Review of immunotherapy in rheumatoid arthritis

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In the present state of knowledge about the immunopathology of rheumatoid arthritis (RA), the failure to eliminate an unknown antigen has been postulated in several models. A defective macrophage function might be the cause of the persistence of non-degradable bacterial fragments (peptidoglycan) in the macrophage after successful phagocytosis and so produce a paradoxical hyperinflammatory response due to the continued existence of a positive tendency to inflammation. In the infective theories, there is either short-term infection altering cells or tissue antigens and the infective agent then disappears leaving a self-perpetuating auto-immune response to altered self-antigens, or the infection can be persistent and is then responsible for perpetuation of pathology.

In the ‘target’ model, the virus infects joint cells. The resulting cell damage, or alteration of cell function, together with an intense but finally ineffective immunological reaction against the infected or altered cell, constitutes the disease. Another possibility is that the virus infects and alters the function of the effector cells of the immune system, T or B lymphocytes or macrophages. Alteration of B cells leads to excessive production of antibodies, and infection of T cells results in a loss of regulation of B-cell functions. If the disordered inflammatory events are considered to be a failure of antigen elimination, new directions for therapeutic intervention in RA become justified and immunomodulating agents such as levamisole have to be investigated for effectiveness in this disease.

LEVAMISOLE PHARMACOLOGY

In therapeutic doses of 2.5 mg/kg, levamisole restores to normal functions of T lymphocytes, polymorphonuclear and mononuclear phagocytes,
especially when these functions are initially impaired. These effects have been shown by in vivo as well as in vitro studies. Levamisole also restores delayed skin hypersensitivity in anergic patients and cell-mediated responses in elderly subjects and in patients with some immune deficiency diseases as well as in animals receiving immunosuppressive therapy. The activity of the drug in adjuvant arthritis in rats has been studied in detail by Trabert et al. The data are contradictory to those mentioned above, since levamisole accentuates the severity of the disease. In this model levamisole consequently not only restores impaired cellular immune responses but also enhances an already activated system. The schedule used is important, since the authors found that continuous therapy may result in a loss of efficacy in adjuvant arthritis. These data may certainly be of paramount importance in the future to explain some kind of responses in patients with RA.

Levamisole seems to have no direct effect on B lymphocytes, but in case of increased B-cell activity it may be reduced to normal as is shown by decreased numbers of Ig-bearing or EAC-rosette forming cells and the normalization of antibody levels. This action seems to result from an improvement in the regulatory function of T cells on B cells, and a stimulatory effect upon T suppressor cells. In vivo the drug is capable of restoring thymic function in nude and thymectomized mice and in children with primary immune deficiencies. Finally, levamisole has a favourable influence on the course of autoimmune diseases in animals. It can, for example, prevent or delay the development of disease in young NZB/NZW mice. In advanced diseases it is less efficient but maintains the remission induced by cyclophosphamide.

CLINICAL ACTIVITY IN RA

Although the multitude of trials performed with levamisole in RA were useful and necessary to establish the activity of the drug in this disease, it must be realized that the majority of information available about activity and toxicity in the short term comes from the EULAR trial and from the Multicenter Study.

In the EULAR Study, two dose schedules for levamisole (150 mg either 3 days per week or 7 days per week) were compared with each other and with placebo over a period of 6 months. The total number of subjects amounted to 110 controls, 124 patients on 7 days per week and 129 patients on 3 days per week. Statistical analysis showed no difference between the two dosage regimens of levamisole for all variables investigated. After 3 months, patients treated with levamisole had improved significantly more than the placebo group. At 6 months the effect was even more pronounced and a highly significant difference was observed for all variables measured (Figure 8.1).

In this trial hardly any factors influencing responsiveness or adverse reac-