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DERLEME REVIEW

Chronic idiopathic urticaria, recent advances in pathophysiology and treatment

Kronik idiopatik ürtiker patofizyolojisi ve tedavisindeki yeni gelişmeler

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ABSTRACT

Chronic urticaria is traditionally defined as recurrent hives for more than 6 weeks. In over 80% of the cases no exogenous allergen trigger or underlying systemic disease is identified, and hence, the condition is referred to as chronic idiopathic urticaria. Several theories have been suggested as the basis of pathogenesis, and because of the lack of evidence of underlying cause or trigger, treatment has been mostly directed toward symptomatic relief, but recently many advances in new therapeutic approaches have been reported. This review will focus on the recent advances in the pathogenesis and treatment of chronic urticaria.

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Key words: Chronic, idiopathic urticaria, treatment, anti-IgE

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ÖZET

Geleneksel olarak kronik ürtiker altı haftadan uzun süren tekrarlayıcı ürtiker olarak tanımlanır. Olguların %80'inden fazlasında dış allerjen uyaran veya altta var olan bir sistemik hastalık saptanamaz, bu durum kronik idiopatik ürtiker olarak tanımlanır. Patogenezin temeli için birçok teori öne sürülmüşse de altta yatan bir nedenin veya tetikleyicinin olmayışı tedaviyi çoğunlukla semptomatik düzelmeye doğru yönlendirmiştir. Yakın zamanda yeni tedavi yaklaşımları bildirilmiştir. Bu derleme kronik ürtikerin patogenezi ve tedavisindeki yeni gelişmelere odaklanacaktır.

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Anahtar kelimeler: Kronik, idiopatik ürtiker, tedavi, anti-IgE

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INTRODUCTION

Chronic urticaria is traditionally defined as recurrent hives for more than six weeks[1]. In over 80% of the cases no exogenous allergen trigger or underlying systemic disease is identified, and hence, the condition is referred to as chronic idiopathic urticaria (CIU). It has been estimated that 15% to 23% of the US populati-

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on will experience acute or chronic urticaria at some point in their lifetime, and there is an approximately 0.5% lifetime prevalence of CIU in the general population[2]. Several theories have been suggested as the basis of pathogenesis, and because of the lack of evidence of underlying cause or trigger, treatment has been mostly directed toward symptomatic relief, but recently many advances in new therapeutic approaches have been reported.

Theories of Pathogenesis or Pathophysiology

Autoimmunity: The idea that chronic urticaria has an autoimmune basis arose from the recognition that thyroid autoantibodies and thyroid dysfunction were more commonly observed in patients with in CIU subjects along with clustered HLA-DR associations[3-5]. It is widely believed that a subset of CIU subjects have pathogenic serum IgG autoantibodies that target the IgE receptor (FcεRI) alpha subunit (30%) or, less commonly, surface-bound IgE (10%)[3]. It is further proposed that these autoantibodies are functional in vivo and preferentially activate skin mast cells on the basis of a high prevalence of complement fixing IgG subclasses (IgG1 and IgG3) that activate via the C5a receptor expressed by skin mast cells and not "mucosal mast cells[3,6]. Although subjects with "autoimmune" CIU are reported to have increased disease severity, there are few differences from non-autoimmune CIU subjects on skin lesion pathology, or the activation status of their blood basophils, a proposed cellular target of autoantibodies[7-12].

The original "autoimmune" assay, termed the autologous serum skin test (ASST), involves the intradermal injection of autologous serum into a subject's skin to demonstrate wheal formation, thus implicating a serum factor that triggers skin mast cells. A positive ASST was felt to represent an immunoglobulin-based factor that selectively activated skin mast cells. Recent concerns raised about the significance of the ASST include its persistence in CIU remission and a high positive rate among (30-47%) in allergic rhinitis patients and healthy controls[13-15]. Further, the persistence of a positive ASST upon IgG depletion of serum samples, raises questions about the nature of the active factor[16]. In fact, active ASST serum fractions of < 30 kDa have also been recognized as selective, non-immunoglobulin, mast cell triggering factors[17]. A recent adaptation of the ASST involving the use of plasma, or APST, was initially reported to have a much higher frequency of positivity among CIU subjects (86%) and suggested the involvement of an activated coagulation cascade in CIU[18]. However, this notion was challenged by a larger study of CIU subjects that reported a rate of skin reactivity by ASST among 37.5% of patients (similar to past studies), with only a slightly higher frequency in CIU patients (43%) with reactivity to APST[19]. Interestingly, patients in this study with a positive ASST were also found to have an increased disease activity score and a greater impairment in quality of life as compared to patients with CIU with negative ASST results. In contrast, patients with positive and negative APST results exhibited no significant differences in disease activity and quality of life.

A second assay for "autoimmunity" in CIU measures serum histamine release activity (HRA) by exposing CIU serum in vitro to a healthy donor's basophils[20,21]. Using purified serum IgG fractions and inhibition studies with soluble FcεRI alpha chain, HRA activity has been shown to indicate functional autoantibodies (mostly IgG1 and IgG3 subclasses) that trigger HRA in a C5a-complement-dependent fashion from healthy donor basophils[22,23]. However, complement deposition is absent in CIU skin lesion biopsies, and serum complement depletion is not a feature of autoimmune CIU[4]. Although serum HRA is often claimed to indicate autoantibody presence, a study of ~250 CIU patients found poor agreement between serum HRA results and serum Western blots using FcεRIα[24]. Likewise, there is variable agreement between HRA and ASST outcomes[18]. HRA is often cited as the "gold-standard" assay to measu-

re functional CIU autoantibodies but also has some problems. The dependence of the assay on the behavior of the normal donor's basophils for readout has hampered the standardization of this method (e.g. variable basophil priming of the donor in vivo by IL-3). Further, the presence of HRA in the serum of nonatopic, non-CIU subjects remains unexplained, and a topic of controversy[11,25]. The lack of established standards, the use of a normal basophil donor, and sensitivity of basophils to other serum factors such as IL-3 also impacts a newer assay testing CIU serum-induced basophil CD203c activation and adds to the confusion about defining the autoimmune CIU subset[3,26]. At the present, studies that predict clinical response to a therapy on the presence or absence of these autoimmune tests are lacking.

An ELISA test for IgG anti-FcεRIα autoantibodies showed similar frequencies in CIU subjects and those with other autoimmune skin diseases such as pemphigus vulgaris and dermatomyositis. However, different IgG subclasses (IgG2 and IgG4) are predominant in non-CIU subjects, suggesting functional differences[27]. Positive results with this ELISA were also seen in other types of urticaria and persisted in remission[28]. More recently, a sensitive immunoenzymetric assay (IEMA) has found similar titers and frequency of IgG anti-FcεRIα and IgG anti-IgE in CIU subjects and healthy controls while others have shown such autoantibodies are part of the natural repertoire of the immune system[29,30].

Role for blood basophils: Blood basophils represent less than 1% of circulating leukocytes. They are characterized by intracellular secretory granules containing histamine and surface IgE receptors. These cells are often recruited to sites of allergen-induced inflammation such as the lung, nose, and skin[31]. In a murine model of chronic allergic skin inflammation that utilizes multivalent allergen injection in the skin of a mouse that has been passively sensitized with allergen-specific IgE, the delayed onset of ear swelling and eosinophilic infiltration occurring two to four days after both early and late phase events was shown to be dependent on basophils[32]. This novel role for basophils in skin inflammation in the mouse is reminiscent of cutaneous hypersensitivity models involving basophils in the guinea pig[33,34].

Blood basopenia is commonly observed in CIU patients, and basophil numbers are inversely related to disease severity measures[35]. Basophils are recruited to both lesional and nonlesional skin biopsies of CIU subjects; this suggests the possibility that basopenia is related to the active recruitment of basophils to skin tissues[9,36]. Although the exact pathways for basophil recruitment to skin tissues in CIU are undefined, systemic corticosteroids are known to inhibit basophil recruitment to allergen-induced skin reactions[37]. Systemic corticosteroids rapidly reduce lesions in CIU and lead to increased blood basophil numbers, suggesting reduced basophil migration to the skin[35]. At present, it is unknown whether blood basophils in CIU reflect the state of the tissue basophil reflect a basophil that has recirculated from skin tissues, or simply a "bystander" of events occurring in the skin. In full disease remission, blood basophil numbers have been noted to rise to normal levels[29,38].

Several studies have also observed the paradoxical suppression of blood basophil FcεRI mediated histamine release in active CIU subjects[39]. Comparisons of blood basophils from active CIU subjects to healthy control subjects have consistently revealed a reduction in IgE receptor-induced histamine release (HR) by CIU basophils using cross-linking anti-IgE or anti-FcεRI antibodies[38,40-42]. In contrast, no significant difference in HR was seen with stimuli independent of the FcεRI pathway such as ionophore, 48/80, N-formyl-methionyl-leucyl-phenylalanine (FMLP), bradykinin, and monocyte chemoattractant protein (MCP-1)[40]. Therefore, a specific defect in the FcεRI signaling pathway of CIU basophils is favored. Further, basophil HR response to histamine-releasing factor (HRF), a distinct measure of hyper-

releasability, was rare among CIU subjects as previously noted in the basophils of atopic and asthmatic subjects[42]. Among the explanations for suppression of the basophil FcεRI pathway are that the basophils are desensitized in vivo to further FcεRI -induced activation. Recent insights into the dysregulated expression of molecules that are critical to signal propagation after IgE receptor activation (spleen tyrosine kinase, Syk) or those that are relevant to inhibition of receptor responses (Src homology 2 (SH2)-containing inositol phosphatases, SHIP-1, and SHIP-2) suggest a more complex picture. There was no significant difference between the amount of histamine per basophil in patients with CIU with or without autoantibodies or healthy control subjects[43].

Recently, a bimodal profile of CIU subjects' blood basophil anti-IgE HR response was reported[42]. Fifty percent of CIU subjects have significant reductions in their basophil HR with optimal anti-IgE stimulation (< 10% of total histamine content) and are designated anti-IgE nonresponders (CIU NR). The remaining 50% of CIU subjects have basophils that release greater than 10% of total histamine content after anti-IgE stimulation and are designated anti-IgE responders (CIU R). These functional differences were also related to altered protein expression of FcεRI inhibitory phosphatases, SHIP-1 and SHIP-2. Although the disease implications of basophil functional phenotypes are not fully apparent, some relevant associations with CIU disease activity have been established. A longitudinal study of CIU subjects has established the stability of the basophil IgE-receptor degranulation phenotypes (CIU R and CIU NR) in subjects with persistent disease[29]. In addition, clinical measures of CIU severity also segregate between CIU R and CIU NR subjects such as heightened itch scores reported by CIU R subjects[44]. In CIU subjects who enter natural disease remission, basophil anti-IgE-induced HR, and blood basophil numbers significantly increase[29,38]. Thus, there is ample evidence that basopenia and suppressed CIU basophil FcεRI -mediated degranulation occur in active CIU disease and improve in CIU remission. In disease remission, the rise in FcεRI -mediated histamine degranulation by blood basophils contrasts with the reduction in hyperreleasability by skin mast cells (see below)[45]. Recent data support the concept that distinct basophil degranulation phenotypes that are present in active disease are associated with an imbalance of FcεRI -regulating phosphatases. However, the status of FcεRI -signaling molecule expression and function during remission remains to be established. Nonetheless, the behavior of blood basophils appears to be a useful biomarker to uncover disease-related activity and pathways.

Role of skin mast cells: A central feature of CIU pathogenesis is mast cell degranulation with release of mediators such as histamine. The exact mechanisms leading to chronic mast cell activation in the generation of CIU lesions are unknown. Human in vivo studies are limited by the difficulties in obtaining large numbers of skin-tissue mast cells for studies. Recent alternatives include the use of cultured human mast cells derived from CD34+ progenitors or isolated from progenitors arising from human skin samples after prolonged culture in a cytokine-rich environment[46].

Skin mast cell numbers are not increased in CIU, but they have heightened releasability of histamine to stimuli such as 48/80 in active disease that reverts in remission[45,47]. Lesional skin biopsies in CIU show tissue edema, vascular dilatation, mast cell degranulation, and a perivascular infiltrate composed of CD3+, CD4+, and CD8+ lymphocytes, eosinophils, neutrophils, and basophils[9,10]. The skin pathology seen in CIU lesions resembles that of allergen-mediated late-phase skin reactions and supports the notion that IgE-receptor (FcεRI) activation of mast cells and basophils is involved in CIU. However, the cytokine profile in CIU shows expression of mRNA for both T-helper type 2 (Th2) [interleukin (IL)-4 and IL-5] and Th1 (interferon γ) cytokines[9].

A recent study on releasability utilizing mast cells cultured from the CD34+ cells in the peripheral blood of CIU R, CIU NR, and normal donors has found an increase in spontaneous HR after IgE sensitization among CIU-derived mast cells[48]. An analysis of the signaling molecules in the FcεRI pathway in these cultured mast cells revealed increased expression of Syk in the CIU R donor subset that is correlated to the degree of spontaneous HR. A study using skin-tissue-derived human skin mast cells examined the impact of IgE levels on IgE receptor function. The findings support the concept that the levels of IgE can contribute to skin mast cell sensitivity for IgE receptor degranulation in that significant release of mediators occurs at low levels of receptor cross-linking[49]. These findings carry implications for therapies involving reduction of IgE levels in CIU.

CIU Therapeutic Management

Traditional therapies: Currently, antihistamines, which generally work by alleviating the symptoms rather than enacting a cure, are the standard treatment for CIU[50]. With the recent advent of non-sedating or minimally sedating H1 receptor antagonists, some patients with CIU have found relief from symptoms without the adverse effect of excessive drowsiness[51]. Unfortunately, there are those whose urticaria does not respond to treatment with antihistamines, with some studies reporting a 5% to 12% failure rate with fexofenadine therapy[51,52]. The failure rate was even higher in a recent study that directly compared two of the modern antihistamines in the treatment of CIU. The failure rate was around 30% with levocetirizine and 40% with desloratidine[53]. Recent European consensus guidelines recommend increased antihistamine doses of up to 4-fold with difficult-to-treat CIU[54]. Increasing the dosage of levocetirizine and desloratadine up to 4-fold was found to improve CIU symptoms without compromising safety in approximately three quarters of patients with difficult-to-treat CIU[55]. For those individuals who fail treatment with H1 receptor antagonists, leukotriene antagonists and systemic corticosteroids may be used, with varying degrees of success[54,56].

Immunomodulators: The potential role of an autoimmune mechanism in some cases of CIU has led to the use of alternative therapies focusing on immunomodulation. Recent randomized trials have demonstrated the efficacy of cyclosporine in subjects with autoimmune features[57]. However, there is no clear evidence that the lack of such autoimmune features would prevent a therapeutic response, and at this time, a routine ASST as a predictive tool is not recommended, because the available large studies have found no correlation with response to cyclosporine[57,58]. There have also been smaller, uncontrolled studies indicating a potential benefit from dapsone, hydroxychloroquine, methotrexate and cyclophosphamide[59-63]. Over the last two decades, there have been sporadic case reports demonstrating successful alleviation of symptoms with the use of sulfasalazine[64,65]. A recent case series evaluating sulfasalazine therapy for fairly severe and recalcitrant CIU patients showed steroid-sparing effects and impressive reduction in urticaria in the majority of patients[66]. Omalizumab (anti-IgE) has now been shown to be dramatically effective in selected patients with chronic spontaneous urticaria[67-69]. Other immunomodulatory therapies, for which less evidence is available, include intravenous immunoglobulins (IVIG), azathioprine, mycophenolate mofetil, and tacrolimus have recently been reviewed[70].

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