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Commentary

Targeted Treatment of Diseases of Immune Dysregulation

Smriti Mohan MD*

Department of Pediatric Rheumatology, University of Michigan, Michigan, USA

DESCRIPTION

Increasing awareness of immune system functioning has led to discovery and understanding of diseases that affect both the innate and adaptive immune systems. Historically, the immune system was considered to have two arms, the innate and adaptive systems. Innate immunity was considered the first and fastest, though less specific line of immunological defense against evolutionarily conserved sequences. Adaptive immunity was considered a more specific, targeted line of immunological defense, mediated by T and B lymphocytes through recognition of foreign antigens with trained tolerance to self-antigens. It is increasingly clear that there is crosstalk between the innate and adaptive immune systems, and disorders of immune dysregulation are caused by impaired regulation of both the innate and/or adaptive arms of the immune system [1,2]. Successful treatment of these conditions relies on increasing our knowledge of the molecular mechanisms leading to disease and targeting these pathways. Currently available biologics are categorized by the cytokines that they inhibit.

Currently available biologics and small molecule inhibitors

Interleukin-1 inhibitors

Approved in treatment of SAIDs, RA and used in sJIA. Injection site reactions, infections, and neutropenia are the main side effects, as well as hepatotoxicity with anakinra, though risks appear to be modest [3-8].

Anakinra: Daily injection, short-acting IL-1 receptor antagonist.

Rilonacept: Weekly injection, soluble IL-1 decoy receptor.

Canakinumab: Long-acting injection, monoclonal antibody.

Interleukin-18 inhibitors

Used for treatment of NLRC4 inflammasome mutations (presents with early onset colitis and MAS). The main side effects are injection site reaction, arthralgia,and upper respiratory infections. There are 2 more monoclonal antibodies still in early clinical trials.

Tadekinig alfa: Recombinant human IL-18 binding protein [4]. Currently in clinical trials [9-13].

Novel inflammasome inhibitors

Currently in various stages of preclinical development to block inflammation at the level of the inflammasome [14-17].

Interleukin-6 inhibitors

Approved in treatment of RA, JIA, sJIA, and is used to treat refractory SAIDs [4]. Neutropenia, thrombocytopenia, hyperlipidemia, and transaminitis are the major side effects of these biologics [18-21].

Tocilizumab: Recombinant humanized IL-6 receptor monoclonal antibody, available as injection or infusion [22].

Sarilumab: Fully human IL-6 receptor alpha monoclonal antibody [12]. Appears to bind with greater affinity than tocilizumab and may help in patients with AOSD who failed tocilizumab therapy [22,23].

TH17 cytokine inhibitors

Block IL-17 and IL-22 which are produced by Th17 cells to recruit neutrophils for defense against extracellular bacteria and fungi. Also blocks IL-23, which is important in proliferation and maintenance of Th17 cells. Approved in treatment of psoriasis and arthritis, and in some cases, inflammatory bowel disease. Main side effects include increased infection risk and antibody development.

Ustekinumab: Fully human monoclonal antibody against IL-12 and IL-23. Approved in Crohn's disease and ulcerative colitis in addition to psoriasis and psoriatic arthritis. Induction dosing is intravenous in IBD, otherwise administered as injections with average maintenance dosing range from 8-12 weeks [24-26].

Secukinumab: Selective IL-17A monoclonal antibody, preventing binding to IL-17 receptor. Administered by monthly injection and approved for ankylosing spondylitis in addition to psoriasis and psoriatic arthritis. It can trigger Crohn's disease and is contraindicated in treatment of IBD [27,28].

Ixekizumab: Humanized monoclonal antibody to IL-17A similar to secukinumab.

Correspondence to: Smriti Mohan, Department of Pediatric Rheumatology, University of Michigan, Michigan, USA, E-mail: smritim@med.umich.edu

Received: 29-Dec-2023, Manuscript No. LOA-23-28833; **Editor assigned:** 03-Jan-2024, PreQC No. LOA-23-28833 (PQ); **Reviewed:** 17-Jan-2024, QC No. LOA-23-28833; **Revised:** 25-Jan-2024, Manuscript No. LOA-23-28833 (R); **Published:** 02-Feb-2024, DOI: 10.35248/2684-1630.24.9.276

Citation: Mohan S (2024) Targeted Treatment of Diseases of Immune Dysregulation. Lupus: Open Access. 9:276.

Guselkumab: Monoclonal antibody against IL-23 administered by injection. [29,30].

Interferon blockade

Anifrolumab

Fully humanized type I interferon monoclonal antibody targeting IFN-αβ receptor. Administered as monthly intravenous infusion [4]. Approved in treatment of systemic lupus erythematosus but may have application in treatment of interferonopathies [31,32].

Emapalumab: Fully human anti-IFN-γ monoclonal antibody to block signal transduction of IFN-γ. May be efficacious in treatment of NRLC4-MAS inflammasomopathy and refractory sJIA/AOSD with MAS and is administered by intravenous infections every 2 weeks [12]. Appears to have mild adverse effects, with increased risk of viral infections, though more data needed [33,34].

Tumor necrosis factor alpha inhibitors

First biologic agents developed as targeted therapy against proinflammatory cytokines, and approved in variety of autoimmune conditions including RA, JIA, AS, IBD, psoriasis and uveitis. Multiple biosimilars are now available in this category [24]. Side effects include increased infection risk, hypersensitivity, malignancy, and autoimmune conditions [4]. They are used in treatment of certain SAIDs, including TRAPS and the vascular phenotype of DADA2 [35-40].

Etanercept

Binds soluble TNF-α administered as weekly injection.

Adalimumab: Fully humanized monoclonal antibody, administered as injection every 2 weeks.

Infliximab: Chimeric monoclonal antibody administered as intravenous infusion, with wider dosing and frequency to optimize disease control than other agents.

Golimumab: Second generation, fully humanized monoclonal antibody available in injection and intravenous forms.

Certolizumab pegol: Pegylated monoclonal antibody administered as injection.

Janus kinase inhibitors

New immunosuppressive agents classified as targeted synthetics DMARDs. Approved for wide indication of treatment of both autoimmune and autoinflammatory diseases, including interferonopathies, RA, JIA, AS, psoriatic arthritis, with increasing use in dermatomyositis. They block a combination of the 4 JAKs in the JAK/STAT pathway [4]. Major side effects include increased infection risk, hyperlipidemia, and among older adults, higher risk of cardiovascular events and malignancy. There is also risk of acute cytokine storm syndrome from abrupt cessation of JAK inhibitors [41-48].

Baricitinib and ruxolitinib: Block JAK1 and JAK2.

Tofacitinib: Blocks JAK1 and JAK3.
Upadacitinib and filgotinib: Selectively block JAK1.

T-cell inhibitors

Abatacept: Recombinant CTLA-4 fusion protein binding CD80 and CD86 on antigen-presenting cells, ultimately blocking T-cell activation. Approved in JIA, RA, and PsA with trials in systemic sclerosis and localized scleroderma. Available in injection and intravenous forms. Has similar infection risk to other biologics [49-54].

B-cell inhibitors

Rituximab: Chimeric monoclonal antibody against CD20, approved for RA and other autoimmune conditions including SLE, ANCA-vasculitis, and autoimmune encephalitis [39]. Administered as intravenous infusion, with maintenance doses usually separated by several months. Side effects include hypersensitivity reaction, hypogammaglobulinemia, and increased malignancy risk [55-61].

Belimumab: Human monoclonal antibody that inhibits B lymphocyte stimulator protein binding to receptors on B lymphocytes. Currently approved in treatment of SLE, and administered as monthly infusions or weekly injections [62-64].

Bortezomib: Plasma cell inhibitor that blocks the 26S proteasome involved in degrading ubiquitinated proteins. Administered by injection or intravenous infusion. Has more side effects with peripheral neuropathy, gastrointestinal issues, thrombocytopenia, and fatigue. Approved in multiple myeloma, but recent studies suggest there may be efficacy in autoimmune diseases [65-67].

CONCLUSION

Abnormalities in both the innate and adaptive immune pathways are increasingly being implicated in pathogenesis of some diseases previously characterized as either autoinflammatory or autoimmune. Treatment of these conditions should be based on the mechanisms of known pathogenesis. Side effects of biologics include increased infection risk, hypersensitivity reaction, and increased malignancy risk. Anakinra, tocilizumab, and JAK inhibitors can also cause hepatotoxicity.

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