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A novel treatment workflow of idiopathic hypereosinophilic syndrome: a single-center retrospective cohort study

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Hypereosinophilic syndrome (HES), a rare systemic disease, was first described in 1968. As a subtype of HES, idiopathic hypereosinophilic syndrome (IHES) is defined as hypereosinophilia of unknown cause, excluding tumor, infection, allergy, and immune system disease. In most cases, more than 1 organ is affected in patients with IHES.[1] The first-line drug for the treatment of IHES is glucocorticoid, which is effective for both hypereosinophilia and clinical manifestations.[2] However, when the outcome of hormone treatment is unsatisfactory, immunosuppressive or antineoplastic agents can also be administered.[3] Due to the low incidence of IHES, there is currently a lack of large-scale retrospective studies of the disease. We aimed to identify factors predictive of prognosis and determine the endpoint eosinophil (EOS) count after pharmacological therapy and the time at which a change of therapy should be considered following the failure of hormone treatment.

Forty-seven patients diagnosed as IHES or "unexplained HES, excluding other possible causes" were included in this study. IHES was diagnosed in accordance with the criteria of the Year 2011 Working Conference on Eosinophil Disorders and Syndromes,[4] which stipulates EOS counts of $>1.5 \times 10^9$/L blood at 2 examinations with an interval of ≥1 month, and/or tissue hypereosinophilia, organ damage and/or dysfunction attributable to tissue hypereosinophilia, and exclusion of other disorders or conditions as major causes of organ damage. The mean age of patients was 43.5 ± 17.2 years and 29.8% were female. Patients were recruited from Peking Union Medical College Hospital from 2002 to 2019. All patients underwent extensive diagnostic workup in accordance with the World Health Organization criteria. Before enrollment, all patients underwent detailed assessments, including medical history, physical examination, and laboratory examination, including complete blood count with differential; routine biochemistries; serology for human immunodeficiency virus, hepatitis B and C viruses; bone marrow biopsy; F/P fusion gene test, and anti-neutrophil cytoplasmic antibodies. We excluded cases of hypereosinophilia caused by medication or dietary supplements. This research was approved by ethic committee of Chinese Academy of Medical Sciences, Peking Union Medical College Hospital (No. S-k1934). Informed consent was waived because the patients did not receive any clinical intervention.

Patients were divided into 2 groups based on the extent of symptomatic improvement: patients who self-reported complete recovery (CR) of the chief complaint were defined as the CR ($n = 31$) group; patients who self-reported no or incomplete recovery (IR) of the chief complaint were defined as the IR ($n = 16$) group.

The normality of continuous data was tested by the Shapiro–Wilk test. Normal variables are presented as the average ± standard deviation and were analyzed by t test. Nonnormal variables are presented as the median (first quartile, third quartile) and were analyzed by nonparametric tests. Significant results were confirmed by multivariate logistic regression to predict prognosis factors. A P value of <0.05 was considered statistically significant. In receiver operating characteristic (ROC) analysis, the optimal cutoff value was selected to maximize the Youden index. Data were analyzed using SPSS v26.0 (Armonk, NY, USA).

The absolute EOS count before treatment was significantly different between CR and IR patients (4.65 [2.91,

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8.09] $\times 10^9$/L in CR; 12.11 [4.92, 19.10] $\times 10^9$/L in IR; $P < 0.01$), indicating that EOS level is relevant to the relief of clinical symptoms. Three binary logistic regression models were then conducted for further analysis. The first model included pretreatment EOS counts only; irrelevant variants were added in model 2 (heart rate and body temperature during acute stage) and model 3 (C-reaction protein and erythrocyte sedimentation rate). In all three models, pretreatment EOS count was regarded as an independent risk factor for IR of clinical symptoms.

The absolute EOS count after treatment was also significantly different between CR and IR groups (0.05 [0.02, 0.12] $\times 10^9$/L in CR; 1.80 [0.97, 3.30] $\times 10^9$/L in IR; $P < 0.01$). To identify the predictive value of EOS for unsatisfactory clinical outcome and the endpoint of treatment, we generated 2 ROC curves based on pretreatment and posttreatment EOS counts. The results indicated that posttreatment EOS was a relatively reliable sign for the endpoint of treatment (area under curve [AUC] = 0.916). We used the maximum Youden Index to select the endpoint of treatment (posttreatment EOS = 0.58 $\times 10^9$/L), with specificity and sensitivity of 96.8% and 87.5%, respectively. Among the patients whose posttreatment EOS level was $<0.58 \times 10^9$/L, approximately 94% recovered completely. However, pretreatment EOS showed unsatisfactory performance (AUC = 0.744). Currently, a clear indicator of treatment endpoint has not been proposed and decisions regarding drug reduction remain empirical in most cases. The endpoint proposed herein provides a subjective basis for clinical decisions.

To determine the time when hormone therapy should be changed to second-line drugs, we conducted survival analysis based on Cox analysis of 28 patients who received hormone therapy and recovered completely. Our findings showed that >80% of patients who ultimately responded to hormone treatment recovered within 10 days of glucocorticoid therapy initiation. Therefore, if clinical symptoms have not improved in 10 days after treatment, hormone therapy should be terminated and replaced by second-line drugs to avoid the side effects caused by prolonged hormone treatment.

In summary, we propose a new workflow for treatment of IHES by analysis of prognostic factors, including pre- and posttreatment EOS counts and determination of treatment endpoint and the optimal time at which to discontinue hormone therapy in favor of second-line drugs [Figure 1]. Our findings indicate an appropriate posttreatment endpoint EOS count of 0.58 $\times 10^9$/L. Previous studies have shown that with symptomatic control and reduction of EOS to below 1.5 $\times 10^9$/L, hormone therapy could be tapered.[5] However, we found that EOS count should be reduced to 0.58 $\times 10^9$/L to ensure the complete resolution of clinical symptoms. We also determined the optimal time at which to change treatment strategy on the basis of Cox survival analysis. Initially, hormone therapy should be recommended for all patients who can tolerate it, among whom approximately 70% could reach the endpoint (EOS level, 0.58 $\times 10^9$/L). In a multicenter study, 85% of HES patients who received corticosteroid monotherapy experienced complete or partial response after 1 month of treatment.[6] However, it has been reported in more recent studies that patients with IHES may respond to hormone therapy more quickly.[7] Our results indicate that if hormone therapy fails to elicit a response within 10 days, second-line drugs, such as antineoplastic/immunosuppressive agents, should be considered. Approximately 30% of patients treated with second-line drugs could also reach the endpoint of treatment. However, patients who recover completely still require maintenance treatment, and glucocorticoid is the most common option. Patients who do not respond to hormone or antineoplastic/immunosuppressive agents are defined as refractory IHES, and novel treatment, such as interferon or monoclonal antibodies should be considered, with Imatinib being the

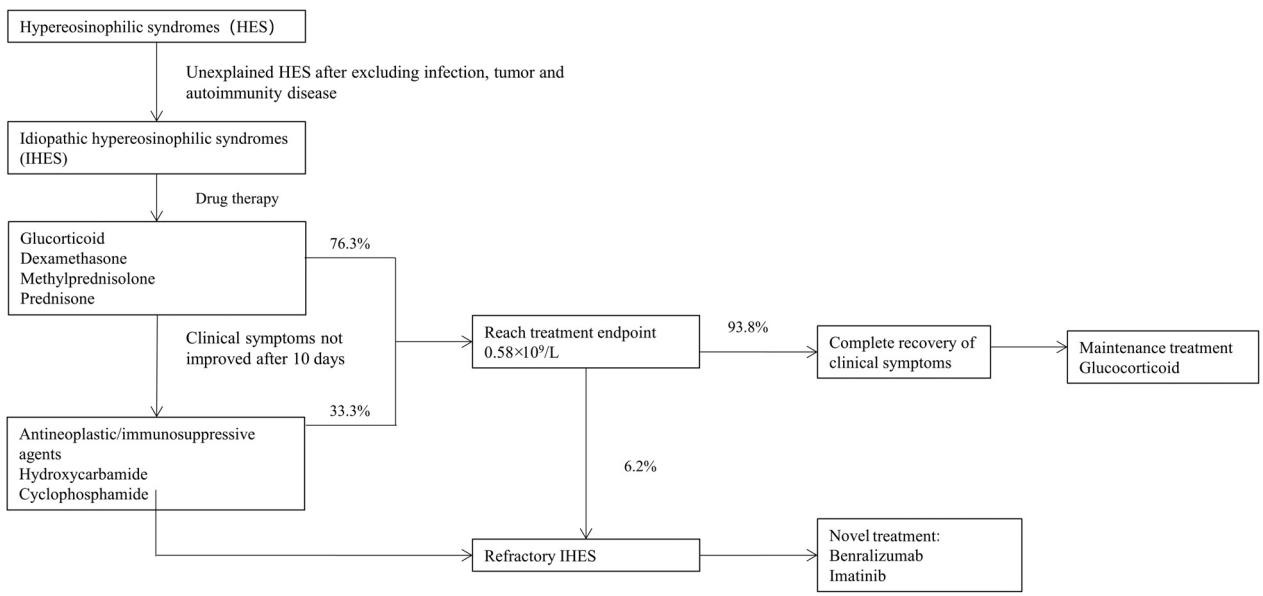

Figure 1: A novel workflow of IHES treatment. IHES: Idiopathic hypereosinophilic syndrome.

most commonly used monoclonal antibody for HES. It has been reported recently that benralizumab is another option for the treatment of IHES.[8]

In conclusion, we have documented the response time in patients receiving hormone therapy based on symptomatic improvement and explored the trends in recovery rate following hormone treatment over time, thus providing valid evidence for the introduction of second-line drugs in clinical practice.

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Conflicts of interest

None.

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