ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

Contraindications in the Use of Biological Therapies -Active or Recent History of Malignancy and Neurological Disorders

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INTRODUCTION:

Biological therapy uses living organisms, substances derived from living organisms, or laboratory-produced versions of such substances to treat disease. Vaccines or bacteria are used to stimulate the body's immune system to act against cancer cells. These are referred to as "immunotherapy" or "biological response modifier therapy" and they do not target cancer cells directly. The body normally produces these substances in small amounts in response to infection and disease. Other biological therapies, such as antibodies or segments of genetic material (RNA or DNA), interfere with specific molecules involved in tumour growth and progression, target cancer cells directly and are also referred to as targeted therapies. For the treatment of cancer, biological therapies are used to treat the cancer itself or the side effects of other cancer treatments. They are also used in the treatment of rheumatoid arthritis and Crohn's disease.

EXAMPLES OF BIOLOGICAL THERAPIES

Forms of biological therapy include Monoclonal antibodies, interferons, interleukin-2, and several types of colony-stimulating factors like CSF, GM- CSF, G-CSF. Interleukin-2 and interferon are examples of BRMs being tested for the treatment of advanced malignant melanoma. Monoclonal antibodies are a common type of biological therapy for many different cancers and other conditions. These are laboratory-produced antibodies that are designed to attack specific proteins expressed by abnormal cells. Examples of monoclonal antibody drugs include rituximab, which is used to treat non-Hodgkin's lymphoma, alemtuzumab to treat chronic lymphocytic leukemia, and ipilimumab for metastatic melanoma. Other kinds of monoclonal antibodies used to treat cancers target proteins that are responsible for cell growth. Examples of these drugs include bevacizumab, which targets vascular endothelial growth factor, cetuximab and panitumumab to target the epidermal growth factor receptor, and trastuzumab and pertuzumab to target the human epidermal growth factor receptor- 2. Modes of biologic therapy that involve blocking the action of specific proteins of inflammation, called tumor necrosis factor (TNF), are being used for the treatment of a number of diseases, including rheumatoid arthritis and Crohn's disease. Etanercept and infliximab are examples of commercially available injectable TNF-blocking treatments for patients with severe rheumatoid arthritis.

TNF-α INHIBITORS

Tumor necrosis factor alpha (TNFα) is a proinflammatory cytokine that exerts multiple effects on different cell types and plays a critical role in the pathogenesis of chronic inflammatory diseases, such as RA, ankylosing spondylitis (AS), psoriatic arthritis (PA), and arthritis associated with inflammatory bowel diseases (enteropathic arthritis)[1]. TNFα exerts cytotoxic action on different types of lymphocytes, stimulating their apoptosis and that of endothelial cells. Currently, there are five different anti-TNF biological agents (also called TNF blockers) marketed: adalimumab, a 100% human monoclonal antibody; certolizumab, a Fab fragment of a humanized anti-TNF antibody with high affinity for TNF, conjugated with two molecules of polyethylene glycol; etanercept, a fusion protein composed of TNF soluble receptor plus Fc region of IgG; golimumab, another human monoclonal antibody; and infliximab, a chimeric monoclonal antibody[2].

Skin tumors are among the possible manifestations associated with the use of anti-TNF agents. Evidence of an increased risk of non-melanoma carcinomata among patients treated with anti-TNF include one registry data meta-analysis, prospective observational studies and randomized trials[3-6]. The most common neoplasms are non-melanoma skin cancers, mainly basal cell carcinoma and, less frequently, squamous cell carcinoma[4-9]. Cases of malignant melanoma, however, have also been described in patients using anti-TNF therapy. Although the exact role of these drugs in the development of melanomas is not well established, one should pay close attention to the appearance of pigmented lesions or changes in the characteristics of preexisting nevi.[3] When in doubt, in order to obtain a correct explanation of the picture, an histopathologic study of the lesion is recommended.

Regarding the recurrence of solid cancer after use of a biological agent, little is known due to the exclusion of these patients in their participation in clinical trials. In patients treated for solid cancer during more than five years, we can recommend the use of any biological agent. In patients under five years of treatment, RTX should be

the biological choice. Thus, although no increased risk was observed for cancer, except for non-melanoma skin cancer[3-6] in patients using anti-TNF agents, surveillance for the occurrence of malignancies (including recurrence of solid tumors) in patients treated with TNF inhibitors remains appropriate.

RITUXIMAB

Rituximab is a genetically engineered chimeric monoclonal antibody that targets CD20-positive B cells. By binding to CD20, rituximab depletes subpopulations of peripheral B cells through different mechanisms, including cell-mediated and complement-dependent cytotoxicity and promotion of apoptosis. B cells can contribute to the initiation and maintenance of the inflammatory cascade in RA by acting on antigen presentation by T cells and through production of pro-inflammatory cytokines and auto-antibodies.

Rituximab treatment requires monitoring of several AEs, including infections, TB, and lymphoma[10]. It is contraindicated in the case of pregnancy and breastfeeding, active infections, live vaccination, severe congestive heart failure, a history of demyelinating disease, and a 5-year history of non-lymphoproliferative cancer[11]. In a meta-analysis assessing the safety of rituximab, including long-term therapy, 123 of 2,578 patients with RA withdrew because of malignancy, infection, a severe infusion reaction, or cardiac event[10].

Oral cancer has also been reported in a patient following rituximab[12]. Although there is no evidence for a causal association, these reports suggest that screening for oral malignancy should also be considered in patients receiving biologics, as is usually performed for patients on conventional immunosuppressive therapy.

OTHER DRUGS

Golimumab is a novel TNF alpha blockers, a fully human monoclonal IgG1 antibody, acting on both soluble and membrane-bound TNF-α[13]. The adverse effect includes hypertension, abnormal liver function, paresthesia, dizziness, constipation, local skin reaction, and some cases of malignancy like basal and squamous cell carcinomas, and prostate, lung, and breast cancers were reported[14-17]. For patients treated with etanercept for up to 6 years, the malignancy incidence was 3%, consistent with that generally seen in patients with RA, but additional cases of lymphoma and breast and lung carcinoma were reported during the post-marketing period[18]. In adalimumab and control groups, respectively, event rates per 1000 PYs were 8.8 *vs* 2.6 for NMSC, 0.8 *vs* 0.9 for lymphoma and 5.9 *vs* 4.3 for other malignancies[19]. In certolizumab-treated patients, event rates per 100 PYs were 0.07 for lymphoma and 0.02 for melanoma[20]. In infliximab-treated and placebo patients, respectively, incidence rates were 0.09% compared with 0% for lymphoma and 0.4% compared with 0.06% for other malignancies [21].

PROGRESSIVE MULTIFOCAL ENCEPHALOPATHY:-

PML is a progressive neurological disorder associated with the John Cunningham virus (JC virus) that is characterized by scattered demyelination of the brain, sparing the spinal cord and optic nerve. There is an association between efalizumab and the development of progressive multifocal leukoencephalopathy and other demyelinating disorders. Tumor necrosis factor-alpha inhibitors have been associated with various demyelinating disorders. The JC virus resides in the latent form in up to 80 percent of healthy adults and typically causes PML only in immunocompromised patients. Hematological malignancies, transplant recipients, and chronic inflammatory diseases have been associated with PML.[21] Patients with human immunodeficiency virus (HIV) are especially vulnerable to PML.

OPTIC NEURITIS:-

Optic neuritis (ON) is defined as the abrupt loss of vision resulting from optic nerve demyelination.[22] It is thought that major histocompatibility complex (MHC) class II antigens are associated with ON, leading some to believe that there is a genetic predisposition for specific immune responses.

ON has been reported with the use of anti-TNF-á therapy as well as with the use of infliximab.[23] ON should be suspected with any patient on biologics who presents with an abrupt loss of vision.

MULTIPLE SCLEROSIS:-

MS is defined by a triad of inflammation, demyelination, and gliosis. Genetics appear to contribute to the development of MS, given that Caucasians have a higher risk of developing the disease when compared to African or Asians. It is likely that there are different causative genes in each individual.[24]

There have been reports of patients presenting with manifestations of MS while on inflixamab and etanercept therapy. In addition to classical manifestations of MS, patients may manifest transverse myelitis.[25] Visual disturbance secondary to ON was the second most common manifestation. Most patients experienced a complete or partial resolution of symptoms upon discontinuation of anti-TNF therapy. MS has also been reported with the administration of adalimumab.[26] MS should be suspected in any patient on TNF-á therapy who develops paresthesias, weakness, blurring, or loss of vision. TNF-á therapy should be avoided in patients with pre-existing demyelinating disorders or a strong family history of multiple sclerosis.

TRANSVERSE MYELITIS:-

Acute transverse myelitis is a focal inflammatory disorder of the spinal cord that leads to sensory, motor, and autonomic dysfunction.[27] Among the many causes of TM are inflammatory, immune-mediated, and demyelinating etiologies. Demyelinating myelopathy may occur as a sequela to MS.[28] Immune-mediated inflammatory TM has been associated with systemic lupus erythematosus (SLE) (often with antiphospholipid antibodies), Sjögren's

syndrome, mixed connective tissue disease, Behcet's syndrome, and vasculitis with perinuclear antineutrophilic cytoplasmic antibodies. Sarcoidosis is another important etiological consideration.[29]

TM has been associated with etanercept. This can occur with other neurological manifestations suggestive of MS. TM should be suspected in a patient on a biologic who presents with back pain, lower extremity weakness, urinary and fecal incontinence, and a "band-like" tightness across the back.

GULLAINE BARRE SYNDROME:-

It is an acute, autoimmune polyradiculoneuropathy characterized by a rapidly evolving symmetrical limb weakness, mild sensory signs, and either areflexia or diminished muscle stretch reflexes, and autoimmune findings.[30] GBS is typically preceded by a viral infection, and has been associated with *Campylobacter jejuni* enteritis, Epstein-Barr virus, CMV, and HIV.

GBS has been associated with efalizumab therapy and is listed in the efalizumab package insert as an adverse reaction.[31] GBS also has been associated with infliximab. Any patient on biologic therapy should be suspected of having GBS with progressive symmetrical limb weakness.

CONCLUSION

The biologic therapies is quickly expanding as a result of better understanding of molecular mechanisms. Experience shows that the most powerful tools may have the most influential adverse consequences. Immunobiological drugs due to the wide spectrum of actions exercised in the intimacy of various immunological mechanisms there is a diversity of adverse events. We emphasize the importance of dedication and surveillance to the safety aspects of this class of drugs.

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