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MONOCLONAL ANTIBODIES - A MINIREVIEW

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ABSTRACT

Monoclonal antibodies have undergone tremendous advancement over the last few decades. They are homogenous biologicals with multiple mechanism of action. With the advancement of hybridoma technique they have become more efficient and safe. However few life threatening adverse reactions of monoclonal antibodies still pose a problem. This review focuses on the applications and adverse effects of monoclonal antibodies commonly used.

KEYWORDS: Adverse Effects, Monoclonal Antibodies, Uses.

INTRODUCTION

Monoclonal antibodies (MA) are biologics with multiple mechanism of action such as direct modulation of the target antigen, complement dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity and delivery of a radio nucleotide or immunotoxins to target cell.[1] The IgG subtype is used for generation of therapeutic MA. Of this IgG1 has the maximum potential for antibody-dependent cell-mediated cytotoxicity and is therefore ideal for eliminating cancer cells. In cases where cytotoxicity is not wanted, IgG4 is commonly used. It is also possible to modify the Fc region to further minimize recruitment of complement or effector cells.[2] With advancement of technology monoclonal antibodies has moved from murine to fully humanised preparations. Their advantages include high specificity, long half-lives, lower immunogenicity, and lower risk for drug-drug interactions as they are not metabolised via hepatic or renal pathways.[3] These drugs are very expensive and exhibit fewer adverse reactions when compared with chemotherapeutic drugs.

The adverse events are due to stimulation or inhibition of the pharmacological action the target or non-target tissue.[4,5] Clinical signs of rashes, weakness, headache, fever, diarrhoea, vomiting and nausea, and sometimes decreased blood pressure are common side effects (Table.1). Acute infusion reactions following infusion of MA include acute anaphylactic reactions, influenza-like syndrome, serum sickness, tumour lysis syndrome and cytokine release syndrome. Muromonab, alemtuzumab and rituximab trigger the release of a range of cytokines, causing a cytokine storm.[2,6] Dermal toxicity manifestations include maculopapular exanthema, pruritus vitiligo, blisters, toxic epidermal necrosis and Stevens-Johnson syndrome and more evident with panitumumab.[2]

There is an increased risk of tuberculosis in patients with inflammatory bowel disease treated with TNF-specific MA. Rituximab, efalizumab has been associated with progressive multifocal leukoencephalopathy. Infliximab, efalizumab bevacizumab has been associated with thrombocytopenia Use of TNF-specific MA for rheumatic diseases has been associated with the development of lupus-like syndromes and drug-related lupus. Other autoimmune complications include cutaneous or systemic vasculitis, nephritis and demyelinating syndromes. Alemtuzumab can cause antibody-mediated thyroid autoimmunity. Some MA such as tositumomab, ibritumomab and TNF-specific infliximab have increased risk of malignancy.[2]

Diarrhoea, intestinal perforation and hepatic toxicity are the immune mediated toxicity caused by ipilimumab. Less frequent immune mediated reactions of ipilimumab are meningitis, uveitis, pneumonitis, pancreatitis, pericarditis, myocarditis, nephritis, angiopathies, haemolytic anaemia and thrombocytopenia. Possible endocrinopathies include hypopituitarism, hypofunction of the adrenals, hypo or hyperfunction of the thyroid gland and hypofunction of the gonads.[5] Trastuzumab causes asymptomatic decrease in left ventricular ejection fraction due to mitochondrial outer membrane permeabilization.[2]

Table. 1. Currently used monoclonal antibodies with their indications and adverse effects

Target	Monoclonal antibody	Indications	Adverse effect
CD20 molecule on B-cells	Rituximab	Lymphoma Autoimmune haematological disorders	Infusion reaction Cytokine release syndrome Tumour lysis syndrome Hypotension Immunogenicity Immunosuppression Hepatitis B reactivation with fulminant hepatitis Progressive multifocal leukoencephalopathy Renal toxicity Cardiac arrhythmias
CD52	Alemtuzumab	Multiple sclerosis Multiple myeloma Leukaemia Graft rejection Vasculitis	Infusion reaction Tumor lysis syndrome Hypersensitivity Immunosuppression Blood dyscariasis Thyroid disorder Cardiotoxicity
CD3	Muromonab	Renal, hepatic and cardiac allograft transplant	Immunogenicity Infusion reaction Hypersensitivity Immunosuppression Cardiovascular side effects Hepatitis
CD5	Eculizumab	Meningoccocal and Neisseria infection	Haemoglobinuria
IgE	Omalixumab	Severe allergic asthma	Anaphylactic reactions Churg Strauss syndrome Immunogenicity Injection site reaction
α4-integrin	Natalizumab	Multiple sclerosis	Hypersensitivity Infusion reactions Hepatotoxicity Immunogenicity Progressive multifocal leukoencephalopathy
Tumor necrosis factor-alpha	Adalimumab, Certolizumab Infliximab	Rheumatoid arthritis, Psoriasis Ulcerative colitis Crohn's diseases	Immunogenicity Infusion reaction Hypersensitivity Immunosuppression Blood dyscariasis Malignancy Worsening heart failure
Platelet glycoprotein IIb/IIIa	Abciximab	Percutaneous coronary interventions of ischaemic cardiac diseases	Hypersensitivity Thrombocytopenia
Vascular endothelial growth factor	Bevacizumab	Colorectal, non-small cell lung, breast and renal carcinoma.	Infusion reactions Haemorrhage Hypertension, Cardiac failure Immunogenicity
	Ranibizumab	Injected for neovascular aged related macular degeneration.	Conjunctival haemorrhage Intra ocular inflammation Endopthalmitis Retinal detachment
Interleukin -2 receptor	Basiliximab, Daclizumab	Prophylaxis of renal allograft transplant rejection	Hypersensitivity Immunogenicity Immunosuppression Local skin reactions
Interleukin -6 receptor	Tocilizumab	Castleman's disease Unresponsive rheumatoid arthritis.	Anaphylaxis Headache Neutropenia
EGFR (Epidermal growth factor receptor)	Cetuximab	Colorectal cancer, squamous cell carcinoma in head and neck.	Severe infusion reaction Bronchospasm Pulmonary toxicity
	Transtuzumab	ERBBR2-positive breast carcinoma	Infusion reaction Hypersensitivity Cardio toxicity Pulmonary toxicity
	Panitumumab	Monotherapy for EGFR-positive meta static colorectal carcinoma.	Infusion reactions Skin reaction, Diarrhoea Nausea vomiting
CTLA4 (cytotoxic T-lymphocyte associated antigen-4)	Ipilimumab	Metastatic melanoma	Immune-related adverse events such as rash and hepatitis
Vascular integrin (alpha-v/beta-3)	Vitaxin	solid tumours	No detrimental side effects.

MA used to treat cancer act by different mechanisms. Alemtuzumab attaches to cancer cells (CD52 antigen on lymphocytes) and acting as a marker for the body's immune system to destroy them. Trastuzumab may attach and block antigens (HER2 protein) on cancer cells that help cancer cells grow or spread. Currently MA targeting immune system checkpoints like ipilimumab, nivolumab and pembrolizumab target programmed cell death 1 receptor (PD-1). Ibritumomab tiuxetan is an example of a radiolabeled MA that is conjugated to radioactive particle. Blinatumomab is bispecific monoclonal antibodies that can attach to two different proteins at the same time. By binding to both of these proteins, this drug brings the cancer cells and immune cells together thus initiating cytotoxicity.[5]

Currently, MA approved for the treatment of cardiological indications are abciximab, digoxin basiliximab.[3] Studies that aims to inhibit the proprotein convertase (subtilisin/kexin) type 9 (PCSK9) to lower LDL-C levels is in clinical trials. Evolocumab and Alirocumab were found to be safe and well tolerated and substantially resulted in favourable changes in other lipids.[4,7] Monoclonal antibodies targeting fatty acid–binding protein aP2 and human glucagon have been successful for preclinical treatment for type 2 diabetes. Monoclonal antibodies are effective against rheumatoid arthritis, Crohn's disease and ulcerative colitis, allergic asthma and rejection of kidney transplants.

It is used in immune diagnosis and metastasis of tumour and to monitor levels of alpha fetoprotein, carcino-embryogenic antigen and HCG secreted by various tumours. It is used to distinguish between myleogenous and lymphocytic leukaemia.[8] They are also used in tissue typing, immunoassay, identification and antigenic characterization of pathogens, serotyping of microorganisms, immunological intervention with passive antibody, anti-idiotype inhibition, or detection and purification of protein.[1,9,10] MA used in diagnosis of plant diseases even before it is visibly evident.[8]

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