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EFFICACY OF INTRAVENOUS IMMUNE GLOBULIN THERAPY IN GIANT CELL HEPATITIS WITH AUTOIMMUNE HEMOLITIC ANEMIA: A PROSPECTIVE MULTICENTER STUDY

Giulia Marsalli[1], Silvia Nastasio [1], Marco Sciveres[2], Pierluigi Calvo[3], Ugo Ramenghi, Veronica Albano[4], Carlo Catassi[4] , Sara Lega[5], Alessandro Ventura[5], Giuseppe Maggiore [1]

1 Department of Clinical and Experimental Medicine, University of Pisa, Pediatric Gastroenterology Unit; University Hospital Santa Chiara, Pisa, Italy
2 Pediatric Hepatology and Liver Transplant Unit, UPMC-IsMett, Palermo, Italy
3 ……Torino
4 ……Ancona
5 Institute for Maternal and Child Health, IRCCS Burlo Garofolo, University of Trieste, Trieste, Italy

Corresponding author:

Giuseppe Maggiore MD
Department of Clinical and Experimental Medicine, University of Pisa
Pediatric Gastroenterology
University Hospital Santa Chiara,
Via Roma 67
56124 Pisa, Italy
e-mail: giuseppe.maggiore@med.unipi.it

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Abbreviations: GCH: giant cell hepatitis; AHA: autoimmune hemolytic anemia; IVIg: intravenous immunoglobulins; ULN: upper limit of the normal; ALT: alanine aminotransferase; GGT: gamma-glutamiltransferase; MMF: micophenolate mofetil; PC: plasma cells;

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ABSTRACT

Background and Objective

Methods

Results

Conclusions

Giant cell hepatitis with autoimmune hemolytic anemia (GCH-AHA) is a rare disease of early childhood of unknown pathogenesis[1]. It is characterized by the association of an acute and severe 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such as Evan's syndrome, the response to immunosuppressive therapy and the constant disease relapse when therapy is withdrawn or tapered in the first years of treatment [2,3].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 is a therapeutic challenge with high mortality despite aggressive immunosuppression[2] and recurrence after liver transplant [4]. High dose corticosteroids associated with azathioprine have been shown to represent the most efficacious first-line treatment for these patients, even though associated with devastating side effects (dwarfism, cataracts, arterial hypertension, vertebral collapse) due to the early beginning in life of high doses of steroids and the need of maintaining it for years[1,2]. For this reason, a wide number of immunosuppressive drugs including, calcineurin inhibitors, sirolimus, micophenolate mophetil and cyclophosphamide have been tried, as an adjunct to corticosteroids, for inducing and maintaining remission, however with 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 liver injury, observed in juvenile autoimmune hepatitis[7]. This hypothesis is supported by a recent study which, by demonstrating of a diffuse C5b-9 complex deposition in giant hepatocytes, suggests that liver cell injury may be autoantibody-driven and complement-mediated, as in the case of the associated Coombs positive hemolytic anemia [8]. This has potential

therapeutic implications and prolonged remission have been recently reported using B cell depletion immunotherapy with chimeric anti-CD20 monoclonal antibody (rituximab) [2,9,10].

Intravenous immune globulins (IVIg) have 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 have been used, in association with cyclosporine[6] plasmapheresis [13,14] or rituximab[15], as second line treatment in patient with liver disease, however with conflicting efficacy, usually limited to a slight reduction of aminotransferase activity. Repeated IVIg infusions at immunomodulatory doses induced remission of the liver disease and allowed corticosteroid discontinuation in two infants with GCH-AHA with severe steroid-related side effects [16,17].

The aim of this prospective, uncontrolled, 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 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. The local ethical committee approved the study. Parents were informed and signed a formal consent. Patients' characteristics at diagnosis are summarized in the table. All patients had clinical and biochemical signs of liver disease with diffuse giant cell transformation on liver biopsy and a Coombs-positive (IgG+C type) hemolytic anemia. Liver-disease related autoantibodies were absent in all. All other known causes of toxic, viral or metabolic 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 a 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 had previously been treated by prednisone, azathioprine and/or cyclosporine from 8 months, 2 and 5 years respectively, before entering in the study. One of these three patients had experienced multiple relapses and had been previously treated also with tacrolimus, rapamicin and rituximab. All patients had an elevation of aminotransferase activities and one patient had a severe reduction of prothrombin activity.

All patients received, as first line therapy, an IVIg infusion (0.5 to 2 g/Kg): four patients at the time of diagnosis and three during a relapse, while treated with different immunosuppressive drugs (prednisone and azathioprine in all, cyclosporine in two and tacrolimus in one).

In a second phase of the study, five of the seven patients received sequential IVIg infusions with a mean of 17 doses (range 7 to 24 doses) administered once a month. All patients were contemporary treated with an immunosuppressive therapy (prednisone in all, associated with azathioprine in four, cyclosporine in two and tacrolimus in one). The two patients who did not progressed to the second part of the study were treated with prednisone and azathioprine, associated with cyclosporine in a case.

Serum aminotransferase and gamma glutamyl-transpeptidase activities, serum albumin and gamma globulins levels, serum immunoglobulins, prothrombin time, blood cell and reticulocyte counts, were regularly checked before every infusion. Eventual side effects of the infusion were recorded.

Results

Administration of a single immunosuppressive dose of IVIg, as a first line therapy, reduced significantly, in all patients, alanine aminotransferase (ALT) activity from a median value of 22,6 x upper limit of normal (N) to 5,6 x N (p=0,03) (figure). Moreover, prothrombin activity, in the single patient in which it was severe reduced (36%), normalized.

Concerning the 5 patients who received sequential infusions of IVIg: three normalized ALT activity in a median time of 4 months (range 3- 5 months) and prednisone could be tapered in all of them. In two other patients, ALT activity significantly decreased, however remaining within 2 times the upper normal limit of normal. In these two patients, immunosuppressive therapy was maintained at the same dosage and in one of them rituximab was associated to therapy.

At the end of follow up (median 17.4 months, range 7-24 months): two of the five patients were still in complete disease remission, after a median time of 23 months from the beginning of IVIg treatment. In these two patients, prednisone could be tapered maintaining the remission of the liver disease. However, in both, hemolytic anemia relapsed. The three other patients relapsed of their liver disease after a median of 7.3 months from the beginning of sequential IVIg infusions on tapering of prednisone.

All children have tolerated IVIg infusions with mild side effects in two patients: urticaria in one and low-grade fever and headache in the other.

Discussion

GCH-AHA is a severe disease of infancy targeting hepatocytes and red blood cells and causing severe anemia and diffuse liver injury often progressing to end stage liver failure. Since its first description, high doses of prednisone have been shown to avoid the progression of the disease, but discontinuation of therapy has been always associated with severe relapse or death[1]. For this reason, patients with GCH-AHA have been treated with a more aggressive immunosuppressive

therapy always including prednisone. This multiple immunosuppressive therapy carries a high risk of developing severe bacterial infections that, together with terminal liver failure, are the main causes of death in such children[2]. The resistance to immunosuppressive therapy, unusual for autoimmune liver diseases of infancy and childhood, that is responsible for the high mortality and high rate of recurrence of GCH-AHA, might be explained by peculiar autoimmune mechanisms of the disease, based on the humoral immunity instead of "classical" T cell autoimmune response[8].

For these reasons, the therapeutic approach of infants with GCH-AHA, up to now empirically based on the experience of few centers on a small number of patients, is today under reconsideration. Rituximab (RTX), which is believed, in particular, to deplete CD20-positive auto-reactive plasma cells sparing protective antimicrobial plasma cells[18], was recently shown to induce and maintain remission in small series of patients with severe liver disease[9,10]. Moreover, RTX has been also shown to act as steroid-sparing drug, allowing the weaning from corticosteroids therapy, particularly in case of an early treatment [10]. However, because of a lack of immediate effect of this drug, attributed to the autoantibodies half-life, with persisting deleterious effects on the liver cells, RTX was suggested to be always associated with a short acting drug, such as corticosteroids[10]. In fact, the almost constant severe and aggressive onset of the disease, induce to obtain a rapid reduction of the activity of the disease to ameliorate liver function. Moreover, liver transplantation is not a safe therapeutic option in GCH-AHA, because of the high risk of recurrence in the graft [4].

This study first demonstrate in a small series of patients with GCH-AHA, that IVIg associated with prednisone, when used as first line therapy, significantly and rapidly reduce the activity of the liver disease, as shown by the decrease of aminotransferase activity in serum and by normalization of prothombin activity in the patient with severe liver dysfunction. Moreover, sequential infusions of IVIg at monthly intervals, were associated with a steroid sparing effect and allow to obtain

complete or partial remission in all patients, confirming previous reports in single cases[16,17] . However the efficacy of periodical infusion of IVIG was temporary and relapse of the hemolytic anemia and/or of the liver disease occurred in all patients.

IVIg acts at different levels of the immune response, neutralizing auto-antigens, inhibiting the activation and proliferation of T and B cells, saturating the Fc receptors of the immune globulins and modulating cytokine network [19-20]. Furthermore, IVIg are able to inhibit complement mediated tissue damage by preventing the generation of C5b-9 membrane attack, scavenging active complement components and diverting complement attack from cellular targets [19,20]. Moreover, IVIg have a few mild adverse effects comparing to steroids, all resolve by stopping the infusion and may be prevented by anti inflammatory drugs infusion before IVIg [20].

The main limit of our study is related to the limited number of patients, but the rarity of the disease strongly limits the feasibility of a study on a larger number of patients.

We thus propose that, in patients with GCH-AHA, infusion, at immunomodulatory dose, of IVIG should be performed, at diagnosis, in association with prednisone and azathioprine to improve the immunosuppressive effect of these drugs, particularly in case of marked increase of aminotransferase activity and liver cell function impairment. IVIg may be also used in case of relapse of the liver disease occurring during the attempt of discontinuation of the steroid treatment.

Although repeated IVIg infusion therapy allows, in our study, to obtain a complete or partial remission of liver disease and to reduce the dose of corticosteroids, we believe that, due to its only temporary efficacy , should not be employed.

Due to the recent results concerning the efficacy and safety of RTX use in patients with the more severe forms of GCH-AHA we believe that RTX treatment should be the second line treatment in patients with early relapse at discontinuation of steroid treatment. RTX should however be

handled with caution due to the potential side effects and in particular of persistent hypogammaglobulinaemia, that may needs periodic IVIG supplementation.

Figure: Aminotransferase activity before and a month after the infusion of IVIG at immunomodulatory dose in 7 children with GCH-AHA

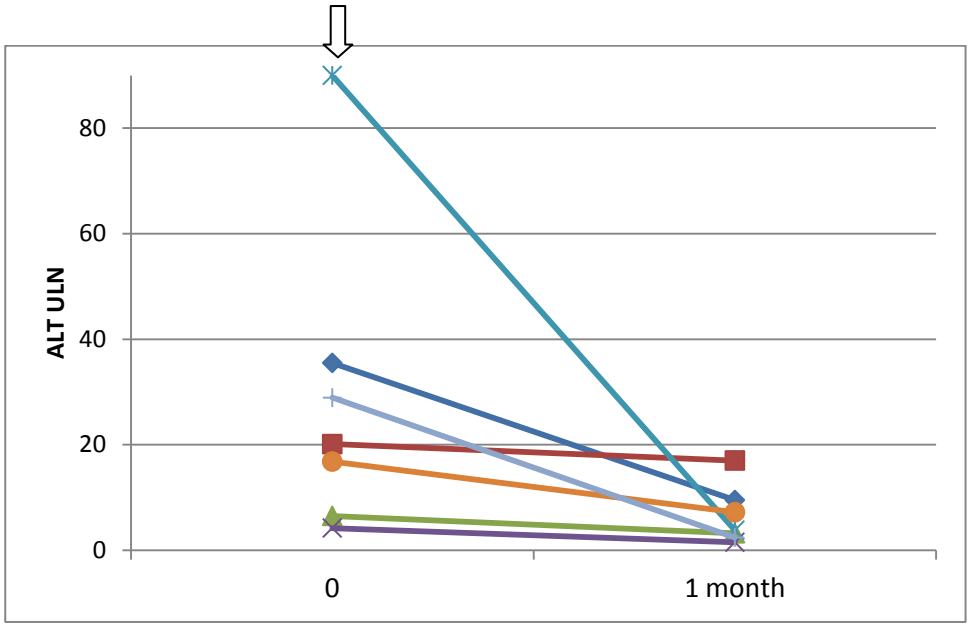

Table: Characteristic of the 7 patients with GCH-AHA at diagnosis.

Patients	n° 1	n° 2	n°3	n° 4	n°5	n° 6	n° 7
Sex	F	M	F	F	F	F	M
Age at onset of AHA *(months)*	5	8	10	10	6	7	8
Age at onset of the liver disease *(months)*	6	8	10	10	6	8	14
Characteristics at diagnosis							
Jaundice	-	+	-	+	+	-	-
Pallor	+	+	+	+	+	-	+
Hepatomegaly	+	-	+	+	-	-	+
Splenomegaly	-	-	+	+		-	-
Hemoglobin (g/dl)	9,8	10,7	9,8	6,3	8,5	11	8,7
ALT (x ULN)	160	16	19	90	39	20	28,9
GGT (x ULN)	4	1,5	2,8	2.8	2,8	N	3,9
Total Bilirubin mg/dl	1,5	3,9	1,5	4.5	5	0,5	1,96
Prothrombin activity %	78	93	43	49	100	100	68
Liver histology							
Giant cell transformation	+++	+++	+++	+++	+++	+++	+++
Portal and periportal inflammation	+	++	++	++	++	+	+
Portal infiltrate	Lymphocytes +	Lymphocytes ++	Lymphocytes ++	Lymphocytes ++	Lymphocytes ++ Neutrophils +	Lymphocytes ++ Neutrophils + Eosinophils +	Lymphocytes +
Portal fibrosis	+	+	++	++	+	+	+

Legend: nd =not performed; ULN = upper limit of normal

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