JMSCR Vol||05||Issue||02||Page 18109-18118||February 2017

www.jmscr.igmpublication.org
Impact Factor 5.84
Index Copernicus Value: 83.27
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v5i2.140

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Immunobiologicals

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Abstract
Immunobiologicals are the biologically active agents with immunological actions that are useful for the management of immunologically mediated diseases of infectious or non-infectious origin.
Keywords: *Immunobiologicals, Epitope, Interferon, Monoclonal antibodies.*

Introduction

Biologicals are molecules that modify the cascade of immunological processes leading to inflammation. Principal Immunobiologicals are Monoclonal Antibodies (Mab), Fusion Inhibitors and Interferons (IFN). Paul Ehrlich first described Monoclonal Antibodies as "magic bullets" in search of toxins.[1]

An antibody is a protein used by the immune system to identify and neutralize foreign objects like bacteria and viruses. Each antibody recognizes a specific antigen unique to its target. Monoclonal antibodies (mAb) are antibodies that are identical because they were produced by one type of immune cell, all clones of a single parent cell.

Polyclonal antibodies are antibodies that are derived from different cell lines. They differ in amino acid sequence.[1]

The antigen associated with tumor cells are called as the" TUMOR MARKER". Antibodies produced as a result of specific tumor markers monoclonally can be conjugated with drug molecule which in turn can be targeted to the specific cells or tumor tissues.

Targeting antibodies with drugs involve the following steps

1. Identification of the new antigen produced by the tumor cells.
2. Production of antibody monoclonally against the identified new antigen.
3. Formation of drug antibody conjugate or complexes. [1]

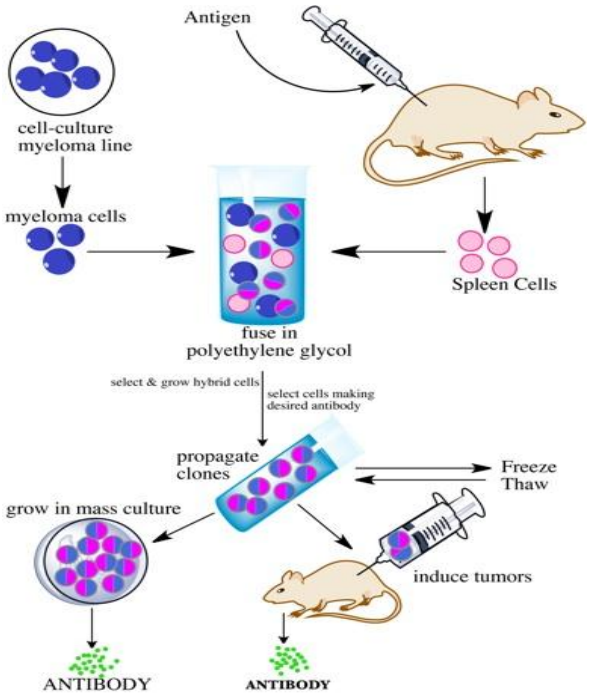
These complexes concentrate at the tumor site and deliver the drug.

There are several advantages when drugs are delivered as antibody conjugates. The conjugates can specifically reach the target cells without causing any damage to the normal tissue. The drug antibody conjugate could be expected to be the ideal agents for drug targeting in chemotherapy.[1]

Production of Monoclonal Antibodies

Kohler and Milstein developed methods for isolation of monoclonal antibodies from hybridoma cells in 1975.[2]

An antigen is injected into a mouse, and after a few weeks its spleen is removed and plasma cells are extracted. The mouse's spleen cells are fused with myeloms cells to create hybrid cells called hybridoma cells. Each hybridoma cell indefinitely produces identical antibody, and the hybridoma cells are then screened using an antigen/antibody assay that will reveal which cells produce the desired antibody. The collection of selected hybridoma cells that produce the preferred antibody are re-screened multiple times until a pure line is isolated. These cells are grown in a culture and/or injected into into mice to induce tumors. The cells can also be frozen and saved for later use. The hybridoma method for producing monoclonal antibodies is useful because large amounts of specifically-tailored identical antibodies can be produced easily.[2]



Production of Monoclonal Antibodies

Monoclonal antibodies are classified according to the decreased order of antigenicity of their components intomurine, chimeric, Primatized and Humanized.

Table 1. Immunobiologicals[2]

Cytokine Blocking Agents	*Target*	*Type*	*Indication*
Afelimomab	Anti TNF-α	Protein	Sepsis
Infliximab (Remicade)	Anti-TNF-α	Chimeric	Behcets Disease Toxic Epidermal Necrolysis
Etanercept (Enbrel)	Anti-TNF-α and TNF-ß	Fusion Protein	Pemphigus
Agents Targeting cell surface epitopes			
Alefacept (Amevive)	CD-2-LFA-3	Fusion Protein	Psoriasis
Alemtuzumab(campath)	CD-52	Humanized	Chronic Lymphocytic Leukemia
Apolizumab	HLA-DR beta	Humanized	Non-Hodgkins Lymphoma
Belimumab (Benlysta)	B cell Activating Factor(BAFF)	Humanized	Sjogrens syndrome Systemic Lupus Erythematosis (SLE)
Bevacizumab (Avastin)	Vascular Endothelial Growth Factor(VEGF)	Humanized	Colorectal Cancer
Belimumab (Benylsta)	Anti BLys	Humanized	Lupus induced Nephritis
Basiliximab (simulect)	CD-25	Humanized Mab	Transplant Rejection
Brentuximab (Adcertis)	CD-30	Chimeric	Hodgkins Lymphoma
Cetuximab(Erbitux)	Epidermal Growth Factor Receptor(EGFR)	Chimeric	Head and Neck cancer
Certolizumab (cimzia)	Inhibition of TNF-α Signalling	Humanized	Crohns Disease
Cixutumumab	IGF-1 receptor	Human	Metastatic Rhabdomyosarcoma Hepatocellular carcinoma
Daclizumab (Zenopax)	CD-25	Humanized Mab	Transplant rejection
Denileukin Diftitox (Ontak)	CD25/Ib 2	Fusion toxin	Cutaneous T-Cell Lymphoma
Denosumab (Prolia)	RANK-L	Humanized	Bone loss

Efalizumab (Raptiva)	CD-11 a/ CD18	Humanized Mab	Psoriasis
Eculizumab (soliris)	Complement System Protein C5	Humanized	Paroxysmal Nocturnal Haemoglobinuria
Epratuzumab (Lymphocide)	CD-22	Humanized	Systemic Lupus Erythematosus (SLE)
Gemtuzumab(Mylotarg)	CD-33	Humanized	Acute Myeloid Leukemia
Golimumab (Simponi)	TNF- α	Humanized	Rheumatoid arthritis, Psoriatric arthritis
Iplimumab (Yervoy)	CTLA-4	Humanized	Metastatic Melanoma
Mepolizumab (Nucala)	IL-5 α of Eosinophil	Humanized	Asthma
Omalizumab (Xolair)	Ig E	Humanized	Asthma
Ofatumumab (Arzera)	CD-20	Humanized	Chronic Lymphocytic Leukemia
Pavilizumab (Synagis)	RSVF	Humanized	Prevention of RSV
Panitumumab (Vectibix)	EGFR	Humanized	Colorectal cancer
Ranibizumab(Lucentis)	VEGF	Humanized	Macular Degeneration
Sifalimumab	Anti-IFN α	Humanized	Systemic Lupus Erythematosus Dermatomyositis Polymyositis
Siplizumab	CD-2	Humanized Mab	Graft vs Host Disease Psoriasis
Tocilizumab (Actemra)	IL-6	Humanized	Rheumatoid arthritis
Trastuzumab (Herceptin)	HER-2	Humanized	Breast cancer
Visilizumab (Nuvion)	CD-3	Humanized	Cohns Disease Ulcerative colitis
Muromonab	CD-3	Murine	Transplant Rejection
Rontalizumab	Anti-IFN α	Humanized	Systemic Lupus Erythematosus
Irbitumomab(Zevalin)	CD-20	Murine	Non-Hodgkins Lymphoma (With Ytrrium-90 or Indium-111)
Tositumomab (Bexxar)	CD-20	Murine	Non-Hodgkins Lymphoma

Table 2. Dosages Of Some Monoclonal Antibodies

Monoclonal Antibodies	Dosages
Infliximab (REMICADE)	5mg/kg/dose i.v alone or in combination with other agents.100mg injection
Etanercept(ENBREL)	25 mg subcutaneously. twice weekly for minimum 12 weeks
Alfacept (AMEVIVE)	10-15 mg intramuscular injection once weekly for 12 weeks
Efalizumab (RAPTIVA)	0.7mg/kg subcutaneous injection (conditioning dose) followed by weekly subcutaneous doses of 1mg/kg (Maximum single dose not to exceed a total of 200 mg).A single vial delivers 125 mg.
DenileukinDiftitox (ONTAK)	9-18 mcg /kg/d intravenous infusion daily for 5 days every 3 weeks, 6 courses are required to show Partial or complete response. A single vial delivers 150 mcg/ml Per vial

Types of Monoclonal Antibodies:[2]

I. Murine monoclonal antibody: Whole antibody is of murine origin produced by Hybridoma technology. Major problems with murine mabs include reduced stimulation of cytotoxicity, formation of complexes after repeated adminis-tration, Allergic reactions, Anaphylactic shock. Eg. Aflimomab

II. *Chimeric monoclonal antibody:* Chimeric antibodies composed of murine variable regions fused onto human constant regions developed by Recombinant DNA technology. Antibodies are Approximately 65% Human origin. This reduces immunogenicity thus increases serum-half life. Eg. Basiliximab, Cetuximab

III. Humanised monoclonal antibody: Humanised antibodies are produced by grafting murine hypervariable domains into human antibodies Antibodies are approximately 90-95% human origin These bind weakly to the antigens. Eg. Apolizumab, Atlizumab

IV. Human monoclonal antibody: Human monoclonal Antibodies are produced by transferring human Immunoglobulin genes into

the murine genome, After which the transgenic mouse is Vaccinated against the desired antigen, leading to the production of monoclonal antibodies. Eg. Belimumab, cixutumumab.

Mechanism of action of Monoclonal Antibodies[3]

1. ADCC: Antibody dependent cell-mediated cytotoxicity ADCC Immunoglobulin's clustered on the surface of the targeted cells and exposes its tail {Fc} region, to be recognized by the Fc receptors present on the surface of the macrophages and neutrophils. This causes Lysis of tumor cell.

2. Radioimmunotherapy: It involves the addition of a radioisotope to a therapeutic monoclonal antibody thereby increasing its activity through targeted radiation. Emitted radiation causes tumor cell lysis.

Table .3. Radionuclides in Radioimmunotherapy

ISOTOPE	RADIATION	HALF-LIFE (Hrs)
Actinium -225	A	240
Astatine-211	A	7
Bismuth-213	A	46 mins
Copper-67	ß	62
Iodine-131	ß or ɤ	193
Lutetium-177	ß	160
Rhenium-186	ß	91
Rhenium-188	ß or ɤ	17
Ytrrium-90	ß	64

3. ADEPT (Antibody mediated Enzyme prodrug therapy):

ADEPT is a two-step antibody targeting system in which the antibody-enzyme conjugate component is first targeted and allowed to localize a tumor followed by clearance of the residual circulating antibody. The cytotoxic agent (prodrug) is then administered, diffuses widely but in the ideal case is activated solely at the tumor following contact with the localized conjugated protein. The potential advantage of ADEPT is amplification of cytotoxic activity by conjugated enzyme.

Table.4. Enzyme and Prodrug Combinations Used in ADEPT

Enzyme	Prodrug	Activity
Alkaline Phosphatase	Etoposide,Doxorubicin,Phenol mustard	Hydrolysis of Phosphate Groups
ß Lactamase	Doxorubicin,Paclitaxel,Mitomycin	Cleavage of Lactam ring, Elimination of substituents attached to 3′ of cephalosporin Derivatives
Cytosine Deaminase	5-Fluorouracil	Deamination of cytosine to uracil
Carboxypeptidase A	Methotrexate	Cleavage of α Glutamyl Peptides
Carboxypeptidase G2	Nitrogen Mustard	Cleavage between Glutamyl moiety and aromatic nucleus

4. Immunoliposomes: [4]

Immunoliposomes are generated by coupling of antibodies to the liposomal surface and allow for an active tissue targeting through binding to tumor cell-specific receptors. Such antibody modified liposomes are attracting great interest for their potential use in specific drug delivery to cancer cells, gene therapy, drug delivery through blood brain barrier, or molecular imaging.

Immunoliposomes show promising results *in vitro* and *in vivo* and appear to be effective systems for improvements in cancer therapy. The targeted liposomes offer various advantages over classic drugs and one of the most compelling of these is that larger drug amounts can be delivered to the target tissue. Likewise, immunoenzymosomes may result in increased prodrug-drug conversion rates. Liposomes can encapsulate drugs, DNA, siRNA, virions (immunovirosomes) or contrast agents with high load capacity and only a few ligand (targeting) molecules per liposome are required to selectively deliver high payloads of drugs *via* receptor mediated endocytosis.

5. Immunotoxins:[5]

Tumor-specific monoclonal antibodies conjugated to tumoricidal substances such as radionuclides or toxins e.g, Diptheria toxin, Ricin. Diptheria antitoxin is prepared in horses by injection of toxoid of corynebacterium diptheriae.

Tetanusantitoxin consists of Human –derived immunoglobulin specific for the toxin of clostridium tetani. Botulism antitoxin is a polyvalent antitoxin made against three types of toxin (Types A,B and E produced by clostridium Botulinum. BCG (Bacille calmette –Guerin) is a live attenuated strain of Mycobacterium Tuberculosis that is used as a vaccination to immunize people against Human Tuberculosis. (The Monoclonal antibodies carry the therapeutic agent directly to the tumor, which lowers toxicity to normal tissues.

Various plant & biological toxins have been genetically fused/chemically conjugated with the antibodies that bind to cancer cells.

6. Antibody drug conjugates:

Antibody drug conjugates are proteins that contain drug along with an antibody, bind specifically to antigen and to be internalized by the target cell, involves release of drug from the antibody and leads to target cell lysis.

Antibody drug conjugates are monoclonal antibodies (mAbs) attached to biologically active drugs by chemical linkers with liable bonds reduces side effects and show wide therapeutic window. Doxorubicin, Chlorambucil etc. can be conjugated with monoclonal antibodies.

7. Fragments of Mabs

Fragments of Mabs Fab and F (ab) 2 are less immunogenic but have greater tumor penetration power than normal antibody and are helpful in detecting smaller lesions (<2cm) not seen on computed tomography ScFv are mainly used as delivery vehicles for cancer therapy.

Problems of Drug Delivery by Monoclonal Antibodies:

1. Slow elimination of monoclonal antibodies from the blood.
2. Poor vascular permeability,
3. Cross reactivity with normal tissues, Metabolism of monoclonal antibody conjugates.
4. May bind with the targeted epitopes present on other tissues, which may lead to the damage of normalcells.
5. Tumor uptake may be increased through administering high doses.

Advantages of Monoclonal antibodies

1. Monoclonal antibodies are extremely valuable in laboratory Procedures because they are easily purified and react with a single epitope of an antigen.
2. Monoclonal antibodies has therapeutic agents and are being used in the treatment of cancer, primarily as carriers of anticancer agents such as radioisotopes or cytotoxic agents.
3. Monoclonal antibodies represent an alternative source of immunogens as anti-idiotypic vaccines.

Disadvantages of monoclonal antibodies

1. Monoclonal antibodies production, a time consuming process because entire process requires 3-4 months for one fusion experiment.
2. Average affinity of Monoclonal antibodies are generally lower.
3. Any physical/chemical treatment will affect all Monoclonal antibodies in that production.

Interferons:

Interferons are a family of glycoproteins which are synthesized by Leukocytes (IFN-α),Fibroblasts (IFN-ß) and Immune cells (IFN-ɤ) against viral infections and other nonviral challenges that in addition to having antiviral properties, also modulate various cellular functions. Interferon α is mainly used for therapeutic purposes.

Interferons synthesised by recombinant techniques have therapeutic value in the treatment of viral infections of the skin and cutaneous malignancies. They are products of bacterial fermentation of particular strain of E.coli consisting genetically engineered plasmid containing a specific interferon gene from Human Leukocytes.

Table 5. Cytokine Therapy for Tumors

INTERFERON	TUMOUR	MODE OF ACTION	RESULT
Interferon-α and ß	Hairy cell Leukemia	Cytostatic,Increased MHC ClassI expression.	Prolonged Remission
Interferon-ɤ	Ovarian carcinoma Renal carcinoma	Cytostatic,T Cell activation,Increased MHC Class I and II Expression. T cell and NK cell activation.	

Interferon α 2 b is supplied as a) Powder for injection/reconstitution, b).Solution for injection in vials. The doses and Preparations of Interferon α2 b is given in the following table 6.

Table 6. Powder Formulation of Interferon α2 b

Vial strength	ML Diluent (sterile water)	Final concentration after reconstitution million IU/ml	Route of administration
10	1	10	IM,SC,IV,IL *
18	1	18	IM,SC,IV*
50	1	50	IM,SC,IV*

IM –Intramuscular, SC- Subcutaneous, IV-Intravenous.

Table.7. Solution Formulations of Interferon α 2 b

Vial strength	concentration	Route of Administration
10 MIU Single Dose	10 million IU /1.0 ml	SC,IL
18 MIU Multi Dose	3 million IU/0.5 ml	IM,SC
25 MIU Multi Dose	5 million IU/0.5 ml	IM,SC,IL

Mechanism of action of Interferons:

Antiviral

Induces enzyme 2′ - 5′ Asynthetase, Polymerises ATP, activates cellular endonuclease, degrade both viral as well as cellular RNA.

Anti proliferative effect:

Inhibits mitosis of the cells and down regulates their growth factors.

Immunoregulatory effect:

Induces expression of class I and class II MHC complexes antigens on immune cells, enhances number of Natural Killer (NK) cells.

Principle Indications of Interferon:

Interferon α 2 A:

Recurrent Aphthous stomatitis:

Interferon α 2 a administered orally once daily in a low concentration (1,200 IU/day) for 1 week (Hutchinson VA et al 1990)[6]

Basal cell carcinoma:

Basal cell carcinomas consecutively expresses CD95 Ligand. Injection of Interferon α 1.5 x 10 (6) IU (13.5 Million IU) 3 times weekly for 3 weeks diminish erythema, improvement in the overall appearance and reduction of size of Basal cell carcinoma (Cornell 1990)[7]

Squamous cell carcinoma:

A single dose of Human Interferon α 2 C 400,000 to 5,000,000 IU given weekly for 3-6 weeks, 5 times per week for 4 weeks (Ikic D 1991)[8]

Bladder cancer:

Induction: 50 MU (With 1/3 vial BCG) Weekly for 6 weeks.

Maintenance: 50 MU (with 1/3 Vial BCG) Weekly for 3 consecutive weeks every month.[9]

Cutaneous T cell Lymphoma (Hairy cell Leukemia) 2 MU/m^2 s.c /i.m[10]

Renal cell carcinoma:

5MU sc thrice daily 2 doses, then 10 MU sc thrice daily for 12 weeks.[11]

Multiple Myeloma:

synergistic activity was observed when IFN was combined with chemotherapeutic agents in vitro and in vivo. The IFN dose ranged between 4.8 and 18.7 MU/week.[12]

Polycythemia vera:

Interferon alpha (IFN) inhibits the growth of the abnormal clone in patients with myeloproliferative disorders, leading to a reduction of the clinical and laboratory signs of the pathologic myelo-proliferation in polycythemia vera (PV)[13]

Hemangioma:

Interferon α 2A 3 million units/m (2) per day should be used only in life threatening Hemang-iomas act by inhibiting angiogenesis in whom high dose corticosteroid therapy failed. (Zhang L 2015)[14]

Chronic Hepatitis B infection:

10 MU/L Pegylated Interferon alpha is used in the treatment of chronic Hepatitis B infection.(Van zonneveld M et al 2004)[15]

Interferon –α 2b

Malignant Melanoma:

20 MU/m^2 i.v over 20 min for 5 consecutive days/week for 4 weeks. (Induction Phase) followed by 10 MU/m^2 s.c injection three times / week for 48 weeks (Maintenance Phase).

Interferon α2 b has a dual effect of TAP1 (Antigen presenting cells of MHC complex) upregulation in antigen presenting cells and in silent metastatic melanoma cells. (Heise Ruth et al 2017)[16]

Herpes simplex:

10,000 IU/ml of Interferon α is used for treatment of Herpes simplex (Hammer 1982).[17]

Herpes zoster:

Interferon α 2 b 5.1 X 10^5 U per kilogram per day effective in limiting cutaneous dissemination, visceral complications and progression within the primary dermatome.[18]

Keratoacanthoma:

The standard dose of Interferon α2 b in the treatment of Keratoacanthoma is 1.5 x 10^6 units (0.3 cc), using a lower dose for the first and second injections—such as 1 x 10^6 units(0.2 cc)—is recommended. The standard dose of 1.5 x 10^6 units is given by the third or fourth injection. For a small tumor (e.g., 1 x 1 cm), the lower dose may be used throughout. For larger tumors, larger doses may be given compatible with patient tolerance. In general, the effective dose range correlates with 1 x 10^6 units form, tumor size 1 cm^2, and increases by 0.5 x 10^6 units for each additional cm^2.[20]

AIDS- related Kaposi sarcoma:

30 MU/m^2/dose subcutaneously or intramuscularly three times a week for 16weeks of treatment till maximum response.[21]

Condyloma acuminatum:

1 MU per lesion (Maximum of 5 lesions in a single course). Intralesional injections should be three times weekly on alternate days for 3 weeks directed towards the centre of the base of the lesion which produce a small wheal if done correctly. An additional course may be administered at 12-16 Weeks.(Boot JM et al 1989)[22]

Behcets disease:

6 MU of IFNα-2a for ocular manifestation of Behcets disease (Kotter 2004)[23]

Interferon ɤ:

Used for the treatment of recalcitrant moderate to severe Atopic dermatitis acts by inhibiting IgE synthesis by promoting proliferation of Th1 cells) administered by weekly subcutaneous injections. (Guttman-yassky et al 2017).[24]

Keloid and Hypertrophic scars:

Interferon ɤ down regulate collagen synthesis invitro and invivo. The recommended dose of Interferon ɤ is 0.05 mg once per week for 10 weeks. (Larrabee WF et al 1990).[25]

Side effects of Interferons:

1) Flu like symptoms can be avoided by the administration of NSAIDs (Non-steroidal Anti-inflammatory Drugs like Paracetamol).
2) Hepatotoxicity.
3) Hypotension,Arrhythmias.
4) Spastic Paraplegia (may be related to the preservatives).
5) Rhabdomyolysis (Rare).

Intravenous Immunoglobulins :[26]

Intravenous immunoglobulins are heterogeneous human gamma globulins consisting IgG with trace of IgA and IgM prepared by cold ethanol fractionalization of pooled human sera harvested from thousands of donors. Intravenous immune-globulins is an important safe, effective therapeutic option as an immunomodulatory agent in the management of skin disorders where corticosteroids and immunosuppressive agents cannot be used.

Mechanism of action of Intravenous immunoglobulins:

1) Neutralization ofMicrobe or toxin.
2) Inhibition of cytokines like IL-1,IL-6 and TNF-α.

3) Superantigen neutralization.
4) Modulation of complement activation.
5) Acceleration of IgG catabolism.
6) Saturation of Fc receptors on Macrophages (Fc receptors play role in cytotoxic cell-mediated immunity and opsonisation).
7) Suppression of antibody production and idiotypic (the variable part of an antibody including the unique antigen binding site is known as idiotype) antibodies.
8) Helps to clear immune complexes from the body in Patients affected with Systemic Lupus Erythematosus.

5% lyophilised powder dissolved in 5 % Dextrose. Available as IMMUGLOB 2.5 g/100ml or 5g/200ml Vial. Since it is not compatible with normal saline, it has to be diluted with 5 % Dextrose in Water.

Table 8. Indications and Doses of Intravenous Immunoglobulins26

Indication	*Doses and Duration*
Pemphigus Vulgaris	2g/kg i.v. single dose monthly or 1 g/kg/day x 3 days every month or 0.5 g/kg/day x5 days every month
Toxic Epidermal Necrolysis	0.8 – 5.8 g/kg for 1-5 days
Dermatomyositis	2g / kg i.v single dose monthly for 2-4 months
Graft Versus Host Disease (GVHD)	250-500 mg/kg weekly from day-8 to day-111 after Bone marrow Transplantation
Autoimmune urticarial	0.4/kg/day for 5 days
Kawasaki disease	2g / kg i.v as single dose
Congenital/Acquired Agammaglobulinemia or Hypogammaglobulinemia	0.25 g/kg every 3 weeks in childhood
Scleromyxedema	2g / kg i.v. monthly for 3 months
PyodermaGangrenosum	1-2 g/kg i.v.monthly for 2-4 months

Disadvantages of Intravenous Immunoglobulins:

1) All intravenous immunoglobulins must be screened to minimise the risk of transmission of HIV,HBV,HCV infection.
2) Can interact with live virus vaccines. Such vaccines should not be given 14 days before or 3 months after Intravenous immunoglobulin administration.
3) Have risk of autoimmunity owing to infusion of antibodies.
4) Rebound flare up can occur after discontinuation of intravenous immunoglobulins.
5) Anaphylactic reactions can occur.

Conclusion

Antibody engineering by amino acid substitutions to increase the efficacy of effect or functions and conjugation of cytotoxic compounds like radionuclides, drugs and toxins is expanding as the next generation of mab based therapeutics for cancer. The main advantage of monoclonal antibodies is that it selectively causes apotosis of the Cancer cells sparing adjacent normal cells and are the future in Cancer therapy.

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