Acute autoimmune hepatitis after fingolimod discontinuation and glatiramer acetate starting in a Relapsing-Remitting Multiple Sclerosis patient

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INTRODUCTION

An association has been described between multiple sclerosis (MS) and autoimmune hepatitis (AIH) (1). AIH has been reported in untreated MS patients (2) and in patients treated with Interferon-beta (βIFN) (3), Glatiramer Acetate (GA) (4) and Natalizumab (NTZ) (5, 6). Fingolimod (FTY) is an oral sphingosine-1-phosphate receptor modulator approved for Relapsing-Remitting Multiple Sclerosis (RR-MS) treatment. It acts retaining certain immune cells in secondary lymphoid organs and preventing their infiltration of central nervous system (7). Increased alanine aminotransferase (ALT) values > 3 times the upper limit of normal is reported to occur in 8% of patients treated with FTY. The causes of hepatic effects are unknown and generally attributed to drug-induced liver injury (DILI).
In our case-report we describe in a MS patient: a) hepatic injury during FTY therapy (DILI), b) withdrawal of FTY and hepatic recovery, c) severe AIH following FTY discontinuation and GA starting.

CASE REPORT

We describe the case of a 52-year-old male patient suffering from MS since 2002. He had no further comorbidities except for cluster headache and hypertension; family history was negative for autoimmune diseases. At the time of MS diagnosis the presence of Anti-Nuclear Antibodies (ANA) at low title (1:80) was demonstrated.
He was first treated with βIFN-1a (Rebif 44 mcg) from May 2003 to July 2011; during this period he developed a trigeminal neuralgia which required chronic treatment with ox-carbazepine. During early βIFN therapy a mild liver enzymes increase was observed, that spontaneously recovered.
In September 2011 NTZ was started because of incomplete recovery from clinical MS activity (with EDSS increase from 2.0 to 3.5). Liver function remained normal during NTZ therapy.
NTZ was stopped in October 2013 (26 infusions) because of increased PML risk and FTY was started in January 2014.
Concomitant medications (ongoing before FTY starting) included enalapril, baclofen, oxcarbazepine and pregabalin.
After 10 months of FTY therapy (November 2014) laboratory findings showed a mild increase in ALT values (61 U/l) and a marked increase in Gammaglutamyl Transferase (GGT; 496 U/l) (see Fig.1). Total bilirubin, International Normalized Ratio (INR) and albumine were normal; hepatic ultrasound did not show any signs of parenchymal injury. Patient was asymptomatic for abdominal pain, nausea or vomiting; physical examination was normal.
Treatment with FTY was stopped according to gastroenterologic advice, with an hypothesis of a FTY-induced DILI.
After a short washout period, GA was started to prevent disease reactivation.
In April 2015 (five months after FTY discontinuation) a consistent elevation of transaminases (AST 321 U/l, ALT 782 U/l) and GGT (190 U/l) was observed. Viral markers for Hepatitis B virus (HBV), Hepatitis C virus (HCV), Hepatitis A virus (HAV), Human Immunodeficiency Virus (HIV), Cytomegalovirus (CMV), Epstein Barr Virus (EBV) were negative.
Anti-Smooth Muscle Antibodies (ASMA), Anti-Liver/Kidney Microsome Antibodies (LKM), Anti-Mitochondrial Antibodies (AMA) and Anti-Neutrophil Cytoplasmic Antibodies (ANCA) were negative, while ANA title raised to 1:320, with homogeneous pattern; gamma-globulins were increased (Ig G 3046 mg/dl; normal 840-1660).

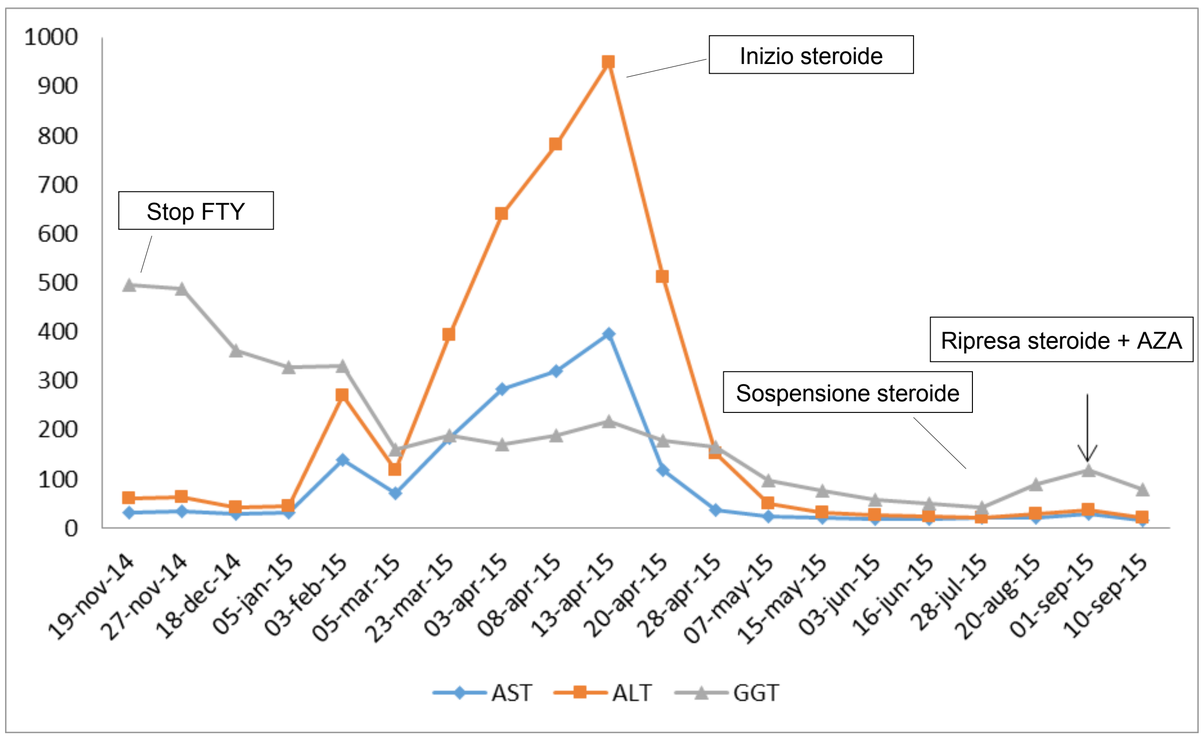

Fig. 1 Liver enzymes values after fingolimod discontinuation

A liver biopsy was performed, which demonstrated a chronic hepatitis with diffuse hepatocellular inflammatory necrosis and plasma cells portal infiltrates. Numerous eosinophils were detected too. The histological features were consistent with AIH.
Patient started corticosteroid therapy (intravenous methylprednisolone 80 mg for two days, followed by oral tapering with prednisone) with progressive normalization of liver enzymes, ANA and gamma-globulins levels.
In August 2015 (one month after prednisone interruption) we observed a new increase of GGT (119 U/l) and a positive ANA title (1:160, homogeneous pattern). Steroid treatment was resumed, GA was stopped and patient was started on azathioprine (50 mg/day), which is still ongoing and well tolerated. One month after azathioprine introduction liver enzymes are normal and ANA title is negative.

DISCUSSION

An association has been described between MS and AIH (1).
This patient was predisposed to autoimmune systemic phenomena, as demonstrated by fluctuating ANA title.
In our case-report, a definite diagnosis of AIH, proved by both histological and serological findings and supported by optimal corticosteroids response, was demonstrated after FTY withdrawal and GA starting.
Hepatic damage during FTY therapy (seemingly by DILI mechanism) and leading to FTY discontinuation might have contributed to triggering a following AIH. Timing of occurrence of autoimmune hepatitis in this patient corresponds to the interval between FTY discontinuation and MS reactivation reported in Literature (8,9). A correlation may exist between T lymphocyte release following FTY cessation and a rebound of disimmune activity, ultimately leading even to autoimmune hepatitis. However this is the first case report of AIH after FTY discontinuation; therefore other hypotheses need to be considered.
GA therapy may have played a role in inducing AIH in this patient. In fact, the mechanism by which GA exerts its therapeutic effects is not fully elucidated. One proposal is that it can induce T-helper type 2 cells releasing cytokines like IL-4, IL-6 and IL-10, which may enhance the production of autoantibodies, thus inducing autoimmune processes in genetically predisposed patients (10).
In conclusion, according to our data, GA therapy or FTY withdrawal (with an excessive T-cells release, usually arising between 2-4 months after FTY discontinuation) may have operated singularly or may have co-operated in inducing an autoimmune hepatitis.

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Disclosure All authors have nothing to disclose

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