

Friend or foe? Mogamulizumab in allogeneic hematopoietic stem cell transplantation for adult T-cell leukemia/lymphoma

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Abstract: Adult T-cell leukemia/lymphoma (ATL/ATLL) is a peripheral T-cell neoplasm associated with human T-lymphotropic virus type-1 (HTLV-1). Even the currently most intensive chemotherapy regimen modified LSG15 (mLSG15, VCAP-AMP-VECP) results in a dismal clinical outcome, with a median overall survival of only around 1 year. Although allogeneic hematopoietic stem cell transplantation (allo-HSCT) may lead to long-term remission in a proportion of patients with aggressive ATL, the clinical outcome in patients with refractory or relapsed ATL is unsatisfactory. The anti-CCR4 antibody mogamulizumab (moga) has been recently approved for ATL in Japan, and it is effective in a significant proportion of patients with refractory or relapsed ATL. However, there are major concerns about the harmful influences of pretransplant moga on the immune reconstitution after allo-HSCT. Specifically, moga depletes regulatory T cells (Tregs) for at least a few months, which may increase the risk of graft-versus-host disease (GVHD) after allo-HSCT. A recent retrospective study from Japan clearly showed that pretransplant moga increased the risk of severe and steroid-refractory GVHD, which led to increases in non-relapse mortality and overall mortality. To improve the overall clinical outcome in patients with relapsed or refractory ATL, more studies are needed to incorporate moga without increasing adverse effects on the clinical outcome after allo-HSCT. In this review, we aim to provide an updated summary of the research related to moga and allo-HSCT.

Keywords: Mogamulizumab; adult T-cell leukemia/lymphoma (ATL/ATLL); regulatory T cells (Tregs); hematopoietic stem cell transplantation; graft-versus-host disease (GVHD)

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Adult T-cell leukemia/lymphoma (ATL/ATLL) and mogamulizumab (moga)

ATL/ATLL is a peripheral T-cell neoplasm that occurs in around 5% of human T-lymphotropic virus type-1 (HTLV-1) carriers and is one of the most aggressive hematologic malignancies (1,2). HTLV-1 is endemic in some areas, such as coastal regions of southwest Japan, South America, and Africa (2). ATL comprises four

clinical subtypes, namely, acute, lymphoma, chronic, and smoldering, the former two of which show more aggressive courses (2). Generally, ATL responds to primary chemotherapy, but it soon becomes refractory to multiple anticancer reagents (3). Therefore, even the currently most intensive chemotherapy regimen modified LSG15 (mLSG15, VCAP-AMP-VECP) results in a median survival of only 13 months (4). Although allogeneic hematopoietic stem cell transplantation (allo-HSCT) may lead to long-

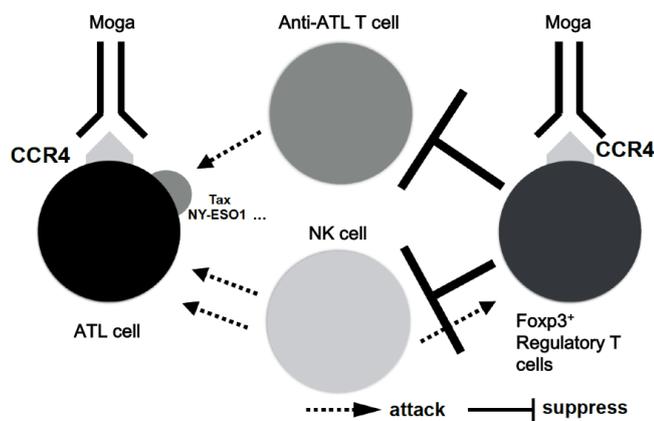


Figure 1 Moga depletes not only ATL cells, but also Tregs. Moga depletes ATL cells through ADCC by NK cells, but also depletes Foxp3⁺ Tregs through ADCC. As a result, moga enhances anti-ATL immunity of anti-ATL NK cells and T cells.

term remission in a proportion of patients with aggressive ATL (5), it can also cause fatal complications such as graft-versus-host disease (GVHD) (6).

Interestingly, there are several lines of evidence that tumor immunity can suppress ATL. Some cases experience spontaneous remission without any anticancer treatment (7-10). The occurrence of mild GVHD correlates with reduced relapse of ATL patients after allo-HSCT (11). Chemotherapy-resistant cases with substantial tumor burdens sometimes achieve long-term remission after allo-HSCT (12). Even relapsing cases after allo-HSCT still respond and achieve complete remission again only following withdrawal of immunosuppressants (13). These observations may be due to the high immunogenicity of ATL cells such as the tumor antigens Tax or NY-ESO-1, and several projects have aimed to treat ATL by enhancing tumor immunity (14,15).

The advent of clinically feasible monoclonal antibodies enabled specific depletion of tumor cells. They enhance antitumor immunity by antibody-dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) (16). As for hematologic malignancies, the anti-CD20 antibody rituximab gained FDA approval for B cell-lineage malignant lymphoma in 1997. Since then, many antibodies have been developed, and their specificities and potentials have been greatly improved. Currently, novel monoclonal antibodies that target immune checkpoint signals such as nivolumab and ipilimumab are about to change cancer therapy (17,18). However, their adverse

effects can result in unknown severe pathology, partly due to incomplete understanding of the human immune system. Therefore, careful and close monitoring of cases that are treated with immunomodulatory reagents is needed.

Chemokines and their receptors play important roles in tumorigenesis and the expansion and migration potentials of tumor cells in the body (19). Moga, a monoclonal antibody that targets the chemokine receptor CCR4, was developed in Japan (20,21). Many T-cell neoplasms including ATL express CCR4 (22,23), for which moga gained approval for clinical use. It binds to CCR4 on ATL cells, inducing ADCC by natural killer (NK) cells (*Figure 1*). The most notable feature of moga is elimination of fucose from sugar chains on the antibody by Potelligent[®] technology, which strikingly enhances its ADCC activity (24).

Moga shows substantial antitumor activity against relapsed/refractory ATL and peripheral T-cell lymphoma. Notably, it is effective even in chemotherapy-resistant or relapsing cases, which means that many unfavorable ATL cases can achieve remission using moga (25,26). Furthermore, its indication may be widened to solid organ malignancies (27). However, there are still some problems to be solved or overcome. Although the effects of moga are often dramatic, some ATL cases are still resistant. There is no clear conclusion regarding the appropriate combination therapy of moga with conventional chemotherapy (28). The effects of moga on extramedullary lesions are limited (25,29). Furthermore, moga has immunomodulatory effects, including depleting regulatory T cells (Tregs) (30). Therefore, concerns have been raised regarding the use of moga, especially prior to allo-HSCT. In this review, the risks of the use of moga in transplant settings and some possible approaches to avoid adverse events are discussed.

Moga and Tregs

Foxp3⁺ Tregs are an indispensable cell subset in human immunity. Because they suppress antitumor immunity in addition to autoimmunity, suppression of Tregs enhances antitumor immunity. Depletion of Tregs reduces the tumor burden *in vivo* in mice (31,32). In humans, the higher density of Tregs among tumor-infiltrating lymphocytes is associated with poor prognosis in several cancers (33-36). Tregs are classified into several subtypes: the most suppressive subset has the CD45RA⁻Foxp3⁺⁺ phenotype, called effector Tregs (37). Effective depletion of effector Tregs may be crucial to achieve strong antitumor immunity (30). It should be noted that effector Tregs

express CCR4 (30) and that depletion of Tregs might mount autoimmune pathology.

Tregs are also important in allo-HSCT. They appropriately modulate immunity, establish graft tolerance, enhance engraftment, and suppress GVHD (38,39). A reduced frequency of Tregs correlates with chronic GVHD (40). Although a reduction in Tregs should mount substantial antitumor immunity, depletion of Tregs may increase severe complications such as GVHD in allo-HSCT.

Several reports have indicated that ATL cells and Tregs share similar features, such as the CD3⁺CD4⁺CD25⁺ phenotype (41). Although they can be differentiated by CADM1 antigen expression (41), they share the CCR4⁺Foxp3⁺ phenotype in many cases. Therefore, moga might deplete Tregs in addition to ATL cells. Moga results in severe autoimmune pathology coincident with depletion of Tregs (41). In addition, T cells with the Th2 phenotype also express CCR4 (42). Theoretically, moga would shift the Th1/Th2 balance to the Th1 axis, which might enhance tissue damage through GVHD, although this has not been sufficiently investigated yet.

Collectively, while moga should enhance antitumor immunity, it may be problematic in cases that subsequently receive allo-HSCT because it can increase the risks of GVHD, graft rejection, impaired immune reconstitution, and other post-transplant complications.

Moga and establishment of tolerance after allo-HSCT

As described above, there are major concerns that pretransplant moga could increase the risk of GVHD. Recently, several groups reported the clinical outcomes of cases that received moga before allo-HSCT. These studies consistently reported that the use of moga before allo-HSCT was associated with an increased risk of severe acute GVHD (43-46), although a case report showed the successful management of acute GVHD (45). However, these studies were rather small to conduct multivariate analyses to adjust for the other risk factors of acute GVHD and other clinical events. Our group recently performed a retrospective analysis using a database of a nationwide survey of aggressive ATL (12). In this study, 82 patients out of 996 allo-HSCT recipients received moga before allo-HSCT. The risk of grade III-IV acute GVHD and steroid-refractory acute GVHD was significantly higher in patients who received moga before allo-HSCT than in those who

did not receive moga before allo-HSCT. The cumulative incidence of non-relapse mortality was significantly higher in the moga group than in the no-moga group (43.7% in the moga group and 25.1% in the no-moga group at 1 year). There was no significant difference in the incidence of relapse between the two groups. As a result, the probability of overall survival in the moga group was significantly inferior to that in the no-moga group (32.2% in the moga group and 49.4% in the no-moga group at 1 year). The median interval between the last moga administration and allo-HSCT was 45 days in this study. Using 50 days as a cut-off, a shorter interval between the last moga administration and allo-HSCT was significantly associated with an increased risk of non-relapse mortality and overall mortality. Sugio *et al.* suggested that an interval of <3 months between the last moga administration and allo-HSCT might be associated with an inferior clinical outcome (46). According to some previous reports, the concentration of moga remains more than 10 µg/mL for weeks even after the last administration of 1.0 mg/kg (25). Although we do not have any data about the correlation of immune recovery and plasma concentrations of moga, we assume that in patients with a shorter interval between the last moga administration and allo-HSCT, the concentration of moga remained high enough to deplete donor-derived Tregs after allo-HSCT, which is expected to induce severe acute GVHD as shown in *Figure 2*. In patients with longer intervals between the last moga administration and allo-HSCT, moga would deplete recipient-derived Tregs, but might not be able to deplete donor-derived Tregs. Recent reports showed that the majority of Tregs in the early period after transplant shows a CD45RA⁻ effector/memory phenotype (30,47). Because effector/memory phenotype Tregs express CCR4, the use of moga might result in a critical decrease in the overall Treg population during the early period after allo-HSCT (47,48). To elucidate the mechanisms *in vivo* further, prospective monitoring of the moga level and immune recovery including Tregs in peripheral blood is warranted.

How to incorporate moga in transplant-eligible patients with ATL

Considering the dismal outcome after allo-HSCT in patients who received moga before allo-HSCT, moga should be cautiously used in transplant-eligible patients with ATL. However, as described above, a proportion of patients with relapsed/refractory ATL could be rescued by

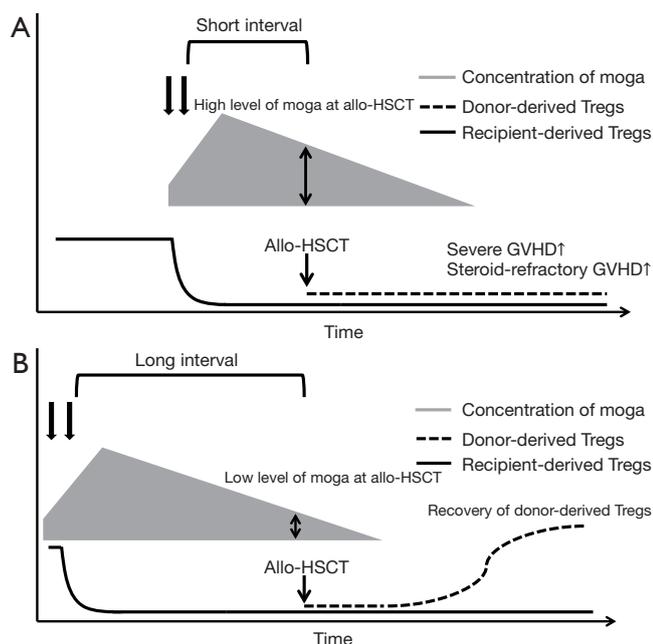


Figure 2 Importance of the interval between the administration of moga and allo-HSCT. (A) With a short interval between moga administration and allo-HSCT, the concentration of moga at allo-HSCT might be high, which is sufficient to deplete donor-derived Tregs as well as recipient-derived Tregs; (B) with a long interval between moga administration and allo-HSCT, the concentration of moga at allo-HSCT might be low, which is no longer able to deplete donor-derived Tregs, although moga has depleted recipient-derived Tregs.

moga (25,26). Therefore, incorporation of moga into the salvage treatment strategy might increase the number of potential candidates for allo-HSCT, and the development of transplant methods to maximize the benefits of moga in the treatment strategy of aggressive ATL is desired.

First, we can prolong the interval between the last moga administration and allo-HSCT. As previously reported and theoretically, the effects of moga could be reduced because the concentration of moga could be lowered as shown in *Figure 2*. Therefore, we could use moga in combination with other chemotherapies or moga alone in patients with relapsed/refractory ATL but only use moga for a short period and continue conventional salvage chemotherapy after sufficient disease control is achieved. The drawback of this strategy is that there is a possibility that disease control could worsen after moga is stopped and that the appropriate interval may depend on each patient. In our experience, this strategy is highly efficient in ATL cases

with tumor cells only in peripheral blood (25,26). As aforementioned, moga is expected to persist for several months *in vivo* as the half-life of moga is approximately 16 to 18 days (26). In addition, the effects of moga may last for more, because its pharmacodynamics may be different from its pharmacokinetics. Thus, we have to pay much careful attention to the development of severe GVHD, even when a long interval exists between administration of moga and allo-HSCT.

Second, we can intensify GVHD prophylaxis in patients who received moga before allo-HSCT. It is expected that a higher ratio of effector T cells/Tregs might lead to the development of acute GVHD (49). Although there are no data regarding how to intensify GVHD prophylaxis in patients who received moga, we could incorporate antithymocyte globulin (ATG) to deplete effector T cells and induce Tregs. ATG was reported to deplete effector T cells but possibly expand Tregs (50-54). The dose of ATG that is practically used differs among centers/countries (55-57). A low dose of ATG (58-61) is usually used in Japan because previous reports showed that the incidence of acute GVHD is lower in the Japanese population than in the Caucasian population (62-64). However, in patients who received moga, it is expected that higher doses of ATG are needed, which should be determined in the future. Although post-transplant cyclophosphamide (PT-Cy) might be an option as a potent GVHD prophylaxis, GVHD prophylaxis using PT-Cy relies heavily on the expansion of Tregs (65,66) and seems ineffective in patients who received moga before allo-HSCT in our experience (personal communication).

Third, we can possibly use adoptive Treg therapy, although it is not usually available in clinical practice. Several studies showed promising results using adoptive Tregs (67-74). However, before adoptive Treg therapy is a cellular therapeutic agent, there are various hurdles to overcome (75). We need to identify and isolate Tregs, and expand them under good manufacturing practice for cellular product manufacturing.

In addition, it is important that some patients do not experience any immunological complications even after a short interval of moga use. This diversity might depend on some polymorphisms such as HLA and KIR, which should be further investigated.

On the other hand, moga might be incorporated as consolidation or salvage therapy “after” allogeneic HSCT. Ipilimumab, a checkpoint inhibitor, was reported to have some beneficial effects in relapses after allogeneic HSCT despite the risk of GVHD (76). Although there have not

been sufficient data about the feasibility and efficacy of posttransplant moga, moga might be safely administered as ipilimumab. In any case, however, we should carefully monitor the incidence of adverse events, as moga could induce GVHD and other alloreaction-related complications.

In summary, because moga might have beneficial effects in a significant proportion of patients, we need to conduct prospective studies to establish a way to inhibit severe/steroid-refractory GVHD in patients who have received pretransplant moga.

Conclusions

Moga has a therapeutic potential in patients with relapsed/refractory ATL. To improve the clinical outcome of relapsed/refractory ATL, we need to develop a treatment strategy incorporating chemotherapy, moga, and allo-HSCT. To optimize such a treatment strategy, more studies are needed to clarify the effects of moga on immune tolerance and tumor immunity.

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Footnote

Conflict of Interest: The authors have no conflicts of interest to declare.

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