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Original article

Mechanism of action and effect of immune-modulating agents in the treatment of psoriasis

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ABSTRACT

Objectives: The aim of this work is to study the possible mechanisms through which different immune-modulating agents can produce their beneficial effects on treatment of psoriasis and to determine whether the supplementation of these agents for psoriasis patients induces regression of psoriasis.
Subjects and methods: One hundred fifty participants were included in this study. The participants were divided into five groups: 1. Normal control group, 2. Psoriasis patients not taking any treatment, 3. Psoriasis patients treated with anti-psoriatic treatment (including coal tar, vitamin D3 analogues and corticosteroids). 4. Psoriasis patients treated with anti-psoriatic treatment and oral metformin (850 mg twice daily) and 5. Psoriasis patients treated with anti-psoriatic treatment and oral pioglitazone (15 mg once a day). Demographic characteristics, diabetic index, lipid profile and liver function tests were monitored. The CD4+ Tcells, CD8+ Tcells, CD4+/CD8+ ratio, interleukin-2 (IL-2), C-reactive protein (CRP) and ceruloplasmin (CP) were assayed.
Results: After treatment of psoriasis patients with a traditional anti-psoriatic drug in combination with metformin and peroxisome proliferator-activated receptor gamma (PPARɣ) agonist (pioglitazone), the CD4+ T cells, IL-2, CRP, CP, ALT and AST levels were statistically significantly decreased compared to psoriasis patients without treatment. Positive and significant correlations between CD4+ % and IL-2, CRP, CP, ALT and AST in psoriasis patients were recorded.
Conclusions: The activation of PPAR-γ receptors by pioglitazone results in reduced formation of the proinflammatory cytokines and infiltration by inflammatory cells. Additionally, metformin acts as a modulator of the immune system in psoriasis patients and has a remarkable effect on the early stages of psoriasis. Therefore, either pioglitazone or metformin in combination with traditional anti-psoriatic drugs provides better results in the treatment of psoriasis than does each alone.

1. Introduction

Psoriasis Vulgaris is a common, chronic, relapsing skin disease characterised by predominant involvement of skin, nails and joints [1]. Recent advances in its pathophysiology have shifted the notion of psoriasis from that of a 'disease of the skin' to a 'T cell mediated systemic disease.' A better understanding of its pathogenesis and co-morbidities along with the development of novel therapeutics, such as biological response modifiers, have changed the approach of dermatologists to the management of psoriasis. Based on the extent of involvement and effect on the quality of life, psoriasis may be mild to moderate in severity. This approach, in turn, forms the basis of treatment in a majority of patients [2].

Psoriasis is an autoimmune disease in which autoreactive CD4+ T cells play an essential role. CD4+ T cells rely on glycolysis for inflammatory effector functions. Yin et al. (2015) showed that mitochondrial metabolism supports their chronic activation. Additionally, both glycolysis and mitochondrial oxidative metabolism are elevated in CD4+ positive T cells in autoimmune disease [5]. The association of psoriasis with metabolic syndrome is now well-documented. Metabolic syndrome is a cluster of risk factors, including central obesity, atherogenicdyslipidaemia, hypertension and glucose intolerance. This syndrome is a strong predictor of cardiovascular diseases, diabetes and stroke [4].

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Topical therapies, such as coal tar, calcipotriol and corticosteroids, are sufficient for mild and localised psoriasis. In more widespread or severe forms that are associated with significant decrease in quality of life of a patient, phototherapy and systemic therapies are indicated either alone or in combination [3]. Although the introduction of biological therapies has revolutionised the treatment of psoriasis in recent years, newer therapeutic options continue to elude the vast majority of patients in the developing and underdeveloped world, where traditional agents, such as methotrexate, cyclosporine, acitretin and phototherapy, still form the backbone of treatment despite serious side effects [4].

The "antidiabetic" effect of metformin, an oral hypoglycaemic agent of the biguanide class, is known for its multitude of actions on various facets of metabolic syndrome. Recently, metformin has also been found to restore normal interleukin-2 (IL-2) production by CD4+ T cells andto inhibit keratinocyte proliferation in a cell culture model of psoriasis [6]. Accordingly, metformincould be useful as an add-on therapy to methotrexate for the treatment of psoriasis as an immune-modulating agent with anti-inflammatory, antineoplastic and anti-proliferative activities. Furthermore, a recent study suggests that the drug reduces the risk of psoriasis [4].

Thiazolidinedione (TZD) peroxisome proliferator-activated receptor gamma (PPAR-γ) agonists, such as pioglitazone, rosiglitazone and lobeglitazone,are used as insulin sensitizers in patients with type 2 diabetes mellitus. Pioglitazone acts as an immune-modulating agent to inhibit proliferation and differentiation in psoriasis. It also has been suggested that the anti-inflammatory and antiangiogenic properties of TZDs underlie their beneficial effects in psoriasis treatment [7].

The aim of this study is to investigate the possible mechanism through which different immune-modulating agents can produce their beneficial effects on treatment of psoriasis, as well as to determine whether supplementation of immune-modulating agents for psoriasis patients ameliorates psoriasis.

2. Subjects and methods

This study was performed with adults from tertiary Saudi Arabian hospitals. One hundred fifty participants were included in the study. Participants were selected according to inclusion and exclusion criteria. The participants are divided into five groups:

1 Normal control group.
2 Psoriasis patients not taking any treatment.
3 Psoriasis patients treated with topical anti-psoriatic treatment including coal tar, vitamin D3 analogues andcorticosteroids.
4 Psoriasis patients treated with topical anti-psoriatic treatment including coal tar, vitamin D3 analogues and corticosteroids-plusoral Metformin 850 mg twice daily.
5 Psoriasis patients treated with topical anti-psoriatic treatment including coal tar, vitamin D3 analogues and corticosteroids plus oral pioglitazone 15 mg once a day.

This study was approved by the hospital committee of the tertiary Riyadh Hospital, KSA. Informed consent was obtained from all included patients. A preliminary examination of all participants consisted of a brief medical history, including details of systemic diseases, drug administration, cigarette smoking, trauma and exposure to ultraviolet radiation.

Patients included in the present study had chronic plaque psoriasis of moderate severity, defined as PASI $\geq$ 6 and/or DLQI $\geq$ 6. They also had metabolic syndrome (By modified ATP III criteria) 4 or impaired glucose tolerance (defined as two-hour glucose levels of 140 to 199 mg per dL on the 75-g oral glucose tolerance test.)

Patients withknown drug allergies to biguanides, psoriatic arthritis, pustular psoriasis, severe psoriasis (PASI > 10, DLQI > 10), diabetes mellitus defined as fasting blood sugar > 126 mg/dL, glucose tolerance test of >200 mg/dL, intake of oral hypoglycaemic or systemic anti-psoriatic medication within the last 4 weeks and patients on medications for cardiovascular, gastrointestinal, hepaticor renal disorders were excluded.

2.1. Sample collection

From each case and control approximately 10 mL was collected from the antecubital vein after overnight fasting to be separated into two aliquots: 5 mL in a vacutainer tube without anticoagulant for obtaining serum and 5 mL in a plain phial containing heparin for obtaining plasma.

2.2. Biochemical analysis

Fasting glucose levels were measured using the colorimetric glucose oxidasemethod of Trinder [8]. Blood glycatedHb was determined according to the method of Little et al. [9] using the Helena GLYCO-Tek affinity column method (Helena Laboratories, USA). Non-esterified fatty acids concentrations were analysed colorimetrically according to the method described by Schuster and Pilz [10]. Serum cholesterol concentration was estimated according to the method of Deeg and Ziegenohrm [11] using a reagent kit (Spinreact Company, Spain). Serum triglycerides (TGs) concentration was determined according to the method ofFossati and Prencipe [12] using a reagent kit purchased from ReactivosSpinreact Company (Spain). SerumHDL cholesterol concentration was calculated according to Nobert [13]. Serum LDL cholesterol level was calculated from the Friedewald [14] formula (LDL-cholesterol = total cholesterol – triglycerides/5–HDL-cholesterol).

2.3. Determination of CD4+ and CD8+

Monoclonal antibodies specific for CD4+ markers of helper/inducer T cells and CD8+ markers of suppressor/cytotoxic T cells were applied to fresh-frozen whole-blood specimens (Dako Co., Glostrup, Denmark). Under 480× magnification, 10 visual fields of the sample were evaluated by a semi-quantitative method. After morphological evaluation of T lymphocytes with positive reactions to the added antibody, the cells were counted [15].

2.4. Determination of serum interleukin-2 (IL-2)

The concentration of IL-2 was determined with Quantikine Human Interleukin Immunoassay ELISA test provided by R&D Systems (Quantikine, R&D Systems, Minneapolis, USA). The test sensitivity was 7 pg/mL [16].

2.5. Determination of plasma ceruloplasmin

Plasma ceruloplasmin was quantitatively measured in accordance with Harris et al. through an enzyme-linked immunosorbent assay (ELISA) using a kit provided by Assaypro (AssayPro, St. Charles, MO, USA) [17].

2.6. Determination of plasma C-reactive protein (CRP)

Plasma CRP was quantitatively measured by ELISA using a kit provided by R&D Systems, Inc. (USA) according to the method of Clearfield [18].