Autoimmune-like hepatitis during masitinib therapy in an amyotrophic lateral sclerosis patient

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CASE REPORT

Abstract

We report a case of acute severe hepatitis resulting from masitinib in a young amyotrophic lateral sclerosis patient. Hepatotoxicity induced by masitinib, a tyrosine kinase inhibitor, is usually transient with mild elevation of transaminases, although acute hepatitis has been not reported to date. The hepatitis was resolved after masitinib was discontinued and a combination of prednisone and azathioprine was started. The transaminases returned to baseline normal values five months later. This is the first case in the hepatitis literature associated with masitinib. The autoimmune role of this drug-induced liver injury is discussed. Physicians should be aware of this potential complication.

Key words: Drug-induced liver injury; Masitinib; Amyotrophic lateral sclerosis; Tyrosine kinase inhibitors; Autoimmunity; Autoimmune-like hepatitis; Idiosyncratic drug hepatotoxicity
Core tip: Physicians must be aware of the possibility of drug-induced liver injury in clinical trials, despite the drug having been shown to be of limited hepatotoxicity when tested in phase I-II trials. We present an example of a patient resembling an autoimmune hepatitis. Despite discontinuing masitinib, the transaminases did not return to their baseline values for five months.

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a rapidly progressive neurodegenerative disorder predominantly affecting motor neurons, leading to generalized muscle paralysis and death from respiratory failure. Mean survival subsequent to clinical onset is 3-5 years, although patients may survive longer if they accept mechanical ventilation and other aggressive life support measures. The pathogenic processes underlying ALS are multifactorial and not yet fully determined. There is no effective treatment for the disease apart from these measures, except for riluzole, which is the only approved drug for the treatment of ALS, and which prolongs survival by a mere three months. Immunomodulatory drugs have recently been suggested as a possible therapeutic approach in ALS. A multicenter, double-blind, randomized placebo-controlled, exploratory phase II/III study of masitinib in patients with ALS treated over 48 wk, with an extension phase, is ongoing. The patients recruited are being randomized to placebo or masitinib at an initial dose of 3 or 4.5 mg/kg per day (in combination with riluzole) administered orally in two daily intakes[1].

We report here a case of a young ALS patient treated with riluzole, who presented high transaminase levels of up to 64 times baseline values, compatible with a hepatitic pattern, 12 wk after the introduction of masitinib.

CASE REPORT

A 40-year-old woman was diagnosed with a predominantly bulbar ALS in October 2011, when she started riluzole 100 mg/d and vitamin E 400 mg/d. Some months later, she started treatment with paroxetine 20 mg due to a reactive depression.

On the 30th December 2013, the patient decided to participate in a clinical trial with masitinib[2]. After signing an informed consent form, and completion and review of all the screening visit assessments, she was randomized to oral masitinib vs placebo 300 mg a day. At that time, alanine aminotransferase (ALT) was 14 IU/L, aspartate aminotransferase (AST) was 25 IU/L, alkaline phosphatase (ALP) was 85 IU/L, gamma-glutamyltransferase (GGT) was 13 IU/L, and total bilirubin was 0.60 mg/dL.

The patient reported mild nausea in the week 12 visit (March 27, 2014). As a result, she was started on metoclopramide 10 mg before meals on demand. Blood test results showed non-clinical significant values. Afterwards, in the scheduled biochemistry blood test in the visit in week 24 (June 16, 2014), she presented elevated transaminases [AST, 228 IU/L (normal values 10-30 IU/L) and ALT, 250 IU/L (normal values 7-34 IU/L). These values were considered severe (grade 3) according to the protocol and administration was consequently discontinued. Riluzole was also discontinued. Treatment was unblinded according to the pharmacovigilance protocol. The patient had been randomized to the masitinib 300 mg/d arm. The transaminase values continued to rise to the following maximum values: AST, 2221 IU/L; ALT, 1166 IU/L; ALP, 240 IU/L; and GGT, 204 IU/L. Bilirubin rose to 10.47 mg/dL.

Laboratory screening for viral hepatitis included IgM anti-HAV, anti-HCV, HBsAg, anti-HBc, IgM anti-HBc, anti-HEV, IgM anti-HEV, were all negative. Antinuclear antibodies (ANA) were negative and immunoglobulins were within normal limits. Liver ultrasonography showed a normal liver parenchyma and normal biliary tract. Hepatic biopsy showed diffuse parenchymal involvement with marked portal lymphohistiocytic infiltrate, with neutrophils, numerous eosinophils and only isolated plasma cells, accompanied by extensive interface hepatitis, occasional bridging necrosis and severe lobular necroinflammatory activity. These features suggest an acute drug-induced liver injury.
with autoimmune-like histological pattern (Figure 1).

After that, the patient started taking oral prednisone 60 mg daily and oral azathioprine 50 mg daily. Treatment with prednisone in combination with azathioprine was chosen, as this combination has been associated with fewer side effects than conventional corticosteroid regimen alone, and reduces exacerbations after discontinuation of immunosuppressive drugs, according to most guidelines and recommendations on managing drug-induced liver injury (DILI) with autoimmune features.[2-5]. The patient’s clinical and biochemical status improved with this treatment. Figure 2 shows the evolution of transaminase and bilirubin values. The laboratory values in February 2015 were 41 IU/L (AST), 25 IU/L (ALT), 38 IU/L (GGT), 97 IU/L (ALP) and 1.01 mg/dL (bilirubin).

**DISCUSSION**

Masitinib is a highly selective tyrosine kinase inhibitor with anti-tumoral and anti-inflammatory activity. Masitinib is a promising treatment option for patients with solid tumors, particularly GIST.[6-9]. Indeed, it is particularly efficient in controlling the survival, migration and degranulation of mast cells (and thus indirectly controlling the array of proinflammatory and vasoactive mediators these cells can release), through inhibition of essential growth and activation signaling pathways[10]. Human clinical trials have been performed in neurological and inflammatory disorders. Promising results have consequently been obtained in Alzheimer’s disease, rheumatoid arthritis, progressive multiple sclerosis, and systemic mastocytosis phase II/III clinical trials.[11-14]. Masitinib has a good safety profile. The maximum tolerated dose has not yet been reached in phase I studies of healthy volunteers or in cancer patients orally administered up to 1000 mg/d[6]. Dose levels of 7.5 mg/kg per day have shown no significant toxicity. The side-effect profile of masitinib appears to be similar to other tyrosine kinase inhibitors. Those commonly observed in long-term administration were gastrointestinal (nausea, vomiting), hematological (anemia, lymphopenia, neutropenia, thrombocytopenia), dermatological (eyelid and facial oedema, rash), and others (pyrexia, jaundice, dehydration, general deterioration in physical health, hypokalaemia, and thrombosis)[1,6-9,11-14]. Liver functions should be closely monitored in patients with impairment, and especially those who are also treated with another cytochrome P450 3A4 inhibitors.

Our patient had an acute icteric hepatitis with elevated transaminases (> 10 ULN) and bilirubin (> 5 ULN), which can be considered a grade IV hepatotoxicity. Six months after beginning masitinib treatment, she developed a marked elevation of ALT; the drug was discontinued but transaminase levels and bilirubin continued rising for 9 wk. After immunosuppressive therapy, the patient improved and a biochemical remission was observed. Grade 3 and 4 liver adverse events, as in our case, have previously been reported with other tyrosine kinase inhibitor drugs. After a literature review, we found at least 16 cases of severe DILI secondary to other members of the TK inhibitors family, predominantly with erlotinib[15-17], but never with masitinib. Interestingly, in four of the cases associated with imatinib, clinical features, time course, histological pattern in the liver biopsy, and a good response to corticosteroids were consistent with an autoimmune DILI[1,6-9,11-14].

The exact hepatotoxicity mechanisms of tyrosine kinase inhibitors are still unknown, and the pathogenesis of most drug-induced autoimmune hepatitis is complex and not fully understood. At present, limited information is available about the mechanisms by which masitinib and other TK inhibitors induce immune-mediated hepatotoxicity, although a hypersensitivity mechanism has been suggested for imatinib. It has been established that reactive metabolites (RM) are formed during the TK metabolism. These RM in genetically susceptible

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**Figure 2** Alanine aminotransferase, aspartate aminotransferase, and bilirubin concentrations before and after treatment with masitinib. AST: Aspartate aminotransferase; ALT: Alanine aminotransferase.

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individuals (within the HLA region on the short arm of chromosome 6, especially those encoding DRB1 alleles) lead to alterations of neighboring host proteins or macromolecules, mainly peptides, and give rise to neoantigens, which are recognized as foreign by the host immune system and able to activate an immune response[4,22,23].

Although in most cases of DILI the patient recovers when the drug is stopped, this is not always the rule. In some cases, hepatic damage continues after treatment with the drug is stopped, as occurred in our patient. One possible explanation for the continuation of liver injury after the administration of the drug has been stopped is that the mechanism involves an autoimmune component, which could continue in the absence of the inciting drug. This mechanism is probably what happened in our case, since the histological pattern was consistent with an autoimmune like histological pattern. Although the existence of autoantibodies was not demonstrated, the excellent response to immunosuppressive treatment, which achieved a biochemical remission of inflammatory activity, suggests that a drug-induced autoimmune-like hepatitis was the type of drug reaction responsible for masitinib hepatotoxicity in our patient[3-5,23-25].

Our patient was taking riluzole (one of the principal criteria for inclusion in this trial). Riluzole is metabolized in the liver via cytochrome P450 (CYP) hydroxylation (principally by CYP1A2) and glucuronidation. Treatment with riluzole has been associated with increases in AST in a small proportion of patients. These increases are usually small and transient and to our knowledge, only 3 cases of icteric toxic hepatitis associated with riluzole have been reported[26,27]. We do not know whether riluzole could increase the risk of hepatotoxicity to masitinib.

These observations mean that it is necessary to investigate the real mechanisms involved in order to explain the hepatotoxicity of these drugs. Meanwhile, taking into account the ongoing clinical trials with masitinib - in our case with Amyotrophic Lateral Sclerosis - and its FDA approval in the treatment of certain types of advanced cancer, it is important that clinicians are aware of this potential complication in practice.

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