Brief report

The CXCR4 antagonist plerixafor is a potential therapy for myelokathexis, WHIM syndrome

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Mutations in CXCR4 cause severe leukopenia in myelokathexis or WHIM syndrome. Plerixafor inhibits binding of CXCR4 to its ligand CXCL12. We investigated the effects of plerixafor (0.04 to 0.24 mg/kg) administered at 2-4 day intervals in 6 patients. Outcome measures were the patients’ complete blood cell counts, CD34+ cell counts and lymphocyte subtypes compared with 5 normal subjects similarly treated with plerixafor. All patients showed prompt leukocytosis with maximum blood neutrophils and lymphocytes at 6-12 hours. Blood neutrophils peaked at 6-12 hours, increasing from a mean baseline of 0.4 ± 0.1 × 10^9/L to mean peak of 4.5 ± 0.78 × 10^9/L. Lymphocytes also increased; the greatest increase was in B cells (CD19+ cells), a > 40-fold increase over baseline at the 0.08 mg/kg dose. None of the patients experienced any significant adverse effects. Plerixafor is a promising therapy for this condition. (Blood. 2011;118(18):4963-4966)

Introduction

WHIM syndrome (warts, hypogammaglobulinemia, immunodeficiency, and myelokathexis) is a rare autosomal dominant immunodeficiency disorder attributable to mutations in CXCR4.1 The WBC is usually < 1.0 × 10^9/L with severe neutropenia and lymphocytopenia. If warts are absent, the condition is usually called “myelokathexis.”2 Marrow examinations show abundant neutrophils with hyper-segmented nuclei and remnants of neutrophils in marrow macrophages.3 Mutations in CXCR4 prevent the normal release of mature neutrophils from the marrow into the blood.4 The mechanism for lymphocytopenia is not known, but it may be attributable to interruption of the normal trafficking of lymphocytes and their retention in the marrow and other lymphoid tissues.5

Plerixafor is a small molecule inhibitor of the binding of CXCR4 to its natural ligand, the chemokine SDF1, also called CXCL12.6 Subcutaneous administration of plerixafor causes dose-dependent leukocytosis and increases circulating leukocytes, including CD34+ cells, and plerixafor is indicated for mobilization of hematopoietic stem cells for autologous transplantation in combination with granulocyte colony-stimulating factor (G-CSF) for patients with non-Hodgkin lymphoma and multiple myeloma.7,8

We and others have hypothesized that plerixafor might also be useful as a molecularly targeted therapy for myelokathexis or WHIM syndrome, increasing circulating leukocytes by overcoming the impaired internalization and receptor dysfunction attributable to mutant CXCR4.9

Results and discussion

All 6 patients showed prompt leukocytosis with maximum blood neutrophils and lymphocytes at 6-12 hours, declining toward baseline by 24 hours (Figure 1). Comparisons of the baseline and 6-hour counts for each type of leukocytes for the patients and normal controls at the 0.08 mg/kg dose are shown in Figure 2. At this dose the patients had significant increase in mean neutrophils (P < .001, Student t test), monocytes (P < .001), B cells (P < .01), T cells (P < .01), NK cells (P < .05), and CD34+ cells (P < .01) in response to plerixafor. As shown in Figure 1, the responses were even greater at higher doses. One patient had neutrophils > 2.0 × 10^9/L 24 hours after the 0.16

Study design

We enrolled 6 patients (4 female, 2 male, ages 28-73 years) in this study, with informed consent, in accordance with the Declaration of Helsinki, and investigational review board approval of the University of Washington and Federal approval for investigational use of plerixafor. Five patients from 3 different families had the same mutation (R334ter); the other patient had a novel mutation (S324F/S365E). Single subcutaneous doses of plerixafor, increasing from 0.04-0.24 mg/kg, were administered at 2-4 day intervals. Complete blood counts were determined at 1, 3, 6, 9 and 24 hours with an automated counter and leukocyte differential counts confirmed manually. CD34+ cells and lymphocyte subtypes were measured by FACS before and 6 hours after the 0.08 mg/kg dose. Plerixafor was discontinued if neutrophils were > 2.0 × 10^9/L at 24 hours, if serious adverse events or illness occurred, or after testing the 0.24 mg/kg dose. Results were compared with 5 similarly studied normal subjects using Student t test for comparisons of means of normal subjects and controls and the ratio paired t test for comparison of baselines and responses for each category of leukocytes.

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Having reached this target for the study, he was not given the final 0.24 mg/kg dose. Another patient achieved 2.0 x 10^9/L 24 hours after the 0.24 mg/kg dose. One patient discontinued the trial after the 0.08 mg/kg dose when she had a recurrence of pneumonia. In the patient group, neutrophils peaked at 4.5 ± 0.78 x 10^9/L (group mean of highest observed values; median: 4.5 x 10^9/L; range: 1.8 to 7.3 x 10^9/L). The absolute increase in neutrophils after single doses of plerixafor was less than for normal subjects, but the relative increase was greater. Comparing peak neutrophil responses, there was a 4.4-fold increase for the controls and an 8.2-fold increase for the patients. For all patients, neutrophils had returned to baseline before the next dose of plerixafor was administered (Figure 1).

Patients’ lymphocyte responses were proportionally greater than their neutrophil responses (Figure 1). Absolute lymphocyte counts transiently reached normal levels in the patients, increasing ~14-fold from baseline to peak levels (P < .01, ratio paired t test). The absolute levels of B cells showed the largest increase over baseline, increasing ~40-fold (P < .01, ratio paired t test). Patients’ CD34+ cells increased almost 6-fold at the 0.08 mg/kg dose.

Hematocrit, hemoglobin and platelet counts were stable through the 10-day testing period, except for 1 patient with severe iron deficiency anemia who responded well to oral iron initiated during the study (data not shown).

None of the patients experienced significant adverse effects, including local reactions to plerixafor injections.

This trial demonstrates that subcutaneous administration of single doses of plerixafor can transiently correct neutropenia and lymphocytopenia in patients with myelokathexis/WHIM syndrome. The patients’ responses were qualitatively similar to those of normal controls. Although the quantitative increase in neutrophils was less than in normal controls, the proportional increase was greater. This suggests that the mechanisms for
release of neutrophils from the mature marrow storage pool are intact, but the “hyper-mature” and apoptotic neutrophils in the marrow have lost the capacity to circulate normally. In this regard, it will be interesting and important to determine whether regular, perhaps daily, plerixafor administration has a greater ability to increase and maintain blood neutrophil levels.

Lymphocyte counts increased much more dramatically, and all lymphocyte subtypes increased in the patients, particularly NK cells. Lymphocytes have far more complex circulatory patterns than neutrophils, entering and leaving the blood in the marrow, spleen and other tissues. Lymphocyte mobilization from the tissues to the blood and apparent correction of lymphocyte trafficking...
may be very important for these patients. As noted in the “Introduction,”
patients with WHIM syndrome have hypogammaglobulinemia, and the
pattern of their infections, particularly their propensity to develop severe
problems with warts, suggests a selective immunodeficiency which
might be corrected with chronic plerixafor therapy. In this brief
dose-response study we did not measure neutrophil functions or
immunoglobulin levels before and after plerixafor, but these will be
important parameters to follow in a study of chronic plerixafor
treatment.

It is not surprising that the observed changes in leukocyte
counts were transient. Plerixafor is a reversible inhibitor of
CXCR4 binding to CXCL12 and has a blood half-life of only
~ 4 hours.\(^\text{10}\) Pharmacokinetic-pharmacodynamic modeling sug-
gests somewhat longer effects, perhaps sufficient to enhance
resistance to infections in these patients.\(^\text{10}\) The optimal dose and
schedule remains to be determined and therapeutic schedules
may depend on the specific infection or other clinical indication.
Because the drug was so well-tolerated in the WHIMS patients it
is a promising molecularly targeted therapy for this condition.
Plans for a therapeutic trial are now underway.

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Authorship

Contribution: D.C.D. directed the study and authored the report;
A.A.B. contributed to planning study, recruited patients, oversaw
clinical study; M.L.K. performed laboratory studies, analyzed data
and assisted in writing paper; E.C.W. assisted in planning study,
performed laboratory studies, assisted in analyzing data; V.M.
performed DNA sequencing and assisted in analyzing data; A.A.
assisted in planning and analyzing data; B.W. was responsible for
FACS analysis; and F.J.H. and D.C.D. planned the study.

Conflict-of-interest disclosure: D.C.D. has received research
funding from Genzyme, served as a consultant for Sanofi-Adventis
(the current owner of Genzyme), and is listed as an inventor on a
University of Washington–Genzyme patent application for the use
of plerixafor for treatment of myelokathexis and related conditions,
and as an inventor on the AnorMED patent for the use of
AMD3100/plerixafor for mobilization of hematopoietic stem cells.
F.J.H. is an employee of Genzyme and is listed as an inventor on a
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