



ORIGINAL ARTICLE

Expression of soluble sCD163 in serum of psoriatic patients is modulated by Goeckerman therapy

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Abstract

Background: CD163 is the monocyte/macrophage receptor for haptoglobin–haemoglobin complexes. The aim of this study was to assess the kinetics in the expression of CD163 on monocytes and the concentration of soluble sCD163 in serum of psoriatic patients in order to examine the effect of Goeckerman therapy.

Methods: sCD163 was measured in 71 patients before and after therapy, and in 57 healthy donors. A subgroup of 40 patients and 25 controls was used to assess the expression of membrane CD163. sCD163 was evaluated by ELISA. Flow cytometry method was used to determine the expression of membrane CD163 on monocytes, expressed as mean fluorescence index (MFI).

Results: Before therapy, the serum level of sCD163 was significantly higher in our patients than in controls ($P=0.0154$). However, we observed a profound decrease in sCD163 in our patients after therapy ($P=0.0037$). Similar to sCD163, pre-treatment expression of CD163 on monocytes was significantly more enhanced in patients than that in controls ($P=0.0078$). There was a trend towards down-regulation of the expression after therapy, nonetheless, the change was not statistically significant compared to the values before therapy ($P=0.8666$). This was also confirmed by comparison with controls which displayed lower expression of CD163 than patients after therapy ($P=0.0019$). The disease activity, expressed as PASI score, was significantly decreased in our patients by GT ($P=0.0001$).

Conclusions: While sCD163 level in psoriatic patients was diminished after GT therapy, CD163 expression on monocytes was altered only to a minor extent.

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Introduction

A variety of cell types and humoral factors constitute the skin immune system. Deregulation of the skin immune system can result in inflammation in the skin. A typical example of such harmful inflammatory reaction is psoriasis. It is a chronic relapsing inflammatory skin disease with still largely unknown aetiology. It affects approximately 2% of the world population. It is suggested that psoriasis is mediated by components of both the innate and adaptive immune system that trigger an abnormal keratinocyte response with dendritic cells, macrophages, T cells and various cytokines and chemokines being involved in the formation of skin lesions.¹ Psoriasis is a multifactorial disease in which both genetic predisposition and many variable incipiting factors such as infection, stress, skin trauma, to list only some, are involved.^{2,3}

Classical approach to treat psoriasis is Goeckerman therapy (GT) which is based on daily application of pharmaceutical grade coal tar on affected skin with subsequent exposition to UV light. GT was described already in 1925 by Dr. William Goeckerman. It is well established that Goeckerman therapy of psoriasis is highly efficient. GT achieves good clinical response followed by a long-term remission in a majority of patients. This therapy is still preferred for its simple application, good clinical response, and low cost^{4,5} regardless of a long-term debate addressing its potential suspicious genotoxicity.

CD163 is the monocyte/macrophage receptor for haptoglobin-haemoglobin (Hp-Hb) complexes.^{6,7} It is a member of the scavenger receptor cysteine-rich (SRCR) superfamily^{8,9}; specifically, it belongs to Group B superfamily.^{7,10,11} Many of the SRCR-proteins have been shown to be directly involved in the development of the immune system and in the regulation of the immune response. CD163 molecule, like most members of the SRCR family, is expressed as a membrane bound protein.¹² CD163 binds with high affinity to the Hp-Hb complex,^{6,13} but not to Hp or Hb separately.¹⁴ Rapid elimination of free haemoglobin is very important to avoid the toxicity of the oxidative heme group of Hb and redox-reactive iron.^{7-9,15} The expression of CD163 is controlled by pro- and anti-inflammatory stimuli. Pro-inflammatory stimuli, such as bacterial lipopolysaccharides, tumour necrosis factor α (TNF- α), transforming growth factor β (TGF- β) or interferon γ (IFN- γ) down-modulate the expression of this receptor, whereas interleukin 6 (IL-6) along with anti-inflammatory interleukin 10 (IL-10) induces a rapid up-regulation of CD163 expression.^{8,10,11,16} Both endogenous and exogenous corticosteroids are very potent inducers of CD163 expression.

CD163 also exists as a soluble protein in normal plasma, resulting from proteolytic shedding of the membrane form. Because of a constant shedding of the receptor from the membrane, the plasma concentration of the receptor may reflect its overall expression level.⁸ Similar to the membrane form of CD163, soluble CD163 (sCD163) also binds Hp-Hb complexes, thus it participates in anti-inflammatory regulatory circuits, exhibiting cytokine-like functions.^{10,17} The level of sCD163 may increase many-fold during sepsis and other conditions affecting macrophage activity.⁶

Besides having a role in the clearance of free Hb from plasma, CD163 has an immunomodulatory role.^{6,18} CD163

immunological function is essentially homeostatic. It is involved in adhesion of monocytes to endothelial cells, in tissues regeneration, and tolerance induction. Monocytes and macrophages are very important cells of the innate immune system, and their study is imperative to better understand the inflammatory nature of psoriasis.¹⁹ Macrophages exist in at least two functionally distinct states that are triggered in response to different stimuli. While classically activated M1 macrophages are engaged in pro-inflammatory responses, alternatively activated M2 macrophages display anti-inflammatory properties, and they are involved in the resolution of inflammation. The characteristic feature of M2 macrophages is the high expression of CD163.^{20,21} Monocytes with up-regulated CD163 resemble these anti-inflammatory macrophages. It can be presumed that M2 macrophages are directly derived from CD163^{high} monocytes. Since the information addressing the influence of GT on CD163 is very sparse, we followed the modulation of both membrane and soluble form of CD163 in psoriatic patients.

Materials and methods

Study groups

The study was approved by the Ethics Committee of the University Hospital in Hradec Kralove, Czech Republic. Informed written consent was obtained from each subject.

The group of patients suffering from psoriasis consisted of 71 patients (33 females, 38 males, average age 39.3 ± 19.0 years). As a control, the group of 57 healthy donors (29 females, 28 males, average age 38.4 ± 13.3 years) was used. sCD163 was measured in all 71 patients (abbreviated as sCD163 group) before and after therapy. The results were compared with the control group. Expression of CD163 on monocytes was assessed in a subgroup of 40 patients (23 males, 17 females, average age 38.3 ± 19.1 years) before and after therapy (abbreviated as CD163 group). Results were compared with a subgroup of 25 controls (18 males, 7 females, average age 39.6 ± 10.8). There was no bias in the selection of probands.

Goeckerman therapy

Goeckerman therapy was indicated by the consulting dermatologist with patient-to-patient adjustments based on the activity of disease expressed as PASI score. The average duration of therapy was 20 days (in sCD163 group) and 22 days (in CD163 group), respectively. The efficacy of Goeckerman therapy was assessed by clinical evaluation of erythema, desquamation, and skin infiltration using PASI score (Psoriasis Area Severity Index). The PASI score was calculated before and after treatment for each patient. GT is ceased when a 30% decrease of PASI is achieved. Coal tar ointment with 5% pharmaceutical grade coal tar was applied daily overnight on the affected skin. Each morning, the excess tar ointment was removed with oil bath. After the tar removal, the patient was irradiated with UV light. The duration of UV irradiation was individual, depending on the disease activity. The light beam density (dose) was controlled by a spectroradiometer Sola-Scope 2000 (Solatell, UK) and was $245.60 \mu\text{W}/\text{cm}^2$ for UV-B radiation

and $134.4 \mu\text{W}/\text{cm}^2$ for UV-A radiation. Previous exposure of patients to UV irradiation and polyaromatic hydrocarbons was assessed by a personal questionnaire. Patients with this positive personal history were excluded from the study. Samples of venous blood were obtained by venipuncture of the cubital vein before treatment and again after completion of Goeckerman therapy (at the day of dismissal from the hospital) using BD Vacutainer sampling tubes. Venous blood was also collected from otherwise healthy blood donors who served as control. Blood sera were isolated by centrifugation. Serum samples were stored under -70°C until they were analysed. Repeated thawing and freezing were avoided.

Flow cytometry and ELISA

The standard whole blood immunophenotypic analysis was performed on peripheral blood using flow cytometer FACSCalibur (Becton Dickinson) with a 3-colour antibody panel: CD163-FITC (Trillium Diagnostics)/CD14-PerCP (BD Biosciences)/CD3-APC (Beckman Coulter). Briefly, $25 \mu\text{l}$ of blood was incubated with the mixture of monoclonal antibodies for 15 min, lysing solution (Beckman Coulter) was added and incubated for an additional 10 min, and physiological solution was added prior to flow cytometric analysis.

The level of soluble CD163 was detected by sandwich enzyme-linked immunosorbent assay (ELISA) using the diagnostic kit Macro163™ (IQ Products, Netherlands). The assay was run according to the instructions for use provided by the manufacturer. Plates were read with a 450 nm filter on the microplate reader.

Statistical analysis

Statistical differences between the groups were evaluated by non-paired and paired *t*-test and Wilcoxon test (MedCalc software, Belgium) after data normality evaluation. To exclude the confounding effect of different age and sex presentation in patients and controls, unpaired *t*-test and chi-square were performed. The results are given as the median (lower to upper quartile) (in sCD163 analysis) and the mean \pm standard deviation (in CD163 analysis). *P* value less than 0.05 was considered as significant.

Results

The therapeutic efficacy of GT was high in our study. A good clinical response was achieved in all patients. In sCD163 group, PASI score dropped significantly from 19.3 before treatment to 10.1 after GT ($P=0.0001$). Similarly, PASI score in CD163 group decreased significantly from 18.2 before therapy to 8.5 after treatment ($P=0.0001$).

When comparing with controls (1128.0 ng/ml (887.8–1325.0)), serum level of sCD163 in patients (1363.0 ng/ml (852.5–1778.5)) was considerably higher before GT ($P=0.0154$). sCD163 was strongly affected by Goeckerman therapy: the serum level decreased from 1363.0 ng/ml (852.5–1778.5) before therapy to 1182.0 ng/ml (850.0–1610.3) after therapy ($P=0.0037$). Comparing the healthy controls (1128.0 ng/ml

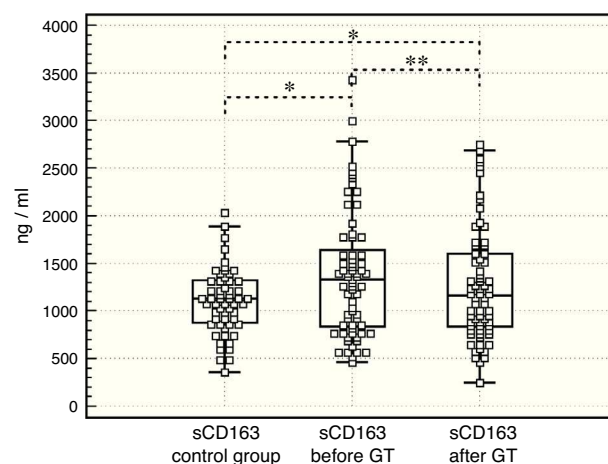


Figure 1 Serum levels of sCD163 in control group and patients with psoriasis before and after GT.

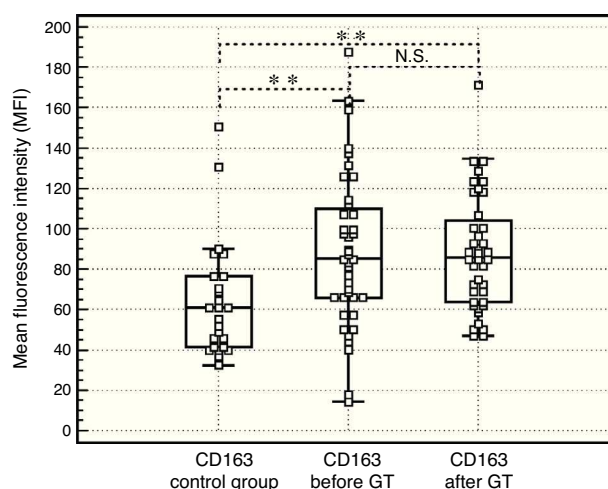


Figure 2 Membrane monocyte CD163 expression in peripheral blood of control group and patients with psoriasis before and after GT.

(887.8–1325.0)) the serum levels of sCD163 in patients with psoriasis after GT (1182.0 ng/ml (850.0–1610.3)) remained slightly elevated ($P=0.0459$).

Intensity of membrane CD163 expression in patients, compared to controls (64.5 ± 28.6), was significantly higher both before (88.9 ± 38.2 , $P=0.0078$) and after (88.1 ± 28.5 , $P=0.0019$) therapy. However, the expression of monocyte membrane CD163 was not significantly affected by GT ($P=0.8666$). Our results are summarised in Fig. 1 (soluble CD163 serum level) and Fig. 2 (membrane CD163 expression).

No correlations between (s)CD163 and disease activity expressed as PASI score were found.

Discussion

Psoriasis is a chronic skin disorder with a substantial adverse impact on patient's health, impairing their physical, psychological, and social life.²² Inflammatory skin diseases, especially psoriasis, are often claimed by patients to be initiated or aggravated by stressful life events.^{23,24}

Goeckerman therapy is highly efficient in inducing remission – measured by the decrease in PASI.²⁵ This therapy reveals an immunomodulatory, immunosuppressive and anti-inflammatory effect. The combination of coal tar ointment and UV light has been reported to be more effective than either therapy alone.⁴ There are some safety concerns addressing Goeckerman therapy. There is the risk of contamination of tar by chemical components with mutagenic activity.²⁵ Coal tar is a mixture of more than 10 000 compounds, including polycyclic aromatic hydrocarbons (PAH).²⁶ Many PAH are recognised as carcinogens with tumour-initiating and/or tumour-promoting properties. It is likely that ultraviolet radiation used in GT pronounces the risk of mutagenicity, carcinogenicity and immunotoxicity.²⁷ The increased risk of non-melanoma skin cancer in patients treated with crude coal tar (with or without exposure to ultraviolet radiation) was found by a few studies,^{28,29} whereas some other studies did not reveal any risk.^{26,27,30}

sCD163 represents a new class of monocyte/macrophage specific biomarkers associated with several clinical conditions, such as atherosclerosis, coronary artery disease, transplantation, cancer, infection and autoimmunity.^{19,31–33} The special attention is given to CD163 in patients who are exposed to a large amount of free heme/hemoproteins due to intravascular haemolysis and tissues damage induced for example by cardiac surgery using cardiopulmonary bypass (CPB).³⁴ CD163 expression is elevated during the late phase of acute inflammation as well as in chronic inflammation.^{35,36} This marker is proposed to be a prognostic marker in selected inflammatory diseases.^{9,10} Apart from other inflammatory markers, CD163 scavenger receptor is exclusively expressed on the monocytes/macrophages.

The effect of GT on CD163 scavenger receptor expression has not been investigated yet. Our study seems to be original in this regard. Our results showed that levels of both membrane expression of CD163 on monocytes and soluble CD163 are significantly higher in patients with psoriasis before Goeckerman therapy compared with healthy controls. This elevation in CD163 scavenger receptor, a specific monocyte/macrophage marker, suggests ongoing inflammatory process in patients with psoriasis. In line with our results, Zaba et al. reported that CD163+ cells show a 3-fold increase in psoriatic lesional skin and return to non-lesional skin levels after effective treatment with etanercept.³⁷ Fuentes-Duculan et al. concluded that macrophages are likely to be contributing to the pathogenic inflammation in psoriasis by releasing the key inflammatory products.¹⁹ We found that the serum level of sCD163, which is increased in patients with psoriasis before therapy, significantly decreases after GT. On the other hand, there are no differences between expression of monocyte membrane CD163 receptor before and after therapy. Moreover, when compared with healthy controls, CD163 monocyte expression in patients with psoriasis is significantly higher, not being substantially affected by GT. This observation might be explained by the benefits of presence of anti-inflammatory macrophages in skin. Therefore membrane CD163 expression remains elevated even after therapy and prolongs its anti-inflammatory activity after GT. On the contrary, sCD163 level in circulation was decreased after therapy because GT down-regulated the activity of metalloproteinases which are responsible for the shedding of CD163 from the membrane surfaces.³⁸ A soluble

CD163 molecule in peripheral blood is now recognised as a new biomarker of inflammation, whereas the expression of CD163 on monocytes is associated with anti-inflammatory phenomena.³⁴

In conclusion, the expression of (s)CD163 reflects ongoing inflammatory process in patients, with psoriasis being significantly higher than in the control group. GT significantly diminished the serum level of sCD163 in patients with psoriasis.

Ethical disclosure

Protection of human and animal subjects: The authors declare that the procedures followed were in accordance with the regulations of the Clinical Research Ethics Committee and in accordance with those of the World Medical Association and the Helsinki Declaration.

Right to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects mentioned in the article. The author for correspondence is in possession of this document.

Confidentiality of data: The authors declare that they have followed the protocols of their work centre on the publication of patient data and that all the patients included in the study have received sufficient information and have given their informed consent in writing to participate in that study.

Conflict of interest

The authors have no conflict of interest to declare.

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