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Eosinophilic Granulomatosis with Polyangiitis: Experiences in Korean Patients

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Eosinophilic granulomatosis with polyangiitis (EGPA) is one form of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. Identical to what has been called Churg-Strauss syndrome, EGPA exhibits both allergic and vasculitis features. EGPA was first described as a syndrome consisting of asthma, fever, eosinophilia, and organ involvement including heart failure, neuropathy, and kidney damage, by Churg and Strauss in 1951. On the basis of the 2012 Chapel Hill Consensus Conferences Nomenclature of Vasculitis, EGPA comprises three typical allergic components, including asthma, peripheral eosinophilia, and eosinophil-rich granuloma of the respiratory tracts. EGPA has three clinical and histological stages. The first is an allergic stage composed of asthma and sinusitis, and the second is an eosinophilic stage characterised by peripheral hypereosinophilia and intra-organ infiltration of eosinophils. The last is a vasculitic stage, including necrotising inflammation of small vessels and end-organ damage. In this review, we describe the classification criteria for EGPA and recommendations for the evaluation and management of EGPA with conventional and newly suggested drugs for EGPA. Also, we discuss a variety of clinical aspects such as predictive values for prognosis and associations with other Th2-mediated diseases and hepatitis B virus.

Key Words: Eosinophilic granulomatosis with polyangiitis, Churg-Strauss syndrome, classification, treatment, clinical aspects

INTRODUCTION

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) comprises a group of systemic necrotising vasculitides, that often involve small vessels, and lead to few or no immune deposits in affected organs.[1] AAV is classified into three variants such as microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), or eosinophilic GPA (EGPA) in accordance with clinical manifestations and histological features.[2] Of the three variants of AAV, EGPA, which is identical to what has been called Churg-Strauss syndrome, exhibits both allergic and vasculitis features. EGPA was first described as a syndrome consisting of asthma, fever, eosinophilia, and organ involvement, including heart failure, neuropathy, and kidney damage, by Churg and Strauss in 1951.[3] On the basis of the 2012 Chapel Hill Consensus Conferences Nomenclature of Vasculitis (the 2012 CHCC definitions), EGPA has been characterised as having three typical allergic components, including asthma, peripheral eosinophilia, and eosinophil-rich granuloma of the respiratory tracts.[1] EGPA has three clinical and histological stages: The first is an allergic stage composed of asthma and sinusitis. The second is an eosinophilic stage characterised by peripheral hypereosinophilia and intra-organ infiltration of eosinophils. The last is a vasculitic stage including necrotising inflammation of small vessels and end-organ damages.[4] For these reasons, in clinical settings, it can occasionally be confusing to distinguish EGPA from other allergic diseases and to select therapeutic regimens. In this review, we describe classification criteria and recommendations for the management of EGPA as well as currently used or attempted therapeutic regimens for EGPA. Also, we outline the results of recent studies on EGPA

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in Korean patients.

CLASSIFICATION CRITERIA AND DEFINITIONS

First, we should clarify our use of the term "definition of disease," "classification criteria," and "diagnostic criteria." Definition of disease means abnormalities in a patient that warrant assignment of a diagnostic term (name of disease), such as eosinophil-rich granuloma of the respiratory tract based on small-vessel necrotising vasculitis compatible with EGPA. Classification criteria are observations that classify a patient into a standardised category for study, such as four or more of the following six items for EGPA. Meanwhile, diagnostic criteria are an observation that demonstrates or confidently predicts the presence of the defining features of a disease in a patient.[1,5] Since 1951, when EGPA was first reported by Churg and Strauss, there have been several definitions and classification criteria for EGPA, and to date, there are no established definitive diagnostic criteria for EGPA.

In 1990, the first classification criteria for Churg-Strauss syndrome (or EGPA) were proposed by the American College of Rheumatology (the 1990 ACR criteria). The 1990 ACR criteria include the following six items: 1) asthma, 2) paranasal sinus abnormality, 3) peripheral blood eosinophilia (>10%), 4) unfixed pulmonary infiltration, 5) mononeuropathy or polyneuropathy, and 6) extravascular eosinophils on histology. When four or more items are satisfied, a patient can firmly be classified as EGPA. The sensitivity and specificity of the 1990 ACR criteria for EGPA have been reported as 85% and 99.7%.[6] Due to their high specificity, the 1990 ACR criteria for EGPA have been most widely used to date.

In 1994, the nomenclature of systemic vasculitis was proposed by CHCC (the 1994 CHCC definitions). The 1994 CHCC definitions first provided standardised nomenclature of vasculitides and subgroups using generally and widely used terminology. The 1994 CHCC definitions described EGPA as exhibiting eosinophil-rich and granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small to medium-sized vessels in association with asthma and eosinophilia.[5]

In 2007, a new algorithm for the classification of AAV and polyarteritis nodosa (PAN) was proposed by the European Medicine Agency (the 2007 EMA algorithm).

The first requirement is a follow-up duration for 3 months or greater. The second requirement is an age of onset over 16 years. The third requirement should meet all three of the following: 1) symptoms and signs compatible with AAV or PAN; 2) at least one of i) histological evidence of vasculitis, ii) ANCA positivity, iii) specific investigations strongly suggestive of vasculitis or granuloma, or iv) eosinophilia (>10% or >1.5×10^9/L); and 3) no other diagnosis to account for symptoms and signs. When all three entry requirements are satisfied, the algorithm may be started. The first step of the 2007 EMA algorithm is to apply the 1990 ACR criteria for Churg-Strauss syndrome (EGPA) to a patient.[7] As mentioned above, their high specificity enabled the 1990 ACR criteria for EGPA to be located on the top of the 2007 EMA algorithm. When a patient meets the 1990 ACR criteria for EGPA, the remaining steps, including GPA, MPA and classic PAN, are not applied any more.

In 2012, the revised nomenclature of systemic vasculitides was proposed by CHCC (the 2012 CHCC definitions). These definitions divided small vessel vasculitis into two groups including AAV and immune complex small vessel vasculitis. Thus, the 2012 definitions mentioned ANCA in the definitions of small vessel vasculitis for the first time. In addition, the 2012 CHCC definitions encouraged to use of myeoloperoxidase (MPO)-ANCA, proteinase 3 (PR3)-ANCA, and ANCA-negative as prefixes. Compared to the 1994 CHCC definitions, the 2012 CHCC definitions added three words (italicized text) as follow: EGPA is described as eosinophil-rich and *necrotizing* granulomatous inflammation *often* involving the respiratory tract, and necrotizing vasculitis *predominantly* affecting small to medium vessels in association with asthma and eosinophilia. This definition for EGPA emphasised concurrently existing necrosis and granulomatosis and suggested the frequencies of occurrence.[1]

In 2017, the ACR/European League Against Rheumatism (EULAR) provisional classification criteria for GPA was proposed by a group of Diagnostic and Classification Criteria for Primary Systemic Vasculitis (DCVAS) and collaborators (presented at 2016 ACR session: New Classification Criteria for ANCA-associated Vasculitis: implications for clinical practice). These criteria consist of nine items and a total score of 5 or greater enables patients to be classified as GPA. Different scores are attributed to each item: the highest score of 5 is assigned to PR3-ANCA or C-ANCA positivity. In contrast, negative scores are allocated to nasal polyp and peripheral blood eosinophilia ≥1 (×10^9/L) because both are clinical features favouring EGPA over GPA.[8] These criteria were initially developed to classify patients as GPA: however, they may be useful to distinguish GPA and EGPA. For instance, when a patient exhibits bloody nasal discharge (1), nasal polyp (-4), peripheral eosinophilia (-3), painful eye (1) and PR3-ANCA (5), the total score becomes 0. Therefore, GPA can be excluded by the ACR/EULAR 2017 provisional classification criteria for GPA in this patient. We suggest that the ACR/EULAR 2017 provisional criteria can be useful to exclude EGPA from GPA. However, these criteria should be applied next to the 2007 EMA algorithm and the 2012 CHCC definitions, as they are not fully validated and published.

RECOMMENDATIONS FOR MANAGEMENT OF AAV

In 2009, the EULAR recommendations for the management of

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primary small and medium vessel vasculitis were published. An expert group consisting of 17 experts from eight European countries and the United States made 15 recommendations.[9] These recommendations have been made for the evaluation, investigation, treatment and monitoring of patients with small and medium vessel vasculitis for use in daily clinical practice based on evidence and expert consensus. However, the strength of the EULAR recommendations was reduced due to the low quality of evidence and by EULAR standardised operating procedure.

In 2015, an international task force representing EULAR and the European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) developed the 2015 updated recommendations for the management of AAV. These new recommendations were based on 1691 papers including licensing of rituximab for AAV in the past 5 years. The 2015 EULAR/ERA-EDTA recommendation statements are modified and described.[10]

Among cases of organs or life-threatening AAV, plasma exchange should be considered in patients with rapidly progressive renal failure [serum creatinine >500 μmol/L (5.7 mg/dL)] or diffuse alveolar haemorrhage. Otherwise, a combination of cyclophosphamide or rituximab with glucocorticoid should be administered. In cases of non-organ threatening AAV, a combination of methotrexate or mycophenolate mofetil with glucocorticoid is recommended. When remission is achieved, azathioprine or methotrexate or rituximab are recommended as maintenance therapy and glucocorticoid should be continuously tapered. A combination of cyclophosphamide or rituximab with glucocorticoid should be started in patients with organ or life-threatening relapse. In patients with non-organ threatening relapse, a higher dose of glucocorticoid (intensification) and an alternative regimen (modification) are recommended. After 2 years from the initiation of treatment, azathioprine or methotrexate should be tapered and rituximab should be stopped if possible.[10]

RECOMMENDATIONS FOR EVALUATION AND MANAGEMT OF EGPA

The EGPA Consensus Task Force of experts from five European countries and the United States developed and provided the 22 EGPA-specific recommendations for the evaluation and management of EGPA. The recommendations are modified and summarised. Among recommendations, the use of glucocorticoids for achieving remission of EGPA was ranked on a level of evidence of A. In addition, two recommendations were ranked at a level of B. A combination of glucocorticoid with an immunosuppressant should be administered to patients with life-threatening EGPA and leukotriene-receptor antagonist can be used to patients with EGPA. Unexpectedly, plasma exchange was not recommended to ANCA positive EGPA patients with rapidly progressive glomerulonephritis or pulmonary–renal syndrome as strongly as MPA or GPA patients with those manifestations (level of evidence of D). Use of rituximab was also limited for ANCA-positive patients with renal involvement or refractory disease at level of evidence of C. These recommendations are important in that they focus on only EGPA patients not AAV.[11] The future updated version of recommendations will be expected to emphasise rituximab use and describe anti-interleukin (IL)-5 and anti-IL-5 receptor monoclonal antibodies, such as mepolizumab, reslizumab and benralizumab.

CONVENTIONAL AND BIOLOGICAL DRUGS FOR EGPA

So far there have been various clinical trials investigating new drugs as induction and maintain therapies beyond traditional immunosuppressive drugs such as cyclophosphamide and azathioprine in AAV patients. Among them, rituximab in ANCA-associated vasculitis (RAVE) and rituximab versus cyclophosphamide in ANCA-associated vasculitis (RITUXVAS) trials demonstrated that rituximab is not inferior to cyclophosphamide as an induction therapy and contributed to the approval of rituximab as a first-line treatment in newly diagnosed patients with severe AAV.[12,13] Cartin-Ceba, et al.[14] reported that rituximab was effective and safe for the induction and maintenance of remission in patients with refractory AAV. The maintenance of remission using rituximab in systemic ANCA-associated vasculitis (MAINRITSAN) 1 trial investigated the efficacy of rituximab as a maintenance therapy in newly diagnosed AAV patients. They compared the therapeutic potentials between rituximab (infusion, 500 mg every 6 months for 18 months) and azathioprine (oral 2 mg/kg/day until 22 months) after the induction therapy of cyclophosphamide, and demonstrated that rituximab was superior to azathioprine in maintenance therapy at 28 months.[15] Moreover, there are several more ongoing clinical trials for maintaining remission such as the RITAZAREM trial (rituximab versus azathioprine), the MAINTANCAVAS trial (rituximab), the REMAIN trial (extended period of azathioprine), and the MAINRITSAN trial (rituximab versus placebo).[16] However, these clinical trials have included only MPA and GPA patients and occasionally renal-limited AAV patients. Until most recently, there have been few clinical trials of new drugs for induction and maintenance therapy in EGPA due to its diverse and heterogeneous clinical features.[4,16]

Although there is no consensus on the strategies for selecting therapeutic regimens for induction and maintenance therapies for EGPA, a five-factor score (FFS), that was proposed by the French Vasculitis Study Group, has been used as a standard for the selection of therapeutic drugs.[17] In the multivariable analysis of various clinical manifestations, age >65 years [hazard ratio (HR) 3.3], renal insufficiency (creatinine ≥150 μmol/L, HR 1.5), gastrointestinal signs (HR 1.5), cardiac insufficiency

(HR 1.5), and ear, nose, and throat (ENT) manifestations (HR 0.5) were significantly associated with 5-year mortality. Accordingly, FFS consists of these five items, and a score of 1 is assigned to each item of age >65 years, renal insufficiency (creatinine ≥150 μmol/L), gastrointestinal signs, cardiac insufficiency and no ENT manifestations. The 5-year mortality rates in patients with FFS=0 and FFS=1 were assessed at 9% and 21%, respectively, whereas it was significantly elevated up to 40% in those with a FFS of 2 or greater.[18] Thus, the therapeutic strategy for EGPA is now being made based on FFS=0 or FFS>1. In non-severe EGPA patients, glucocorticoid has been recommended as both induction and maintenance therapies.[17,19] Azathioprine might be considered effective as a maintenance therapeutic regimen for EGPA, like MPA and GPA. However, a recent study reported that adding azathioprine to induction therapy with glucocorticoid did not increase remission rates, diminish relapse risk, or spare the dose of glucocorticoid in non-severe EGPA patients. The initial remission rate was assessed as 100% for azathioprine and 96.2% for placebo. Furthermore, a combination of glucocorticoid with azathioprine did not reduce the exacerbation rates of EGPA-related asthma and rhinosinusitis.[20] Thus, in patients with FFS=0, a monotherapy of glucocorticoid is currently recommended in both induction and maintenance therapy, whereas in severe EGPA patients with FFS >1, a combination of cyclophosphamide with glucocorticoid has been widely used as the first-line induction therapeutic regimen, with azathioprine as the maintenance therapeutic regimen.[21]

In patients with EGPA refractory to a combination induction therapy of cyclophosphamide and glucocorticoid, particularly in EGPA patients at a vasculitic stage, rituximab may be recommended in MPA and GPA.[17] In general, EGPA has been classically considered a Th2-mediated autoimmune disease.[22] Upregulated production of Th-2 cell-associated cytokines such as interleukin (IL)-4, IL-5, and IL-13, were demonstrated in peripheral T cells from active EGPA patients.[23,24] In contrast, in late EGPA patients at a vasculitic stage, the alteration of T cell populations occurs from Th2 cells to Th1 and Th17 cells and furthermore, an increased concentration of IL-17A was confirmed in late EGPA patients.[25] Therefore, it can be reasonably assumed that the use of rituximab in late EGPA patients may be as effective as in MPA and GPA patients.

There are currently two ongoing clinical trials of the efficacy of rituximab in EGPA patients. The first ongoing clinical trial is the rituximab in eosinophilic granulomatosis with polyangiitis (REOVAS) trial (phase III, comparative, multicentre, randomised, controlled, double-blind and superiority research).[26] The REOVAS trial has four arms, including rituximab with FFS=0, conventional therapy with FFS=0, rituximab with FFS≥1, and conventional therapy with FFS≥1, and seeks to compare its potential in induction therapy for EGPA (NCT 02807103). Another ongoing clinical trial (NCT 03164473) is seeking to compare the efficacy of rituximab with azathioprine as a maintenance therapeutic regimen for EGPA.[26] Rituximab has occasionally been tried for induction therapy in a few cases of EGPA refractory to cyclophosphamide and glucocorticoid in Korea despite no official published case reports. However, the use of rituximab has not been approved in Korea until now, and thus it is not covered by Korean National Health Insurance Service. We expect that based on positive results of currently conducted clinical trials on rituximab, the use of rituximab will be approved for use in EGPA patients in Korea soon.

IL-5 regulates the proliferation, maturation, and differentiation of eosinophils, and it plays a crucial role in the development and progression of EGPA.[27,28] Therefore, inhibiting IL-5-mediated signals may theoretically improve clinical symptoms of EGPA. Mepolizumab is an anti-IL-5 monoclonal antibody that binds to IL-5 and blocks the interaction between IL-5 and IL-5 receptor on the eosinophil surface.[29] Pilot studies have demonstrated that mepolizumab is effective in the treatment of EGPA.[30,31] Recently, the results of phase III randomized, placebo-controlled, double-blind, parallel-group clinical trial investigating the efficacy and safety of mepolizumab in relapsing or refractory EGPA have been reported. Mepolizumab (300 mg subcutaneous every 4 weeks) versus placebo, based on glucocorticoid with/without immunosuppressive therapy, had been administered to 68 participants for each group for 52 weeks. The two primary endpoints were the accrued weeks of remission during the study period and the proportion of participants in remission at weeks 36 and 48. Mepolizumab showed significantly more accrued weeks of remission than placebo (28% vs. 3% of the participants having ≥24 weeks of accrued remission [odds ratio (OR) 5.9] and a higher proportion of participants in remission at week 36 and 48 [32% vs. 3% (OR 16.7)]. Remission occurred in 53% of the participants in the mepolizumab group, whereas it occurred in only 19% of those in the placebo group. The time to first relapse over the 52-week period was significantly longer in participants with mepolizumab than in those with placebo. The annualized relapse rate was 1.14 in the mepolizumab group, compared to 2.27 in the placebo group (rate ratio 0.50). In addition, mepolizumab reduced the proportion of participants who had an average daily dose of prednisolone or prednisone of 4.0 mg or less per day during weeks 48 through 52 (OR 0.20). There were several limitations such as various doses of glucocorticoid or difficulty in observing the effect of mepolizumab on inflammatory markers due to glucocorticoid at entry and no standard assessment tool for EGPA. However, this trial contributed to the extended approval of the use of mepolizumab to treat adult patients with EGPA by the United States Food and Drug Administration.[32] In addition to mepolizumab, reslizumab (a monoclonal antibody against IL-5) and benralizumab (a monoclonal antibody against IL-5 receptor α) are being evaluated through clinical trials (NCT 02947945 and NCT 03010436).[26] Mepolizumab is only approved by the Korean Food and Drug Administration for severe asthma. In the near future, we expect that mepolizumab will be approved by the Korean Food and Drug Administration

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and may be a solution for refractory EGPA.

PREDICTIVE FACTORS FOR PROGNOSIS IN KOREAN PATIENTS WITH EGPA

A previous study investigated independent predictive factors for the prognosis of EGPA in Korean patients in 2013. They retrospectively reviewed the medical records of 52 Korean patients with EGPA. The most common organ affected by EGPA was the respiratory tract, followed by nerves. Clinical remission was achieved in 95.3% of patients, among whom 16.3% experienced relapse. Remission for more than 6 months was more often observed in patients with older age, diagnosis in an earlier stage, pulmonary manifestations, generalized symptoms, and high C-reactive protein than those without.[33] We included 30 Korean patients with EGPA and investigated the initial predictors at diagnosis of relapse during follow-up. Respiratory symptoms were common clinical manifestations, such as asthma (86.7%) and lung parenchymal involvement (76.7%). The mean FFS was 0.9, and a FFS of 1.0 was calculated as a cut-off to predict relapse of EGPA by a receiver operator characteristic curve. Finally, we demonstrated that relapse was more frequent in patients with FFS ≥1 than those with FFS <1 (68.8% vs. 7.1%, relative risk 28.6).[34]

COMPARISON BETWEEN ANCA-POSITIVE VERSUS ANCA-NEGATIVE EGPA

Cottin, et al.[35] retrospectively reviewed the medical records of 157 EGPA patients. They divided all patients into two groups based on the presence of ANCA and compared clinical and laboratory variables between the two groups. ANCA-positive EGPA patients more frequently exhibited weight loss, myalgia, and arthralgia than ANCA-negative EGPA patients. Also, ANCA-positive EGPA patients exhibited increased frequencies of definitive vasculitis, biopsy-proven necrotising vasculitis, necrotising glomerulonephritis or crescentic glomerulonephritis, haematuria, and leukocytoclastic capillaritis and/or eosinophilic infiltration of the arterial walls, compared to ANCA-negative EGPA patients. In addition, mononeuritis multiplex, myocarditis and renal disease were more often observed in ANCA-positive EGPA patients than those without ANCA. Sokolowska, et al.[36] also compared clinical features between 15 ANCA-positive and 3 ANCA-negative EGPA patients. At the time of diagnosis, ANCA-positive EGPA patients showed a higher rate of renal, cutaneous, and peripheral nervous manifestations than ANCA negative patients. However, ANCA positivity was not proven to affect the frequency of relapse.

In terms of Korean patients with EGPA, Kim, et al.[33] compared clinical features between ANCA-positive and negative patients. ANCA-positive EGPA patients showed a higher frequency of renal involvement than ANCA-negative EGPA patients. Meanwhile, we subdivided EGPA patients into MPO-ANCA-positive, PR3-ANCA-positive and ANCA-negative EGPA groups, and compared clinical features among them. A total of 36.7% of patients had MPO-ANCA and 10.0% had PR3-ANCA. Among clinical manifestations, MPO-ANCA-positive patients with EGPA exhibited a higher frequency of cutaneous manifestations than PR3-ANCA-positive and ANCA-negative patients (72.7% vs. 0% and 72.7% vs. 31.3%, respectively). Proteinuria (>1 g/day) was significantly more often observed in both MPO-ANCA-positive and PR3-ANCA-positive patients than in ANCA-negative patients (27.3% vs. 6.3% and 66.7% vs. 6.3%, respectively). In addition, MPO-ANCA-positive patients with EGPA showed a higher relapse rate than ANCA-negative patients with EGPA (54.6% vs. 25.0%).[34] Taking the results of the two previous studies together, in Korean patients with EGPA, ANCA positivity may be associated with skin and renal involvement for EGPA at diagnosis and with the occurrence of relapse during follow-up.

HYPEREOSINOPHILIC SYNDROME VERSUS EGPA

In daily clinical practice, it is not easy to distinguish between hypereosinophilic syndrome (HES) and EGPA, because they share similar clinical features, such as eosinophilia in the peripheral blood, paranasal sinusitis, and acute or chronic eosinophilic lung involvement.[6,37,38] The currently used diagnostic criteria for HES are the refined definitions of HES, which were proposed in 2010 (the 2010 definition of HES). The 2010 definition of HES consists of two items: one is peripheral blood eosinophilia >1500/mm^3 on at least two separate occasions or histological confirmation of tissue eosinophil infiltration associated with symptoms, and the other is exclusion of secondary aetiology of peripheral blood eosinophilia.[37] Thus, hypereosinophilia is not obligatory in cases of evident eosinophil infiltration in damaged end organs. So far, asthma or asthmatic history has been considered as a clue favouring EGPA based on the 2010 definition of HES and the 1990 ACR criteria for EGPA,[6,37] as asthma is one of the pre-existing aetiologies of hypereosinophilia. However, asthma can occur as end-organ damage of HES.[39] ANCA positivity can be definite evidence to distinguish EGPA from HES; however, the frequency of ANCA in EGPA has been reported as 40% approximately.[17] Thus, in a majority of cases, ANCA is not a good parameter for distinguishing between HES and ANCA-negative EGPA.

Meanwhile, HES is currently classified into six categories, such as myeloproliferative HES, lymphocytic HES, undefined HES, overlap HES, associated HES, and familial HES. The category of associated HES, which is composed of significant peripheral eosinophilia under the conditions known to provoke eosinophilia, includes EGPA, systemic mastocytosis, inflam-

matory bowel disease, sarcoidosis and human immunodeficiency virus infection.[40] Thus, because EGPA is included in the category of associated HES, and immunosuppressive drugs for allergic diseases, such as mepolizumab, are now approved for the treatment of EGPA, the boundary between the two diseases is becoming gradually obscure. We are now conducting a retrospective study to investigate a new laboratory value with which to help to distinguish HES from EGPA in Korean established patients. We have tentatively concluded that initial white blood cell and eosinophil counts may be useful markers with which to differentiate between the two diseases (unpublished).

IMMUNOGLOBULIN G4 AND EGPA

Humans express four subclasses of immunoglobulin (IgG), such as IgG1, IgG2, IgG3, and IgG4, and the proportion of IgG4 is at most approximately 5%.[41] Since both IgG4 production and early stage EGPA are primarily associated with the up-regulation of Th2 cytokines, enhanced serum IgG4 levels in patients with EGPA has been often reported.[42] A previous study investigated whether serum IgG4 levels might be associated with the disease activity or prognosis of EGPA. They included 24 patients with active EGPA and 22 patients with inactive EGPA. They also included 26 patients with GPA, 25 with atopic asthma, and 20 healthy people as controls. Serum IgG4 levels were significantly increased in patients with active EGPA, compared to controls, and furthermore, they were well correlated with the extent of organ damage and disease activity.[43] However, another previous longitudinal cohort study obtained blood samples from 25 patients with EGPA (105 visits) and demonstrated that serum IgG4 levels and IgG4/IgG ratio did not significantly reflect the current activity of EGPA in established patients.[44] Therefore, the role of serum IgG4 level as a biomarker to predict the current activity of EGPA still remains elusive.

Researchers have wondered whether elevated serum IgG4 levels in EGPA result in IgG4-related disease (IgG4-RD). High serum IgG4 level is one of the comprehensive diagnostic criteria for IgG4-RD: organ involvement, serum IgG4 level >135 mg/dL and $IgG4^+/IgG^+$ cells >40% or $IgG4^+$ cells/high power field >10 on tissues.[45] A previous study determined the frequency of IgG4-RD and other disease in patients with elevated serum IgG4 levels. Of 3300 patients, 158 (4.8%) patients showed elevated serum IgG4 levels (>140 mg/dL) and 29 of 158 patients (18.4%) were classified as definite and possible IgG4-RD.[46] Accordingly, in approximately 20% of patients with elevated serum IgG4 levels, IgG4-RD may occur.

Nonetheless, there have been few studies reporting the concomitant occurrence of IgG4-RD in EGPA patients. A previous multicentre observational study included 13 patients who were diagnosed with AAV and IgG4-RD. Of 18 patients, 13 patients were concomitantly diagnosed with both diseases. Among 18 patients, 14 patients were classified as GPA, 3 patients as MPA and only one patient as EGPA.[47] We reviewed the medical records of 12 EGPA patients who had serum IgG4 levels and histological results. The mean level of IgG4 was 1983.3 mg/dL and all EGPA patients exhibited serum IgG4 levels >135 mg/dL (min 151.1, max 5420.0). None of 12 EGPA patients satisfied comprehensive diagnostic criteria for IgG4-RD.[45] Therefore, we conclude that IgG4-RD rarely occurs in EGPA patients despite elevated serum IgG4 levels. We hypothesise that similar pathogenic mechanisms of EGPA and IgG4-RD may shift towards only one disease entity rather than both diseases simultaneously.

On the other hand, we wondered if IgG4-RD may be associated with AAV, excluding EGPA. We investigated whether elevated serum IgG4 levels are associated with concurrent IgG4-RD in Korean patients with MPA and GPA. Interestingly, 37% of MPA and GPA patients had elevated serum IgG4 levels at diagnosis. However, no patient with elevated serum IgG4 levels was classified as IgG4-RD based on comprehensive diagnostic criteria for IgG4-RD. We also provided an assumption that the cross-sectional IgG4 levels might reflect activity and inflammatory burden of Korean patients with MPA and GPA.[48] Taken together with these results, while serum IgG4 levels may be elevated in EGPA patients, they do not seem to be associated with the concurrent occurrence of IgG4-RD. In addition, serum levels of IgG4 may reflect the cross-sectional activity of AAV.

RESOLVED HEPATITIS B VIRUS IN EGPA

The prevalence of patients with resolved hepatitis B virus (HBV) infection, which refers to conditions of clearance of circulating hepatitis B surface antigen (HBsAg) and appearance of antibody to hepatitis B core antigen (anti-HBc) with or without antibody to HBsAg (anti-HBs) is approximately 60% in endemic areas, particularly in Korea.[49] Therefore, patients with resolved HBV infection had been exposed to HBV and achieved an immune response to control viral replication. So far, HBV has been known to be associated with polyarteritis nodosa and recently a new category of HBV associated vasculitis was established in 2012.[1,50] We previously reported that resolved HBV infection may influence vasculitis activity at diagnosis and subsequently relapse after remission in EGPA patients.[51] We referred to a previous report on Churg-Strauss vasculitis after hepatitis B vaccination[52] and assumed that resolved HBV infection might act as HBV vaccination. Resolved HBV infection might trigger the deterioration of the immune system, and initiate insidious allergic features and clinical symptoms of EGPA with a considerable time gap. If EGPA occurs after HBV reactivation, however, how do we classify this case? The satisfaction of four or more items of the 1990 ACR criteria for EGPA may assign this case as EGPA. However, given that antiviral agent

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should be necessary to control reactivated HBV, we believe that classifying this case as HBV associated vasculitis may be safer to the patient.

CONCLUSION

A considerable number of clinical features and pathogenic mechanisms of EGPA, HES and IgG4-RD overlap in that they are regulated by Th2 cell-mediated immune response. Moreover, EGPA belongs to small vessel vasculitis related to ANCA including GPA and MPA. Therefore, it is clinically important to distinguish EGPA from other diseases due to their different therapeutic and preventive strategies. So far, there have been noticeable advancements and changes in the classification criteria for GPA and MPA, although the 1990 ACR criteria for EGPA are still widely used due to their high sensitivity and specificity. In contrast with treatment strategies for GPA and MPA, those for EGPA have not keep pace. Recently, several clinical trials have demonstrated the efficacy of biological agents, such as rituximab and mepolizumab in EGPA patients. In the near future, we expect to be able to better cope with the maintenance of remission and prevention of relapse for EGPA with the new drugs that are currently being evaluated in clinical trials.

AUTHOR CONTRIBUTIONS

Conceptualization: Sang-Won Lee. Data curation: Chan-Bum Choi and Sang-Won Lee. Formal analysis: Chan-Bum Choi and Sang-Won Lee. Funding acquisition: Yong-Beom Park and Sang-Won Lee. Investigation: Chan-Bum Choi and Sang-Won Lee. Methodology: Sang-Won Lee. Project administration: Sang-Won Lee. Resources: Chan-Bum Choi and Sang-Won Lee. Software: Chan-Bum Choi and Sang-Won Lee. Supervision: Sang-Won Lee. Validation: Yong-Beom Park. Visualization: Chan-Bum Choi and Sang-Won Lee. Writing—original draft: Chan-Bum Choi and Sang-Won Lee. Writing—review & editing: Chan-Bum Choi, Yong-Beom Park and Sang-Won Lee.

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