USE OF IPRIFLAVONE TO REDUCE THE NUMBER OF CD8 + CELLS

The invention relates to pharmaceutical compositions suitable to decrease the number of CD8+ cells containing 7-isopropoxyisoflavone (IPRIFLAVONE) as active ingredient.

IPRIFLAVONE is a known antiosteoporotic agent. Its preparation is described in Hungarian patent specifications Nr. 162377 and 196981. It is known that the organism has two basic protective functions, the humoral and the cell-mediated immune responses. The so-called cell-mediated immune response is primarily directed against endogen antigens on cells infected with a virus or with an intracellular parasite, tumor cells, chemically modified cells and foreign tissues.

Cell-mediated immune response is attached to the so-called thymus dependent (cells maturing in the thymus) lymphocytes (T lymphocytes).At the end of the maturation process two types of T lymphocytes -based on their surface markers clearly differentiable subgroups- will be released to the periphery. The CD4+ cells. the so-called helper cells are activated upon the presentation of exogen antigens and help the immune response by increasing their cytokine production. The CD8+ cells. the so-called cytotoxic cells are activated upon recognition of the endogen antigen then they destroy the cells recognized as foreign by cytolysis.

Approximately 2/3 of the peripheral lymphocytes are CD4+ and 1/3 CD8+. Corresponding to this the normal CD4+/CD8+ ratio is 2:1.

(András Falus; Immunology pages 111-138 TEMPUS ITC Bp./1993)

The cytotoxic immune response is a basic protective mechanism in case of intracellular infections because by the destruction of the infected cell it eliminates the possibility for the pathogenic agent to reproduce. Similarly it has an important role in the destruction of tumor cells. In these cases the cytotoxic immune response serves to protect the integrity of the organism.

Cases are also known where with respect to the organism cytotoxic immune response is undesired or even harmful. In case of certain autoimmune diseases cytotoxic reaction is directed towards own cells of the organism causing severe functional disturbances as a result. Characteristic example of T cell mediated immune disease is rheumatoid arthritis.

Pathologic cytotoxic reaction can be seen in case of certain aplastic anemias and chronic active hepatitis. Rejection reaction following tissue or organ transplantations is also based on the cytotoxic immune response. In case of special organ transplantation -bone marrow- the so-called „graft versus host" is also based on the cytotoxic reaction.

In these cases CD4+/CD8+ ratio decreases, in certain cases reverses which is mainly the result of the increase of CD8+ cells and less the result of the decrease of the CD4+ cells. In cases of autoimmune diseases and rejection reactions following tissue/organ transplantations it is a usual treatment procedure to moderate the immune response, in certain cases even to drastically reduce it (immunosuppressive treatment).

Immunosuppressive treatment causes not only a decrease in the number of T lymphocytes but it also has an effect toward normalization of the CD4+/CD8+ cell ratio. In case of an allogen bone marrow transplant which does not contain CD8+ cell „graft versus host" reaction can be observed in significantly less numbers. Therefore, in the mentioned diseases a therapy that decreases specifically the number of CD8+ cells could be advantageous.

Based on the above theoretical considerations and practical experiences we examined the kind of effect ipriflavone treatment has on T lymphocytes responsible for the cell-mediated immune response and on the number of CD4+ helper and CD8+ cytotoxic cells. To separate certain types of lymphocytes and subgroups we used flow cytometry.

In a clinical trial the absolute lymphocyte count and the change in certain lymphocyte subpopulations were studied in 60 patients taking a daily dose of 400 mg ipriflavone.

In 51 patients a mild or moderate decrease of absolute lymphocyte count was observed. The mean absolute lymphocyte count of patients was 0.85×10^9/l (range 0.25-0.89) following the treatment. (Normal range: 0.9-3.22x10^9/l) In 9 patients the mean absolute lymphocyte count was found within the normal range, 1.84×10^9/l. In the 51 patients with lymphopenia the decrease was characteristic only for the so called T lymphocytes and among them primarily and pronounced for the CD8+ subpopulation. The mean CD8+ count was 0.08×10^9/l (range 0.02-0.23), which represents a rather significant cell count reduction taking into account the normal range of 0.3-1.44x10^9/l.

In the 9 patients showing normal lymphocyte count the mean CD8+ count was 10.43×10^9/l (range 0.28-0.64). Although this value is within the normal range, it falls in its lower quartilis, which finding supports the selectivite nature of the effect.

We found that under ipriflavone treatment the number of T lymphocytes decreased on the average by 66.6%. Considering CD4+ helper and CD8+ cytotoxic subgroups the average decrease was significantly different. Next to the 50% CD4+ helper cell decrease, the decrease of CD8+ cytotoxic cells was 77%. CD4+/CD8+ ratio characterizes the differing number of Cd4+ and CD8+ cells, the ratio of which changed to 5:1 upon ipriflavone treatment.

The decrease in the number of T lymphocytes, CD4+ helper and CD8+ cytotoxic cells and the basic change in their ratios are considerable in two aspects. In the course of customary immunosuppressive treatments the observed decrease in cell number was as a rule smaller than experienced in case of ipriflavone. Further significant difference is the more pronounced decrease in the number of CD8+ cytotoxic cells than in the number of CD4+ helper cells. Based on the results it can be assumed that ipriflavone is capable to decrease or to inhibit specifically the cytotoxic reaction.

Subject of the invention is a pharmaceutical composition suitable to decrease the number of CD8+cells comprising as active ingredient 7-isopropoxyisoflavone in admixture with suitable inert, solid or liquid carriers and optionally with usual therapeutic additives and auxiliary agents.

The above composition can be used for the treatment of a human or animal subject being in a condition where selective suppression of CD8+lymphocytes is desirable.

The compositions according to the invention may be prepared in the form of injection, infusion, capsule, tablet, solution, syrup, transdermal preparation, etc. by methods known per se.

In diseases or states of condition where inhibition of the cytotoxic reaction has a therapeutic value are rather different in their nature, appearance and course of disease. Therefore the dose has to be determined in knowledge of the diagnosis, initial number of lymphocytes and the ratio of Cd4+/CD8+ cells.

What we claim is:

1. Pharmaceutical composition suitable to decrease the number of CD8+ cells comprising a therapautically active amount of 7-isopropoxyisoflavone as active ingredient in admixture with suitable inert, solid or liquid carriers and optionally with usual therapeutic additives and auxiliary agents.

2. Composition according to claim 1 prepared as injection, infusion, capsule, tablet, solution, syrup or transdermal preparation.

3. Use of the composition according to claims 1 and 2 in clinical conditions where selective suppression of CD8+lymphocytes is desirable.

4. Method of treatment of a human or animal subject being in a condition where selective suppression of CD8+ lymphocytes is desirable which comprises the step of administering in an effective amount 7-isopropoxyisoflavone in admixture with suitable inert, solid or liquid carriers and optionally with usual therapeutic additives and auxiliary agents.

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