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Mogamulizumab for the treatment of cutaneous T-cell lymphoma: recent advances and clinical potential

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***Abstract*:** Mogamulizumab (KW-0761) is a humanized immunoglobulin G1 (IgG1) monoclonal antibody (mAb) that targets CC chemokine receptor 4 (CCR4). It has shown promising therapeutic potential in phase I and II clinical trials and is currently being investigated for efficacy in treating cutaneous T-cell lymphoma (CTCL). We review the mechanism of action of mogamulizumab and its role in treating CTCL. We also discuss the results of major clinical trials.

Keywords: cutaneous T-cell lymphoma, mogamulizumab, peripheral T-cell lymphoma

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Background

Mogamulizumab (KW-0761) is a humanized immunoglobulin G1 (IgG1) monoclonal antibody (mAb) that targets CC chemokine receptor 4 (CCR4). This antibody possesses a defucosylated Fc region that enhances its antibody-dependent cellular cytotoxicity (ADCC) *via* high-affinity binding with the Fc receptor on effector cells [Ishida *et al.* 2004a]. CCR4 is a novel target for immunotherapy, as it is expressed on surface of tumor cells of most patients with adult T-cell leukemia–lymphoma (ATLL), and is selectively expressed in other subtypes of peripheral T-cell lymphoma (PTCL) and cutaneous T-cell lymphoma (CTCL) [Ishida *et al.* 2004b].

Approximately 30–40% cases of PTCL not otherwise specified (NOS) are CCR4+ and the CCR4+ expression is an independently and significantly unfavorable prognostic factor [Ohshima *et al.* 2004]. Previous studies have proposed that CCR4 expression is an important prognostic factor in the PTCL-nodal group and that positivity for chemokine receptor CXCR3 and negativity for CCR4 demonstrate better prognosis [Tsuchiya *et al.* 2004].

CTCL is the second most common extranodal non-Hodgkin's lymphoma (NHL) after marginal zone B-cell lymphoma. It represents a series of skin-based neoplasms of T-cell origin, predominantly of peripheral CD4+ T-cells. There are 13 distinct CTCL subtypes, and mycosis fungoides (MF) is the most common. MF is a mature, indolent T-cell lymphoma with potential for nodal, blood and visceral involvement. Sézary syndrome (SS) is the most aggressive form of CTCL characterized by erythroderma and blood involvement by atypical clonal T-cells [Willemze *et al.* 1997]. Advanced CTCL has been associated with poor prognosis and an estimated 5-year overall survival rate between 42% and 63% [Vidulich *et al.* 2009].

The CCR4 expression in CTCL indicates that mogamulizumab has promising therapeutic potential, which has been elucidated clinically. Phase I and II clinical trials investigating the use of mogamulizumab in ATLL, PTCL and CTCL have already been published. A phase III trial is currently recruiting, with an estimated completion date at the end of 2015. The drug has already been approved for use in Japan for relapsed or refractory CCR4+ ATLL in 2012, and for relapsed or refractory CCR4+ PTCL or CTCL in 2014. Thus, mogamulizumab represents the first approved and clinically-tested antibody drug against a chemokine receptor being used for cancer therapy.

Overview of mogamulizumab

Mogamulizumab is a humanized anti-CCR4 defucosylated IgG1 mAb that eliminates tumor

cells *via* ADCC. Using the mechanism, nonspecific effector cells, including natural killer (NK) cells and macrophages/monocytes, possess membrane-bound FcγRs that crosslink with the Fc region of the IgG molecule, bound to a specific target cancer cell, such as the CCR4+ lymphoma cell. FcγR binding increases the activity of the cytotoxic cells, facilitating the release of cytoplasmic lytic enzymes, granzymes, perforin-containing granules and tumor necrosis factor (TNF) that induce lysis of the antibody-targeted cell [Shinkawa *et al.* 2003].

The IgG Fc domain of mogamulizumab contains two N-linked asparagine oligosaccharide sites with a β-mannose core, bisecting N-acetylglucosamine (GlcNAc), and a glycan moiety of branching sugar residues containing fucose, galactose or sialic acid. Recombinant DNA-based glyco-engineering technology has altered the glycan moiety by depletion of fucose residues (defucosylation), significantly changing the IgG activity [Shinkawa *et al.* 2003].

Removing fucose on the Fc region of the mogamulizumab IgG enhances ADCC, by means of increasing the binding affinity to the activating FcγRIIIa. Of all the sugar components in the antibody, fucose has been found to be the most important in affecting ADCC. This is based on studies documenting >50-fold higher ADCC with humanized anti-IL-5 receptor IgG1 and chimeric anti-CD20 IgG1 with a low fucose content of oligosaccharides compared with antibodies with high fucose oligosaccharides [Shields *et al.* 2002]. Later studies have validated this finding in mouse T-cell lymphoma cell line EL4-derived transfectants with different levels of exogenous human CD20 expression used as target cells. Compared with high fucose IgG1, the low fucose IgG1 showed potent ADCC through improved binding of FcγRIIIa on activated effector NK cells at low antigen densities; fucose depletion reduced by threefold the amount of antigen required on target cells for the same level of ADCC [Shinkawa *et al.* 2003].

Role of mogamulizumab in CTCL

Patients with CTCL experience an immunodeficiency as their disease progresses, which is the result of immunosuppressive cytokine secretion, by dysregulation of immunoregulatory protein expression by the malignant T-cells, and by loss of T-cell receptor repertoire complexity. It is also possible that some CTCL cells may act as regulatory T-cells (Tregs) and effectively impede host antitumor immunity [Krejsgaard *et al.* 2012]. CCR4 facilitates T-cell migration to the skin through skin-associated chemokines, including thymus and activation-regulated cytokine (TARC) and monocyte-derived chemokine (MDC), which are the ligands to CCR4 [Ishida *et al.* 2003].

CCR4 and its chemokine ligands are universally overexpressed in CTCL skin lesions at all stages of disease [Sugaya *et al.* 2015]. The receptor is also selectively expressed at high levels in skin-homing Tregs compared with other T-cell subsets [Ni *et al.* 2015]. A study using a CCR4+ CTCL mouse model demonstrated NK-mediated ADCC of CTCL cells in vitro and inhibition of MDC-induced chemotaxis of CD4+ CD25 high Tregs with in-house engineered anti-CCR4 mAbs [Ito *et al.* 2009]. Therefore, the use of mogamulizumab in CTCL is supported by the expression of CCR4 on clonally expanded lymphoma cells.

There are no reports regarding the resistance to mogamulizumab therapy, which exerts its activity on CCR4 expressing T-cells through an indirect effector mechanism, ADCC [Ishi *et al.* 2010]. CCR4 molecules could be involved in the resistance to mogamulizumab by loss of expression. Several mechanisms ranging from gene to protein level have been explained for loss of CD20 [Duman *et al.* 2012], similar mechanisms might cause loss of CCR4 expression. Ohno and colleagues showed a loss of CCR4 expression on the same adult TCLL clones. Loss of CCR4 expression is one mechanism; others can be mutation, or deletion within epitope coding region of mogamulizumab, increase in soluble CCR4 and reduced ADCC [Ohno *et al.* 2013].

Efficacy of mogamulizumab in CTCL *in vivo*

The effectiveness of mogamulizumab in CTCL has been demonstrated in separate phase I and II randomized controlled trials. The initial phase I/II multicenter, dose-escalation study included relapsed patients with PTCL and CTCL. The results were presented at the American Society of Hematology meeting in 2010 and have recently been published. Subjects in this study with either a complete response (CR), partial response (PR), or stable disease (SD) could receive additional infusions of KW-0761 every 2 weeks until disease progression (PD). A total of 40 pretreated patients received at least four doses of KW-0761 at 0.1 mg/kg ($n = 3$), 0.3 mg/kg ($n = 3$) and 1 mg/kg

(n = 34). A total of 38 patients (23 with MF; 15 with SS) were evaluable for efficacy. The objective response rate (ORR) was 39% with two patients achieving CR (5%), and 13 achieving PR (34%). Twelve of 15 (80%) SS patients had a response in the blood, including seven (47%) CRs. SD was observed in 19 patients (50%); PD occurred in four patients (11%) [Duvic *et al.* 2015].

A phase II multicenter Japanese study investigating mogamulizumab in previously treated patients with PTCL or CTCL was published in 2014. Of the 37 patients who received mogamulizumab, the ORR was 35%, with a CR of 14%. Subgroup analysis showed an ORR of 34% in PTCL patients and 38% in CTCL patients. Median progression-free survival was 3.0 months [95% confidence interval (CI) 1.6–4.9], and median overall survival was not reached [Ogura *et al.* 2014].

A phase III randomized clinical trial comparing mogamulizumab with the histone deacetylase inhibitor vorinostat in patients with relapsed/refractory CTCL is currently underway and is expected to conclude in late 2015.

Efficacy of mogamulizumab in CTCL *in vitro*

A study published in 2015 demonstrated a reduction of Tregs in CTCL patients receiving mogamulizumab as part of the initial phase I/II clinical trial. Peripheral blood of 24 patients was analyzed for CCR4 expression on different T-cell subsets by flow cytometry, before and after one course of mogamulizumab. Malignant T-cells in peripheral blood were 20.8–100% positive for CCR4 at baseline. A total of 14 patients who achieved a response in blood had high baseline CCR4 expression on malignant T-cells, which underwent a significant reduction upon treatment. Furthermore, Tregs in blood were 58.6–100% positive for CCR4 at baseline and showed decreased numbers and CCR4 expression after treatment. CD8+ T-cells in blood were 3.2–23.2% positive for CCR4 at baseline and showed limited reduction of CCR4 expression with increased percentages of CD8+ T-cells after treatment. This study ultimately provided proof of concept that mogamulizumab is responsible for depleting circulating malignant cells in CTCL patients, while also decreasing their overall Treg populations [Ni *et al.* 2015].

Adverse events most frequently observed in the phase I/II study for CTCL [Duvic *et al.* 2015] included nausea (31.0%), chills (23.8%), infusion-related reaction (21.4%), headache (21.4%), pyrexia (19.0%), fatigue (16.7%), and cutaneous drug eruption (16.7%). Thirteen patients (30.9%) had at least one skin infection, only one of which was considered related to treatment. Patients who experience rash were withdrawn from study and the biopsies frequently showed perivascular lymphocytic infiltrate with eosinophils, with or without epidermal spongiosis. All of the infections seen were those frequently encountered in patients with CTCL [Talpur *et al.* 2008].

Conclusion

Mogamulizumab is a third-generation glyco-engineered mAb that targets CCR4, which is selectively expressed on aggressive T-cell neoplasms. It has shown efficacy in CCR4+ PTCL and CTCL, achieving significant response rates in these heterogeneous diseases. Most recently, it has been shown quantitatively to reduce circulating CCR4+ circulating malignant cells through a mechanism that also depletes native Treg cells. Given the results of the preliminary clinical trials, as well as the most recent proof-of-concept analysis, the results of the ongoing phase III study are eagerly anticipated. It is conceivable that the next generation of clinical trials will involve combination regimens in initial treatment, as well as other studies directly comparing different targeted agents. Nonetheless, mogamulizumab has already shown its clinical efficacy in CTCL and is likely to remain an integral part of a physician's approach to treating this disease.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

References

Duman, B., Sahin, B., Ergin, M. and Guvenic, B. (2012) Loss of CD20 antigen expression after rituximab therapy of CD20 positive B cell lymphoma: a case report review of the literature. *Med Oncol* 29: 1223–1226.

Duvic, M., Pinter-Brown, L., Foss, F., Sokol, L., Jorgensen, J., Challagundla, P. *et al.* (2015) Phase 1/2

study of mogamulizumab, a defucosylated anti-CCR4 antibody, in previously treated patients with cutaneous T-cell lymphoma. *Blood* 125: 1883–1889.

Ishida, T., Iida, S., Akatsuka, Y., Ishii, T., Miyazaki, M., Komatsu, H. *et al.* (2004a) The CC chemokine receptor 4 as a novel specific molecular target for immunotherapy in adult T-cell leukemia/lymphoma. *Clin Cancer Res* 10: 7529–7539.

Ishida, T., Inagaki, H., Utsunomiya, A., Takatsuka, Y., Komatsu, H., Iida, S. *et al.* (2004b) CXC chemokine receptor 3 and CC chemokine receptor 4 expression in T-cell and NK-cell lymphomas with special reference to clinicopathological significance for peripheral T-cell lymphoma, unspecified. *Clin Cancer Res* 10: 5494–5500.

Ishida, T., Utsunomiya, A., Iida, S., Inagaki, H., Takatsuka, Y., Kusumoto, S. *et al.* (2003) Clinical significance of CCR4 expression in adult T-cell leukemia/lymphoma: its close association with skin involvement and unfavorable outcome. *Clin Cancer Res* 9: 3525–3634.

Ishi, T., Ishida, T., Utsunomiya, A., Ingaki, A., Yano, H., Komatsu, H. *et al.* (2010) Defucosylated anti-CCR4 monoclonal antibody KW-0761 as a novel immunotherapeutic agent for adult T-cell leukemia/lymphoma. *Clin Cancer Res* 16: 1520–1531.

Ito, A., Ishida, T., Yano, H., Inagaki, A., Suzuki, S., Sato, E. *et al.* (2009) Defucosylated anti-CCR4 monoclonal antibody exercises potent ADCC-mediated antitumor effect in the novel tumor-bearing humanized NOD/Shi-scid, IL-2Rgamma(null) mouse model. *Cancer Immunol Immunother* 58: 1195–1206.

Krejsgaard, T., Odum, N., Geisler, C., Wasik, M. and Woetmann, A. (2012) Regulatory T cells and immunodeficiency in mycosis fungoides and Sézary syndrome. *Leukemia* 26: 424–432.

Ni, X., Jorgensen, J., Goswami, M., Challagundla, P., Decker, W., Kim, Y. *et al.* (2015) Reduction of regulatory T cells by mogamulizumab, a defucosylated anti-CC chemokine receptor 4 antibody, in patients with aggressive/refractory mycosis fungoides and Sézary syndrome. *Clin Cancer Res* 21: 274–285.

Ogura, M., Ishida, T., Hatake, K., Taniwaki, M., Ando, K., Tobinai, K. *et al.* (2014) Multicenter phase II study of mogamulizumab (KW-0761), a defucosylated anti-cc chemokine receptor 4 antibody, in patients with relapsed peripheral T-cell lymphoma and cutaneous T-cell lymphoma. *J Clin Oncol* 32: 1157–1163.

Ohno, N., Kobayashi, S., Ishigaki, T., Yuji, K., Kobayashi, M., Sato, K. *et al.* (2013) Loss of CCR4 antigen expression after mogamulizumab therapy in a case of adult T-cell leukaemia-lymphoma. *Br J Haematol* 163: 683–685.

Ohshima, K., Karube, K., Kawano, R., Tsuchiya, T., Suefuji, H., Yamaguchi, T. *et al.* (2004) Classification of distinct subtypes of peripheral T-cell lymphoma unspecified, identified by chemokine and chemokine receptor expression: analysis of prognosis. *Int J Oncol* 25: 605–613.

Shields, R., Lai, J., Keck, R., O'Connell, L., Hong, K., Meng, Y. *et al.* (2002) Lack of fucose on human IgG1 N-linked oligosaccharide improves binding to human Fcgamma RIII and antibody-dependent cellular toxicity. *J Biol Chem* 277: 26733–26740.

Shinkawa, T., Nakamura, K., Yamane, N., Shoji-Hosaka, E., Kanda, Y., Sakurada, M. *et al.* (2003) The absence of fucose but not the presence of galactose or bisecting N-acetylglucosamine of human IgG1 complex-type oligosaccharides shows the critical role of enhancing antibody-dependent cellular cytotoxicity. *J Biol Chem* 278: 3466–3473.

Sugaya, M., Morimura, S., Suga, H., Kawaguchi, M., Miyagaki, T., Ohmatsu, H. *et al.* (2015) CCR4 is expressed on infiltrating cells in lesional skin of early mycosis fungoides and atopic dermatitis. *J Dermatol* 42: 1–3.

Talpur, R., Bassett, R. and Duvic, M. (2008) Prevalence and treatment of Staphylococcus aureus colonization in patients with mycosis fungoides and Sézary syndrome. *Br J Dermatol* 159: 105–112.

Tsuchiya, T., Ohshima, K., Karube, K., Yamaguchi, T., Suefuji, H., Hamasaki, M. *et al.* (2004) Th1, Th2, and activated T-cell marker and clinical prognosis in peripheral T-cell lymphoma, unspecified: comparison with AILD, ALCL, lymphoblastic lymphoma, and ATLL. *Blood* 103: 236–241.

Vidulich, K., Talpur, R., Bassett, R. and Duvic, M. (2009) Overall survival in erythrodermic cutaneous T-cell lymphoma: an analysis of prognostic factors in a cohort of patients with erythrodermic cutaneous T-cell lymphoma. *Int J Dermatol* 48: 243–252.

Willemze, R., Kerl, H., Sterry, W., Berti, E., Cerroni, L., Chimenti, S. *et al.* (1997) EORTC classification for primary cutaneous lymphomas: a proposal from the cutaneous lymphoma study group of the European Organization for Research and Treatment of Cancer. *Blood* 90: 354–371.