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REVIEW

Thalidomide-induced severe hepatotoxicity

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Introduction

Thalidomide was introduced in Europe during the 1950s as a sedative agent and was found to alleviate symptoms of morning sickness. However, it was withdrawn in 1961 due to its teratogenic properties. Around that time, the immunomodulatory effects of thalidomide were recognized, and it became the drug of choice for erythema nodosum leprosum [1]. It is also being used to alleviate symptoms of HIV-induced cachexia, presumably via its suppression of tumor necrosis factor-a [2, 3]. In the field of hematology, thalidomide appeared to inhibit the growth and survival of myeloma cells via its immunomodulatory and antiangiogenic properties. It was approved by the Food and Drug Administration (FDA) in May of 2006 for use in combination with dexamethasone for treatment patients with of newly diagnosed multiple myeloma [4–6].

Common side-effects during treatment with thalidomide are sedation, constipation, skin rash and peripheral neuropathy [7]. Less frequently bradycardia, hypotension and hypothyroidism have been described. Deep vein thromboses has been reported in patients receiving the combination of thalidomide and cytotoxic agents [8]. More severe toxicity in the form of Stevens–Johnson syndrome and toxic epidermal necrolysis has also been reported [9]. Hepatotoxicity is listed as an extremely rare adverse effect, though a limited number of reports have demonstrated it to be a potentially serious adverse effect [10–12]. Post marketing surveillance of thalidomide since reintroduction in 1998 has identified one case where the cause of death was thought to be directly due to treatment with thalidomide [13]. Thalidomide induced fulminant hepatic failure, which proved to be fatal in a 64-year-old woman has also been described in Mayo clinic proceedings [14]. Lenalidomide induced severe hepatotoxicity was recently described by Hussain et al. in Blood in 2007 [15], cautioning regarding the use of immunomodulatory group of drugs. We describe two such cases treated with thalidomide, one serious enough to be fatal.

Case report

A 79-year-old African American woman with a prior history of hypertension, chronic kidney disease and monoclonal gammopathy of undetermined significance for 2–3 years, was diagnosed recently with IgA lambda multiple myeloma, when she was admitted with acute renal failure and hypercalcemia. With aggressive hydration, her kidney function returned to baseline with normalization of her calcium, and she was started on treatment with thalidomide and dexamethasone; the former was started at 50 mg a day which she took for a week. The dose was increased by 50 mg every week till she reached a maximum of 200 mg a day. Each treatment cycle lasted 28 days with thalidomide given daily and dexamethasone started on day 1 of each cycle and dosed as pulse dexamethasone, i.e. 40 mg daily 4 days on and 4 days off schedule as per standard. Her other medications included memantine 10 mg twice daily, amlodipine 10 mg daily, metoprolol 25 mg twice daily, omeprazole 20 mg daily, and warfarin (for DVT prophylaxis). The dose of warfarin was adjusted to maintain therapeutic international normalized ratio (INR). She denied any history of alcohol or illicit drug use. She denied using over the counter medications or herbal supplements at this time.

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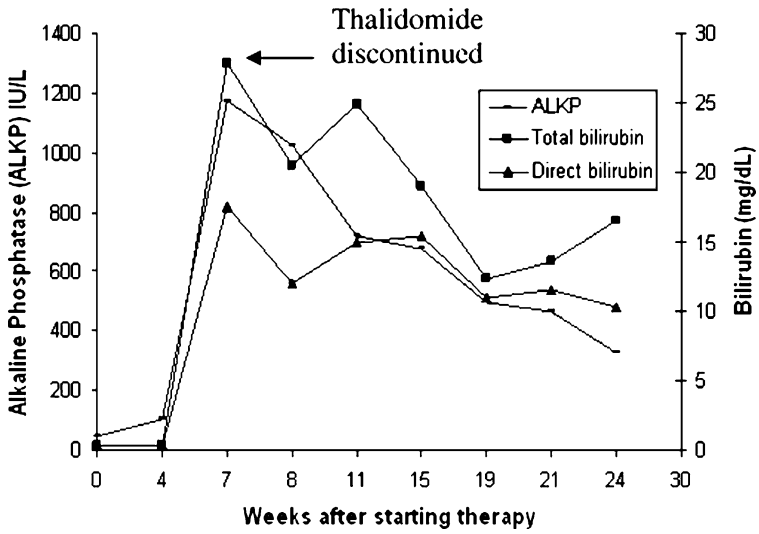

Fig. 1 Rise in liver enzymes, mainly alkaline phosphatase and bilirubin within 7 weeks after starting therapy. Thalidomide was discontinued at that time but note that the liver functions never returned to baseline

She tolerated her first cycle of treatment well, and was prescribed her second cycle, each cycle for duration of 4 weeks. At the end of 4 weeks she was noticed to have a high INR of 19.8 requiring holding off her warfarin therapy and the need for parenteral vitamin K. Liver function tests were normal at baseline, however since hepatotoxicity was not suspected to be the cause of elevated INR, and since her INR was decreasing with above interventions, LFT's were not recorded at this time. Towards the end of her second cycle, about 7 weeks after starting treatment with thalidomide, she was admitted to the hospital with a couple of weeks history of worsening jaundice, fatigue, decreased appetite, abdominal discomfort, and 9–10 pounds of weight loss. She was found to have abnormal liver function tests, with her INR at 3.74 and her warfarin still on hold since week 5, a high total bilirubin of 27.9 mg/dl, direct bilirubin of 17.5 mg/dl, alkaline phosphatase of 1172 IU/L, with borderline elevated SGOT of 187 IU/L and SGPT of 392 IU/L, as shown in Fig. 1, suggesting a cholestatic picture. Her liver function tests checked a month prior to this hospitalization had been normal. Thalidomide was considered as a potential cause, and was placed on hold. None of the other medications she was taking is commonly known to cause significant liver damage.

Diagnostic evaluation consisted of serological tests, all of which were negative for acute and chronic hepatitis including hepatitis A, B and C, Epstein–Barr virus, herpes simplex virus, and cytomegalovirus. Liver architecture appeared to be normal on ultrasound and MRI examination, with no fatty infiltration. Doppler ultrasound failed to show any evidence of portal vein thrombosis. Liver functions tests improved only slightly over the course of 10–14 days and hence a liver biopsy was performed, which showed cholestasis with a decreased number and destruction of bile ducts. In view of the clinical history, cholestasis and bile duct injury, the architectural appearance was felt to be consistent with drug related damage. Pathological manifestations of various drugs causing liver injury vary widely from hepatocellular injury, cholestasis, to autoimmune or vascular/venoocclusive diseases. The classic pattern of liver involvement by thalidomide has not been studied and our knowledge is based only on the few case reports that have been published in the literature. However, the clinical setting of occurrence of the hepatic insult within weeks after starting thalidomide, and lack of any alternative causative factor, made us believe that this was consistent with thalidomide induced hepatotoxicity.

Evaluation with the Naranjo adverse drug reaction probability scale indicated a possible relationship between administration of thalidomide and elevated liver function tests [16]. Regular follow up for the next few months continued to demonstrate elevated liver enzymes. She was felt to be hospice appropriate due to her liver failure from which she never recovered and her underlying untreated multiple myeloma, treatment of which was on hold on account of her liver injury. She died after 3 months.

Our second case is a 57-year-old woman with a prior history of diabetes, hypertension, and high cholesterol, recently diagnosed with IgG kappa multiple myeloma, and started on thalidomide and dexamethasone as first line treatment. Thalidomide was started at 100 mg daily for 14 days, increasing to a maximum of 200 mg daily with pulse dexamethasone of 40 mg a day, 4 days on and 4 days off schedule as per standard. Her other medications included nifedipine 90 mg daily for hypertension, glucophage 1 g daily for diabetes, multivitamin daily and ibuprofen and hydrocodone with acetaminophen for pain from her osteoarthritis. She tolerated the first cycle of therapy well. We hence decided to continue with her second cycle; however treatment had to be discontinued due to an elevation in her liver enzymes. Her baseline liver tests were within normal limits, while after one month of starting her on

thalidomide, alkaline phosphatase was up to 175 IU/L, about twice the upper limit of normal, while SGOT and SGPT were 214 and 398 IU/L, respectively, about 10 times the upper limit of normal. Though her liver profile seemed to indicate more hepatic damage rather than the cholestatic picture as was seen with patient 1, given the abnormal liver function tests shortly after starting thalidomide, we felt it prudent to hold the medication. Whether exposure to longer duration of thalidomide would cause more of a cholestatic liver damage remains unknown. Hepatitis serology for hepatitis A, B and C were negative. No further work up was done. The patient was on ibuprofen and hydrocodone with acetaminophen for arthritis for at least 4–5 years without changes in her liver functions prior to this episode and hence though acetaminophen is well known to cause liver damage, was not felt to be the likely causative factor for her liver damage. Also her liver function tests were followed closely over the next few weeks, and they returned to baseline within about 2 weeks after stopping thalidomide. Her treatment thereafter was switched to bortezomib, and she is currently doing well.

Discussion

Though unlike lenalidomide, thalidomide does not undergo significant hepatic metabolism and reports have shown minimal involvement of cytochrome P450 system. Thus clinically important interactions between thalidomide and other drugs that are also metabolized by this enzyme system are unlikely. The major route of thalidomide breakdown in humans and animals is through spontaneous hydrolysis with subsequent elimination in the urine. This together with the clinical course, liver biopsy findings and timeline in our patients strongly suggest thalidomide as a causative factor for the severe and fatal drug-induced hepatotoxicity (first patient). Neither of our patients received more than 2 units of blood transfusion in their course of treatment and hence we do not think, transfusion induced graft verses host disease like condition would be suspected to have any role in the liver damage. None of the medications either of our patients was on are commonly associated with severe hepatotoxicity. The exact mechanism for thalidomide induced liver damage remains unclear. However, review of the literature of the few case reports published, support the possibility of thalidomide induced severe liver injury. To our knowledge 2 case reports, one during the post marketing surveillance and one recently described in the Mayo clinic proceedings have indicated thalidomide induced hepatotoxicity to be potentially fatal. Since approval of thalidomide in treatment of multiple myeloma, its use has been increasing. Hence, rare and possibly unrecognized side effects are likely now being increasingly recognized.

Based on our findings, we would like to alert clinicians to this potential complication and recommend regular monitoring of liver function tests during treatment with the drug. No standard algorithm exists for LFT monitoring, we, on our part, include monitoring of LFTs along with other labs, usually every week for first 4 weeks, followed by on a every other week schedule throughout the course of their therapy.

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