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Possible exacerbation of autoimmune hepatitis in patient with chronic hepatitis C during therapy with direct acting antivirals

Prawdopodobne zaostrzenie autoimmunologicznego zapalenia wątroby u pacjentki z przewlekłym wirusowym zapaleniem wątroby C w trakcie terapii lekami działającymi bezpośrednio przeciwwirusowo

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Słowa kluczowe

HCV, przewlekłe zapalenie wątroby typu C, autoimmunologiczne zapalenie wątroby, leki działające bezpośrednio przeciwwirusowo

S u m m a r y

Chronic hepatitis C (CHC) infection may be associated with several features of autoimmunity, autoimmune hepatitis being one of them. During the time of interferon-based antiviral therapies, CHC therapy in patients with AIH was extremely difficult to perform, as interferon could lead to an exacerbation of the coincident autoimmune disease, or even induce another one. Nowadays, highly specific and effective therapeutic options are available, in the form of direct antiviral agents (DAA) against HCV. However, the data about HCV treatment with DAA in patients with autoimmune hepatitis are still scarce. Potential pitfalls of AIH therapy in chronic hepatitis C patients with DAA include a deregulation of immunity after rapid clearance of HCV-RNA, but also potential drug to drug interactions with DAA and immunosuppressive therapy. Here we report two cases of patients with coincidence of autoimmune hepatitis and HCV infection treated with DAA therapy. Both cases share similarity in AIH type and advancement, used immunosuppressive therapy but also DAA regiment. On the other hand, one was complicated with severe exacerbation while in second no complications during DAA therapy were observed. We postulate that patients with chronic hepatitis C and autoimmune hepatitis are important group due to the faster disease progression and with availability of novel anti-HCV antiviral their treatment should not be deferred. On the other hand, caution is warranted since potential drug to drug interaction between DAA and immunosuppressant as well as potential exacerbations AIH cannot be ruled out.

S t r e s z c z e n i e

Przewlekłe zapalenie wątroby typu C (PZW C) może być powiązane z wieloma procesami autoimmunizacyjnymi, jednym z nich jest autoimmunologiczne zapalenie wątroby (AIH). W czasach terapii przeciwwirusowych opartych na interferonie, leczenie PZW C u pacjentów z AIH było znacznie utrudnione, ponieważ stosowanie interferonu mogło prowadzić do zaostrzenia współistniejącej choroby autoimmunologicznej lub nawet wywołać kolejną. Obecnie dostępne są wysoce swoiste i skuteczne terapie, pod postacią leków działających bezpośrednio przeciwwirusowo (DAA) przeciwko HCV. Jednakże dane na temat stosowania tych leków u pacjentów z autoimmunologicznym zapaleniem wątroby są wciąż ograniczone. Potencjalne niepowodzenia w terapii AIH u zakażonych HCV obejmują zaburzenia równowagi immunologicznej po szybkim wyeliminowaniu HCV-RNA, ale również potencjalne interakcje lekowe, pomiędzy DAA a lekami immunosupresyjnymi. Przedstawiamy dwa przypadki pacjentek z współistniejącym autoimmunologicznym zapaleniem wątroby oraz zakażeniem HCV leczonym za pomocą DAA. Oba przypadki były podobne w zakresie typu AIH oraz zaawansowania choroby, użytej immunosupresji, jak również zastosowanego schematu DAA. Z drugiej strony, jeden z przypadków był powikłany ciężkim zaostrzeniem, podczas gdy w drugim przypadku nie zaobserwowano żadnych komplikacji. Sugerujemy, że pacjenci z przewlekłym wirusowym zapaleniem wątroby C oraz autoimmunologicznym zapaleniem wątroby są ważną grupą w związku z szybszą progresją choroby wątroby, a wraz z dostępnością nowych leków anty-HCV, ich leczenie nie powinno być opóźniane. Z drugiej strony, zalecana jest ostrożność, gdyż potencjalne interakcje lekowe pomiędzy DAA, a lekami immunosupresyjnymi oraz możliwe zaostrzenie AIH mogą wikłać terapie.

Conflict of interest
Konflikt interesów

None
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INTRODUCTION

Hepatitis C virus (HCV) is the RNA virus responsible for the hepatitis C disease. Total global HCV prevalence is estimated at 2.5% (177.5 million of HCV infected adults), ranging from 2.9% in Africa to 1.3% in Americas (1). In European Union number of viremic HCV cases of HCV is estimated to be more than 3.2 million, while in Poland exceeds 200,000 with around 80% being not aware of their infection (2, 3). Chronic hepatitis C infection may be associated with several features of autoimmunity, autoimmune hepatitis being one of them. Hepatitis C is also associated with other autoimmune diseases, such as autoimmune thyroiditis, lichen ruber planus, and membranous glomerulonephritis. One of the indicators of autoimmune disease is the presence of autoantibodies in serum and among them, antinuclear antibodies (ANA) – usually present in serum of patients with autoimmune hepatitis. Data indicate that serum ANA are positive in 6% general population and even more among women and over 50 years old populations (4). However, reported incidence rates of AIH are around 1 per 100,000 population per year. Prevalence of serum autoantibodies in chronic hepatitis C patients is known to be higher than that in the general population. Data indicate that ANA may be positive in 9% of the chronic hepatitis C patients (5). Nevertheless, isolated ANA positivity is not a factor in chronic HCV disease progression and does not affect the treatment response (6). Because of that, the coincidence of chronic hepatitis C with an autoimmune hepatitis usually have to be confirmed by liver biopsy and characteristic histological features in the bioptate. During the time of interferon-based antiviral therapies, hepatitis C treatments in patients with AIH were extremely difficult to perform, as interferon could lead to an exacerbation of the coincident autoimmune disease, or even induce another one (7). In these cases, a prophylactic immunosuppression had to be started before initiation of interferon therapy. Even then, the risk of AIH exacerbation was high and many clinicians were resigning from treating such patients for HCV infection. Nowadays, highly specific and effective therapeutic options are available, in the form of direct antiviral agents (DAA) against hepatitis C. However, the data about HCV treatment with DAA in patients with autoimmune hepatitis are still scarce. Potential pitfalls of AIH therapy in chronic hepatitis C patients with DAA include a deregulation of immunity after rapid clearance of HCV-RNA, but also potential drug to drug interactions with DAA and immunosuppressive therapy. We present two cases of patients with coincidence of autoimmune hepatitis and HCV infection treated with DAA therapy. Both cases share similarity in AIH type and advancement, used immunosuppressive therapy but also DAA regiment. On the other hand, one was complicated with severe exacerbation while in second no complications during DAA therapy were observed.

CASE PRESENTATIONS

First patient (#1) is a 67 years old female with an anamnesis of atrial hypertension. Her HCV genotype 1b infection was diagnosed over 15 years ago. At the same time autoantibodies: ANA (1:1280) and ASMA were revealed with accompanying high gamma-globulins (27%) and increased ALT (81 IU/mL), higher than AST (73 IU/mL). Other hepatic comorbidities were excluded. Liver biopsy performed in 2001 confirmed a diagnosis of AIH but also revealed advanced bridging fibrosis (F3 in Metavir scale). Just after diagnosis of AIH prednisone (standard dose) with azathioprine (AZT – 50 mg/day) were introduced and significant reduction of ALT activity was observed 6 weeks after the start of immunosuppressive therapy. This therapy was well tolerated. Due to the advanced fibrosis and definite diagnosis of AIH she was not treated with interferon based anti-HCV regiments. In 2016 with availability of direct acting antivirals she was qualified for the therapy with ombitasvir/paritaprevir/ritonavir with dasabuvir (OBV/PTV/r + DSV) without ribavirin. Prior to anti-HCV therapy her HCV-RNA was 1.195.170 IU/mL, ALT 53 IU/mL and gamma-globulins of 33%. No increase in bilirubin, INR, creatinine or decrease in platelets were observed. OBV/PTV/r + DSV in standard doses was introduced and therapy with prednisone (5 mg/day) with azathioprine (50 mg/day) sustained. After two weeks of therapy her ALT increased to 120 IU/mL, although patient was asymptomatic and therapy was continued. In the fourth week of therapy (wk 4) ALT increase was 782 IU/mL and patient reported general weakness. Coinfection with HAV, HBV, EBV, CMV as well as other obvious reasons for ALT elevation were excluded. She did not take any additional co-medications beside valsartan at the lowest dose of 80 mg/day. Patient was hospitalized and azathioprine stopped after suspicion of potential drug to drug interaction between OBV/PTV/r + DSV and azathioprine. Following this ALT activity remained unchanged and highly elevated (fig. 1), while there was no alteration in liver function parameters and only minor general weakness was present. Patient insisted on continuation of anti-HCV therapy, therefore prednisone dose was increased to 1 mg/kg of body weight to control exacerbation of AIH. Two weeks later (wk 10) ALT activity decreased 374 IU/mL and AZT was reintroduced in a dose of 50 mg/day. Patient returned to Department two weeks later for end of therapy visit (EOT) again with high ALT of 664 IU/mL but without any symptoms. Therapy with OBV/PTV/r + DSV has been terminated according to the schedule and AZT (50 mg/day) with prednisone which has doses were eventually reduced to 5 mg/day continued. Four weeks after the EOT her ALT was already within normal range (24 IU/mL), patient did not complain of any symptoms and the most importantly her HCV-RNA was not detected.

Second case (patient #2) is a 51 years old female without significant comorbidities in anamnesis. Again chronic hepatitis C (genotype 1b) as well as autoimmune hepatitis were diagnosed simultaneously in 2009. The diagnosis of AIH was based on high ALT levels 840 IU/mL with lower AST of 654 IU/mL, presence of autoantibodies in high titer (ANA 1:3200, ASMA 1:1000),

increased level of gamma-globulins (21%). The diagnosis was confirmed by a liver biopsy showing typical features of AIH and also chronic hepatitis C with fibrosis stage F2. She was started on prednisone (1 mg/kg of body weight) with azathioprine (100 mg/day) with biochemical remission of disease. Her control liver biopsy in 2014 showed an improvement in fibrosis (F1) but immunotherapy (AZT 50 mg/day, prednisone 5 mg/day) was continued. Finally with availability of anti-HCV DAA she started a therapy with OBV/PTV/r + DSV for 12 weeks, with baseline HCV-RNA of 5.622.677 IU/ml and ALT activity of 42 IU/mL. During the course of anti-HCV therapy ALT activity further declined to 15 IU/mL and remained low until end of therapy (fig. 2). HCV-RNA was not detected at the end of therapy and sustained viral response (SVR) was achieved. Currently she continues only AZT at low dose of (50 mg/day) with ALT activity within normal range.

DISCUSSIONS

In this paper we have presented two clinical cases with coexisting autoimmune hepatitis and chronic hepatitis C. Both cases shared significant similarities with respect to AIH (type 1, high activity of disease, moderate advancement of fibrosis and good response to AZT and prednisone) but also chronic HCV infection (HCV genotype 1, high HCV-RNA levels). Furthermore, in both cases the diagnosis of AIH was made simultaneously with chronic hepatitis C, and since both were treatment naïve the case of autoimmune triggering by IFN can be excluded. Type 2 AIH with presence of anti-LKM antibodies as a complication of chronic hepatitis C is well described in literature since 1990 (8), on the other hand the nature of influence of chronic hepatitis C and type 1 AIH is less known. It is well know that chronic liver damage might trigger autoimmunity which could further influence progression of disease, for example in alcoholic liver damage (9). Importantly, anti-HCV therapy was deferred in majority of patients with HCV, since the risk of exacerbation during IFN-based therapies. In the recent years novel classes of anti-HCV direct antiviral allowed to treat chronic hepatitis C with high efficacy (> 95%) without the use of interferon. In patients infected with HCV genotype 1 and 4 a regimen of ombitasvir/paritaprevir/ritonavir ± dasabuvir ± ribavirin reached efficacy 99% in real world study including 56% with liver cirrhosis (10). Such high efficacy with no significant safety concerns in patients with compensated cirrhosis allowed to widen profile of patients treated for chronic hepatitis C.

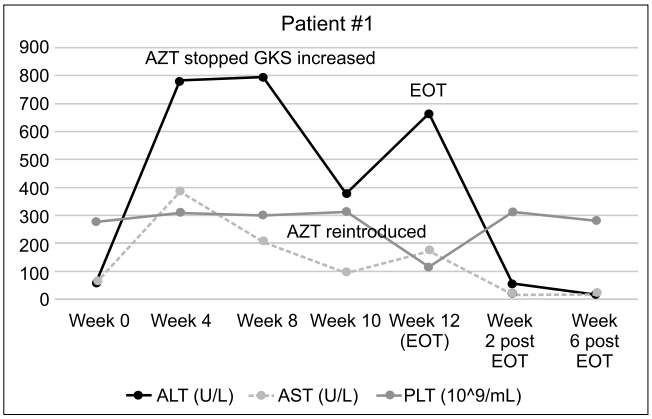

Fig. 1. ALT, AST activity as well platelet count in patient with chronic hepatitis C and autoimmune hepatitis during therapy with ombitasvir/paritaprevir/ritonavir + dasabuvir (case #1)
AZT – azathioprine; EOT – end of therapy; GKS – glucocorticosteroids

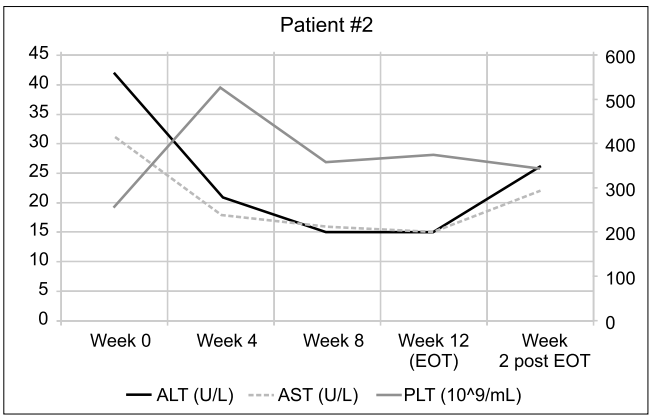

Fig. 2. ALT, AST activity as well platelet count in patient with chronic hepatitis C and autoimmune hepatitis during therapy with ombitasvir/paritaprevir/ritonavir + dasabuvir (case #2)

Without any doubt, chronic hepatitis C with other coexisting liver disorder should be treated as priority due to the faster progression of disease. On the other hand, there is still limited evidence of the fate of autoimmune diseases in HCV-infected patients after successful eradication of the virus with DAA. In presented in this manuscript case #1 unexpected high increase in ALT activity occurred after two weeks of antiviral therapy. Additional possible causes of this increase, including co-infection with other viruses (also HBV) has been excluded. Among possible explanations one is a drug to drug interaction between immunotherapy and OBV/PTV/r + DSV. According to the most valuable source on drug interactions (11) azathioprine does not induce interactions with OBV/PTV/r + DSV without RBV since there is no overlap in metabolic pathways. Nevertheless, AZT has been terminated and no reduction of was ALT observed. Another co-medication was prednisone. Prednisone is a substrate of CYP3A4 and its exposure may increase due to CYP3A4 inhibition by ritonavir. Toxicity of prednisone cannot be ruled out in this case but still is unlikely since its dose elevation to better control inflammation during AIH caused a decline of ALT activity. Next potential explanation could be that rapid decline of HCV-RNA which is usually observed within first 1-2 weeks of DAA therapy caused immune disbalance and exacerbation of AIH. The most important issue is long-term consequence of successful antiviral therapy with DAA. There are emerging but still limiting reports on remission of some autoimmune phenomena after SVR with DAA. They include remission of lichen planus (12) or a high rate of complete clinical response hepatitis C virus-associated cryoglobulinaemia vasculitis (13).

On the other hand, exacerbation of ulcerative colitis most likely due to ribavirin in patient treated with sofosbuvir was described (Ohta). In both cases described in this manuscript EOT HCV response was achieved, ALT activity normalized and AIH remission could be maintained with low doses of immunosuppressant.

CONCLUSIONS

In conclusion, patients with chronic hepatitis C and autoimmune hepatitis are important group due to the faster disease progression and with availability of novel anti-HCV antiviral their treatment should not be deferred. On the other hand, caution is warranted since potential drug to drug interaction between DAA and immunosuppressant as well as potential exacerbations AIH cannot be ruled out. Further long-term observation after obtaining SVR is necessary to evaluate an influence of HCV-eradication on activity of autoimmune hepatitis.

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