Allergology International 66 (2017) 116–122

Contents lists available at ScienceDirect

Allergology International

journal homepage: http://www.elsevier.com/locate/alit

Original article

Serum TARC levels are strongly correlated with blood eosinophil count in patients with drug eruptions

Takayoshi Komatsu-Fujii [a], Sakae Kaneko [a], Yuko Chinuki [a], Yohji Suyama [b], Masataka Ohta [a], Hiroyuki Niihara [a], Eishin Morita [a, *]

[a] Department of Dermatology, Shimane University Faculty of Medicine, Shimane, Japan
[b] Department of Laboratory Medicine, Shimane University Hospital, Shimane, Japan

ARTICLE INFO

Article history:
Received 16 March 2016
Received in revised form
2 June 2016
Accepted 7 June 2016
Available online 4 August 2016

Keywords:
Drug eruptions
Drug-induced hypersensitivity syndrome (DIHS)
Drug reaction with eosinophilia and systemic symptoms (DRESS)
Th2-type immune reaction
Thymus and activation-regulated chemokine (TARC)

Abbreviations:
TARC, thymus and activation-regulated chemokine; DIHS, drug-induced hypersensitivity syndrome; DRESS, drug reaction with eosinophilia and systemic symptoms; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; MPE, maculopapular exanthema; EM, erythema multiforme; WBC, white blood cell; RBC, red blood cell; TP, total protein; Alb, albumin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; Alp, alkaline phosphatase; γ-GTP, gamma-glutamyl transpeptidase; CK, creatinine kinase; BUN, blood urea nitrogen; Cr, creatinine; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein; ROC curve, receiver-operating characteristic curve; SD, standard deviation; CLEIA, chemiluminescent enzyme immunoassay

ABSTRACT

Background: This study aims to evaluate the relationship between serum thymus and activation-regulated chemokine (TARC) levels with various clinicopathological conditions in patients with drug eruptions. The value of TARC in diagnosing drug-induced hypersensitivity syndrome (DIHS) was also examined.

Methods: Study participants included 84 patients who presented with generalized eruptions suspected to be drug-related, including DIHS, Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), maculopapular exanthema (MPE), erythema multiforme (EM), erythroderma, and toxicoderma. The correlation coefficients between serum TARC levels and clinical parameters in peripheral blood samples were calculated.

Results: Serum TARC levels in patients with DIHS were higher than those found in patients with SJS/TEN, MPE, EM, and toxicoderma. TARC levels had 100% sensitivity and 92.3% specificity in diagnosing DIHS, with a threshold value of 13,900 pg/mL. Serum TARC levels positively correlated with age, white blood cell (WBC) count, neutrophil count, eosinophil count, monocyte count, atypical lymphocyte (Aty-ly) count, serum blood urea nitrogen (BUN) levels, and creatinine (Cr) levels. It negatively correlated with serum total protein (TP), albumin (Alb), and estimated glomerular filtration rate (eGFR). Among these clinical parameters, blood eosinophil counts were most strongly correlated with serum TARC levels, with a correlation coefficient of 0.53.

Conclusions: Serum TARC levels are well correlated with blood eosinophil counts in patients with generalized drug eruptions, indicating that Th2-type immune reactions underlie TARC production. Serum TARC measurements also have potent diagnostic value for DIHS, with high sensitivity and specificity.

* Corresponding author. Department of Dermatology, Shimane University Faculty of Medicine, 89-1 Enya-cho, Izumo, Shimane 693-8501, Japan.
E-mail address: emorita@med.shimane-u.ac.jp (E. Morita).
Peer review under responsibility of Japanese Society of Allergology.

http://dx.doi.org/10.1016/j.alit.2016.06.003

Introduction

Drug-induced hypersensitivity syndrome (DIHS) is a severe adverse drug eruption, which has biphasic aspects of allergic reaction to a drug and immune response to reactivation of a virus such as the human herpes virus type-6 (HHV-6). The diagnostic criteria for DIHS include seven clinical features: maculopapular rash, prolonged clinical symptoms, high fever, leucocyte abnormalities, liver dysfunction, lymphadenopathy, and HHV-6 reactivation.[1] However, early diagnosis of DIHS may prove difficult, not only because diagnostic criteria include prolonged symptoms, but also because its clinical features mimic maculopapular rash-type drug reactions or eruptions due to viral infection.[1]

Recently, thymus and activation-regulated chemokine (TARC), also known as CC chemokine ligand 17, has attracted attention as a potential biomarker for DIHS diagnosis. TARC is one of the CC chemokines that stimulates CC chemokine receptor 4 (CCR4), which is expressed on type 2 helper T (Th2) lymphocytes.[2] It recruits CCR4+ Th2-polarized T lymphocytes into sites of local inflammation, leading to a Th2-type immune response.[3–5] Regulatory T cells (Tregs) are also reported to express CCR4.[6] Since patients with atopic dermatitis (AD) show increased numbers of Th2 lymphocytes, serum TARC levels correlate with disease severity in AD.[7,8] In addition, stratum corneum TARC levels correlate with severity of local skin inflammation in patients with AD.[9]

Recently, it has been reported that serum TARC levels are higher in patients with DIHS than in patients with other severe drug eruptions including Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) and maculopapular exanthema (MPE).[10,11] It has also been reported that serum TARC levels can be used as a disease-specific diagnostic indicator of DIHS because elevated levels are observed, especially at an early stage.[12,13] However, studies to confirm the diagnostic value of serum TARC level for DIHS among patients with various types of drug eruptions, including erythema multiforme (EM) and erythroderma, are scarce. The association of serum TARC levels with pathophysiological aspects of drug eruptions also remains unknown.

In the current study, serum TARC levels were examined in 67 patients who presented with generalized drug eruptions, including DIHS, to confirm the diagnostic value for DIHS and to investigate the relationship of TARC to various clinical and laboratory parameters. Seventeen patients with toxicoderma, arising independently from drug eruptions, were also included.

Methods

Patients

Study participants included 84 patients (2–99 years; mean age 60.7 years) who presented with generalized eruptions suspected to be drug-related at Shimane University Hospital from April 2014 to September 2015. Of the 84 patients, 36 were male (3–89 years; mean age 61.4 years), and 48 were female (2–99 years; mean age 60.1 years). The diagnoses of DIHS and SJS/TEN were performed according to appropriate clinical criteria.[1,14] The diagnosis of toxicoderma was assigned when no causal relationship to a drug was detected, although initial clinical history and symptoms were suggestive of a drug eruption. Final diagnoses were assigned as follows: DIHS, 6 patients; SJS/TEN, 5 patients; MPE, 14 patients; EM, 37 patients; erythroderma, 5 patients; and toxicoderma, 17 patients. The background profiles of these patients are presented in Table 1 and Supplementary Table 1

The details of the study were fully explained to each patient or his/her guardian and written informed consent was obtained. This study was approved by the ethics committee of Shimane University Faculty of Medicine (Approval No. 1746).

Measurement of serum TARC levels

In order to measure serum TARC levels, a chemiluminescent enzyme immunoassay (CLEIA) was conducted, utilizing the HISCL® system (Sysmex, Hyogo, Japan) with a TARC assay kit (Shionogi, Osaka, Japan).[13] Serum TARC levels were examined at first visit to our clinic and at several time points thereafter. Maximum serum TARC levels represent the value reported for each patient.

Laboratory tests

Peripheral blood testing and biochemical examination were performed during the study and results obtained within the same week. From these results, maximum TARC levels were evaluated for correlation with serum TARC levels. The following biological parameters were evaluated: white blood cell (WBC) count; neutrophil count; eosinophil count; basophil count; monocyte count; lymphocyte count; atypical lymphocyte (Aty-ly) count; red blood cell (RBC) count; haemoglobin (Hb) level; platelet count; serum total bilirubin (T-bil) level; total protein (TP) level; albumin (Alb) level; aspartate aminotransferase (AST) level; alanine aminotransferase (ALT) level; lactate dehydrogenase (LDH) level; alkaline phosphatase (Alp) level; gamma-glutamyl transpeptidase (γ-GTP) level; creatinine kinase (CK) level; blood urea nitrogen (BUN) level; creatinine (Cr) level; C-reactive protein (CRP) level; total IgE level; and estimated glomerular filtration rate (eGFR). The eGFR was calculated according to the following equations, which were proposed for estimating renal function of Japanese patients: $194 \times Cr^{-1.094} \times Age^{-0.287}$ for male patients; $194 \times Cr^{-1.094} \times Age^{-0.287} \times 0.739$ for female patients.[15]

Data analysis

Unless otherwise indicated, data are presented as mean ± standard deviation (SD). Statistical analysis was conducted with SPSS software (version 22, Chicago, IL, USA). The Mann–Whitney *U*-test was used for analysis between two groups. The Spearman's rank correlation test was used for analysis of correlation. Results were considered significant when $^{*}P < 0.05$, $^{**}P < 0.02$ and $^{***}P < 0.002$.

Table 1
Background of the patients ($n = 84$).

	DIHS	SJS/TEN	MPE	EM	Erythroderma	Toxicoderma
n	6	5	14	37	5	17
TARC (pg/mL)	31,713.8 ± 28,310.7	4702 ± 3582.1	5822.5 ± 9990.4	3748.6 ± 6561.9	11,605.5 ± 7341.9	1209.7 ± 1186.8
Age (years)	76.0 ± 13.3	68.0 ± 24.0	53.7 ± 20.8	62.8 ± 22.4	69.0 ± 11.9	52.3 ± 26.7
Time lag of TARC measurement after onset (days)	11.6 ± 5.0 ($n = 5$)	11.0 ± 12.0 ($n = 5$)	5.5 ± 8.5 ($n = 13$)	7.9 ± 9.5 ($n = 34$)	8.0 ± 5.7 ($n = 2$)	8.0 ± 11.3 ($n = 17$)

Data are presented as mean ± standard deviation (SD). DIHS, drug-induced hypersensitivity syndrome; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; MPE, maculopapular exanthema; EM, erythema multiforme. TARC, thymus and activation-regulated chemokine.