Secondary Immunodeficiencies with Biologics: What every physician should know

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Disclosures

› I have no relevant disclosures

Objectives

- Understand the global effects of biological therapies on immune functioning
- Identify important intermediate and long-term risks
- Develop management strategies for complication prevention for patients while taking biological therapies and post therapy risk assessment and treatments.

Case Vignettes

- **8 year old girl with a history of nephrotic syndrome. The initial treatments were not successful at controlling her disease and she was started on rituximab. Her disease became controlled and she was well. Eight months later she developed shingles.**
- **14 year old boy treated for lymphoma 2 years ago in Ukraine including Rituximab with chemotherapy. He now presents with septic arthritis of right knee**

Case Vignette 3

- 14 year old female with IBD, on treatment with anti-TNF-R inhibitor. In March, because of fears of severe COVID-19 in immunosuppressed patients, she stopped taking the medication and now has a significant flair of her disease.
- What do you advise?
- Will the COVID vaccine be effective?

What are Biologics

- Specific immune components implicated in the etiology or pathogenesis of disease lend themselves to targeted therapies
- Biological therapies are designed to target specific components and are in general modifiers of immune responses
- Examples include monoclonal antibodies, peptides and small molecules, and modified immune cells, changing activity
- These agents are costly and carry risks, some of which are as yet unknown or not fully understood.

Knowledge gaps

- Biologics are used for increasing number of indications
- Intermediate effects on the developing immune system of children are largely unknown
- High risk of infectious complications
  - Risks of malignant and autoimmune complications are unknown
- When and how do we vaccinate these patients?
- Duration of effects of treatment largely unknown for most of this class of medications

Case in Point

- SARS Co-V2 arrived in March 2020.
- Early reports suggested patients with immune system disorders were at higher risk for severe disease
- Effects of infection in patients with immune compromise because of biologic therapies were unknown leading to anxiety and clinical decisions were made with very limited information.
- After almost a year of study, much is known about immunity in COV2. Still few studies on children using biologic therapies.
- Now the biggest question: how should patients on biologic therapy be vaccinated? What are the potential effects of the different types of vaccines on patients with compromised immunity. Do all patients need boosters? Will they help?

BIOLOGICS IN USE 2021

Here is a partial list of the biological therapies.

This large group of medications are used to control diseases and commonly affect the way the immune system operates.

They have been studied in adults but rarely have any studies been done in children and there are no studies about the long-term effects of their use.

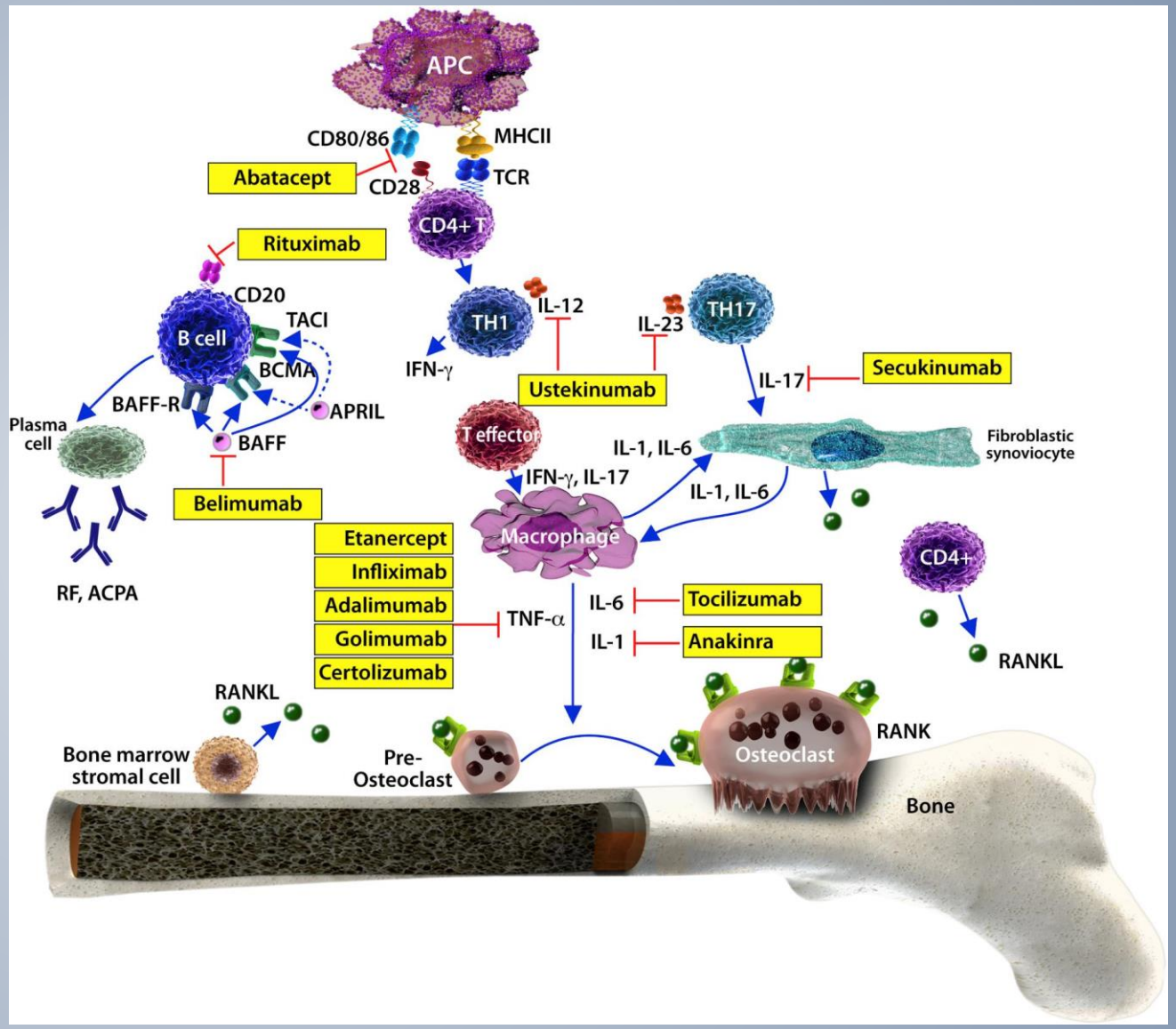
Diseases currently treated with immune response modifying biologic therapies (partial list)

- Arthritis
- Inflammatory bowel disease
- cancer
- Glioblastoma
- Autoinflammatory disease
- PNH
- HUS
- Immune Deficiency
- Eczema
- Psoriasis
- COVID 19
- Autoimmune hemolytic anemia
- Crohn's
- Kidney Disease
- Melanoma
- Periodic Fever
- Intractable seizures
- Sepsis
- Asthma
- encephalitis
- Lupus
- ITP
- coronary artery disease
- **1/5 patients are predicted to receive biologics within the next 5-10 years**

BIOLOGICS AND IMMUNITY

Biologics used for many autoimmune diseases act on key elements in a normal immune response creating a form of secondary immune deficiency both during and after treatment.

How do you diagnose patients taking anakinra with acute bacterial sepsis?



Adverse effects of therapies blocking IL1, IL6 and TNFα

- Increased risk of infection, reactivation of tb, invasive fungal infection; viral infection including herpes zoster, PJP pneumonia
- Formation of anti-drug antibodies limiting efficacy and increasing complications
- Development of the paradoxical inflammatory response
- Potential increased risk of specific types of cancer in some studies
- Increased mortality with bacterial infections

Anti-TNF and vaccination

- Modest impairment in response to influenza vaccination with lower anti-influenza antibodies detected in treated versus control group
  - This study did not address efficacy
- Pneumovax 23 vaccination resulted in 30-40% seroconversion in patients on anti TNF therapy
- Pre-TNF therapy: In 1 study patients received Prevnar 13 x1, followed by Pneumovax 1 month later, hepatitis B x3, DT and influenza vaccine before initiation of anti-TNF therapy and compared the frequency of admissions to hospital in the years preceding the vaccination program versus the same number following the initiation of vaccination for anti-TNF therapies
  - Significant decrease in hospitalizations for invasive pneumococcal disease in vaccinated group suggesting that pneumococcal vaccination should be given ideally prior to starting anti-TNFs but if not then during treatment.
- What about live viral vaccines? Increased risk of herpes zoster with treatment makes vaccination a complex discussion

Different types of biologics affecting T cells

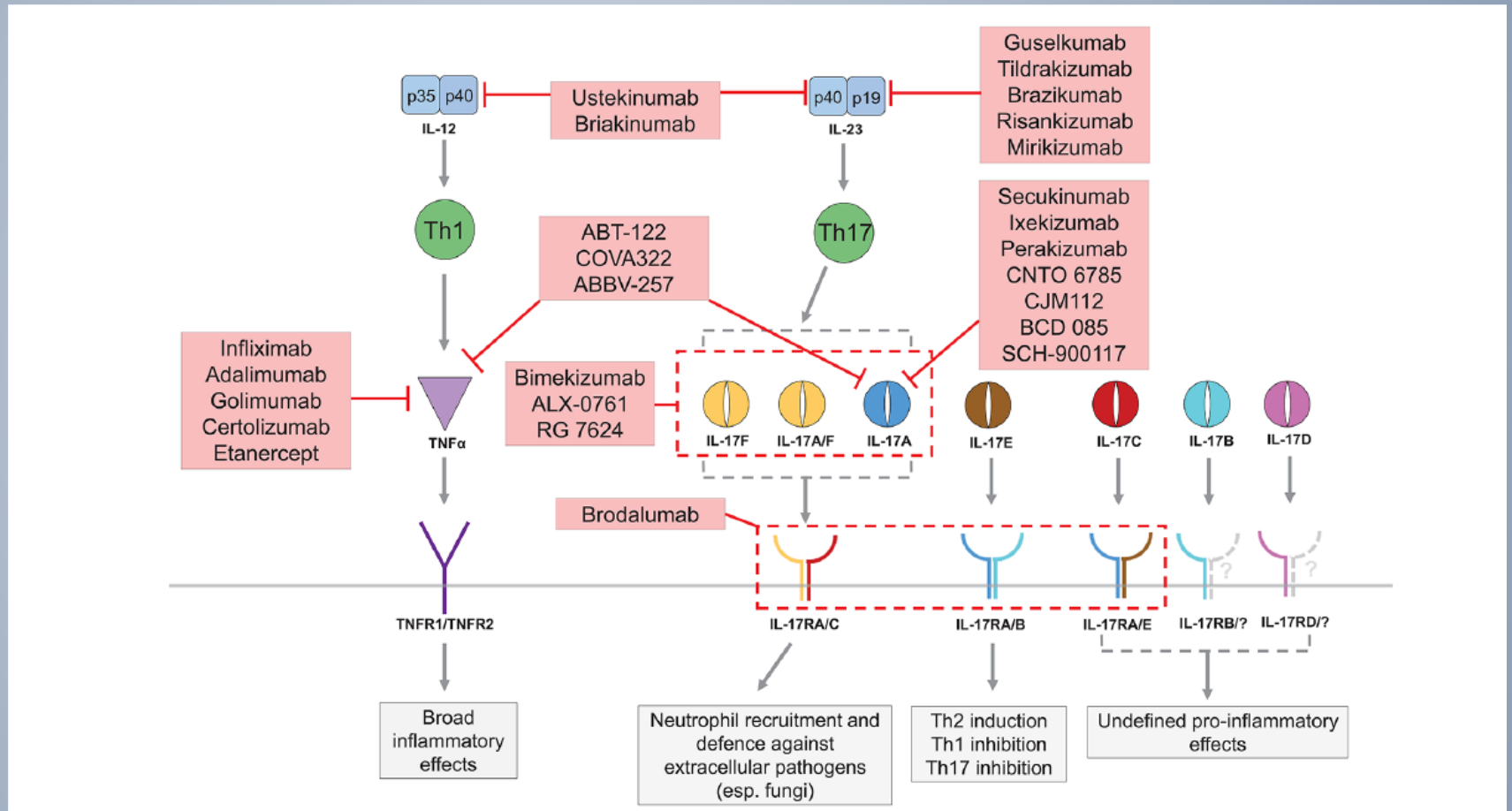


Figure 1 Overview of biologics targeted against elements of the T-helper (Th)17/interleukin (IL)-17 and tumour necrosis factor-α (TNF-α) axes. Adapted from Bartlett and Million[5] and Beringer *et al*.[6]

Baker and Isaacs, 2017

T cell deficiencies

- Infection risk from all sources is increased using biologics targeting T cell function. Opportunistic, virus and fungal infections are especially problematic to manage in this patient population.
- Increased risk for autoimmunity
- Increased risk for malignancy

[a]: including thymus-derived $CD4^{+}CD25^{high}FoxP3^{+}$ and other CD52-bearing regulatory T cells, such as $CD52^{high}CD4^{+}$ T cells; BAFF: B cell activating factor; Th: T helper cell; Treg: regulatory T cell.

Example of T cell inhibition: alemtuzumab

Table 3. Lymphopenia-associated secondary autoimmune disease after alemtuzumab.

Potential Mechanism	Consequences	References
Homeostatic proliferation ↑	Chronically activated, oligoclonal, auto-reactive T cells ↑	[56,59,60]
IL-21 ↑	Homestatic proliferation ↑	[22]
	Th17 cells ↑	[61]
	B cell differentiation, antibody production	[62]
	Treg function ↓	[63,64]
Thymopoiesis ↓	Clonal restricted T cell receptor repertoire	[56]
IL-7 ↓	Thymic output ↓, homeostatic proliferation > thymopoiesis	[65,66]
Faster B cell recovery than T cell recovery, BAFF ↑	Unregulated B cell expansion in response to self-antigens	[3,74]
Low absolute Treg numbers, potentially compromised Treg function [a]	Diminished control of autoimmune responses	[13,72,73]
Genetic risk profile	Susceptibility to autoimmunity ↑	[67,69,70]
Smoking	Susceptibility to autoimmunity ↑	[70]

Table 2. Adverse events of alemtuzumab, frequency, monitoring and management.

Adverse Event	Prevalence [a]	Highest Incidence	Risk-Monitoring	Management
IARs	>90%	During infusion and 24 h thereafter	Clinical and technical monitoring of vital signs	Corticosteroids (first 3 days of infusion), antihistamines and/or antipyretics (prior and as needed)
Infections	66%–77%	Year 1	Frequent follow-up visits	Herpes prophylaxis ≥1 month after alemtuzumab
Thyroid disorders	30%–41%	Year 3 Onset 6–61 months	Thyroid function test (e.g., TSH)	Prior to alemtuzumab and quarterly after alemtuzumab for 48 months
ITP	1%–3%	Onset 1–34 months	CBC and differential	Prior to alemtuzumab and monthly after alemtuzumab for 48 months
Glomerulo-nephritis	0.3%	Onset 4–39 months	Serum creatinine and urinalysis with microscopy	Prior to alemtuzumab and monthly after alemtuzumab for 48 months

Taken from Ruck et al 2015

Targeting B cells: Rituximab
Which of the following is false?

- A) Rituximab targets B cells and eliminates lymphoma cells that are CD20 positive
- B) rituximab is effective for AIHA and ITP as it targets B cells and reduces the production of autoantibodies.
- C) After rituximab administration B cell levels remain low for at least 6 months and rituximab levels can be detected in serum > 6 months after treatment
- D) Infectious complications are primarily sino-oto-pulmonary and medium time to development of first infection is approximately 12 months

Hypogammaglobulinemia after Rituximab

- retrospective study from 1998 to 2009 of patients with B cell lymphoma
- serial serum IgG levels before and subsequent to rituximab administration
- 211 patients
- 179 (85%) had normal IgG before rituximab
  - 38.5% had hypogamm after rituximab
- 32 (15%) had low IgG before rituximab
- symptomatic hypogammaglobulinemia needing IVIg developed in 6.6% of patients
  - in the pediatric population persistent hypogammaglobulinemia occurs in >30% of patients

INFECTIONS AND HYPOGAMMAGLOBULINEMIA

A STUDY OF RITUXIMAB FOR EBV REACTIVIATION POST HSCT (PETROPOLOU ET AL 2012)

TABLE 2. Bacteria-causing late infections (after 3 months) in EBV patients and controls

	Rituximab	Controls
No. patients with at least one infection	29	18
No. infections	47	25
Gram-negative bacilli		
Pseudomonas	8	6
Hemophilus influenza	3	0
Other	13	8
Gram-positive cocci		
Coagulase-negative staphylococcus	7	0
Pneumococcus	2	1
Other	9	3
Clostridium	0	1
Atypical mycobacteria	1	0
Unspecified	4	6

- BY 36 MONTHS: PROBABILITY OF BACTERIAL INFECTION IN R GROUP VS CONTROL: 55% VS 35% (*P*=0.048)
- 3 MONTHS AFTER RITUXIMAB AND 6 MONTHS AFTER TRANSPLANT IN CONTROL GROUP: HYPOGAMMAGLOBULINEMIA IN 29/40 (69%) VS 10/25 (40%) (*P*=0.002)
- 13 PATIENTS IN R GROUP (26%) RECEIVED IGG REPLACEMENT VS 2 (4%) IN CONTROL GROUP (*P*=0.002)

RITUXIMAB AND IMMUNIZATIONS LIMITED DATA

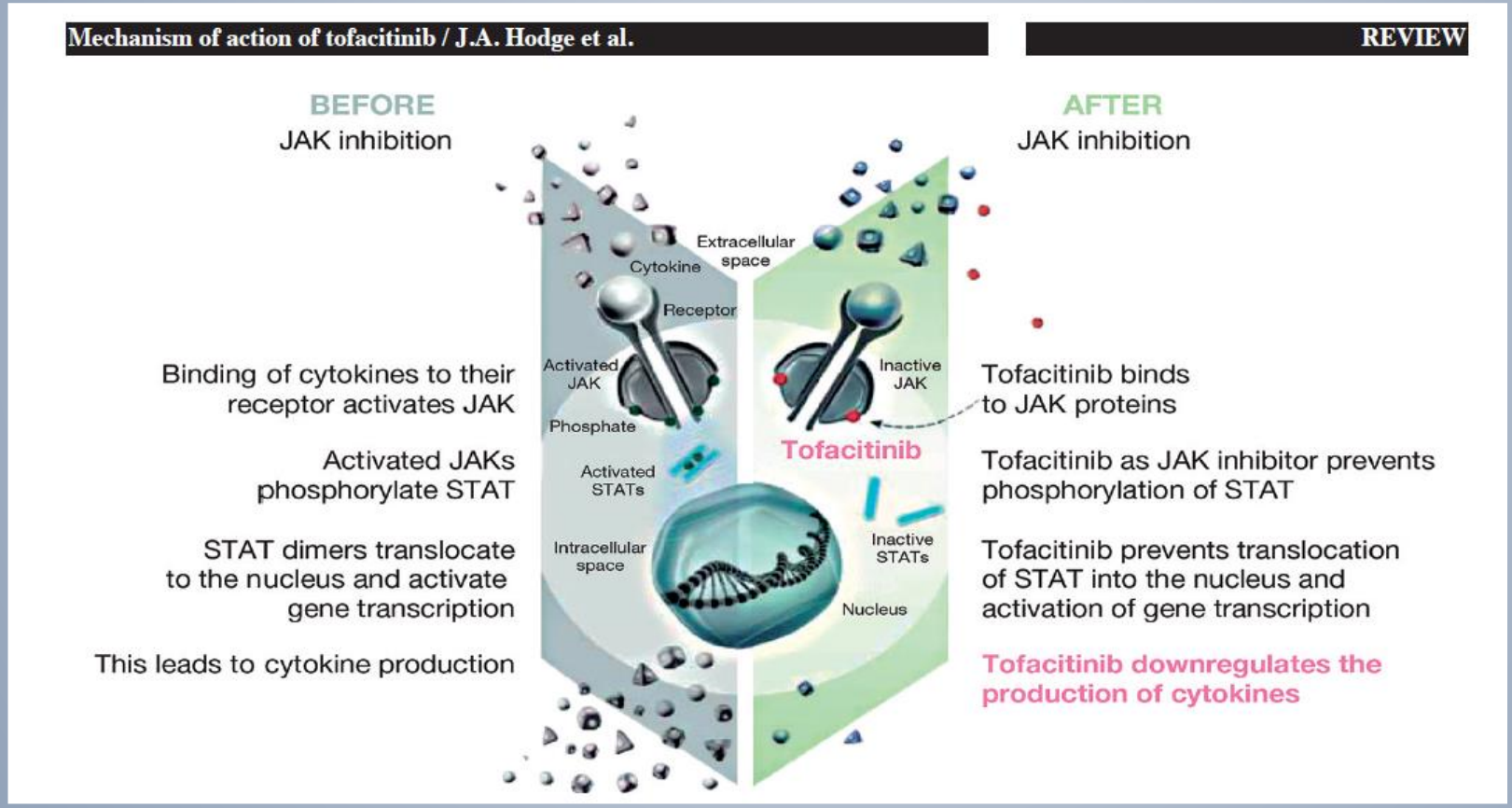
- 9/15 patients with SLE failed to show a response to either tetanus or the pneumococcal vaccine at 7 months post-rituximab
- patients with RA who were immunized with the influenza vaccine at various times after treatment with rituximab responded less than control patients with RA

ALBERT ET AL. OREN ET AL
ARTHRITIS RHEUM 2006

- 0/7 patients responded adequately to pneumovax after Rituximab
- low anti-tetanus and anti-diphtheria antibodies, but all responded well post revaccination

KAPLAN ET AL. J ALLERGY CLIN IMMUNOL PRACT. 2014
RITUXIMAB AND IMMUNE DEFICIENCY: CASE SERIES AND REVIEW OF THE LITERATURE

Small molecule inhibitors: new drugs tofacitinib (Jak 1/3 inhibitor)



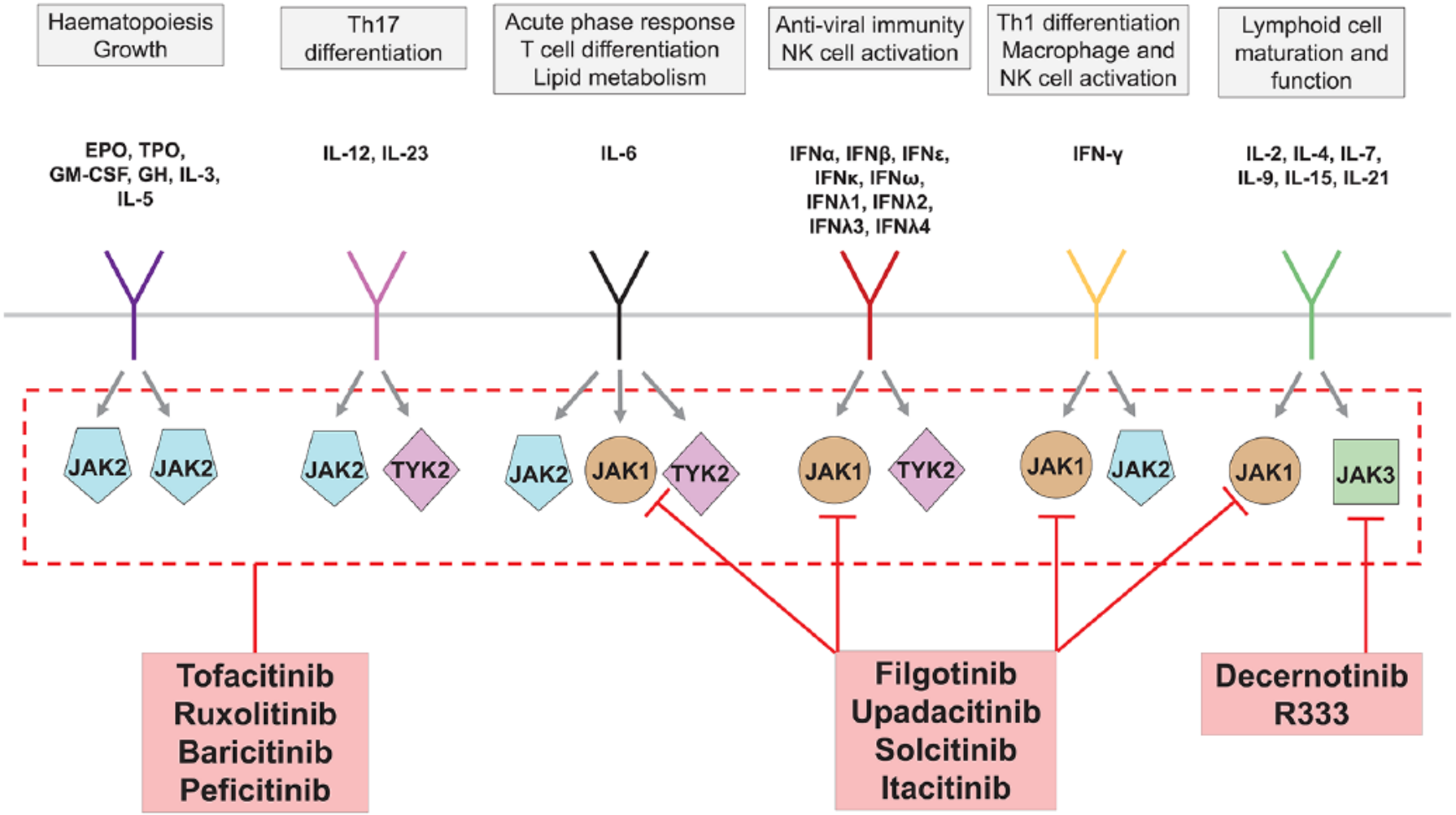


Figure 4 Overview of Janus kinase (JAK) inhibitors developed for the treatment of immune-mediated inflammatory diseases. JAK2-specific inhibitors have been developed for the treatment of haematological malignancy, although are omitted here for simplicity. EPO, erythropoietin; GH, growth hormone; IFN, interferon; GM-CSF, granulocyte macrophage colony-stimulating factor; TPO, thrombopoietin; Tyk2, tyrosine kinase 2. Adapted from reference.[77]

Baker and Isaacs, 2017

Risks for JAK-inhibitors

- Double the frequency of herpes zoster compared with other biologics
- Evidence for direct effect on T cell proliferation and innate interferon signaling.
- Immunoglobulin levels decrease by 20%
- Increased frequency of cellulitis and pneumonia

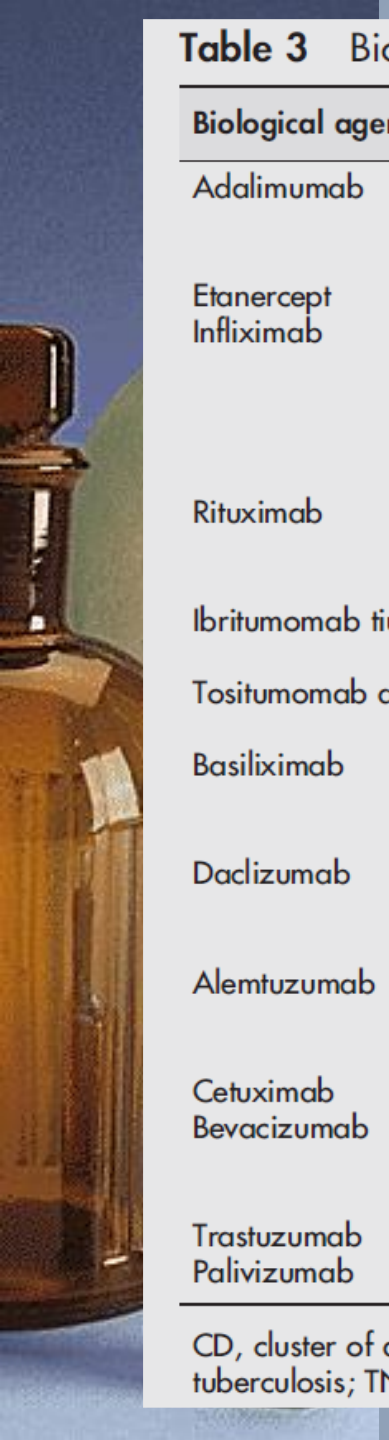


Table 3 Biologicals warnings—consult summary of product characteristics

Biological agent	Molecular target	Specific warnings
Adalimumab	TNFα	Risk of infection, especially TB Patients should be assessed for active/latent TB before treatment. Treatment of latent TB should be initiated before treatment with adalimumab, contraindicated in active TB
Etanercept	TNFα	Infection
Infliximab	TNFα	Risk of infection, especially TB. Patients should be assessed for active/latent TB and treatment should be initiated before treatment with infliximab, contraindicated in active TB Invasive fungal and other opportunist infections. Hypersensitivity reactions
Rituximab	CD20	Infusion reactions Tumour lysis syndrome Severe mucocutaneous reactions
Ibritumomab tiuxetan	CD20	Fatal infusion reactions Prolonged and severe cytopenias
Tositumomab and ^{131}I tositumomab	CD20	Hypersensitivity reactions Prolonged and severe cytopenias
Basiliximab	CD25	Only administered by doctors experienced in immunosuppressive treatment and management of organ transplantation. Facilities must be equipped and staffed with adequate laboratory and supportive medical resources
Daclizumab	CD25	Only administered by doctors experienced in immunosuppressive treatment and management of organ transplantation. Facilities must be equipped and staffed with adequate laboratory and supportive medical resources
Alemtuzumab	CD52	Haematological toxicity (ITP alert, November 2005) Infusion reactions Infection/opportunist infection
Cetuximab	EGFR	Infusion reactions
Bevacizumab	VEGF	Gastrointestinal perforation Wound-healing complications Haemorrhage
Trastuzumab	HER2	Cardiomyopathy especially when given with anthracyclines and cyclophosphamide
Palivizumab	RSV F protein	Anaphylaxis (rare)

CD, cluster of differentiation; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; RSV, respiratory syncitial virus; TB, tuberculosis; TNF, tumour necrosis factor; VEGF, vascular endothelial growth factor.

Conclusions

- Biologics are used for increasing number of indications
- Intermediate and long term effects on immune responses are largely unknown
- High risk of infectious complications
  - Infections are difficult to diagnose
- Pre-treatment vaccination would be considered the ideal
- Careful pre and post treatment monitoring should be undertaken
- Duration of effects of treatment unknown for most of this class of medications
- Combinations are used but not studied
- Vigilance is important.

References

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Recent Papers Rituximab complications

- **Ong et al. 2020 (Boston)**
  - 96 children treated with RTX for rheumatologic diseases
    - **25 (26%)** pts developed hypogammaglobulinemia within 12 months of RTX
      - **11 (44%)** of them developed infectious complications
- **Khojah et al. 2019 (Chicago)**
  - 63 children treated with RTX for autoimmune diseases
    - **28 pts (44%)** developed hypogammaglobulinemia, most within 6 months of RTX
- **Ottaviano et al. 2019 (Italy)**
  - 53 children treated with RTX for ITP, AHA and ES
    - **17 (32%)** pts developed *persistent* hypogammaglobulinemia (>12 months post-RTX)
      - 9 (53%) were subsequently diagnosed with PID
- **Deyà-Martinez et al. 2020 (Spain)**
  - 20 children treated with a single-dose RTX for autoimmune diseases
    - **5/14 (36%)** developed dysgammaglobulinemia