https://doi.org/10.22416/1382-4376-2024-34-1-31-36
UDC 616.36-002.2-092.19-097:612.017.1

Immunological Remission as a Basis for Dose Reduction of Immunosuppressors in Autoimmune Hepatitis: Results of Monocenter Surveillance Study

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Aim of the study: evaluate the role of normalization of humoral immunity to address dose reduction or discontinuation of immunosuppressors in patients with autoimmune hepatitis (AIH).
Patients and methods. The data of 47 patients with AIH who received immunosuppressive therapy from April 2001 to August 2023 were analyzed: 10 men (21 %), 37 women (79 %); the average age was 37 (17–66) years. The follow-up period was 10–180 months. Type 1 AIH was diagnosed in 37 patients, type 2 AIH — in 7 patients, seronegative AIH — in 3 patients. The diagnosis was established according to the IAIHG point system. To confirm the diagnosis, a liver biopsy was performed in 17 patients, a histological picture of AIH was detected in all of them. The most used combination was prednisolone and azathioprine — in 25 patients (53.2 %), as well as methylprednisolone and azathioprine — in 8 patients (17 %).
Results. In some patients, when the immunosuppressive therapy decreased below the recommended dose, a relapse of the disease developed (Group 1), and in others, remission persisted (Group 2). The concentration of гамма-globulins in patients of Group 1 was 22.5 mg%, in Group 2 — 17.95 mg% (p = 0.00055). IgG level after achieving remission in Group 1 was 1709.7 mg/dL, in Group 2 — 1381.7 mg/dL (p = 0.000001). The terms of ALT normalization in Group 1 were 2.14 months, in Group 2 — 1.47 months (p = 0.037); AST normalization in Group 1 made 2.22 months, in Group 2 — 1.48 months (p = 0.026).
Conclusions. Normalization of humoral immunity, as well as rapid normalization of ALT and AST can be considered as markers of maintaining AIH remission when immunosuppressor doses are reduced below standard doses, and in individual patients — the possibility of immunosuppressive therapy withdrawal. This will reduce the risk of adverse events and increase adherence to the therapy. We propose introducing the term “immunological remission” into the clinical lexicon, which, along with biochemical and histological remission, acts as a predictor of persistent remission of AIH.
Keywords: autoimmune hepatitis, treatment, remission, relapse, gamma globulins, immunoglobulin G
Conflict of interest: the authors declare that there is no conflict of interest.

For citation: Bueverov A.O., Koblov S.V., Bogomolov P.O. Immunological Remission as a Basis for DoseReduction of Immunosuppressors in Autoimmune Hepatitis: Results of Monocenter Surveillance Study. RussianJournal of Gastroenterology, Hepatology, Coloproctology. 2024;34(1):31–36. https://doi. org/10.22416/1382-4376-2024-34-1-31-36

Иммунологическая ремиссия как основание для снижения доз иммуносупрессоров при аутоиммунном гепатите: результаты моноцентрового наблюдательного исследования

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Цель исследования: оценить роль нормализации показателей гуморального иммунитета для решения вопроса о снижении дозы или отмены иммуносупрессоров у пациентов с аутоиммунным гепатитом (АИГ).
Пациенты и методы. Проанализированы данные 47 больных АИГ, получавших иммуносупрессивную терапию в период с апреля 2001 по август 2023 г.: 10 мужчин (21 %) и 37 женщин (79 %); средний возраст — 37 (17– 66) лет. Период наблюдения составил от 10 до 180 месяцев. АИГ 1-го типа диагностирован

у 37 пациентов, 2-го типа — у 7, серонегативный АИГ — у 3 пациентов. Диагноз устанавливался согласно балльной системе IAIHG. С целью подтверждения диагноза биопсия печени выполнена 17 пациентам, гистологическая картина АИГ выявлена у всех. Наиболее часто применялась комбинация преднизолона и азатиоприна — у 25 пациентов (53,2 %), а также метилпреднизолона и азатиоприна — у 8 пациентов (17 %).
Результаты. У части пациентов при снижении иммуносупрессивной терапии ниже рекомендуемой дозы развился рецидив заболевания (группа 1), у другой — ремиссия сохранялась (группа 2). Концентрация гамма-глобулинов у пациентов группы 1 была 22,5 мг%, в группе 2 — 17,95 мг% (p = 0,00055). Уровень IgG после достижения ремиссии в группе 1 составил 1709,7 мг/дл, в группе 2 — 1381,7 мг/дл (p = 0,000001). Срок нормализации АЛТ в группе 1 был 2,14 мес., в группе 2 — 1,47 мес. (p = 0,037); сроки нормализации АСТ в группе 1 составили 2,22 мес., в группе 2 — 1,48 мес. (p = 0,026).
Выводы. Нормализация показателей гуморального иммунитета, а также быстрая нормализация АЛТ и АСТ могут рассматриваться в качестве маркеров поддержания ремиссии АИГ при снижении доз иммуносупрессоров ниже стандартных, а у отдельных пациентов — возможности отмены иммуносупрессивной терапии. Это позволит снизить риск развития нежелательных явлений и повысит приверженность к проводимой терапии. Мы предлагаем ввести в клинический лексикон термин «иммунологическая ремиссия», которая, наряду с биохимической и гистологической ремиссиями, выступает в качестве предиктора стойкой ремиссии АИГ.
Ключевые слова: аутоиммунный гепатит, лечение, ремиссия, рецидив, гамма-глобулины, иммуноглобулин G
Конфликт интересов: авторы заявляют об отсутствии конфликта интересов.

Для цитирования: Буеверов А.О., Коблов С.В., Богомолов П.О. Иммунологическая ремиссия как основание для снижения доз иммуносупрессоров при аутоиммунном гепатите: результаты моноцентрового наблюдательного исследования. Российский журнал гастроэнтерологии, гепатологии, колопроктологии. 2024;34(1):31–36. https://doi.org/10.22416/1382-4376-2024-34-1-31-36

The prevalence of autoimmune hepatitis (AIH) in Europe and the United States ranges from 4 to 24.5 cases per 100,000 population with an annual incidence of 0.6 to 2.0 cases per 100,000 [1–3]. Despite its relative rarity, timely diagnosis of AIH is extremely important due to the often-aggressive course with rapid formation of cirrhosis of the liver. In 2019, the American Association for the Study of Liver Diseases (AASLD) published detailed guidelines for the diagnosis and treatment of AIH, updating the previous version published in 2010 [1, 2]. According to these recommendations, verification of the diagnosis of AIH requires: 1) histological picture of interstitial hepatitis; 2) laboratory data: increased activity of alanine (ALT) and aspartic (AST) aminotransferase, elevated serum immunoglobulin G (IgG); 3) diagnostic titers of autoantibodies characteristic of the disease; 4) exclusion of other liver diseases similar in course to AIH [1, 4]. The International AIG Study Group (IAIHG) developed a point-based diagnostic system for this disease, which was slightly modified in subsequent years; along with it, a simplified system of diagnostic signs was proposed. In both cases, the key indicators are autoantibodies, IgG, histological changes, and the absence of viral markers [5]. Based on the profile of serological markers, two types of AIH are distinguished. Isolation of the third type of AIG is not supported by most specialists, since its serological marker (antibodies to soluble hepatic antigen, and hepatic-pancreatic antigen, anti-SLA/LP) is found in both type 1 AIG and type 2 AIG [3, 6, 7]. Seronegative AIH is considered separately [8]. It should be noted that in real clinical practice, liver biopsy is performed relatively rarely due to, firstly, the lack of qualified morphologists, and secondly, the sufficiency of non-invasive diagnostic criteria in many patients.

For the treatment of AIH, the drugs of choice are glucocorticosteroids (corticosteroids) — prednisone or methylprednisolone; the use of the latter is associated with fewer side effects with prolonged use due to the practically absent mineralocorticoid activity. To increase the effectiveness of immunosuppressive therapy (IST) and reduce the dose, azathioprine, which has antiproliferative activity, is often added to corticosteroids. The main purpose of prescribing prednisone is to induce remission, while azathioprine is to maintain it [1, 5, 6]. The lack of sufficient effect or poor tolerability of prednisone and azathioprine give grounds for an attempt to prescribe other immunosuppressants, such as cyclophosphamide, mycophenolate mofetil, cyclosporine, tacrolimus [9, 10].

An important but little-discussed problem in the literature is patient adherence to treatment, primarily related to corticosteroid therapy. Young patients refuse therapy mainly due to weight gain, cushingoid, acne and menstrual disorders. In patients of older age groups, the question of reducing the dose of corticosteroids is usually raised due to the progression of osteoporosis, arterial hypertension, and steroid diabetes.

Aim of the study: to evaluate the role of normalization of humoral immunity indicators in deciding whether to reduce the dose or discontinue immunosuppressants in patients with AIH.

Patients and methods

Data from 47 AIH patients treated with IST in the period from April 2001 to August 2023 were analyzed. Among the participants, there were 10 men (21 %) and 37 women (79 %), the average age was 37 (17–66) years: the average age of men — 43 years, of women — 35 years. The follow-up period ranged from 10 to 180 months. Type 1 AIG was diagnosed in 37 patients, type 2 — in 7, and seronegative AIG — in 3 patients. The diagnosis was made according to the IAIHG score system. To confirm the diagnosis, liver biopsy was performed in 17 patients, the histological picture of AIH was revealed in all of them. Control liver biopsy to assess the achievement of histological remission was performed in 6 patients, all of whom were confirmed to have no histological activity. The most frequently used combination was prednisone and azathioprine — in 25 patients (53.2 %), and methylprednisolone and azathioprine — in 8 patients (17 %). Other IST regimens were used less frequently: prednisolone in monotherapy — in 4 patients (8.5 %), methylprednisolone in monotherapy — in 3 (6.4 %), prednisolone + cyclophosphamide — in 2 (4.3 %), azathioprine in monotherapy — in 2 patients (4.3 %). One patient was receiving a combination of prednisolone and mycophenolate mofetil (2.1 %), 1 — a combination of methylprednisolone and mycophenolate mofetil (2.1 %), and 1 — methylprednisolone + cyclophosphamide (2.1 %).

Methods of statistical processing. Data analysis was carried out using the statistical software package Statistica 12.0. Statistical comparison of mean values between two parallel groups was carried out using the two-way Student's criterion (for the normal distribution of the trait). In the case of a non-normal feature distribution, its nonparametric counterpart, the Mann — Whitney — Wilcoxon test, was used. The probability of a type I error (two-way significance level) was set at 5 %.

Inclusion criteria:

- at least 18 years of age;
- definite diagnosis of AIH according to IAIHG;
- IST with achievement biochemical remission;
- duration of drug-induced remission for at least 6 months.

Exclusion criteria:

- cross syndrome with primary biliary cholangitis (cirrhosis), primary sclerosing cholangitis;
- combined pathology (chronic viral hepatitis, alcoholic liver disease, metabolic associated fatty liver disease, etc.);
- severe combined diseases other organs and systems.

Results

Before treatment, 34 patients met the diagnosis of "definite AIH" (> 15 points), 14 — the diagnosis of "probable AIH" (14–15 points). After IST, all study participants met the diagnosis of "definite AIH" (> 17 points). The average ALT activity was 19.2 upper limits of normal (ULN; 5.8–36.4); in men, ALT activity was 20.2 ULN, in women — 19.1. AST activity averaged 17.7 ULN (6.0–32.7): 17.4 ULN — in men and 17.8 — in women. The average level of serum gamma globulins was 31.2 mg % (26.5–39.1) and was almost the same in both men and women. Level of IgG averaged 2584.7 mg/dL (1887–3673; in the male cohort — 2558.4 mg/dL, in the female cohort — 2591.9 mg/dL), no statistically significant differences were found between the groups.

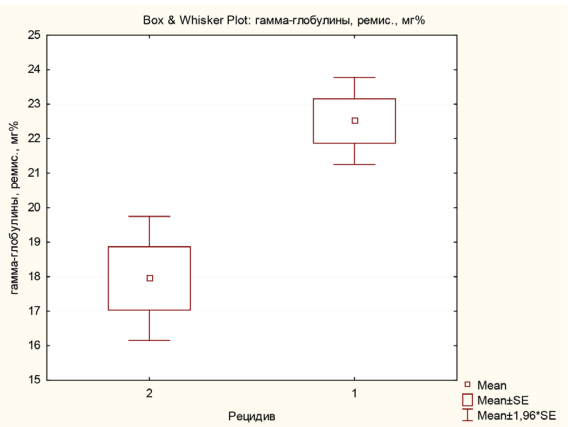
According to the results of the analysis, patients were divided into two groups: Group 1 consisted of patients with recurrent AIH on the background of reducing the dose of immunosuppressants or discontinuing IST, Group 2 — of patients without relapse.

When comparing the indicators of humoral immunity markers after achieving remission, it was found that in the relapse group, the levels of gamma globulins and immunoglobulin were significantly higher. Thus, the average concentration of gamma globulins in Group 1 was 22.5 mg/dL, in Group 2 — 17.95 mg/dL. These values were statistically significant ($p = 0.00055$) (Fig. 1). The IgG level after achieving remission in Group 1 was 1709.7 mg/dL, in Group 2 — 1381.7 mg/dL ($p = 0.000001$) (Fig. 2).

There were also differences in the time of normalization of cytolysis indicators in the study groups. The duration of ALT normalization in Group 1 was 2.14 months, in Group 2 — 1.47 months ($p = 0.037$). The duration of AST normalization in Group 1 was 2.22 months, in Group 2 — 1.48 months ($p = 0.026$) (Fig. 3).

In most patients ($n = 42$; 89.4 %), liver density was assessed by elastometry performed at the stage of diagnosis and after achieving remission of AIH. At the onset of the disease, the liver density averaged 11 kPa, while the liver density of patients in Group 1 was 11.28 kPa, in Group 2 — 10.0 kPa, there was no statistically significant difference between the groups ($p = 0.385$). After achieving remission, the average liver density index in Group 1 was 7.27 kPa, in Group 2 — 6.21 kPa. However, these differences were not statistically significant ($p = 0.3$) (Fig. 4).

When comparing the activity of ALT and AST at the onset of the disease, it was found that in the group of patients with relapse, the activity of ALT and AST was slightly higher, but there was no statistically significant difference ($p > 0.05$). Thus, ALT activity in Group 1 was 19.5 ULN, while in Group 2 it was 18.4 ULN ($p = 0.68$). AST activity in Group 1 was 18 ULN, in Group 2 — 16.8 ULN ($p = 0.64$). Similar results were obtained when analyzing the level of gamma globulins and immunoglobulin: the



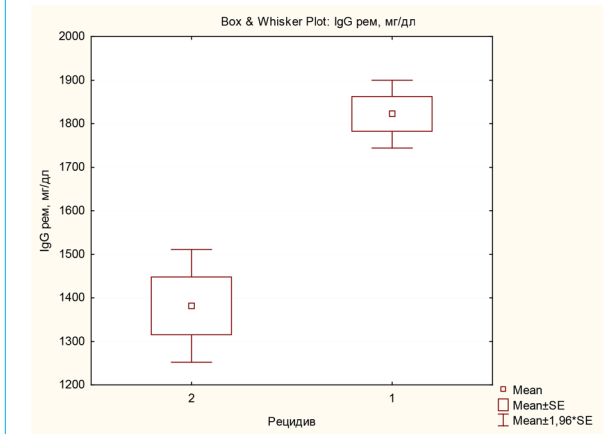


Figure 1. Differences in gamma globulin levels in groups after achieving remission of autoimmune hepatitis: box whisker plot — box diagram with outlier limiters; Mean — average value; SE — standard error

Рисунок 1. Различия уровня гамма-глобулинов в группах после достижения ремиссии аутоиммунного гепатита: box whisker plot — блочная диаграмма с ограничителями выбросов; Mean — среднее значение; SE — стандартная ошибка

Figure 2. Differences in immunoglobulin G levels in groups after achieving remission of autoimmune hepatitis: box whisker plot — block diagram with outlier limiters; Mean — average value; SE — standard error

Рисунок 2. Различия уровня иммуноглобулина G в группах после достижения ремиссии аутоиммунного гепатита: box whisker plot — блочная диаграмма с ограничителями выбросов; Mean — среднее значение; SE — стандартная ошибка

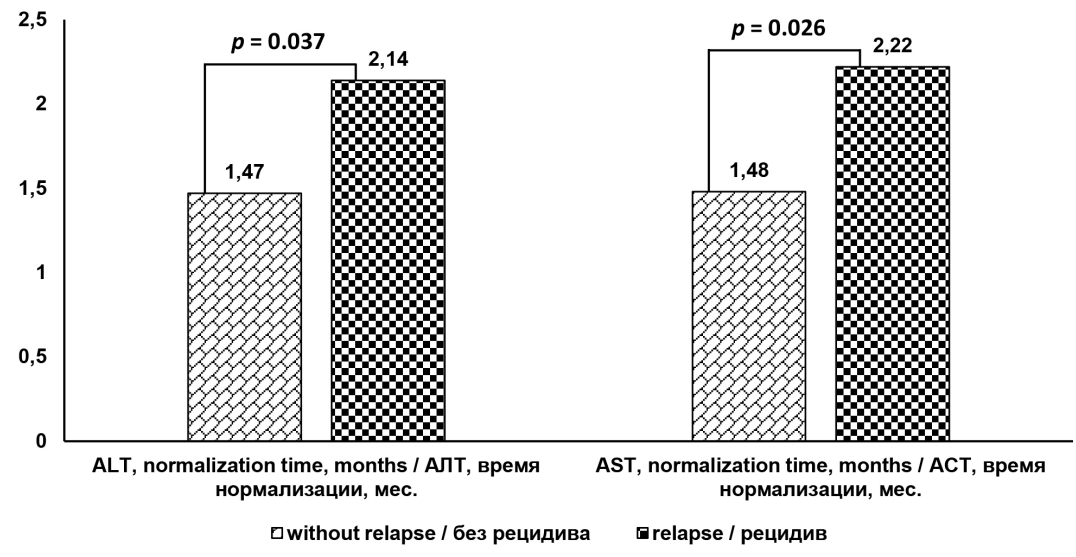


Figure 3. Differences in time to normalization of ALT and AST in groups

Рисунок 3. Различия времени нормализации АЛТ и АСТ в группах

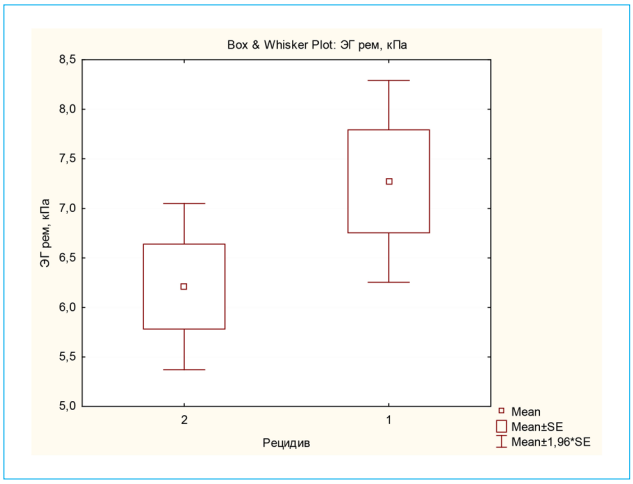


Figure 4. Differences in liver density in groups after achieving remission of autoimmune hepatitis: box whisker plot — block diagram with outlier limiters; Mean — average value; SE — standard error; Student's *t*-test was used for independent groups

Рисунок 4. Различия плотности печени в группах после достижения ремиссии аутоиммунного гепатита: box whisker plot — блочная диаграмма с ограничителями выбросов; Mean — среднее значение; SE — стандартная ошибка; использовался *t*-критерий Стьюдента для независимых групп

concentration of gamma globulins in Group 1 was 31.05 g/L, in Group 2 — 31.74 g/L (p = 0.51); IgG in Group 1 — 2546.6 mg/dL, in Group 2 — 2695.9 mg/dL (p = 0.4).

Discussion

In patients with AIH, before the withdrawal of immunosuppressants, which is possible in 20–30 % of patients not earlier than three years of treatment, it is recommended to perform a liver biopsy to determine the disappearance of histological signs of hepatitis activity, and after withdrawal — regular clinical and biochemical examination at least once every 6 months [1, 5]. Non-invasive criteria for reducing the dose of immunosuppressants below standard maintenance or their withdrawal are not covered in the literature available to us. A single study reported that normalization of serum IgG levels, along with normalization of ALT activity, is a negative predictor of relapse; all patients who achieved sustained remission within > 1 year after discontinuation of IST were characterized by ALT values < 0.5 upper limit of normal and IgG < 1200 mg/dL [11].

The most important result of our study is the identification of differences in the indicators of humoral immunity markers after achieving remission. In patients with normalization of the level of gamma globulins and IgG in the majority of cases, it is possible to reduce the doses of immunosuppressants below the standard maintenance ones, while in those who maintain increased activity of indicators of the humoral immune response, this tactic quickly leads to biochemical relapse. Therefore, we believe that there are grounds for introducing the term "immunological remission", which, along with biochemical and histological remission, allows us to consider a reduction in the dose of immunosuppressants below the standard maintenance dose, and in some patients — complete cancellation of IST. This will reduce the risk of adverse events and increase adherence to therapy. Of course, all patients with AIH, regardless of their remission status, should be under the supervision of a specialist for life since the risk of relapse persists for life due to the persistence of a pathological clone of immune cells [12].

In addition, there were differences in the time of normalization of cytolysis indicators in the study groups. The duration of ALT normalization in Group 1 was 2.14 months, in Group 2 — 1.47 months (p = 0.0237). The duration of AST normalization in Group 1 was 2.22 months, in Group 2 — 1.48 months (p = 0.026). When determining liver density by elastometry performed at the stage of diagnosis and after achieving remission of AIH, at the onset of the disease, the liver density averaged 11 kPa; while the liver density of patients in Group 1 was 11.28 kPa, in Group 2 — 10.0 kPa, there was no statistically significant difference between the groups (p = 0.385). After achieving remission, the average liver density index in Group 1 was 7.27 kPa, in Group 2 — 6.21 kPa (p = 0.3). When interpreting the elastometry data, it is necessary to consider that the density of liver tissue can be determined not only by the degree of fibrosis, but also by the severity of inflammation, which gives grounds for a cautious interpretation.

Thus, normalization of humoral immunity parameters (gamma globulins, IgG), as well as rapid normalization of ALT and AST can be considered as additional markers of persistent remission of AIH.

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Submitted: 29.10.2023 Accepted: 14.11.2023 Published: 29.02.2024
Поступила: 29.10.2023 Принята: 14.11.2023 Опубликована: 29.02.2024

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