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ORIGINAL ARTICLE

Efficacy of intravenous immunoglobulin therapy in giant cell hepatitis with autoimmune hemolytic anemia: A multicenter study

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Summary

Background and objective: Giant cell hepatitis with autoimmune hemolytic anemia (GCH-AHA) is a rare disease of infancy, of possible autoimmune mechanism with poor prognosis due to its scarce response to immunosuppressive drugs. The aim of this retrospective multicenter study was to evaluate the efficacy and safety of intravenous immunoglobulin (IVIg) treatment in inducing and maintaining remission of the liver disease, in patients with GCH-AHA.

Methods: Seven children with GCH-AHA, four newly diagnosed, and three in relapse, being treated with different therapies, received one to three IVIg infusions (0.5 to 2 g/kg) in association with other immunosuppressive drugs. Subsequently five of them received monthly sequential IVIg infusions (mean 13.4, range 7—24).

Abbreviations: GCH-AHA, Giant cell hepatitis with autoimmune hemolytic anemia; IVIg, Intravenous immunoglobulin; ULN, Upper limit of the normal; ALT, Alanine aminotransferase; GGT, Gamma-glutamiltransferase.

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Results: IVIg infusions as first-line therapy associated with prednisone and other immunosuppressive drugs significantly ($P = 0.04$) reduced the aminotransferase activity in all patients and normalized prothombin activity in the only patient with severe liver dysfunction. Sequential monthly IVIg infusions determined a steroid-sparing effect and allowed a complete or partial remission in all patients, although with temporary efficacy, since relapse of the hemolytic anemia and/or of liver disease occurred in all patients. IVIg infusions were associated with mild side effects in two patients.
Conclusions: IVIg infusion can be safely and effectively administered in patients with severe GCH-AHA at diagnosis, or in case of relapse, in association with other immunosuppressive drugs. Repeated IVIg infusions may help maintain remission, however, due to their temporary efficacy, they should not be routinely employed.

Giant cell hepatitis with autoimmune hemolytic anemia (GCH-AHA) is a rare and severe disease of unknown pathogenesis, affecting early childhood [1]. It is characterized by the association of an acute liver injury with a diffuse giant cell transformation of hepatocytes and a Coombs-positive hemolytic anemia [1,2]. Although autoimmune liver disease-related autoantibodies are usually absent [2], an autoimmune mechanism explaining liver injury has been hypothesized, because of the constant association with an autoimmune disease, the possible association with other immune-mediated disorders, such as Evan's syndrome, the response to immunosuppressive therapy and the constant disease relapse when therapy is withdrawn or tapered in the first years of treatment [2,3]. Moreover, GCH-AHA represents a therapeutic challenge because of a high mortality despite aggressive immunosuppression [2] and recurrence after liver transplant [4]. High-dose corticosteroids associated with azathioprine have been shown to be the most effective treatment for these patients, even though associated with severe side effects (growth impairment, cataracts, hypertension, vertebral collapse) due to the early life initiation of corticosteroid therapy and the need to maintain it at considerable doses for years [1,2]. For this reason, several immunosuppressive drugs, including, calcineurin inhibitors, sirolimus, micophenolate mophetil and cyclophosphamide have been administered, in addition to corticosteroids, for inducing and maintaining remission, with only partial success [2,5,6]. The incomplete response to these immunosuppressive drugs, that are usually effective in the treatment of juvenile autoimmune hepatitis, might be explained by a different immune-mediated mechanism of liver injury in GCH-AHA, as compared to ''classical'', T cell mediated injury, observed in juvenile autoimmune hepatitis [7]. A recent study demonstrated a diffuse C5b-9 complex deposition on the membrane of giant hepatocytes, suggesting that liver cell injury might be autoantibody-driven and complement-mediated, as in the case of the associated Coombs-positive hemolytic anaemia [8]. Moreover prolonged remission has been recently reported using B cell depletion immunotherapy with chimeric anti-CD20 monoclonal antibody (rituximab) [2,9,10].

Intravenous immunoglobulin (IVIg) has been empirically used in patients with GCH-AHA, mainly at replacement dose and in single administration, for treating the autoimmune hemolytic anemia before the onset of liver disease, but without proof of efficacy [3,6,9,11,12]. In a few patients, IVIg has been used, in association with cyclosporine [6], plasmapheresis [9,14], rituximab [15] for the treatment of the liver disease. Results, however, were not conclusive and usually limited to a slight reduction of aminotransferase activity. Repeated IVIg infusions at immunomodulatory doses were reported to induce remission of the liver disease and to allow corticosteroid discontinuation in two infants with GCH-AHA with severe steroid-related side effects [16,17] (Table 1).

The aim of this multicenter study was to evaluate the efficacy and safety of IVIg treatment in inducing and maintaining remission of the liver disease, in infants with GCH-AHA, as first-line therapy in association with other immunosuppressive drugs and as a steroid-sparing treatment.

Patients and methods

Seven patients diagnosed with GCH-AHA, in 5 pediatric gastroenterology and hepatology units in Italy were included in the study and their charts retrospectively reviewed. Patients' characteristics at diagnosis are summarized in the Table 2. All patients had clinical and biochemical signs of liver disease with diffuse giant cell transformation on liver biopsy (biopsies were revised locally at each different center) and a Coombs-positive (IgG + C type) hemolytic anemia. Liver disease-related autoantibodies were absent in all. All other known causes of liver disease were excluded. Five of the seven children were girls and median age at the beginning of the study was 2.1 years (range 7 months—6.2 years). In six patients, the onset of AHA preceded that of the liver disease by less than a month, and in one patient by 6 months. Three of the six patients were jaundiced at presentation and two infant girls developed a severe interstitial pneumonia requiring intensive care.

Four patients were newly diagnosed, while three were experiencing a relapse, and had already been in treatment for a mean time of 2.3 years (range 0.6—4.5 years) with different immunosuppressive drugs, such as prednisone, azathioprine, cyclosporine and one patient, who had experienced multiple relapses, with tacrolimus, sirolimus and rituximab (rituximab was administered 3.6 years prior to