ENGLISH

SUMMARY

Biological therapy

Cytokines are a heterogeneous group of proteins, variously termed lymphokines, monokines, interleukines and interferons, which act on cell surface receptors to regulate and modify cell growth, maturation and repair. In addition to their longer term effects on cell growth and differentiation, cell mediated host-defence mechanisms and chronic diseases such as rheumatoid arthritis, cytokines also mediate several acute effects such as the inflammatory response. Cytokines are produced from activated leucocytes, in particular monocytes, and also from activated fibroblasts and endothelial cells.

Cytokines play a pivotal role in the coordination and regulation of immune responses. Surgical trauma and anesthesia are associated with a complex dysregulation of the immune system with the activation of both proinflammatory and anti-inflammatory responses. Interleukin-1, tumor necrosis factor (TNF) α and Interleukin-6 have local and systemic effects that may limit injury and the spread of infection and provide a suitable environment for tissue healing and repair.

Cytokines may show the following features; Pleiotropy Ambiguity, Redundancy, Synergy and Antagonism.

Systemic inflammatory response syndrome (SIRS) is defined as 2 or more of the following variables:

- Fever of more than 38°C or less than 36°C

- Heart rate of more than 90 beats per minute
- Respiratory rate of more than 20 breaths per minute or a PaCO2 level of less than 32 mm Hg
- Abnormal white blood cell count (>12,000/μL or <4,000/μL or >10% bands).

Biological therapy refers to the use of medication that is tailored to specifically target an immune or genetic mediator of disease. Even for diseases of unknown cause, molecules that are involved in the disease process have been identified, and can be targeted for biological therapy; many of these molecules, which are mainly cytokines, are directly involved in the immune system. Biological therapy has found a niche in the management of cancer, autoimmune diseases,[4] and diseases of unknown cause that result in symptoms due to immune related mechanisms.

Inflammatory bowel disease, or IBD, is a collection of systemic diseases involving inflammation of the gastrointestinal tract. IBD includes two (or three) diseases of unknown causation: ulcerative colitis, which affects only the large bowel; Crohn's disease, which can affect the entire gastrointestinal tract; and, indeterminate colitis, which consists of large bowel inflammation that shows elements of both Crohn's disease and ulcerative colitis. Although the causes of these diseases are unknown, genetic, environmental, immune and other mechanisms have been proposed. Of these, the immune system plays a large role in the

development of symptoms. Given this, a variety of biological therapies have been developed for the treatment of these diseases. These have changed the way physicians treat Crohn's disease and ulcerative colitis.

The monoclonal antibody infliximab is a mouse-human chimeric antibody to TNF-α. It first was used in the treatment of rheumatoid arthritis, and was the first biological agent used in the treatment of IBD. It is also used in the treatment of psoriasis and ankylosing spondylitis. Infliximab has shown significant success in treating Crohn's disease.

Other biological therapy agents and monoclonal antibodies have not showed as much efficacy in the treatment of IBD. These include etanercept (which is the soluble receptor for TNF. Adalimumab (which is a humanized recombinant antibody to TNF) showed effectiveness in patients with moderate-to-severe Crohn's disease, but less than that of infliximab. It however conveys an advantage in that it is given by subcutaneous injection as opposed to infliximab, which is given by intravenous infusion.

There have been concerns about the side effects of monoclonal antibodies, and specifically of infliximab, but these are rare. Early side effects include the risk of allergic reactions (including anaphylaxis which may be life-threatening), and reactions to the infusion. These are often treated with medications given before treatment. Infliximab also carries a risk of worsening infection, and can cause reactivation of old infections, like tuberculosis. Over time, there is the risk of serum sickness, which is a delayed hypersensitivity response to the medication. Later complications

may include multiple sclerosis and lymphoma. Finally, the medication is quite expensive, with treatment costs ranging from US$3000 to $8000 per infusion.