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Anti-class II -DR humanized monoclonal antibody, IMMU-114, blocks allogeneic immune response

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KEYWORDS:
IMMU-114;
Human leukocyte antigen;
HLA;
Class II;
Mixed lymphocyte reaction;
MLR

Abstract

BACKGROUND: The effect of a humanized anti–human leukocyte antigen–DR monoclonal antibody, IMMU-114, on the allogeneic immune response was investigated in vitro.

METHODS: Responder peripheral blood mononuclear cells were cocultured with inactivated self or allogeneic stimulator peripheral blood mononuclear cells in the presence of control antibody or IMMU-114. Thymidine incorporation rates were then measured. Phenotypic changes in peripheral blood mononuclear cells and the intracellular Th1-type cytokines interleukin-2, interferon-γ, and tumor necrosis factor–α were analyzed using flow cytometry. The concentrations of interleukin-2, interferon-γ, and tumor necrosis factor–α in the mixed lymphocyte reaction culture medium were measured.

RESULTS: Thymidine incorporation rates at a 1:1 responder/stimulator ratio of allogeneic, allogeneic + IMMU-114, self, and self + IMMU-114 were 22,080.7 ± 602.4, 2,254.5 ± 118.1, 1,284.0 ± 227.8, and 494.5 ± 27.5 cpm, respectively ($P = .038$). IMMU-114 decreased the frequencies of human leukocyte antigen–DR–expressing CD16+56+ NK cells, CD19+ B cells, and CD3+25+ activated T cells.

CONCLUSION: Intracellular cytokine assay and measurement of Th1-type cytokines in the mixed lymphocyte reaction culture medium revealed that IMMU-114 significantly decreased the titers of interleukin-2, interferon-γ, and tumor necrosis factor–α. IMMU-114 significantly suppresses the allogeneic immune response in vitro, partly through inhibition of the Th1 response.
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The immunologic dogma that CD4+ T cells recognize antigen on major histocompatibility complex (MHC) class II and that CD8+ T cells recognize antigen on MHC class I is a central tenet of transplantation immunity.[1,2] Recognition of allogeneic antigens by host T cells occurs in 2 main ways: after presentation by donor MHC on donor antigen-presenting cells or endothelial cells of grafts (direct recognition) and after presentation along with self MHC after processing of donor antigens by host antigen-presenting cells (indirect recognition).[3,4] In both recognition systems, CD4+ T cells play a major role. CD4+ T cells are activated upon recognition of allogeneic antigens and MHC class II complex and develop into Th1 or Th2 cells, producing specific cytokines.[5–7] Previous studies have shown that Th1

Dr Goldenberg has a management role and stock ownership in Immunomedics, Inc.

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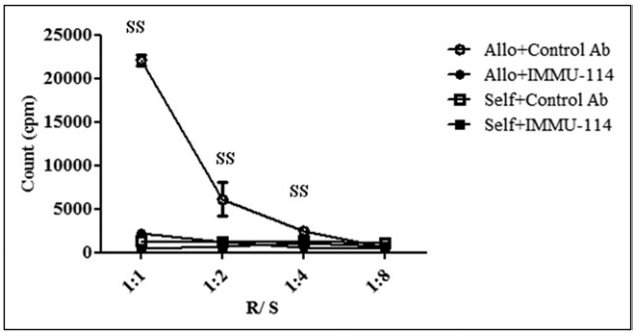

Figure 1 In vitro MLR. Responder (R) cells were cocultured with self (Self) or allogeneic (Allo) stimulator (S) cells at responder/stimulator ratios of 1:1, 1:2. 1:4, and 1:8 for 6 days. The cells were cultured in the presence of 10 nmol/L control antibody (Ab) or IMMU-114. Statistical analysis was performed using 1-way ANOVA. SS = statistically significant.

cells mediate rejection and that Th2 cells mediate tolerance of grafts,[8] although this simple paradigm is still questionable.[9–11]

Blocking of the interaction between CD4+ T cells and MHC class II is an attractive strategy and has been investigated.[12] Treatment with anti–MHC class II antibody has been shown to prolong graft survival in allogeneic[13] and concordant xenogeneic[14] transplantation models. However, for human leukocyte antigen (HLA) class II, very few antibodies have been clinically available,[15] and this has hampered the clinical introduction of such antibodies.

IMMU-114 is an anti–class II -DR humanized monoclonal antibody designed for use in class II -DR–overexpressing B-cell malignancies.[16,17] It was recently reported that IMMU-114 can deplete human antigen-presenting cells, leading to suppressed T-cell proliferation in allogeneic mixed lymphocyte reaction (MLR), suggesting that it may have therapeutic potential against graft-versus-host disease.[18]

It is anticipated that IMMU-114 will be the first anti–class II antibody used in a clinical setting.[19] A previous study demonstrated that IMMU-114 killed various types of leukemia cell lines, but not all.[17] The cytotoxicity of IMMU-114 requires the activation of specific intracellular signals, including Jun kinase 1/2 and extracellular signal-regulated kinase 1/2 mitogen-activated protein kinases.

In this study, we investigated the effect of IMMU-114 on the human allogeneic immune response in vitro and found that it was strongly inhibitory.

Methods

IMMU-114

The anti–class II -DR humanized monoclonal antibody IMMU-114 was obtained from Immunomedics, Inc (Morris Plains, NJ), and the anti–human immunoglobulin G4 control antibody (HCA050A) was from AbD Setotec (Oxford,

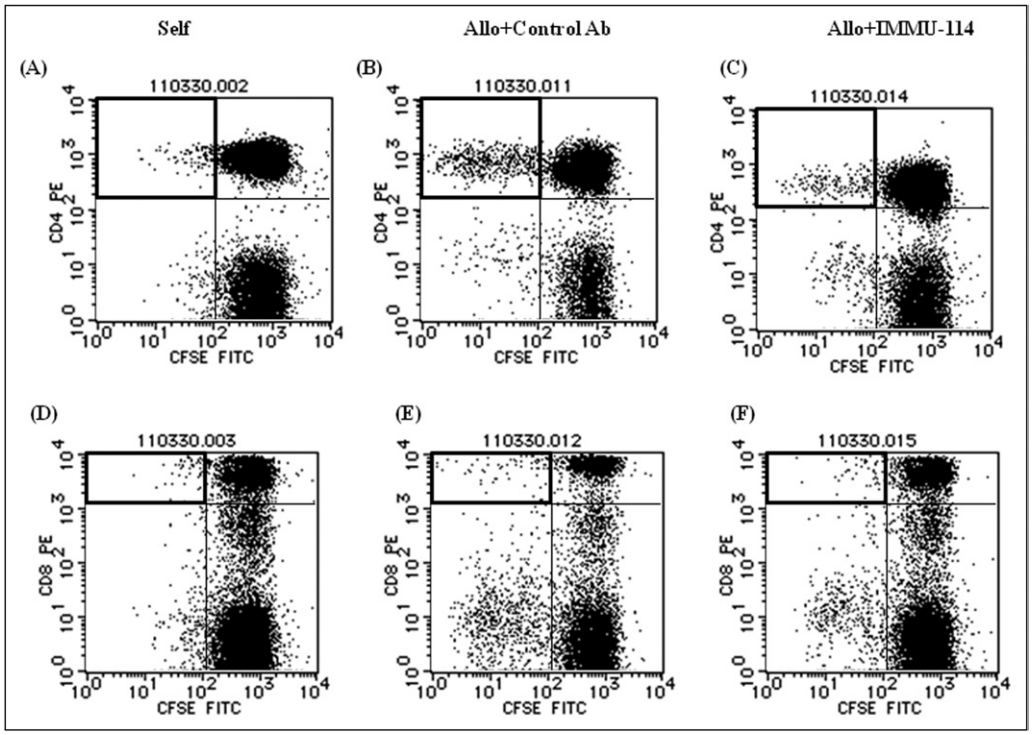

Figure 2 CFSE MLR. Responder cells were cocultured for 6 days, with self (Self) stimulators (A,D), allogeneic (Allo) stimulators with control antibody (Ab) (B,E), or allogeneic stimulators with IMMU-114 (C,F). Proliferating CD4+ or CD8+ T cells were visualized by a low intensity of CFSE fluorescence (area surrounded by thick square).

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