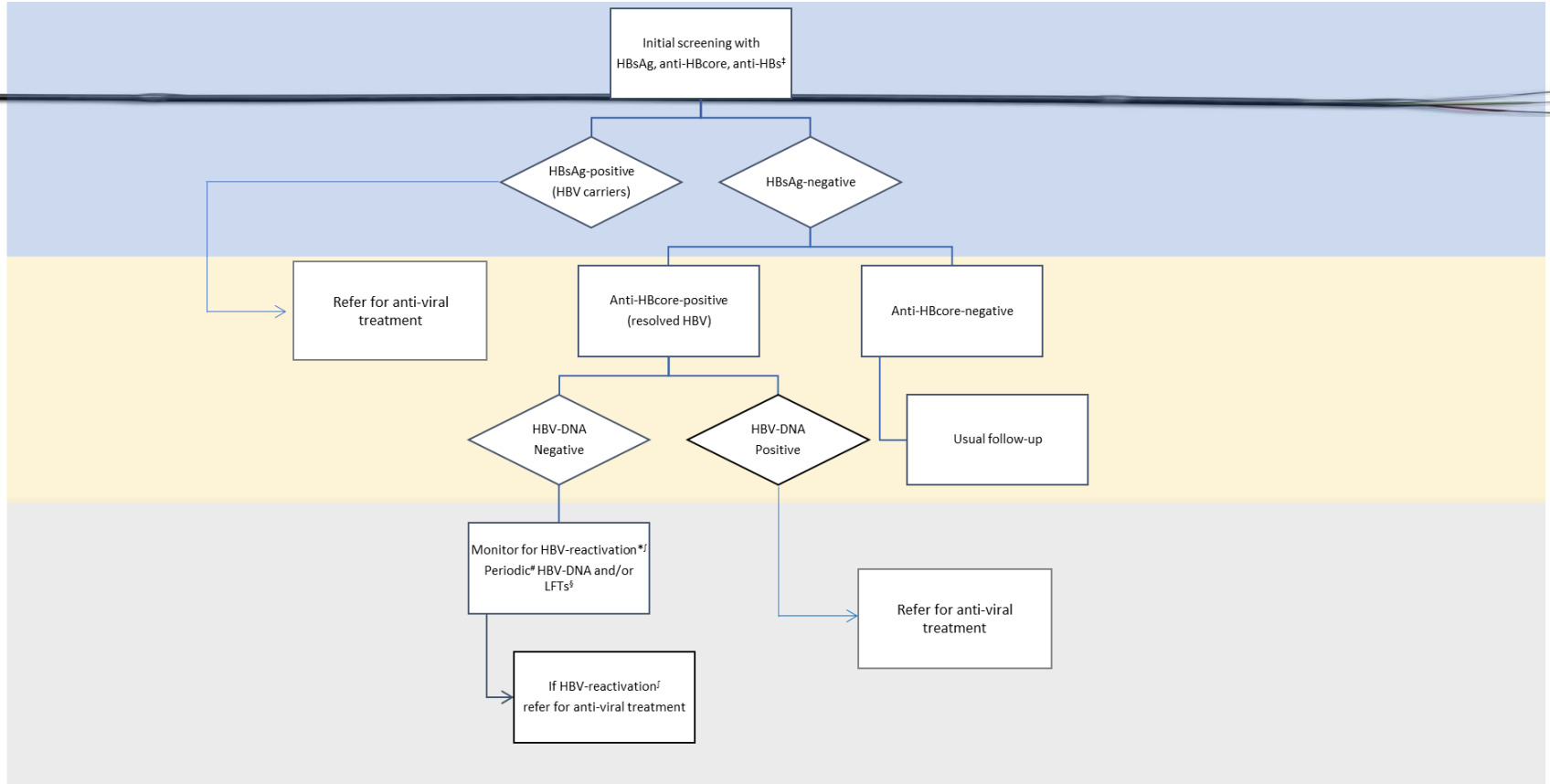
Stamatia Katelani[1,‡], George E. Fragoulis[2,3,‡], Athanasios-Dimitrios Bakasis[1], Abraham Pouliakis[4], Elena Nikiphorou[5], Fabiola Atzeni[6,§], Theodoros Androutsakos[1,*,§]

372 RA patients

HBVr in RA patients with chronic HBV: 6.7% increasing to 37% when no antiviral prophylaxis

HBVr was close to 0% in RA patients with resolved HBV infection, irrespective of antiviral prophylaxis.

Hepatitis B Algorithm



‡ positive anti-HBs without positive HBsAg or anti-HBcore is consistent with prior vaccination. If all three (HBsAg, anti-HBcore, anti-HBs) are negative, means no previous exposure to HBV, * Consider referral for anti-viral prophylaxis for those commencing rituximab, having also low titers of anti-HBs. Risk is assessed on an individual basis, ʃ HBV-reactivation: rise or appearance of HBV-DNA, or conversion from HBsAg-negative to HBsAg-positive, # periodic: there are no data to specify the exact time at which re-screening for HBV-reactivation should be performed. However, every 3-6 months is the standard for many national guidelines. Risk factors and cost should also be considered. § referral to hepatologists is also recommended,

Hepatitis C

Evidence

- Increases in HCV viral load
- Can occur but….
- ….Low frequency for bDMARDs
  - No data for GC, cDMARDs, immunosuppressives

Table 5 Hepatotoxicity and reactivation of hepatitis C in patients treated with DMARDs or immunosuppressants

Author-year/country	Patients (N)	Concurrent antivirals* (%)	Disease	Treatment	Increase in LFTs N (%)	Increase in viral load N (%)	RoB
Iannone *et al*[164] 2014/ Italy†	29	0%	RA	Etanercept or MTX or combination	0 (0)	0 (0)	Some concerns
Burton *et al*[165] 2017/USA	748‡	4.6%	RA	DMARDs	37 (3.4)	0 (0)	7
Chen et al[166] 2015/ Taiwan	26§	NS	SLE	Immunosuppressants	10 (38.5)¶	10 (38.5)¶	6
Costa *et al*[160] 2014/Italy	15	NS	PsA	TNFi	0 (0)	0 (0)	6
Parke *et al*[161] 2004/USA	5	0%	RA	TNFi	0 (0)	1 (20)**	6
Peterson *et al*[162] 2003/ USA	24	0%	RA	Etanercept or Infliximab	0 (0)	6/22 (27.3)††	6
Gandhi et al[163] 2017/ USA	14‡‡	14.3%	RA, PsA	Etanercept	7 (50.0)	5/10 (50.0)	5

*Patients concurrently treated with antivirals.
†Randomised controled trial.
‡1097 treatment-episodes.
§Anti-HCV+, baseline RNA not stated.
¶Increase in viral load or LFTs.
**Was not combined with liver injury.
††No significant differences were seen between the mean viral loads at baseline and follow-up.
‡‡5/7 were RNA-positive.

Fragoulis et al RMDOpen 2022

RHEUMATOLOGY

Rheumatology 2011;50:1700–1711
doi:10.1093/rheumatology/ker190
Advance Access publication 20 June 2011

Original article

Safety of anti-tumour necrosis factor agents in patients with chronic hepatitis C infection: a systematic review

Alexandra M. G. Brunasso[1,2], Matteo Puntoni[3], Andrea Gulia[4] and Cesare Massone[5]

- SLR 1990-2010
- TNFi in patients with chronic HCV
- 153 patients, 37 publications
- Most used: Etanercept
- In 2 (<0.5%) patients, worsening

TABLE 1 Numbers of patients treated with anti-TNF-α agents in the setting of HCV infection

Baseline pathology in association with HCV infection	Patients treated with etanercept	Patients treated with infliximab	Patients treated with adalimumab	Patients treated with infliximab or etanercept	Mean duration of anti-TNF-α therapy	References
RA	59	23	8	5	13.15 months	[22–34]
PsA	6	1	1	NA	9.8 months	[21, 30, 35–37]
Psoriasis	8	NA	NA	NA	12 months	[38–42, 55, 56]
PsA and psoriasis	8	NA	NA	NA	14.5 months	[39–41, 55, 57]
CD	NA	6	NA	NA	15.3 weeks	[46–50]
AS	NA	1	NA	NA	13 months	[37]
Cryoglobulinaemia	NA	1	NA	NA	NA	[50]
Vasculitis	NA	2	NA	NA	4 weeks	[51]
None	19	NA	NA	NA	24 weeks	[52]
HCV-related oligo- and polyarthritis	9	NA	NA	NA	3 months	[53]
PM	1	NA	NA	NA	14 months	[30]

NA: not available.

HCV

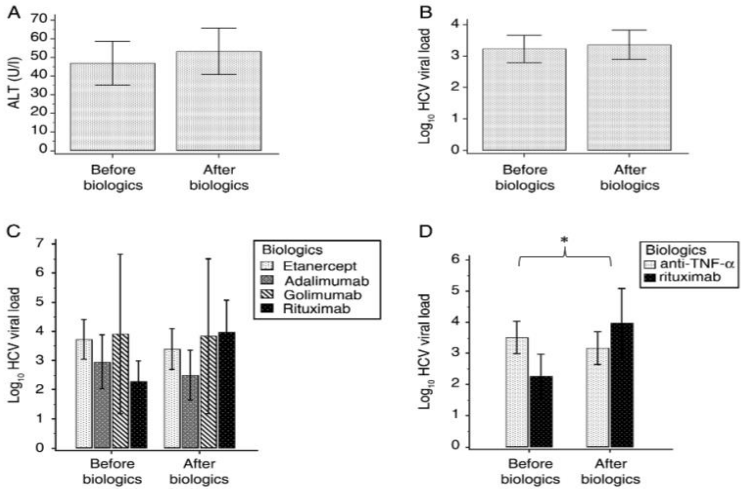
RTX

bDMARDs

26 pts with RA and HCV

20 TNFi and 6 RTX

- Small increases in HCV RNA > TNF



Chen YM et al. Ann Rheum Dis. 2015 Mar;74(3):626-7

HCV

Newer bDMARDs, other drugs

Table 1. Descriptive characteristics of HCV- RNA positive patients

	n=9
Age, years (median, IQR)	63 (55- 81)
Female, n (%)	5 (55)
Inflammatory Arthritis, n (%)	7 (77)
Disease duration, years (median, IQR)	6.5 (4-13.5)
HCV treatment, n (%)	9 (100)
- Sofosbuvir/ledipasvir, n (%)	3 (33.3)
-Sofosbuvir/velpatasvir, n (%)	2 (22.2)
-IFN, n (%)	2 (22.2)
-Dasabuvir, n (%)	1 (11.1)
-other, n (%)	1 (11.1)
HCV treatment duration, months (median, IQR)	3 (3-7)
Hydroxychloroquine, n (%)	2 (22.2)
(b-ts-)-DMARDs, n (%)	5 (55.5)
-anti-TNF-a, n (%)	2 (22.2)
-anti-IL-17 or- Il23, n (%)	2 (22.2)
-CTLA4 inh, n (%)	1 (11.1)
Immunosuppressants^, n (%)	3 (33.3)
Current prednisolone dose (median, IQR)	5 (0-15)
HCV reactivation *, n (%)	0 (0)

^ *Methotrexate, cyclosporine A*

**HCV reactivation defined as an increase in HCV-RNA of at least 1 logarithm or an increase in liver function tests of at least two times the upper limit of normal*

Pappa M et al MJR (In Press 2025)

HCV

Practical recommendations

- In the interest of public health, screening (anti-HCV and if positive HCV-RNA) for HCV is recommended
  - More intense when risk factors exist
- Landscape changed with newer anti-virals
- If HCV-RNA are negative, no further action required
- Avoid hepatotoxic drugs like Methotrexate/Leflunomide

Recommendations #4-5

Hepatitis B & Hepatitis C

Recommendations	LoE	GoR	LoA mean (SD)
4. All patients being considered for treatment with csDMARDs, bDMARDs, tsDMARDs*, immunosuppressants* and glucocorticoids (according to dose and duration) should be screened for HBV.	2a 2b*	C C*	9.1 (1.3)
5. Screening for chronic hepatitis C should be considered in patients prior to starting csDMARDs, bDMARDs, tsDMARDs*, immunosuppressants and glucocorticoids* (according to dose and duration). Screening is recommended for patients with elevated alanine aminotransferase (ALT) or those with known risk factors.	2b 5*	C D*	9.0 (1.3)

Considering also cost-effectiveness and geographical variations, the threshold for screening should be lower for patients with concurrent HCV risk factors (eg, intravenous use of drugs) and/or abnormal LFTs, especially ALT.

AIIRD: autoimmune inflammatory rheumatic diseases, bDMARDs: biologic DMARDs, csDMARDs: conventional synthetic disease modifying anti-rheumatic drugs, GoR: grade of recommendation, HBV: hepatitis B virus, LoA: level of agreement, LoE: level of evidence, tsDMARDs: targeted synthetic DMARDs, NA: not applicable, SD (standard deviation) *denotes separate LoE and GoR, where this is different from the rest of the statement

HIV/VZV
Evidence

- HIV
- Only a small study (n=8), CD4 cells>200/mm3 and viral load<60 000 copies/mm3, treated with TNF-inhibitors
  - showed stable CD4 counts and viral load over a 2-year follow-up
- VZV
  - importance of establishing VZV-immunity status
    - a detailed past medical history of previous exposure
    - Screening in some countries
    - Vaccination
  - Patient who are non-immune should be informed about post-exposure prophylaxis
    - This will change in the update of the recommendations

Cepeda et al Ann Rheum Dis 2008

Recommendations #6-7
Other Viruses (HIV, VZV)

Recommendations	LoE	GoR	LoA mean (SD)
6. Screening for HIV is recommended prior to treatment with bDMARDs and should be considered prior to treatment with csDMARDs, tsDMARDs, immunosuppressants and glucocorticoids (according to dose and duration).	5	D	8.9 (1.6)
7. All patients commencing csDMARDs, bDMARDs, tsDMARDs, immunosuppressants and/or glucocorticoids (according to dose and duration) who are non-immune to VZV should be informed about post-exposure prophylaxis following contact with VZV.	5	D	8.9 (1.5)

AIIRD: autoimmune inflammatory rheumatic diseases, bDMARDs: biologic DMARDs, csDMARDs: conventional synthetic disease modifying anti-rheumatic drugs, GoR: grade of recommendation, HIV: human immunodeficiency virus, LoA: level of agreement, LoE: level of evidence, tsDMARDs: targeted synthetic DMARDs, NA: not applicable, SD (standard deviation), VZV: varicella zoster virus. *denotes separate LoE and GoR, where this is different from the rest of the statement

PCP

Evidence

- Prophylaxis
  - GC in daily doses >15–30 mg of prednisolone or equivalent for >2–4 weeks
  - Data lacking for DMARDs
  - Higher risk when Immunosuppressants are co-administered with GC
- most commonly used scheme
  - TMP-SMX 480 mg/day (single-strength) or 960 mg three times a week;
    - there is some evidence that reduced doses (eg, half-strength, daily) may also be effective

Table 6 Prophylaxis with trimethoprim-sulfamethoxazole for PCP in patients treated with GC

Author-year/country	Patients (N)	GC scheme	Prophylaxis* N (%)	Outcome of prophylaxis	RoB
Park et al[170] 2018/South Korea	1092 (1522 episodes†)	≥30 mg/day for ≥4 weeks	262 (24.0)	Reduced PCP incidence HR=0.07 (95% CI 0.01 to 0.53), p=0.01	8
Honda et al[168] 2019/Japan	437	≥50 mg/day	376 (86.0)	Reduced PCP incidence OR=0 (95% CI 0.00 to 0.38), p=0.003	7
Park *et al*[169] 2019/South Korea	735 (1065 episodes†)	≥15 mg and <30 mg for ≥4 weeks	45 (6.1)	Reduced PCP incidence in high risk-group‡ HR=0.2 (0.001–2.3)	7
Ogawa *et al*[171] 2005/Japan	124	≥30 mg/day	46 (37.1)	Effective in high-risk patients§, p=0.039	7
Vananuvat *et al*[172] 2011/ Thailand	132 (138 episodes†)	≥20 prednisolone for >2 weeks	59 (44.7)	Reduced PCP incidence, p=0.038	6

*Prophylaxis given in (% episodes): trimethoprim-sulfamethoxazole 480 mg/day or three tablets of 480 mg, weekly.
†Episode: a patient could be treated with these doses of glucocorticoids more than once.
‡High-risk group: GC-pulse treatment and/or lymphopenia.
§Risk was calculated using a prediction model.
AIIRD, autoimmune inflammatory rheumatic diseases; GC, glucocorticoids; PCP, pneumocystis pneumonia; RoB, risk of bias.

Park et al Arthr Res Ther 2019

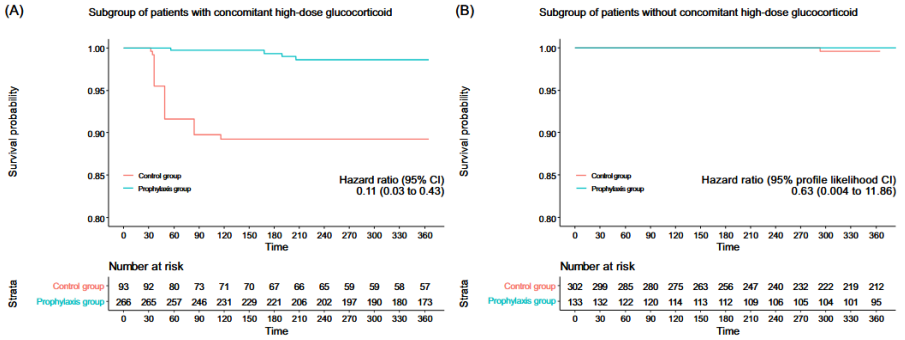
Park et al Ann Rheum Dis 2018

Vananuvat et al Seminars 2011

PCP

Ritxuximab

- 818 ARD patients treated with RTX
  - 419 received prophylactic TMP/SMX, the remainder did not
  - 663.1 person-years, there were 11 PCP cases
  - Concomitant use of high-dose GC (≥30 mg/day) was the most important risk factor.
  - TMP/SMX reduced the PCP incidence (HR 0.11 [95% CI 0.03–0.43])
    - NNT to prevent 1 case of PCP (146) was higher than the NNH (86)
      - ✓ NNT fell to 20 (95% CI 10.7–65.7) in patients receiving concomitant high-dose glucocorticoids.

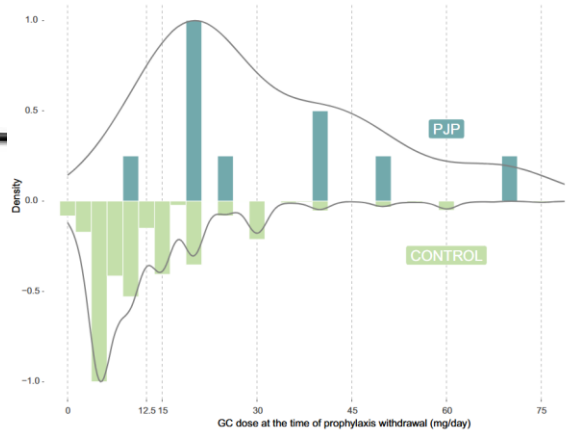


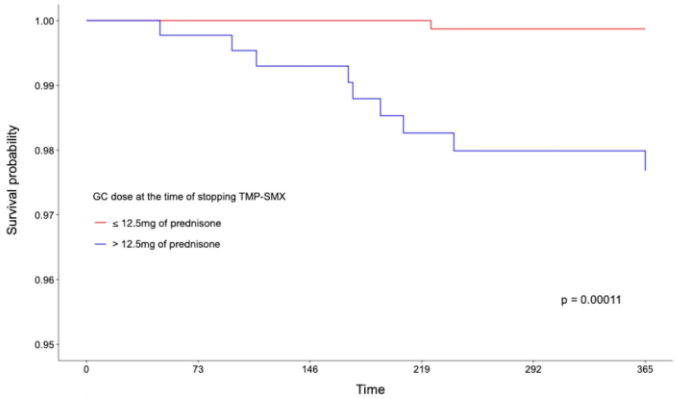
Park et al Arthr Rheumatol 2023

PCP

at which dose to stop?

- 1294 prophylactic episodes in 1148 patients with various ARDs
- Primary outcome
  - 1-year incidence of PCP
  - Incidence rate of 0.85/100 person-years
  - Discontinuing TMP-SMX while on a GC dose >12.5 mg/day increased the risk of PCP
    - adjHR 13.84; 95% confidence interval, 1.71–111.80





Kim et al Arthr Rheumatol 2025

Recommendation #8

Pneumocystis Jirovecii

Recommendations	LoE	GoR	LoA mean (SD)
8. Prophylaxis against PCP should be considered in patients with AIIRD in whom high doses of glucocorticoids are used, especially in combination with immunosuppressants* and depending on the risk-benefit ratio.	2b 5*	B D*	9.2 (1.1)

AIIRD: autoimmune inflammatory rheumatic diseases, bDMARDs: biologic DMARDs, csDMARDs: conventional synthetic disease modifying anti-rheumatic drugs, GoR: grade of recommendation, LoA: level of agreement, LoE: level of evidence, PCP: pneumocyctis jirovecii pneumonia, tsDMARDs: targeted synthetic DMARDs, NA: not applicable, SD (standard deviation), VZV: varicella zoster virus. *denotes separate LoE and GoR, where this is different from the rest of the statement

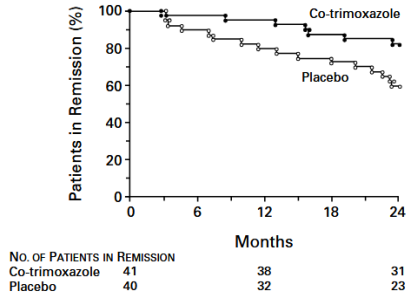
Recommendation

EULAR recommendations for the management of ANCA-associated vasculitis: 2022 update

Bernhard Hellmich [1], Beatriz Sanchez-Alamo [2], Jan H Schirmer [3], Alvise Berti [4, 5], Daniel Blockmans [6], Maria C Cid [7], Julia U Holle [8], Nicole Hollinger [1], Omer Karadag [9], Andreas Kronbichler [10, 11], Mark A Little [12], Raashid A Luqmani [13], Alfred Mahr [14], Peter A Merkel [15], Aladdin J Mohammad [11, 16], Sara Monti [17, 18], Chetan B Mukhtyar [19], Jacek Musial [20], Fiona Price-Kuehne [11], Mårten Segelmark [21], Y K Onno Teng [22], Benjamin Terrier [23], Gunnar Tomasson [24, 25], Augusto Vaglio [26], Dimitrios Vassilopoulos [27], Peter Verhoeven [28], David Jayne [11]

17	For patients with AAV receiving rituximab, cyclophosphamide and/or high doses of glucocorticoids, we recommend the use of trimethoprim–sulfamethoxazole as prophylaxis against *Pneumocystis jirovecii* pneumonia and other infections.	3b	B	100	9.5±1.1

- Prophylactic use of TMP/SMX
  - Has been associated with lower frequency of severe infections (HR 0.30, 95% CI 0.13 to 0.69)
- Therapeutic dose of TMP/SMX
  - Associated with fewer relapses
  - Lower frequency of infections (p=0.005)



Kronbichler A et al Ann Rheum Dis 2018

Stageman et al NEJM 1996

Research agenda

Box 1 Research agenda

General

⇒ Does the risk of opportunistic and chronic infections differ between the different classes of disease-modifying antirheumatic drugs (DMARDs) or immunosuppressive drugs?

⇒ What is the dose and duration of glucocorticoids above which the risk of opportunistic and chronic infections starts to increase compared to those patients not receiving glucocorticoids? Does this differ by pathogen?

⇒ How often should people with autoimmune inflammatory rheumatic diseases (AIIRD) receiving antirheumatic therapies be rescreened for chronic and opportunistic infections?

⇒ Is screening and prophylaxis for opportunistic and chronic infections in people with AIIRD receiving antirheumatic therapies cost-effective?

Tuberculosis

⇒ Should patients starting immunosuppressants (eg, cyclophosphamide) be screened routinely for latent tuberculosis (TB)?

⇒ Should patients starting antirheumatic therapies be screened for non-tuberculous mycobacteria? What is the most effective way to screen for these infections?

⇒ How often should patients who have already been tested for tuberculosis, be rescreened? In relation to that, is there a need to rescreen patients who switch biological DMARDs or targeted synthetic-DMARDs?

Hepatitis

⇒ When should hepatitis antiviral treatment be started in people living with AIIRD commencing antirheumatic treatment found to be at risk of hepatitis reactivation?

⇒ For how long should hepatitis antiviral prophylaxis be continued in patients at risk for hepatitis reactivation after antirheumatic treatment is stopped?

⇒ Should patients with chronic or resolved hepatitis B also be screened for hepatitis D?

Other viruses

⇒ Is it safe to treat people living with HIV with antirheumatic treatments?

⇒ When should antiviral prophylaxis be considered in people with AIIRD who have recurrent herpes zoster infections?

⇒ Is postexposure prophylaxis for patients non-immune to VZV who are exposed to VZV beneficial?

⇒ Should patients with AIIRD starting antirheumatic therapy be screened for cytomegalovirus?

Task Force Members

Convenors: Kimme Hyrich, James Galloway

Methodologists: Elena Nikiphorou (senior), Delphine Courvoisier (junior)

Fellows: George Fragoulis (main), Mini Dey (co-fellow), Steven Zhao (co-fellow)

TF Members: Laurent Arnaud, Fabiola Atzeni, Georg Behrens, Hans Bijlsma, Peter Boehm, Costas Constantinou, Silvia Garcia-Diaz, Meliha Kapetanovic, Kim Lauper, Mariana Luis, Jacque Morel, Gyorgy Nagy, Eva Polverino, Jef van Rompay, Marco Sebastiani, Anja Strangfeld, Annette de Thurah

- 22 members, from 15 different countries
- Rheumatologists/epidemiologists (including two EMEUNET members)
- 2 patient research partners
- 2 health-care professionals in rheumatology
- 2 infectious disease doctors with an interest in rheumatology
- 1 pulmonologist

Thank you for your attention ☺

Friday, 30 January

16:00 Arrival
17:00 Welcome and introduction
17:30 Keynote Lecture | Treatment recommendations of PsA – the same as RA?
Laure Gossec
18:30 Disease Intercetption in PsA
Dennis McGonagle
19.30 Dinner and dinner talk | SpA in the era of AI
Diego Benavent

Sunday, 1 February

09.30 Syndemics in inflammatory arthritis. Current and future concepts
Elena Nikiphorou
10.30 Treatment recommendations of axSpA – where are we and what can we expect?
11:30 Break
12:00 Imaging workshop in axSpA / PsA
Nikos Kougkas, Apostolos Karantanas
13:30 End of workshop & Evaluation

Saturday, 31 January

09:00 Comorbidities in SpA. Affecting treatment choice
George Fragoulis
10:00 National registries and the application of knowledge in daily practice
Pedro Machado
11.00 Break
11:15 D2T concepts in PsA and AxSpA. What are they? Why we need them?
Ennio Lubrano
12:15 Screening algorithms for early detection of axSpA
Victoria Navaro
13:15 Lunch
14:00 Axial SpA vs. axial PsA: one entity, different entities or just semantics?
Xenofon Baraliakos
15:00 Workshops: main aspects in diagnosis and treatment of extra-musculoskeletal manifestations. What the rheumatologist needs to know

- Uveitis and SpA | Dimitris Ladas
- Inflammatory bowel disease and SpA | Konstantinos Karmiris
- Dermatological aspects of SpA | Elena Sotiriou
- Management of cardiometabolic risk in SpA | Stefan Siebert