Novel approach to treatment of scleroderma lung disease with anti-LFA3 therapy

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Summary

This pilot trial shows the feasibility of depleting T cells from scleroderma patients, including both the blood and lungs. Alefacept was well tolerated, and T cell depletion was associated with stability in lÅuÅng function over the period of the protocol. The data suggest that, at least in part, T cells may drive the non-specific inflammatory response in the lungs of these patients.

Introduction

Restrictive lung disease is a major cause of death in scleroderma. Our work and that of others have shown that progressive restrictive lung disease and death are associated with the presence of non-specific lung inflammation on bronchoalveolar lavage (BAL) cell differential. This non-specific inflammation is defined as = 3% neutrophils or = 2.2% eosinophils on BAL cell differential, but it is total numbers of macrophages, neutrophils, and eosinophils per ml BAL fluid are also increased in these individuals. Our data also show that progressive restrictive lung disease in scleroderma is associated with increased numbers of activated CD8+ T cells in the BAL fluids from scleroderma patients. It is unknown whether there is any link between the activation of CD8+ T cells and non-specific lung inflammation in scleroderma.

The purpose of this open label pilot trial was to determine whether treatment of scleroderma patients with lung inflammation with alefacept (LFA-3/IgG1 fusion protein, Biogen, Cambridge, MA) would reduce T cells in the lungs, including CD8+ T cells, and whether this reduction in T cells would be associated with a decrease in non-specific lung inflammation, as measured by alveolar neutrophils and macrophages. Alefacept serves as a molecular bridge between CD2+ cells (largely T cells, especially activated and CD8+ T cells) and FcgRIII+ cells (mostly NK cells), leading to Ig-dependent cellular cytotoxicity of the CD2+ T cell targets.

Results

Eight scleroderma patients with lung inflammation were treated with 12 weekly intravenous infusions of 7.5 mg alefacept, with bronchoalveolar lavage (BAL) done at time 0, 14 weeks (2 weeks after the end of therapy), and 26 weeks (3 months after the end of therapy). There were 5 women, 3 men, 6 Caucasians, and 2 African Americans, with median age 46 years (range 36-72 years). Seven patients had diffuse disease.

Alefacept was well tolerated, with only one serious adverse event related to the protocol, which was hospitalization for transient fever after the second bronchoscopy, with no infection found. All patients completed the protocol, with the exception that the last BAL procedure was not done in the patient who had developed fever after the second bronchoscopy.

Studies of T cells in the blood and lungs were done. In Table 1, data are given as median (25^{th}, 75^{th} percentile) change from time 0, with negative values indicating decreases from baseline. Patients had depletion of $CD3^+$, $CD4^+$, and $CD8^+$ T cells in

both peripheral blood and BAL fluids by week 14, with recovery underway by week 26. There was greater depletion of memory ($CD45RO^+$) than naive ($CD45RA^+$) T cells in the blood, and reduction in both in the lungs, with relatively few $CD45RA^+$ T cells in the lungs at baseline.

A reduction in alveolar macrophages and BAL neutrophils accompanied the decrease in BAL T cells. During this 26 week period, forced vital capacity (FVC) and diffusing capacity for carbon monoxide (DLco) were stable, with little overall change in patient and physician global assessment scores (0-10 scale).

Table 1. CHANGES IN IMMUNE CELLS AND CLINICAL PARAMETERS IN SCLERODERMA PATIENTS TREATED WITH ALEFACEPT

Parameter	Blood - 14 weeks	Blood - 26 weeks	BAL - 14 weeks	BAL - 26 weeks
$CD3^+$ T cells /ml	-29% (-34, -21)	-3% (-11, 1)	-32% (-77, -4)	15% (-29, 77)
$CD4^+$ T cells/ml	-22% (-35, -14)	2% (-19, 7)	-46% (-73, -10)	8% (-41, 123)
$CD8^+$ T cells/ml	-35% (-46, 28)	-10% (-29, -2)	-17% (-72, 6)	25% (-4, 52)
$CD4CD45RO^+$ T cells/ml	-42% (-47, -37)	-4% (-25, 2)	-46% (-71, 5)	14% (-35, 168)
$CD4CD45RA^+$ T cells/ml	10% (2, 18)	30% (16, 70)	-64% (-80, -50)	-25% (-75, 42)
$CD8CDRO^+$ T cells/ml	-42% (-64, -31)	-13% (-48, 9)	-16% (-70, 8)	39% (-4, 551)
$CD8CDRA^+$ T cells/ml	-7% (-9, -1)	25% (8, 44)	-41% (-86, -3)	2% (-43, 67)
Monos/macs/ml	-13% (-33, 9)	-5% (-12, 3)	-32% (-52, 0)	0% (-23, 23)
Neutrophils/ml	-6% (-14, 0)	-9% (-17, 12)	-28% (-52, -4)	2% (-20, 34)
FVC,%			-1% (-7, 2)	-1% (-8, 3)
TLC,%			-3% (-8, -1)	-2% (-4, 1)
DLco, %			-3% (-8, 0)	-8% (-10, 2)
Physician Global			-8% (-31, -3)	-26% (-45, -5)
Patient Global			-4% (-17, 11)	2% (-10, 8)

Data are given as median % change (25^{th}, 75^{th} percentile).