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MONOCLONAL ANTIBODIES: A REVIEW

Pradnya Deolekar[1]*, Kavitha Dongerkery[2], Pramila Yadav[3] and Prathmesh Deolekar[4]

[1,2,3]Pharmacology Department, D.Y. Patil School of Medicine, Navi Mumbai.

***Corresponding Author: Pradnya Deolekar**

Pharmacology Department, D.Y. Patil School of Medicine, Navi Mumbai.

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INTRODUCTION

Monoclonal antibodies are a relatively new type of "targeted" cancer or biologic therapy. A variety of mechanisms are thought to play important roles in mediating the anti-tumor effects of mAb. These include signaling mediated by cross-linking of surface antigen that leads to cell death, blocking an activation signal that is necessary for continued cell growth, antibody-dependent cellular cytotoxicity (ADCC), complement mediated cytotoxicity (CMC) and the ability of mAb to alter the cytokine milieu or enhance development of an active anti-tumor immune response.[1]

Cancer cells share many similarities with the normal host cells and this presents a challenge for achieving high levels of selective cytotoxicity. Chemotherapeutic monoclonal antibodies were engineered with the predicted advantage of specificity, thus acting as 'targeting missiles' toward cancer cells.[2]

Monoclonal antibodies originally derived from a nonhuman species (mouse, rat) can be "humanized" to various degrees by engineering amino acid substitutions that make them more similar to the human sequence. This is done using recombinant DNA technologies. Humanized mAbs are those in which the larger constant regions of the immunoglobulin heavy and light chains are human-derived. Chimeric antibodies are generally those in which the Fc part of the immunoglobulin molecule is of a human sequence.

Monoclonal antibody that had been humanized was designated by inclusion of the stem "zu" in its name (eg, trastu**zu**mab), and chimeric mAbs were designated as chimeric by the addition of "xi" (eg, ritu**xi**mab).

Atezolizumab: Atezolizumab is a humanized monoclonal antibody used to prevent the interaction of PD-L1 and PD-1. Programmed death 1 (PD-1) and its ligands PD-L1 and PD-L2 are key co-inhibitory molecules in the modulation of T-cell mediated immune responses. PD-L1 is often overexpressed in different tumors, and its interaction with PD-1 on T cells enables cancer cells to evade T-cell-mediated immune responses.[3] Thus, blocking the PD-1/PD-L1 interaction can restore T-cell activation and antitumor responses.[4]

Indicated for first-line treatment of metastatic non-small cell lung cancer (NSCLC):, urothelial carcinoma and triple-negative breast cancer.[5]

Canakinumab: is a recombinant, human anti-human-IL-1β monoclonal antibody that belongs to the IgG1/κ isotype subclass. It is expressed in a murine Sp2/0-Ag14 cell line.

In inflammatory diseases involving Cryopyrin-Associated Periodic Syndromes (CAPS), interleukin-1 beta (IL-1β) is excessively activated and drives inflammation. The protein cryopyrin controls the activation of IL-1β, and mutations in cryopyrin's gene, NLRP-3, up-regulate IL-1β activation. Canakinumab binds to human IL-1β and neutralizes its inflammatory activity by blocking its interaction with IL-1 receptors, but it does not bind IL-1α or IL-1 receptor antagonist (IL-1ra).[6]

Canakinumab is used to treat Periodic Fever Syndromes such as Cryopyrin-Associated Periodic Syndromes (CAPS) and Familial Mediterranean Fever (FMF), and also to treat active Systemic Juvenile Idiopathic Arthritis (SJIA).[7]

Daclizumab: is a humanized, monoclonal antibody that blocks CD25, a critical element of the high-affinity interleukin-2 receptor (IL-2R). Blockade of CD25 inhibits effector T cell activation, regulatory T cell expansion and survival, and activation-induced T-cell apoptosis.[8]

It is specifically indicated for the treatment of adult patients with relapsing forms of multiple sclerosis, for the prophylaxis of acute organ rejection in patients receiving renal transplants. It is used as part of an immunosuppressive regimen that includes cyclosporine and corticosteroids.[9]

Dinutuximab: Dinutuximab is an IgG1 monoclonal antibody against GD2, a disialoganglioside expressed on tumors of neuroectodermal origin, including human neuroblastoma and melanoma, with highly restricted expression on normal tissues.

By binding to GD2, dinutiximab induces antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity of tumor cells thereby leading to apoptosis and inhibiting proliferation of the tumour.[10, 11] It is specifically indicated for use in combination with granulocyte-macrophage colonystimulating factor (GM-CSF), interleukin -2 (IL-2) and 13-cis-retinoic acid (RA), for the treatment of paediatric patients with high risk neuroblastoma.[12]

Eculizumab: is a targeted therapy that targets and binds to the complement protein C5, this in turn prevents the splitting of this protein interfering with the formation of membrane attack complex (MAC). This interference prevents the destruction of red blood cells (hemolysis) and therefore results in stabilization of hemoglobin and a decrease in the need for blood transfusions in persons with paroxysmal nocturnal hemoglobinuria (PNH).[13] It has approved for atypical hemolytic uremic syndrome (aHUS). It is used for paroxysomal nocturnal hemoglobinuria.[14] It has orphan-drug designation status for treatment of refractory myasthenia gravis and neuromyelitis optica.[15]

Gemtuzumab: Monoclonal antibody against CD33 for AMI. By binding to the CD33 antigen on tumors, leads to internalization of the drug-antigen complex and hydrolytic release of the toxic calicheamicin component. The cytotoxic agent blocks the growth of cancerous cells and causes cell death.[16] Indicated for the treatment of patients with CD33 positive acute myeloid leukemia.[17]

Golimumab: A human anti-tumor necrosis factor (TNF)-alpha monoclonal antibody. Inhibition of TNFα prevents it binding to its receptors, which prevents both leukocyte infiltration through prevention of cell adhesion proteins and pro-inflammatory cytokine secretion.[18] In areas such as the joints and blood, increased TNFα is associated with chronic inflammation and thus golimumab decreases the inflammation.[19] It is administered once-monthly for the treatment of rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis. It is also indicated (v) for the treatment of active polyarticular juvenile idiopathic arthritis (pJIA) in patients 2 years of age and older.[20]

Ipilimumab: is a fully humanized IgG1 monoclonal antibody that blocks cytotoxic T lymphocyte antigen-4 (CTLA-4), which is an inhibitory molecule that competes with the stimulatory CD28 for binding to B7 on antigen presenting cells. By binding with CTLA-4, it also blocks the interaction of CTLA-4 with its ligands, CD80 and CD86.[21]

By blocking this function, ipilimumab potentiates the antitumor T-cell response, resulting in unrestrained T-cell proliferation,[22] preventing the inhibition of T-cell mediated immune responses to tumors.[23]

It is indicated for the treatment of unresectable or metastatic melanoma.[24]

Ixekizumab: humanized IgG4 monoclonal antibody that selectively binds the Interleukin -17 A cytokine and inhibits its interaction with the IL-17 receptor. It inhibits the release of proinflammatory cytokines and chemokines.[25] IL-17A has been found to be implicated in a variety of autoimmune diseases including Rheumatoid Arthritis and plaque psoriasis.It is indicated for the treatment of adults with moderate-to-severe plaque psoriasis.[26]

Nivolumab: is a genetically engineered anti-PD-1 mAb. It binds PD-1 with high affinity, blocks its interactions with both PD-L1 and PD-L2, and stimulates memory response to tumor antigen-specific T cell proliferation.[27] It is specifically indicated for the treatment of patients with metastatic squamous nonsmall cell lung cancer (NSCLC) with progression on or after platinum based chemotherapy. It is also approved for the treatment of patients with unresectable or metastatic melanoma and disease progression following Ipilimumab. Nivolumab in combination with ipilimumab, is indicated for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma and patients with intermediate or poor risk advanced RCC.

Obiltoxaximab: is a chimeric IgG1 kappa monoclonal antibody (mAb) that binds the PA component of B. anthracis toxin. ETI-204 is an affinity-enhanced, de-immunized antibody. ETI-204 targets and binds to Protective Antigen, which prevents the anthrax toxins from binding to and entering the cells in the body, thereby preventing death.It is specifically indicated for use in adult and pediatric patients for the treatment of inhalational anthrax due to Bacillus anthracis in combination with appropriate antibacterial drugs and for prophylaxis of inhalational anthrax due to Bacillus anthracis when alternative therapies are not available.[28]

Obinutuzumab: It is a humanized anti-CD-20 monoclonal antibody of the IgG1 subclass. It is more potent than rituximab in depleting B-cells, antitumor activity, and tumor regression. It binds to type II CD20 antibodies. This allows obinutuzumab to have a much higher induction of antibody-dependant cytotoxicity and a higher direct cytotoxic effect than the classic CD20 antibodies.[29] It is specifically indicated for use in combination with chlorambucil for the treatment of patients with previously untreated chronic lymphocytic leukemia.[30] There is a black box warning of fatal Hepatitis B Virus (HBV) reactivation and fatal Progressive Multifocal Leukoencephalopathy (PML).

Ofatumumab: is a fully humanized, high-affinity monoclonal antibody whose epitope on CD20 is distinct from rituximab's target.[31] The membrane proximal epitope reognized by ofatumumab encompasses both the small and large loops of CD20. In contrast, rituximab's binding site on CD20 is distal to ofatumumab's epitope and involves only the large loop. It is specifically indicated for the treatment of patients with chronic lymphocytic leukemia refractory to fludarabine and alemtuzumab.[32]

Olaratumab: It is a platelet derived growth factor receptor alpha (PDGFR- α) blocking antibody. It exerts an anti-tumor activity in vivo and in vitro against selected sarcoma cells by inhibiting tumor growth by binding to PDGFR-alpha that is present on several types of cancer on transformed cells and in tumor stroma.[33] PDGFR signalling is a type of tyrosine kinase-mediated pathway that normally regulates cell growth, chemotaxis, and mesenchymal stem cell differentiation. It also promotes internalization of PDGFR thus alters the surface levels of PDGFR.When used in a combination therapy with doxorubicin, olaratumab improves progression-free survival in patients with advanced soft-tissue sarcoma.[34]

Pembrolizumab: It is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1and PD-L2, releasing PD-1 pathway mediated inhibition of the immune response, including the anti-tumour immune response. It is specifically indicated for the treatment of patients with unresectable or metastatic melanoma and disease progression following Ipilimumab, also used for the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma with disease progression on or after platinum containing chemotherapy.[35]

Pertuzumab: It is a HER2/neu receptor antagonist compound**.** Human epidermal growth factor receptor-2 (HER2) is a tyrosine kinase receptor that plays an integral role in cell proliferation, differentiation, and survival. HER2 becomes active following dimerization with another HER2 receptor, another member of the HER protein family (e.g. HER3), or with a ligand - this dimer then phosphorylates and activates numerous intracellular signaling proteins, initiating signal transduction via several pathways. HER2 is also a known oncogene - it is overexpressed or gene-amplified (i.e. HER2-positive) in approximately 20% of breast cancers and these cancers carry a generally poorer prognosis than HER2-negative breast cancers. Pertuzumab targets the extracellular dimerization domain (subdomain II) of HER2, thereby inhibiting ligand-initiated intracellular signaling via the MAP kinase and PI3K pathways. Inhibition of these pathways results in inhibition of cell growth and the initiation of apoptosis, respectively.[36] It is specifically indicated for the first line treatment of HER2+ metastatic breast cancer in combination with trastuzumab and docetaxel.[37]

Ramucirumab: It is a recombinant human IgGI monoclonal antibody that specifically binds to vascular endothelial growth factor receptor 2 (VEGFR2). By binding to VEGFR2, ramucirumab prevents binding of its ligands (which are secreted by solid tumors to promote angiogenesis and enhance tumor blood supply), thereby preventing VEGF-stimulated receptor phosphorylation and downstream ligand-induced proliferation, permeability, and migration of human endothelial cells.[38] Thus, it is an angiogenesis inhibitor that blocks the blood supply to tumours.[39] It is specifically indicated for advanced gastric cancer or gastro-oesophageal junction adenocarcinoma, as a single agent after prior fluropyrimidine or platinum containing chemotherapy.

Ranibizumab: is a recombinant humanized monoclonal antibody and VEGF-A antagonist. It binds to the receptor binding site of active forms of VEGF-A, including the biologically active, cleaved form of this molecule, VEGF110. The binding of ranibizumab to VEGF-A prevents the interaction of VEGF-A with its receptors (VEGFR1 and VEGFR2) on the surface of endothelial cells, reducing endothelial cell proliferation, vascular leakage, and new blood vessel formation.[40] It was first approved for the treatment of patients with macular edema after retinal vein occlusion, age-related macular degeneration (wet), and diabetic macular edema.[41]

Raxibacumab: A human monoclonal antibody inhibits the binding of protective antigen (PA) to its cellular receptors, preventing the intracellular entry of the anthrax lethal factor and edema factor, the enzymatic toxin components responsible for the pathogenic effects of anthrax toxin. It does not have direct antibacterial activity.[42] Raxibacumab used in conjunction with an antibacterial regimen to treat patients with inhalational anthrax caused by Bacillus anthracis and for prophylaxis of inhalational anthrax. It targets the protective antigen component of the lethal toxin of Bacillus anthracis.[43]

Reslizumab: It is an anti-interleukin-5 antagonist monoclonal antibody (IgG4 kappa). IL-5 is a pro-inflammatory cytokine that is responsible for the growth and differentiation, recruitment, activation, and survival of eosinophils. Elevated levels of eosinophils increase the risk for asthma exacerbationst. By targeting the IL-5 and disrupting its signalling pathways, reslizumab aims to inhibit eosinophil maturation and promote programmed cell death.[44] It is specifically indicated for the add-on maintenance treatment of patients with severe asthma aged 18years and older with an eosinophilic phenotype. Reslizumab is not indicated for use in other eosphinophilic conditions or for the relief of acute bronchospasm or status asthmaticus.[45]

Siltuximab: It is an anti-interleukin-6 (IL-6) chimeric monoclonal antibody that binds to human IL-6 and neutralizes human IL-6 directly, thereby decreasing levels of unbound IL-6 and preventing binding to its

receptor. IL-6 is a multifunctional cytokine produced by various cells such as T cells, B cells, monocytes, fibroblasts and endothelial cells.[46]

It is specifically indicated for the treatment of patients with multicentric Castleman's disease who are human immunodeficiency virus (HIV) negative and human herpes virus-8 (HHV-8) negative. Dysregulated overproduction of IL-6 from activated B cells in affected lymphnodes has been implicated in the pathogenesis of Castleman's disease.[47]

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