Findings that shed new light on the possible pathogenesis of a disease or an adverse effect

Exacerbation of AIH in a patient with an AIH/systemic sclerosis overlap syndrome and pulmonary arterial hypertension treated with the endothelin-1 receptor antagonist sitaxentan

Reinhild Klein,¹ Eva Hintz,² Gerd Staehler³

¹Department of Internal Medicine II, University of Tuebingen, Tuebingen, Germany

²Praxis Winnenden, Winnenden, Germany

³Klinik Loewenstein, Loewenstein, Germany

Correspondence to Professor Reinhild Klein, reINHILD.klein@med.uni-tuebingen.de

Summary

Increase of liver enzymes during therapy with endothelin receptor antagonist (ERA) because of pulmonary arterial hypertension (PAH) has been observed quite frequently the cause of which is unknown. Here we describe a female patient who suffered from autoimmune hepatitis (AIH) type I [positive for antinuclear (ANA) and antiactin antibodies] who developed systemic sclerosis (SSc) with PAH. AIH was treated with corticosteroids and azathioprine, and PAH with the ERA sitaxentan. Reactivation of AIH was observed in the course of therapy with sitaxentan as shown by an increase of liver enzymes, immunoglobulin G globulins, the reappearance of antinuclear and antiactin antibodies and the induction of a further AIH marker antibody reacting with the soluble liver/liver pancreas antigen. Therapy with ERA for pulmonary hypertension may increase the risk for development or exacerbation of AIH.

BACKGROUND

Excess synthesis of endothelin-1 (ET-1) plays a central role in the pathogenesis of pulmonary arterial hypertension (PAH), and endothelin receptor antagonists (ERA) have, therefore, become important drugs for its treatment.¹ The most encouraging outcome has been the approval of bosentan and, recently, sitaxentan and ambrisentan.^{1–3} However, elevation of liver function tests (aspartate aminotransferase—AST, alanine aminotransferase—ALT and bilirubin) to greater than three times the upper limit of normal (ULN) can be seen in 10–15% of patients treated with bosentan, and in lower incidences in patients treated with sitaxentan or ambrisentan.^{2–4} Although these adverse reactions are in most instances reversible, there are quite a few case reports describing serious liver injury associated with bosentan or sitaxentan.⁴

Herein, we present a patient suffering from autoimmune hepatitis (AIH) type I who developed in the follow-up additionally systemic sclerosis (SSc). Because of PAH as a consequence of lung involvement in SSc the patient was treated with sitaxentan which led to a relapse of AIH.

CASE PRESENTATION

The patient, a woman born in 1948, presented in 1995 with icterus, nausea, fatigue and an elevation of AST and ALT to five times ULN (figure 1). Histologically, the typical features of chronic active hepatitis with piecemeal necrosis were observed. The patient had no history of drug or alcohol abuse, viral hepatitis could be excluded.

Serological analysis revealed high antibody titres to smooth muscle antigens (SMA) and actin (1:640) in the immunofluorescence test (IFT) using an in-house test with cryostat sections from rat stomach, kidney, liver and heart (cut-off: 1:40). The antibodies were only of the IgG type and had IgG1 specificity. IgG2, IgG3, IgG4 and IgM antibodies were negative. Antibodies to nuclei (ANA), liver-kidney microsomes (LKM), soluble liver/liver pancreas antigen (SLA/LP) and mitochondria (AMA) were negative. Also serum IgG globulin levels were elevated (2.000 mg%; normal values <1.600 mg%) and were due to an increase of IgG1 globulins; IgG2, IgG3 and IgG4 globulins were normal. According to the revised criteria of the Autoimmune Hepatitis Group for the diagnosis of AIH including the four parameters absence of viral markers, liver histology, IgG concentration and autoantibody serology, the patient had a score of 8 (definite AIH).⁵ She was treated with prednisolone starting with 70 mg/day (1 mg/kg body weight/day).⁶ Liver enzymes and IgG globulins normalised within 3 months; antiactin antibodies were still positive (1:640). Within the next 12 months, steroids were reduced to 5 mg/day.

In 2000, the patient complained of exercise-induced fever and arthralgia; she developed pneumonia that was not influenced by antibiotics. Furthermore, the patient reported about an increasing Raynaud syndrome, signs of sclerodactylia and dry mouth and eyes. CT revealed pulmonary fibrosis; in the bronchial lavage eosinophils, neutrophils and lymphocytes showed evidence of non-specific alveolitis. Autoantibody screening revealed for the

Figure 1 Clinical course and levels of transaminases in a patient with autoimmune hepatitis followed by systemic sclerosis and relapse of autoimmune hepatitis by treatment with sitaxentan because of pulmonary arterial hypertension. Also treatment, autoantibody (ab) pattern (antiactin antibodies, antibodies to nucleoli/fibrillar) and IgG-globulins (normal <1600 mg%) are given. CAH—chronic active hepatitis.

first time antibodies to nucleoli (fibrillar) in the IFT (titre >1:280). Antibodies to topoisomerase (Scl70) and centromeres remained negative; also antiactin antibodies were negative at that time. Systemic sclerosis (SSc) was diagnosed with predominant pulmonary involvement, other organs were not affected. Because of the diagnosis of SSc, the corticosteroid dose was initially raised up to 50 mg/day and additionally azathioprine (100 mg/day) was introduced, liver enzymes were normal at that time. Then once more steroids were slowly reduced to 5 mg/day, azathioprine was reduced to 50 mg/day.

In the following 4 years there was no evidence of progression of the AIH or SSc. During this time, antibodies to fibrillar remained negative while antiactin antibodies remained negative. In 2006, an increase of AST and ALT up to 3×ULN was observed, probably due to the treatment of bronchitis with antibiotics. Also IgG globulins increased to 1.870 mg%, antiactin antibodies were still negative. Azathioprine was increased to 100 mg/day while the steroid dose was maintained at 5 mg/day. Again the liver enzymes normalised.

Since 2007, the patient complained about exercise-induced dyspnoea. Complete pulmonary function tests, blood gas analysis, colour Doppler echocardiography and right heart catheterisation were performed that revealed mild pulmonary arterial hypertension (pulmonary arterial pressure 35–40 mm Hg). According to the updated treatment guidelines for PAH accompanying mixed connective tissue disease⁷ in January 2008 treatment with an ERA was started which had been suggested to be effective in this condition.⁸ Because of the underlying liver disease, sitaxentan was chosen because elevation of liver function tests have been reported to be seen in a lower incidence than in patients treated with bosentan.^{2–4}

Transaminases and IgG globulins began slightly to rise under the treatment in May 2009. Antiactin antibodies

increased up to 1:1280, but antifibrillar antibodies persisted at the same level. In April 2010, ALT and AST had reached 5–8×ULN and IgG globulins 2.440 mg%. Sitaxentan was, therefore, withdrawn. Then, after a decrease of liver enzymes, the therapy was changed to the ERA ambrisentan (figure 1). However, the patient did not tolerate ambrisentan because of severe headache and nausea, and also liver enzymes again began to rise. It was replaced by sitaxentan after 10 days, once more, but again, ALT, AST and IgG globulins increased. A relapse of autoimmune hepatitis was assumed.

OUTCOME AND FOLLOW-UP

Sitaxentan treatment was stopped after 14 days, and the patient received 20 mg corticosteroids and 100 mg azathioprine. Under this therapy, liver enzymes normalised by August 2010. Therapy was then reduced to 5 mg/day of steroids and 75 mg/day of azathioprine. At her last visit in January 2011, the laboratory values were normal, although antiactin antibodies were still present (titre 1:640) and IgG globulins were slightly elevated. PAH has remained stable since 2007. At that time complement fixing anti-SLA/LP antibodies reacting in the western blot with a 48 kDa protein were detected for the first time (figure 2) using an in-house assay as recently described.⁹ All patient's sera were also tested by an in-house ELISA using a chromatographically purified antigen fraction,⁹ which confirmed the appearance of anti-SLA/LP antibodies in January 2011.

DISCUSSION

This case report has several interesting aspects. First, although the association of AIH with SSc has been described in a few case reports (for a literature survey, see ref.¹⁰) the manifestation of SSc during the course of AIH

Figure 2 Appearance of antibodies to the soluble liver/liver pancreas antigen (SLA/LP) antibodies reacting with a 48-kDa protein during the follow-up in a patient with an overlap autoimmune hepatitis (AIH)/systemic sclerosis and relapse of AIH due to treatment with sitaxentan. Serum 1: patients' serum sample from 1995; serum 2: serum sample from April 2010; serum 3: serum sample from Jan. 2011; and serum 4: serum from an anti-LP/SLA positive control revealing the typical 52 and 48 kDa determinant.

is rather exceptional and has, to our knowledge, not been presented before. Second, from the follow-up there is evidence that the AIH relapse may have occurred as the consequence of sitaxentan therapy. Third, anti-SLA/LP antibodies appeared in the late period of the follow-up and in a phase, where the patient experienced remission being treated with immunosuppressive drugs. The LP antigen consists of two determinants at 52 and 48 kDa;⁹ the 52 kDa protein has been identified as a UGA suppressor tRNA-associated antigenic protein (tRNP(Ser)Sec)¹¹ recently renamed as SepSecS,¹² the identity of the 48 kDa protein recognised by the patient's sera is still unknown.¹³

Diagnosis of AIH was based on typical histological, clinical and serological features including high titres of

antiactin antibodies and elevated IgG globulins typical for AIH type 1. At the time of first diagnosis of AIH there was neither clinically nor serologically any evidence for a collagen disorder and especially antibodies specific for SSc were lacking. SSc was diagnosed 4 years later due to typical clinical symptoms and the presence of antifibrillar antibodies, which are one of the three autoantibodies that are relevant for the diagnosis of SSc, the other two being antibodies to Scl70 and centromeres.¹⁴ At that time, AIH was in remission.

An increase of transaminases was observed in March 2009, 14 months after therapy with sitaxentan had been started because of SSc-related PAH. There are three explanations; first, the increase of transaminases and IgG globulins reflects the natural course of AIH which is known to be rather fluctuating, particularly in anti-SLA/LP positive cases, and therapy with 5 mg steroids and 50 mg azathioprine at that time was not sufficient to suppress the inflammatory process. Second, it was due to a drug-allergic reaction towards sitaxentan; third, the relapse of AIH was triggered by sitaxentan. The fact that transaminases immediately fell after the withdrawal of sitaxentan although immunosuppressive therapy was not intensified and again increased after re-inducing the drug (figure 1) speaks rather against the hypothesis of the natural fluctuating course. Since no features of allergic reactions (elevation of IgE-globulins, eosinophilia, rash, fever, etc) were observed, also a drug-allergic reaction seems to us rather unlikely. Considering the increase of IgG globulins and reappearance of antiactin antibodies we, therefore, favour the concept that sitaxentan led to an exacerbation. Of course, one could object that the interval between introduction of therapy with the ET-1 antagonist and increase of transaminases is too long to argue for a causal relationship with ERA therapy. However, there are studies showing that the risk of developing abnormal liver function tests after 1 year on sitaxentan is still about 4%.¹⁵ Moreover, for the whole time the patient received low-dose immunosuppression, which may also have delayed the onset of the AIH relapse.

We have also no explanation for the pathomechanisms of the postulated ERA-induced liver damage. Genetic polymorphism and/or formation of neoantigens with the induction of autoimmune reactions may be one cause as postulated for other forms of drug-induced hepatitis.¹⁶ Thus, sitaxentan is metabolised by P450 hepatic enzymes and is an inhibitor of cytochrome P450 (CYP)2C9, 2C19 and 3A4.¹⁵ Binding of sitaxentan to these enzymes—as already shown for antibiotics¹⁶ (and in this respect it is of interest that also treatment with antibiotics induced an increase of transaminases in this patient)—would be one explanation for the postulated formation of neoantigens despite the fact that we did not detect antibodies to any microsomal antigens by IFT or ELISA (not shown) as described in patients with drug-induced hepatitis as, for instance, tielinic acid or hydralazine-induced hepatitis developing antibodies to CYP2C9 or CP1A2, respectively.¹⁷ Nevertheless, the induction of anti-SLA/LP antibodies in this context is of interest, but its cause still remains unknown.

In the meantime, sitaxentan has been withdrawn from the market; however, increase of liver enzymes has been also described for other ERA. Therefore, monitoring of

patients developing liver injury due to treatment with ET inhibitors for signs and serological features of AIH seems to be justified as this case report suggests.

Learning points

- ▶ An increase of liver enzymes can occur during therapy with endothelin inhibitors.
- ▶ In this case, the development or exacerbation of an underlying autoimmune process of the liver has to be taken into consideration.
- ▶ Antisoluble liver/liver pancreas antigen antibodies can newly appear in the course of autoimmune hepatitis type I showing antibodies to nuclei and/or actin.

Competing interests None.

Patient consent Obtained.

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Please cite this article as follows (you will need to access the article online to obtain the date of publication).

Klein R, Hintz E, Staehler G. Exacerbation of AIH in a patient with an AIH/systemic sclerosis overlap syndrome and pulmonary arterial hypertension treated with the endothelin-1 receptor antagonist sitaxsentan. *BMJ Case Reports* 2012;10.1136/bcr-01-2012-5494, Published XXX

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