

## Successful rituximab therapy in refractory autoimmune hepatitis and Evans syndrome

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### ABSTRACT

A 44-year-old woman was found to have elevated aminotransferases, twice the upper limit of normal. Liver biopsy demonstrated a mixed inflammatory process suggestive of both primary biliary cirrhosis and autoimmune hepatitis (AIH). Prednisone and azathioprine were started, with normalization of aminotransferases. Six months later, she returned with worsening pruritus and re-evaluation demonstrated probable reactivation of AIH with acute elevation of liver injury tests. Repeat liver biopsy was suggestive of a flare of AIH which did not respond to prednisone, azathioprine, or mycophenolate mofetil. One month later the patient was hospitalized for sudden onset of anemia and thrombocytopenia, suggestive of autoimmune hemolytic anemia and idiopathic thrombocytopenic purpura consistent with Evans syndrome. Rituximab was initiated and mycophenolate mofetil discontinued. After one infusion of rituximab, liver injury tests significantly improved. Within four weeks of rituximab infusion (4 doses) the patient's Evans syndrome completely resolved with normal hemoglobin and platelet levels; aminotransferases also significantly improved to less than twice the upper limit of normal.

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**Key words:** Anemia, hemolytic, autoimmune; Evans syndrome; Hepatitis, autoimmune; Rituximab.

### Tratamiento exitoso de hepatitis autoinmune y síndrome de Evans con rituximab

Una mujer de 44 años de edad se presentó para la evaluación de una elevación de aminotransferasas, dos veces sobre lo normal. La biopsia hepática demostró un proceso inflamatorio mixto sugerente de cirrosis biliar primaria, así como de hepatitis autoinmune (HAI). Se comenzó tratamiento con prednisona y azatioprina, con normalización de las aminotransferasas. Sin embargo, 6 meses después la enferma regresó por presencia de prurito progresivo y tras nueva evaluación clínica se sospechó una reactivación de la HAI, con elevación aguda de las pruebas de lesión hepática. Una nueva biopsia sugirió agudización de la HAI, la cual fue refractaria a tratamiento con prednisona, azatioprina y micofenolato de mofetilo. Un mes después la paciente fue hospitalizada tras el desarrollo agudo de anemia y trombocitopenia, sugerentes de una anemia hemolítica autoinmune y púrpura trombocitopénica idiopática consistentes con el síndrome de Evans. Se discontinuó el micofenolato de mofetilo y se inició tratamiento con infusiones endovenosas de rituximab. Tras la primera infusión, las pruebas de función hepática mejoraron significativamente. Tras 4 semanas de rituximab (4 dosis), el síndrome de Evans se resolvió completamente, con cifras normales de hemoglobina y plaquetas; además, las aminotransferasas mejoraron a niveles menores a dos veces lo normal.

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**A**utoimmune hepatitis (AIH) is a chronic disease characterized by hepatocellular inflammation and necrosis<sup>1</sup>. Although the exact etiology is unknown, it is often associated with elevated immune markers and seen in the setting of other autoimmune disorders such as rheumatoid arthritis, Graves's disease, Sjogren's syndrome and lupus<sup>1,2</sup>. The onset of AIH is thought to be an immunological cell mediated process triggered by several potential factors including viral prodromes, chemical agents and even genetic predisposition. The presentation ranges from fulminant hepatic failure to chronic asymptomatic hepatitis to stable cirrhosis<sup>1,3</sup>. AIH is also linked to other cell mediated processes including autoimmune hemolytic anemia (AIHA) and idiopathic thrombocytopenic purpura (ITP).

The mainstay of treatment for AIH has been corticosteroids with or without azathioprine<sup>4</sup>. About two thirds of patients respond to initial therapy with this combination but about half relapse after drug withdrawal. Once remission has been achieved, prednisone or azathioprine can be used for maintenance therapy to prevent relapse<sup>3,4</sup>. Cases of AIH refractory to standard therapy must be treated with alternative methods as untreated AIH can lead to cirrhosis and liver failure<sup>1</sup>. For patients refractory to corticosteroid therapy and/or azathioprine combination therapy, other immunosuppressive drugs such as tacrolimus, methotrexate, and mycophenolate mofetil have been attempted with inconsistent outcomes<sup>4, 5</sup>. Rituximab, with CD20 targeted, has not previously been a common mode of treatment for refractory AIH. Although there are documented cases of its effectiveness in AIHA and ITP, the data on efficacy of rituximab specifically in AIH are limited<sup>6-12</sup>. We describe a case of severe AIH and Evans syndrome successfully treated with rituximab.

### Case report

A 44 year old woman with Sjogren's syndrome and systemic lupus erythematosus presented with severe headaches; diagnostic evaluation revealed elevated serum aminotransferases twice the upper limit of normal. Liver biopsy demonstrated a mixed inflammatory process suggestive of both primary biliary cirrhosis (PBC) and AIH: mixed portal and pericellular infiltrates of lymphocytes,

plasma cells and eosinophils with areas of granulomatous inflammation. Antinuclear antibody, antimitochondrial antibody and smooth muscle antibody were all positive. The liver histology in conjunction with laboratory values suggested an AIH-PBC overlap syndrome and she was treated with prednisone 20mg daily, azathioprine 100 mg daily, and ursodeoxycholic acid 500mg twice daily. After four weeks of therapy the aminotransferases returned to normal. Rifampin 150mg three times a day was started for management of pruritus.

Six months later the patient complained of worsening pruritus. Re-evaluation demonstrated probable reactivation of AIH with acute elevation of liver injury tests (total bilirubin 1.3 mg/dL, alkaline phosphatases 124 IU/L, ALT 1145 U/L, AST 630 U/L) despite ongoing therapy with prednisone 10mg daily and azathioprine 100mg daily. The differential diagnosis included flare of AIH, an idiopathic allergic reaction, or drug toxicity related to rifampin or meloxicam (prescribed for arthritic pain). A repeat liver biopsy demonstrated that the portal changes of PBC were stable but that periportal hepatitis with marked active lobular changes was more pronounced, suggestive of a flare of AIH. Prednisone was increased from 10mg daily to 40mg daily and azathioprine was increased to 150mg daily with minimal response in liver enzymes over a four week period. Out of concern for uncontrolled AIH, azathioprine was discontinued and mycophenolate mofetil was initiated at 1 gram twice daily. Although there was some initial improvement in liver enzymes they remained consistently elevated over another four week period (total bilirubin 1.7 mg/dL, alkaline phosphatases 152 IU/L, ALT 519 U/L, AST 363 U/L). Four weeks later, the total bilirubin was 4.6 mg/dL, alkaline phosphatases 133 IU/L, ALT 245 U/L and AST 166 U/L. The lack of response to adequate immunosuppression prompted reevaluation of the possibility of drug toxicity so rifampin and meloxicam were discontinued. One week after stopping rifampin and meloxicam, minimal improvement was seen with total bilirubin 2.1 mg/dL, alkaline phosphatases 144 IU/L, ALT 221 U/L, AST 198 U/L.

One month after discontinuation of rifampin and meloxicam, the patient was hospitalized for sudden onset of anemia and thrombocytopenia of unknown etiology. Hematologic workup revealed a Coombs test positive for IgG and complement,

elevated serum lactate dehydrogenase, and decreased haptoglobin. Bone marrow biopsy was positive for erythroid hyperplasia. These findings were suggestive of AIHA and idiopathic ITP consistent with Evans syndrome. In the setting of a flare of AIH, this patient had also developed Evans syndrome despite immunosuppression with prednisone and mycophenolate mofetil. After multidisciplinary discussion, rituximab was initiated at a dosage of 375 mg/m<sup>2</sup> infused once a week for a four week course of therapy. Prednisone was increased from 40 mg daily to 80 mg daily and mycophenolate mofetil discontinued. After one infusion of rituximab, which the patient tolerated well, liver injury tests improved considerably: total bilirubin 1.4 mg/dL, alkaline phosphatases 125 IU/L, ALT 92 U/L and AST 79 U/L. Within four weeks, the anemia and thrombocytopenia completely resolved with hemoglobin and platelet levels returning to normal. Liver tests also significantly improved over another three week period to less than twice the upper limit of normal with a total bilirubin 0.7 mg/dL, alkaline phosphatases 63 IU/L, ALT 64 U/L and AST 50 U/L. Prednisone was tapered down by increments of 5 mg every two weeks to 30 mg daily. A year after completion of rituximab, the serum aminotransferases remain within normal range without evidence of AIH reactivation and hemoglobin and platelet counts continue to remain normal.

## Discussion

In this case, a 44-year-old woman with several autoimmune disorders including Evans syndrome and AIH refractory to multiple immunosuppressive regimens responded favorably to treatment with rituximab. The effectiveness of rituximab in Evans syndrome has been established in a number of cases<sup>6,7,13</sup>. However, the successful treatment with rituximab for patients with a combination of Evans syndrome and concurrent autoimmune hepatitis is limited.

Rituximab is a human monoclonal antibody that targets the CD20 antigen which is a transmembrane protein on pre-B and mature B lymphocyte surfaces that regulate the cell cycle<sup>14</sup>. Rituximab has been linked to apoptosis induction, an antiproliferative effect, Fc receptor polymorphism and antibody-dependent cytotoxicity.

It is most effective in B lymphocyte mediated autoimmune disorders such as AIH because the binding process results in apoptotic lysis of the B cell and reduction in B lymphocytes and immunoglobulins<sup>11,14,15</sup>. The effects of a once weekly infusion with rituximab for four weeks can be effective for up to one year. With the extensive use of rituximab for other chronic disorders including Non-Hodgkin's lymphoma, ITP, Waldenström's macroglobulinemia and chronic lymphocytic leukemia, the infusions have been well tolerated without significant adverse reactions<sup>11</sup>. Notable side effects include hypotension, flushing, urticaria and angioedema. These most commonly occur with the first infusion. Although rare, serious adverse reactions including progressive multifocal leukoencephalopathy, Stevens-Johnson syndrome, serious infection from cytopenias, aplastic anemia or lymphocytopenia can occur<sup>9</sup>. Rituximab is considered an effective alternative therapy for refractory ITP based on the number of successful cases documented<sup>6-9</sup>. In this case rituximab was found to be effective against a combination of not only AIHA and ITP but also AIH.

The treatment of AIH with rituximab is an emerging alternative therapy. In AIH, B cell expansion and hyperactivity is a notable aspect of activated plasma cell proliferation and immunoglobulin activation that damages the hepatocyte through targeted natural killer cell activity<sup>4</sup>. The rationale for using monoclonal CD20 antibody therapy is that by targeting the CD20 cell surface receptor on B lymphocytes and inducing apoptosis, the reduction in the number of activated plasma cells will reduce hepatocyte damage and contain the inflammatory process<sup>11,15</sup>. On presumption of this theory, there have been a number of cases reported on the overall favorable outcomes of rituximab therapy on patients with refractory AIH<sup>4,8</sup>.

Our patient had AIH and Evans syndrome that were refractory to standard therapy. However, she responded well to rituximab with minimal side effects. The hemoglobin, platelets and aminotransferases were within normal range and rapidly responsive to rituximab even prior to completion of the four week treatment course. A year after completion of the rituximab therapeutic course, she remains in remission from AIH as well as from Evans syndrome. She continues to be on maintenance therapy with prednisone 30mg daily to prevent relapse.

Although the benefits of rituximab in several autoimmune diseases have been demonstrated, there are only a few successful cases reported specifically for AIH and concurrent ITP. Given the remarkable response seen with rituximab infusion in our patient, we propose that further research in the form of clinical trials be undertaken to consider rituximab as a potential cornerstone therapy for AIH.

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