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.\textsuperscript{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.\textsuperscript{1}

The antigen associated with tumor cells are called as the" TUMOR MARKER". Antibodies produced as a result of specific tumor markers monoclonoally 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.\textsuperscript{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.\textsuperscript{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 myeloma 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

Table 1. Immunobiologials2

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

Monoclonal antibodies are classified according to the decreased order of antigenicity of their components intomurine, chimeric, Primatized and Humanized.
Table 2. Dosages Of Some Monoclonal Antibodies

<table>
<thead>
<tr>
<th>Monoclonal Antibodies</th>
<th>Dosages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab (REMICADE)</td>
<td>5mg/kg/dose i.v alone or in combination with other agents.100mg injection</td>
</tr>
<tr>
<td>Etanercept(ENBREL)</td>
<td>25 mg subcutaneously. twice weekly for minimum 12 weeks</td>
</tr>
<tr>
<td>Alfacept (AMEVIVE)</td>
<td>10-15 mg intramuscular injection once weekly for 12 weeks</td>
</tr>
<tr>
<td>Efalizumab (RAPTIVA)</td>
<td>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.</td>
</tr>
<tr>
<td>DenileukinDiftitox (ONTAK)</td>
<td>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</td>
</tr>
</tbody>
</table>

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 administration, 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**

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**

<table>
<thead>
<tr>
<th>ISOTOPE</th>
<th>RADIATION</th>
<th>HALF-LIFE (Hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actinium-225</td>
<td>A</td>
<td>240</td>
</tr>
<tr>
<td>Astatine-211</td>
<td>A</td>
<td>7</td>
</tr>
<tr>
<td>Bismuth-213</td>
<td>A</td>
<td>46 mins</td>
</tr>
<tr>
<td>Copper-67</td>
<td>β</td>
<td>62</td>
</tr>
<tr>
<td>Iodine-131</td>
<td>β or γ</td>
<td>193</td>
</tr>
<tr>
<td>Lutetium-177</td>
<td>β</td>
<td>160</td>
</tr>
<tr>
<td>Rhenium-186</td>
<td>β</td>
<td>91</td>
</tr>
<tr>
<td>Rhenium-188</td>
<td>β or γ</td>
<td>17</td>
</tr>
<tr>
<td>Yttrium-90</td>
<td>β</td>
<td>64</td>
</tr>
</tbody>
</table>

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**

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Prodrug</th>
<th>Activity</th>
</tr>
</thead>
</table>
| Alkaline Phosphatase          | Etoposide, Doxorubicin, Phe
ol mustard                  | Hydrolysis of Phosphate Groups                                                        |
| β 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**: 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**: 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.
Tetanus antitoxin 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 normal cells.
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 have 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-idiotype 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-β) and Immune cells (IFN-γ) 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

<table>
<thead>
<tr>
<th>INTERFERON</th>
<th>TUMOUR</th>
<th>MODE OF ACTION</th>
<th>RESULT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon-α and β</td>
<td>Hairy cell Leukemia</td>
<td>Cytostatic, Increased MHC Class I expression.</td>
<td>Prolonged Remission</td>
</tr>
<tr>
<td>Interferon-γ</td>
<td>Ovarian carcinoma</td>
<td>Cytostatic, T Cell activation, Increased MHC Class I and II expression. T cell and NK cell activation.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Renal carcinoma</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Vial strength</th>
<th>ML Diluent (sterile water)</th>
<th>Final concentration after reconstitution million IU/ml</th>
<th>Route of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>1</td>
<td>10</td>
<td>IM, SC, IV, IL*</td>
</tr>
<tr>
<td>18</td>
<td>1</td>
<td>18</td>
<td>IM, SC, IV*</td>
</tr>
<tr>
<td>50</td>
<td>1</td>
<td>50</td>
<td>IM, SC, IV*</td>
</tr>
</tbody>
</table>

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

Table 7. Solution Formulations of Interferon α 2 b

<table>
<thead>
<tr>
<th>Vial strength</th>
<th>Concentration</th>
<th>Route of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 MIU Single Dose</td>
<td>10 million IU/1.0 ml</td>
<td>SC, IL</td>
</tr>
<tr>
<td>18 MIU Multi Dose</td>
<td>3 million IU/0.5 ml</td>
<td>IM, SC</td>
</tr>
<tr>
<td>25 MIU Multi Dose</td>
<td>5 million IU/0.5 ml</td>
<td>IM, SC, IL</td>
</tr>
</tbody>
</table>

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)

**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)

**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)

**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.

Cutaneous T cell Lymphoma (Hairy cell Leukemia) 2 MU/m² s.c /i.m.

**Renal cell carcinoma:**
5MU sc thrice daily 2 doses, then 10 MU sc thrice daily for 12 weeks.

**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.

**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)

**Hemangioma:**
Interferon α 2A 3 million units/m (2) per day should be used only in life threatening Hemangiomas act by inhibiting angiogenesis in whom high dose corticosteroid therapy failed. (Zhang L 2015)
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)

Interferon –α 2b

Malignant Melanoma:
20 MU/m² i.v over 20 min for 5 consecutive days/week for 4 weeks. (Induction Phase) followed by 10 MU/m² 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)

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

Herpes zoster:
Interferon α 2 b 5.1 X 10⁵ U per kilogram per day effective in limiting cutaneous dissemination, visceral complications and progression within the primary dermatome.

Keratoacanthoma:
The standard dose of Interferon α2 b in the treatment of Keratoacanthoma is 1.5 x 10⁶ units (0.3 cc), using a lower dose for the first and second injections—such as 1 x 10⁶ units(0.2 cc)—is recommended. The standard dose of 1.5 x 10⁶ 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 10⁶ units form, tumor size 1 cm², and increases by 0.5 x 10⁶ units for each additional cm².

AIDS- related Kaposi sarcoma:
30 MU/m²/dose subcutaneously or intramuscularly three times a week for 16 weeks of treatment till maximum response.

Condyloma acuminatum:
1 MU per lesion (Maximum of 5 lesions in a single course). Intrallesional 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)

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

Interferon γ:
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).

Keloid and Hypertrophic scars:
Interferon γ down regulate collagen synthesis invitro and invivo. The recommended dose of Interferon γ is 0.05 mg once per week for 10 weeks. (Larrabee WF et al 1990).

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:
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 immunoglobulins 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 of Microbe 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 Immunoglobulins

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

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 apoptosis of the Cancer cells sparing adjacent normal cells and are the future in Cancer therapy.

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