Opportunistic infections among biologic users

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History

- Since the late 1990s, a variety of biological and synthetic drugs have been developed to treat rheumatoid arthritis, psoriatic arthritis and IBD as well as other autoimmune disorders
- In recent years, the incidence of severe infection in these patients has been reported by observational studies, reviews and metaanalyses
- Although Severe infection is defined as infection that requires hospitalization for treatment, every early nonserious infection must be taken potentially fatal
- although JAK inhibitors are targeted synthetic DMARDs and not real biologics here they will be dealed as biological agents

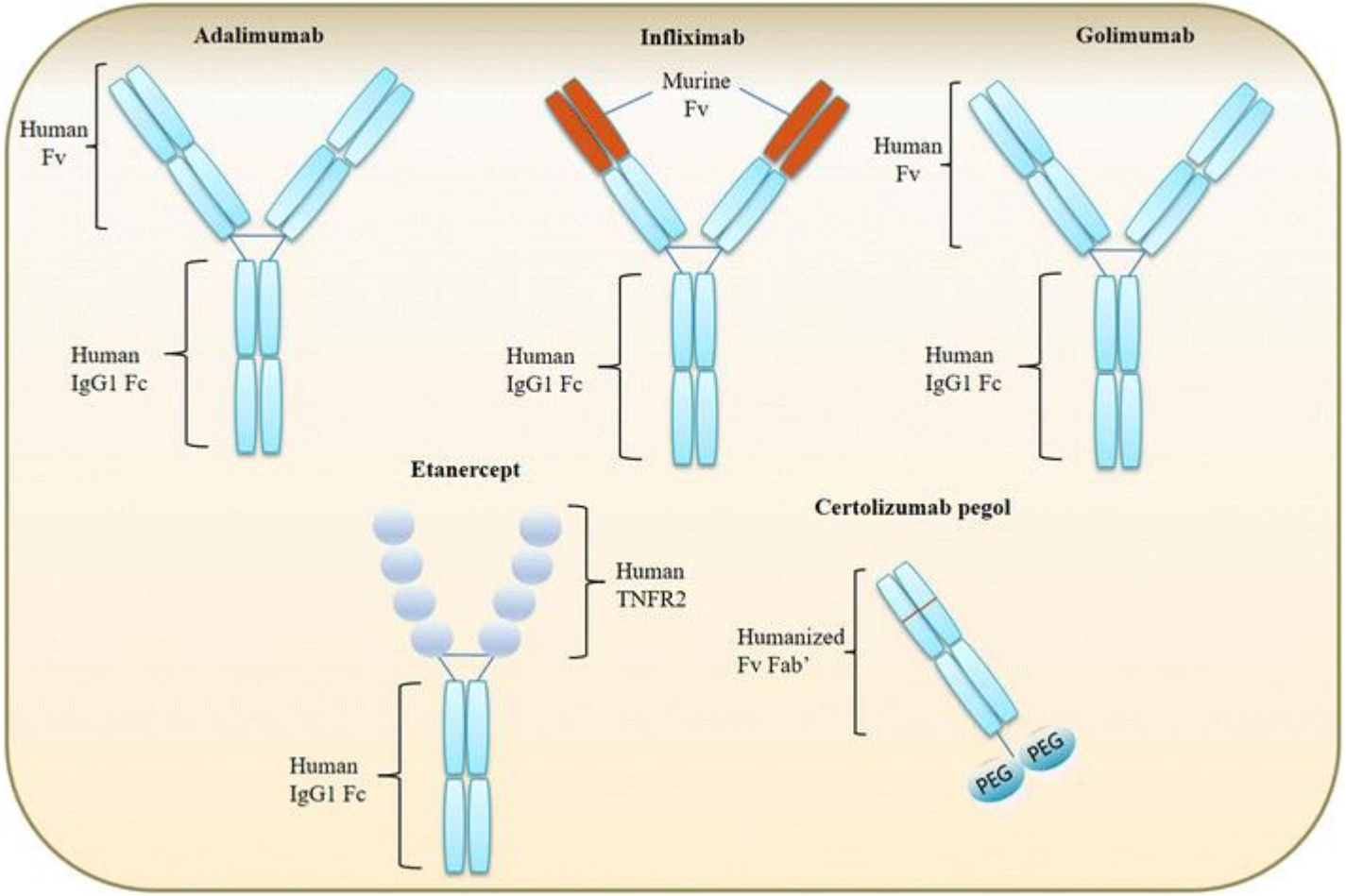
Definition of current status

- Biologics are monoclonal antibodies or fusion proteins that target essential components in immune pathways related to RA pathogenesis
- TNF-alpha inhibitors were introduced first, in the late 1990s (infliximab, etanercept, adalimumab, certolizumab pegol, golimumab)

Other biologicals followed:

- anti-CD20 (B-cell) agents (rituximab, ocrelizumab, Belimumab)
- T-cell co-stimulation inhibitors (abatacept)
- interleukin1 antagonists (anakinra)
- IL6 rec. blocker (tocilizumab)
- Anti IL23 (Guselkumab)
- Anti IL12/23 (Ustekinumab)

- Five tumor necrosis factor (TNF) inhibitors are available for the treatment of rheumatoid arthritis, spondyloarthritides including IBD and psoriatic arthritis, Behcet disease, uveitis of different causes, large vessel vasculitis, sarcoidosis and a number of other rheumatic diseases worldwide



TNF inhibitor induced infections

- Tuberculosis (TB) and other mycobacterial infections
- *Listeria monocytogenes*, *Nocardia* spp, and *Legionella* spp
- Hepatitis B virus (HBV) and hepatitis C virus (HCV)
- Herpes zoster virus
- Endemic mycoses
- Candidal infections
- Cryptococcal infection
- Aspergillosis
- Toxoplasmosis (rare)
- Common viral and bacterial infections (sinopulmonary infections, pneumonia, urinary tract infections, cellulitis

Evaluation and prevention of infections associated with TNF-alpha inhibitors (TNFi), abatacept, and janus kinase (JAK) inhibitors

Medication	Effect on immune system	Associated infections*	Pre-treatment testing¶	Pre-treatment vaccinations$^{\Delta}$
TNFi				
Infliximab Etanercept◇ Adalimumab Certolizumab pegol Golimumab	Inhibits macrophage activation and granuloma formation and function	Bacterial: ▪ **Tuberculosis◇ and other mycobacterial infections** ▪ Listeria monocytogenes ▪ *Nocardia* spp. ▪ *Legionella* spp. Viral: ▪ **HBV** ▪ HCV ▪ Herpes zoster virus Fungal: ▪ **Endemic mycoses** (histoplasmosis, blastomycosis, coccidioidomycosis, paracoccidioidomycosis, talaromycosis) ▪ Candidal infections ▪ Cryptococcal infection ▪ Aspergillosis Parasitic: ▪ Toxoplasma gondii (rare)	Test for: ▪ TBI ▪ HBV ▪ HCV ▪ In endemic regions, obtain history of possible recent (eg, in the last two years) infection with endemic fungi. If history is concerning, obtain a chest radiograph. ▪ In coccidioidomycosis-endemic regions, obtain *Coccidioides* serology	▪ Routine age-appropriate vaccinations ▪ Pneumococcal vaccine(s) ▪ RZV

ABATACEPT

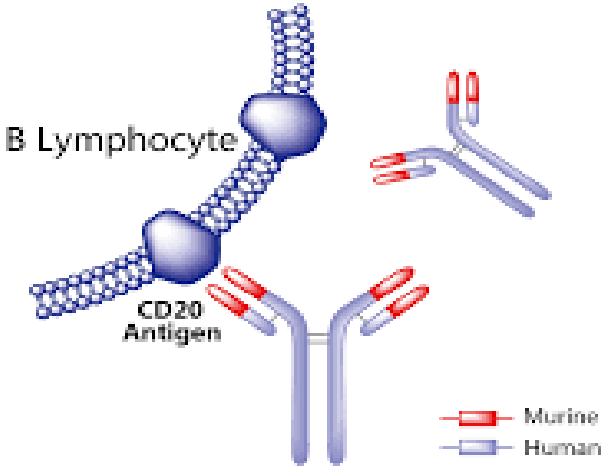
- abatacept is not thought to be severely immunocompromising but might predispose to:

- Tuberculosis (TB) and other mycobacterial infections
- Hepatitis B virus (HBV) and hepatitis C virus (HCV)
- EBV and cytomegalovirus (CMV) infection
- Common viral and bacterial infections (sinopulmonary infections, pneumonia, urinarytract infections, cellulitis)

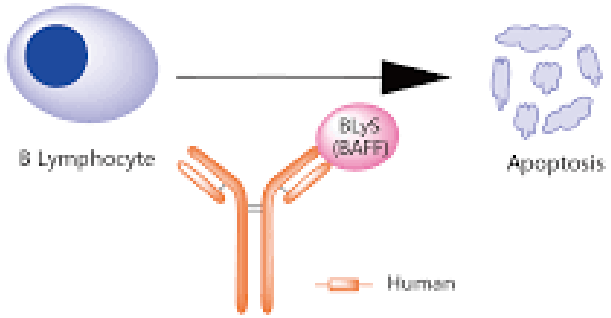
Blocking B-cells

- Biologic agents that can deplete B cells or inhibit factors that activate B cells are used for the treatment of a range of rheumatic and other autoimmune diseases
- In addition to their central role in antibody production, B cells present antigen to T cells, activate T cells, and promote the production of proinflammatory cytokines, including interleukin (IL)-1, 4, 6, 8, 10, and 12; tumor necrosis factor (TNF)-alpha (VEGF), (MCP) and macrophage migration inhibitory factor (MIF)

rituximab



belimumab



ANTI-B CELL AGENTS

Rituximab and other anti-B cell antibodies (eg, ocrelizumab, ofatumumab) are monoclonal Abs that bind to the CD20 receptor on B cells cause B cell depletion while B-cell activation factor(Blys) inhibitors like Belimumab are less risky because they prevent activation of B cells instead of depleting them

Wallace DJ, Navarra S, Petri MA, et al. Safety profile of belimumab: pooled data fromplacebo-controlled phase 2 and 3 studies in patients with systemic lupus erythematosus.Lupus 2013; 22:144

Infection with SARS-CoV-2 has been a serious complication for those on anti-CD20, which increases the risk of COVID-19-related hospitalization and death

Andersen KM, Bates BA, Rashidi ES, et al. Long-term use of immunosuppressive medicinesand in-hospital COVID-19 outcomes: a retrospective cohort study using data from theNational COVID Cohort Collaborative. Lancet Rheumatol 2022; 4:e33.

- Pts with HIV receiving anti-CD20 therapies should be closely monitored and strictly adhere to antiviral therapy, guidelines recommend stopping anti-CD20 therapies in patients with CD4 cell counts ≤50 cells/µL

anti-B cell agents predisposes to the following infections

- Tuberculosis (TB) and other mycobacterial infection
- Hepatitis B virus (HBV) and hepatitis C virus (HCV)
- Herpes zoster virus (HZV)
- Pneumocystis pneumonia (only rituximab)
- Common viral and bacterial infections (sinopulmonary infections, pneumonia, urinarytract infections, cellulitis)
- Epstein-Barr virus and cytomegalovirus CMV infection
- Severe coronavirus disease 2019 (COVID-19) (except belimumab)
- Progressive multifocal leukoencephalopathy (PML; mostly rituximab, although has been reported with belimumab)
- Endemic mycoses
- Cryptococcal infection

Timing of vaccinations

- before initiating biologics age appropriate routine vaccinations including SARS-CoV-2 vaccine (if its needed in future) and annual influenza vaccination should be completed prior to starting therapy because vaccinations may be less effective during and after therapy or may be contraindicated (eg, live vaccines)
- Routine vaccinations should be administered at least two weeks before starting these immunomodulatory therapies if possible, and timing should be extended to at least four weeks for live vaccines
- Vaccine responses may be attenuated while on anti B-cell therapy for 6 to 12 months after cessation of therapy.

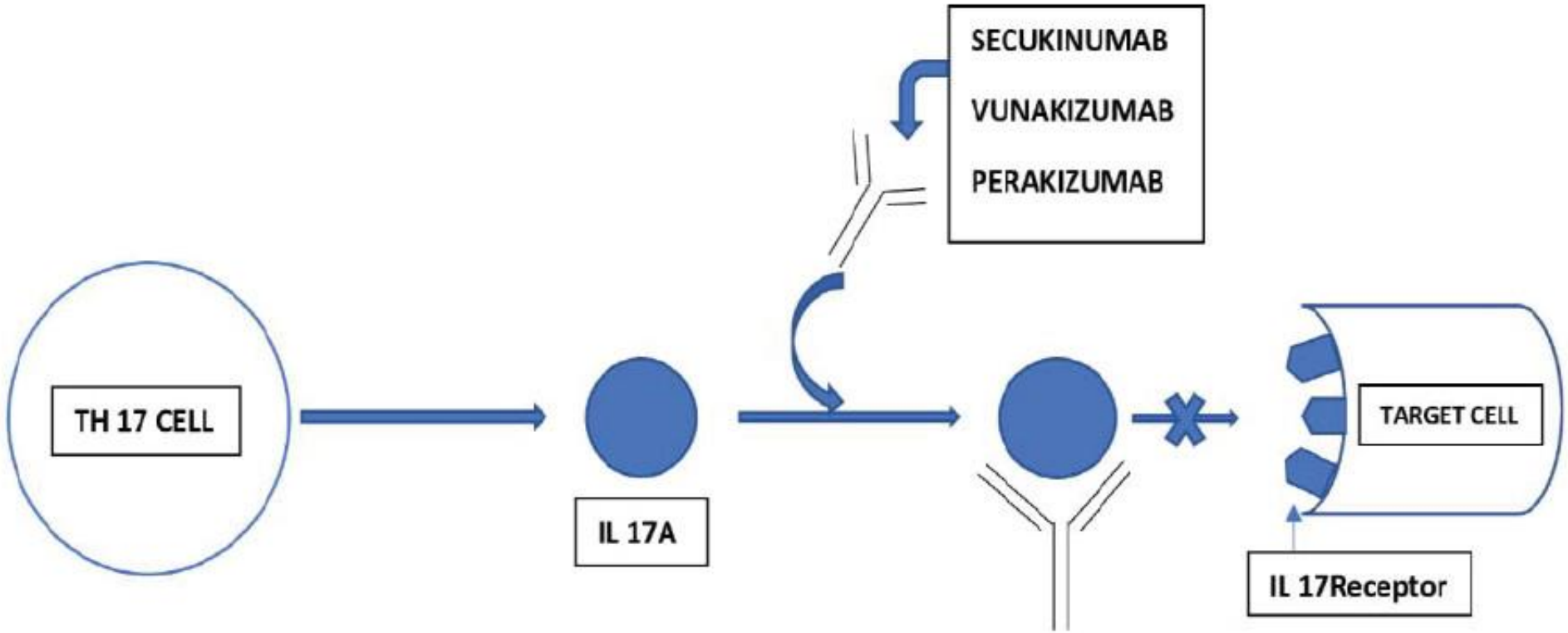
Park JK, Lee MA, Lee EY, et al. Effect of methotrexate discontinuation on efficacy of seasonalinfluenza vaccination in patients with rheumatoid arthritis: a randomised clinical trial. AnnRheum Dis 2017; 76:1559

Santibodies: weighing up the benefit-risk assessment for natalizumab. J TravelMed 2021; 28. chwob JM, Samer CF, Lalive PH, Eperon GA. Live vaccines and immunosuppressive monoclonal

Not become Nl so early!

- Mean time of recovery for B cells numbers to Nl after discontinuing rituximab is 6-9 months
- In a study of 120 patients with different types of vasculitides , B cell recovery occurred over a range of 8 to 44 months
- Even after normalization of B cell numbers, vaccine response may be attenuated. In a study of 75 patients who received four injections of rituximab or placebo over one month, titers to vaccines administered 12 months after rituximab therapy were lower in patients who received rituximab versus placebo Pescovitz MD, Torgerson TR, Ochs HD, et al. Effect of rituximab on human in vivo antibodyimmune responses. J Allergy Clin Immunol 2011; 128:1295
- Pre-existing immunity to vaccinations administered previously is not affected by treatment. in a study of 75 patients treated with four injections of rituximab or placebo over one month and then followed for 12 mo. measles, mumps, and rubella titers before rituximab and after were unchanged between the rituximab group and placebo Thiel J, Rizzi M, Engesser M, et al. B cell repopulation kinetics after rituximab treatment inANCA-associated vasculitides compared to rheumatoid arthritis, and connective tissuediseases: a longitudinal observational study on 120 patients. Arthritis Res Ther 2017;19:101.
- beside transient hypogammaglobulinemia (common) after Rituximab, "late-onset" neutropenia also appears one to five months after the end of infusion

IL 17 inhibitors Mechanism of action



IL17 inhibitors

➢Patients treated with IL-17 inhibitors(secukinumab, brodalumab) are at increased risk of the following infections:

- TB and other mycobacterial infections
- Candida infections, especially oral candidiasis
- Dermatologic fungal infections (eg, tinea)
- Common viral and bacterial pathogens (eg, nasopharyngitis, upper respiratory tract infections, urinary tract infections)

Secukinumab has been used in patients with HBV and HCV infection without viral reactivation and very few cases of TB and other mycobacterial infections have been reported with these agents, so the overall risk is very low

Hindawi
International Journal of Clinical Practice
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https://doi.org/10.1155/2022/2442603

Review Article

Risk of *Candida* Infection and Serious Infections in Patients with Moderate-to-Severe Psoriasis Receiving Biologics: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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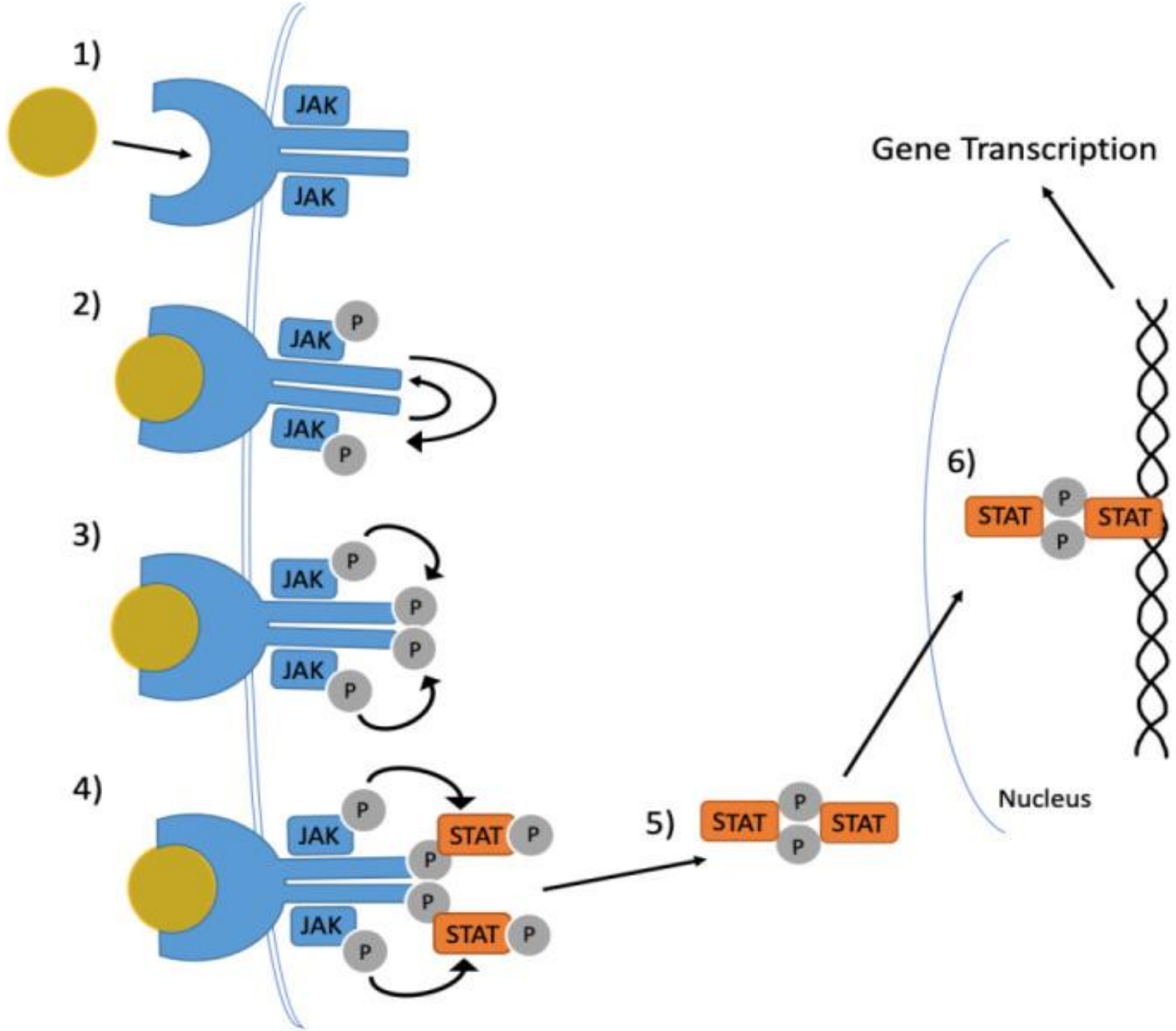
Results

- this systematic review and meta-analysis included 48 published articles that consisted of data from 52 RCTs
- pooled analysis of 11 RCTs using placebos and anti-IL-17 agents, showed that they significantly increased the risk of Candida infection compared with placebos Previously, Candida infections were most commonly found in the oral cavity and vulvovaginal mucosal surfaces, with only one ear infection reported
- In a separate analysis, it was found that secukinumab, but not ixekizumab or brodalumab, significantly increased the risk of Candida infection
- patients with psoriasis had significantly higher Candida species colonization than controls and patients with psoriasis are more likely to get Candida infection
- In patients with psoriasis, anti-IL-17 agents, but not anti-IL-12/23 agents, may have significantly increased the risk of Candida infection

JAK inhibitors new players in field

- As they quickly enter the systemic circulation, they have a rapid onset of action and can induce fast clinical response
- Compared to TNF-α inhibitors or anti-α4β7 integrin inhibitors that block a single or a few specific molecules, JAK inhibitors can block multiple cytokines from different inflammatory pathways simultaneously, thus potentially improving the therapeutic response
- JAK inhibitors do not elicit anti-drug antibodies; thus, immunogenicity is not an issue concerning JAK inhibitor therapy
- They are administered orally and don't need special infusion settings

Mechanism of action in JAK/STAT signaling



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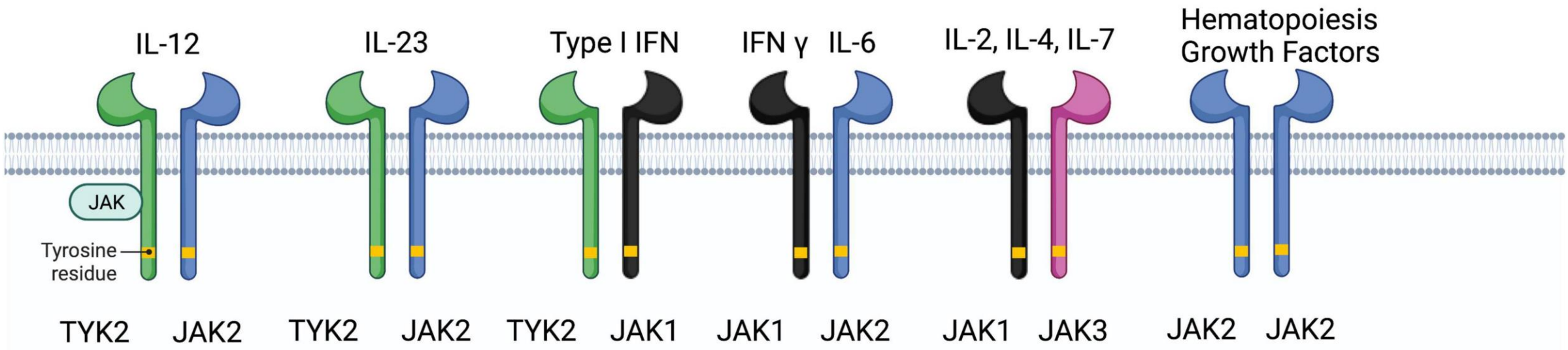

STATs PROTEINS binding to their receptor in nucleus

Th1 differentation

Th17 differentation

B cell differentation

Lipid Metabolism
Th1 differentation

Treg maintenance
Th2 differentation

Hematopoiesis

Risk of infection in JAKi users

- Tuberculosis (TB) and other mycobacterial infections
- Hepatitis B virus (HBV) and hepatitis C virus (HCV)
- Herpes zoster virus
- Epstein-Barr virus and cytomegalovirus (CMV)
- Progressive multifocal leukoencephalopathy (PML)
- Endemic mycoses
- Cryptococcal infection
- *Pneumocystis* pneumonia
- Common viral and bacterial infections (sinopulmonary infections, pneumonia, urinary tract infections, cellulitis)

Baricitinib

- Baricitinib, and ruxolitinib, are JAK1/JAK2 inhibitors that block plasmablast, Th1, and Th17 differentiation and innate stimulation of T cells
- Patients receiving baricitinib most commonly report respiratory infections, bronchitis, and UTI
- Herpes zoster occurred more frequently in patients receiving baricitinib compared with placebo in clinical trials

Tofacitinib

- Tofacitinib inhibits pan jak/stat signaling that comes from IFNY, IL17,IL23 and TNF altogether
- Infections reported in patients treated with tofacitinib include pneumonia, cellulitis, herpes zoster, urinary tract infections and upper respiratory tract infections
- Opportunistic infections have been reported, including *M. tuberculosis*, *P.jirovecii* pneumonia, and cryptococcosis, as well as the reactivation of other viruses. Patients with HBV and HCV were excluded from clinical trials, but HBV reactivation has been observed
- It is unclear if risk of TB reactivation is lower with JAK inhibitors compared with TNF inhibitor or other biologic agents
- Decreased responses to pneumococcal immunization, especially in combination with methotrexate, have been observed

Janus Kinase (JAK) inhibitors				
Ruxolitinib Tofacitinib Baricitinib Other (upadacitinib, filgotinib, peficitinib, abrocitinib)	Inhibits JAK signaling and disrupts signaling pathways involved in immune cell (eg, NK cells, macrophages, T cells) activation and migration	Bacterial: ▪ Tuberculosis and other mycobacterial infections Viral: ▪ **Hepatitis B virus** ▪ Hepatitis C virus ▪ EBV and CMV ▪ **Herpes zoster virus** ▪ PML (JCV reactivation) Fungal: ▪ Endemic mycoses ▪ Cryptococcal infection ▪ Pneumocystis pneumonia	Test for: ▪ TBI ▪ HBV ▪ HCV ▪ In coccidioidomycosis-endemic regions, obtain *Coccidioides* serology (only ruxolitinib)	▪ Routine age-appropriate vaccinations ▪ Pneumococcal vaccine(s) ▪ RZV

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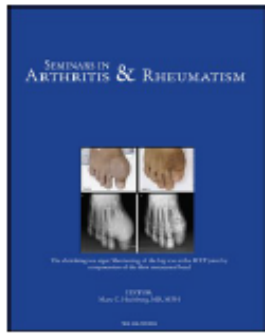

Opportunistic infections associated with Janus kinase inhibitor treatment for rheumatoid arthritis: A structured literature review

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Crude frequency rates per 100 patients (ranges) for OIs in RA patients on approved doses of JAK inhibitors

OI of interest	All JAKi	Tofacitinib	Baricitinib	Upadacitinib	Filgotinib
4–12 weeks[a]	$N = 2273$	$N = 672$	$N = 96$	$N = 638$	$N = 98$
OI (any)	0.0%	0.0% for 5 mg BD	-	-	0.0% for 100 mg OD; 0.0% for 200 mg OD
Tuberculosis	0.0%	0.0% for 5 mg BD	0.0% for 2 mg OD; 0.0% for 4 mg OD	-	0.0% for 100 mg OD; 0.0% for 200 mg OD
HZ (any form)	0.0%–3.6%	1.6%–1.9% for 5 mg BD	0.0% for 2 mg OD; 0.0% for 4 mg OD	1.8% for 15 mg OD	0.0% for 100 mg OD; 0.0% for 200 mg OD
PCP	0.0%	-	0.0% for 2 mg OD; 0.0% for 4 mg OD	-	-
HSV infection	0.0%	0.0% for 5 mg BD	0.0% for 2 mg OD; 0.0% for 4 mg OD	-	-
13–24 weeks[a]	$N =$ 6,580	$N = 1,520$	$N = 3,095$	$N = 735$	$N = 1,230$

OI of interest	All JAKi	Tofacitinib	Baricitinib	Upadacitinib	Filgotinib
25–52 weeks[a]	*N* = 8,031	*N* = 2,392	*N* = 1,462	*N* = 1,281	*N* = 1,788
OIs (any)	0.0%–2.0%	-	-	2.0% for 15 mg OD	0.0% for 100 mg OD; 0.0%–0.2% for 200 mg OD
Tuberculosis	0.0%–0.5%	0.0%–0.5% for 5 mg BD	0.0% for 2 mg OD; 0.0% for 4 mg OD	0.15% for 15 mg OD	0.0% for 100 mg OD; 0.0% for 200 mg OD
HZ (any form)	0.8%–7.5%	1.0%–2.9% for 5 mg BD	3.5% for 2 mg OD; 2.1%–2.5% for 4 mg OD	0.8% for 15 mg OD	0.8%–1.5% for 100 mg OD; 1.3%–1.9% for 200 mg OD
Candidiasis	0.0%–1.2%	-	0.0% for 2 mg OD; 0.0%–0.7% for 4 mg OD	1.2% for 15 mg OD	0.0% for 100 mg OD; 0.0–0.2% for 200 mg OD
PCP	0.0%–0.5%	-	NR for 2 mg OD; 0.5% for 4 mg OD	-	0.0% for 100 mg OD; 0.0% for 200 mg OD
Cryptococcosis (pulmonary)	0.0%	-	-	-	0.0% for 100 mg OD; 0.0% for 200 mg OD
Aspergillosis	0.15%	-	-	0.15% for 15 mg OD	-
LM infection	0.15%	-	-	0.15% for 15 mg OD	-
CMV infection	0.3%	0.3% for 5 mg BD	-	-	-
Other OIs	0.2%–0.9%	-	NR for 2 mg OD; 0.9% for 4 mg OD	0.3% for 15 mg OD	0.2% for 100 mg OD; 0.2% for 200 mg OD

- The infection profile of tumor necrosis factor (TNF) inhibitors and JAK inhibitors has been shown to be similar with regard to serious infection, although JAK inhibitors have been reported to carry a several fold higher risk of herpes zoster (HZ)

Winthrop KL, Cohen SB. Oral surveillance and JAK inhibitor safety: the theory of relativity. Nat Rev Rheumatol 2022;18(5):301–4. https://doi.org/10.1038/ s41584-022-00767-7

Why zoster?

- Although the exact pathogenic mechanism by which JAK inhibitors increase the risk of developing OI (and HZ in particular) is not clear
- it is hypothesized that this probably relates to its inhibitory effect on the intracellular signaling of cytokines acting via the JAK/STAT signaling pathway and is likely correlated with impairment in cell-mediated immunity
- Blocking signaling via JAKs could dampen antiviral defenses involving the induction of type 1 (IFN-α) and type 2 (IFN-γ) signaling via JAK-mediated signaling pathways, and also inhibit lymphocyte proliferation and functioning
- Inhibition of IL15 also disrupts NK cell development and innate immunity against viral infection

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The incidence of opportunistic infections in patients with psoriatic arthritis treated with biologic and targeted synthetic agents: A systematic review and meta-analysis

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Pt size of review

- In total, more than 17000 Psa patients were assigned to receive different doses of the tested agents and 6,425 patients were assigned to receive placebo during the placebo-controlled period (range12–48 weeks) total follow-up duration ranging from 12 to 268 weeks
- the cumulative incidence of OIs was less than 3% across all mechanism of actions examined

TABLE 1 Opportunistic infections cumulative incidence and relative risk (RR) for bDMARDs, tsDMARDs during placebo-controlled period.

Mechanism of action	No of studies	No of patients	No of placebo	Range of follow-up (weeks)	RR	95% CI	Cumulative incidence %	95% CI
TNF inhibitors	17	2621	1984	12–48	0.87	0.37–2.01	0.00	0.00–0.00
IL-17 inhibitors	9	2578	1312	12–24	2.27	1.03–4.99	0.26	0.01–0.70
JAK inhibitors	6	1957	1003	12–24	2.25	1.16–4.35	1.10	0.53–1.83
IL-23 inhibitors	6	1744	1217	24	0.88	0.26–3.02	0.02	0.00–0.25
PDE4 inhibitors	6	1595	848	12–24	1.00	0.31–3.24	0.00	0.00–0.04
IL-12/23 inhibitors	3	693	380	12–24	0.99	0.17–5.67	0.00	0.00–0.27
CTLA4-Ig	3	464	315	12–24	1.18	0.22–6.23	0.02	0.00–0.66

Results cont’d

- Among Pts received anti-IL-17 The incidence of opportunistic Candida spp. infections was 0.97%, which is in concordance with previous studies
- Anti-IL-17 therapies, by either blocking the IL-17 receptor or IL-17A and/or IL-17F homodimers or heterodimers, increase the incidence of Candida infections but not systemic, disseminated or invasive candidiasis
- The incidence of OIs in anti-TNF treated patients was 0.01% That was in contrast to data from a study that found the increased RR of OI among Anti-TNF treated RA Pts
- In this study, 5 cases of M. tuberculosis infection among well-screened and monitored patients with PsA were reported, emphasizing the need for increased surveillance during anti-TNF treatment.

Anti TNF vs. jaki for risk of herpes zoster

- Evidence from real-world data and the Phase 3b/4 ORAL Surveillance study, suggest that HZ occurs more frequently among tofacitinib initiators compared with those using TNFi or other biologics
- Available evidence demonstrates a higher incidence of HZ in Asian countries compared with Western Europe and North America
- This is consistent with the incidence rates we observed in systematic reviews, where TNFi comparator arms were studied. Incidence rates were consistently 2–3-fold lower for TNFi arms within these trials
- unlike TNFi therapy, where the risk of HZ (any form) is greater within the first 6 months of treatment the zoster frequency observed in the current review appears to be persistent and relatively stable over time

Curtis JR, Xie F, Yun H, Bernatsky S, Winthrop KL. Real-world comparative risks of herpes virus infections in tofacitinib and biologic-treated patients with rheumatoid arthritis. Ann Rheum Dis 2016;75(10):1843–7. https://doi.org/10.1136/ annrheumdis-2016-209131.

results

- Herpes zoster infection was the most common OI among patients treated with JAKi
- The cumulative incidence of herpes zoster infection was almost 2.5% in JAKi-treated patients
- Age comorbidities, and the effect of JAKi on T cell function and inhibition of IFN-γ and IL-15 are potential risk factors for varicella zoster virus reactivation
- Among the 130 herpes zoster infections reported, occurrence of disseminated herpes zoster or permanent drug discontinuation due to herpes zoster infection were rare

Counterregulatory measures

- As the risk for TB-reactivation with JAK inhibitors is likely similar

to that for TNF inhibitors, screening for TB per national guidelines is

recommended in clinical practice

unless already done prior to initial bDMARD commencement without a subsequent risk of exposure Routine screening for any other OI is not recommended based on these data

- Furthermore, PCP prophylaxis is not indicated based on the small number of cases reported in this review

Herpes Zoster vaccination status

- Very few trials either collected or reported data on shingles vaccination status
- Interestingly, in the Phase 3b/4 tofacitinib ORAL Strategy study (*N* = 1146, of which 216 received live zoster vaccine [Zostavax], 4 weeks in advance of study treatment
- the incidence rates of HZ were numerically slightly higher in the tofacitinib live zoster vaccinated [Zostavax] groups (IR = 1.5/100 PY with tofacitinib 5 mg BD ± GC and IR = 3.0/100 PY with tofacitinib 5 mg BD + MTX ± GC) than in the non-vaccinated groups (IR = 1.0/100 PY with tofacitinib 5 mg BD ± GC and 2.2/100 PY with tofacitinib 5 mg BD + MTX ± GC)
- However, in the comparator arms of those studies where Pts used adalimumab + MTX ± GC, the rates were numerically lower among vaccinated vs. unvaccinated patients (0/100 PY vs 2.1/100 PY)

Rheumatol Ther (2023) 10:1147–1165
https://doi.org/10.1007/s40744-023-00571-z

ORIGINAL RESEARCH

Infections in Biological and Targeted Synthetic Drug Use in Rheumatoid Arthritis: Where do We Stand? A Scoping Review and Meta-analysis

Barbara J. M. Bergmans · Biniyam Y. Gebeyehu · Eugène P. van Puijenbroek · Katrijn Van Deun · Bennett Kleinberg · Jean-Luc Murk · Esther de Vries

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study design

- since 1999 till 2020, 242 studies containing 512 study arms and a total of 293,431 patients were selected
- TNF inhibitors were the most often administered biological class, with 117 studies (44%), 205 study arms (42%) and 170,826 patients (58%)most patients were female (79.0%)The weighted mean age was 57 years
- Across all study arms, this comprised 58,789 (totally infected) and 168,042 (seriously infected) participants, as there were more studies reporting on serious infections only

Type of infections among biologic users

- Across all biological/targeted synthetic therapy classes, upper respiratory tract (URT) infections were the most prevalent (12.7%, 95% CI 10.6-15)followed by genitourinary tract infections (3.5%, 95% CI 2.9–4.2) and lower respiratory tract (LRT) infections (2.2%, 95% CI 1.9–2.7)
- Individual infection proportions were comparable across biological classes
- TNF inhibitors were associated with an increased proportion of mycobacterial infections (0.9%, 95% CI 0.6–1.0) compared to other drug classes
- Overall, the proportion of seriously infected patients was highest in rituximab users (6.7%, 95% CI 4.5–9.7)
  The proportion of LRT infections (3.3%, 95% CI 1.6–6.5), and skin and soft tissue infections (2.3%, 95% CI 0.4–13.4) was also relatively high in this group, as was the proportion of Herpes Zoster (11.8%, 95% CI 3.1–35.4 Compared to other drug classes

Barbara J. M. Bergmans . Biniyam Y. Gebeyehu . Euge `ne P. van Puijenbroek . Katrijn Van Deun . Bennett Kleinberg . Jean-Luc Murk . Esther de Vrie Rheumatol Ther (2023) 10:1147–1165 https://doi.org/10.1007/s40744-023-00571-z

Nonserious vs. Serious infections

- non-serious infections outnumbered serious infections in a ratio of approximately 10:1 in RA patients using biological/targeted synthetic therapies
- In particular, RA patients on molecular-targeted treatment have shown an increased risk of opportunistic infections (OIs), such as Pneumocystis pneumonia (PCP), tuberculosis (TB), nontuberculous mycobacterial infection (NTM), and herpes zoster (HZ)
- For example tofacitinib use was associated with an increased proportion of Herpes Zoster (2.8%, 95% CI 1.3–6.0) and Pneumocystis jirovecii pneumonia (PJP) (1.5%, 95% CI 0.4–4.5)

372 Case reports & case series

- Most described patients (398, 82%) used TNFi The median onset of an infectious adverse event was 9 months after start of biological/targeted therapy
- Of all reported pathogens, 326 (64%) were bacterial (of which 143 mycobacterial infections), 19.4% (99) fungal, 7.9% [40] parasitic and 8.6% viral
- Overall, the most frequently reported infections (187, 32%) occurred in the lower respiratory tract (LRT)
- The most frequently reported pathogens were Mycobacterium tuberculosis (85, 16.7% of pathogens), nontuberculous mycobacteria (50, 9.8%), Pneumocystis jirovecii (28, 5.5%), Salmonella spp (28, 5.5%), Listeria monocytogenes (24, 4.7%), Histoplasma capsulatum (22, 4.3%) and Leishmania spp (21, 4.1%)
- The largest proportion of these infections were reported in TNF-alpha inhibitor users, who are known to have difficulty clearing mycobacterial and intracellular bacterial infection

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- A meta-analysis of 70 clinical trials identified an overall increased risk of OIs (odds ratio = 1.79 compared with control patients) in patients treated with bDMARDs

Kourbeti IS, Ziakas PD, Mylonakis E. Biologic therapies in rheumatoid arthritis and the risk of opportunistic infections: a meta-analysis. Clin Infect Dis 2014;**58**:1649–57

most of the data are from limited facilities or short time periods within 1 year, and reports. covering the whole country or OIs over the long term are scarce

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Original Article

Incidence of opportunistic infections in patients with rheumatoid arthritis treated with different molecular-targeted drugs: A population-based retrospective cohort study

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Selection of patients with OI from the national database of japan 2010-2017

	PCP	TB	NTM	HZ	Total patients
(1) RA patients with both MTAT and OI in 7 years	893	1347	904	24,406	205,906
(2) RA patients with OI which occurred after MTAT in 7 years	765	1158	834	18,336	205,906
(3) Naïve patients among (2) cases	406	538	437	7892	121,288
(4) Among naïve patients OI occurred during MTAT	303–311	353	323	5067	121,288
(5) Among (4) cases eliminated previous OI just before MTAT started	302	300	199	5051	121,288

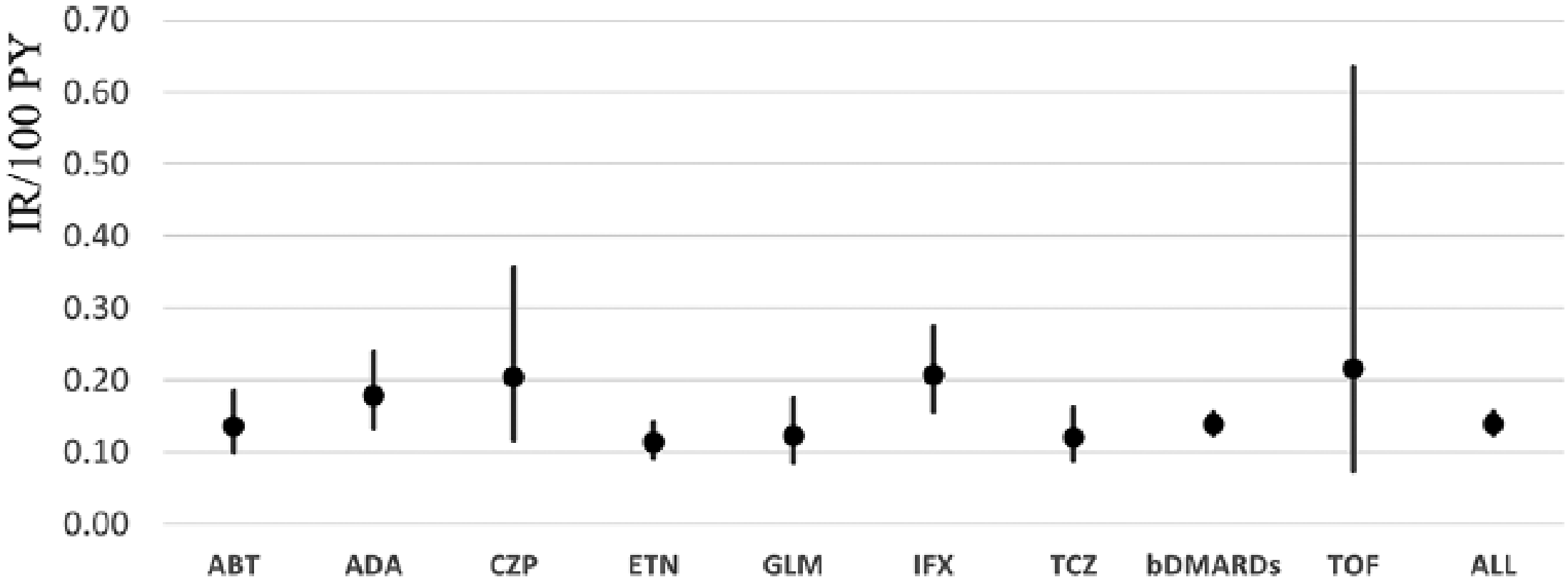
- using the NDB which covers the whole country. The resultant incidences of PCP, TB, NTM, and HZ were 765, 1158, 834, and 18,336 in 7 years, respectively, which implied 109, 165, 119, and 2619, respectively, per year in the whole of Japan
- The biggest difference in IR among them was seen in HZ: TOF shows a higher HZ IR of 7.00 (95% CI = 5.70–8.59) than that of the bDMARDs as a whole [2.40 (95% CI = 2.31–2.44)], which has also been reported by others
- There was no big difference in IRs of OIs between TNF and non-TNF, although there were statistically significant differences between a few TNF

Incidence ratio of OIs for each molecular-targeted drug

Table 3. IRs of OIs for each molecular-targeted drug.

		bDMARDs							JAKi	
		ABT	ADA	CZP	ETN	GLM	IFX	TCZ	TOF	All
PCP	Patients	17,647	14,248	4797	36,887	15,197	12,000	19,314	120,090	1182	121,272
	Events	40	44	12	84	30	47	42	299	<10	300–308
	IRs (/100PY)	0.14	0.18	0.20	0.11	0.12	0.21	0.12	0.14	0.22	0.14
	95% CI	0.1–0.18	0.13–0.24	0.12–0.36	0.09–0.14	0.09–0.17	0.16–0.28	0.09–0.16	0.12–0.15	0.07–0.63	0.12–0.16
TB	Patients	17,622	14,241	4791	36,869	15,196	11,997	19,311	120,027	1181	121,208
	Events	36	41	16	82	36	44	42	297	<10	298–306
	IRs (/100PY)	0.12	0.17	0.27	0.11	0.15	0.19	0.12	0.14	0.22	0.14
	95% CI	0.09–0.17	0.12–0.23	0.17–0.44	0.09–0.14	0.11–0.2	0.14–0.26	0.09–0.16	0.12–0.15	0.07–0.64	0.12–0.15
NTM	Patients	17,566	14,243	4794	36,867	15,193	11,999	19,309	119,971	1180	121,151
	Events	56	20	<10	50	17	14	38	196–204	<10	197–205
	IRs (/100PY)	0.19	0.08	0.05	0.07	0.07	0.06	0.11	0.09	0.07	0.09
	95% CI	0.15–0.25	0.05–0.13	0.02–0.15	0.05–0.09	0.04–0.11	0.04–0.1	0.08–0.15	0.08–0.11	0.01–0.41	0.08–0.11
HZ	Patients	17,609	14,227	4793	36,845	15,177	11,982	19,287	119,920	1180	121,100
	Events	737	571	125	1542	605	533	847	4960	91	5051
	IRs (/100PY)	2.6	2.4	2.2	2.2	2.6	2.4	2.5	2.4	7.0	2.4
	95% CI	2.42–2.79	2.21–2.6	1.83–2.6	2.05–2.26	2.36–2.77	2.24–2.66	2.35–2.68	2.31–2.44	5.7–8.59	2.34–2.47

PCP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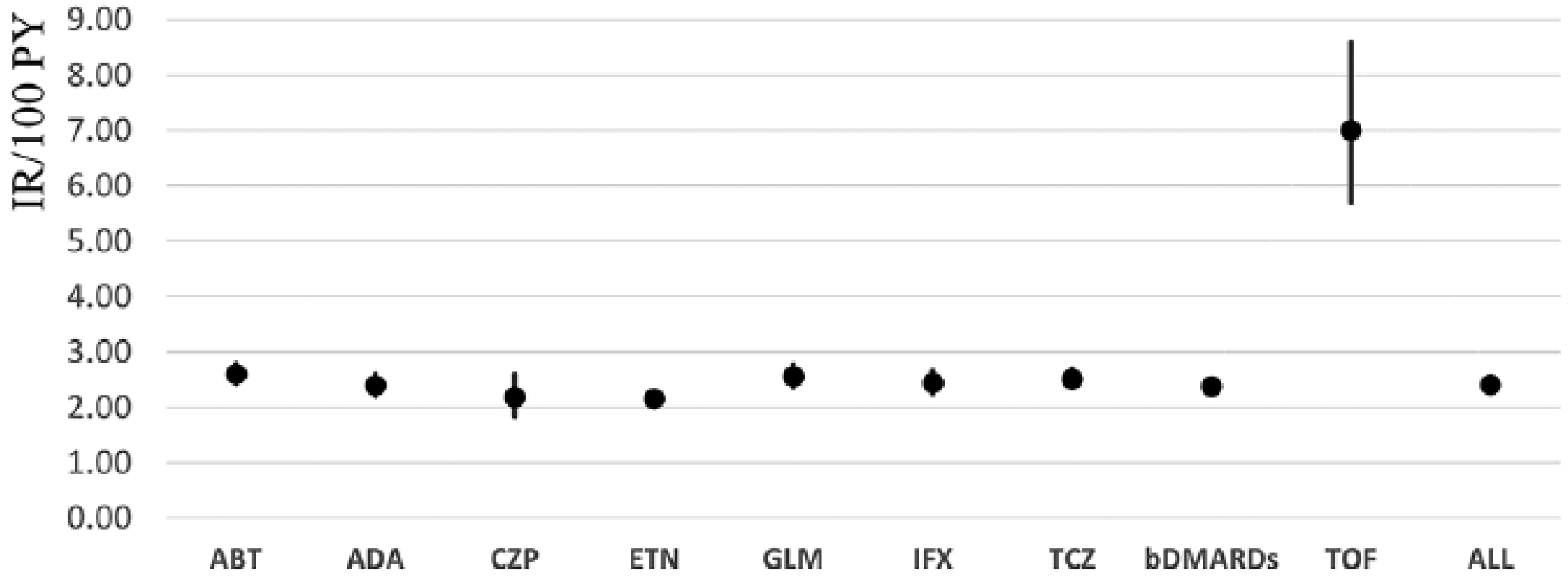
ETN
GLM
IFX
TCZ
bDMARDs
TOF
ALL

HZ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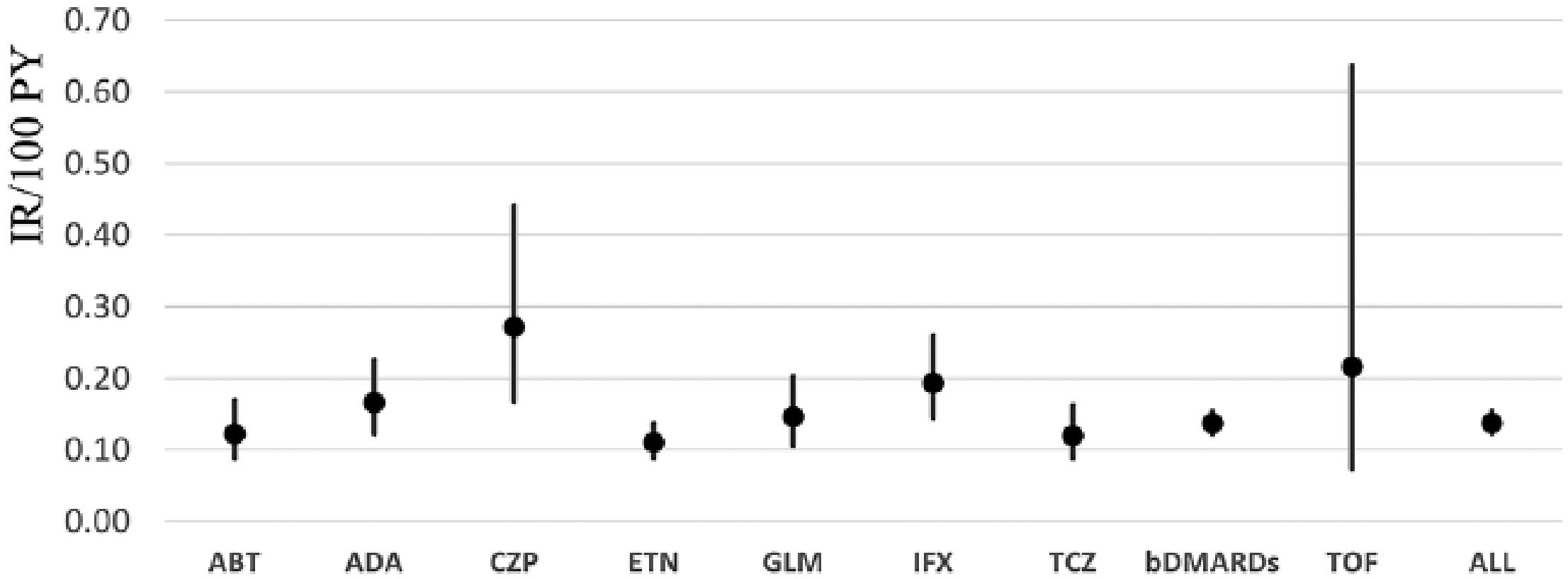
ALL

TB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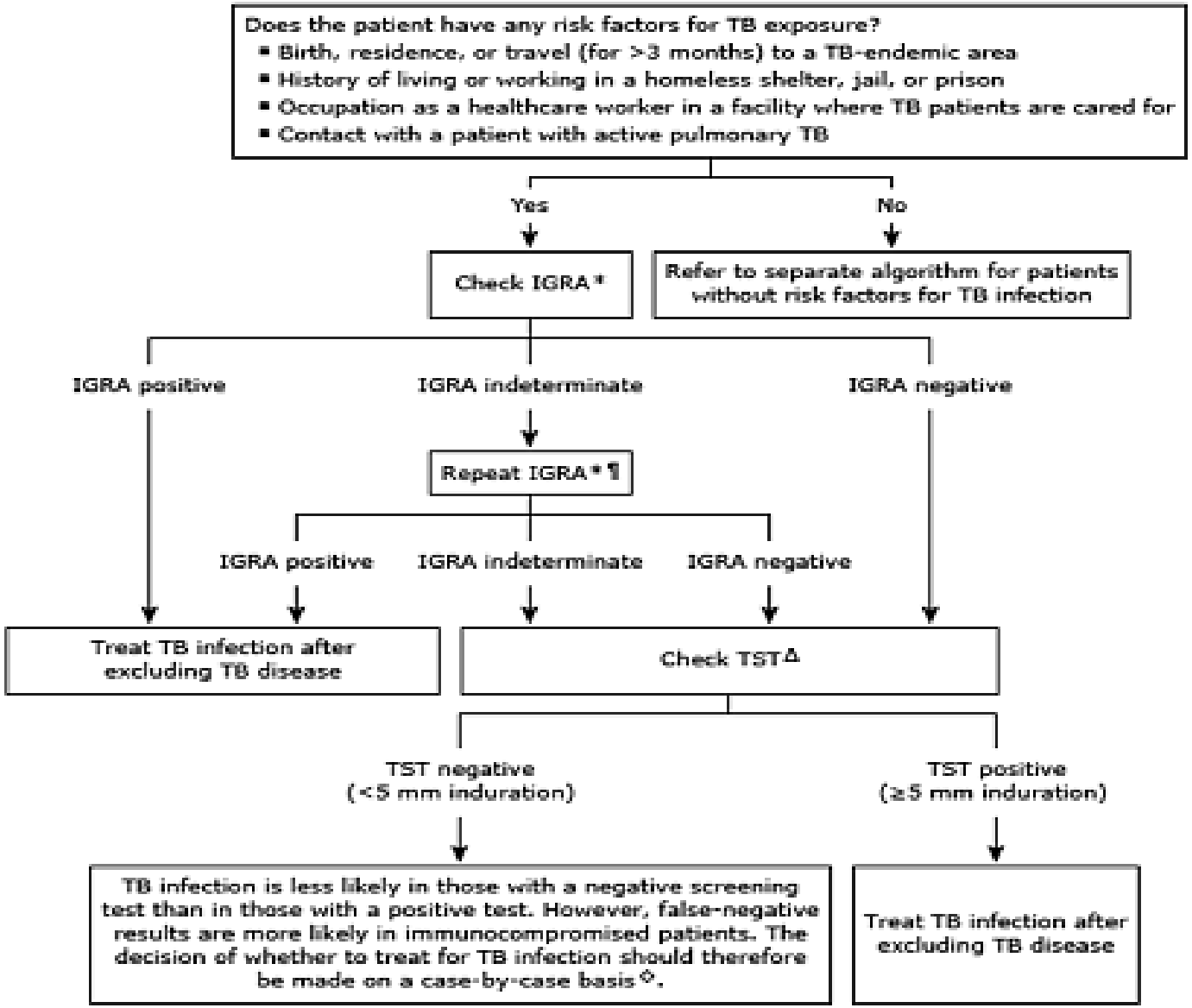
TCZ
bDMARDs
TOF
ALL

Does age matters?

- Regarding ages, OIs showed a higher IR in the elderly as many papers previously reported. However, there was little difference between 65–74 years old and those >75 years old, except for TB

TB screening prior to receipt of a biologic agent or JAK inhibitor for patients with TB risk factors



Thanks for your attention