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CORRELATION ANALYSIS OF THE TH17/TREG RATIO, LECT2, CXCL10 AND LIVER FUNCTION IN PATIENTS WITH AIH

ANALIZA KORELACIJE ODNOSA TH17/TREG, LECT2, CXCL10 I FUNKCIJE JETRE KOD PACIJENATA SA AUTOIMUNIM HEPATITISOM

Wei Zhang[1], Anqing Luo[2], Yanfang Wei[3], Xue Su[3], Zhengdeng Li[3], Huimei Yao[4], Xin Tian[4], Sheng Zheng[5]

[1]Department of Hepato-Biliary Surgery, the First People's Hospital of Chuzhou, No. 369, Zuiweng West Road, Nanqiao District, Chuzhou City 239001, China
[2]Department of General Surgery, Lianshui People's Hospital of Kangda College Affiliated to Nanjing Medical University, No. 6 Hongri Avenue, Lianshui County, Huaian City 223400, China
[3]Graduate School of Clinical Medicine, Dali University, No. 2 Hongsheng Road, Ancient City, Dali City 671000, China
[4]Department of Gastroenterology, Peking University Shenzhen Hospital, No. 1120, Lianhua Road, Futian District, Shenzhen City 518036, China
[5]Department of Gastroenterology, the Third People's Hospital of Yunnan Province, No. 292 Beijing Road, Guandu District, Kunming City 650011, China

Summary

Background: To analyse the relationships between the ratios of helper T-cell 17/regulatory T-cell (Th17/Treg), serum leukocyte-derived chemokine 2 (LECT2), and chemokine ligand 10 (CXCL10) and liver function and posttreatment response in patients with autoimmune hepatitis (AIH).
Methods: For the case group, 102 AIH patients admitted to our hospital between January 2022 and January 2024 were selected. The control group consisted of an additional 100 healthy people who were examined throughout the same time period. The Th17/Treg ratios, serum LECT2 and CXCL10 levels, and indicators of liver function were examined between the case and control groups. Pearson correlation analysis was used to examine correlations among peripheral blood Th17/Treg ratios, serum LECT2 and CXCL10 levels, and liver function indicators. Additionally, based on their responses after treatment, all patients were divided into two groups: 25 patients had poor responses, and 77 had good responses. Using multivariate logistic regression, the risk factors for a poor reaction were examined.

Kratak sadržaj

Uvod: Analiziran je odnos između racija pomoćničkih T ćelija 17/regulatornih T ćelija (Th17/Treg), nivoa leukocitima derivisanog hemoatraktanta 2 (LECT2) i hemokinskog liganda 10 (CXCL10) sa funkcijom jetre i postterapijskim odgovorom kod pacijenata sa autoimunim hepatitisom (AIH).
Metode: U posmatranu grupu su uključena 102 pacijenta sa AIH primljena u našu ustanovu između januara 2022. i januara 2024. Kontrolnu grupu je činilo dodatnih 100 zdravih osoba pregledanih u istom periodu. Upoređivani su odnosi Th17/Treg, nivoi LECT2 i CXCL10 u serumu, kao i parametri funkcije jetre između posmatrane i kontrolne grupe. Korišćena je Pirsonova korelaciona analiza za ispitivanje povezanosti odnosa Th17/Treg u perifernoj krvi, nivoa LECT2 i CXCL10 u serumu sa pokazateljima funkcije jetre. Dodatno, na osnovu odgovora na terapiju nakon lečenja, svi pacijenti su podeljeni u dve grupe: 25 pacijenata sa slabim odgovorom i 77 sa dobrim odgovorom. Multivarijantnom logističkom regresijom analizirani su faktori rizika za slab terapijski odgovor.

Address for correspondence:

Sheng Zheng
Department of Gastroenterology, the Third People's Hospital of Yunnan Province
No. 292 Beijing Road, Guandu District, Kunming City 650011, China
e-mail: zheng_sheng523@sina.com

Results: The Th17/Treg ratio and the serum LECT2, CXCL10, aspartate aminotransferase (AST), and the case group's alanine aminotransferase (ALT) levels were greater than the control group's ($P<0.05$). Patients in the case group had reduced Th17/Treg ratios, LECT2, CXCL10, AST, and ALT levels after 4 weeks of treatment compared to those who started treatment 1 day earlier ($P<0.05$). Pearson correlation analysis revealed that AST and ALT levels were positively correlated with the Th17/Treg, LECT2, and CXCL10 ratios ($P<0.05$). Univariate analysis revealed that the Th17/Treg ratio and LECT2, CXCL10, AST, ALT, and IgG levels were associated with the response of AIH patients after treatment ($P<0.05$). An increased Th17/Treg ratio was one of the risk variables for poor treatment response in AIH patients, according to multivariate logistic regression analysis, elevated LECT2, elevated CXCL10, elevated AST, elevated ALT, and elevated IgG ($P<0.05$).

Conclusions: The Th17/Treg ratio, serum LECT2, and CXCL10 levels are closely related to liver function and post-treatment response in patients with AIH. They can be used as biological indicators to assist in diagnosing AIH patients and evaluating posttreatment response.

Keywords: autoimmune hepatitis, the ratio of helper T cells 17 to regulatory T cells, leukocyte-derived chemokine 2, chemokine ligand 10, immune response

Rezultati: Odnos Th17/Treg, kao i nivoi LECT2, CXCL10, aspartat aminotransferaze (AST) i alanin aminotransferaze (ALT) u posmatranoj grupi su bili viši u poređenju sa kontrolnom grupom ($P<0,05$). Nakon 4 sedmice terapije, pacijenti su pokazali sni ene vrednosti odnosa Th17/Treg, kao i nivoe LECT2, CXCL10, AST i ALT u poređenju sa prvim danom lečenja ($P<0,05$). Pirsonova analiza je pokazala da su vrednosti AST i ALT pozitivno korelirane sa odnosom Th17/Treg, te nivoima LECT2 i CXCL10 ($P<0,05$). Univarijantna analiza je pokazala da su odnos Th17/Treg, te nivoi LECT2, CXCL10, AST, ALT i IgG povezani sa terapijskim odgovorom pacijenata sa AIH nakon lečenja ($P<0,05$). Prema multivarijantnoj logističkoj regresiji, povećan odnos Th17/Treg, kao i povišeni nivoi LECT2, CXCL10, AST, ALT i IgG predstavljaju faktore rizika za slab terapijski odgovor kod pacijenata sa AIH ($P<0,05$).

Zaključak: Odnos Th17/Treg, kao i nivoi LECT2 i CXCL10 u serumu su blisko povezani sa funkcijom jetre i terapijskim odgovorom kod pacijenata sa AIH i mogu se koristiti kao biološki pokazatelji pri dijagnostici AIH i proceni odgovora na terapiju.

Ključne reči: autoimuni hepatitis, odnos pomoćničkih T ćelija 17 i regulatornih T ćelija, hemoatraktant 2 poreklom iz leukocita, hemokinski ligand 10, imuni odgovor

Introduction

Autoimmune hepatitis (AIH) mainly refers to chronic liver disease caused by abnormal autoimmune function (1). This disease is more common in women and is to some extent influenced by genetic, environmental and other factors. With the deepening of related research in recent years, some studies (2–4) have shown that immune dysregulation may drive autoreactive lymphocytes to produce autoantibodies and various cytokines, leading to liver damage and ultimately triggering a series of clinical symptoms. Helper T 17 (Th17) and regulatory T (Treg) cells are in a dynamic balance that is essential for preserving the body's immunological milieu and is implicated in the onset and progression of several autoimmune and hepatic disorders (5). At present, leukocyte-derived chemokine 2 (LECT2) is generally believed to be a liver factor. It can mediate the pathogenesis of AIH by regulating cell growth and differentiation, thereby exerting immunoregulatory effects (6). Other studies (7–9) have shown that Chemokine ligand 10 (CXCL10) is a key proinflammatory factor in the onset and progression of several autoimmune disorders.

The body's own immune response mediates the chronic inflammatory liver condition known as autoimmune hepatitis (AIH) (10). Its exact cause is unknown, and it is characterised mainly by liver cell damage, elevated serum transaminase, hyperimmunoglobulinemia and positive autoantibodies. If AIH is not diagnosed in time and is effectively controlled, it can progress to liver cirrhosis or even liver failure, seriously threatening the patient's health (11). At present, the diagnosis of AIH mainly relies on a comprehensive assessment of clinical manifestations, biochemical markers, autoantibody profiles, and liver histopathology. However, its pathogenesis is complex and highly heterogeneous, and specific, ideal biomarkers that accurately reflect disease activity, predict treatment response, and predict prognosis are lacking (12–14). In recent years, imbalances in immune regulation have played a core role in the pathogenesis and progression of AIH. Th17 cells promote inflammatory damage, whereas Treg cells exert immunosuppressive effects. In addition, several novel cytokines and chemokines are attracting increasing attention (15). Leukocyte chemokine 2 (LECT2) is highly expressed in the liver and is involved in the progression of various liver diseases. CXC chemokine ligand 10 (CXCL10), a key chemokine induced by interferon-γ, plays a significant role in recruiting immune cells to the inflammatory site (16). All of these factors may be closely related to liver inflammatory activity and the immune microenvironment (17).

To explore the correlation between the serum Th17/Treg ratio and the concentrations of LECT2 and CXCL10 and key liver function indicators (ALT, AST, TBil, Alb, etc.) in patients with AIH, to understand the immunopathological mechanism of AIH in detail. To evaluate the potential value of these indicators in reflecting disease activity, predicting the severity of liver injury and monitoring treatment response, and to provide a new theoretical basis and possible clinical tools for the precise diagnosis, treatment, and individualised management of AIH.

Materials and Methods

General information

From January 2022 to January 2024, 102 patients with AIH were admitted to our hospital; 30 males and 72 females were selected as the case group. The ages ranged from 22 to 58 years, with an average of 38.43±5.06 years.

Inclusion criteria: (1) Adhere to the »Consensus on the Diagnosis and Treatment of Autoimmune Hepatitis (2022)« about the diagnostic criteria for autoimmune hepatitis (AIH); (2) Age >18 years old; (3) No relevant treatment was received before enrolment; (4) The medical records are complete. Exclusion criteria: (1) Combined with other types of liver diseases or (and) other autoimmune diseases; (2) Accompanied by cardiovascular and cerebrovascular complications; (3) Poor compliance; (4) Abnormal consciousness.

With an average age of 38.57±5.12 years, the ages varied from 21 to 58. The two groups were equivalent (P>0.05). Each research participant signed an informed consent form, and the hospital ethics review committee approved this study (AZWJC18059).

Laboratory testing methods

(1) Specimen collection:

After admission, 10 mL of fasting venous blood was collected from each subject and divided into two equal parts. One part was reserved for the detection of Th17 and Treg cells in peripheral blood, and the other was centrifuged to obtain serum, which was stored at -80 °C in a low-temperature refrigerator for future use. The centrifugation radius was 8 cm, the speed was 3,500 r/min, and the duration was 10 minutes.

Detection of Th17 and Treg cells in peripheral blood:

Ficoll isolation solution was used to isolate and obtain peripheral blood mononuclear cells, and the number of cells was adjusted to 2×106 cells/mL as appropriate. Then, 100 ng/mL verboxylate and 1 μg/mL ionomycin were added, the mixture was mixed well, and the mixture was incubated in a carbon dioxide incubator for 60 minutes. Then, one μL/mL monensin was added, and the mixture was cultured for 5 hours. The cells were evenly divided into two parts, and the relevant monoclonal antibodies were added. Th17 and Treg cells were detected by flow cytometry, and the ratio of these two cell types was calculated.

Serum LECT2 and CXCL10 detection:

Serum levels of LECT2 and CXCL10 were measured by enzyme-linked immunosorbent assay. Every procedure was completed in compliance with the reagent kits' instructions. The relevant reagent kits were all purchased from Shanghai Jianglai Biotechnology Co., Ltd.

Liver function test:

An AU5800 fully automatic biochemical analyser (purchased from Beckman Coulter, USA) was used to measure the levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT).

Serum immunoglobulin (Ig) detection:

Serum IgG levels were measured by enzyme-linked immunosorbent assay. The kit was purchased from Wuhan Saipei Biotechnology Co., Ltd. The above indicators for the case group were measured once daily before treatment and 4 weeks after treatment.

Posttreatment response assessment

All patients with AIH were given combined treatment consisting of prednisolone and azathioprine. After 4 weeks of treatment, the response was evaluated, and the response determination criteria were based on the relevant standards formulated in the »Consensus on the Diagnosis and Treatment of Autoimmune Hepatitis (2022)«. Based on their responses after treatment, all patients were divided into two groups: 25 patients had poor responses, and 77 had good responses.

Statistical analysis

Data analysis was conducted using SPSS 26.0. Measurement data conforming to a normal distribution are expressed as $\bar{x}\pm s$, and a t-test was used for comparisons between groups. Count data were expressed as counts or percentages, and the χ^2 test was used for comparisons between groups. Pearson correlation analysis was used to examine correlations among Th17/Treg ratios in peripheral blood, serum LECT2 levels, CXCL10 levels, and liver function indicators. Analysis of the variables predicting poor response was done using univariate and multivariate logistic regression models.

Results

Comparison of the Th17/Treg ratio, serum LECT2 and CXCL10 levels, and liver function indices between the case group and the control group

The case group's Th17/Treg ratio, LECT2, CXCL10, AST, and ALT levels were higher than the control group's (P<0.05), as shown in *Table I*.

The patients in the case group exhibited obvious characteristics of immune imbalance. The ratio of

Table I Comparison of Th17/Treg ratio, serum LECT2, CXCL10 and liver function index levels.

Group	n	Th17/Treg ratio	LECT2 (ng/mL)	CXCL10 (pg/mL)	AST (IU/L)	ALT (IU/L)
Case group	102	0.17±0.03	27.48±4.39	62.74±4.19	416.55±42.38	450.71±50.68
Control group	100	0.13±0.01	20.58±3.11	23.48±2.62	20.62±5.14	21.50±5.27
t		12.661	12.867	79.664	92.753	84.241
P		<0.001	<0.001	<0.001	<0.001	<0.001

Table II Comparison of Th17/Treg ratio, serum LECT2, CXCL10, and liver function index levels before and after treatment in the case group.

Time	n	Th17/Treg ratio	LECT2 (ng/mL)	CXCL10 (pg/mL)	AST (IU/L)	ALT (IU/L)
1 day before treatment	102	0.17±0.03	27.48±4.39	62.74±4.19	416.55±42.38	450.71±50.68
After 4 weeks of treatment	102	0.14±0.02	24.12±3.62	45.10±3.45	139.26±10.45	155.69±14.78
t		8.403	5.964	32.824	64.159	56.440
P		<0.001	<0.001	<0.001	<0.001	<0.001

helper T cell 17 to regulatory T cell (Th17/Treg) in their peripheral blood was significantly higher than that in the healthy control group, suggesting that the homeostasis of proinflammatory and anti-inflammatory immune responses was disrupted in the patients. Meanwhile, the levels of leukocyte-derived chemokine 2 (LECT2) and CXC chemokine ligand 10 (CXCL10) in the serum of patients in the case group were also significantly increased, reflecting a more active inflammatory response state. In terms of liver function, the levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in the case group were significantly higher than those in the control group, directly reflecting the intensification of liver cell damage in patients with AIH.

Comparison of the Th17/Treg ratio, serum LECT2 and CXCL10 levels, and liver function indices before and after treatment in the patient group

Patients in the case group had reduced Th17/Treg ratios, LECT2, CXCL10, AST, and ALT levels after 4 weeks of treatment compared to 1 day before treatment ($P<0.05$), as shown in *Table II*.

After short-term standardised treatment, the patient's multiple key biological indicators showed a significant improvement trend. The imbalance between helper T cell 17 and regulatory T cells (Th17/Treg) in the patient's peripheral blood decreased significantly after treatment compared with before, suggesting that immunosuppressive therapy helps restore the balance between proinflammatory and anti-inflammatory immune responses. Meanwhile, the levels of serum markers reflecting inflammatory responses – leukocyte-derived chemokine 2 (LECT2) and CXC chemokine ligand 10 (CXCL10) – also significantly decreased after treatment, indicating that the treatment effectively inhibited the activation of related inflammatory pathways. Most intuitively, the serum liver function indicators representing the degree of liver cell damage, including alanine aminotransferase (ALT) and aspartate aminotransferase (AST), also showed a significant decrease simultaneously after treatment, directly reflecting the repair of liver parenchymal damage and the improvement of liver function.

Correlation analysis of the Th17/Treg ratio, serum LECT2 and CXCL10 levels and liver function indicators

Pearson correlation analysis revealed that AST and ALT levels were positively correlated with the Th17/Treg ratio and LECT2 and CXCL10 levels ($P<0.05$), as shown in *Table III*.

The changes in the levels of core serological markers reflecting hepatocyte injury – alanine aminotransferase (ALT) and aspartate aminotransferase (AST) – showed a significant positive correlation with multiple immune-inflammatory indicators. The increase in the ratio of helper T cells 17 to regulatory T cells (Th17/Treg) in peripheral blood, the rise in serum leukocyte-derived chemokine 2 (LECT2) levels,

Table III Correlation analysis between Th17/Treg ratio, serum LECT2, CXCL10 levels and liver function indicators.

Indicator	AST		ALT	
	r	P	r	P
Th17/Treg ratio	0.581	<0.001	0.574	<0.001
LECT2	0.624	<0.001	0.562	0.001
CXCL10	0.606	<0.001	0.507	0.025

Table IV Univariate analysis of factors influencing treatment response in AIH patients [n (%)].

Group	n	Gender		Th17/ Treg ratio	LECT2 (ng/mL)	CXCL10 (pg/mL)	AST (IU/L)	ALT (IU/L)	IgG (g/L)
		Male	Female						
Poor response group	25	7 (28.00)	18 (72.00)	0.20±0.04	32.34±4.85	72.31±6.28	488.27±44.15	507.37±58.97	27.54±3.25
Good response group	77	23 (29.87)	54 (70.13)	0.16±0.02	25.86±4.05	59.53±4.02	392.17±30.49	43240±34.58	22.78±2.95
t		0.032		6.625	6.615	11.905	12.183	7.800	6.837
P		0.858		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Table V Analysis of factors influencing poor treatment response in AIH patients by multivariate logistic regression.

Factor	β	SE	Wald x^2	P	OR	95% CI
Th17/Treg ratio	0.783	0.278	14.586	<0.001	2.189	1.395 6.208
LECT2	0.621	0.258	16.289	<0.001	1.860	1.455 5.278
CXCL10	0.645	0.359	17.341	<0.001	1.906	1.204 6.179
AST	0.871	0.267	6.209	0.008	2.389	1.495 3.849
ALT	0.778	0.209	7.291	<0.001	2.178	1.596 3.116
IgG	0.584	0.341	7.991	<0.001	1.794	1.204 2.389

and the increase in the concentration of CXC chemokine ligand 10 (CXCL10) were all accompanied by a significant increase in AST and ALT levels. This significant positive association indicates that the disruption of the Th17/Treg immune balance in patients and the activation degree of inflammatory responses mediated by LECT2 and CXCL10 are closely related to the severity of liver parenchymal injury.

Univariate analysis of factors influencing treatment response in patients with AIH

According to *Table IV*, univariate analysis showed that the Th17/Treg ratio and LECT2, CXCL10, AST, ALT, and IgG levels were unrelated to sex (P>0.05) but were associated with treatment response in AIH patients (P<0.05).

There is a significant correlation between the baseline levels of multiple biological indicators of patients before treatment and their final therapeutic effects. The higher ratio of helper T cells 17/ regulatory T cells (Th17/Treg) in peripheral blood before treatment, the level of serum leukocyte-derived chemokine 2 (LECT2), the concentration of CXC chemokine ligand 10 (CXCL10), and the levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), which reflect the degree of hepatocyte injury All were found to be associated with poorer treatment responses. In addition, an increase in serum immunoglobulin G (IgG) levels before treatment was associated with adverse treatment outcomes.

Multivariate logistic regression analysis of the factors influencing poor treatment response in AIH patients

The treatment response of AIH patients was used as the dependent variable, with values assigned as follows: poor response = 1, good response = 0. Using the univariate analysis's indicators that show statistically significant differences as independent variables, the values are assigned as follows: an increase in the Th17/Treg ratio =1 and a decrease =0; LECT2 increase =1 and no =0; CXCL10 increase =1 and no =0; an increase in AST =1 and a decrease =0; elevated ALT =1 and no =0; and elevated IgG =1 and no =0. Multivariate logistic regression analysis revealed that the risk factors for poor treatment response in AIH patients included an elevated Th17/Treg ratio, elevated LECT2, elevated CXCL10, elevated AST, elevated ALT, and elevated IgG ($P<0.05$), as shown in *Table V*.

Discussion

At present, the specific pathogenesis of AIH is not yet clear. Currently, it is generally believed to be related to factors such as autoantigens, genetics and immunity. Some studies suggest that if the transaminase level of AIH patients remains twice the upper limit of normal after treatment, the treatment has failed; that is, the response is poor (18–20). Among them, steroid-based immunosuppressive therapy is the standard of care for AIH treatment. However, some patients receiving this protocol may have a poor response, increasing the economic burden on patients' families and society (21–23). Therefore, it is extremely important to identify potential biomarkers to evaluate poor treatment response in patients with AIH effectively. The Th17/Treg ratio is a reliable indicator of the body's immune function. It mainly regulates the expression of proinflammatory cytokines and anti-inflammatory cytokines in the body, further mediating the occurrence and development of immune diseases (24). LECT2 was first widely studied because of its abnormal expression in liver cancer, and is an effective marker for diagnosing liver cancer. It exerts a regulatory effect on inflammation and may play a crucial role in the development and progression of AIH. CXCL10 mediates processes such as cell adhesion and migration, possibly regulating the recruitment of effector and regulatory cells, and further participates in the body's immune response (25).

Th17 cells are closely associated with the release of proinflammatory cytokines, including IL-17, IL-6, and IL-23. Tregs are related to the secretion of anti-inflammatory cytokines such as IL-10 and transforming growth factor (TGF)-β (26–28). The dynamic balance between the two maintains the stability of the immune function of the body. When the above balance is disrupted, the body's immune function becomes abnormal, which, in turn, leads to the development of immune diseases. The occurrence of AIH leads to the excessive secretion of various inflammatory cells, further stimulating the onset of inflammation (29). As a liver factor, LECT2 can regulate inflammation and is thus abnormally overexpressed in AIH patients. As a Th1-related chemokine, CXCL10 mediates the inflammatory response of Th1-type cells, further aggravates liver injury, and indirectly participates in the occurrence and development of AIH (30). After 4 weeks of treatment, the Th17/Treg ratio and LECT2, CXCL10, AST and ALT levels of the patients in the case group were lower than those 1 day before treatment. Pearson correlation analysis revealed that AST and ALT levels were positively correlated with the Th17/Treg, LECT2, and CXCL10 ratios, suggesting that the abnormally high Th17/Treg ratios and elevated serum LECT2 and CXCL10 levels were closely associated with liver function in patients with AIH. In addition, multivariate logistic regression analysis revealed that an elevated Th17/Treg ratio, elevated LECT2, elevated CXCL10, elevated AST, and elevated ALT. Th17 cells are closely associated with the expression of proinflammatory cytokines such as IL-6 and IL-23, whereas Treg cells are associated with the expression of cytokines such as IL-10 and TGF-β. An increase in the ratio of the two often reflects a shift in the dynamic balance toward Th17, leading to a significant increase in proinflammatory cytokine secretion and exacerbating liver injury (31–33). This increases the difficulty of treatment and prevents patients from benefiting from it. The elevated level of LECT2 may be due to the body's ability to resist the erosion of inflammatory cytokines, suppress inflammatory responses, and enhance its self-protective immune regulatory mechanisms. Therefore, the increase in its expression often reflects the intensification of inflammatory responses within the body. CXCL10 can induce various chemotactic cells, such as mononuclear macrophages, T lymphocytes and basophils, and promote the synthesis and secretion of multiple proinflammatory cytokines, thereby intensifying the local inflammatory response of the liver and inducing liver injury (34). An increase in AST and ALT levels indicates that liver damage in patients intensifies, and even severe liver fibrosis symptoms may occur, which in turn leads to poor responses to related treatments in patients (35). IgG is a reliable indicator of the body's immune function. When its expression level rises, the body's immune response becomes more intense, accelerating the course of the patient's illness and eventually making it more difficult for the patient to respond to related treatments (36).

Conclusion

The Th17/Treg ratio and LECT2 and CXCL10 levels play significant roles in liver injury in patients

with AIH and can, to a certain extent, reflect the response status after treatment.

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Conflict of interest statement

All the authors declare that they have no conflict of interest in this work.

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