BIOLOGICAL THERAPIES AND LATENT INFECTION REACTIVATION

Masoud Mardani MD, MPH,FIDSA
Prof of Infectious Diseases
Fellowship in Immune Compromised Host and Transplant patients
Shahid Beheshti Medical University

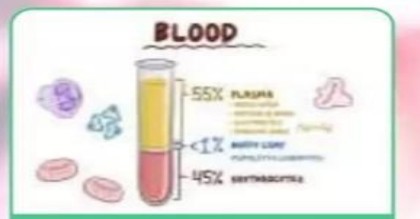
TYPES OF BIOLOGICS:

Blood derivatives

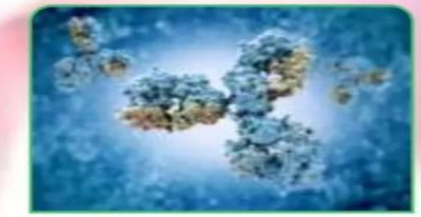
Vaccines

Allergenic extracts

Whole blood



Blood components



Proteins

Human tissues

Cellular and gene therapies

Xenotransplantation product

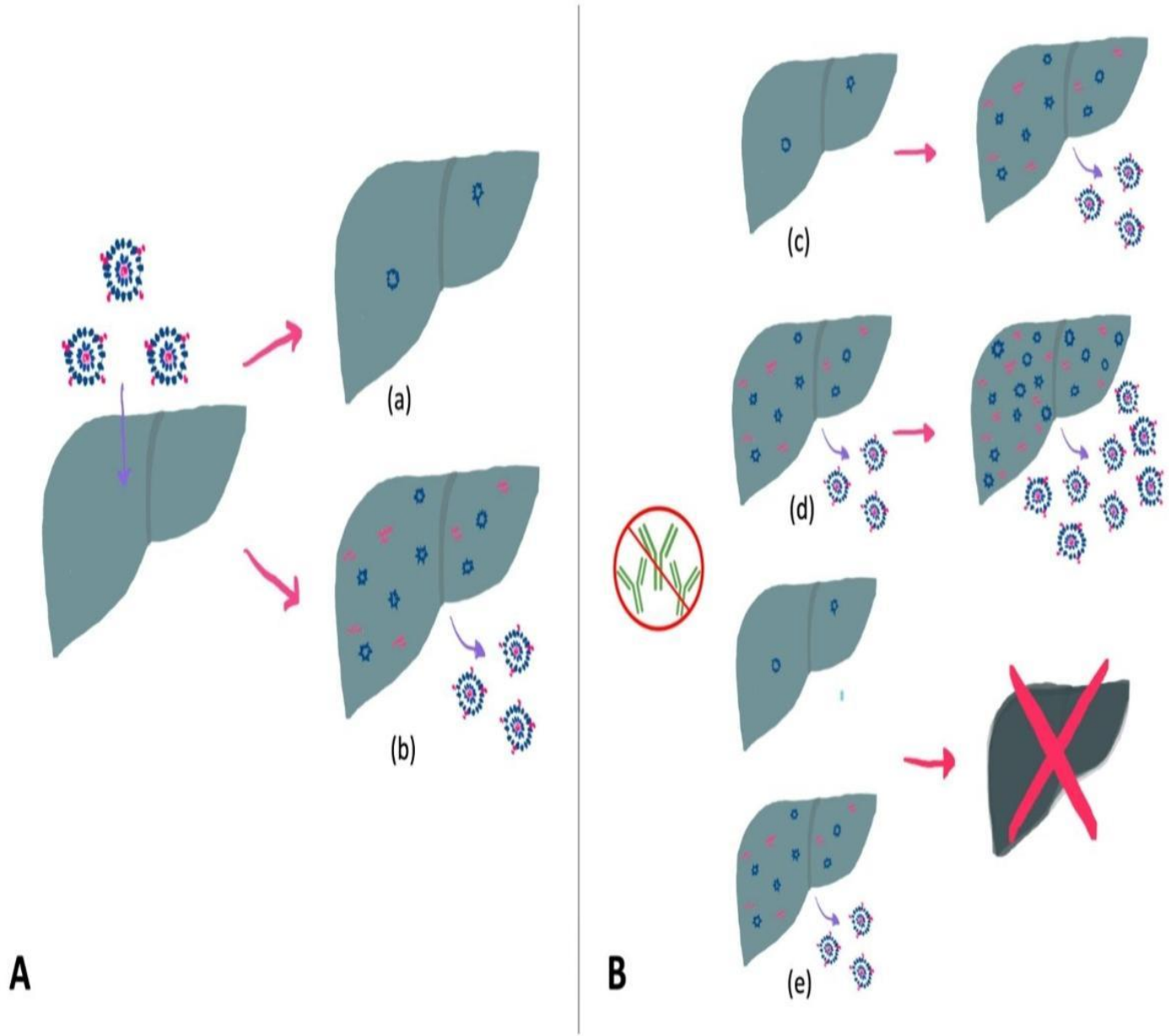
Category	Representative Drugs	Primary Target	Immunosuppressive Mechanism	Clinical Applications	
				Autoimmunity Diseases	Cancers
TNF-α Inhibitors	Infliximab (Remicade), Adalimumab (Humira), Etanercept (Enbrel)	TNF-α	Inhibits TNF-α, reducing inflammation	Rheumatoid arthritis, Crohn's disease, Psoriasis	-
B-Cell Targeting Agents	Rituximab (Rituxan), Obinutuzumab (Gazyva), Ofatumumab (Arzerra)	CD20	Depletes B cells, impairing humoral immune response	Rheumatoid arthritis, Systemic lupus erythematosus, Vasculitis	Non-Hodgkin lymphoma, Chronic lymphocytic leukemia
Checkpoint Inhibitors	Pembrolizumab (Keytruda), Nivolumab (Opdivo), Ipilimumab (Yervoy)	PD-1, PD-L1, CTLA-4	Activates the immune system, potentially causing immune dysregulation	-	Melanoma, Lung cancer, Renal cell carcinoma, Hodgkin's lymphoma, Head and neck squamous cell carcinoma
IL-6 Inhibitors	Tocilizumab (Actemra), Sarilumab (Kevzara)	IL-6	Inhibits IL-6, affecting acute phase response and systemic immune reactions	Rheumatoid arthritis, Giant cell arteritis, Systemic juvenile idiopathic arthritis	-
IL-17 Inhibitors	Secukinumab (Cosentyx), Ixekizumab (Taltz)	IL-17	Inhibits IL-17, affecting neutrophil recruitment and function	Psoriasis, Psoriatic arthritis, Ankylosing spondylitis	-
JAK Inhibitors	Tofacitinib (Xeljanz), Baricitinib (Olumiant), Upadacitinib (Rinvoq)	JAK-STAT signaling pathway	Inhibits multiple cytokines signaling pathways, broadly suppressing the immune system	Rheumatoid arthritis, Psoriatic arthritis, Ulcerative colitis	-
CCR4 Inhibitors	Mogamulizumab (Poteligeo)	CCR4	Depletes Tregs and Th2 cells, impairing immune regulatory functions	-	Adult T-cell leukemia/lymphoma, Cutaneous T-cell lymphoma

T-Cell Costimulation Blockers	Abatacept (Orencia) Belatacept (Nulojix)	CD80/CD86	Inhibits T-cell costimulatory signals, weakening T-cell-mediated immune responses	Rheumatoid arthritis, Organ transplantation, Psoriasis, Psoriatic arthritis	-
IL-1 Inhibitors	Anakinra (Kineret), Canakinumab (Ilaris)	IL-1	Inhibits IL-1, reducing inflammation	Rheumatoid arthritis, Neutrophilic dermatoses	Multiple myeloma
IL-12/IL-23 Inhibitors	Ustekinumab (Stelara)	IL-12/IL-23 p40 subunit	Inhibits IL-12 and IL-23, reducing Th1 and Th17 responses	Psoriasis, Crohn's disease	-
IL-4/IL-13 Inhibitors	Dupilumab (Dupixent)	IL-4Rα	Inhibits IL-4 and IL-13 signaling, reducing inflammation	Atopic dermatitis, Eosinophilic esophagitis, Asthma	-
IL-5 Inhibitors	Mepolizumab (Nucala), Reslizumab (Cinqair), Benralizumab (Fasenra)	IL-5	Inhibits IL-5, reducing eosinophil activity	Eosinophilic asthma	-
Complement Inhibitors	Eculizumab (Soliris)	C5	Inhibits complement component C5, preventing complement-mediated damage	Paroxysmal nocturnal hemoglobinuria, Atypical hemolytic uremic syndrome	-
Integrin Inhibitors	Natalizumab (Tysabri), Vedolizumab (Entyvio)	α4-integrin, α4β7-integrin	Inhibits integrin-mediated cell adhesion, reducing immune cell infiltration	Multiple sclerosis, Crohn's disease, Ulcerative colitis	-
CD52 Inhibitors	Alemtuzumab (Lemtrada)	CD52	Depletes CD52-positive cells, broadly suppressing the immune system	Multiple sclerosis	Chronic lymphocytic leukemia
GM-CSF Inhibitors	Sargramostim (Leukine)	GM-CSF	Modulates GM-CSF signaling, affecting immune cell activation	Bone marrow transplantation	Chronic myelogenous leukemia
IL-2 Receptor Antagonists	Basiliximab (Simulect), Daclizumab (Zinbryta)	IL-2Rα (CD25)	Blocks IL-2 signaling, reducing T-cell proliferation	Prevention of organ transplant rejection, Multiple sclerosis	-

Introduction to Biological Therapies

- Biological therapies target specific immune pathways, altering the body's immune response.
- They are used to treat conditions like autoimmune diseases, cancers, and transplants.
- However, they can lead to the reactivation of latent infections.

Hepatitis B Virus Reactivation with Immunosuppression



Hepatitis B Virus (HBV) Reactivation

Category	HBsAg+ Risk	HBsAg-/Anti-HBc+ Risk
Anti-CD20	High	Moderate
Anti-TNF	High	Low
Anti-IL-6	High	Moderate
Other cytokine inhibitors	High	Moderate
Anti-CCR4	Moderate	Moderate
Immune checkpoint inhibitors	High	Low
JAK inhibitors	High	High

Hepatitis B Virus (HBV) Reactivation

Biological therapies associated with reactivation:

- Anti-CD20 monoclonal antibodies, such as Rituximab, Obinutuzumab, and Ofatumumab, are strongly linked to HBV reactivation due to their effect on B cells, which are crucial for controlling HBV.
- JAK inhibitors like Tofacitinib also increase the risk of HBV reactivation, especially in patients with past HBV infection.
- TNF-α inhibitors have also been reported to contribute to HBV reactivation, albeit with a lower risk.

Preventive measures:

HBV screening and antiviral prophylaxis are recommended before starting these therapies.

Anti-TNF Agents (Infliximab, Adalimumab, Certolizumab, and Etanercept)

- There is also a different risk of reactivation associated with higher-potency agents in patients with positive HBsAg (e.g., Infliximab, 12–39%) compared to lower potency agents (e.g., Etanercept, 1–5%)
- Overall, most experts agree that prophylaxis is warranted in patients with positive HBsAg, whereas those with negative HBsAg and positive anti-HBc may be evaluated on a case-by-case basis.

Checkpoint Inhibitors, Tyrosine Kinase Inhibitors, and mTOR Inhibitors

- Anti-HBV prophylaxis may be recommended in patients with positive HBsAg
- Unlikely to be necessary in patients with negative HBsAg and positive anti-HBc.

solid-organ transplant recipients

- Current AASLD guidelines recommend solid-organ transplant recipients with positive HBsAg receive lifelong anti-HBV therapy starting at the time of transplant surgery
- Though the evidence is less clear in patients with negative HBsAg and positive anti-HBc; a limited period of anti-HBV therapy is reasonable

Liver Transplant Recipients

- In liver transplantations involving recipients and/or donors who test positive for anti-HBc, providing lifelong HBV prophylaxis to recipients in conjunction with their immunosuppression is recommended.

- TAF and ETV stand as the preferred HBV prophylactic agents, and their administration is recommended for patients at the time of transplantation

- CDC recommends a triple-panel screening (HBsAg, anti-HBc, and anti-HBs) for all high-risk individuals .

- Recent systematic review suggested that higher anti-HBs titers (>100 IU/L) may be protective against HBV reactivation
- while low or negative titers may be associated with reverse seroconversion

Hepatitis C Virus (HCV) Reactivation

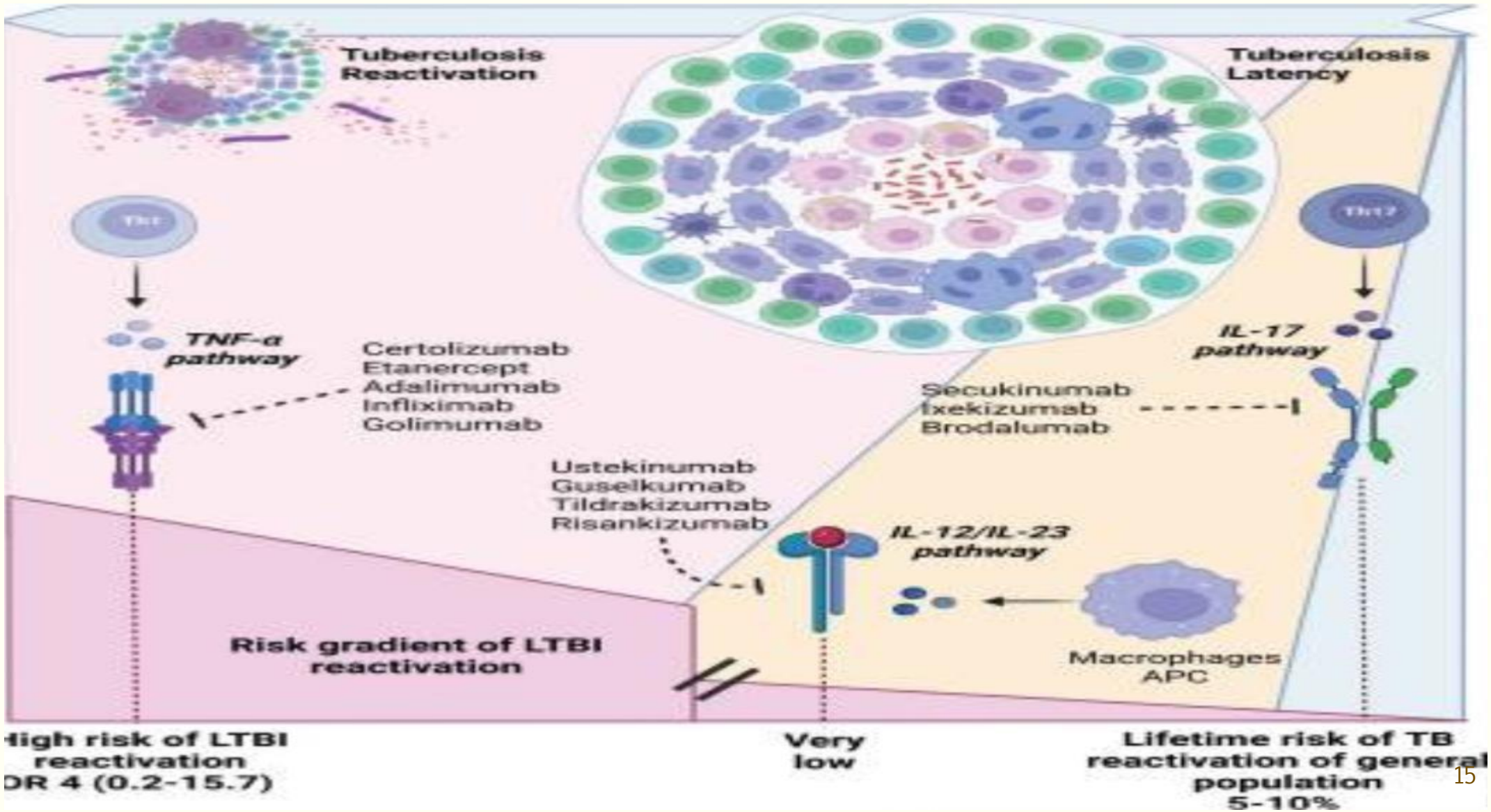
Biological therapies associated with reactivation:

- Anti-CD20 antibodies, including Rituximab, can lead to HCV reactivation, particularly in cancer patients receiving immunosuppressive therapy.
- However, TNF-α inhibitors are not strongly associated with HCV reactivation.

Preventive measures:

Monitoring HCV-RNA levels during therapy is essential for early detection of reactivation.

Targeted Immunotherapies and TB Risk, 2024



Tuberculosis (TB) Reactivation

Biological therapies associated with reactivation:

- TNF-α inhibitors (such as Infliximab, Adalimumab, and Etanercept) increase the risk of TB reactivation by inhibiting the formation of granulomas, which are crucial for containing latent TB bacteria.
- JAK inhibitors, like Tofacitinib, also pose a risk by broadly suppressing immune functions.
- IL-6 inhibitors, including Tocilizumab, may contribute to TB reactivation, though the risk is lower than that of TNF-α inhibitors.

Preventive measures:

TB screening and prophylaxis are essential for patients receiving these therapies.

Targeted Immunotherapies and TB Risk, 2024

University of California San Francisco TB Targeted Immunotherapy Group (TB-TIG)

TB testing with interferon-gamma release assay or tuberculin skin test is recommended for the following targeted immunotherapies (per the manufacturers drug insert)

Drug Name	Mechanism/Target
Abatacept	Selective T-cell co-stimulation modulator, CTLA-4
Abrocitinib	Kinase inhibitor (JAK1)
Adalimumab	Anti-TNF-alpha mAb
Alemtuzumab	Anti-CD-52 mAb
Anakinra	IL-1 receptor antagonist
Baricitinib	Kinase inhibitor (JAK1/JAK2)
Bimekizumab	Anti-IL-17 receptor mAb
Brodalumab	Anti-IL-17 receptor mAb
Canakinumab	Anti-IL-1beta mAb
Certolizumab	Anti-TNF-alpha mAb

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TB testing with interferon-gamma release assay or tuberculin skin test is recommended for the following targeted immunotherapies (per the manufacturers drug insert)

Drug Name	Mechanism/Target
Guselkumab	Anti-IL-23 mAb
Inebilizumab	Anti-CD-19 mAb
Infliximab	Anti-TNF-alpha mAb
Ixekizumab	Anti-IL-17 mAb
Mirikizumab	Anti-IL-23 mAb
Rilonacept	Soluble IL-1 receptor
Risankizumab	Anti-IL-23 mAb
Ritlecitinib	Kinase inhibitor (JAK3)
Rituximab	Anti-CD-20 mAb
Ruxolitinib	Kinase inhibitor (JAK1/JAK2)
Sarilumab	Anti-IL-6 receptor mAb

Targeted Immunotherapies and TB Risk, 2024

University of California San Francisco TB Targeted Immunotherapy Group (TB-TIG)

TB testing with interferon-gamma release assay or tuberculin skin test is recommended for the following targeted immunotherapies (per the manufacturers drug insert)

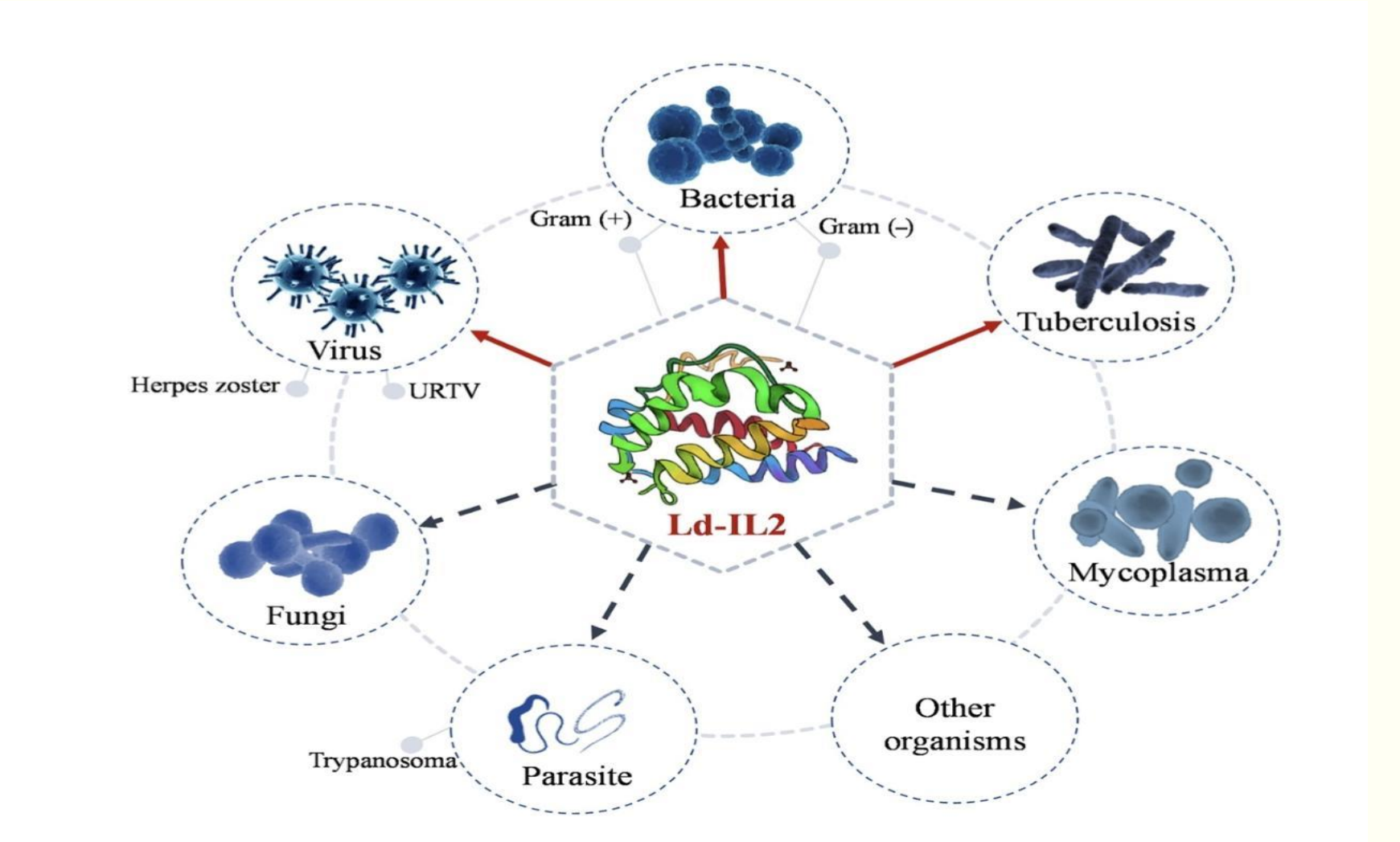
Drug Name	Mechanism/Target
Tocilizumab	Anti-IL-6 receptor mAb
Tofacitinib	Kinase inhibitor (JAK1/JAK2/JAK3)
Upadacinitib	Kinase inhibitor (JAK1)
Ustekinumab	Anti-IL-12 and IL-23 mAb
Vedolizumab	Anti-integrin (a4B7) mAb
Deucravacitinib	Kinase inhibitor (TYK2)
Emapalumab	Anti-IFN-gamma mAb
Etanercept	Soluble TNF-alpha receptor
Golimumab	Anti TNF-alpha mAb

- PD-1/PDL1 inhibitors, CTLA-4 inhibitors, JAK kinase inhibitors, and IL-6 and IL-23 inhibitors are also associated with increased risk of TB reactivation.

- These targeted immunotherapies should be treated similarly as for a TNF-inhibitor.

- SFDPH recommends that patients with a diagnosis of LTBI should be initiated on treatment for at least 1 month, if possible, prior to starting those targeted immunotherapies where a risk for TB progression has been identified.

Infectious Complications of Multiple Sclerosis Therapies: Implications for Screening, Prophylaxis, and Management



Drug	LTBI Screening	Acyclovir Prophylaxis[a]	Other
Natalizumab	Consider[b]	Consider[c]	Universal screening for HCV and HIV
Alemtuzumab	Yes	Yes[d]	Universal screening for HCV and HIV
Ocrelizumab	No[e]	No[f]	Universal screening for HCV and HIV
Mitoxantrone	Consider[b]	No[f]	Universal screening for HCV and HIV
Fingolimod	Consider[b]	Consider[g]	Universal screening for HCV and HIV
Dimethyl fumarate	Consider[b]	No[f]	Universal screening for HCV and HIV
Teriflunomide	Yes	No[f]	Universal screening for HCV and HIV

Drug	Risk of HBV Reactivation or Flare	HBsAg (+)	HBsAg (-) Anti-HBc (+)	Duration of Preemptive or Prophylactic Management
Natalizumab	Moderate	Prophylaxis	Prophylaxis or preemptive	During and for 6 mo after therapy
Alemtuzumab	High	Prophylaxis	Prophylaxis or preemptive	During and for 6 mo after therapy
Ocrelizumab	Very high	Prophylaxis	Prophylaxis	During and for 12 mo after therapy
Mitoxantrone	Moderate	Prophylaxis	Prophylaxis or preemptive	During and for 6 mo after therapy
Fingolimod	Low	Prophylaxis or preemptive	Preemptive or periodic LFT monitoring	During and for 6 mo after therapy
Dimethyl fumarate	Low	Prophylaxis or preemptive	Preemptive or periodic LFT monitoring	During and for 6 mo after therapy
Teriflunomide	Low	Prophylaxis or preemptive	Preemptive or periodic LFT monitoring	During and for 6 mo after therapy

Abbreviations: anti-HBc, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; LFT, liver function test.

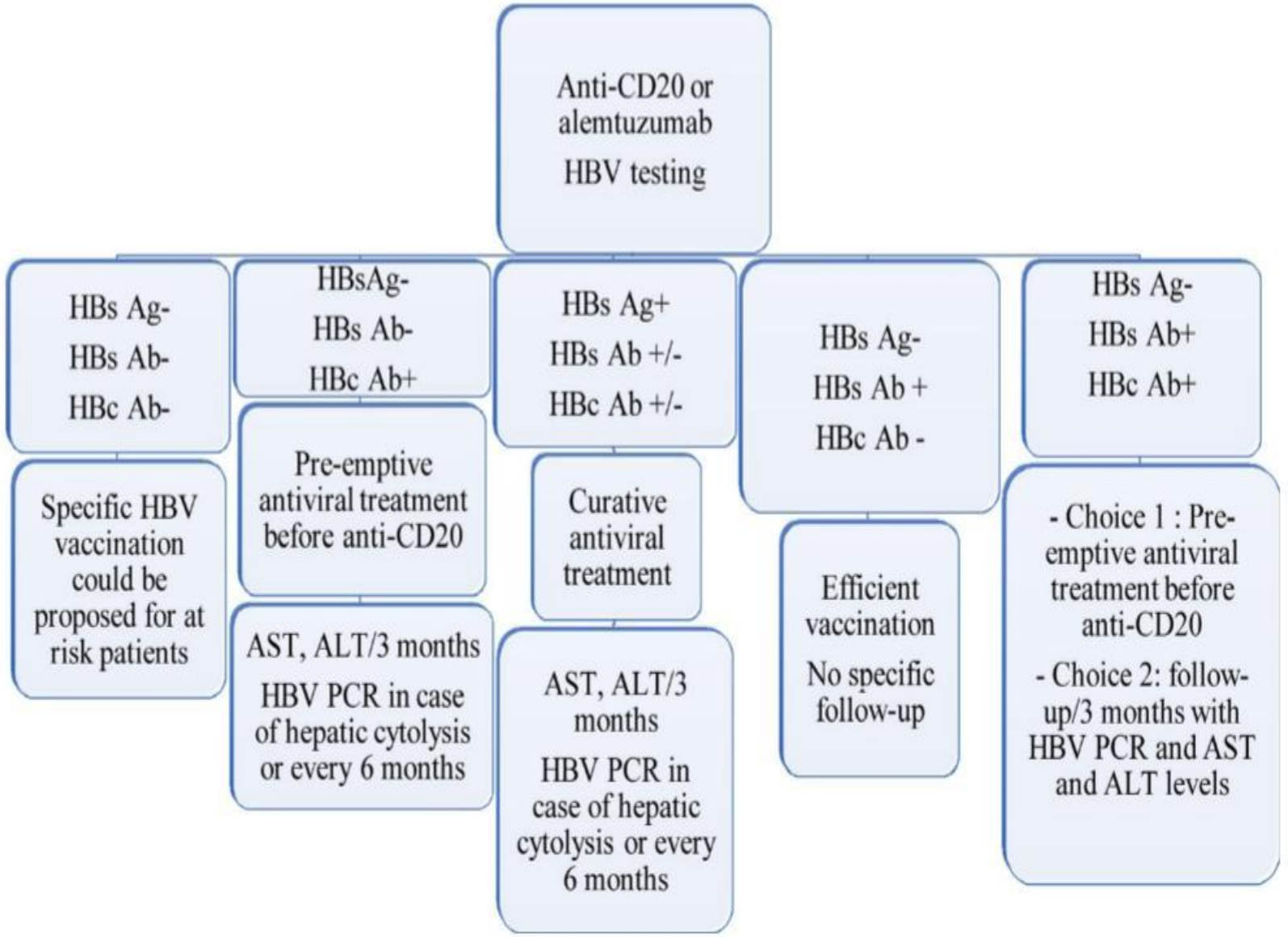


Fig. 1 – Algorithm of HBV management before anti-CD20 and alemtuzumab therapy according to results of HBV testing (Ab: antibodies; Ag: antigens).

Cytomegalovirus (CMV) Reactivation

Biological therapies associated with reactivation:

- Alemtuzumab, which targets CD52, depletes T and B cells and is associated with a high risk of CMV reactivation in immunocompromised patients.
- Mogamulizumab, an anti-CCR4 antibody, is also linked to CMV reactivation.
- Anti-CD20 antibodies, such as Rituximab, can increase the risk of CMV reactivation, though to a lesser extent.
- TNF-α inhibitors, while primarily associated with bacterial reactivations, have also been linked to CMV reactivation in some cases.

Preventive measures:

Regular monitoring and antiviral prophylaxis are important for managing CMV reactivation.

Herpes Simplex Virus (HSV) Reactivation

Biological therapies associated with reactivation:

- Anti-TNF therapies, such as Infliximab, can lead to the reactivation of latent HSV, resulting in oral or genital herpes outbreaks.
- Anti-CD20 antibodies, such as Ocrelizumab, have also been associated with HSV reactivation in clinical trials, with an increased incidence of oral HSV infections.

Preventive measures:

Patients undergoing these treatments should be closely monitored for HSV reactivation and managed with antiviral therapy if necessary.

Varicella Zoster Virus (VZV) Reactivation

Biological therapies associated with reactivation:

- VZV reactivation, which leads to shingles, is commonly reported in patients receiving TNF-α inhibitors (such as Infliximab), JAK inhibitors (such as Tofacitinib), and anti-CD20 antibodies (such as Rituximab and Obinutuzumab).
- The suppression of immune surveillance mechanisms under these therapies allows latent VZV to reactivate.

Preventive measures:

Vaccination against VZV and antiviral prophylaxis are advised in high-risk patients.

Polyomaviruses Reactivation (BK and JC Viruses)

Biological therapies associated with reactivation:

- JC Virus reactivation can lead to progressive multifocal leukoencephalopathy (PML), a serious and often fatal demyelinating disease.
- Natalizumab, a drug used for multiple sclerosis, is strongly associated with JC virus reactivation.
- Other biological therapies, including Rituximab and Alemtuzumab, have also been linked to JC virus reactivation.

Preventive measures:

Regular monitoring for neurological symptoms and MRI screening are recommended for patients at risk of PML.

Human Immunodeficiency Virus (HIV) Reactivation

Biological therapies associated with reactivation:

- While most biological therapies are considered safe for HIV-positive patients with well-controlled infections, the immunosuppressive effects of therapies like TNF-α inhibitors and anti-CD20 antibodies require careful monitoring.
- There is no direct link to HIV reactivation, but immune suppression can exacerbate the progression of HIV infection.

Preventive measures:

HIV screening and maintaining stable antiretroviral therapy are crucial for managing patients on biological therapies.

HTLV-1 (Human T-Cell Leukemia Virus) Reactivation

Biological therapies associated with reactivation:

- While rare, HTLV-1 reactivation has been reported in patients receiving TNF-α inhibitors (such as Adalimumab) and IL-6 inhibitors (such as Tocilizumab).
- Rituximab has also been linked to reactivation in isolated cases of adult T-cell leukemia (ATL), a disease caused by HTLV-1.

Preventive measures:

Screening for HTLV-1 and monitoring for symptoms of ATL are important for patients at risk.

Take home message

- Biological therapies are highly effective but carry risks of latent infection reactivation.
- Proper screening, prophylaxis, and monitoring are essential for patient safety.

Varicella Vaccine

Dosage and Administration

- **Each dose is approximately 0.5 mL and is administered intramuscularly or subcutaneously.**

  - ***Children (12 months to 12 years of age):*** **The first dose is administered between 12 and 15 months of age. The second dose is administered between 4 to 6 years of age. There should be a minimum interval of 3 months between doses.**

  - ***Adolescents (≥13 years of age) and Adults*****: Two doses are administered with a minimum interval of 4 weeks between doses.**

Dosage and Administration

•Due to the concern for transmission of vaccine virus, vaccine recipients should attempt to avoid, whenever possible, close association with susceptible high-risk individuals for up to 6 weeks following vaccination.

VARIVAX CONTRAINDICATIONS

Immunodeficient or immunosuppressed.

Active febrile illness with fever >101.3° F (>38.5° C).

Active untreated tuberculosis.

During pregnancy or individuals who are planning on becoming pregnant in the next 3 months.

VARIVAX CONTRAINDICATIONS

Do not give varicella vaccine to a person with severe immunodeficiency (e.g., hematologic and solid tumors, receipt of chemotherapy, congenital immunodeficiency, long-term immunosuppressive therapy or patients with HIV infection who are severely immunocompromised).

Note: Long-term immunosuppressive therapy is defined as at least 2 weeks of daily receipt of 20 mg or 2 mg/kg body weight of prednisone or its equivalent.

VARIVAX CONTRAINDICATIONS

Do not give varicella vaccine to a person with a family history of congenital or hereditary immunodeficiency in first-degree relatives (e.g., parents, siblings) unless the immune competence of the potential vaccine recipient has been clinically substantiated or verified by a laboratory


Thank
You