Editorial

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What are the clinical usefulness and scientific value of intramuscular injection of autologous serum (autologous serum therapy) in patients with atopic dermatitis?

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See "Clinical efficacy and safety of autologous serum intramuscular injection in patients with mild-to-moderate atopic dermatitis: a prospective, open-label, uncontrolled study" by Gil-Soon Choi, Jong Bin Park, Young-Ho Kim, Hee-Kyoo Kim

Atopic dermatitis (AD) is a chronic allergic skin disorder characterized by itching and eczema [1]. Standard therapies for AD currently include topical treatments, such as corticosteroids or calcineurin inhibitors, and systemic therapies with oral immunosuppressants, such as cyclosporine or methotrexate [1-3]. The monoclonal antibody dupilumab, which targets the interleukin (IL)-4 receptor alpha and simultaneously inhibits IL-4 and IL-13, and Janus kinase inhibitors (abrocitinib, ruxolitinib, upadacitinib, etc.) can significantly reduce clinical severity in patients with moderate-to-severe AD who do not respond adequately to standard therapies [3]. However, these new medications for AD are only effective during the treatment period, and there is an ongoing debate about the feasibility of administering these expensive treatments for a lifetime. Consequently, there is a need for trials to find alternative treatments that can be easily applied to the management of patients with AD in real clinical practice.

Autologous blood therapy and autologous serum therapy, also known as autohemotherapy and autoserum therapy, involve the repeated administration of autologous blood or serum (1–5 mL) to the same subjects via intramuscular injections [4-9]. These therapies have been utilized in the treatment of AD and chronic urticaria as complementary and alternative medicine modalities for over a century [5-9]. A double-blind, randomized, placebo-controlled clinical trial (RCT) has shown the clinical effectiveness of autologous blood therapy in patients with AD [6]. Similarly, another double-blind RCT has confirmed the clinical effectiveness of autologous serum therapy in patients with chronic urticaria [8]. However, the clinical efficacy of autologous serum therapy for AD had not been rigorously tested in either pilot or RCT until the recent publication of two clinical studies: an uncontrolled pilot clinical trial [10] and an RCT (Table 1) [11]. Therefore, further studies are needed to assess the clinical usefulness of autologous serum therapy for AD and to elucidate its mechanism of action.

In the current issue of the *Kosin Medical Journal*, Choi et al. [10] assessed the clinical efficacy and safety of intramuscular injection of autologous serum (autologous serum

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Table 1. Clinical trials on the clinical efficacy of intramuscular injections of autologous blood or autologous serum for AD

No. of enrolled patients (completed patients)	Inclusion criteria	Design of study	Intervention	Efficacy parameters (clinical severity score of AD)	Author (year)
31 (30)	Mild-to-moderate AD	DBPC-RCT	- Intramuscular injection of autologous whole blood (n=15) or saline (n=15) - Intervention period: 5 wk (total 5 injections)	SASSAD ↓, DLQI ↓ at wk 9	Pittler et al. (2003) [6]
23 (21)	Moderate-to-severe AD	DBPC-RCT	- Intramuscular injection of autologous serum (n=11) or saline (n=12) - Intervention period: 4 wk (total 8 injections)	SCORAD ↓, DLQI ↓, EASI ↔ at wk 8	Nahm et al. (2023) [11]
23 (22)	Mild-to-moderate AD	Uncontrolled pilot clinical trial	-Intramuscular injection of autologous serum - Intervention period: 4 wk (total 5 injections)	SCORAD ↓, DLQI ↓, EASI↔ at wk 4	Choi et al. (2024) [10]

AD, atopic dermatitis; DBPC-RCT, double-blind placebo-controlled randomized clinical trial; SASSAD, six area, six sign AD; DLQI, Dermatology Life Quality Index; SCORAD, Scoring Atopic Dermatitis; EASI, Eczema Area and Severity Index.

therapy) in patients with mild-to-moderate AD. They conducted a prospective pilot clinical trial, administering treatments once a week for 4 weeks, with a follow-up period extending to week 8, involving 23 patients. The study reported the clinical effectiveness of autologous serum therapy in patients with mild-to-moderate AD, showing significant improvements in the clinical severity score (Scoring Atopic Dermatitis; SCORAD), pruritus, sleep difficulty, and the patient-reported subjective Dermatologic Life Quality Index (DLQI) score [10]. Similarly, another double-blind RCT reported significant clinical effectiveness, as evidenced by improvements in SCORAD and DLQI scores, of autologous serum therapy in patients with moderate-to-severe AD [11]. These results suggest that autologous serum therapy is clinically useful in patients with AD. However, neither of these clinical trials on autologous serum therapy for AD reported significant changes in another objective clinical severity parameter, the Eczema Area and Severity Index (EASI) [10,11]. Based on data from clinical studies on autologous blood therapy and autologous serum therapy for AD, these treatments appear to be more clinically beneficial for patients with mild-to-moderate AD than for those with severe AD (Table 1). Therefore, further research is needed to evaluate the clinical usefulness of autologous serum therapy in patients with AD.

The primary scientific limitation of autologous blood therapy and autologous serum therapy, as standard treatment methods for AD, is the insufficient understanding of the specific blood or serum component responsible for their therapeutic efficacy. An analysis of clinical trials on the therapeutic efficacy of both autologous blood therapy and autologous serum therapy suggests that the therapeutic component mediating the clinical efficacy of autologous blood therapy is present in the serum fraction rather than the cellular fraction (red blood cells, leukocytes, or platelets) of autologous blood (Table 1). On the basis of this reasoning, Nahm et al. [12,13] hypothesized that an autologous immunoglobulin G (IgG) could be the effective component in autologous blood therapy, with anti-idiotypic immunomodulation serving as the therapeutic mechanism. To prove the concept, Nahm et al. [12,13] conducted a pilot study on the clinical efficacy of intramuscular injections of autologous total IgG (purified from autologous plasma using Protein A beads) in 20 patients with severe AD, and the study showed significant decreases in the clinical severity score of AD (SCORAD) after the intervention. An RCT demonstrated that intramuscular injection of autologous total IgG could significantly decrease the clinical severity of AD and increase serum IL-10 and interferon-gamma levels in patients with moderate-to-severe AD [14]. Moreover, long-term clinical improvements lasting more than 9 months were observed in two out of three adult patients with severe AD who were followed for over 2 years after receiving 4 weeks of intramuscular administrations of autolo-

gous total IgG [15]. Intramuscular injections of autologous total IgG also increased the population of CD4+/IL-10+ T cells (type 1 regulatory T cells) in the peripheral blood samples of 13 healthy human subjects [16]. These findings indicate that intramuscular injections of autologous total IgG have the potential to be developed as a novel personalized immunomodulatory therapy. This approach could lead to long-term clinical improvement in AD by activating regulatory T cells and inducing immune tolerance [1,17,18].

The studies on autologous serum therapy for AD may provide insights for the evolution of empirically developed alternative and/or complementary medicine—such as autologous blood therapy and autologous serum therapy—toward a therapy that targets specific immunomodulatory components, like autologous IgG therapy. Historically, aspirin was discovered through efforts to isolate a therapeutic component, salicin, from willow bark, which had been used as an analgesic since ancient times [19]. Efforts to identify the therapeutic component in autologous serum that mediates its clinical efficacy, as well as to understand its mechanism of action, could unexpectedly lead to the discovery of new immunomodulatory therapies for individuals with various immune disorders, including allergic diseases, in the near future [18].

Further studies are needed to test the clinical efficacy and the mechanisms of action of autologous serum therapy and autologous IgG therapy in patients with AD.

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