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Review

Role of abatacept in the prevention of graft-*versus*-host disease: current perspectives

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***Abstract*:** Administration of abatacept following transplantation has been reported to inhibit graft rejection and graft-*versus*-host-disease (GvHD) in mouse models associated with allogeneic hematopoietic stem cell transplant (HSCT). This strategy has recently been adopted in clinical practice for GvHD prevention in human allogeneic HSCT and offers a unique approach to optimizing GvHD prophylaxis following alternative donor HSCTs. When combined with calcineurin inhibitors and methotrexate, abatacept had shown to be safe and effective in preventing moderate to severe acute GvHD in myeloablative HSCT using human leukocyte antigen (HLA) unrelated donors. Equivalent results are being reported in recent studies using alternative donors, in reduced-intensity conditioning HSCT and nonmalignant disorders. These observations have led to hypothesizing that even in the setting of increasing donor HLA disparity, abatacept when given with traditional GvHD prophylaxis does not worsen general outcomes. In addition, in limited studies, abatacept have being protective against the development of chronic GvHD through extended dosing and in the treatment of steroid-refractory chronic GvHD. This review summarized all the limited reports of this novels approach in the HSCT setting.

Keywords: abatacept, allogeneic hematopoietic stem cell transplantation, graft-*versus*-host disease

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Introduction

Graft-*versus*-host disease (GvHD) is still a major problem in patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT).[1] It results from immune reactions associated with donor T-cells toward dissimilar host histocompatibility antigens.[2] Traditionally, unrelated HSCT or partially HLA-mismatched has been reported to result in an increased risk of severe GvHD, in addition to graft failure, profound immune dysregulation, and non-relapse mortality, hence limiting the use of alternative donors.[3] Thus, strategies to prevent GvHD are essential to ensure successful results of unrelated allogeneic HSCT. Conventionally, GvHD prophylaxis includes calcineurin inhibitor (CNI), combined with a short course of methotrexate (MTX).[4] Anti-lymphocyte antibodies either polyclonal (anti thymocyte globulin) or monoclonal (alemtuzumab) are also being used as GvHD prophylaxis due to their effects on T-cell surface antigens or *in vivo* T-cell depletion by depleting CD4 lymphocytes.[5–7] Recent progress in GvHD pathophysiology research has supplied comprehensive knowledge of associated signaling pathways. Consequently, leading to the development of targeted agents which are under study (Phase II and III trials).[8]

Primarily, aGvHD is mediated by alloreactive T-lymphocytes. Therefore, several treatment approaches have been developed to target donor T-cell activation, which is achieved through two stimulatory signals (Figure 1). The first signal happens through the T-cell receptor (TCR). The TCR recognizes the antigen and is HLA restricted but not enough to ensure complete activation of the T-cells. The second stimulatory signal, also known as co-stimulation, is mediated by various molecules, especially those

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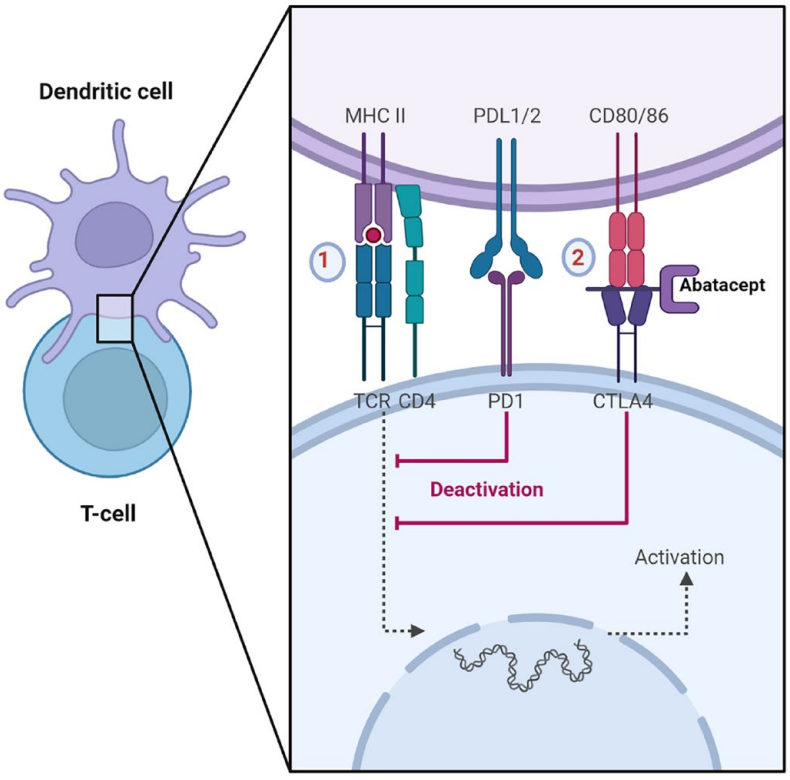

Figure 1. Inhibition of T-cell co-stimulation by abatacept.

expressed on antigen-presenting cells (APCs), such as adhesion molecules like LFA-1, TNF receptor, and the B7-CD28 family.[9] This signal is necessary to stimulate cytokine secretion, T-cell proliferation, and effector function after TCR activation, and is controlled by various inhibitory molecules such as programmed death-1 (PD-1) and cytotoxic T-lymphocyte antigen 4 (CTLA-4).[10] Since co-stimulation is fundamental to most functions of T-cells, incomplete or improper activation can make T-cells unresponsive or die due to programmed cell death (apoptosis).[10] Therefore, regulation of co-stimulatory and co-inhibitory signals presents novel approaches to target the prevention of GvHD, such as blocking the CD28/CTLA-4 axis.[11] Abatacept is a recombinant soluble fusion protein that inhibits antibody-dependent, cell-mediated cytotoxicity and/or complement fixation.[12] It consists of the extracellular domain of human cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) connected to the modified Fc (hinge, CH2, and CH3 domains) of the human immunoglobulin G1. The CTLA-4 binds to CD80 and CD86 (co-stimulatory receptors) on APCs with a higher affinity than CD28 (their native co-stimulatory ligand). This binding leads to attenuation of T-cell activation, offering the underlying principle for abatacept as GvHD prophylaxis given the abundance of evidence that GvHD is driven by the activities of CD4+ CD8+ T-cells[4,11,12] (Figure 1). The effect of abatacept treatment on T-cell subsets population has been investigated in patients with rheumatoid arthritis (RA).[13–17] However, these studies are limited and conflicting, this is due to different time points when T-cell subsets frequencies were analyzed and different patient cohorts. Picchianti *et al.* analyzed the frequency of T-cell subsets and T regulatory cell (Treg) inhibitory function in 20 RA patients that did not respond to a TNF-α blocking agent and then received abatacept with methotrexate. Immune studies were done before and 6 months after therapy. Abatacept therapy was able to rescue immune function and led to an effective and safe clinical outcome.[13] In an observational cohort study, Conigliaro *et al.* reported their findings on 48 RA patients treated with abatacept. All clinical data were collected at baseline and after 3 months of treatment. The percentage and the absolute number of CD3+ CD4+

CD45+ (helper) T-cells did not show any significant difference after the treatment but the percentage and absolute number of CD3+ CD8+ CD45+ (cytotoxic) T-cells significantly decreased after 3 months of abatacept treatment.[14] Alvarez-Quiroga *et al.*[15] described an enhanced suppressive ability of Treg cells, isolated from the periphery after abatacept therapy, in contrast, Pieper *et al.*[16] could not detect an increased suppressive ability of synovial Treg cells. Meanwhile, Bonelli *et al.*[17] saw a diminished suppression of T-cell proliferation *in vitro*.

Abatacept was approved by US Food and Drug Administration (FDA) in 2005 to treat adult patients with rheumatoid arthritis. Later in 2008, the drug was approved to treat children ($\leq$6 years) with juvenile idiopathic arthritis.[18] Recently, the US FDA-approved abatacept combined with a CNI and MTX to prevent aGvHD in patients aged $\geq$2 years undergoing HSCT from an unrelated donor with a matched or single allele mismatch.[19] This article will address abatacept's development and clinical applications in GvHD treatment. This article will also review the results of various clinical trials studying this treatment approach in HLA-matched and mismatched allogeneic HSCT.

Preclinical studies

Blazar and colleagues were the first to show that *in vivo* infusion of recombinant soluble CTLA4 linked to Fc of Ig could prevent effective activation of T-cells, thereby reducing the severity of GvHD.[20] The Ig heavy chains serve as a substitute ligand to block CD28/CTLA-4 co-stimulation. In the study, lethally irradiated B10.BR recipients of major histocompatibility complex disparate C57BL/6 donor grafts received intraperitoneal injections of human CTLA4-lg (hCTLA4-lg) or murine CTLA4-lg (mCTLA4-lg) at different doses and schedules after undergoing bone marrow transplantation (BMT) (on day -1 or day 0). The mice injected with CTLA4-Ig showed up to 67% survival rates, surviving three months after BMT while untreated recipients only had 0% survival rate. The recipients of CTLA4-Ig also showed no difference between those that received hCTLA4-Ig and those that were injected with mCTLA4-Ig. Thymic flow cytometry analysis did not show any reductions in the absolute number of mature CD3+ CD4+ CD8− T-cells. In addition, flow cytometry studies showed that CD8+ T-cell repopulation was not inhibited by hCTLA4-Ig injection. CD8+ T-cells were the predominant T-cell population at all time periods post-BMT in hCTLA4-Ig-treated mice even though the donor spleen used to generate GvHD has twofold more CD4+ compared with CD8+ T-cells. They concluded that CTLA4-Ig consistently and significantly decreases lethal GvHD in murine recipients of fully allogeneic donor cells. However, because GvHD prevention was incomplete, Blazar *et al.*[20] suggested combining CTLA4-Ig administration with other agents that block co-stimulatory ability to optimize the effects of CTLA4-Ig in preventing GvDH.

Comparable results were replicated by Wallace *et al.*[21] who used CTLA4Ig to increase the survival rate of lethally irradiated (C57BL/6X DBA/2) F1 recipient mice after undergoing injection of parent C57BL/6 bone marrow and spleen cells. They found that short courses of CTLA4Ig extended the survival of recipients after BMT, even after delaying the treatment for 6 days post-BMT. Wallace and colleagues concluded that the severity of aGvHD seems to be more reliant on CD28/CTLA-4 co-stimulation pathway.

Furthermore, Miller *et al.*[22] sought to figure out the impact of blocking CD28/CD40-directed co-stimulation and sirolimus (CoBS) in a primate model (rhesus macaque) after undergoing haploidentical transplant. Their study noted that at the 30-day primary endpoint, the recipients treated with CoBS had a 100% survival rate compared with untreated recipients who had 0% survival. This CoBS treatment increased the recipients' survival from 11.6 to 62 days (p value < 0.01) by reducing the activation and proliferation of T-cells. In addition, although CoBS was able to significantly impede the T-cell activation that occurred in untreated animals after transplant, GvHD occurred in some treated animals. Using flow cytometric analysis of BCl-2 and Ki-67, Miller *et al.* observed breakthrough activation and proliferation despite CoBS treatment. This showed that although most T-cell subpopulations remained dormant during CoBS treatment, the CD28− CD8 + T-cell subpopulation showed breakthrough activation (loss of BCl-2) and proliferation (gain of Ki-67).

Other animal studies on non-myeloablative conditioning and BMT have shown the efficacy of CTLA4Ig in preventing the T-cell-mediated host *versus* response and inducing tolerance to help

achieve stable chimerism without increasing cytoreductive toxicities in host.[23–26]

All the above preclinical studies formed the basis for the hypothesis that blocking this co-stimulatory signal using short courses of treatment with CTLA4Ig(abatacept) can result in reducing incidence of acute GvHD (aGvHD) in patients following HSCT.

Clinical transition of abatacept in treatment of GvHD: initial studies

Koura *et al.*[27] carried out a feasibility study in humans and documented promising results in using traditional GvHD prophylaxis with abatacept in 10 pediatric and adult patients with leukemia. All patients underwent unrelated HSCT. Six donor-recipient pairs were 7/8 HLA-matched, while four had 8/8 HLA-matched (MLA-A, HLA-B, HLA-C, and HLA-DBRB1 loci). Subjects were conditioned with either total body irradiation (TBI) (1200 cGy) + cyclophosphamide (Cy) (120 mg/kg); busulfan (Bu) (900–1300 mmol*min/L for each of 16 doses) + Cy (120 mg/kg); or fludarabine (Flu) (125 mg/m^2 + melphalan (Mel) 140 mg/m^2. The cyclosporine was started 3 days prior to transplant, with doses titrated to maintain a trough level of 100 to 300 ng/mL and continued at full dose up to 100 days after the HSCT. Methotrexate was given at 15 mg/m^2 at day +1 and 10 mg/m^2 on day +3, +6, and +11. Abatacept was given intravenously over 30 min at 10 mg/kg (maximum dose, 100 mg) day 1 and day +5, +14, and +28. In their results, Keen and colleagues noted that the median time to neutrophil engraftment was 16.5 days. Patients had a reduced rate of aGvHD, with a 20% rate of grades II to IV and an impressive 10% of grades III and IV even in robust immune reconstitution. No graft failures, no deaths due to infection, and no cases of transplant-associated mortality were recorded. Seven out of 10 patients survived to a median follow-up of 16 months. Keen *et al.* further observed that blocking co-stimulation using abatacept could impact the activation and proliferation of CD4+ after transplantation. They concluded that using abatacept in treating aGvHD in individuals undertaking unrelated-donor HSCT was feasible and encouraging.[27] This report served as proof of concept for further studies in patients with hematologic malignancies and those with nonmalignant hematologic diseases.

Extended studies: malignant

Watkins *et al.* further explored Koura *et al.*[27] proof-of-concept observations. In a Phase II Trial study (ABA2, NCT01743131), they investigated the role of abatacept in reducing aGvHD after unrelated donor HSCT in malignant disorders.[28] The study involved pediatric and adult patients with hematologic malignancies grouped into two categories: a randomized, double-blind, placebo-controlled group with 8/8-HLA-matched unrelated donor (MUD) and a single-arm group with 7/8-HLA-mismatched unrelated donor (MMUD). The MUD group compared calcineurin inhibitor (CNI)/methotrexate (MTX) plus abatacept with CNI/MTX plus placebo, while the MMUD group compared CNI/MTX plus abatacept with CNI/MTX CIBMTR controls. The MUD group involved 142 recipients, while MMUD had 43 recipients. The primary endpoint was day 100 grade III-IV aGvHD, while the secondary endpoint was day 180 severe-aGvHD-free-survival (SGFS). In the MUD category, Watkins *et al.* noted that grades III and IV was 6.8% (CNI/MTX plus abatacept group) compared with 14.8% (CNI/MTX plus placebo group) (p value = 0.13; hazard ratio = 0.45). In the same group, they found the SGFS to be 93.2% (CNI/MTX plus abatacept) compared with 82% (CNI/MTX plus placebo; p value = 0.5). However, for patients in the MMUD category, grade III-IV aGvHD was 2.3% (CNI/MTX plus abatacept), which contrasted with CNI/MTX (30.2%; p value $<$ .001), and the SGFS was better (97.7% *versus* 58.7%; p value $<$ 0.001). Based on these results, Watkins and colleagues concluded that adding abatacept to unrelated HSCT is safe and effective in reducing moderate to severe GvHD and improving overall survival. These remarkable results have resulted in the FDA innovating designation of this drug to prevent aGvHD in 2021.[19]

A *post hoc* analysis of the ABA2, NCT01743131, was conducted by Qayed and colleagues hypothesizing that abatacept could nullify the risks associated with HLA mismatching.[29] They compared outcomes in patients with MMUD receiving CNI/MTX and abatacept to patients with MUD receiving CNI/MTX alone. The study's primary endpoint was the cumulative incidence of severe (grade III-IV) aGvHD at day +100. A total of 112 patients (median age 40.0 years) that underwent HSCT were analyzed, 43 patients were treated with MMUD/CNI/MTX plus abatacept, while 69 patients got MUD CNI/MTX alone,

82.1% of them had a diagnosis of acute myeloid leukemia, myelodysplastic, or acute lymphoblastic leukemia. Seventy-three percent of the entire group received myeloablative conditioning and 58.0% received peripheral blood stem cell transplantation. No differences were detected between groups in age, disease, and conditioning intensity. However, the groups differed only in distribution across conditioning regimens ($p = 0.04$). Most patients (18.6% *versus* 2.9%) of MMUD/CNI/MTX and abatacept received busulfan and fludarabine, while a few of MMUD/CNI/MTX plus abatacept received TBI and cyclophosphamide (25.6% *versus* 37.7%). The MMUD/CNI/MTX and abatacept group had 30.2% non-White compared with 11.6% non-Whites in MUD/placebo patients ($p = 0.09$). No difference in platelet engraftment or neutrophils was seen. In their results, they noted a cumulative incidence of grade III-IV aGvHD by day +100 of 2.3% (95% CI = 0.2–10.7) in the MMUD/CNI/MTX and abatacept group compared with 14.8% (95% CI = 7.5–24.3) in MUD/CNI/MTX alone group (p value = 0.03). However, in MMUD/CNI/MTX and abatacept, they noted a 57.9% (95% CI, 40.7–71.8) cumulative incidence of moderate to severe chronic GvHD compared with 41.3% (95% CI, 27.7–54.4) in the MUD/CNI/MTX alone group ($p = 0.12$). There were no significant differences between the two study groups in the day +180 cumulative incidence of Epstein-Barr virus or cytomegalovirus viremia. With a median follow-up of 25 months comparing the MMUD/CNI/MTX and abatacept group to the MUD/CNI/MTX alone group, they observed a 2-year cumulative incidence of transplant-related mortality (16.7% *versus* 16.1%), relapse rate (9.3% *versus* 23.6%), relapse-free survival (74% *versus* 60.3%), SGFS through day +180 (97.7% *versus* 82.0%), and 2-year overall survival (73.6% *versus* 64.0%). Overall, these results show that adding abatacept to standard CNI/MTX alleviates the issues of mismatching by reducing the risks associated with severe aGvHD and non-relapse mortality (NRM) without increasing relapse. Nevertheless, Qayed and colleagues saw that risk of cGvHD was not reduced as they noted 57.9% in 1-year cumulative incidence of moderate to severe cGvHD in MMUD/CNI/MTX and abatacept group compared with 41.3% in MUD/CNI/MTX alone group. Therefore, a multicenter, randomized controlled trial (ABA3, NCT04380740) will be performed to address this issue, investigating whether an eight-dose regimen of abatacept (last dose at day 150) can prevent cGvHD.[29]

In a recent observational study, Kean *et al.* analyzed 216 patients from the Center for International Blood and Marrow Transplant Research registry. Patients, 6 years of age or older with malignancy whose first allogeneic HSCT was with a 7/8 MMUD between 2011 and 2018 were included. Patients were treated with standard of care aGvHD prophylaxis [CNI/MTX, without anti thymocyte globulin (ATG)] with or without abatacept. Overall survival rates at day 180 post transplant were 98% for patients treated with abatacept and standard of care compared with 75% for those treated with standard of care only. Further exploratory analysis showed that patients who were treated with abatacept and standard of care did better than those treated with standard of care alone (either CNI/MTX/ATG or post transplant cyclophosphamide).[30] The noted advantage of abatacept over ATG is interesting and should be explored because even though a recent meta-analysis reported that the addition of ATG to GvHD prophylaxis in patients undergoing HSCT resulted in a significantly lower risk of grade III-IV aGvHD, however ATG treatment was correlated with a high incidence of Epstein-Barr virus (EBV) reactivation and did not appear to affect overall survival.[7]

Extended studies: nonmalignant

HSCT is used to treat nonmalignant diseases affecting the lymphohematopoietic system, particularly sickle cell anemia, which is limited, due to a lack of appropriate donors.[31] Alternative donor transplants with abatacept show promising results in patients suffering from life-threatening nonmalignant hematologic diseases and lacking an HLA-matched sibling donor.

Ngwube *et al.*[32] documented a part of the Phase I study (NCT03128996) involving unrelated donor HSCT in 14 recipients aged 4- 21 years with severe sickle cell anemia. In the study, they used a reduced-intensity conditioning regimen (RIC) involving melphalan (day -3), fludarabine (days -8 to -4), distal alemtuzumab (days -22 to -19), and hydroxyurea (days -50 to -21). Thiopeta was added on day -4 for patients who got mismatched bone marrow and cord blood transplants. GvHD treatment included tacrolimus and short-course mycophenolate mofetil (cord blood) or

methotrexate (bone marrow). In the study, seven patients got 8/8 HLA-matched (HLA-A, HLA-B, HLA-C, and HLA-DRB1) bone marrow, five got 7/8 matched bone marrow, and two got 5/6 matched (HLA-A, HLA-B, and HLA-DRB1) cord blood. The administration of abatacept was performed intravenously on days -1, + 5, + 14, + 28, + 100, + 180, + 270, and + 365. However, the abatacept was given to patients receiving cord blood transplants until day + 28 (four total doses). One patient had secondary graft rejection on day + 30; the patient had CMV reactivation. The other patients engrafted with a median time of 19.5 days in platelet recovery and 14 days in neutrophil recovery. The two-year probability of disease-free and overall survival was 92.9% and 100%, respectively. Twenty-nine percent of patients developed grades II-IV aGvHD and only 7% with grades III to IV. They also noted that only one out of nine patients who received unrelated bone marrow and abatacept doses beyond day + 100 developed extensive cGvHD. They concluded by postulating that GvHD prophylaxis with abatacept improves survival after unrelated HSCT in SCD.[32]

In a retrospective study, Khandelwal *et al.*[33] explored the role of adding abatacept to reduce the severity of aGvHD in 32 children with Beta-thalassemia major transplanted in their institution. All patients received a myeloablative conditioning regimen comprising of a combination of busulfan given daily for four days according to pharmacokinetic-targeted dosing, fludarabine, and thiopeta intravenously. In the study, they compared the clinical outcomes of eight patients who received a standard GvHD prophylaxis which included calcineurin inhibitor combined with corticosteroids (1 mg/kg/d from 1 day after the HSCT to days +28), to 24 patients who received abatacept given at a dose of 10 mg/kg (maximum dose of 100 mg) intravenously on days −1, + 5, + 14, and +28 following stem cell infusion in addition to their standard GvHD prophylaxis. Donor types were similar in both groups (63% related donors and 37% unrelated donors). With no difference in platelets and neutrophils engraftment between both groups, the rate of aGvHD was 50% in the standard GvHD prophylaxis group *versus* 0% in the standard GvHD prophylaxis with abatacept group ($p = 0.001$), chronic GvHD (25% *versus* 25%, $p = 1$) and viral reactivation (62.5% *versus* 83%, $p = 0.3$) rates. Overall survival at 1 year in the standard GvHD prophylaxis group was 62.5% *versus* 100% in the group with standard GvHD prophylaxis group and abatacept ($p = 0.007$). Therefore, they concluded that adding abatacept to routine GvHD prophylaxis can reduce the incidence of aGvHD post-HSCT with durable engraftment and improved survival.[33]

In 2017, Jaiswal *et al.*[34] reported their experience using abatacept in severe aplastic anemia (SAA) following HLA-mismatched haploidentical HSCT. They rationalized that in haploidentical transplants, adding abatacept to prior to graft infusion would eliminate predominant alloreactive T-cell population and a minority of abatacept resistant T-cells which might be activated during the 72 hours window could be effectively eliminated by PTCy. In addition, they also postulated that combining sirolimus and abatacept might enhance transplantation tolerance through *via* Tregs. They conducted a retrospective study comparing two different GvHD prophylaxis approaches in pediatric patients. The conditioning regimen used in both groups comprised fludarabine, low dose Cy and melphalan, and Anti-thymocyte Globulin (ATG). In the control group (same site historical control), GvHD prophylaxis consisted of post-transplantation cyclophosphamide (PTCy) at 50 mg/kg on days +3 and 4 with sirolimus from day −7 (with trough levels of 8–14 ng/ml on day 0) until 9 months in addition to cyclosporine (CSA) and mycophenolate mofetil (MMF). In the study group, CSA and MMF were replaced with the co-stimulation blockade, abatacept (COSBL group). Abatacept was administered at 10 mg/kg on days −1, +5, +20, +35 and then every 4 weeks until day +180. Ten patients with a median age of 12 were in the COSBL group, compared with 10 patients, with a median age of 10 years in the control group. There was a rapid and sustained recovery of Tregs (CD4 + CD25 + CD127dim/−) in the COSBL group compared with the control group. The incidence of aGvHD was 10.5% in the COSBL group compared with 50% in the control group ($p = 0.04$), chronic GvHD (12.5% *versus* 56%, $p = 0.02$) and CMV reactivation (30% *versus* 80%, $p = 0.03$). Overall survival at 1 year in the COSBL group was 88.9% *versus* 50% in the control group ($p = 0.09$). They concluded that abatacept combined with PTCy and sirolimus might augment transplantation tolerance and reduce aGvHD in children with SAA.[34]

In another study from the same group, Jaiswal *et al.*[35] reported their experience, this time in

patients with thalassemia major (TM, $n=5$) and sickle cell disease ($n=5$), aged 3 to 19 years. This small cohort of patients underwent pretransplant immunosuppressive therapy for ten weeks. Conditioning was myeloablative, and abatacept was given to patients every 2 weeks during the treatment, on days −1, +5, +20, +35, and every 4 weeks after that for 6 months, together with sirolimus. In addition, a short course of low-dose dexamethasone was administered from day + 6 for 2 weeks. Jaiswal and colleagues observed nine patients engrafted at a median of 15 days, with 1 patient dying due to sepsis on day + 19. No acute or chronic GvHD has been documented in the study. Only four patients have been reported having cytomegalovirus reactivation. All remaining nine patients are still alive and free from disease at a median follow-up of 28 months.[35]

Finally, in another study highlighting the effects of abatacept in nonmalignant HSCT, Chaudhury *et al.*[36] reported their initial experience in an ongoing multicenter trial through the Sickle Transplant Alliance for Research (STAR), looking at the use of abatacept in pediatric patients with sickle cell disease at elevated risk of GvHD. They used a RIC combination of distal alemtuzumab, Fludarabine, Thiopeta, and Melphalan. The T-cell replete bone marrow grafts were obtained from matched related ($n=8$) or unrelated ($n=5$) donors. Abatacept was administrated at 10 mg/kg/dose intravenously on days −1, + 5, + 14, and + 28 in addition to a standard GvHD prophylaxis involving tacrolimus and methotrexate. After a median follow-up of 8 months, the first 13 recruited patients were alive and reported no acute or chronic GvHD, and three are now off immune suppression.[36]

Using abatacept to treat and prevent chronic GvHD

In a preclinical study, Via *et al.*[37] using mouse models showed that CTAL4Ig administered early can prevent the development of acute and chronic GvHD by inhibiting the activation of T-cells of the donor. On the other hand, delayed administration of CTAL4Ig after the development of T-helper type 1 and 2 effector responses (day 7) had no impact on aGvHD. However, this delayed administration was noted to reverse cGvHD as showed by fewer donor CD4 memory T-cells, reduced donor T-cell expression of CD40 ligand, standard host B cell numbers, and normal serum levels of auto-antibodies.[37] Watkins *et al.*[28] showed that, although abatacept reduced the incidence of aGvHD in ABA2 patients, 4-doses schedule of abatacept did not improve cGvHD prevention. Koura and colleagues, had earlier, showed that abatacept treated patients when compared with control patient proved a profound decrease in absolute and relative percentage of CD4+ T but not CD8+ cells early after transplantation. This decrease was clear in both unfractionated T-effectory memory and T central memory subsets. However, by day + 60 post-HSCT, these differences were no longer seen between the two cohorts. There was also a decrease in the number of CD4 + /CD25 high/CD127 low/FoxP3 + putative Tregs cells in the abatacept arm compared with control. As FoxP3 + can also mark proliferating and activated CD4+ T-cells the authors could not determinate this was due to a true difference in functional regulatory cells. In addition, this difference in FoxP3+ cells were transient and confined to early time points post-HSCT.[27] Chronic GvHD is in part helped by host reactive T-cells stimulated by allogeneic antigens, and these early findings imply that extending abatacept beyond the 4-doses schedule may continue to suppress CD4 memory T-cells, improving cGvHD prevention. Based on this rationale, Jaiswal *et al.* gave eight doses of abatacept (every month through day +180) in SAA patients undergoing a haploidentical transplant and showed decreased incidence of cGvHD compared with control. In addition, Ngwube *et al.*[32] increased the number of abatacept doses (every 3 months through day + 365 for eight doses) in SCD patients undergoing a matched unrelated or mismatch related HSCT and showed decreased incidence of cGvHD, hence showing the need for clinical trials, exploring the benefits of intermediate-duration (eight doses) abatacept on the risk of cGvHD in HSCT.

In a recent phase I clinical trial, abatacept was used to treat patients with steroid-refractory cGvHD. These patients were treated with two increasing doses of abatacept administrated at 3 and 10 mg/kg in a 3 + 3 design with an expansion cohort given only 10 mg/kg. The results of the study showed abatacept to be safe. The results also led to improved chronic scores (44%) and a significant reduction (51.3%) in prednisone use. The sites with considerable improvement in the studied 16 patients were the

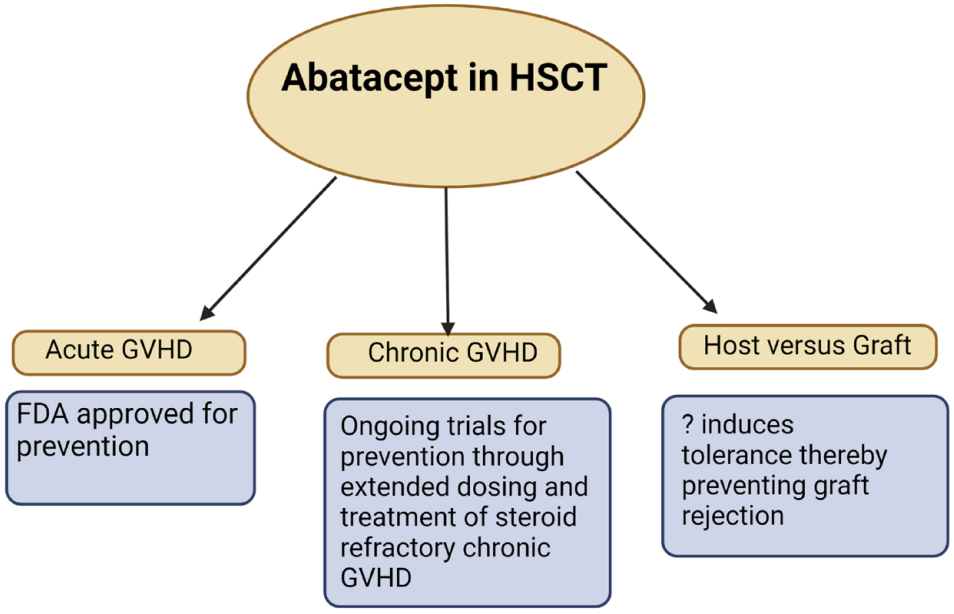

Figure 2. Current state and future role of abatacept in allogenic HSCT.
HSCT, hematopoietic stem cell transplant.

gastrointestinal tract (40%) and mouth (42%), followed by joints, skin, and lungs. Remarkably, a full recovery of grade II pulmonary cGvHD was reported in one patient.[38]

In another retrospective study, 15 patients (median age of 49 years) who underwent HSCT and received abatacept for cGvHD were analyzed. They reported an overall response rate of 40%, mostly, in patients with lung GvHD (bronchiolitis obliterans syndrome). Abatacept was noted to have significant, durable clinical improvement as measured by an 89% improvement based on lung severity score or lung function measured by pulmonary function test.[39]

Conclusion

Together, these clinical results show that abatacept has effectively evolved its role from the bench to the bedside in HSCT (Figure 2). These early clinical studies though limited by their sample size, demonstrate the potential abatacept may have in helping alleviate negative impacts associated with HLA disparity in transplantation in both malignant and nonmalignant disorders regardless of conditioning type. In a recent registry study, increased incidence of GvHD and inferior outcomes in patients receiving haploidentical HSCT with PTCy, tacrolimus and mycophenolate mofetil for GvHD prevention as opposed to matched unrelated donor HSCT with PTCy-based GvHD prevention was reported signaling a need for improvement.[40] Future studies should explore extensively, the use of abatacept in conjunction with post-transplant cytoxan and compared with ATG for GvHD prevention. It has also been noted that there is little to no effect on cGvHD incidence with just four doses of abatacept, suggesting adding more doses of abatacept, may also prevent moderate to severe cGvHD. Although reports from these limited studies have been convincing, they call for further studies, especially in preventing cGvHD. Several ongoing and previously completed clinical trials exist and are focusing on expanding and bridging the knowledge gap on this novel approach of using abatacept in transplantation. Table 1 provides a summary of ongoing actives clinical trials based on clinicaltrials.gov. In combination with other immunosuppressive agents, abatacept has supplied a practical and safe pharmacologic choice for GvHD prevention in malignant and nonmalignant diseases while using HLA-matched or alternative donors. However, there are some limitations to its effectiveness. Speculations remains on how abatacept as an effective aGvHD prophylaxis could impact on relapse rates in malignant disorders. However, as successful studies in this novel approach increases, this will guarantee effective and prompt HSCTs are accessible to everyone, including populations traditionally lacking donors, such as patients with hemoglobinopathies.

Table 1. Selected registered studies of abatacept based GvHD prevention in hematopoietic stem cell transplantation.

ClinicalTrials.gov identifier (Title acronym) and location	Study title	GvHD prophylaxis including abatacept drug schedule if available	Status
Phase I NCT02867800 USA	Abatacept for GvHD Prophylaxis After Hematopoietic Stem Cell Transplantation for Pediatric Sickle Cell Disease	Abatacept on days –1, +5, +14 and +28. Updated study includes extended dosing to Day +60, +90, +120 and +150	Active not recruiting
Phase 1 NCT01917708 USA	Bone Marrow Transplant With Abatacept for Nonmalignant Diseases Patients with nonmalignant disease	Four doses of abatacept 10 mg/kg/dose given on days –1, +5, +14, and +28 with cyclosporine and MMF	Completed
Phase1/Phase2 NCT03128996 USA	Reduced Intensity Conditioning and Familial HLA-Mismatched BMT for Nonmalignant Disorders	Day +3 to +4: Cyclophosphamide (50 mg/kg/day) Day +5: Tacrolimus and MMF Days +5, +14, +30, +60, +90: abatacept (10mg/kg/day IV) Days +120 to +390: abatacept monthly (5mg/kg/day IV)	Recruiting
Phase1/Phase2 NCT05426252	Thal-Fabs: Reduced Toxicity Conditioning for High-Risk Thalassemia	Abatacept and sirolimus	Recruiting
Phase2 NCT01012492 USA	Pilot of Abatacept based immunosuppression for prevention of aGvHD during unrelated donor HCT.	Cyclosporine, Methotrexate and Abatacept	Completed with results PMIDs: 24047754 and 25852054
Phase2 NCT03680092 USA	Comparing Cyclophosphamide and Abatacept With Standard of Care Treatment Following Stem Cell Transplantation in Patients With Hematologic Malignancy	Experimental arm: Cyclophosphamide on Days + 3 and + 4 followed by abatacept for 6 months. Abatacept at a dose of 10mg/kg will be administered on days + 5, + 14 and + 28, + 56, + 84, + 112, + 140, + 168 Active Comparator: Methotrexate on Days + 1,+3, + 6 and + 11 and tacrolimus	Active Recruiting
Phases 1 and 2 NCT04503616 USA	Cyclophosphamide, Abatacept, and Tacrolimus for GvHD Prevention Adult patients with hematological malignancies undergoing HLA-haploidentical HSCT from first-or second-degree family donors.	Tacrolimus Cyclophosphamide 50 mg/kg IV over 2 hours on day +3 and +4 Abatacept 10 mg/kg IV on days +5, +14, and +28	Active, recruiting
Phase 3 NCT04000698 Russia	Personalized Targeted Preparative Regimen Before T-depleted Allogeneic HSCT in Children With Chemo resistant Acute Leukemia. GvHD prophylaxis: Plerixafor, abatacept, tocilizumab, rituximab, HSCT from the haploidentical donor, *ex vivo* depleted of alpha/beta T lymphocytes	Not reported	Active, Recruiting
Phases 1 and 2 NCT00920972 USA	Campath/Fludarabine/Melphalan Transplant Conditioning for Nonmalignant Diseases	Tacrolimus or cyclosporine and MMF along with Abatacept 10mg/kg IV Day +1. Day +6, Day +14, Day +28, Day +60, Day +100, Day +180, Day +270, and Day +365.	Active, Recruiting

(Continued)

Table 1. (Continued)

ClinicalTrials.gov identifier (Title acronym) and location	Study title	GvHD prophylaxis including abatacept drug schedule if available	Status
Phase 2 NCT03924401 USA	Acute GvHD Suppression Using Co-stimulation Blockade to Expand Nonmalignant Transplant (ASCENT)	Stratum 1 ($n = 14$) will be for patients with 7/8 donors and stratum 2 ($n = 14$) will be for those with 8/8 (matched) donors. All participants will receive eight doses of abatacept (10 mg/kg intravenously on days −1, +5, +14, +28, +56, +84, +112, and +150).	Active and recruiting
Phase1/Phase 2 NCT05289167 USA	High-Dose Post-Transplant Cyclophosphamide, Bortezomib and Abatacept for the Prevention of Graft-*versus*-Host-Disease (GvHD) Following Allogenic Hematopoietic Stem Cell Transplantation (HSCT) Study	Cyclophosphamide(50 mg/kg IV) Day +3 and +4 Abatacept: Dose level 0: 10 mg/kg IV over 30 minutes on day + 5 Dose level 1: 10mg/kg IV over 30 minutes on day +5 and +14 Dose level 2: 10mg/kg IV over 30 minutes on day +5, +14, and +28 Bortezomib: 1.3 mg/m2 IV 6 hours after graft infusion completion and 72 hours thereafter	Recruiting
Phase 1 NCT01954979 USA	A Phase I Study of Abatacept in the Treatment of Patients With Steroid Refractory Chronic Graft *Versus* Host Disease (cGvHD).	The study will follow a standard 3 + 3 design with two escalating doses of abatacept to determine the maximum tolerated dose (MTD): 3 mg/kg (dose level 1) and 10 mg/kg (dose level 2)	Active, not recruiting PMID: 29549175
Phase 2 NCT01743131 USA	Abatacept as GvHD Prophylaxis Phase 2	Placebo Comparator: CNI with Methotrexate + placebo Experimental: CNI with methotrexate + abatacept	Active, not recruiting, has results PMID: 33449816
NCT05421299 USA	A Study to Assess 7/8 HLA-matched Hematopoietic Stem Cell Transplantation Participants Treated With or Without Abatacept in Combination With a Calcineurin Inhibitor and Methotrexate	CNI plus MTX (with or without ATG and with or without abatacept); or	Completed Observational Retrospective study
Phase 2 NCT04380740 USA	Extended *versus* Short-term Abatacept Dosing for Graft *Versus* Host Disease Prophylaxis (ABA3)	Placebo Comparator: Standard GvHD Prophylaxis(cyclosporine or tacrolimus) and methotrexate + Abatacept short term + Placebo Experimental: Standard GvHD Prophylaxis + Abatacept Extended dosing Standard GvHD prophylaxis of calcineurin inhibitor (cyclosporine or tacrolimus) and methotrexate + 8 doses of Abatacept.	Not yet recruiting
Phases 1 and 2 NCT04686929 China	Abatacept subcutaneous (sc). for aGvHD Prevention in Haplo-HCT Experimental: Cohort 1	Cohort 1: Subcutaneous abatacept: 250 mg (d −1), 125mg (d +5, +14, +21, +28, +35, +42, +49, +56) combined with CsA, MTX, and MMF. Cohort 2: Subcutaneous abatacept: 250 mg (d −1, +5, +14, +21, +28, +35, +42, +49, +56) combined with CsA, MTX, MMF.	Active and recruiting

ASCENT, acute GvHD suppression using co-stimulation blockade to expand nonmalignant transplant; BMT, bone marrow transplantation; cGvHD, chronic graft *versus* host disease; CNI, calcineurin inhibitor; HCT, Hematopoietic Stem Cell Transplantation; HSCT, Hematopoietic Stem Cell Transplantation; MMF, mycophenolate mofetil; MTD, maximum tolerated dose; MTX, methotrexate.

Declarations

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Not applicable.

Consent for publication
Not applicable.

Author contributions
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