‘B’ for Biologicals

1. **What are biologicals? How is it relevant in day-to-day pediatric practice?**

- Biologicals are biotechnology-derived products of biological origin which can modulate our immune system.
- Biological drugs are a class of medications that target specific molecules in the immune system that contribute to inflammation and damage in autoimmune and inflammatory diseases
- Often referred to as biological DMARDS (“**bDMARDS**”) ,these are specific and target a specific pathway of the immune system.
- These are drugs which are used when conventional synthetic DMARDS csDMARD) fail to achieve control over various rheumatological conditions.

Though not in extensive details, a pediatrician should be broadly aware of the common molecules used, the mechanisms of action and adverse drug reactions vis a vis these drugs.

It is important to note that the use of biological drugs in pediatric rheumatology requires careful monitoring and management by a specialist in this field. Administration of these medications is best left to the specialists.

A joint team effort on the part of pediatrician and the pediatric rheumatologist is critical in managing these children subsequently specially with respect to ongoing care ,the risk of infections ,vaccinations etc

2. How do biologics work? How are these molecules named?

These drugs are either monoclonal, chimeric/ humanized fusion antibodies, or are receptors that have been fused to a part of the human immunoglobulin.

These agents primarily work by

- Interfering with cytokine function, signal transduction, or production
- Inhibiting the "second signal" required for T-cell activation
- Depleting B cells

Nomenclature: -

Abbreviations placed at the ends of the names of therapeutic agents convey specific information relating to their structure

"-cept" refers to fusion of a receptor to the Fc part of human immunoglobulin G1 (IgG1) eg. : Etanercept (spelt "ETA… NER…CEPT")

"-mab" indicates a monoclonal antibody (mAb) eg. Rituximab (spelt "RITUX…IMAB")

"-ximab" indicates a chimeric mAb eg. Infliximab (spelt "IN…FLIXI...MAB")

"-zumab" indicates a humanized mAb eg. Tocilizumab (spelt "To... ci…li…zu…mab")

"-umab" indicates a fully human mAb eg. Adalimumab (spelt "ADAA...LIMU….MAB")

3. What are the commonly used biologicals in pediatric rheumatology?

Some of the commonly used bDMARDS *(Table 1)* include

Group	MOA/Type	Methodology Freq	ADRs	Indications
TNF Alpha Blocker				
Etanercept	TNFR-IgG1 fusion Protein	S.C weekly	Injection-site reactions, infections (especially reactivation of latent tuberculosis), lymphomas	JIA
Infliximab	Chimeric antibody (IgG1κ monoclonal antibody)	I.V 2-4 weekly	Induction of human chimeric auto-antibodies (HACAS), infusion reactions	JIA/ERA/ Uveitis/IBD/Resistant KD
Adalimumab	Fully Humanized Mab	S.C q2 weekly	Reactivation of latent TB, local site reaction	JIA/ERA/PSA/Uveitis/ PAN/ Autoinflammatory
Cytokine /Cytokine receptor Blocker				
Tocilizumab	Humanized IL-6 receptor blocker	I.V/S.C Once in 2 weeks	Upper respiratory tract infections, headache, hypertension, and increased liver enzymes. gastrointestinal perforation, hypersensitivity reactions, and neutropenia.	SJIA/ Takayasu arteritis
Anakinra (Not available in India)	IL-1receptor antagonist	S.C daily	Hypersensitivity, Pain, swelling at site, diarrhea, infections	SJIA/MAS/ Resistant KD
B Cell Depletion				
Rituximab	Chimeric immunoglobulin G1 (IgG1) monoclonal antibody (mAb)	I.V once in a wk/ once in 2 weeks	Infusion reaction, Infection, neutropenia, PML	SLE/JIA/ AAVs (ANCA associated vasculitis)
Co-Stimulation Blockade				
Abatacept	Soluble fusion protein (CTLA-4-Ig)	I.V monthly/S.C weekly	Hypersensitivity	JIA

Table 1 . **Characteristics and posology of commonly used bDMARDS**

i. ***Tumor necrosis factor (TNF) inhibitors****:* These drugs, such as etanercept, adalimumab, and infliximab, block the activity of TNF, a molecule that promotes inflammation. They are often used to treat juvenile idiopathic arthritis (JIA) and psoriatic arthritis.

ii. ***Interleukin-1 (IL-1) inhibitors***: These drugs, such as anakinra and canakinumab, block the activity of IL-1, a molecule that promotes inflammation. They are often used to treat systemic juvenile idiopathic arthritis (sJIA).

iii. ***Interleukin-6 (IL-6) inhibitors*****:** These drugs, such as tocilizumab, block the activity of IL-6, a molecule that promotes inflammation. They are often used to treat sJIA.

iv. ***B-cell inhibitors****:* These drugs, such as rituximab and belimumab, target B-cells, a type of immune cell that produces autoantibodies. They are often used to treat lupus, vasculitis, and other autoimmune conditions.

v. ***Interferon inhibitors:*** These drugs, such as anifrolumab, block the activity of interferons, molecules that promote inflammation and contribute to the development of autoimmune diseases. They are often used to treat systemic lupus erythematosus (SLE).

vi. ***Co stimulation Blockade****:* Drugs like abatacept works by T cell co-stimulation blockade. It is used in resistant JIA

4. What are the main side-effects of bDMARDS?

TNF inhibitors - Injection-site reactions, infections (especially reactivation of latent tuberculosis) , lymphomas, induction of auto-antibodies, and rarely development of lymphomas, demyelinating disease, and lupus-like syndrome. Therefore, it is important to screen for tuberculosis, HIV, hepatitis B and hepatitis C viruses (ideally)before initiation of anti-TNF agents.

****Kochs/Latent Kochs work up mandatory before commencement***

Tocilizumab-Upper respiratory tract infections, headache, hypertension, and increased liver enzymes. Other adverse effects include gastrointestinal perforation, hypersensitivity reactions, and neutropenia.

****LFTs and blood counts to be monitored stringently***

Rituximab- Infusion reactions, infections, and neutropenia. Other side effects include hypotension, angioedema, and bronchospasm. Rare long-term side effects include predisposition to develop lymphoma and progressive multifocal leukoencephalopathy.

Infusion reactions common (ensure infusion over atleast 6 hours with precautions)

5. What about vaccinations and b DMARDS?

Concerns usually revolve round two issues, Flare of disease /infection and 2. Adequate immunogenicity. Broad recommendations are

1. Live vaccine to be avoided as a routine whilst on bDMARDS
2. In high-risk situations /outbreaks, VZV / MMR booster can be administered safely to patients on glucocorticoids and specified b DMARDS (TNF alpha blockers, anti-IL1 and anti-IL6 therapy)
3. Seasonal annual Influenza vaccination should be given to all children on biologicals including Rituximab. Vaccination 4 weeks prior to rituximab cycle is recommended.
4. Rest vaccines to be given 6 months after last dose of rituximab.

If in doubt, it is always a good approach to discuss with the pediatric rheumatologist /ID expert prior to vaccination

References

- *Jansen MHA, Rondaan C, Legger GE, Minden K, Uziel Y, Toplak N, et al. EULAR/PRES recommendations for vaccination of paediatric patients with autoimmune inflammatory rheumatic diseases: update 2021. Ann Rheum Dis. (2022). 10.1136/annrheumdis-2022-222574.*
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NEXT COMING – C, D, E for " Crp anD Esr"

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