European Medicines Agency

London, 4 August 2009
Doc. Ref: EMEA/493705/2009

EMEA 2010 Priorities for Drug Safety Research

Long term adverse effects of immunomodulators

Immunomodulators, and in particular monoclonal antibodies, are important therapies for the treatment of severe rheumatoid arthritis, multiple sclerosis and other serious diseases where imbalance of the immune system is suspected of causing the disease process. They are also used for the prevention of transplant rejection. A number of these products, including abatacept, adalimumab, basaliximab, daclizumab, efalizumab, etanercept, infliximab, leflunamide, natalizumab, rituximab and tocilizumab are licensed in the EU for use in a variety of clinical situations.

Cases of adverse neurological effects, opportunistic infections and malignancies have caused concern regarding the long term use of these therapies. Use of these products in adolescents and young adults is of particular concern because of the increased likelihood of long term immunosuppression.

A plausible biological mechanism for the adverse effects exists. Immunosurveillance is an important mechanism by which the body protects itself against infection and oncogenesis. Immunomodulators decrease immune function by a variety of mechanisms including inhibition of T-cell activation, stimulation, proliferation and migration, impairment of cytokine function and B lymphocyte depletion. As a result opportunistic infections, including reactivation of latent viruses may occur. Oncogenesis could occur by either infection with oncoviruses and/or by failure to identify and eliminate malignant cells.

Areas of particular interest for research include:

- Identification of risk factors for developing neurological effects, opportunistic infections or malignancy in patients treated with immunomodulators e.g. indication for treatment, age, sex, disease (including severity), prior treatment.
- The effect of time and/or intensity of immunosuppression on likelihood of developing neurological effects, opportunistic infection or malignancy
- Elucidation of mechanisms e.g. latent infection reactivation, cancer initiation/promotion
- Methodologies for early clinical detection of virus/bacterial reactivation/infection eg JC virus and other polyoma viruses.
- Methodologies for screening/predicting patients at high risk of developing opportunistic infections or malignancy.

Suitable research methodologies could include long-term epidemiological follow-up studies of these adverse effects, subgroup analyses to study risk factors and important effect modifiers, intensive monitoring studies as methods to capture early stages of diseases, and non-clinical mechanistic studies.

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 68
E-mail: mail@emea.europa.eu http://www.emea.europa.eu.