Polymorphism of Fc Receptor (FcyRII) Is Reflected in Cytokine Release and Adverse Effects of mlgG1 Anti-CD3/TCR Antibody During Rejection Treatment After Renal Transplantation


Anti-CD3 monoclonal antibody (MAb) OKT3 is immunosuppressive, but the first injection usually evokes severe adverse effects that are related to a massive release of cytokines in vivo. The high serum levels of tumor necrosis factor (TNF-α), interferon-gamma (IFN-γ), and to a lesser extent interleukin-2 (IL-2), that are observed a few hours after the first injection, presumably result from T-cell activation in vivo. Previous studies have demonstrated that in vitro T-cell activation and proliferation induced by anti-CD3 MAb are dependent on the presence of monocytes bearing Fcy receptors that bind murine IgG. The Fcy receptor responsible for binding of murine IgG1 (mlgG1) is FcyRIIa, an isoform of FcyRII that occurs on monocytes, macrophages, and granulocytes. FcyRIIa is known to be polymorphic: mlgG1 anti-CD3 MAb induces T-cell proliferation in vitro in only 70% of normal Caucasian individuals ("high-responders" [HR]) but not in "low-responders" (LR) individuals. This genetic polymorphism of FcyRII is also reflected in the release of cytokines (IFN-γ, IL-2) observed in vitro when mononuclear cells are incubated with mlgG1 anti-CD3 MAb.

We investigated the role of this FcyRII polymorphism in the release of cytokines in vivo and the occurrence of adverse effects after the administration of WT31, a mlgG1 MAb directed against the CD3-associated T-cell receptor (TCR).

PATIENTS AND METHODS

The large-scale production of WT31 was performed at the Dutch National Institute of Public Health and Environmental Protection as described elsewhere.

We measured the T-cell proliferation in vitro induced by WT31 to determine whether patients to be treated with WT31 were HR or LR. WT31 was administered by intravenous infusion, after informed consent, to nine patients with a rejection episode after kidney transplantation. The diagnosis of rejection was confirmed by histology of allograft biopsy (except in one case in which no biopsy could be taken). Four patients were HR, and five were LR.

Blood samples were collected in EDTA tubes at regular intervals after the start of the first administration of WT31. Plasma was obtained by immediate centrifugation at 4°C, and aliquots were stored at −70°C until tested. An immunoradiometric assay (IRMA) was used to measure TNF-α, IFN-γ, IL-6, and IL-2 (Medgenix Diagnostics, Fleurus, Belgium).

RESULTS AND DISCUSSION

This pilot study was set up primarily to investigate whether or not the anti-TCR antibody WT31 induces the release of cytokines in vivo and the cytokine-associated “first-dose reaction” usually observed with anti-CD3 antibodies. Furthermore, in case these phenomena occurred, we wanted to find out if their occurrence was related to the known polymorphism of FcyRII, the human Fc receptor that can bind mlgG1.

Administration of WT31 (6 mg) to the first HR patient induced a typical “first-dose reaction.” In plasma samples obtained from this patient during the first hours after the start of WT31, very high concentrations of circulating cytokines were measured (eg, a peak value of 1750 pg/mL for TNF-α). In addition to the cytokine-related adverse effects, we observed a marked decrease in the number of peripheral lymphocytes and, surprisingly, a profound granulocytopenia which necessitated the interruption of WT31 treatment for several days. In view of the side effects observed in this patient, the other HR patients received a much lower initial dose (1 mg) of WT31, and 50 mg of intravenous prednisolone 1 hour before WT31 administration. Despite this, all HR patients except one had a first-dose reaction and granulocytopenia (although to a lesser extent than the first HR patient). One HR patient had some symptoms of cytokine-related syndrome, but only the day after the start of WT31 and not immediately following it. In complete contrast, none of the five LR patients showed any sign of first-dose reaction (or granulocytopenia), despite the fact that the first dose of WT31 was 6 mg and four of them received no premedication with prednisolone. An increase of TNFα was measured in plasma samples from all HR patients but not in the three LR patients analyzed until now. No increase of IFN-γ or IL-6 was observed in the LR patients, whereas increased concentrations were measured in all HR patients except the one who showed no immediate first-dose response. The serological and clinical findings in HR and LR patients are summarized in Table 1.

It is remarkable that one of the HR patients showed no immediate side effects of WT31 administration, despite an adverse effect after the start of WT31, very high concentrations of circulating cytokines were measured (eg, a peak value of 1750 pg/mL for TNF-α). In addition to the cytokine-related adverse effects, we observed a marked decrease in the number of peripheral lymphocytes and, surprisingly, a profound granulocytopenia which necessitated the interruption of WT31 treatment for several days. In view of the side effects observed in this patient, the other HR patients received a much lower initial dose (1 mg) of WT31, and 50 mg of intravenous prednisolone 1 hour before WT31 administration. Despite this, all HR patients except one had a first-dose reaction and granulocytopenia (although to a lesser extent than the first HR patient). One HR patient had some symptoms of cytokine-related syndrome, but only the day after the start of WT31 and not immediately following it. In complete contrast, none of the five LR patients showed any sign of first-dose reaction (or granulocytopenia), despite the fact that the first dose of WT31 was 6 mg and four of them received no premedication with prednisolone. An increase of TNFα was measured in plasma samples from all HR patients but not in the three LR patients analyzed until now. No increase of IFN-γ or IL-6 was observed in the LR patients, whereas increased concentrations were measured in all HR patients except the one who showed no immediate first-dose response. The serological and clinical findings in HR and LR patients are summarized in Table 1.

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Table 1. Cytokine Release and "First-Dose Reaction"
Following the First Administration of WT31 to HR and LR Patients

<table>
<thead>
<tr>
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<th>HR</th>
<th>LR</th>
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<tbody>
<tr>
<td>Increase of TNFα</td>
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<td>0/3</td>
</tr>
<tr>
<td>Increase of IFNγ</td>
<td>3/4</td>
<td>0/3</td>
</tr>
<tr>
<td>Increase of IL-6</td>
<td>3/4</td>
<td>0/3</td>
</tr>
<tr>
<td>First-dose reaction</td>
<td>3/4*</td>
<td>0/5</td>
</tr>
<tr>
<td>Granulocytopenia</td>
<td>3/4</td>
<td>0/5</td>
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*Adverse effects including fever and myalgia were also observed in the fourth HR patient, but only on the second day of treatment.

increase of plasma TNF-α. In this patient there was no increased IFN-γ or IL-6. These findings are reminiscent of those obtained by Chatenoud and coworkers, who observed only mild or no side effects after administration of BMA031 (a mIgG2b anti-TCR MAb), despite a sharp increase of isolated TNF-α (in the absence of IFN-γ).9 Apparent, IFN-γ is required to induce the characteristic "first-dose reaction." This hypothesis is supported by the protective effect of anti–IFN-γ antibodies on anti-CD3–induced morbidity and mortality in mice.10

We have recently reviewed the clinical significance of the polymorphism of human Fc receptors for immunotherapy.11,12 Our current data indicate that WT31 can induce cytokine release in vivo and the cytokine-associated syndrome, and that the polymorphism of human FcγRII determines whether or not this will occur. Furthermore, WT31 induced granulocytopenia in three of the four HR patients, but in none of the LR patients. This granulocytopenia might be related to the expression of FcγRII on granulocytes. These findings imply that the HR/LR polymorphism defined by in vitro experiments indeed has direct implications for the in vivo use of mIgGl MAb. Previously published data obtained from a small group of patients treated with a mIgGl anti-CD8 antibody already suggested that elimination of CD8-positive cells only occurred in HR patients.13 Knowledge obtained from such pilot studies performed with mouse MAb may be helpful in designing suitably modified antibodies for optimal efficacy and minimal toxicity.14

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REFERENCES