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Forma aguda da doença enxerto contra o hospedeiro após transplante de fígado. Existe opção terapêutica para as formas refratárias ao tratamento com esteróides?

Acute graft versus host disease after liver transplantation. Do we have an option for treatment of steroid-refractory forms?

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Chaib E, Coimbra BGMM, Silva FD, Kanas AF, Tatebe ER, Shinzato MS, Galvão FHF, D'Albuquerque LAC. Forma aguda da doença enxerto contra o hospedeiro após transplante de fígado. Existe opção terapêutica para as formas refratárias ao tratamento com esteróides?/ Acute graft versus host disease after liver transplantation. Do we have an option for treatment of steroid-refractory forms? Rev Med (São Paulo). 2012 abr.-jun.;91(2):110-6.

ABSTRACT: Background: Acute graft-versus-host disease (GVHD) usually occurs by 8 weeks after liver transplantation (LT) usually is an uncommon complication but has both high mortality and major diagnostic challenge in addition most of them are associated with resistance to steroid therapy. Objective: Discuss the pathogenesis, treatment and long-term results of Acute Graft versus Host Disease after Liver Transplantation. Methods: A PubMed search was performed to identify all reported cases of GVHD following LT. The medical subject heading GVHD disease was used in combination with LT, including adults (19 + years) and children. The bibliographies of the articles found though PubMed were then searched for further reports of GVHD. Results: We reviewed 102 cases of acute GVHD, 96 (94.1%) adults and 6 (5.8%) children. After treatment 24 (25%) adults and 3 (50%) children were alive only. As far as the treatment of GVHD is concern the therapy used in adults and in children patients was respectively : anti-thymocyte globulin + prednisolone – 19 (19.5%); interleukin-2 receptor blocker – 17 (17.5%); OKT3 – 12 (12.3%); cyclosporine – 9 (9,2%); others – 39 (40.2%) and in children anti-thymocyte globulin – 1 (20%); anti-thymocyte globulin + prednisolone – 1 (20%); prednisolone – 1 (20%); anti-thymocyte globulin + prednisolone + interleukin-2 receptor blocker-1 (20%); not mentioned – 1.There was no standard treatment of acute GVHD for both children and adults. Conclusion: Although acute GVHD following LT is rare complication and mortality is still very high, there is no consensus for the treatment of steroid-refractory forms. Further researches are needed to provide new approach for treating effectively such condition.

KEYWORDS: Liver transplantation; Graft vs host disease/etiology; Grafts vs host disease/therapy; Pathogenesis/treatment; Steroids/therapeutic use.

RESUMO: Introdução: A forma aguda da doença do enxerto contra o hospedeiro ocorre geralmente até oito semanas após o transplante de fígado, é rara, porém tem mortalidade alta e constitui-se em um grande desafio terapêutico principalmente naqueles casos que são resistentes ao tratamento com corticóides. Objetivo: Discutir a patogênese, tratamento e resultados a longo prazo da Forma Aguda da Doença Enxerto contra o Hospedeiro após Transplante de Fígado. Métodos: Fizemos uma pesquisa na base de dados do PubMed procurando identificar todos os casos de doença Enxerto contra o Hospedeiro após Transplante de Fígado incluindo adultos com mais de 19 anos e crianças. Resultados: Revisamos 102 casos desta doença e encontramos 96 (94,1%) adultos e 6 (5,8%) crianças. Após o tratamento, 24 (25%) adultos e 3 (50%) crianças estavam vivos. Com relação ao tratamento da doença do enxerto contra o hospedeiro em adultos e crianças encontramos respectivamente: globulina anti-timocítica + prednisolona – 19 (19,5%); bloqueador do receptor da interleucina 2 – 17 (17,5%); OKT3 – 12 (12,3%); ciclosporina – 9 (9,2%); outros – 39 (40,2%) e em crianças globulina anti-timocítica – 1 (20%); globulina anti-timocítica + prednisolona – 1 (20%); prednisolona – 1 (20%); globulina anti-timocítica + prednisolona + bloqueador do receptor da interleucina 2 -1 (20%); não mencionado – 1. Conclusão: Pesquisas devem ser aprofundadas nos mecanismos que desencadeiam esta patologia. Não existe consenso para o tratamento da doença do enxerto contra o hospedeiro após o transplante de fígado naqueles doentes que são refratários ao uso de esteróides.

DESCRITORES: Transplante de fígado; Doença enxerto-hospedeiro/etiologia; Doença enxerto-hospedeiro/terapia; Patogênese/tratamento; Esteróides/uso terapêutico.

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INTRODUCTION

Acute graft-versus-host disease (GVHD) usually occurs by 8 weeks after liver transplantation (LT)[1], and its prevalence has been estimated to be 0.3 to 1.9%[8,45,56,58].

Acute GVHD following LT is an uncommon complication but has both high mortality and major diagnostic challenge and in addition to that most of them are associated with resistance to steroid therapy.

We reviewed 102 cases of acute GVHD in the past 23 years, discussing the pathogenesis, treatment and long-term results of this condition after LT.

METHODS

A PubMed search was performed to identify all reported cases of GVHD following LT. The medical subject heading GVHD disease was used in combination with LT, including adults (19 + years) and children. The bibliographies of the articles found though PubMed were then searched for further reports of GVHD.

The mean age of affected patients was 52 years in 96 adult patients and 5 years in 6 children. The onset of GVHD was similar in both groups, averaging approximately 1 month after LT for both adults and children. The clinical manifestations of GVHD were similar in both adult and children and consist of rash, fever, diarrhea and bone marrow involvement manifested by cytopenias.

RESULTS

We reviewed 102 cases of acute GVHD, 96 (94.1%) adults and 6 (5.8%) children. The primary difference seen between pediatric and adults patients was in mortality with 75% death rate in reported adult patients with GVHD vs. a 50% mortality rate for patients younger than 18 years. Of the 102 patients reported to have experienced of GVHD, only 27 were reported to be alive at the time of publication of their case (Table 1). 94 (92.15%) patients demonstrating chimerism for confirming the diagnosis of GVHD after LT.

Table 1. Literature review. Acute graft vs host disease after liver transplantation. Treatment and results

Reference	Patients	Basic IS	Onset	Chimerism	Therapy	Outcome
Burdick et al. (1988)[5]	1	CsA,AZA,PSL	21	+	ATG, PSL	Alive
Bhaduri et al. (1990)[3]	1 child	AZA, PSL	23	+	ATG, PSL	Dead
Marubayashi et al. (1990)[36]	1	CsA,AZA,PSL	13	+	ATG, PSL	Dead
Merle et al. (1990)[39]	1	-	30	+	Anti-IL2R	Dead
Jamieson et al. (1991)[25]	2	CsA,PSL,AZA,IL2-R blocker	18 / 30	+	CsA, PSL, ATG	1x dead
Roberts et al. (1991)[64]	4	CsA,AZA,PSL	18-42	ND	3x IS increase with PSL	4x dead
Comenzo et al. (1992)[13]	1 child	CsA,PSL	95	+	IS increase	Alive
Collins et al. (1992)[12]	1	CsA,AZA,PSL	35	+	PSL	Dead
De Paoli et al. (1992)[15]	1	-	14	+	ATG, PSL	Dead
Joysey et al. (1992)[27]	1	-	38	+	ATG, PSL	Dead
Mazzaferro et al. (1993)[37]	1	CsA,PSL	17	+	PSL	Dead
Rosen et al. (1993)[51]	1	-	24	-	Anti L-AB	Dead
Redondo et al. (1993)[49]	1	-	25	+	OKT3, PSL	Alive
Neumann et al. (1994)[40]	1	CsA,AZA,PSL	32	+	ATG, OKT3	Dead
Cattral et al. (1994)[9]	1 child	CsA,PSL	16	+	PSL	Alive
Pageaux et al. (1995)[42]	1	CsA,AZA,PSL	18	+	ATG, PSL	Dead
Connors et al. (1996)[14]	1	FK506,PSL	24	+	-	Dead
Sanchez et al. (1996)[52]	1	CsA,AZA,PSL	34	+	OKT3	Dead
Whitington et al. (1996)[68]	1 child	CsA,AZA,PSL	34	+	ATG	Alive
Burt et al. (1996)[6]	1	-	28	+	PSL	Dead

Continua

Table 1. Literature review. Acute graft vs host disease after liver transplantation. Treatment and results *continuação*

Reference	Patients	Basic IS	Onset	Chimerism	Therapy	Outcome
Kiuchi et al. (1998)[31]	1 child	-	27	+	-	Dead
Aziz et al. (1998)[2]	1	CsA,AZA,PSL	15	-	ATG	Alive
Paizis et al. (1998)[41]	1	-	21	+	OKT3	Alive
Schmuth et al. (1999)[55]	1	FK506,PSL	7	+	AZA, PSL	Dead
Joseph et al. (1999)[26]	1	CsA,AZA,PSL	35	+	CsA, Cyclophosphamide	Dead
Merhav et al. (1999)[39]	1	FK506,PSL	30	+	CsA, PSL, ATG	Dead
Hahn et al. (2000)[20]	2	CsA,PSL/ FK506,PSL	35 / 21	+	OKT3 / Stop IS	Dead /Alive
Au et al. (2000)[1]	1	FK506,PSL	20	+	AZA,PSL	Dead
Hanaway et al. (2001)[21]	1	-	18	-	ATG,PSL	Dead
Romognoulo et al. (2000)[50]	1	PLS, CsA	23	-	AZA,PSL	Dead
Knox et al. (2002)[33]	1	FK506,MMF,PSL	17	+	PSL	Alive
Lehner et al. (2002)[34]	1	MMF, IL-2R	21	+	Stop IS	Alive
Smith et al. (2003)[56]	13	FK506,AZA,PSL	8-115	+	IS increase PSL, GM-CSF	12x dead
Sudhindran et al. (2003)[59]	2	FK506, PSL, AZA	24 / 31	+	PSL, IL-2R Blocker	Alive / Dead
Soejima et al (2004)[57]	4	CsA,PSL,FK506	27-114	+	IS increase FK506, PSL, CsA, ATG	2x Dead
Key et al. (2004)[30]	7	FK506,AZA,PSL	14-56	+	IS increase PSL, ATG, IL-2R Blocker	5x Dead
Hara et al. (2004)[22]	1	CsA,PSL	20	+	Change CsA to FK506, ATG	Dead
Walling et al. (2004)[66]	1	FK506,PSL	70	+	MMF, PSL	Alive
Pollack et al. (2005)[47]	1	FK506,MMF,PSL	240	+	OKT3, SCT	Dead
Kamei et al. (2006)[28]	8	-	14-114	-	-	8x Dead
Sun et al. (2006)[560]	1	FK506, MMF, PSL	122	+	PSL	Dead
Schappi et al. (2006)[54]	1 child	MMF, FK506, PSL, IL2-R Blocker	1	+	IL-2R Blocker, Alemtuzumab, ATG, PSL	Dead
Ghali et al. (2007)[17]	1	IL2-R Blocker, MMF, and PSL, FK506	ND	+	ATG, PSL, IL-2R Blocker, G-CSF, Erythropoietin	Dead
Chinnakotta et al. (2007)[10]	3	2x MMF, FK506, PSL / 1x CsA, PSL, RAPA	07-70	+	Stop IS	2x Alive
Perri et al. (2007)[45]	5	Standard IS	23-35	+	PSL, ATG and IL-2R	5x Dead
Wang et al. (2007)[67]	2	FK506, PSL, MMF / CsA, PSL	24 / 32	ND	PSL, GM-CSF	Dead /Alive
Cho et al. (2007)[11]	1	FK506, PSL	56	+	IS increase	Dead
Guo et al. (2008)[19]	2	FK506,PSL	40-59	+	PSL	2x Dead
Kohler et al. (2008)[32]	5	1x IL2-R Blocker,CSA,AZA,PSL / 4x PSL,FK506	20-60	+	ATG, OKT3 / PSL, ATG / PSL, ATG / PSL	5x Dead
Thin et al. (2008)[63]	1	PSL,FK506, AZA	20	+	GM-CSF, PSL, CsA, MMF, Etanercept	Alive
Grosskreutz et al. (2008)[18]	1	FK506,PSL	45	+	PSL	Alive
Lu et al. (2008)[35]	1	Radiosone, PSL, FK506	18	ND	Stop IS, Thymosin Alpha 1, ATG, IL-2R Blocker	Alive
Stotler et al. (2009)[58]	1	-	20	+	Alefacept	Alive
Piton et al. (2009)[46]	1	FK506,PSL	21	+	PSL,ATG, Infliximab	Alive
Gao et al. (2010)[16]	1	FK506	9	ND	decreased FK506	Alive
Chaib et al. (2011)[7]	1	FK506,PSL	31	+	ATG, PSL	Dead

Legenda: IS: Immunosuupression; CsA: Cyclosporine; AZA: Azathioprin; PSL: Prednisolone; FK506: Tacrolimus; MMF: Mycophenolate Mofetil; RAPA: Rapamycin; IL-2R Blocker, Interleucin-2 Receptor Blocker; ATG: Anti-Thymocyte Globulin; SCT: stem cell transplantation; GM-CSF: Granulocyte Macrophage Colony Stimulating Factor; ND: Not Described.

The literature describes several approaches used to treat GVHD after LT. These involve the use of available immunossupressive medications and of biological agents aimed at modulating the pathogenic lymphocytes.

Basic immunossupression used in adults and children patients after LT was respectively: FK506 + prednisolone – 49 (50.5%); cyclosporine + prednisolona + azathioprine – 19 (19,5%); cyclosporine + prednisolone – 5 (5.1%); others – 23 (23.7%); and cyclosporine + prednisolone – 2 (40%); cyclosporine + prednisolone + azathioprine – 1(20%); FK506 + prednisolone – 1 (20%); azathioprine + prednisolone – 1 (20%); not mentioned – 1 (20%).

As far as the treatment of GVHD is concern the therapy used in adults and in children patients was respectively: anti-thymocyte globulin + prednisolone – 19 (19.5%); interleukin-2 receptor blocker – 17 (17.5%); OKT3 – 12 (12.3%); cyclosporine – 9 (9.2%); others – 39 (40.2%) and anti-thymocyte globulin – 1 (20%); anti-thymocyte globulin + prednisolone – 1 (20%); prednisolone – 1 (20%); anti-thymocyte globulin + prednisolone + interleukin-2 receptor blocker-1 (20%); not mentioned – 1.

DISCUSSION

Acute GVHD after LT was first described by Burdick et al.[6], occurs when immunocompetent donor lymphocytes originating from the transplanted liver undergo activation and clonal expansion, allowing them to mount a destructive cellular immune response against recipient tissues.

The essential requirements for development of GVHD was described by Billigham as early as 1966[4]; first the graft must contain immunologically competent cells; second, the recipient must be recognized as foreign by the graft; and third the recipient must be unable to reject the graft before it mounts an effective immune response.

The aim of therapy for GVHD after LT is to allow the elimination of the unwanted donor lymphocytes by the host immune system. Many drugs and antibodies have been used in the past years such as: corticosteroids (increased or decreased immunossupression); anti-lymphocyte therapy (antithymocyte globulin, antilymphocyte globulin and the monoclonal anti-lymphocyte agent OKT3); anti-interleukin-2 receptor antibodies (the humanized antibody daclizumab and the murine/human chimeric monoclonal antibody basiliximab) and others like infusion of host immune cells or autologus bone marrow transplant.

The literature describes 28 adult patients treated primarily with corticosteroids and/ or an increased in standard immunosuppressive medications after the diagnosis of GVHD after LT[30,55,56,64]. Of these patients all were reported to die of complications of GVHD with the exception of one who was reported to be alive only 11 days after therapy was initiated. On the basis of the above results it is evident that treatment of GVHD after LT exclusively with corticosteroids or increase in immunosupression is inadequate long-term therapy.

There have been 37 adult patients reported to have been treated with ATG or OKT3. Of these only 7 (18,9%) patients were reported to be alive at least > 8 months after LT[2,5,15,21,22,25,27,30,32,35,38,40-42,45-47,49,52,57].

Of course this represents an improvement over results that use corticosteroids therapy alone, survival is still poor and the development of a complication of immunosupression such as posttransplantation proliferative disease raises the concern.

There have been 17 adult patients reported to have been treated with anti-interleukin-2 receptor antibodies Of these only 5 (29,4%) patients were reported to be alive after LT[17,30,35,45,59,63]. Main complication of using these agents are sepsis, pancytopenia and gastrointestinal bleeding.

Six adult patients have been reported to have been primarily treated for GVHD after LT by a reduction or discontinuation of immunossupression[7,47,61]. Five of these patients were reported to be alive at the time of report with their recovery attributed to reduction in immunosupression. The theoretical benefit of this approach is that by reducing or discontinuing immunosupression, the host immune system may be enabled to rejected the donor lymphocytes mediating the GVHD[56].

The largest series of GVHD after LT reported in this review was from Smith et al.[4] and Key et al.[30] 13 and 7 adults patients respectively. The basic immunossupression after LT was very much the same in the two groups, FK506, azathioprine and prednisolone. The treatment of GVHD was basically increase of prednisolone associated with GM-CSF and interleukin-2 receptor blocker in the former and the latter respectively. All of patients but one[56] have died after the treatment of this condition for different reasons, demonstrating clearly that there was no standard treatment of acute GVHD so far. The most popular treatment in 96 adults patients were stop immunosupression, prednisolone and anti-thymocyte globulin. Also there is no consensus to date for treating steroid-refractory forms of acute GVHD after LT.

Finally, since TNF-alpha is secreted by monocytes and macrophages leading to donor T-cell activation and inducing a cascade of inflammatory cytokine and cell activation in acute GVHD following LT the use of infliximab (a chimerical mouse/human immunoglobulin G antibody directed against soluble

and transmembrane forms of human TNF-alpha) has been successfully reported in treatment of this condition[46].

In conclusion, although acute GVHD following LT is rare complication and mortality is still very high, there is no consensus for the treatment of steroid-refractory forms. Further researches are needed to provide new approach for treating effectively such condition.

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