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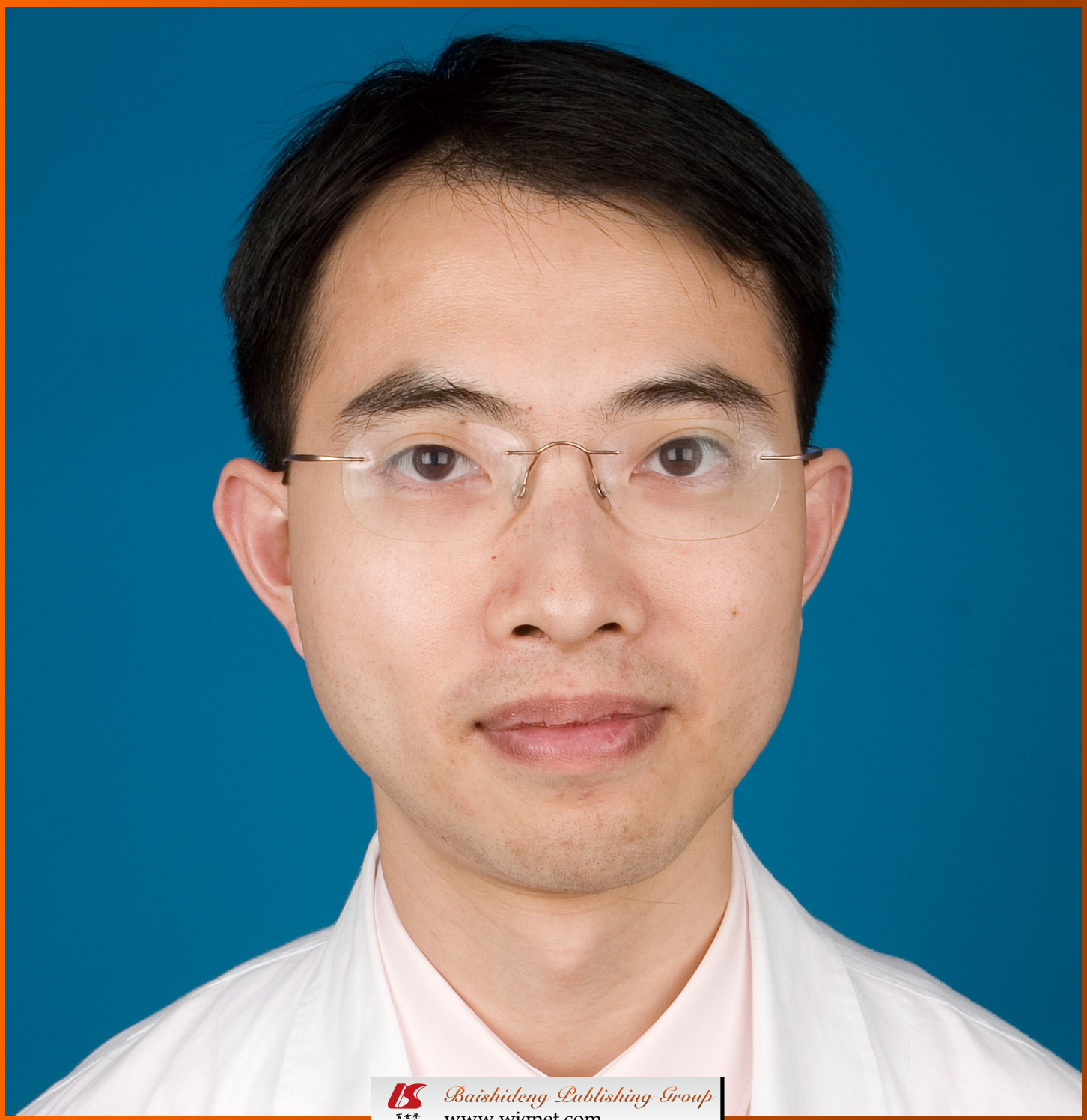

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EDITORIAL

Antibody induction therapy in adult kidney transplantation: A controversy continues

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Abstract

Antibody induction therapy is frequently used as an adjunct to the maintenance immunosuppression in adult kidney transplant recipients. Published data support antibody induction in patients with immunologic risk to reduce the incidence of acute rejection (AR) and graft loss from rejection. However, the choice of antibody remains controversial as the clinical studies were carried out on patients of different immunologic risk and in the context of varying maintenance regimens. Antibody selection should be guided by a comprehensive assessment of immunologic risk, patient comorbidities, financial burden as well as the maintenance immunosuppressives. Lymphocyte-depleting antibody (thymoglobulin, ATGAM or alemtuzumab) is usually recommended for those with high risk of rejection, although it increases the risk of infection and malignancy. For low risk patients, interleukin-2 receptor antibody (basiliximab or daclizumab) reduces the incidence of AR without much adverse effects, making its balance favorable in most patients. It should also be used in the high risk patients with other medical comorbidities that preclude usage of lymphocyte-depleting antibody safely. There are many patients with very low risk, who may be induced with intravenous steroids without any antibody, as long as combined potent immunosuppressives are kept as maintenance. In these patients, benefits with antibody induction may be too small to outweigh its adverse effects and financial cost. Rituximab can be used in desensitization protocols for ABO and/or HLA incompatible transplants. There are emerging data suggesting that alemtuzumab induction be more successful than other antibody for promoting less intensive maintenance protocols, such as steroid withdrawal, tacrolimus monotherapy or lower doses of tacrolimus and mycophenolic acid. However, the long-term efficacy and safety of these unconventional strategies remains unknown.

Key words: Induction; Kidney transplant; Thymoglobulin; Basiliximab; Alemtuzumab; Acute rejection; Graft survival

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INTRODUCTION

Appropriate immunosuppression is a key component of

successful kidney transplantation. It is generally accepted that more intensive immunosuppression is required initially to prevent acute rejection (AR) and graft loss from AR, and less immunosuppression is subsequently maintained to allow the recipient to tolerate allograft and to minimize the adverse effects of immunosuppressive drugs. Many transplant centers in the USA routinely use an antilymphocyte antibody peri-operatively as induction therapy in addition to a maintenance regimen. In the year of 2008, 81.5% of kidney transplant recipients were given one of the following antibody inductions: thymoglobulin (44.8%), basiliximab (17.8%), daclizumab (10.9%), alemtuzumab (10.7%), and other 18.5% of patients do not receive any antibody induction[1]. The modern maintenance typically consists of a combination of two of the three classes of agents, calcineurin inhibitor (CNI, tacrolimus or cyclosporine), mycophenolic acid (mycophenolate mofetil or enteric coated mycophenolate sodium) and mammalian target of rapamycin inhibitor (sirolimus or everolimus), with or without steroids[1]. In this review, we will discuss the controversial issue of various antibody induction therapies, which were studied on adult patients of different immunologic risk in the context of varying maintenance immunosuppressive regimens.

OKT-3

OKT-3 is a murine monoclonal antibody against CD3 molecule. It depletes T cells by binding to the T-cell receptor-associated CD3 glycoprotein. Though historically used, it was never approved in the USA by the food and drug administration (FDA) as an induction agent. OKT-3 is associated with many side effects, including first-dose effect[2], pulmonary edema[3], nephropathy[4], infection[5,6] and malignancy[7]. Antithymocyte globulin (ATG) preparations were demonstrated to be superior than OKT-3 in terms of decrease in the incidence of AR and better tolerability[8-10]. The use of OKT-3 was subsequently decreased and led to cessation of its production in 2009.

ATG

There are two forms of ATG that are polyclonal immunoglobulins against human thymocytes from either horses (ATGAM) or rabbits (thymoglobulin). ATG binds to various cell surface markers, including CD2, CD3, CD4, CD8, CD11a and CD18, and leads to complement dependent lysis of lymphocytes. ATG as well as OKT-3 and alemtuzmab are often referred as lymphocyte-depleting antibodies. ATGAM was approved by FDA for both treatment and prevention of AR whereas thymoglobulin was only approved to treat AR episodes. ATG use is associated with cytokine release syndrome, myelosuppression and rarely anaphylactic reaction[11]. Several studies found that thymoglobulin was more effective in preventing AR and was associated with better graft survival than ATGAM[12-14]. Subsequently, ATGAM was used less frequently as induction therapy.

Dose of thymoglobulin induction has ranged from 1 to 4 mg/kg per day for 3 to 10 d. One study compared 3-d induction regimen (n = 40) with the historic 7-d course (n = 48). With 3-d course, thymoglobulin was administered at 3 mg/kg intra-operatively followed by 1.5 mg/kg on post-operative day 2 and 3. The 7-d course consisted of 1.5 mg/kg intra-operatively followed by same daily dose for next 6 d. Shorter initial hospital stay (6.1 d *vs* 8 d) and more profound lymphocyte depletion were observed in the 3-d group[15]. There was no difference in AR (5% *vs* 4.2%), graft survival (95% *vs* 98%) and patient survival (95% *vs* 98 %) at the end of 1 year in the 3-d *vs* 7-d group. Intraoperative administration of thymoglobulin was found to be associated with a lower incidence of delayed graft function (DGF) and shorter hospital stay[16]. Doses less than 3 mg/kg may not effectively prevent AR[16]. Higher dose and longer duration of induction was associated with increased risk of infection and lymphoma[17-21]. Therefore, the optimal dose of thymoglobulin induction might be a total of 6 mg/kg administered as 1.5 mg/kg per day in 3 to 5 d[17-21].

To compare thymoglobulin *vs* placebo induction, 89 sensitized renal transplant recipients received induction with (47 patients) or without (42 patients) thymoglobulin. The maintenance regimen consisted of cyclosporin, steroids and azathioprine. At the end of 1 year, the incidence of AR was 38% in thymoglobulin group and 64% in the placebo group. Both graft survival (89% *vs* 76%) and graft function were better in thymoglobulin group than the placebo group[22]. Similar benefits with ATG induction were reported by a meta-analysis of seven comparative studies[23]. Further analysis indicated that ATG induction might reduce the risk of graft loss greater in sensitized patients with high panel-reactive antibody (PRA) than in unsensitized patients[24].

These studies were performed in the era of less potent old maintenance immunosuppressives. The introduction of modern more potent maintenance drugs has successfully decreased the incidence of rejection and has improved graft survival[25-28]. The independent use of either mycophenolic acid[25,26] or tacrolimus[27,28] was found to have advantages over azathioprine or cyclosporine, respectively. In a 3-group comparative study with 6-mo follow up, AR was highest in the group receiving tacrolimus, azathioprine and prednisone without induction (25.4%) compared to the group receiving tacrolimus, azathioprine, prednisone and thymoglobulin induction (15.1%) and the group receiving cyclosporine, azathioprine, prednisone and thymoglobulin (21.2%)[29]. In the two thymoglobulin induction groups, tacrolimus arm had a lower incidence of AR than cyclosporine arm. The patient and graft survival were similar in all three groups. Both thymoglobulin groups had more side effects including leukopenia, thrombocytopenia and CMV infection. In the era of modern potent maintenance regimen including tacrolimus and mycophenolic acid, it is unlikely that ATG induction can still provide that much benefits as it was previously demonstrated in the context of less potent maintenance of cyclosporine and azathioprine.

INTERLEUKIN-2 RECEPTOR ANTIBODY

Daclizumab and basiliximab are the two interleukin (IL)-2 receptor antibodies (IL-2R Ab). Daclizumab is a humanized antibody and basiliximab is a chimeric monoclonal antibody. Both bind to the α chain of IL-2 receptor complex (CD25) expressed on activated T lymphocytes. This prevents the T cell activation and proliferation without causing cell lysis. Therefore, they are also known as non-depleting antibodies. IL-2R Ab was first introduced in 1997 and was FDA approved for induction therapy. They have the best safety profile compared to other available induction antibody without increased risk of infection or malignancy[30-32].

IL-2R Abs have been subjected to numerous placebo-controlled, randomized trials, which have showed a reduction in AR rate compared with placebo (28% *vs* 42%)[33-36]. In a meta analysis, the risk of AR is significantly reduced in patients who received IL-2R Ab induction than in those with placebo at 6 mo (12 trials: relative risk 0.66, 95% CI: 0.59-0.74) and at 1 year (10 trials: relative risk 0.67, 95% CI: 0.60-0.75)[37]. The incidences of CMV infection and malignancy at 1 year were similar to placebo control[37]. Both IL-2R Abs have similar efficacy and safety profile, but basiliximab is administered as 2 doses within 4 d of transplantation, whereas daclizumab is administered as 5 doses over 8 wk[19,32]. This difference in convenience of administration led to more frequent use of basiliximab than daclizumab. Subsequently, Roche pharmaceuticals withdrew daclizumab from market in October 2008.

Our center's decade - long experience has indicated that basiliximab induction is safe and adequate for kidney transplant, including the high risk transplants, such as deceased donor kidney transplants in highly sensitized African Americans[38], simultaneous kidney pancreas transplant in African Americans[39] and splitting single pediatric donor kidney transplant[40], as long as the conventional triple regimen consisting of tacrolimus, mycophenolic acid and steroids are used as maintenance. A recent analysis based on USRDS data from 2000 to 2005 also indicated that both patient and graft survival were similar in African Americans and Caucasian patients using either thymoglobulin or IL-2R Ab induction[41].

IL-2 RECEPTOR ANTIBODY *VS* ATG

The safety and efficacy of thymoglobulin and basiliximab induction were compared in 278 high risk patients who received deceased donor kidneys[42]. High risk was determined according to the duration of cold ischemia and various other donor and recipient risk factors including donor age > 50 years, donation after cardiac death, donor with ATN or requiring high dose of ionotropic support, repeat transplant, PRA > 20%, black race and one or more HLA mismatches. Both groups received cyclosporine, mycophenolate mofetil and prednisone as maintenance. At 12 mo, there were fewer biopsy-proven AR in the thymoglobulin group than in the basiliximab group (15.6% *vs* 25.5%, $P = 0.02$). Severe rejection, as indicated by the need for antibody treatment, was less frequent in thymoglobulin group than basiliximab group (1.4% *vs* 8.0%, $P = 0.005$). The incidence of DGF (40.4% *vs* 44.5%, $P = 0.54$), graft loss (9.2% *vs* 10.2%) and death (4.3% *vs* 4.4%) was similar in both groups. However the incidences of infection and malignancy were significantly higher in thymoglobulin group than basiliximab group. A 5-year follow-up of these patients showed that AR remained lower in thymoglobulin than basiliximab group, but graft and patient survival were still not different[43]. Similar result was also reported by Noël *et al*[44] in 227 high risk patients who received modern maintenance of tacrolimus, mycophenolate mofetil and corticosteroid. High risk was defined as PRA > 30% and/or peak PRA > 50%, loss of a first renal transplant to rejection within 2 years or history of two or more previous transplants. Compared to the daclizumab group, thymoglobulin group had lower incidence of AR (15.0% *vs* 27.2%), and steroid-resistant AR (2.7% *vs* 14.9%) and also delayed the time to AR (35 d *vs* 13 d) in 1 year[44]. However, there was no difference in either graft or patient survival. The number of bacterial infection per patient (2.5 ± 1.8 *vs* 1.7 ± 1.2, $P = 0.01$) and the incidence of CMV infection (18.6% *vs* 10.5%, $P = 0.09$) was significantly higher in the thymoglobulin group than in the daclizumab group. These clinical trials show that thymoglobulin induction reduces the risk of AR, but it increases the risk of infection and possible malignancy. There is no convincing clinical evidence of superior graft or patient survival with thymoglobulin induction than the IL-2R antibody induction in high-risk patients.

Using SRTR database, Patlolla *et al*[45] analyzed a total of 48 948 recipients of first renal transplants who were discharged on CNI (cyclosporine or tacrolimus) and anti-metabolite (mycophenolic acid or azathioprine). Induction with IL-2R Ab (basiliximab or daclizumab, $n = 17\,472$) was associated with a reduction in both AR (odds ratio 0.81, 95% CI: 0.75-0.87) and graft loss (hazard ratio 0.90, 95% CI: 0.84-0.95) compared with no antibody induction ($n = 22\,008$). The greater the HLA mismatch, higher the efficacy of IL-2R Ab in reducing AR. Compared to IL-2R Ab induction, lymphocyte - depleting antibody (thymoglobulin, ATGAM or OKT-3, $n = 9468$) was associated with lower risk of AR (OR: 0.90, 95% CI: 0.83-0.99) at 1 year, but not associated with any better graft survival (OR 1.08, 95% CI: 1.00-1.18). Several studies directly compared thymoglobulin with IL-2R Ab induction in patients with low immunologic risk[46-48]. Similar rejection rate and graft survival, but higher incidence of infection was reported in those received thymoglobulin than IL-2R Ab induction. These clinical data, taken together with other trials comparing IL-2R Ab induction with placebo[33-37] supports use of IL-2R Ab rather than thymoglobulin for induction in low risk patients.

ALEMTUZUMAB

Alemtuzumab is a humanized anti-CD52 monoclonal

antibody, which triggers the antibody-dependent lysis of lymphocytes (both B and T cells), monocytes and NK cells. Alemtuzumab is FDA approved for treating B cell lymphomas. It was first introduced to kidney transplant by Calne *et al*[49] in late 1990s. As an induction agent, it produces a profound depletion of lymphocytes and is associated with more frequent and severe adverse effects, such as neutropenia, thrombocytopenia, autoimmune hemolytic anemia and other autoimmune diseases[50,51]. However, it did not appear to affect the incidence of recurrent glomerulonephritis[52]. Two doses of alemtuzumab were initially administrated for induction[53,54]. Due to its profound immunosuppression, single dose (30 mg, given intraoperatively) has been subsequently studied[55,56]. It is also hoped that alemtuzumab induction could permit patients to be maintained on less intensive immunosuppression, such as tacrolimus monotherapy[57,58], steroid-free regimen[59,60], or lower doses of tacrolimus and mycophenolic acid[59,61].

Margreiter *et al*[57] assessed the efficacy of alemtuzumab induction with tacrolimus monotherapy (n = 65) as compared to no induction with tacrolimus, mycophenolate mofetil and steroid maintenance (n = 66) for deceased donor kidney transplant. At 12 mo, the incidence of AR was not statistically different (20% *vs* 32%, P = 0.09). The graft and patient survival were similar, but alemtuzumab group had more CMV infection. This protocol was also studied in living donor kidney transplant by Tan *et al*[62,63]. A total of 205 living donor recipients were treated with alemtuzumab induction followed by tacrolimus monotherapy and 47 controls were treated with conventional triple therapy of mycophenolate, tacrolimus and prednisone without induction. At 1 year, the incidence of AR was much lower in the alemtuzumab group (6.8% *vs* 17%, $P < 0.05$)[62]. The 1, 2, and 3-year patient survival (99%, 98% and 96.4%) and the graft survival (90.8%, 93.3% and 86.3%) in the alemtuzumab group, are similar to the SRTR data for living donor kidney transplantation[63].

Induction with alemtuzumab (n = 123) and basiliximab (n = 155) were compared in a steroid-free maintenance consisting of mycophenolate acid and tacrolimus[64]. Early rejection (< 3 mo) rates were higher in the basiliximab group (11.6% *vs* 4.1%) but were equal at 1 year in the two groups (13.5% *vs* 14.9%, P = NS). The 1-year death censored graft survival was 99.2% for the alemtuzumab and 99.4% in the basiliximab group (P = NS). The incidence of CMV disease (4% *vs* 5%) and malignancy (2 recipients in each group) were also similar in the two groups. Therefore, in steroid-free maintenance, alemtuzumab induction is associated with lower incidence of early rejection, but similar graft survival compared to basiliximab induction.

ALEMTUZUMAB *VS* BASILIXIMAB *VS* THYMOGLOBULIN

These three antibody induction agents were first compared by Ciancio *et al*[59] in 90 deceased donor kidney transplants. Maintenance immunosuppression was tacrolimus (target trough level of 8-10 ng/mL), mycophenolate mofetil (1000 mg twice daily) and prednisone in thymoglobulin and daclizumab groups, while alemtuzumab group received lower doses of tacrolimus (target trough level of 4-7 ng/mL) and mycophenolate mofetil (500 mg twice daily). At 1 year, there was no significant difference in the three groups for AR, graft survival or patient survival. At 2 years, cumulative incidences of AR were 20%, 23% and 23% in thymoglobulin, alemtuzumab and daclizumab groups, respectively[61]. The overall patient and graft survival were similar, but there was a trend towards worse death censored graft survival and more chronic allograft nephropathy in alemtuzumab group[61]. In another study of rapid steroid withdrawal in a total of 474 kidney recipients, 139 high risk patients (African American, PRA $\geqslant$ 20% or re-transplants) were induced with alemtuzumab or thymoglobulin, while 335 low risk patients (non African American, PRA < 20% or primary transplant) were induced with alemtuzumab or basiliximab[60]. At 2 years, alemtuzumab induction has lower incidence of AR than basiliximab (8.9% *vs* 21.7%, $P < 0.05$) for low risk patients. The high-risk patients experienced same rejection rates with either thymoglobulin or alemtuzumab induction (13% in both groups). Patient and graft survival at 2 years were similar between the groups in both high risk patients (98.6% *vs* 93% and 92.2% *vs* 88.4%, alemtuzumab *vs* thymoglobulin, P = NS) and low risk patients (97.4% *vs* 98% and 96.2% *vs* 92.3%, alemtuzumab *vs* basiliximab, P = NS). A 3-year follow up showed similar results in terms of lower incidence of AR with alemtuzumab than basiliximab (10% *vs* 22%, P = 0.003) in low risk patients, while no difference in AR between alemtuzumab and thymoglobulin (18% *vs* 15%, P = 0.63) in high risk patients[65].

From these data, alemtuzumab induction appears to be more successful than other induction for unconventional protocols, such as steroid withdrawal, tacrolimus monotherapy or lower doses of tacrolimus and mycophenolic acid. However, these studies are small, short-term and should be considered as experimental. The long-term efficacy of these protocols remains to be vigorously investigated[53,61,66]. One obvious concern is that lymphocytes could recover from the initial depletion if insufficient maintenance immunosuppression is left over long term, which potentially leads to development of AR and/or chronic rejection. Late development of *de novo* donor specific antibodies (DSA) is increasingly recognized as an independent and detrimental factor for accelerated transplant glomerulopathy and graft loss[67,68].

RITUXIMAB

Rituximab is a chimeric monoclonal Ab against CD20, which is expressed on the majority of B cells. It was first approved in 1997 for refractory B cell lymphomas and it is increasingly applied for autoimmune diseases. In the realm of kidney transplant, rituximab has been used for the treatment of AMR and desensitization in

ABO and/or HLA incompatible transplants[69,70]. Takagi *et al*[70] reported rituximab induction in desensitization of 78 ABO and/or HLA incompatible transplants, all of them also received 3-4 sessions of double-filtration plasmapheresis before transplant. Compared with the non-rituximab group of 66 compatible transplants, rituximab group had significantly lower incidence of ACR (8.2% *vs* 23.3%, $P < 0.05$), but not higher incidence of AMR (6.8% *vs* 8.3%, $P = 0.75$). Anti-HLA Ab to class 1 and class 2 were depleted by 70% and 83%, respectively for more than 2 years after rituximab induction. The incidences of CMV infection (26% *vs* 29%, $P = 1.0$) or leukopenia (23% *vs* 14%, $P = 0.25$) were not different, and the 2-year survival rates of patient (100% *vs* 98%, $P = 0.28$) and graft (99% *vs* 100%, $P = 0.91$) were excellent in both groups[70]. Therefore, rituximab appears to be a safe and effective induction Ab for the desensitization protocol of ABO or HLA incompatible transplants.

In the setting of non-desensitization, Clatworthy *et al*[71] reported that 5 of 6 patients (83%) induced with rituximab had ACR in the first 3 mo after transplant as compared with 1 of 7 patients (14%) induced with daclizumab ($P = 0.01$). However, Tydén *et al*[72] reported a randomized, doubleblind multicenter study that included 68 rituximab and 68 placebo patients. All patients received conventional maintenance of tacrolimus, mycophenolic acid and steroids. During the first 6 mo, there were 10 treatment failure (defined as AR, graft loss or death) in rituximab group *vs* 14 in placebo group ($P = 0.35$). There was a tendency toward fewer AR (8/68 *vs* 12/68, $P = 0.32$) and milder AR without increase in infections or leukopenia in the rituximab group. Long-term study is needed to further determine the benefits of rituximab induction for non-sensitized patients.

OTHER CONSIDERATION

Apart from the immunologic risk, many other medical and physical factors should also be considered in the choice of induction therapy. Depleting antibody (thymoglobulin, ATGAM, OKT-3 and alemtuzumab) induction should be avoided in patients with history of malignancy, severe viral infection (including HIV, HBV or HCV), hematological disorder of leucopenia or thrombocytopenia and elderly with cardiac or pulmonary comorbidities[73-75]. For these patients, we do not use any antibody induction if they do not have high immunologic risk, and we use IL-2R Ab induction (not lymphocyte depleting antibody) for those who do have high immunologic risk. A recent study of 150 HIV-infected patients who underwent kidney transplant indicated that ATG induction significantly increased the risk of graft loss (HR 2.5, 95% CI: 1.1-5.6, $P = 0.03$). ATG induction was also associated with twice as many serious infections per follow-up year as patients received IL2R Ab induction or no induction (0.9 *vs* 0.4, $P = 0.002$)[74]. Another study reported that 2-year patient survival was less than 50% in the elderly (more than 60 years old) who had DGF and received thymoglobulin induction[75].

The financial costs of antibody induction therapies are significantly different. In US, the average whole sale price for the typical dose of alemtuzumab (30 mg × 1 dose) is $1982.70; basiliximab (20 mg × 2 doses) is $5338.66; while thymoglubulin (1.5 mg/kg × 4 doses for a 70 kg patient) costs $10 200.00[76]. A financial analysis indicated that IL-2R Ab (basiliximab/daclizumab) was more cost effective than placebo (no induction) or induction with lymphocyte-depleting antibody (OKT3/ATG/ATGAM)[77].

CONCLUSION

Published data support the usage of antibody induction therapy in adult patient with immunologic risk to reduce the incidence of AR and possible graft loss from rejection. However, the choice of antibody remains controversial. Antibody selection should be guided by a comprehensive assessment of immunologic risk of recipient and donor organ, patient comorbidities, financial burden, and more importantly, the maintenance immunosuppressive regimen. Lymphocyte-depleting antibody is recommended for those with high immunologic risk as outlined in the 2009 KDIGO clinical practice guidelines[78] (sensitized patient, presence of DSA, ABO incompatibility, high HLA mismatches, DGF, cold ischemia time > 24 h, African-American ethnicity, younger recipient age, older donor age), though it increases the risk of infection and malignancy. For low risk patients, IL-2R Ab induction reduces the incidence of AR and graft loss without much adverse effects, making its balance favorable in most patients. IL-2R Ab induction should also be used in the high risk patients with other medical comorbidities that preclude usage of any lymphocyte-depleting antibody safely. We believe that many patients with very low risk (non-sensitized, Caucasian, Asian, well HLA matched, living related donor transplant) may be induced with intravenous steroids without using any antibody, as long as combined potent immunosuppressives are kept as maintenance. In these patients, benefits with antibody induction may be too small to outweigh its adverse effects and the financial cost. Rituximab induction is useful in desensitization protocols for ABO and/or HLA incompatible transplants. Alemtuzumab induction might be more successful than other antibody induction for adopting less intensive maintenance protocols, such as steroids withdrawal, tacrolimus monotherapy or lower doses of tacrolimus and mycophenolic acid. However, the long-term safety and efficacy of these unconventional strategies remains to be determined.

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REVIEW

Hepatic veno-occlusive disease after hematopoietic stem cell transplantation: Prophylaxis and treatment controversies

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Abstract

Hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome, is a major complication of hematopoietic stem cell transplantation and it carries a high mortality. Prophylaxis for hepatic VOD is commonly given to transplant recipients from the start of conditioning through the early weeks of transplant. However, high quality evidence from randomized controlled trials is scarce with small sample sizes and the trials yielded conflicting results. Although various treatment options for hepatic VOD are available, most have not undergone stringent evaluation with randomized controlled trial and therefore it remains uncertain which treatment offers real benefit. It remains controversial whether VOD prophylaxis should be given, which prophylactic therapy should be given, who should receive prophylaxis, and what treatment should be offered once VOD is established.

Key words: Hepatic veno-occlusive disease; Hematopoietic stem cell transplantation; Prophylaxis; Treatment; Randomized controlled trial

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INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is a standard therapeutic modality for many different malignant and non-malignant diseases. However, complications from HSCT may result in severe morbidity and mortality. Major complications of HSCT include hepatic veno-occlusive disease (VOD), also known as hepatic sinusoidal obstruction syndrome. It is one of the major causes of non-relapse, transplant-related mortality. Hepatic VOD can occur after autologous or allogeneic HSCT, regardless of the underlying disease, stem cell source, or type of pre-transplant conditioning. The incidence of hepatic VOD after HSCT varies from 0 to 77%, depending on the risk of the patient cohort; and the median incidence is 13.3%[1]. The mortality of severe VOD is high at average of 84%[1]. Because of its high incidence and mortality, prophylaxis for hepatic VOD is widely practiced, using different regimens in different centers. However, whether prophylaxis alters the occurrence of VOD and which regimen is effective remains controversial. When hepatic VOD is established, specific therapy is usually given in addition to general supportive care, especially in moderate or severe cases. Different treatment strategies are tried with variable success, and no consensus regarding standard treatment is currently available. We therefore briefly review the existing evidence base for prophylaxis and treatment of hepatic VOD in this editorial and highlight the uncertainties and deficiencies in the evidence.

DIAGNOSIS OF HEPATIC VOD

Diagnosis of hepatic VOD is based on a constellation of symptoms and signs and serum bilirubin level. Hepatic VOD is clinically characterized by jaundice caused mainly by conjugated hyperbilirubinemia, tender hepatomegaly, fluid accumulation manifested as rapid weight gain and ascites. Most commonly used diagnostic criteria for VOD includes the Seattle criteria[2], the modified Seattle criteria[3], and the Baltimore criteria (also called Jones criteria)[4]. Since different studies on prophylaxis and treatment of hepatic VOD might have used different criteria for diagnosis of VOD, comparisons of effectiveness of prophylaxis and treatment regimens across different studies may be difficult.

The severity of VOD is usually categorized into 3 grades: mild, moderate, or severe, depending on adverse effect from VOD, treatment required, duration of disease and mortality[3]. While mild hepatic VOD may resolve without specific therapy, severe VOD caries a high mortality despite intensive therapeutic efforts. Because of variability and subjectivity in the definition of disease severity and the distribution of different severities within different cohorts of patients, comparisons of treatment results in different studies may be misleading.

PATHOGENESIS AND RISK FACTORS

The pathogenesis of hepatic VOD is incompletely understood. The clinical manifestations of hepatic VOD are thought to be caused by hepatic sinusoidal obstruction with or without occlusion of intrahepatic central venules, resulting from dysfunction of hepatic sinusoidal endothelial cells (SEC)[5,6]. The cause of SEC dysfunction is multifactorial, and includes cytotoxic chemotherapy and radiotherapy, with concomitant glutathione and nitric oxide depletion, increased matrix metalloproteinases and vascular endothelial growth factor, and disturbances of inflammatory cytokines and coagulation and fibrinolytic system. Prophylaxis and treatment of VOD therefore generally aims at preventing or relieving possible thrombotic obstruction of hepatic sinusoids and venules, or trying to prevent or restore the function of SEC, replenish anti-oxidants, promote vasodilation, and counterbalance proinflammatory cytokines.

Many different risk factors of VOD have been described, and they can be classified into patient factors, disease factors, and treatment factors (Table 1). Since many risk factors for hepatic VOD are not modifiable, prophylactic therapy is commonly administered to selected high-risk transplant recipients to prevent its occurrence. Some centers routinely give VOD prophylaxis to all transplant patients. However, the benefits and risks of VOD prophylaxis in different situations are not entirely clear.

Table 1 Risk factors of hepatic veno-occlusive disease

Risk factors	Ref.
Patient factors	
Younger age in children	[75-77]
Older age in adults	[78]
Poor performance status	[13,79,80]
Glutathione S-transferase M1 null genotype	[81]
Hemochromatosis C282Y allele	[82]
Pre-existing hepatic dysfunction	[2-4,79]
Hypoalbuminemia	[83]
Hyperbilirubinemia	[83]
High serum ferritin	[84]
Positive CMV serology	[85]
Elevated plasma transforming growth factor β level	[86]
Hepatitis B or C infection	[7,87-90]
History of pancreatitis	[85]
Disease factors	
Thalassemia major	[76]
Advanced malignancy	[83,91]
Acute leukemia	[89]
Neuroblastoma	[75,77]
Delayed platelet engraftment	[75,76]
Presence of acute graft-*vs*-host disease	[83]
Treatment factors	
Interval between diagnosis and transplantation greater than 13 mo	[83]
Allogeneic HSCT	[75,79]
Unrelated donor HSCT	[3,13,85,91]
Mismatched donor	[3,83]
Second or subsequent transplants	[7,84]
Prior use of gemtuzumab ozogamicin	[92]
Prior use of norethisterone	[93]
Prior abdominal irradiation	[3,7,77,79]
Use of total parenteral nutrition within 30 d before HSCT	[85]
High dose cytoreductive therapy	[79]
Conditioning regimen containing busulfan with or without cyclophosphamide	[3,75,76,84,85]
Conditioning regimen containing fludarabine	[85]
Conditioning regimen containing melphalan	[94,95]
Total body irradiation	[83,84]
Graft-*vs*-host disease prophylaxis with cyclosporin with or without methotrexate	[80,83,85]
Use of sirolimus	[96]
Use of tranexamic acid	[97]
Platelet transfusion containing ABO-incompatible plasma	[95]

HSCT: Hematopoietic stem cell transplantation.

VOD PROPHYLAXIS

Prophylactic medications that have been used for hepatic VOD with some success include heparin[7-10], low molecular weight heparin[11-13], danaparoid[14], ursodeoxycholic acid[15,16], prostaglandin E1[10,17,18], glutamine[19], defibrotide[20-25], and fresh frozen plasma (FFP)[7]. Some of these have also been tried in combination[7,13]. Prophylaxis is generally given continuously from the commencement of conditioning till neutrophil engraftment or 1-3 mo after HSCT, during which hepatic VOD is most likely to develop. Some centers administer VOD prophylaxis to all patients who are undergoing HSCT while others only give prophylaxis to high risk patients, but the criteria for "high risk" is variable. High level evidence from randomized controlled trials supporting VOD prophylaxis is limited, and is only available for ursodeoxycholic acid, heparin, enoxaparin, glutamine, and FFP. They are briefly summarized below.

Table 2 Randomized controlled trials of ursodeoxycholic acid for hepatic veno-occlusive disease

Trial reference	Essell *et al*[26] 1998	Ohashi *et al*[27] 2000	Ruutu *et al*[28] 2002	Park *et al*[29] 2002
Blinding	Double-blind	Non-blind	Non-blind	Non-blind
Type of transplants	Allogeneic	Allogeneic or autologous	Allogeneic	Allogeneic or autologous
Donor	Related	Variable	Variable	NA
Stem cell source	Bone marrow	NA	Variable	NA
Conditioning	Busulfan and cyclophosphamide or busulfan alone	Variable	Variable	Variable
No. of patients (treatment *vs* control)	35 *vs* 32	71 *vs* 65	124 *vs* 120	82 *vs* 83
Treatment regimen	Ursodeoxycholic acid 300 mg BD (< 90 kg) or 300/600 mg BD (> 90 kg), given before conditioning till Day+80	Ursodeoxycholic acid 600 mg daily, given from Day-21 till Day+80	Ursodeoxycholic acid 6 mg/kg per day BD, given 1 d before conditioning till Day+90	Ursodeoxycholic acid 300 mg BD, heparin 5 units/kg per hour, given 12-24 h before conditioning till Day+30
Control	Placebo	No drug	No drug	Heparin alone
Age of patients (yr, treatment *vs* control)	Mean 38 (22-56) *vs* 37 (21-56)	Mean 34.5 *vs* 35.7	Median 38 (5-59) *vs* 40 (1-58)	Median 39 *vs* 38
VOD criteria	Seattle	Seattle	Baltimore, Seattle	Modified Seattle
Frequency of VOD (treatment *vs* control)	14.3% *vs* 40.6%	2.8% *vs* 18.5%	Baltimore 2.4% *vs* 4.2%; Seattle 11.3% *vs* 11.7%	15.9% *vs* 19.3%
Mortality at Day+100 (treatment *vs* control)	22.9% *vs* 40.6%	NA	NA	11.0% *vs* 10.8%

NA: Data not available; VOD: Veno-occlusive disease.

Ursodeoxycholic acid

There were 4 randomized controlled trials evaluating ursodeoxycholic acid for prophylaxis of hepatic VOD in HSCT recipients. Their characteristics and results are summarized in Table 2. The first randomized controlled trial was the only double-blind, placebo-controlled trial[26]. Five of 35 patients (14.3%) who received ursodeoxycholic acid compared with 13 of 32 patients (40.6%) who received placebo developed hepatic VOD, which was significantly different (RR 0.35, 95% CI: 0.14-0.88, P = 0.02). Survival at Day+100 appeared higher in the ursodeoxycholic acid group, but the difference was not statistically significant (77% *vs* 59%, P = 0.15). The second randomized controlled trial compared ursodeoxycholic acid with no ursodeoxycholic acid[27]. Two of 71 patients (2.8%) in the ursodeoxycholic acid group and 12 of 65 patients (18.5%) in the control group developed hepatic VOD, which was significantly different (RR 0.15, 95% CI: 0.04-0.66, P = 0.01). None of the patients in both groups died with hepatic VOD. The overall mortality was similar in both groups (21.1% *vs* 24.6%, RR 0.86, 95% CI: 0.46-1.59, P = 0.63). The third randomized controlled trial again compared ursodeoxycholic acid with no ursodeoxycholic acid[28]. Three of 124 patients (2.4%) in the ursodeoxycholic acid group compared with 5 of 120 patients (4.2%) in the control group developed hepatic VOD according to the Baltimore criteria, which was not significantly different (RR 0.58, 95% CI: 0.14-2.38, P = 0.45). If the Seattle criteria for VOD diagnosis were used, 14 patients in each group developed hepatic VOD, again not significantly different between the 2 groups (RR 0.97, 95% CI: 0.48-1.94, P = 0.93). Hyperbilirubinemia occurred in 18 and 31 patients in the 2 groups respectively, which was significantly less frequent in patients who received ursodeoxycholic acid (RR 0.56, 95% CI: 0.33-0.95, P = 0.03). There were 2 deaths related to hepatic VOD in the control group but none in the treatment group, but the difference was not statistically significant (RR 0.19, 95% CI: 0.01-3.99, P = 0.29). The fourth trial compared ursodeoxycholic acid plus heparin with heparin alone[29]. Thirteen of 82 patients (15.9%) in the combined treatment group compared with 16 of 83 patients (19.3%) in the heparin alone group developed hepatic VOD, which was not significantly different (RR 0.82, 95% CI: 0.42-1.60, P = 0.56). There was also no significant difference in the frequency of severe VOD (2.4% *vs* 6.0%, RR 0.40, 95% CI: 0.08-2.03, P = 0.27). Survival at Day+100 was also similar between the 2 groups (89.0% *vs* 89.2%).

Heparin

There were 2 open-label randomized controlled trials evaluating heparin for hepatic VOD prophylaxis. The first trial comparing low dose heparin infusion (1 mg/kg per day from Day 0 till discharge) with no heparin for VOD prophylaxis in autologous bone marrow transplant recipients showed no significant difference in the incidence of hepatic VOD between the 2 groups[9]. Four of the 52 patients (7.7%) in the heparin group developed hepatic VOD and 1 of the 46 patients (2.2%) in the control group had hepatic VOD (RR 3.54, 95% CI: 0.41-30.53, P = 0.25). However, patients with increased risk to develop VOD were excluded from randomization and it was not clear what constituted "increased risk". In contrast, the second trial comparing low dose heparin infusion (100 units/kg per day from Day-8 to Day+30) with no heparin in both allogeneic and autologous HSCT recipients showed a significantly lower incidence of VOD in the heparin group[30]. Only 2 of 81 patients (2.5%) in the treatment group developed hepatic VOD, which was significantly less frequent compared to the control group,

in which VOD occurred in 11 of 80 patients (13.7%) (RR 0.18, 95% CI: 0.04-0.78, $P = 0.02$). Two patients in the heparin group and 7 patients in the control group died with VOD, which was not significantly different (RR 0.28, 95% CI: 0.06-1.32, $P = 0.11$). On subgroup analysis, none of the 39 patients (0%) who received heparin after allogeneic transplant developed hepatic VOD, but 7 of the 38 allogeneic transplant recipients (18.4%) who did not receive heparin had hepatic VOD, giving a relative risk of 0.07 favoring the heparin group (95% CI: 0.00-1.10), with borderline statistical significance ($P = 0.06$). For autologous or syngeneic transplants, the difference between the 2 groups was not significant, as 2 of 42 patients (4.8%) in the heparin group and 4 of 42 patients (9.5%) in the control group developed hepatic VOD (RR 0.50, 95% CI: 0.10-2.58, $P = 0.1$).

Low molecular weight heparin

There was one double-blind randomized controlled trial assessing the efficacy of enoxaparin for prevention of hepatic VOD in allogeneic and autologous bone marrow transplant recipients above 15 years of age[31]. Sixty-one patients were randomized to receive enoxaparin 40 mg daily by subcutaneous injection from 1 d before conditioning till Day+40 (28 patients) or placebo (33 patients). The incidence of hepatic VOD was not reported in this study. However, it was found that 23 patients (82.1%) in the enoxaparin group and 28 patients (84.8%) in the control group had hyperbilirubinemia (RR 0.97, 95% CI: 0.77-1.21, $P = 0.78$); 17 patients (60.7%) in the enoxaparin group and 27 patients (81.8%) in the control group had hepatomegaly (RR 0.74, 95% CI: 0.53-1.04, $P = 0.08$); 6 patients (21.4%) in the enoxaparin group and 13 patients (39.4%) in the control group had right upper quadrant abdominal pain (RR 0.54, 95% CI: 0.24-1.24, $P = 0.15$); 20 patients (71.4%) in the enoxaparin group and 21 patients (63.6%) in the control group had weight gain (RR 1.12, 95% CI: 0.79-1.59, $P = 0.52$); and 2 patients (7.1%) in the enoxaparin group and 2 patients (6.1%) in the control group had ascites (RR 0.59, 95% CI: 0.12-2.98, $P = 0.52$). None of these outcomes were significantly different between the 2 groups. However, the duration of hyperbilirubinemia and hepatomegaly appeared shorter in the enoxaparin group compared to the control group (mean 7.4 d *vs* 15.3 d, $P = 0.008$; and mean 2.4 d *vs* 5.5 d, $P = 0.03$, respectively). All patients in this study survived.

Glutamine

There was one double-blind randomized controlled trial that compared glutamine with isonitrogenous amino acid mixture for protection of hepatic function in allogeneic or autologous bone marrow transplant recipients[19]. Eighteen patients received daily infusion of 50 g glutamine and 16 patients received daily infusion of isonitrogenous amino acid mixture. Treatment was given from the start of conditioning till discharge from the transplant unit. No hepatic VOD was observed in both groups of patients. One patient in the control group died from sepsis and acute graft-*vs*-host disease, while all patients in the glutamine group survived. There was no significant difference between the 2 groups in overall mortality (RR 0.3, 95% CI: 0.01-6.84, $P = 0.45$). Of note is that 4 patients in each group withdrew from treatment, among whom one was due to abdominal discomfort.

FFP

One open-label randomized controlled trial compared FFP infusion with no FFP for prophylaxis of hepatic VOD in allogeneic HSCT recipients[32]. The patients were stratified into children and adults for randomization. Patients allocated to the FFP group (23 patients) received twice weekly FFP infusions from the start of conditioning till Day+28 after HSCT and patients in the control group (20 patients) did not receive FFP. Hepatic VOD occurred in none of the patients (0%) in the FFP group and 3 adult patients (15%) in the control group. The difference was not statistically significant (RR 0.13, 95% CI: 0.01-2.28, $P = 0.16$). Mortality was not reported in this trial.

VOD TREATMENT

Fluid restriction, diuretics, and avoidance of hepatotoxic medications are essential supportive care for patients who developed hepatic VOD. Specific therapeutic options on top of these include tissue plasminogen activator[33-44], heparin[36], thrombomodulin[45], antithrombin Ⅲ[46-49], protein C[50], prostaglandin E1[51], glutamine[52,53], acetylcysteine[54], methylprednisolone[55], and defibrotide[56-63]. Some of the above have also been tried in combination[36,51,64-66]. Treatment is usually given until hepatic VOD resolves or the treatment is considered ineffective. In some cases, charcoal hemofiltration[67], transjugular intrahepatic portosystemic shunt[68-71] or liver transplantation is performed as last resort[72,73]. However, little high level evidence on the treatment of hepatic VOD exists and only one randomized controlled trial is available which evaluated 2 different doses of defibrotide for treatment of hepatic VOD.

This multicenter open-label randomized controlled trial compared defibrotide at 25 mg/kg per day (arm A, 76 patients) with 40 mg/kg per day (arm B, 75 patients), both divided into 4 daily doses, given for at least 2 wk or until complete response[74]. Both pediatric and adult patients with either autologous or allogeneic HSCT were included. This trial found no significant difference in complete response rate between arms A and B (49% *vs* 43%), survival at Day+100 (44% *vs* 39%), or treatment-related adverse events (7% *vs* 10%).

SUMMARY OF EVIDENCE

High level evidence from randomized controlled trials supporting prophylaxis for hepatic VOD is scarce. Most trials were not double-blind and therefore susceptible to performance and assessment biases. The sample sizes

were also small, limiting generalizability of results and the statistical power to make definitive conclusion. Ursodeoxycholic acid might reduce the incidence of hepatic VOD but trial results were conflicting. It is also uncertain which sub-group of patients is more likely to benefit. Nevertheless, all trials failed to show any survival benefit in those who received ursodeoxycholic acid. Trial results on low dose heparin infusion for VOD prophylaxis were also conflicting, with 1 trial showing reduction of VOD with heparin while the other trial showing no difference between the treatment and the control groups. It seemed that heparin was more likely to benefit allogeneic transplant recipients as compared to autologous transplant recipients but there was insufficient statistical power to draw a more definitive conclusion. Similar to trials on ursodeoxycholic acid, both trials on heparin prophylaxis failed to show survival benefit. Trials on enoxaparin, glutamine and FFP all failed to demonstrate efficacy on reduction of VOD or overall mortality when given prophylactically.

High level evidence on treatment options for hepatic VOD is even less. Only one randomized controlled trial was available. However, this trial just demonstrated that different doses of defibrotide resulted in similar response rate and survival, without informing us whether defibrotide itself was really effective or not. We are also uncertain to what extents treatment benefits patients with different severities of VOD.

CONCLUSION

High quality clinical evidence on prophylaxis and treatment of hepatic VOD in hematopoietic stem cell transplant recipients is scarce. Although anecdotal reports and some clinical trials suggested certain strategies may be effective for preventing and treating hepatic VOD, it remains controversial whether any of these is indeed effective. It is also unclear who should receive prophylaxis and which treatment is most likely to offer the best risk-benefit ratio. Large, double-blind, randomized controlled trials evaluating prophylactic and treatment options for hepatic VOD is therefore urgently needed.

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Events Calendar 2012

January 29 - 31, 2012
2nd Joint AIDPIT and EPITA Winter Symposium & 31st AIDPIT Workshop
Innsbruck, Austria

February 1 - 5, 2012
2012 BMT Tandem Meetings
American Society for Blood and Marrow Transplantation
Manchester Grand Hyatt,
San Diego, CA, United States

February 22 - 24, 2012
British Transplantation Society 15th Annual Congress
Glasgow, Scotland

February 23 - 25, 2012
2012 Canadian Society of Transplantation Annual Scientific Conference
Fairmont Château Frontenac,
Québec, Canada

March 8 - 10, 2012
3rd International Conference on Transplantomics and Biomarkers in Organ Transplantation
La Jolla/San Diego,
CA, United States

April 18 - 21, 2012
The International Society for Heart and Lung Transplantation (ISHLT), 32nd Annual Meeting and Scientific Sessions
Prague, Czech Republic

April 25 - 27, 2012
United Network for Organ Sharing's 20th Annual Transplant Management Forum
Wyndham Rio Mar Beach Resort,
Puerto Rico

June 2 - 6, 2012
2012 American Transplant Congress
John B. Hynes Convention Center,
Boston, MA, United States

July 15 - 19, 2011
24th International Congress of the Transplantation Society
Berlin, Germany

September 13 - 15, 2012
ELITA - LICAGE LIVER MEETING and 4th ELITA Split-Liver Course
Ghent, Belgium

September 29 - 30, 2012
Advances in nephrology, dialysis, Kidney Transplantation
Odessa, Ukraine

October 5 - 7, 2012
V Congress of Transplantologists
Kharkiv, Ukraine

October 5 - 7, 2012
2012 European Organ Donation Congress, 24th ETCO-EDC
Dubrovnik, Croatia
October 12 - 14, 2012
ESOT and AST Joint Meeting - Transformational therapies and diagnostics in transplantation
Nice, France

November 2 - 4, 2012
5th ELPAT Invitational Working Groups Meeting
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5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

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6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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