Increased Risk of Herpes Zoster with JAK Inhibitors vs Biologics in Atopic Dermatitis: *A Real-World Comparative Study*

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Why Compare JAKi and Biologics?

- Atopic dermatitis affects ~10% of adults in the US
- **Dupilumab (FDA 2017):** mainstay treatment with favorable safety profile
- **JAKi (FDA 2022):** oral, rapid onset, effective in refractory cases or inadequate response with biologics
  - JAKi carry boxed warnings for infections including **herpes zoster**.

Evidence to Date

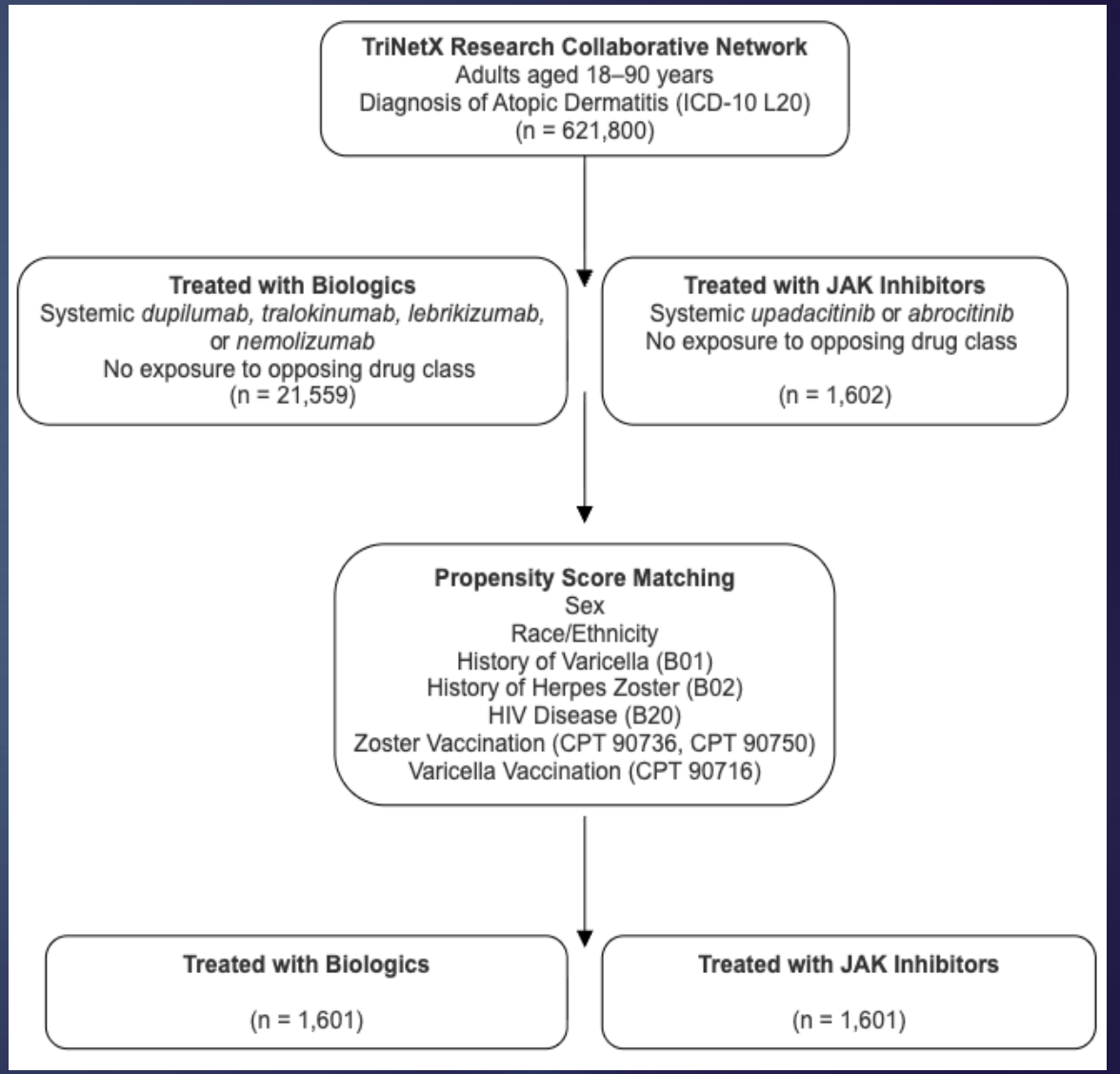
- HZ reported in ~2–4% of JAKi users vs <1% with biologics.
- JAK blockade → ↓ IFN-mediated antiviral defense → VZV reactivation.
- Prior studies limited by **short follow-up**, **exclusion of high-risk patients**, **mixed drug indications**, or **off-label agents**
- Our TriNetX study incorporated **all FDA-approved systemic agents** in a matched, **national-level analysis**

Methods – Study Design

Design: Retrospective cohort (TriNetX, ~105 U.S. health systems).

Cohort

- Adults **18–90 years** with **AD**
  - **Biologics:** dupilumab, tralokinumab, lebrikizumab, nemolizumab
  - **JAK inhibitors:** upadacitinib, abrocitinib
- **Index date:** first qualifying systemic therapy
- **Outcome:** first case of HZ
- **Follow-up:** 1-day post-index until last encounter or censoring.



Propensity-Score Matching and Analysis

1:1 PSM (nearest neighbor) on:

- Age, sex, race/ethnicity
- Prior varicella/zoster, HIV
- Zoster and varicella vaccination status

- **Balance achieved** across covariates (SMD< 0.05).

Analysis

- **Risk ratio**
- **Cox proportional HR analysis**
  - **Subgroup analyses:** Age 18–49; 50–90 yrs
  - **Sensitivity analysis:** Limited to 1-year follow-up

Table 1. Baseline Patient Characteristics Before and After PSM

	Before PSM				After PSM			
Characteristic	Total (n= 23,161)	Biologic (n= 21,559)	JAKi (n= 1,602)	P-value	Total (n= 3,202)	Biologic (n= 1,601)	JAKi (n= 1,601)	P-value
Age, mean ± SD	—	49.3 ± 18.6	48.3 ± 17.3	**0.046**	—	48.7 ± 17.5	48.3 ± 17.3	0.597
Sex								
Male	9,602 (41.9%)	9,025 (41.9%)	577 (36.0%)	**<0.001**	1,154 (36.0%)	577 (36.0%)	577 (36.0%)	1.000
Female	12,547 (58.1%)	12,524 (58.1%)	1,023 (63.9%)	**<0.001**	2,046 (63.9%)	1,023 (63.9%)	1,023 (63.9%)	0.971
Race								
White	13,741 (59.3%)	12,779 (59.3%)	962 (60.0%)	0.542	1,930 (60.3%)	968 (60.5%)	962 (60.1%)	0.828
Black	4,140 (17.9%)	3,920 (18.2%)	220 (13.7%)	**<0.001**	442 (13.8%)	222 (13.9%)	220 (13.7%)	0.918
Asian	2,232 (9.6%)	2,018 (9.4%)	214 (13.4%)	**<0.001**	427 (13.3%)	214 (13.4%)	213 (13.3%)	0.959
AI/AN	165 (0.7%)	154 (0.7%)	11 (0.7%)	0.899	21 (0.7%)	10 (0.6%)	11 (0.7%)	0.827
NH/PI	191 (0.8%)	181 (0.8%)	10 (0.6%)	0.358	20 (0.6%)	10 (0.6%)	10 (0.6%)	1.000
Other	996 (4.3%)	933 (4.3%)	63 (3.9%)	0.452	125 (3.9%)	63 (3.9%)	62 (3.9%)	0.927
Unknown	1,699 (7.3%)	1,574 (7.3%)	125 (7.8%)	0.457	248 (7.7%)	123 (7.7%)	125 (7.8%)	0.895
Ethnicity								
Not Hisp	17,196 (74.2%)	15,993 (74.2%)	1,203 (75.1%)	0.421	2,407 (75.2%)	1,205 (75.3%)	1,202 (75.1%)	0.902
Hispanic	1,282 (5.5%)	1,197 (5.6%)	85 (5.3%)	0.677	170 (5.3%)	85 (5.3%)	85 (5.3%)	1.000
Unknown	4,683 (20.2%)	4,369 (20.3%)	314 (19.6%)	0.523	625 (19.5%)	311 (19.4%)	314 (19.6%)	0.894
Prior Dx								
Varicella	73 (0.3%)	63 (0.3%)	10 (0.6%)	**0.022**	20 (0.6%)	10 (0.6%)	10 (0.6%)	1.000
HZ	901 (3.9%)	829 (3.8%)	72 (4.5%)	0.195	130 (4.1%)	58 (3.6%)	72 (4.5%)	0.210
HIV	189 (0.8%)	179 (0.8%)	10 (0.6%)	0.376	20 (0.6%)	10 (0.6%)	10 (0.6%)	1.000
Vaccines								
HZV-Live	152 (0.7%)	142 (0.7%)	10 (0.6%)	0.869	20 (0.6%)	10 (0.6%)	10 (0.6%)	1.000
HZV-Rec	402 (1.7%)	367 (1.7%)	35 (2.2%)	0.154	77 (2.4%)	43 (2.7%)	34 (2.1%)	0.299
VAR	74 (0.3%)	64 (0.3%)	10 (0.6%)	**0.025**	20 (0.6%)	10 (0.6%)	10 (0.6%)	1.000

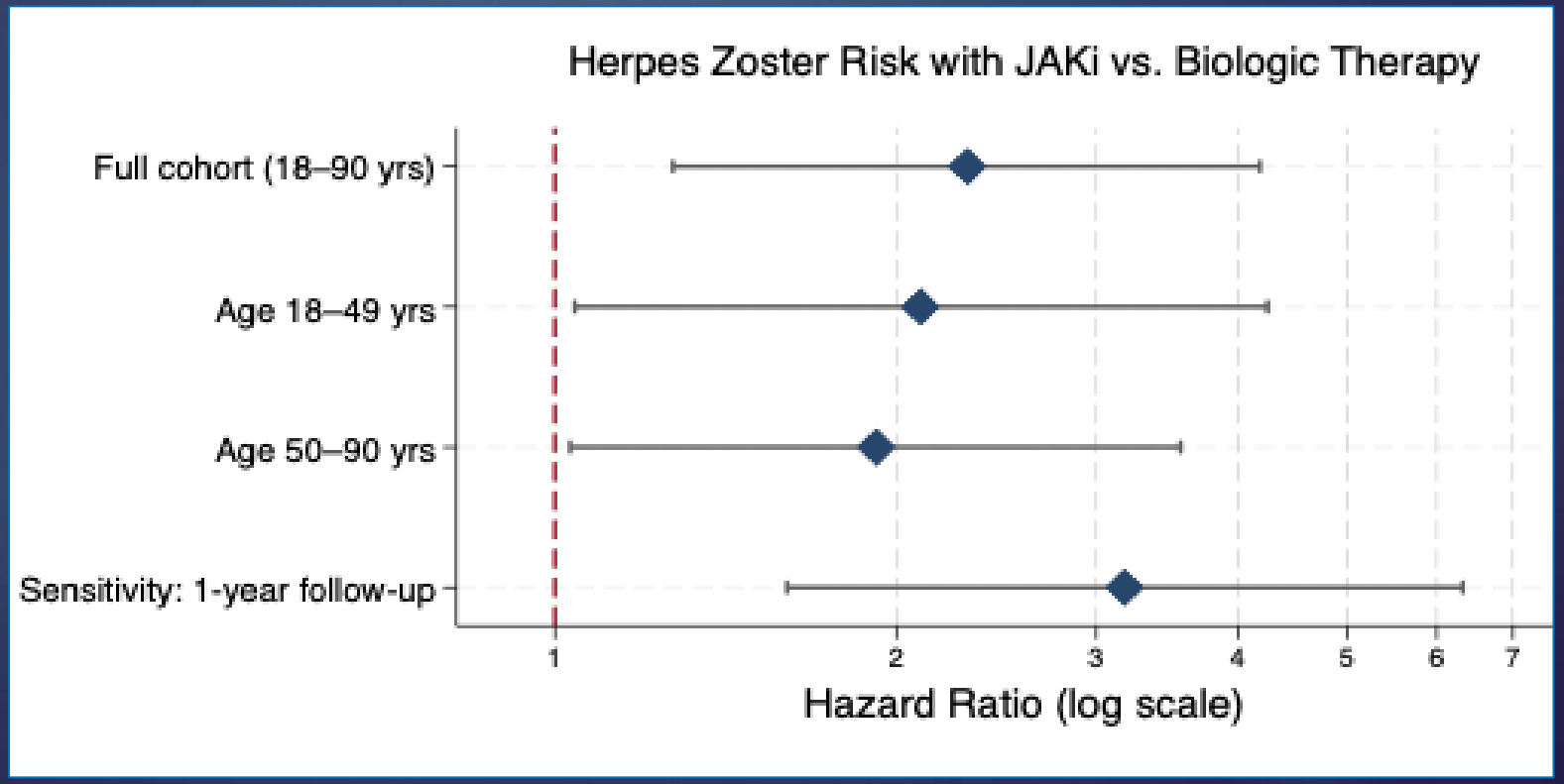
Cohort Characteristics

- **n = 3,202 total** (1,601 per group)
- **Mean age ≈ 48 years** (SD 17.5)
- **~64% female**
- **Predominantly Non-Hispanic White**
- **Low prevalence of prior HZ (<5%) or HIV (<1%)**

Results

Summary Table. Risk Estimates After PSM: JAK Inhibitors vs. Biologic Therapy

Cohort	N per group (after PSM)	HZ Events Biologic (%)	HZ Events JAKi (%)	Risk Diff. (%, 95% CI)	RR (95% CI)	HR (95% CI)	*p*-value
Full cohort	1,601	16 (1.0%)	47 (2.9%)	+1.9 (1.0–2.8)	2.89 (1.64–5.08)	**2.31 (1.27–4.19)**	<0.001
Age 18–49 yrs	808	10 (1.2%)	26 (3.2%)	+2.0 (0.5–3.4)	2.63 (1.29–5.38)	**2.10 (1.04–4.25)**	0.007
Age 50–90 yrs	705	13 (1.8%)	23 (3.3%)	+1.5 (–0.2–3.1)	1.83 (0.94–3.57)	**1.92 (1.03–3.56)**	0.04
1-year follow-up	1,601	11 (0.7%)	31 (1.9%)	+1.2 (0.5–2.0)	2.71 (1.41–5.20)	**3.18 (1.60–6.32)**	0.002



Takeaways and Next Steps

- **JAKi associated with a ~2–3× higher HZ risk** compared with biologics, after adjusting for prior HZ and vaccination status
- **Association persisted across subgroups** and after restricting follow-up to one year, indicating an **early and consistent risk**
- **Limitations:** limited information on **prescription dose**, **adherence**, **and disease course**, which may influence observed risk estimates.
- **Next steps:** Contextualize HZ risk within the broader **safety–efficacy profile** of JAKi, correlating adverse-events with **clinical metrics (IGA**, **EASI**, **SCORAD)** to guide individualized treatment decisions.

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Thank You