
بسم الله الرحمن الرحيم

Varicella-Zoster Virus and Autoimmune Diseases

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Agenda

- VZV and Autoimmune Disease Link
- Immunosuppressive Therapies and VZV
- Vaccination Guidelines Overview

VZV and Autoimmune Disease Link

Rheumatoid Arthritis and VZV

- **RA patients** *exhibit* doubled shingles risk
  - Incidence: 12.1 vs. 5.4/1,000 person-years
  - Immunosuppression increases VZV reactivation likelihood
- *Environmental factors* **contribute** to RA susceptibility
  - Smoking, periodontal disease linked to RA
  - **VZV transmission via respiratory droplets**; unclear link to RA onset/exacerbation.

- Rare cases: RA remission post-varicella or HZ, mechanism unclear.
- Glucocorticoids, DMARDs suppress immune responses
  - **JAK inhibitors** particularly increase risk
- HZ Risk:
  - Incidence: 12.1 (US) and 9.1 (Japan) cases per 1000 person-years vs. 5.4 and 4.15 in controls.
- RA patients: 2x HZ risk compared to general population.
- Medication influences HZ risk.

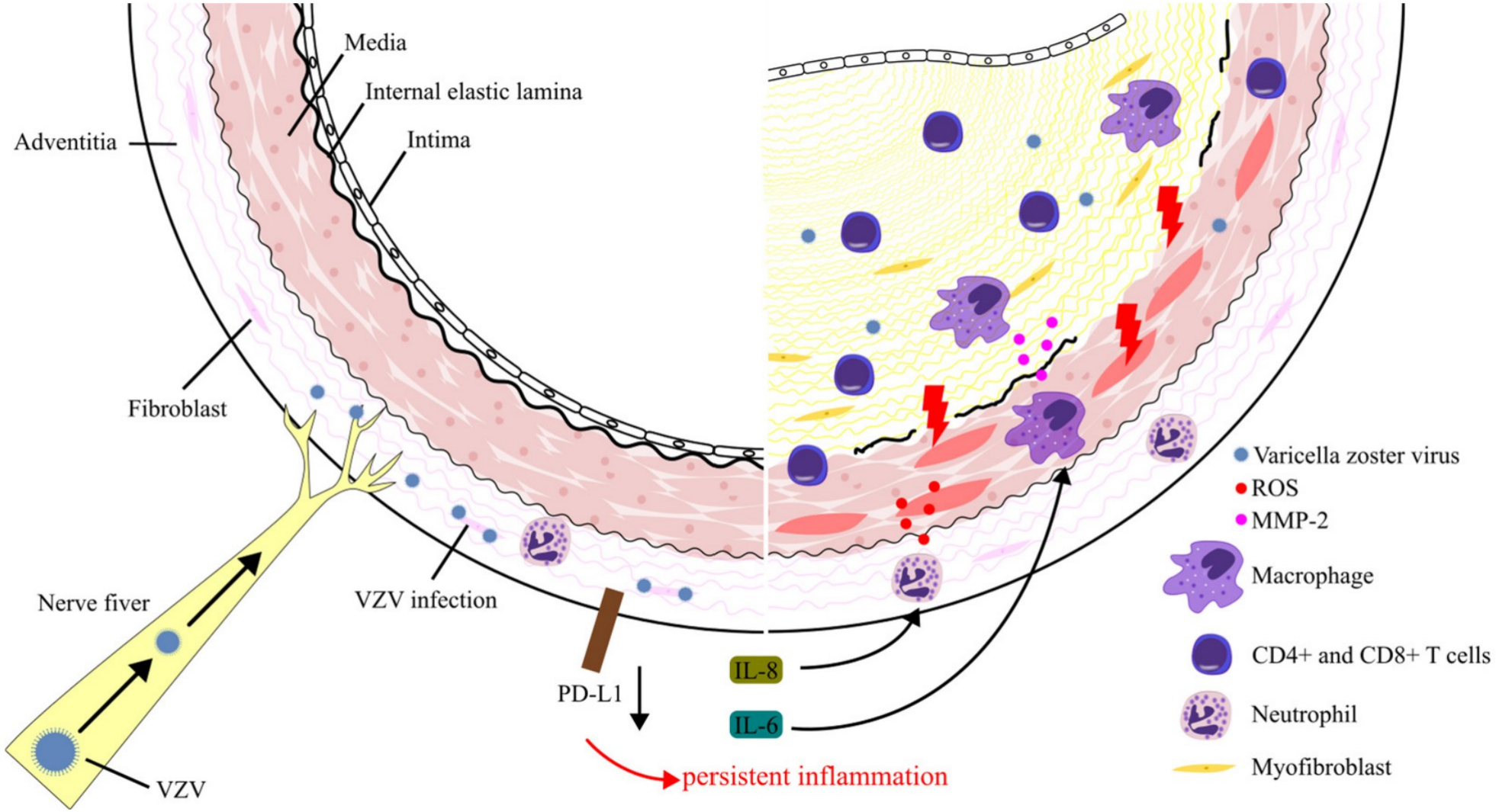
Systemic Lupus Erythematosus and VZV

- **SLE patients** *face* high shingles incidence
  - Rates**: 6.4–91.4 per 1,000 person-years**
  - Particularly elevated in Asian populations
  - ▶ Prevalence in Japan: 43% vs. 5–6% in Western populations.
  - ▶ Fewer severe HZ complications and mortality in SLE patients
- *Immune dysregulation* **impairs** VZV-specific T-cell responses
  - Reduced CD4+ T-cell IFN-γ production
  - Higher IgG levels do not protect
- **Shingles** *occurs* during SLE remission phase
  - Half of cases in inactive SLE
  - Not solely linked to immunosuppression
- *Therapies* **increase** shingles risk in SLE

Vasculitis and VZV Connection

- **VZV** *infects* arteries causing vasculopathy
  - ***Intracranial arteritis*** leads to ischemic stroke
  - Elevated IL-6, MMP-9 in CSF
- ***Giant cell arteritis*** **linked** to VZV
  - VZV antigens in 75% GCA biopsies
  - Antiviral therapy proposed with glucocorticoids
- **ANCA vasculitis** *shows* no immune difference
  - VZV antibody levels similar to controls
  - Rare cases link VZV to flares
- *Pathogenesis overlap* **suggests** VZV-GCA connection
  - IL-6, MMPs critical in both
  - PD-L1 downregulation promotes arterial inflammation

VZV Vasculopathy Mechanisms



Immunosuppressive Therapies and VZV

Glucocorticoids and Shingles Risk

- **Glucocorticoids** *increase* shingles risk dose-dependently
  - ≥1,000 mg prednisone equivalent risky
  - Risk persists post-administration
- *Low doses* **still** elevate shingles incidence
  - <500 mg prednisone increases risk
  - 1.32 hazard ratio reported

- **Monitoring** *essential* during glucocorticoid therapy
  - Early shingles detection improves outcomes
  - Antiviral prophylaxis may be considered
- *RZV vaccination* **mitigates** glucocorticoid-related shingles
  - Administer before high-dose therapy
  - Serology confirms vaccine necessity

Conventional DMARDs and Shingles

- **Methotrexate**, **salazosulfapyridine, leflunomide**: No increased HZ risk.

- *Azathioprine* **increases** shingles risk moderately
  - Hazard ratio: 1.57–2.0 reported

- **Hydroxychloroquine** *linked* to shingles risk
  - Odds ratio: 1.77–1.95 in RA
  - Close monitoring during treatment

- ***Cyclophosphamide*** **significantly** elevates shingles incidence
  - Oral administration riskier than intravenous
  - RZV recommended before therapy

- ***Mycophenolate Mofetil*** (MMF):
  - HZ risk: 2x higher than glucocorticoids and AZP in lupus nephritis and organ transplant patients.

bDMARDs and Herpes Zoster (HZ) Risk

- ***bDMARDs Usage***:
  - ❑ Adjunctive therapy to csDMARDs for autoimmune/rheumatic diseases.
  - ❑ Targets: Cytokines, B cells, costimulatory molecules.
  - ❑ Favorable efficacy and safety profile.

▶ ***Infection Risk:***

- ❑ Higher infection risk compared to csDMARDs.
- ❑ HZ risk: bDMARDs (monotherapy/combination) aHR: 5.53 [95% CI: 2.03–3.16] vs. csDMARDs aHR: 1.48 [95% CI: 1.33–1.66].

▶ ***TNF Inhibitors***:

- ❑ 2x HZ risk vs. csDMARDs.
- ❑ Soluble TNF receptors: Lower risk than anti-TNF monoclonal antibodies.
- ❑ Mechanism: Anti-TNF antibodies cross-link transmembrane TNF, inducing T-cell apoptosis

Targeted Synthetic DMARDs: JAK Inhibitors

▶ JAK Inhibitors (JAKis): Immunosuppressive agents targeting intracellular signaling pathways critical in autoimmune diseases.

Clinical Data: Upadacitinib (UPA) trial showed HZ incidence per 100 patient-years: 0.8 (MTX alone), 1.1 (adalimumab + MTX), 3.0 (UPA 15 mg), 5.3 (UPA 30 mg)

Class Effect: Higher HZ incidence with JAKis compared to csDMARDs and bDMARDs; *dose-dependent* risk observed.

▶ Comparison: *Filgotinib may have a lower HZ risk than* upadacitinib and baricitinib (network meta-analysis findings).

Anifrolumab and Shingles Risk

- ***Anifrolumab*** *targets* type I interferon receptor
  - Approved for moderate-severe SLE treatment
  - Inhibits IFNα, IFNβ signaling pathways
- *Shingles incidence* **higher** with anifrolumab therapy
  - HZ incidence: 13.4% (anifrolumab) vs. 3.6% (placebo). ▶
  - Japanese subgroup: 24.2% (anifrolumab) vs. 5.3% (placebo).

- **Monitoring** *essential* during anifrolumab treatment
  - Early detection of shingles critical
  - First months of therapy riskiest
- *Vaccination strategies* **mitigate** anifrolumab-related shingles
  - RZV recommended before therapy initiation
  - Serology guides vaccine necessity

Vaccination Guidelines Overview

ACR Guideline

- For RMD patients aged ≥ 65 years, and RMD patients aged >18 and <65 years who are on immunosuppressive medication, giving high-dose or adjuvanted influenza vaccination is conditionally recommended over giving regular-dose influenza vaccination.
- For patients with RMD aged <65 years who are on immunosuppressive medication, pneumococcal vaccination is strongly recommended.
- **For patients with RMD aged >18 years who are on immunosuppressive medication, administering the recombinant zoster vaccine is strongly recommended.**
- For patients with RMD aged >26 and <45 years who are on immunosuppressive medication and not previously

  vaccinated, vaccination against HPV is conditionally recommended.

Indications for Varicella Vaccine in Patients with Autoimmune Diseases

- **Target Population:**
  - ❑ **Children and adults without a history of varicella**
  - ❑ **Patients prior to initiating immunosuppressive therapy**
  - ❑ **Patients with stable autoimmune diseases**

1. **Pre-Vaccination Assessment:**
    - ***Serological testing for anti-VZV IgG*** to identify susceptible individuals.

Evaluation of ***disease activity and immunosuppression severity*** using metrics such as

- SLEDAI for SLE
- DAS28 for RA

Dosing and Timing Guidelines

- **dosing**
  - administered as a two-dose series, given 4–8 weeks apart
  - In patients with AIDs, the immune response may be attenuated due to the disease or therapy, so **post-vaccination serology** to confirm immunity is recommended.
- **Timing**
  - administered before initiating immunosuppressive therapies or during periods of disease remission
  - at least 14 days before starting immunosuppressive therapies

CDC

- (CDC) recommendations, the definition of the ‘immunosuppressive therapy’ includes
- GC usage for ≥2 weeks in dosages equivalent to prednisone of 20mg/d or 2mg/kg body weight are
- methotrexate (MTX) ≥0.4mg/kg/week
- azathioprine ≥3.0mg/kg/day or 6-mercaptopurine ≥1.5mg/kg/day
- whereas dosages below these levels may be considered as a **‘low grade’ immunosuppression**
- bDMARDs and tsDMARDs are likewise defined as immunosuppressive therapy.

Immunosuppressive medication	Hold before live-attenuated virus vaccine administration	Hold after live-attenuated virus vaccine administration
Glucocorticoids[a]	4 weeks	4 weeks
Methotrexate, azathioprine[b]	4 weeks	4 weeks
Leflunomide, mycophenolate mofetil, calcineurin inhibitors, oral cyclophosphamide	4 weeks	4 weeks
JAK inhibitors	1 week	4 weeks
TNF, IL17, IL12/23, IL23, BAFF/BLyS inhibitors	1 dosing interval[c]	4 weeks
IL6 pathway inhibitors	1 dosing interval[d]	4 weeks
IL1 inhibitors Anakinra Rilonacept Canakinumab	 1 dosing interval[d] 1 dosing interval[d] 1 dosing interval[d]	 4 weeks 4 weeks 4 weeks
Abatacept	1 dosing interval[c]	4 weeks
Anifrolumab	1 dosing interval[c]	4 weeks
Cyclophosphamide IV	1 dosing interval[c]	4 weeks
Rituximab	6 months	4 weeks
IVIG[e] 300-400 mg/kg 1 gm/kg 2 gm/kg	 8 months 10 months 11 months	 4 weeks 4 weeks 4 weeks

Post-Vaccination Monitoring:

- Monitoring for adverse effects such as vesicular rashes or signs of disseminated VZV disease.
- Serological evaluation 4–8 weeks post-vaccination to confirm immunity.


THANK
YOU!