PICO 8. IS THERE ANY EVIDENCE FOR HERPES ZOSTER VACCINATION BEFORE STARTING tsDMARD (JAK INHIBITOR) TREATMENT?

The clinical question is: “Is the use of herpes zoster vaccination in patients with rheumatoid arthritis and with indication for the use of Janus Kinase inhibitors, is it effective and safe”?

The eligibility elements of the studies are:

1. Adult patients with rheumatoid arthritis with indication for the use of JAK inhibitors;
2. Vaccinated for Herpes Zoster prevention with live attenuated zoster vaccine [LZV] or recombinant zoster vaccine [RZV];
3. Compared with unvaccinated for Herpes Zoster;
4. Clinical outcomes - incidence of herpes zoster, adverse events related to vaccination, humoral immune response, cell-mediated immune response;
5. Intermediate outcomes excluded;
6. Randomized clinical trial (RCT), observational cohort, before and after, case series;
7. No period or language limit;
8. Abstracts with data or full texts available for access.

The search for evidence was carried out in the virtual scientific information bases using the search strategies:

Medline/PubMed: #1 (Herpes OR Zoster OR Herpesvirus) AND (JAK inhibitor OR JAK inhibitors OR Janus Kinases Inhibitors OR Janus Kinase Inhibitors OR Upadacitinib OR Protein Kinase Inhibitors OR Tofacitinib OR Baricitinib) – 1.189

#2 (Herpes OR Zoster OR Herpesvirus) AND (JAK inhibitor OR JAK inhibitors OR Janus Kinases Inhibitors OR Janus Kinase Inhibitors OR Upadacitinib OR Protein Kinase Inhibitors OR Tofacitinib OR Baricitinib) AND (Vaccine OR Vaccines OR prophylaxis OR (prevention and control)) – 78

#3 (Arthritis, Rheumatoid OR Rheumatoid Arthritis OR Sjogren's Syndrome OR Caplan Syndrome OR Felty Syndrome OR Rheumatoid Nodule OR Rheumatoid Vasculitis OR Still Disease OR Arthritis, Juvenile OR Juvenile Arthritis OR Polyarthritis, Juvenile) AND (Herpes OR Zoster OR Herpesvirus) AND (Vaccine OR Vaccines OR prophylaxis OR (prevention and control)) – 393

CENTRAL (Cochrane): (Herpes OR Zoster OR Herpesvirus) AND (JAK inhibitor OR JAK inhibitors OR Janus Kinases Inhibitors OR Janus Kinase Inhibitors OR Upadacitinib OR Protein Kinase Inhibitors OR Tofacitinib OR Baricitinib) AND (Vaccine OR Vaccines OR prophylaxis OR (prevention and control))

EMBASE: #2. #1 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)
#1. ('herpes'/exp OR herpes OR 'zoster'/exp OR zoster OR 'herpesvirus'/exp OR herpesvirus) AND ('jak inhibitor'/exp OR 'jak inhibitor' OR (jak AND ('inhibitor'/exp OR inhibitor)) OR 'jak inhibitors' OR (jak AND ('inhibitors'/exp OR inhibitors)) OR 'janus kinases inhibitors' OR (janus AND ('kinases'/exp OR kinases) AND ('inhibitors'/exp OR inhibitors)) OR 'janus kinase inhibitors'/exp OR 'janus kinase inhibitors' OR (janus AND ('kinase'/exp OR kinase) AND ('inhibitors'/exp OR inhibitors)) OR 'upadacitinib'/exp OR upadacitinib OR 'protein kinase inhibitors'/exp OR 'protein kinase inhibitors' OR (('protein'/exp OR protein) AND ('kinase'/exp OR kinase) AND ('inhibitors'/exp OR inhibitors)) OR 'tofacitinib'/exp OR tofacitinib OR 'baricitinib'/exp OR baricitinib) AND ('vaccine'/exp OR vaccine OR 'vaccines'/exp OR vaccines OR 'prophylaxis'/exp OR prophylaxis OR (('prevention'/exp OR prevention) AND ('control'/exp OR control)))

LILACS: (Herpes OR Zoster OR Herpesvirus) AND (JAK inhibitor OR JAK inhibitors OR Janus Kinases Inhibitors OR Janus Kinase Inhibitors OR Upadacitinib OR Protein Kinase Inhibitors OR Tofacitinib OR Baricitinib) AND (Vaccine OR Vaccines OR prophylaxis OR (prevention and control))

Searches ended on June 23, 2020.

RESULTS

Figure 01 - FLOW DIAGRAM

The selection of works retrieved from the virtual databases of scientific information is detailed in the flowchart below:

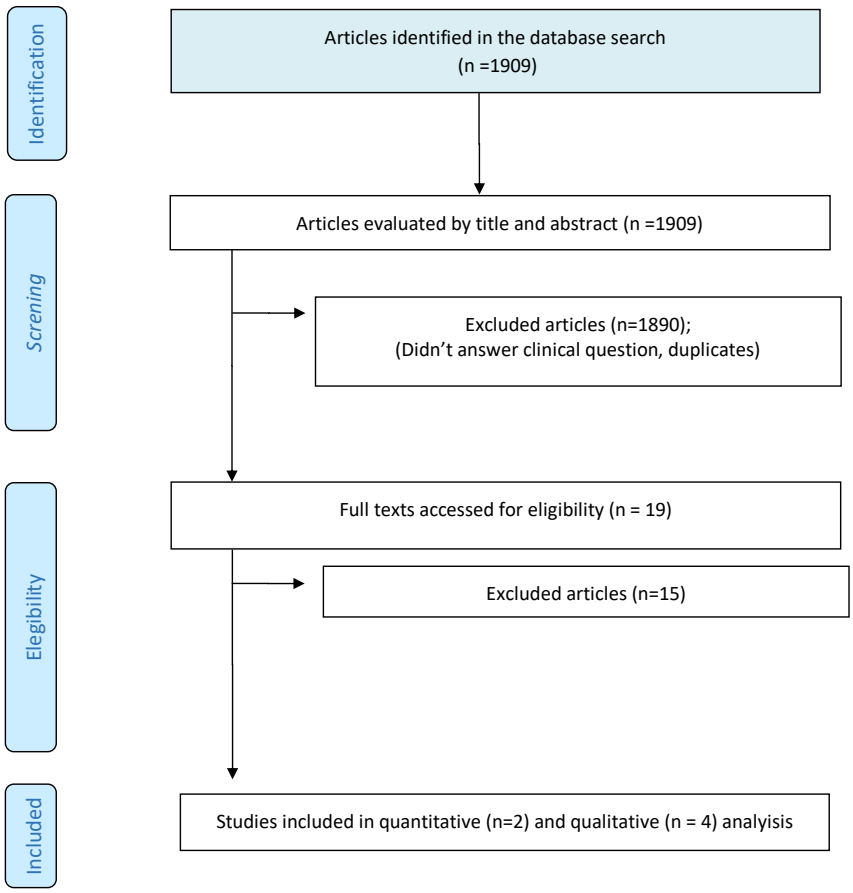

Table 1. Characteristics of the included studies

Author,yr	Design	Pacient	Intervention	Comparator	Outcome	Follow-up
Calabrese LH, 2020	Analysis of ECR ORAL Strategy patient subgroups	Age ≥ 18 years with active RA, inadequate response to MTX. ≥50 years old could choose to receive LZV 28 days before starting treatment, at the	Total = 216 LZV + TOFA 5 mg BID, N =69 TOFA 5 mg BID + MTX, N = 75	Total = 930 Non vaccinated TOFA 5 mg BID, N =315 TOFA 5 mg BID + MTX, N = 301	HZ incidence rates (IR); opportunistic infections (multidermatomus / disseminated), severe HZ events and LZV-related adverse events	1 year

		investigator's discretion	ADA 40 mg EOW + MTX N = 72	ADA 40 mg EOW + MTX, N = 314		
Winthrop KI, 2017	RCT	112 patients ≥50 years old with active RA and who were receiving MTX	N = 55 LZV + TOFA 5 mg BID + MTX 2 to 3 weeks post vaccination	N = 57 LZV + Placebo + MTX 2 to 3 weeks post vaccination	- Humoral immune response (VZV specific IgG levels) - Cellular immune response (VZV-specific T cell responses) Adverse events in 6 weeks post vaccination	14 weeks post vaccination or 12 weeks after the start of treatment
Winthrop KI, 2020	Follow-up of the previous study in a long-term open-label extension	100 RA patients who took tofacitinib after receiving LZV	N = 46 TOFA 5 mg BID N = 50 TOFA 10mg BID 14 weeks post vaccination	NO CONTROL GROUP	HZ incidence Adverse events from vaccination	27 months
Stevens E, 2020	Case series	Patients with RA (n=239) or systemic rheumatic diseases (SRD), [n=164]	RZV vaccination 52 = 12.9% received TOFA	NO CONTROL GROUP	HZ incidence Incidence of AR flare (up to 12 weeks after vaccine administration) and adverse events of vaccination	1 40 weeks post administration

ACR =American College of Rheumatology; EULAR = European League Against Rheumatism; BID = twice daily; EOW = every other weeks; IR = participants with events per 100 patient-years; LZV = live zoster vaccine; RZV = recombinant zoster vaccine; SRDs include psoriatic arthritis, systemic lupus erythematosus, spondylitis, Sjogren's syndrome, giant cell arthritis, and other diseases.

Regarding the risk of bias of the 2 RCTs included[11,12]: one study[11] performed a subgroup analysis of the ORAL Strategye RCT, therefore, with a high risk of bias despite the proportions of patients who received LZV being similar between the patients who received monotherapy with tofacitinib and tofacitinib plus MTX; another study[12] showed no risk of bias in the 14-week post-vaccination analysis. (Table 2).

Table 2. Description of the biases of the included studies

HZ vaccination in RA and treatment with JAK inhibitors									
STUDY	RANDOM	ALOCATION	DOUBLE BLIND	LOSSES	PROGNOSTIC FACTORS	OUTCOME	CALCULATION SAMPLE	ITA	EARLY INTERRUPTION
Calabrese LH, 2020									
Winthrop KI, 2017									

ITA = INTENTION-TO TREAT ANALYSIS

LOW BIAS RISK HIGH BIAS RISK UNCERTAIN BIAS RISK

Considering that the approved dose of tofacitinib for the treatment of RA in Brazil and the United States is 5 mg twice a day, we will consider this value for the analysis of the results, answering the clinical question.

LIVE ZOSTER VACCINE [LZV]

In the RCT *Oral Rheumatoid Arthritis Trial Strategy ("ORAL Strategy")*[11] , 216 of 1.146 patients (18.8%) received LZV. Overall, 18 patients (1.6%) developed HZ (vaccinated: n = 3; unvaccinated: n = 15). In vaccinated patients, the incidence rates (IRs - patients with events per 100 patient-years) for HZ were 1.5 (95%CI 0.0-8.3) for tofacitinib monotherapy, 3.0 (95%CI 0 .4-10.8) for tofacitinib plus MTX and 0 (95%CI 0.0-5.8) for ADA plus MTX. In unvaccinated patients, HZ IRs were 1.0 (95%CI 0.2-3.0) for tofacitinib monotherapy, 2.2 (95%CI 0.8-4.7) for tofacitinib plus MTX, and 2, 1 (95%CI 0.8-4.5) for ADA plus MTX. The IRs were generally similar for patients who received LZV (18.8% patients were vaccinated) versus those who did not (81.2%).In patients ≥50 years of age who were vaccinated, the HZ IRs were 1.6 (95% CI 0.0-8.9) for tofacitinib monotherapy, 3.1 (95% CI 0.4-11, 4) for tofacitinib plus MTX and 0 (95% CI 0.0-5.8) for ADA plus MTX. In unvaccinated patients, HZ RIs were 0.9 (95%CI 0.0-4.7) for tofacitinib monotherapy, 4.0 (95%CI 1.3-9.3) for tofacitinib plus MTX, and 2 .4 (95%CI 0.5-7.1) for ADA plus MTX. Quality of evidence - GRADE - for these outcomes in Appendices - Tables 3 and 4). The effectiveness of LZV could not be fully evaluated, as a minority (<20%) of patients received LZV in the "ORAL Strategy".
There were three multidermatomus, 1 disseminated and 2 severe HZ events. No vaccinated patient had zoster-like lesions within 42 days after vaccination; 1 patient had erythema at the vaccination site.

Wintrop Kl, et al (2017)[12] in a study included 112 patients, aged 50 years or older with active rheumatoid arthritis using methotrexate, who were vaccinated (LZV) and randomized to receive tofacitinib or placebo, started 2 to 3 weeks after vaccination for up to 12 weeks. The primary endpoint was the assessment of the mean geometric duplication rate (MGDR - considering 80% CI) in the varicella-zoster virus (VZV) specific IgG titer six weeks after vaccination. The geometric mean for TOFA at 6 weeks (post-vaccination) for the IgG level was 2,105 (80%CI 1,871 to 2,369) and for placebo 1,736 (80%CI 1,546 to 1,950), with a Ratio of MGDRs (Tofacitinib/Placebo) equal to 1,213 (IC80% 1,033 to 1,424).The GMFR VZV-specific T cells were similar in the tofacitinib group and in the placebo group (1.50 and 1.29, respectively).Secondary outcomes included the proportion of patients who achieved a ≥1.5-fold increase in VZV-specific IgG titer (defined as responder) at six weeks post-vaccination. The TOFA group had a higher number of responders (ARA 14%, 95%CI -0.05 to 0.33), however, without statistical significance. Tofacitinib therapy after vaccination had no negative impact on the established immune response.

Serious adverse events occurred in 3 patients in the tofacitinib group (5.5%) and 0 patients (0.0%) in the placebo group. One patient had disseminated chickenpox infection after starting tofacitinib. This patient was the only participant who did not have chickenpox in the past, which emphasizes the importance of giving the vaccine only to patients who had chickenpox, because herpes zoster arises when chickenpox virus is reactivated.

A follow-up of these patients in an open-label long-term extension study[13] included 46 patients on a mean dose of TOFA 5 mg and 54 patients on a mean dose of 10 mg twice a day. Five patients developed herpes zoster at 218, 280, 748, 741 and 544 days after vaccination, respectively. All cases were mild to moderate in severity and resolved with antiviral treatment. Three of the five patients who developed herpes zoster during the study had undetectable cell-mediated cellular immunity to varicella zoster virus (VZV) after vaccination, both at baseline and at week 6. The other two patients who developed herpes zoster responded adequately to vaccination for both IgG and ELISPOT measurements, but had lower than mean VZV IgG levels at baseline and at week 6. These results suggest that LZV may not provide adequate long-term protection, as previously demonstrated in healthy individuals with age ≥60 years 3 years after vaccination, in which the risk of HZ was reduced by 51%[15].

ZOSTER RECOMBINANT VACCINE [RZV]

Stevens E, et al (2020)[14] retrospectively evaluated the impact of recombinant zoster vaccine on RA and other patients with systemic rheumatic disease (SRD) by measuring the risk of an outbreak and the

incidence of side effects. Data from 403 patients (239 with RA and 164 with SRD) were included at a mean follow-up of 12.5 weeks, ranging from 1 to 40 weeks, after administration. Only 52 (12.9%) patients received tofacitinib. Three cases of HZ have been reported. One patient had RA and was taking tofacitinib and methotrexate, a second patient with RA was taking only tofacitinib, and a third patient with lupus was taking mycophenolate mofetil and belimumab. All cases were self-limited, occurred in a single dermatome and were successfully treated with antiviral therapy.

Table 3. LZV vaccine compared to not vaccinating, before starting JAKs

Outcomes/n	Relative effect (95% CI)	**Potential absolute effects (95% CI)**			Certainty	What happens
		Unvaccinated (LZV)	Vaccinated (LZV)	Difference		
HZ incidence n: 760 (1 RCT)	**RR 1.40** (0.38 to 5.09)	1.5%	**2.0%** (0.6 to 7.4)	**0.6% more** (0,9 minus to 6 more)	⊕⊕⊕◯ MODERATE[a]	nothing
HZ - incidence TOFA 5 mg BID n: 384 (1 RCT)	**RR 1.52** (0.16 to 14.41)	1.0%	**1.4%** (0.2 to 13.7)	**0.5%** more (0,8 minus to 12,8 more)	⊕⊕⊕◯ MODERATE [b]	nothing
HZ - incidence TOFA 5 mg BID+ n: 376 (1 RCT)	**RR 1.34** (0.28 to 6.50)	2.0%	**2.7%** (0.6 to 13)	**0.7%** more (1,4 minus to 11 more)	⊕⊕⊕◯ MODERATE [c]	nothing
Responders (achieved a ≥1.5-fold increase in VZV-specific IgG titer) n: 107 (1 RCT)	**RR 1.32** (0.90 to 1.94)	43.4%	**57.3%** (39.1 to 84.2)	**13.9%** more (4,3 minus to 40,8 more)	⊕⊕⊕◯ MODERATE [d]	nothing

Explanations
a,b,c,d Subgroup analysis of an RCT without description of randomization, blindfolded allocation, and blinding. There was no sample calculation and analysis by intention to treat

Table 4. Patients ≥50 years vaccinated (LZV) compared to unvaccinated before starting JAKI

Outcomes/n	Relative effect (95% CI)	**Potential absolute effects (95% CI)**			Certainty	What happens
		Unvaccinated (LZV)	Vaccinated (LZV)	Difference		
HZ incidence n: 400 (1 RCT)	**RR 0.96** (0.24 to 3.85)	2.3%	**2.2%** (0.5 to 8.8)	**0.1% minus** (1,7 minus to 6,5 more)	⊕⊕⊕◯ MODERATE[a]	nothing
Incidência HZ - TOFA 5 mg Nº de participantes: 194 (1 RCT)	**RR 1.98** (0.13 to 31.22)	0.8%	**1.5%** (0.1 to 24.2)	**0.8%** more (0,7 minus to 23,4 more)	⊕⊕⊕◯ MODERATE[b]	nothing
Incidência HZ - TOFA 5 mg + MTX Nº de participantes:	**RR 0.74** (0.15 to 3.74)	3.7%	**2.8%** (0.6 to 14)	**1.0% minus** (3,2 minus to 10,2 more)	⊕⊕⊕◯ MODERATE[c]	nothing

Table 4. Patients ≥50 years vaccinated (LZV) compared to unvaccinated before starting JAKI

Outcomes/n	Relative effect (95% CI)	Potential absolute effects (95% CI)			Certainty	What happens
		Unvaccinated (LZV)	Vaccinated (LZV)	Difference		
206 (1 RCT)						

* The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk of the comparator group and the relative effect of the intervention (and its 95% CI)

References

1. Schmader KE, Dworkin RH. Natural history and treatment of herpes zoster. J Pain. 2008;9(1 Suppl 1):S3-9.
2. Thyregod HG, Rowbotham MC, Peters M, et al. Natural history of pain following herpes zoster. Pain. 2007;128(1-2):148-56.
3. Moffat J, Ku CC, Zerboni L, Sommer M, Arvin A. VZV: pathogenesis and the disease consequences of primary infection. In: Arvin A, Campadelli-Fiume G, Mocarski E, et al., eds. *Human Herpesviruses: Biology, Therapy, and Immunoprophylaxis*. Cambridge: Cambridge University Press; 2007. PMID: 21348076
4. Kawai_K, Gebremeskel_BG, Acosta_CJ. Systematic review of incidence and complications of herpes zoster: towards a global perspective. *BMJ* 2014;**4**(6):e004833. [DOI: 10.1136/bmjopen-2014-004833]
5. Yun H, Yang S, Chen L, et al. Risk of herpes zoster in autoimmune and inflammatory diseases: implications for vaccination. Arthritis Rheumatol 2016;68:2328–37.
6. Winthrop KL, Furst DE. Rheumatoid arthritis and herpes zoster: risk and prevention in those treated with anti-tumour necrosis factor therapy. Ann Rheum Dis 2010;69:1735–7.
7. Curtis JR, Xie F, Yun H, et al. Real-world comparative risks of herpes virus infections in tofacitinib and biologic-treated patients with rheumatoid arthritis. Ann Rheum Dis 2016;75:1843–7.
8. Winthrop KL, Curtis JR, Lindsey S, et al. Herpes Zoster and Tofacitinib: Clinical Outcomes and the Risk of Concomitant Therapy. *Arthritis Rheumatol*. 2017;69(10):1960-1968. doi:10.1002/art.40189
9. Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.
10. GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University, 2015 (developed by Evidence Prime, Inc.). Available from gradepro.org.
11. Calabrese LH, Abud-Mendoza C, Lindsey SM, Lee SH, Tatulych S, Takiya L, et al. Live Zoster Vaccine in Patients With Rheumatoid Arthritis Treated With Tofacitinib With or Without Methotrexate, or Adalimumab With Methotrexate: A Post Hoc Analysis of Data From a Phase IIIb/IV Randomized Study. Arthritis Care Res (Hoboken) 2020;72:353-359. PMID: 31207152
12. Winthrop KL, Wouters AG, Choy EH, Soma K, Hodge JA, Nduaka CI, et al. The Safety and Immunogenicity of Live Zoster Vaccination in Patients With Rheumatoid Arthritis Before Starting Tofacitinib: A Randomized Phase II Trial. Arthritis Rheumatol 2017;69:1969-1977. PMID: 28845577
13. Winthrop KL, Wouters A, Choy EH, Chen C, Biswas P, Wang L, et al. Long-term effectiveness of live herpes zoster vaccine in patients with rheumatoid arthritis subsequently treated with tofacitinib. Ann Rheum Dis 2020;79:669-671. PMID: 32161057
14. Stevens E, Weinblatt ME, Massarotti E, Griffin F, Emani S, Desai S. Safety of the Zoster Vaccine Recombinant Adjuvanted in Rheumatoid Arthritis and Other Systemic Rheumatic Disease Patients: A Single Center's Experience With 400 Patients. ACR Open Rheumatol 2020 May 15. doi: 10.1002/acr2.11150. PMID: 32412669.
15. Winthrop KL, Furst DE. Rheumatoid arthritis and herpes zoster: risk and prevention in those treated with anti-tumour necrosis factor therapy. *Ann Rheum Dis*. 2010;69(10):1735-1737. doi:10.1136/ard.2010.133843