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# Allele and Antigen-Specific Treatment of Rheumatoid Arthritis: A Double Blind, Placebo Controlled Phase 1 Trial

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***ABSTRACT.*** ***Objective.*** Human cartilage glycoprotein 39 (HC gp-39) appears to be a relevant autoantigen in patients with rheumatoid arthritis (RA). Administration of major histocompatibility complex (MHC) Class II complexed antigens without requisite costimulatory signals can induce immunologic tolerance. We evaluated the safety, pharmacokinetics, and preliminary efficacy of AG4263 in patients with RA. AG4263 is a soluble complex of native HLA-DR4 (ß*0401) complexed to Org 36601, a 13-mer peptide derived from HC gp-39 (also referred to as CDP263).

***Methods.*** Thirty-one HLA-DRB1*0401 positive patients with persistent RA disease activity despite concurrent methotrexate were randomized to 7 infusions of AG4263 (n = 24) or placebo (n = 7) over 6 weeks. The initial dose of 0.5 µg/kg was escalated in subsequent cohorts to a maximum of 150 µg/kg. Safety analyses included recording of adverse events and measurement of CD4/CD8 counts, reactivity to recall antigens, and development of antibodies to HLA-DR4. Efficacy was assessed using the Paulus 20 criteria.

***Results.*** Treatment was well tolerated, with injection site reaction the most common adverse event. There was no loss of reactivity to recall antigens, change in cell counts, or antibodies to HLA-DR. The mean half-life of AG4263 was 12.5 h. Some evidence of clinical response was seen; responses were more common among patients receiving the highest doses of AG4263 and among those with baseline T cell reactivity to CDP263.

***Conclusion.*** AG4263 was safe, well tolerated, and without evidence of generalized immune suppression. Along with the observed trend toward clinical efficacy, the results suggest that this therapeutic approach warrants further investigation in patients with RA. (J Rheumatol 2003;30:449–54)

*Key Indexing Terms:*
RHEUMATOID ARTHRITIS HLA-DR ANTIGENS T CELL ANTIGEN RECEPTORS
MAJOR HISTOCOMPATIBILITY COMPLEX AUTOANTIGENS T LYMPHOCYTES

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory disease characterized by infiltration of the synovium by various immunocompetent cells. Among the immunoregulatory abnormalities described in patients with RA has been the production of antibodies with reactivity to self antigens, many of which are constituents of the normal joint. Relevant putative autoantigens include type II collagen, which is the major component of articular cartilage, and human cartilage glycoprotein 39 (HC gp-39)[1-4]. A potential role for autoantigens in perpetuating arthritis in patients with RA is supported by their ability to induce chronic arthritis in animal models[1-3]. HC gp-39, an impor-

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tant secretory product of synovial fibroblasts, is also produced by articular chondrocytes and peripheral blood mononuclear cells (PBMC). A potential role for HC gp-39 as an important target antigen in RA is supported by several lines of evidence. These include the presence of HC gp-39 mRNA and protein in rheumatoid synovium, increased concentrations of HC gp-39 in plasma from patients with RA, a correlation between plasma levels of HC gp-39 and some measures of disease activity in RA, and the observation of reactivity of peripheral blood T cells from patients with RA to a peptide (CDP263; Org 36601) derived from HC gp-39[1-3,5].

According to the "2 signal" model of T cell activation, T cells in a cognate immune reaction require not only the trimolecular complex of antigen/MHC molecule/T cell receptor (TCR), but also a second signal that could be provided by other costimulatory molecules. It was observed that provision of antigen/MHC to T cells in the absence of such costimulatory signals led to T cell inactivation and immunologic tolerance[6-8]. This observation paved the way for various therapeutic approaches, including the use of soluble MHC:self-peptide complexes that interact with the TCR, sending only the primary signal to the T cell. This approach has been utilized in animal models such as experimental allergic encephalomyelitis (EAE) and experimental allergic myasthenia gravis (EAMG)[9-12]. Treatment in these models results in a state of T cell anergy and ultimately, when evaluated *in vitro*, T cell clonal apoptosis.

There is a genetic component to RA, with the strongest genetic contribution provided by MHC Class II alleles[13,14]. More specifically, alleles such as HLA-DRB1*0401, *0404, *0405, and *0101 that contain the "shared epitope" consensus motif in their third hypervariable region have been associated with the development and/or severity of RA in diverse populations. These findings have led to the hypothesis that a HLA-DR4:autoantigenic peptide complex could induce anergy and/or apoptosis of a selected autoaggressive T cell subset in patients with RA, thereby improving their clinical prognosis without causing nonspecific immune suppression. Subsequently, a soluble complex of DR4:CDP263 (AG4263) has been developed for study.

## MATERIALS AND METHODS

*Patients.* Patients with RA between the ages of 18 and 75 years who were heterozygous or homozygous for HLA-DRB1*0401 were eligible for the study. Subjects were required to have previously failed treatment with at least one disease modifying antirheumatic drug (DMARD) and to have active disease despite the concurrent use of methotrexate (MTX) at a stable dose of 5–20 mg/week for at least 6 weeks preceding the study, and consecutive use of MTX for at least 3 months prior to study enrollment. Subjects were also required to take folic acid for at least 4 weeks prior to the first dose of study drug and throughout the study. Stable concurrent doses of nonsteroidal antiinflammatory drugs (NSAID) and low dose prednisone (≤ 10 mg/day) were permitted during the trial. In addition, patients receiving concurrent therapy with hydroxychloroquine (HCQ) or sulfasalazine (SSZ) at stable doses for 4 or more weeks prior to study entry were allowed to continue those medications during the study (HCQ, n = 8/31 patients; SSZ, n = 1/31 patients).

Activity of RA was defined as the presence of swelling in ≥ 6 of 66 diarthrodial joints in addition to 2 of the following 3 measures: ≥ 9/68 tender joints; Westergren erythrocyte sedimentation rate (ESR) ≥ 28 mm/h or C-reactive protein (CRP) ≥ 15 ng/l; early morning stiffness of at least 45 min. Before entry into the trial, subjects were required to have adequate renal, hepatic, hematological, and immunological function, confirmed by serum creatinine < 1.8 mg/dl, aspartate aminotransferase (AST) < 1.5 times upper limit of normal, hemoglobin ≥ 9.5 g/dl, platelet count ≥ 100,000/µl, white blood cell (WBC) count ≥ 3000/µl, and CD4 count ≥ 320/µl. Eight of 11 patients in the 2 highest dose cohorts were also required to have baseline T cell reactivity to CDP263 as measured by Elispot assay. Pregnant patients, those with a history of malignancy, and those with active infection were also excluded from the trial.

*Study drug*. The active drug, AG4263, is a soluble complex of native HLA-DR4 complexed to CDP263, a 13-mer peptide derived from HC gp-39. HLA-DR4 is a heterodimer composed of one 34 kDa and one 29 kDa glycoprotein subunit. The molecules were detergent-extracted from an Epstein-Barr virus (EBV) transformed lymphoblastoid cell line, GM06821, and then purified to remove extraneous contaminants. All manufacturing procedures were carried out under Good Manufacturing Practice (GMP) conditions at the Corixa Corporation pilot manufacturing facility (Redwood City, California, USA). The 1311 Da peptide that corresponds to amino acid residues 263–275 of HC gp-39 was also manufactured under current GMP conditions by Diosynth BV, a division of Akzo Nobel (Oss, The Netherlands). Loading of the peptide into the HLA-DR4 dimer was performed under conditions that favor the coupling of the peptide to the HLA-DR4 complex to achieve a 1:1 ratio (> 90% of the HLA-DR4 binding sites loaded with the CDP263 peptide).

*Treatment protocol*. The study was a randomized, double blind, placebo controlled, dose escalation safety and tolerability trial with separate cohorts for each dose. The institutional review boards at each participating site reviewed and approved the study and all amendments.

Three subjects were enrolled, regardless of CDP263 reactivity, in each of the first 3 cohorts (0.5, 2.5, 12.5 µg AG4263/kg). Two subjects received AG4263 and one received placebo consisting of the AG4263 diluent. A total of 3 nonreactive and 8 reactive subjects were enrolled in each of the 2 highest dose cohorts (60 and 150 µg AG4263/kg). In each of these higher dose cohorts, 2 of the 3 nonreactive subjects and 7 of the 8 reactive subjects were randomized to AG4263; one of the 3 nonreactive subjects and one of the 8 reactive subjects in each cohort was randomized to placebo. Subjects were randomized after completion of the screening visit and confirmation of eligibility. To fully evaluate the safety at each dose level, the last subject in each dose group was followed for at least 21 days before the next dose level was administered to a new cohort.

Five identical doses of AG4263 or placebo were given by intravenous infusion on alternate days over 2 consecutive weeks as an induction course. Subjects were observed for 4 weeks and then received a single maintenance cycle consisting of 2 identical doses of AG4263 or placebo on alternate days in Week 6. Subjects were then observed through Week 10.

*Safety.* Safety criteria comprised adverse event reports, routine laboratory data, measurement of antibodies to HLA-DR by ELISA, and measurement of T cell secretion of interferon-γ (IFN-γ) in response to tetanus toxoid and purified protein derivative (TT/PPD) of tuberculin by Elispot assay.

*Elispot assay.* The Elispot protocol used in this study was developed by Corixa Corporation[15,16]. In brief, patient PBMC were isolated from heparinized blood by Ficoll density gradient centrifugation, washed, and set up in culture in a 96 well U-bottom plate at $2 \times 10^5$ cells/well in 200 µl complete medium in the presence of specific antigens including TT/PPD and CDP263 peptide. Cells were boosted with recombinant interleukin 2 (IL-2) on Day 4 and restimulated with antigen and autologous antigen-presenting cells on Day 7. The following day, cells were transferred to Elispot plates that were precoated with IFN-γ capture antibody and incu-

bated 24 h at 37°C in 5% $CO_2$. The detection of secreted IFN-γ was identified by the progressive binding of a secondary biotinylated anti-IFN-γ antibody and streptavidin-horseradish peroxidase; the spot color was then developed by adding 100 µl/well of aminoethyl carbazol (AEC) substrate. Plates were observed for spot development for a maximum of 1 h, washed 3 times, and dried overnight at room temperature. The number of spots/well was then enumerated on an ImmunoSpot analyzer (Cellular Technology Ltd., Cleveland, OH, USA). To allow for variability in sampling, 6 wells were used for each antigen and for the media control. Reactivity to specific antigens was obtained by determining the ratio of the median number of spots among the 6 wells indicating the presence of IFN-γ after stimulation to the median number of spots observed when no peptide was added. A sample was considered positive or reactive if that ratio was ≥ 2 (a ratio sensitive enough to detect statistically significant differences in reactivity).

*Efficacy. Biological activity.* The biological effects of AG4263 were assessed by measurement of the reactivity of T cells to CDP263 by the Elispot assay as described. Blood samples were obtained prior to treatment and on Days 14, 28, 44, 56, and 74 posttreatment. Elispot assays for individual cohorts were performed when the last subject in each cohort completed the trial. T cell reactivity represented the ability of T cells to secrete IFN-γ in response to the specific CDP263 stimulation. Baseline reactivity (i.e., before study drug treatment) was quantified as positive or negative, with a reactivity index of 2 as criteria for positive reactivity.

*Clinical disease activity.* The response to therapy was assessed using the Paulus 20 criteria[17], which was the standard assessment tool at the time the study was designed. Variables measured included painful and swollen joint score (none = 0, mild = 1, moderate = 2, severe = 3), duration of morning stiffness, the subject's global assessment of disease activity, the investigator's global assessment of disease activity, and ESR. These variables were assessed on Days 7, 14, 28, 44, 56, and 74 posttreatment. To reduce variability, the same individual performed all assessments for a given subject. Response was defined as 20% improvement in at least 4 of the 6 variables measured.

*Pharmacokinetics.* Serum samples were obtained from 7 subjects in the 150 µg/kg dose cohort and assayed for HLA-DR content above background. The pharmacokinetic variables estimated included maximum concentration ($C_{max}$), time to reach maximum concentration ($T_{max}$), area under the concentration-time curve ($AUC_{0-\infty}$), total clearance ($CL_t$), half-life ($T_{½}$), and volume of distribution ($V_d$).

*Statistical analysis.* There were 2 populations for analysis. The intent-to-treat (ITT) population was used for the safety, biological activity, clinical disease activity, and pharmacokinetic analyses, and consisted of subjects who were randomized and had at least one dose of study medication. The per-protocol population was used for confirmatory analyses of biological and clinical disease activity, and consisted of ITT subjects who completed the study according to the protocol with no relevant protocol violations. All descriptive and inferential statistical analyses were performed using SAS software. Statistical tests were 2 tailed unless otherwise stated. No adjustments for multiplicity were performed for this exploratory study because the comparisons are considered independent from one another and the sample size does not support such adjustments. The first 3 cohorts (AG4263 0.5, 2.5, and 12.5 µg/kg; n = 2 for each dose of active study drug) were too small to support inferential statistical comparisons. Inferential statistics were applied to compare placebo (n = 7), AG4263 60 µg/kg, and AG4263 150 µg/kg (n = 9 for each dose of active study drug). For continuous data, an analysis of variance (ANOVA) model with an effect for treatment was used. Type III sum of squares from the SAS GLM output was used when assessing treatment effects in all models.

## RESULTS

*Patients.* Two hundred twenty-three patients considered to be eligible for the study on clinical grounds were HLA-DR phenotyped and assessed for reactivity to CDP263 by Elispot assay. Sixty-four of 223 patients (29%) were found to be HLA-DRB1*0401 positive; of these, 90% were heterozygous. Among HLA-DRB1*0401 positive patients, 39% were found to have T cell reactivity to CDP263.

Baseline demographic and disease characteristics of patients enrolled in the trial are shown in Table 1.

Thirty-one patients enrolled in the study, and 29 completed all planned evaluations. One patient discontinued the study due to lack of efficacy, and one discontinued due to thrombophlebitis. Both patients received all 5 doses in the induction arm before exiting the study, and both were in the 150 µg/kg group.

*Safety.* Multiple doses of AG4263 (0.5, 2.5, 12.5, 60, and 150 µg/kg) were found to be safe and well tolerated in 24 subjects with RA, and no maximally tolerated dose was reached. Adverse events tended to be of mild severity. No clinically meaningful changes in vital signs were observed. Subjects in the placebo group and the groups that received active study drug had a similar incidence of adverse events. The most frequently occurring adverse events are presented in Table 2. The most commonly occurring events were mild infusion site reactions such as bruising, redness, and pain.

One adverse event, thrombophlebitis at the infusion site, was considered by the investigator to be probably related to administration of study drug and resulted in study discontinuation. There were no trends that suggested important differences among treatments for any clinical laboratory abnormalities. The changes in the groups treated with active drug and the placebo group were similar. Of the 6 subjects who experienced Grade 3 laboratory toxicities (National Institutes of Health Common Toxicity Criteria, version 2.0, NIH, Bethesda, MD, USA) after dosing with active drug, 5 had decreases in lymphocytes (0.5–0.9) and one had an elevated AST (277 U/l). One serious adverse event, pleuritis resulting in hospitalization, was considered possibly related to the study drug in view of its temporal relationship to the maintenance cycle doses (onset one day prior to the seventh infusion). The subject completed the study, and the event had resolved by the end of the study.

There was no evidence of suppression of recall cellular immune responses to TT/PPD and no evidence of development of antibodies to DR4 (data not shown).

*Efficacy. Clinical disease activity.* Clinical efficacy, measured by the Paulus 20 criteria, is illustrated in Figure 1. Data are shown for all patients in the 60 and 150 µg/kg groups and CDP263 reactive patients as well as for the combined placebo treated patients.

At day 28, 17 days after the last of 5 induction doses, 67% of patients in the 150 µg/kg cohort were responders, compared with 44% of those in the 60 µg/kg cohort and 14% of placebo treated patients; this trended toward clinical significance (p = 0.107). Of note, when only patients experiencing baseline reactivity to CDP263 are considered, 86% of those in the 150 µg/kg group were responders, compared

*Table 1*. Demographics and baseline characteristics.

| Variable | Result | Placebo, n = 7 | AG4263, µg/kg 0.5, n = 2 | 2.5, n = 2 | 12.5, n = 2 | 60, n = 9 | 150, n = 9 |
|---|---|---|---|---|---|---|---|
| Age, yrs | Mean | 60.4 | 61.0 | 62.5 | 66.0 | 45.4 | 48.9 |
| Baseline Elispot reactivity*, n (%) | Reactive | 3 (43) | 0 (0) | 0 (0) | 1 (50) | 7 (78) | 7 (78) |
| | Nonreactive | 4 (57) | 1 (100) | 1 (100) | 1 (50) | 2 (22) | 2 (22) |
| ß*0401, n (%) | Heterozygous | 6 (86) | 2 (100) | 1 (50) | 2 (100) | 8 (89) | 9 (100) |
| | Homozygous | 1 (14) | 0 (0) | 1 (50) | 0 (0) | 1 (11) | 0 (0) |
| Westergren ESR, mm/h | Mean | 22.6 ± 18.6 | 18.5 ± 6.4 | 2.0 | 2.0 | 29.0 ± 19.9 | 20.3 ± 10.7 |
| C-reactive protein, mg/dl | Mean | 1.1 ± 0.6 | 0.8 | 4.0 ± 4.5 | 2.1 ± 1.8 | 2.0 ± 1.6 | 1.3 ± 1.2 |
| Painful/tender joint score (0–204) | Mean | 46.6 ± 27.3 | 41.5 ± 19.1 | 56.0 ± 58.0 | 15.5 ± 9.2 | 31.0 ± 24.6 | 26.0 ± 13.7 |
| Swollen joint score (0–198) | Mean | 20.4 ± 10.3 | 36.0 ± 21.2 | 18.5 ± 2.1 | 15.0 ± 1.4 | 25.8 ± 14.5 | 31.1 ± 13.1 |
| Disease duration, yrs | Mean | 9.9 | 6.5 | 9.0 | 12.5 | 7.8 | 12.9 |
| % RF+ | | 100 | 50 | 100 | 50 | 78 | 100 |
| Concomitant steroid use, % | | 43 | 50 | 50 | 50 | 56 | 56 |

* Baseline reactivity not assessed in one patient in each of the 0.5 and 2.5 µg/kg dose groups.

*Table 2*. Number (%) of subjects with most frequent adverse events.

| | Placebo, n = 7 | AG4263, µg/kg 0.5, 2.5, 12.5, n = 6 | 60, n = 9 | 150, n = 9 |
|---|---|---|---|---|
| At least one adverse event (%) | 5 (71.4) | 6 (100) | 9 (100) | 8 (88.9) |
| Infusion site reaction (%) | 2 (28.6) | 1 (16.7) | 3 (33.3) | 4 (44.4) |
| Fatigue (%) | 1 (14.3) | 0 (0.0) | 2 (22.2) | 2 (22.2) |
| RA aggravated (%) | 0 (0.0) | 2 (33.3) | 2 (22.2) | 0 (0.0) |
| Nausea (%) | 2 (28.6) | 0 (0.0) | 1 (11.1) | 1 (11.1) |
| Upper respiratory tract infection (%) | 1 (14.3) | 1 (16.7) | 1 (11.1) | 1 (11.1) |
| Dyspepsia (%) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 3 (33.3) |

with 29% of those in the 60 µg/kg group and none taking placebo (p = 0.03). Clinical efficacy at Day 74, nearly a month after the last maintenance dose, was not significantly different among the treatment groups.

*Biological activity.* Biological activity was assessed by reactivity of T cells to CDP263 in the Elispot assay. Data from the patients in the higher dose groups (60 and 150 µg/kg) who were reactive at the start of the study are shown in Table 3.

Among patients receiving 60 µg/kg of AG4263, 2 of 5 had converted from reactive to nonreactive at Visit 8, 6 days after the last of 5 induction doses. The numbers of patients shifting from reactive to nonreactive increased to 4 of 9 at Days 28 and 44 (20 and 36 days after the last induction dose, respectively), 5 of 8 at Day 56 (11 days after the second of 2 maintenance doses), and 3 of 9 at Day 74 (29 days after the last maintenance dose). Among patients receiving the 150 µg/kg dose, 6 of 9 went from reactive to nonreactive at Day 14, 5 of 9 remained so at Day 28, 5 of 8 were still nonreactive at Day 44, 5 of 6 at Day 56, and 4 of 7 at Day 74. Corresponding numbers for placebo treated patients in all the treatment cohorts are shown in Table 3. There is a trend toward greater biologic activity at Day 56, 11 days after the last maintenance dose.

It appeared that there was a possible correlation between loss of CDP263 reactivity and achievement of Paulus 20 response in the 150 µg/kg dose group (data not shown).

*Pharmacokinetics.* The mean volume of distribution was 1708 $mm^3$ and the mean clearance was 103 ml/min. After a single infusion of 150 µg/kg AG4263, there was an initial increase in plasma concentration of HLA-DR, with mean peak concentration of 15 mg/ml 1 h after dosing. This pattern was consistent across the 7 subjects studied. The mean half-life was 12.5 h.

## DISCUSSION

RA is a complex disease in which the etiopathogenesis and the factors driving perpetuation of the illness are poorly understood. In RA, the presentation of antigenic self-peptides to autoreactive T cells is presumed to be either an initiating event or a process through which an aberrant immune response is perpetuated. A peptide postulated to be one of the autoantigens involved in the development of RA is CDP263 (a 13-mer peptide) derived from a putative autoantigen HC gp-39. One therapeutic strategy in the treat-

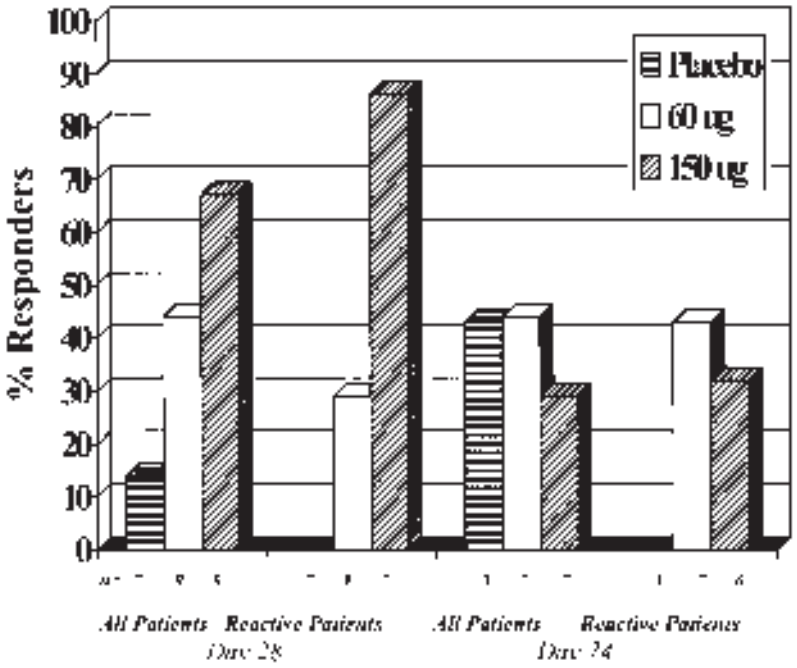


*Figure 1*. Clinical efficacy, measured by the Paulus 20% criteria, for all patients in the 60 and 150 µg/kg groups and CDP263-reactive patients as well as for the combined placebo treated patients.

*Table 3*. Number of subjects who shifted from CDP263 reactive at baseline to CDP263 nonreactive at subsequent times, by treatment group.

| Visit | Placebo | AG4263 60 µg/kg | AG4263 150 µg/kg | p |
|---|---|---|---|---|
| Day 14 | 2/6* | 2/5 | 6/9 | 0.580 |
| Day 28 | 2/6 | 4/9 | 5/9 | 0.873 |
| Day 44 | 1/7 | 4/9 | 5/8 | 0.377 |
| Day 56 | 1/6 | 5/8 | 5/6 | 0.077 |
| Day 74 | 3/7 | 3/9 | 4/7 | 0.865 |

* Denominator is the number of subjects who were CDP263+ at baseline and had data available at baseline and the subsequent timepoints.

ment of RA is through administration of soluble MHC class II:self-peptide complexes that in turn could deliver tolerizing signals to autoreactive T cells. MHC:peptide complexes can interact with the T cell receptor in a manner that could induce T cell anergy or apoptosis in the absence of costimulatory signals. This approach has shown efficacy in rodent models[12,18].

The MHC:peptide complex AG4263 makes use of a peptide derived from HC gp-39 in concert with HLA-DRB1*0401, a genetic background identified to increase the severity and potential risk of developing RA. This MHC:peptide complex has now been studied as an antigen directed therapeutic approach to disease therapy.

In this dose-finding safety study, this molecule appeared safe and well tolerated, with no differences seen between the active arm of the study and the placebo group. There were no deaths in this study and no malignancies or development of any opportunistic infections. Nevertheless, this was a short term study and the safety profile of this approach will need to be established in a larger sample size and longer term controlled trial.

While designed as a safety study, this Phase 1/2 study allowed some evaluation of therapeutic benefit. With the highest dose group, 67% of patients appeared to have achieved a Paulus 20% response by Day 28. There was also a suggestion of higher clinical efficacy among those patients with baseline T cell reactivity against the peptide. Looking at clinical responsiveness and reactivity to CDP263, it appeared that there may have been a correlation between biologic and clinical efficacy. Among patients in the highest dose group who had baseline reactivity to CDP263, clinical efficacy may have been achieved more commonly on those visits when there was loss of reactivity than when there was not.

With the introduction of anticytokine approaches to the treatment of RA the standard has been raised regarding the necessary or expected therapeutic benefit needed to establish the utility of a new therapy. However, these approaches suppress disease without curing it, as evidenced by the recurrence of disease activity upon discontinuation of treatment with TNF inhibitors. In addition, many patients have residual disease activity despite impressive improvements with TNF inhibitors. Therefore, the need remains for further research for potentially tolerogenic therapies.

Fundamental to the treatment of RA is the concept of inducing immunologic tolerance. The use of soluble MHC:peptide complexes may be one such approach to the possible induction of anergy or tolerance. HC gp-39 may prove to be an important target in this approach, as targeting HC gp-39 has been shown to induce tolerance in animal models.

However, difficulties with this approach exist. HLA-DRB1*0401 is expressed by a minority of patients with RA (about 40%), and this approach may prove to be useful only in those patients. While data suggest the possibility of greater efficacy among those patients with T cell reactivity to CDP263, it is far from clear that T cell reactivity is either necessary or sufficient to produce a response. Additionally, while HC gp-39 is a putative autoantigen, there may be limited prevalence of HC gp-39 as the dominant autoantigen in the greater population of patients with RA. Moreover, the efficacy of MHC:peptide therapy in a diversified autoimmune response or in the setting of epitope spreading is uncertain.

Nonetheless, given the apparent safety profile observed to date, additional studies to optimize the dosing regimen and to further evaluate safety and the potential clinical efficacy with possible induction of tolerance are worthwhile and should be explored.

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