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(57) Abstract

A glucocorticoid, such as cortisol or a derivative or analogue thereof, and an anti-glucocorticoid, such as dehydroepiandrosterone (DHEA) or a derivative or analogue thereof, are used simultaneously, separately or sequentially in treatment of chronic infections such as tuberculosis, HIV infection, leishmaniasis and syphilis.

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COMPOSITIONS AND METHODS FOR THE TREATMENT OF CHRONIC INFECTIONS

The present invention relates to the treatment of chronic infections, particularly those in which the metabolism of steroid hormones is disturbed, and more specifically to the provision of methods and compositions comprising combinations of steroidal compounds for the treatment of such infections.

Certain chronic infections such as tuberculosis, HIV[19-21], are characterised by increased adrenal activity in the early phase of the disease, followed by under-activity in the late stages (adrenal insufficiency). Moreover, late stages of certain chronic infections such as tuberculosis, syphilis (Parker CR, *et al.* Proc. Soc. Exp. Biol. Med. (1991); 197: 165-167) and HIV are characterised by a fall in the ratio of DHEA to cortisol (both steroid hormones produced by the adrenal glands), and an immune response biased away from Th1 towards a Th2 pattern of lymphocyte response. The Th1 pattern is characterised by lymphocytes that release interleukin 2 and interferon gamma, whereas the Th2 lymphocytes release interleukin 4 and their activity is often accompanied by release of interleukin 10 from lymphocytes and other cell types. The effect of interleukins 10 and 4 is to decrease anti-microbial efficiency of the immune response to the infecting organisms (Rook GAW, *et al.* Bloom BR. Mechanisms of pathogenesis in tuberculosis. In: Bloom BR, ed. Tuberculosis; pathogenesis, protection and control. Washington DC: ASM Press, 1994: 485-501; Clerici M, *et al.* Immunol. Today. (1993); 14: 107-111; Rook GAW, *et al.* Immunol. Today (1993); 14: 568-569; Levy JA, *et al.* Immunol. Today (1996); 17: 217-224). This biasing may, at least in some cases, be a result of an illness-induced imbalance in the hormones and other signals e.g. cytokines which control the production and function of T cells. For example, in tuberculosis, some patients have infected adrenal glands, resulting in severe adrenal

insufficiency and disrupted production of steroidal hormones. Even those patients who do not have tuberculous adrenals commonly have abnormal adrenal function, commonly a reduced 24 hour output of steroids (Rook GAW, *et al.* Q. J. Med. (1996); 89: 333-341), and abnormal peripheral metabolism of steroid hormones. This reduction in output is often by as much as 50%. It is not uncommon for such patients to die suddenly, apparently as a result of acute adrenal failure (Scott GM, *et al.* J. Infect. (1990); 21: 61-69; Onwubalili JK, *et al.* Q. J. Med. (1986); 59: 599-610). Tuberculous mice show adrenal atrophy in the chronic phase of infection (which parallels the human disease)with reductions in weight of the adrenals of up to 50% (Hernandez-Pando R, *et al.* FEMS Immunol. Med. Microbiol. (1995); 12: 63-72) (Fig. 2).

The adrenal glands secrete numerous steroid hormones with a variety of physiological regulatory functions. These include the glucocorticoids such as cortisol (hydrocortisone) in humans (but mostly corticosterone in rodents), the mineralocorticoids and pregnancy-related steroids. The steroid hormones secreted by the adrenals may be further modified in peripheral tissues, particularly by a series of dehydrogenase, reductase and hydroxylase enzymes, to yield compounds with decreased, increased or otherwise altered activity.

Glucocorticoids may be defined by reference to their binding to the glucocorticoid receptor. Some glucocorticoids also bind the mineralocorticoid receptor.

Glucocorticoids modulate the immune response by causing dysfunction of T lymphocytes. Pharmacological (i.e. very high) doses will suppress cytokine secretion by mature lymphocytes whether they are Th1 or Th2. On the other hand raised physiological levels of glucocorticoids present during the recruitment of an immune response from naive T lymphocytes favour the *development* of a Th2 cytokine profile. Thus,

conventional treatments for Th-2-mediated diseases such as asthma and hay fever may work via anti-inflammatory effects, and by reducing cytokine production by mature Th2 cells and yet at the same time encourage perpetuation of the underlying problem by driving newly recruited T cells towards Th2 (Daynes RA, *et al.* J. Invest. Dermatol. (1995); 105: 14S-19S; Rook GAW, *et al.* Immunol. Today (1993); 14: 568-569; Brinkmann V, *et al.* J. Immunol. (1995); 155: 3322-8; Ramirez F, *et al.* J. Immunol. (1996); 156: 2406-2412). Glucocorticoids also cause direct inactivation of anti-mycobacterial mechanisms within macrophages (Brown DH, *et al.* Infect. Immun. (1995); 63: 2983-2988; Rook GA, *et al.*Eur. J. Respir. Dis. (1987); 71: 286-291) and death by apoptosis of thymocytes (Vacchio MS, *et al.* J. exp. Med. (1994); 179:1835-1846) and some peripheral T lymphocytes. As a result, glucocorticoids have been used as immunosuppressants, for example in inhibition of transplant rejection. They have also found use in the treatment of T lymphocyte leukaemias and as anti-inflammatory drugs in the treatment of e.g. rheumatoid arthritis, however the immunosuppressive action of glucocorticoids severely limits their anti-inflammatory use in tuberculosis and other infectious disease.

Tuberculosis is caused by *Mycobacterium tuberculosis* infection which may take hold in various organs, most commonly the lungs. In tuberculosis meningitis, infection causes inflammation of the membranes (meninges) surrounding the brain. This inflammation must be brought under control as a matter of urgency, as the brain is particularly delicate and inflammation within the confined space of the cranial cavity can lead rapidly to compression of the brain and to brain damage. The anti-inflammatory effect of glucocorticoids has been exploited in the treatment of tuberculosis meningitis, however, their immunosuppressive effects can lead to severe side effects such as re-activation of latent tuberculosis and

rapid progression of ongoing disease, and these effectively restrict their use to the acute emergency posed by tuberculous meningitis.

The Th1 immune response mechanism, which is particularly important in the control of *M.tuberculosis* and *Leishmania Major* (Leishmaniasis) infection, is particularly sensitive to suppression by glucocorticoids (Lurie MB. Resistance to tuberculosis; experimental studies in native and acquired defensive mechanisms. Cambridge Massachussetts: Harvard University Press, 1964; McCune RM, *et al.* J. Exp. Med. (1966); 123: 469-486; McCune RM, *et al.* J. Exp. Med. (1966); 123: 445-468; Brown DH, *et al.* Infect. Immun. (1995); 63: 2983-2988; Brown DH, *et al.* Infect. Immun. (1993); 61: 4793-4800), which tend to drive the Th2 and suppress the Th1 response. Furthermore, glucocorticoids down-regulate the function of macrophages (Rook GA, *et al.*Eur. J. Respir. Dis. (1987); 71: 286-291), which are the cells that limit the growth of and, when activated by Th1 lymphocytes, perhaps actually kill the *M.tuberculosis* organism. For this reason, administration in tuberculosis treatment must be combined with very effective anti-bacterial drugs administered in tandem (Kumarvelu S, *et al.* Tuber. Lung. Dis. (1994); 75: 203-207), to help in reducing the side-effects.

The inflammatory damage in pulmonary tuberculosis contributes to permanent destruction of lung tissue and to fibrosis and cavitation, but it is slowly evolving, rather than an acute emergency. In this condition there is no convincing evidence that co-administration of glucocorticoids with the standard anti-bacterial drugs provides any additional benefit rather, because of the side-effects, they can be detrimental.

Other products of the adrenals, or metabolites of those products, can oppose the effects of glucocorticoids, acting either directly, through the same receptors and signalling mechanisms, or via different

receptors (Blauer KL, *et al*. Endocrinology (1991); 129: 3174-3179; Daynes RA, *et al*. J. Invest. Dermatol. (1995); 105: 14S-19S). The precursor of these "anti-glucocorticoid" steroids, dehydroepiandrosterone (3β-ol-androstene-17-one or DHEA) is the most abundant adrenal steroid in the blood of normal, healthy humans, present mostly as the sulphate (DHEAS). Chronic physical ill-health or more acute events, such as surgery, result in an elevated cortisol level, lowered DHEA and thus altered cortisol-DHEA ratios (Parker, L.N., *et al*. Journal of Clinical Endocrinology and Metabolism (1985); 60: 947-952; Parker, L., *et al*. Hormone Metabolism Research (1985); 17: 209-212; Spratt, D.I., *et al*. J. Clin. Endcrin. Metab. (1993); 76: 1542-1547). DHEA levels in adults decrease with advancing age. DHEA is an inflammatory agent and has been proposed as a stimulant of the Th1 T cell response (Daynes RA, *et al*. J. Invest. Dermatol. (1995); 105: 14S-19S), which is the pattern required for immunity to tuberculosis (Rook GAW, *et al*. Bloom BR. Mechanisms of pathogenesis in tuberculosis. In: Bloom BR, ed. Tuberculosis; pathogenesis, protection and control. Washington DC: ASM Press, 1994: 485-501). However, administration of DHEA in tuberculosis may be dangerous as a certain level of glucocorticoid activity is necessary for life. Administration of DHEA to patients already suffering from depressed adrenal function and therefore glucocorticoid insufficiency can therefore be expected to be detrimental.

An anti-glucocorticoid is a molecule, which may be a steroid, which opposes one or more effects of a glucocorticoid. As noted, glucocorticoids bind the glucocorticoid receptor.

From the above it can be seen that it is not beneficial to treat tuberculosis patients (apart from TB meningitis) with glucocorticoid steroids in order to exploit their anti-inflammatory effect, nor to treat them with steroids that show anti-glucocorticoid activity,

such as DHEA or its derivatives, in order to exploit their Th1 lymphocyte-promoting effect. Both steroids accelerate death, for different reasons. The same can be expected to be true for other chronic infections such as HIV, leishmaniasis, syphilis and the like, in which a low DHEA/cortisol ratio may occur and in which the immune response is biased away from the Th1 and toward the Th2 pattern of T cell response.

Although there has been a claim that glucocorticoids may have a therapeutic effect in the treatment of HIV infection (Andrieu JM, *et al*. J. Infect. Dis. (1995); 171: 523-530), the conclusions drawn from this small study are not generally accepted. In fact there is evidence that glucocorticoids may enhance susceptibility to and growth of Kaposi's sarcoma, a major complication of HIV infection (Guo WX, *et al*. Am. J. Pathol. (1995); 146: 727-734). Similarly, following the observation that progression to AIDS correlates with a fall in DHEA levels (Wisniewski TL, *et al*. Am. J. Med. Sci. (1993); 305: 79-83) and reports that DHEA has some anti-retroviral activity, there has been a study of DHEA treatment in HIV positive individuals (Yang JY, *et al*. AIDS. Res. Hum. Retroviruses. (1993); 9: 747-754; Yang JY, *et al*. Biochem. Biophys. Res. Commun. (1994); 201: 1424-1432; Dyner *et al*. *J. Acquir. Immune Defic. Syndr*. (1993) 6: 459-465). This would clearly be dangerous in advanced disease when adrenal insufficiency is common (Abbott M, *et al*. J. Infect. (1995); 31: 1-4).

The present invention has arisen from the surprising finding that the combined administration of a glucocorticoid steroid and an anti-glucocorticoid steroid has a significantly more beneficial effect than would be expected if the detrimental effects of the two compounds simply cancelled each other out, i.e. the combined preparation exhibits an unexpected synergy.

In a first aspect, the present invention provides a pharmaceutical composition comprising i) a glucocorticoid

steroid, preferably cortisol, prednisolone or another synthetic analogue of cortisol and ii) an anti-glucocorticoid steroid, preferably DHEA, AED or an anti-glucocorticoid derivative thereof, as a combined preparation for simultaneous, separate or sequential use in the treatment of a chronic infection.

In a second aspect, the present invention provides the use of an anti-glucocorticoid steroid in the manufacture of a medicament for treating a chronic infection.

In a third aspect, the present invention provides use of a glucocorticoid steroid in the manufacture of a medicament for treating a chronic infection.

In a fourth aspect, the present invention provides use of a glucocorticoid steroid, preferably cortisol or prednisolone, and an anti-glucocorticoid steroid, preferably DHEA, AED or a derivative thereof, in the manufacture of a medicament for the treatment of a chronic infection by simultaneous, separate or sequential administration.

In another aspect, the present invention provides a method of treating an individual suffering from a chronic infection, comprising administration of a glucocorticoid steroid, preferably cortisol, alternatively prednisolone or another analogue of cortisol, and an anti-glucocorticoid steroid, preferably DHEA, AED or a derivative thereof to the individual, simultaneously, separately or sequentially.

Another aspect of the present invention provides a method of making a combined medicament for treatment of a patient with a chronic infection, the method comprising use of a glucocorticoid steroid, preferably cortisol or prednisolone, and an anti-glucocorticoid steroid, preferably DHEA, AED or a derivative thereof, e.g. by admixing DHEA and cortisol, separately or together, with a pharmaceutically acceptable component or vehicle such as an excipient, carrier, buffer, stabiliser or other

material, as discussed below, to produce a pharmaceutical composition suitable for simultaneous, separate or sequential administration.

Further aspects of the present invention provide a glucocorticoid steroid, preferably cortisol (hydrocortisone) or an analogue thereof such as prednisolone, and an anti-glucocorticoid steroid, preferably DHEA, AED or a derivative thereof, for use in the manufacture of a medicament for simultaneous, separate or sequential administration, or for use in the treatment of a chronic infection. Also provided is a kit or pack containing components A and B, wherein component A includes a glucocorticoid steroid, preferably cortisol or an analogue thereof such as prednisolone, and component B includes an anti-glucocorticoid steroid such as DHEA, AED or a derivative thereof, components A and B being formulated for simultaneous, separate or sequential delivery in the treatment of a chronic infection.

The chronic infections with which the present invention is concerned may be characterised by the infected individual having one or more of; disturbed metabolism of steroid hormones; adrenal insufficiency, atrophy or other abnormality of the adrenal glands; low DHEA/cortisol ratio in the blood, preferably reflected by altered levels of steroid metabolites in the urine; and biasing of the immune response away from the Th1 response and towards the Th2 response.

The chronic infection may be one in which the Th1 immune response plays a greater role in control of infection than does the Th2 response.

Particular infections to which the methods and compositions of the present invention may be applied include tuberculosis, HIV, leishmaniasis, syphilis and the like.

As discussed above, the present inventors have surprisingly found that the combined administration of a glucocorticoid steroid and an anti-glucocorticoid

steroid has a strikingly beneficial effect on the progression of tuberculous infection. In animal models, combined treatment increases the response to *M.tuberculosis* in skin tests, and increases survival times for tuberculosis infected animals whilst decreasing inflammation. These effects would not be seen if the Th1 and Th2 effects were simply cancelled out. There is evidence of increased Th1 response; the Th2-enhancing effect of the glucocorticoid has been removed, but the Th1 enhancing effect of the anti-glucocorticoid has not. Conversely, since DHEA derivatives increase inflammation while glucocorticoids decrease it, the anti-glucocorticoid effect is removed but the glucocorticoid effect remains because the inflammation is decreased. The effect is significantly more beneficial than would be expected if the detrimental effects of the two compounds simply cancelled each other out, i.e. the combined preparation exhibits a synergy which could not have been predicted, and is surprising.

The compositions provided herein may comprise a glucocorticoid and an anti-glucocorticoid steroid as combined (simultaneous or sequential) actives. However, compounds may be employed which mimic a given active in improving diagnostic status and/or ameliorating one or more symptoms in a chronic infection (mimetics). Such compounds and their use are within the scope of the present invention. Mimetics may be identified or obtained by screening of other compounds or by more rational design, and this is discussed further below.

Also within the scope of the present invention are derivatives or analogues of DHEA or cortisol which retain the anti-glucocorticoid or glucocorticoid activity, respectively. Preferred derivatives of DHEA include 7OH-DHEA (3β,7 diolandrostene-17-one) (with the 7OH in α or β form), 3β,17β-androstenediol (AED), 3β,7,17β-androstenetriol (AET) (with the 7OH in α or β form), and other 7-hydroxylated derivatives of DHEA or AED. As

alternatives to cortisol, synthetic glucocorticoids may be used, for example prednisone or prednisolone, or dexamethasone, (all available as tablets), methylprednisolone, dexamethasone or triamcinolone (all available for injection). Hydrocortisone sodium succinate or hydrocortisone acetate are also available glucocorticoid injectables and cortisone could also be used since it is rapidly metabolised to active cortisol.

The designing of mimetics to a known pharmaceutically active compound is a known approach to the development of pharmaceuticals based on a "lead" compound e.g. DHEA, AED or cortisol. Mimetic design, synthesis and testing is generally used to avoid randomly screening large number of molecules for a target property.

There are several steps commonly taken in the design of a mimetic from a compound having a given target property. Firstly, the particular parts of the compound that are critical and/or important in determining the target property are determined. These parts or residues constituting the active region of the compound are known as its "pharmacophore".

Once the pharmacophore has been found, its structure is modelled according to its physical properties, eg stereochemistry, bonding, size and/or charge, using data from a range of sources, eg spectroscopic techniques, X-ray diffraction data and NMR. Computational analysis, similarity mapping (which models the charge and/or volume of a pharmacophore, rather than the bonding between atoms) and other techniques can be used in this modelling process.

In a variant of this approach, the three-dimensional structure of the ligand and its binding partner are modelled. This can be especially useful where the ligand and/or binding partner change conformation on binding, allowing the model to take account of this the design of the mimetic.

A template molecule is then selected onto which

chemical groups which mimic the pharmacophore can be grafted. The template molecule and the chemical groups grafted on to it can conveniently be selected so that the mimetic is easy to synthesise, is likely to be pharmacologically acceptable, and does not degrade *in vivo*, while retaining the biological activity of the lead compound. The mimetic or mimetics found by this approach can then be screened to see whether they have the target property, or to what extent they exhibit it. Further optimisation or modification can then be carried out to arrive at one or more final mimetics for *in vivo* or clinical testing.

In accordance with the present invention, compositions provided may be administered to individuals. Administration is preferably in a "therapeutically effective amount", this being sufficient to show benefit to a patient. Such benefit may be at least amelioration of at least one symptom. The actual amount administered, and rate and time-course of administration, will depend on the nature and severity of what is being treated. Prescription of treatment, eg decisions on dosage etc, is within the responsibility of general practitioners and other medical doctors. Dose regimens for the glucocorticoids may be within the range used for the anti-inflammatory treatment of acute rheumatoid arthritis, or TB meningitis. For instance, using prednisolone, a maximal dose may be 1mg/kg or more, although doses of about 40-70mg/kg or 50-60mg/kg, possibly as low as 0.25mg/kg, or even less, may be suitable. For the anti-glucocorticoids, DHEA has been given orally to humans in other indications at 50mg/day which corresponds to about 0.8mg/kg which was also the approximate level at which AED was administered to mice in the experimental work discussed below (25µg AED three times/week in 25g mice). About 25-100mg/day may be a suitable dose range, however doses of 200mg every four weeks may be a suitable alternative dosage regime in

certain circumstances.

Pharmaceutical compositions according to the present invention, and for use in accordance with the present invention, may comprise, in addition to active ingredient, a pharmaceutically acceptable excipient, carrier, buffer, stabiliser or other materials well known to those skilled in the art. Such materials should be non-toxic and should not interfere with the efficacy of the active ingredient. The precise nature of the carrier or other material will depend on the route of administration, which may be oral, or by injection, e.g. cutaneous, subcutaneous or intravenous. Clearly patients prefer oral drugs, but when people are very sick, injection is preferred (intravenous or intramuscular), because it is more accurate, the drug is not vomited up, etc. For instance, one embodiment of the present invention may provide an intravenous injection of hydrocortisone sodium succinate plus dehydroepiandrosterone (DHEA) sulphate or androstenediol (AED) sulphate. The DHEA and AED derivatives can all also be given orally, as the free compound e.g. in oil, or as water soluble sulphates.

Pharmaceutical compositions for oral administration may be in tablet, capsule, powder or liquid form. A tablet may comprise a solid carrier such as gelatin or an adjuvant. Liquid pharmaceutical compositions generally comprise a liquid carrier such as water, petroleum, animal or vegetable oils, mineral oil or synthetic oil. Physiological saline solution, dextrose or other saccharide solution or glycols such as ethylene glycol, propylene glycol or polyethylene glycol may be included.

For intravenous, cutaneous or subcutaneous injection, or injection at the site of affliction, the active ingredient will be in the form of a parenterally acceptable aqueous solution which is pyrogen-free and has suitable pH, isotonicity and stability. Those of relevant skill in the art are well able to prepare

suitable solutions using, for example, isotonic vehicles such as Sodium Chloride Injection, Ringer's Injection, Lactated Ringer's Injection. Preservatives, stabilisers, buffers, antioxidants and/or other additives may be included, as required.

Further aspects and embodiments of the present invention, and modifications to those disclosed herein, will be apparent to persons skilled in the art. Illustration of embodiments of the present invention, by way of example, follows with reference to the figures. All documents mentioned herein are incorporated by reference.

Figure 1 Shows the % survival of mice with pulmonary TB after treatment with AED alone, corticosterone alone or AED with corticosterone compared to untreated mice. The % surivival figures are shown at days after intratracheal infection with *M. tuberculosis*. AED 25 μg was given by subcutaneous injection dissolved in olive oil, 3 times/week (Mon, Wed, Fri). Corticosterone was added to drinking water at 3 μg/ml. (Triangles - AED; squares - corticosterone; closed circles - AED and corticosterone; open circles - controls.)

Figure 2 Shows the effect of *M.tuberculosis* infection in mice on the weight of the adrenal gland. The weight of the right adrenal (mg) is shown at days after intratracheal infection with 10^6 *M. tuberculosis*.

Figure 3 shows the effect of treatment with corticosterone (3 μg/ml in the drinking water) and and AED (25 μg s.c. x3 each week - Mon, Wed and Fri - from day 60 after infection) on delayed hypersensitivity to tuberculin. Foot-pad swelling in microns is shown at days since intratracheal infection with *M. tuberculosis*. (Closed circles - AED + corticosterone; open circles - controls.)

Figure 4 shows the therapeutic effect in murine tuberculosis of corticosterone (3μg/ml in drinking water; physiological level) and androstenediol (50μg x3/ week,

in olive oil, s.c.). (Closed circles - corticosterone + androstenediol; open squares - untreated.)

Figure 4A shows the % of lung affected by pneumonia at days since intratracheal infection with *M. tuberculosis*.

Figure 4B shows area of granuloma of lung (μ^2) at days since intratracheal infection with *M. tuberculosis*.

Experimental

Murine tuberculosis was used as a model tuberculous system. Mice were infected (intra tracheal infection) with 10 (Swartz SL, *et al*. Drugs. (1978); 16: 238-255) *M.tuberculosis* and the weight of the right adrenal gland was monitored through the progression of the infection. After an early phase of adrenal hypertrophy lasting only 3 weeks (Fig.2) the gland atrophies so that in the chronic phase the glands have reduced to 50% of their normal size (Hernandez-Pando R, *et al*. FEMS Immunol. Med. Microbiol. (1995); 12: 63-72).

Animals in this phase of the disease (from day 60 post infection) were treated with AED (25μg in olive oil, administered by subcutaneous injection 3 times a week) or with corticosterone (3μg/ml in drinking water) or with both. As can be seen from Fig.1, the mice treated with AED alone died more rapidly than did untreated infected animals. This treatment was initiated at day 60 when the adrenals are already atrophied (see Fig. 2). In the absence of normal adrenal function and glucocorticoid production, the AED is detrimental, causing not only accelerated death, but also increased tissue-damaging pathology in the lungs. The same detrimental result would be obtained if AED or DHEA were given to human patients at the stage of disease where adrenal function is reduced. The same dose of AED given to normal mice, or to mice at the start of their tuberculosis when the adrenals are increased in size (Fig. 2), does not cause any detrimental effect and can delay progress of the

disease (data not shown).

Similarly the mice receiving corticosterone alone from day 60 also died rapidly. It should be noted that the mice were receiving no antibacterial drug therapy so the immune dysfunction caused by the glucocorticoid therapy is very apparent. This is equivalent to giving glucocorticoids to a human patient with multidrugresistant disease.

In contrast to the consequences of giving either steroid alone, survival of the mice given combined therapy was strikingly improved relative to untreated controls.

The results of a delayed type hypersensitivity test to tuberculin (Fig.3), carried out by injection of tuberculin into the footpads of the mice, reflected the survival results. The immune response (measured by swelling of the footpad) is indicative of macrophage and Th1 lymphocyte accumulation at the injection site and was markedly greater for mice receiving the combined treatment than for those receiving no steroid at all.

In further experiments mice were infected by the intraacheal route with *M. tuberculosis*, and then treated from day 60 with either placebo (saline) three times/week, or with AED (50μg three times/week) and corticosterone (3μg/ml) in drinking water. The lungs of representative animals were studied at intervals by microscopy and morphometry. Treatment with the steroids decreased the percentage of the lung affected by pneumonia and increased the area of granuloma. It is known that areas of pneumonia contain equal numbers of Th2 and Th1 lymphocytes, and correlate with rapid death. On the other hand areas of granuloma are dominated by Th1 lymphocytes, and correlate with control of bacterial replication (Hernandez-Pando, *et al. Infect. Immun.* (1997), Volume 65).

Other intra-tracheal infected tuberculous mice were treated with AED from the time of infection. The results show that, during this phase of disease when the adrenals are not atrophied (and are in fact enlarged), AED is partly protective, increasing survival rates. This correlates with the theory that AED boosts the Th1 immune response, which is important for tuberculosis resistance.

CLAIMS

1. A product including a glucocorticoid and an anti-glucocorticoid as a combined preparation for simultaneous, separate or sequential use in treatment of a chronic infection.

2. A product according to claim 1 wherein the glucocorticoid is cortisol or a glucocorticoid derivative or analogue thereof.

3. A product according to claim 1 wherein the glucocorticoid is prednisone, prednisolone, dexamethasone, methylprednisolone, triamcinolone, cortisone, hydrocortosone sodium succinate, or hydrocortisone acetate, or a glucocorticoid derivative or analogue of any of these.

4. A product according to any preceding claim wherein the anti-glucocorticoid is dehydroepiandrosterone or an anti-glucocorticoid derivative thereof.

5. A product according to any of claims 1 to 3 wherein the anti-glucocorticoid is 3β,7 diolandrostene-17-one, 3β,17β-androstenediol, or 3β,7,17β-androstenetriol, a 7-hydroxylated anti-glucocorticoid derivative of dehydroepiandrosterone or 3β,17β-androstenediol, or an anti-glucocorticoid derivative or analogue of any of these.

6. A product according to any preceding claim wherein the chronic infection is tuberculosis, HIV infection, leishmaniasis, or syphilis.

7. A kit including a product according to any preceding claim and instructions for administration of the glucocorticoid and the anti-glucocorticoid in treatment of a chronic infection.

8. Use of a glucocorticoid and an anti-glucocorticoid in the manufacture of a medicament for treatment of a chronic infection.

9. Use according to claim 8 wherein the glucocorticoid is cortisol or a glucocorticoid derivative or analogue thereof.

10. Use according to claim 8 wherein the glucocorticoid is prednisone, prednisolone, dexamethasone, methylprednisolone, triamcinolone, cortisone, hydrocortosone sodium succinate, or hydrocortisone acetate, or a glucocorticoid derivative or analogue of any of these.

11. Use according to any of claims 8 to 10 wherein the anti-glucocorticoid is dehydroepiandrosterone or an anti-glucocorticoid derivative thereof.

12. Use according to any of claims 8 to 10 wherein the anti-glucocorticoid is 3β,7 diolandrostene-17-one, 3β,17β-androstenediol, or 3β,7,17β-androstenetriol, a 7-hydroxylated anti-glucocorticoid derivative of dehydroepiandrosterone or 3β,17β-androstenediol, or an anti-glucocorticoid derivative or analogue of any of these.

13. Use according to any of claims 8 to 12 wherein the chronic infection is tuberculosis, HIV infection, leishmaniasis, or syphilis.

14. A method of treatment of a chronic infection, the method including administration to a mammal of a glucocorticoid and an anti-glucocorticoid.

15. A method according to claim 14 wherein the glucocorticoid is cortisol or a glucocorticoid derivative

or analogue thereof.

16. A method according to claim 15 wherein the glucocorticoid is prednisone, prednisolone, dexamethasone, methylprednisolone, triamcinolone, cortisone, hydrocortosone sodium succinate, or hydrocortisone acetate, or a glucocorticoid derivative or analogue of any of these.

17. A method according to any of claims 14 to 16 wherein the anti-glucocorticoid is dehydroepiandrosterone or an anti-glucocorticoid derivative thereof.

18. A method according to any of claims 14 to 16 wherein the anti-glucocorticoid is 3β,7 diolandrostene-17-one, 3β,17β-androstenediol, or 3β,7,17β-androstenetriol, a 7-hydroxylated anti-glucocorticoid derivative of dehydroepiandrosterone or 3β,17β-androstenediol, or an anti-glucocorticoid derivative or analogue of any of these.

19. A method according to claim 14 wherein the chronic infection is tuberculosis, HIV infection, leishmaniasis, or syphilis.

Figure 1

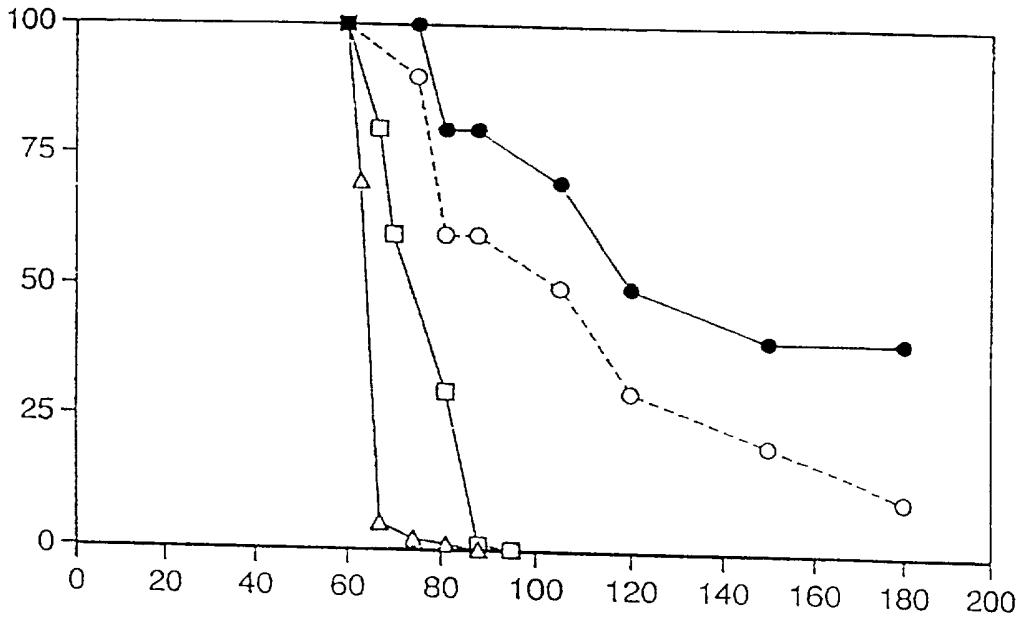

Figure 2

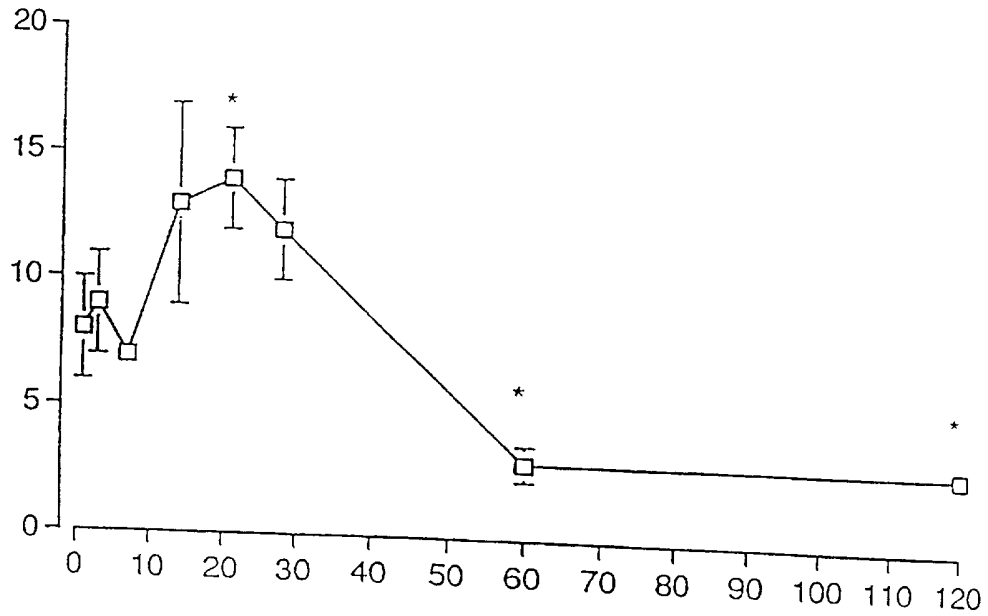

Figure 3

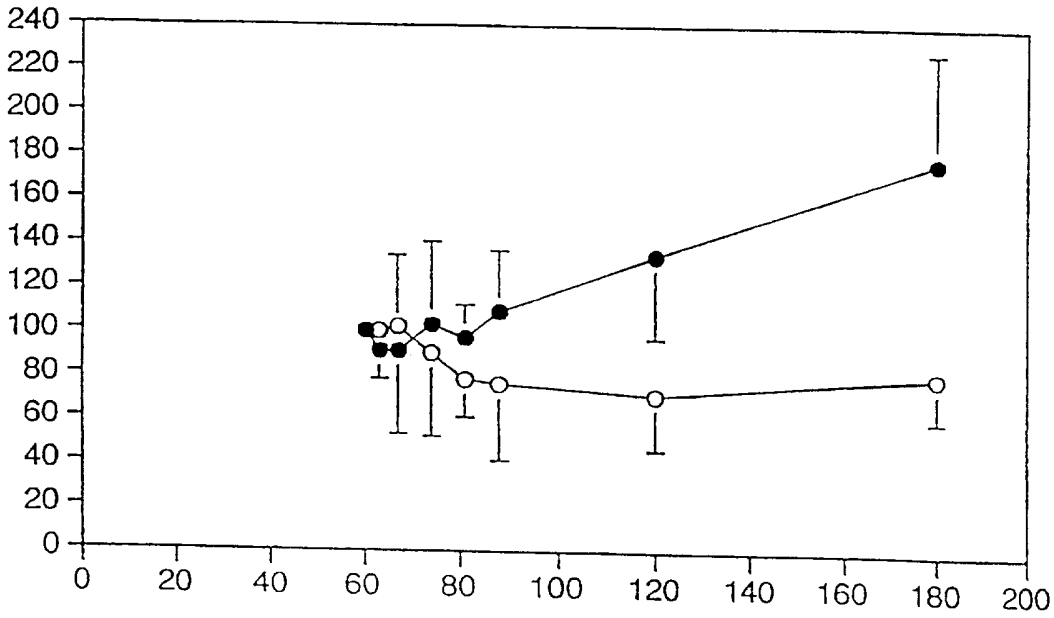
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Figure 4A

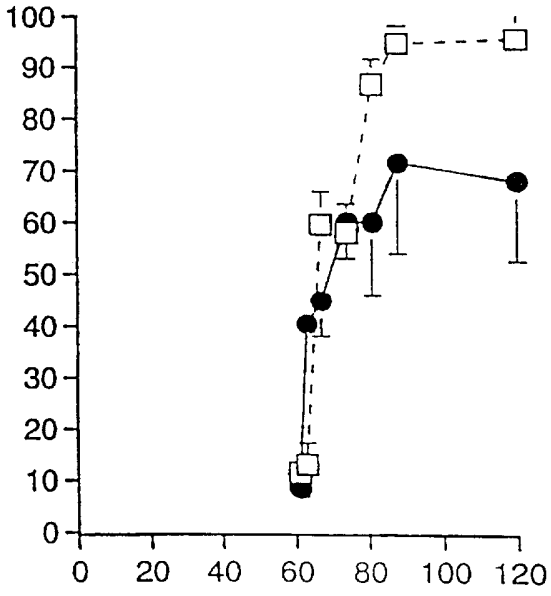

Figure 4B