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Oral administration of acarbose ameliorates imiquimod-induced psoriasis-like dermatitis in a mouse model

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ABSTRACT

Psoriasis is a chronic autoimmune disease of undefined etiology that involves dysregulated interplay between immune cells and keratinocytes. Acarbose was found to decrease inflammatory parameters in diabetic patients in addition to its anti-diabetic effects. Here, we report that imiquimod (IMQ)-induced epidermal hyperplasia and psoriasis like-inflammation were significantly inhibited by acarbose treatment. Real-time PCR showed that mRNA levels of the cytokines TNF-α, IL-6, IL-1β IL-17A, and IL-22 in skin were also decreased significantly by acarbose. In addition, we found that acarbose reduced infiltration of $CD3^+$ T cells and $GR\text{-}1^+$ neutrophils in lesional skin and also reduced the percentage of IL-17-producing $CD4^+$ T cells (Th17) and IL-17- and IL-22-producing γδ T cells in the spleen. In contrast, acarbose increased the frequency of IL-10-producing $CD4^+$ regulator Tr1 T cells in the spleen and small intestine. These results indicate that oral administration of acarbose can attenuate the severity of imiquimod-induced psoriasis with local and systemic anti-inflammatory and immune modulation effects, thus suggesting that acarbose is an effective therapeutic strategy for psoriasis regulation.

1. Introduction

Psoriasis is a chronic autoimmune inflammatory skin disorder affecting approximately 2 to 3% of the population worldwide [1]. Psoriasis is associated with of cardiovascular risk factors including diabetes [2,3], hypertension [4], dyslipidemia [5], and obesity [6]. Psoriasis is also a likely independent risk factor of cardiovascular disease [7]. The psoriasis skin lesion is usually characterized by raised erythematous scaly plaques, skin infiltration with leukocytes, epidermal hyperproliferation (acanthosis), aberrant differentiation of keratinocytes (parakeratosis), and increased tortuous capillaries (angiogenesis) [1,8].

Accumulating evidence suggests that many innate and adaptive immune cells and derived cytokines, such as TNF-α, IL-6, IL-1β, IL17, IL-22 and IL-23, are involved and interact as a network in the pathogenesis of psoriasis [1,9–11]. In addition, the proven therapeutic efficacy of targeted biologics, including TNF-α inhibitors [12], mAbs against IL-23/IL-12 p40 such as ustekinumab [13], or selective Abs against either IL-17 [14] or IL-23 p19 [15] confirmed the critical role of TNF-α and the IL-23/IL-17 axis in the pathogenesis of psoriasis. However, the high costs and immunosuppressive effects of these novel biologics confine their use to psoriasis patients with inadequate response to conventional synthetic disease-modifying antirheumatic drugs (csDMARDs). Therefore, the development of cheap and well-tolerated immunemodulatory drugs, which target the mechanisms described above, can offer an alternative treatment option for psoriasis patients.

Acarbose, a pseudo-carbohydrate that competitively interferes with alpha-glucosidases in the brush border of the small intestine to retard carbohydrate breakdown, is a commonly used antidiabetic drugs. Acarbose is well-tolerated and does not lead to hypoglycemia if no other anti-diabetes drugs are used concurrently [16]. Notably, recent studies have shown that acarbose may decrease inflammatory markers in diabetic patients [17,18]. In addition, it also reduces the risk of cardiovascular disease, a major diabetes mellitus (DM) complication characterized by high levels of circulating inflammatory mediators, through anti-inflammatory effects [19]. Therefore, we hypothesize that acarbose is of potential value for the treatment of psoriasis.

Imiquimod (IQM)-induced psoriasis-like inflammation in mice and humans has been reported [20,21]. Experimental data show that daily

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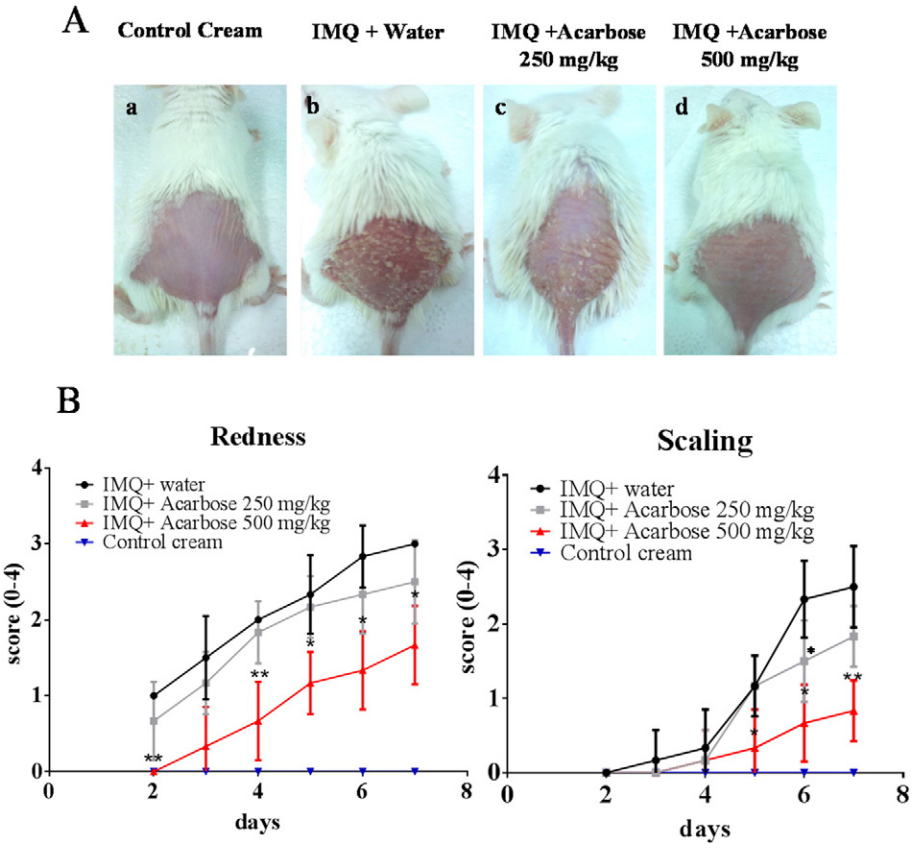

Fig. 1. Acarbose reduced psoriasis-like skin lesions in IMQ-treated mice. (A) Representative images of IMQ-induced psoriasis-like skin lesions in mice treated with IMQ (mouse b, c, d) or control cream treated mouse (mouse a) at day 7. Mouse b was treated with IMQ/water and mouse c, d was treated with 250 mg/kg or 500 mg/kg acarbose, respectively. (B) Daily mean disease severity is depicted as back skin erythema, and scaling scores for mice grouped. Symbols represent mean score ± SD of five mice per group. *$p < 0.05$, **$p < 0.01$ (Mann–Whitney U test) versus IMQ/water group. Data shown are representative of three experiments.

application of imiquimod (IMQ)-induced dermatitis in mice. This condition resembles human psoriasis lesions not only in terms of phenotypic and histological characteristics (acanthosis, parakeratosis and neoangiogenesis), including of $CD4^+$ T cells and neutrophils but also in the development of the dermatitis, which is immunologically mediated via the IL-23/IL-17 axis, IL-22, and TNF-α, which that are involved and interact as a network in the pathogenesis of psoriasis [21–23]. This study was designed to investigate the effect of acarbose on an IMQ-induced psoriasis-like mouse model to assess the therapeutic efficacy of acarbose in treating psoriasis.

2. Materials and methods

2.1. Mice

6–8 week-old BALB/c mice were purchased from the National Laboratory Animal Center (Taipei, Taiwan). The mice were housed at the facility of National Chung Hsing University (Taichung, Taiwan). All protocols involving live animals were approved by the Institutional Animal Care and Use Committee of National Chung Hsing University (IACUC NO. 104-096).

2.2. IMQ-induced psoriasis-like skin inflammation protocol

Naive BALB/c mice were randomly divided into 4 groups. Based on previous reports [21,24], the psoriasis-like skin inflammation mouse mode was generated by daily topical application of 62.5 mg Imiquimod (IMQ) cream (Aldara; 3M Pharmaceuticals St Paul, MN) on the shaved back skin for 6 consecutive days. In the experimental groups, the mice were fed orally with either 200 μl of water (n = 6) or acarbose (250 or 500 mg/kg) for treated group (n = 6 per each group), respectively, 1 week before imiquimod treatment and twice daily at approximately 12-h intervals until the end of the experiment. As a control group, the mice were given vaseline cream (62.5 mg) topically on the shaved back skin for 6 consecutive days and fed orally with either 200 μl of water (n = 6).To evaluate the severity of inflammation of the back skin, a modified target lesion psoriasis severity score was applied. Mice were evaluated daily and individually regarding back redness (erythema) and presence of scales (scaling) on a scale from 0 (no alteration) to 4 (very distinct alteration).

2.3. Histopathological and immunohistochemical analysis

At the end of experiment (day 7), the back skin samples were fixed in 4% formaldehyde and cut longitudinally into 6 μM-thick sections. Tissue sections were stained using hematoxylin and eosin (H&E) to study their microarchitecture. For immunohistochemical analyses, sections were fixed with formalin; then antigen retrieval was performed in the EDTA buffer (pH 9, epitope retrieval solution) at 95–98 °C for 20 min by microwave; endogenous peroxidase was removed with 0.02% H_2O_2 for 10 min; sections were washed with PBS and incubated overnight at 4 °C with primary rabbit antibodies against mouse Ki67 (16A8, Biolegend, San Diego, CA), $CD3^+$ T cells (GK1.5, Biolegend, San Diego, CA), and $Gr1^+$ neutrophil (RB6-8C5, Biolegend, San Diego, CA) in PBS/0.1% BSA. HRP-conjugated goat anti-rat secondary antibody was applied in PBS/0.1% BSA for 30 min at room temperature. Enzyme activity was detected by using DAB substrate kit (Leica Microsystems Nussloch GmbH, Nussloch, Germany), stained lightly with Hematoxylin. Staining was analyzed independently by two investigators in a blind fashion. For quantification of immune infiltrating cells, a light microscope with a