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STEM CELL TRANSPLANTATION FOR RESISTANT LUPUS. Ann E Traynor, James Schroeder, Robert M Rosa, Salim Mujais, Steve Rosen, Suzanne Bowyer, Lawrence Jung, Richard Burt Chicago, IL, Indianapolis, IN Omaha, NE

Five patients who experienced persistence of aggressive systemic lupus despite cyclophosphamide therapy were treated by dose intense immune suppression and autologous hematopoietic stem cells. Stem cells were mobilized with cyclophosphamide (2.0 g/m2) and granulocyte colony stimulating factor (GCSF) 10 ug/kg/day, enriched using CD34 positive selection, and reinfused following immune suppression with cyclophosphamide (200 mg/kg) and anti-thymocyte globulin (ATG) 90 mg/kg. Results: Median time to an absolute neutrophil count greater than 500/ul and non-transfused platelet count greater than 20,000/ul in these five transplanted patients were day 10 and 12 respectively. The first five patients to undergo transplant have now been followed for 60-800 days. All are well and without evidence of active lupus. Renal, cardiac, CNS and pulmonary functions and all serologic parameters have normalized or markedly improved. No patient has received chemotherapy or any immune modulatory agent since transplant other than a continuous prednisone taper. Among the four patients who have been followed for over one year, the median prednisone dose is 5 mg daily (0-15 mg/d). The median SLEDAI score is 1. The first four patients have now been followed a median of 18 months (14-27 months) and all are without evidence of active lupus. Conclusion: Despite failure of available therapies and serious organ dysfunction, each patient is without active lupus and continues to improve following stem cell transplant. Durability of these remissions remains to be determined.

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SUCCESSFUL TREATMENT OF REFRACTORY SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) BY AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT) WITH IN VIVO IMMUNOABLATION AND EX VIVO DEPLETION OF MONONUCLEAR CELLS. Falk Hiepe, Oliver Rosen, Andreas Thiel, Gero Massenkeil, Hartmut Radtke, Thomas Haupl, Erika Gromnica-Ihle, Andreas Radbruch, Renate Arnold Berlin, Germany

ASCT is a new experimental approach to treat patients with severe refractory autoimmune diseases. Various strategies for immunosuppression and processing of transplants have been proposed. Our hypothesis is that effective in vivo immunoablation and ex vivo depletion of mononuclear cells including autoimmune cells with subsequent ASCT can lead to long-lasting remission in severe autoimmune disease. Until now 3 patients with a refractory SLE (2 female, 1 male, age between 27 and 48 years) have been treated. These patients failed multiple conventional therapeutic strategies and had active life-threatening disease at the time of transplant. All SLE patients exhibited high disease activity with severe organ involvement especially lupus-nephritis and positive anti-dsDNA antibodies. Peripheral stem cells were mobilized with cyclophosphamide (2 g/sqm) and G-CSF. The transplant was CD34 positive selected by CliniMacs and contained 2.4 to 7.3 x 10e6 CD34+/kg b.w. and 1.0 to 1.6 x 10e4 CD3/kg b.w. The conditioning regimen included 200 mg/kg cyclophosphamide and 90 mg/kg antithymocyte globulin. The patients received antibacterial and antiviral prophylaxis. The efficient depletion of T cells from the transplant did not lead to life-threatening infections during the time of lymphopenia. All 3 SLE patients with a follow-up time of 5, 9 and 13 months after transplant are in clinical and serological remission. Antinuclear antibodies, anti-dsDNA antibodies and other autoantibodies (anti-Ro/SS-A, anti-La/SS-B, anti-cardiolipin) are still negative. The activity index ECLAM decreased from 7 to 2, 6 to 2, and 10 to 2, respectively. An increase of low complement levels to normal values was observed. Moreover, the dosage of steroids could be markedly reduced.

In conclusion, clinical and serological remission in patients with refractory SLE can be achieved by successful immunoablation in vivo combined with highly effective purging of the transplant. The duration of the remissions is unknown and needs to be studied.

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HIGH-DOSE IMMUNOABLATIVE CYCLOPHOSPHAMIDE IN SLE. M Petri, A Jones, R Brodsky Baltimore, MD

High-dose immunoablative cyclophosphamide (HDIC; 200 mg/kg) without stem cell rescue results in durable, complete remissions in the majority of pts with aplastic anemia and other refractory autoimmune diseases. Stem cell rescue is not necessary, because early stem cells are resistant to HDIC. HDIC delivers the same dose of cytoxan used in bone marrow transplantation preparation regimens, but avoids the problem of re-infusion of autoreactive lymphocytes with stem-cell rescue. We have followed 11 pts with SLE after HDIC. **Methods:** 11 SLE pts refractory to other regimens underwent HDIC. Complete remission is defined as no disease activity, on physiologic or no prednisone and no immunosuppressive therapy. Partial response is defined as mild disease activity, on physiologic or no prednisone and no immunosuppressives.

		Previous Therapies	Follow up (mths)	
Pt.	Indication			Response
GB	Skin	Methotrexate, Cellcept	1.53	Complete Remission
DD	Kidney	Cellcept	3.57	None
JG	Skin (pyod. Gang.)	Cellcept, cyclosporin	4.17	None
YH	Kidney	Cellcept	2.87	None
CK	Kidney	Cellcept	7.93	Complete Remission
PK-T	CNS, Heme	Imuran	25.63	Partial Response
GL-T	Skin, Kidney	Imuran, cytoxan	19.75	Complete Remission
PL-E	Kidney	Cytoxan	10.25	None
MO-N	CNS	Imuran	8.50	Complete Remission
LT	CNS, Pulm HTN	Imuran, Cellcept, Cytoxan	9.17	Pulm HTN-Com. Rem.
BG	Kidney	Cytoxan, Cellcept	3.10	None

Example of Renal Complete Remission for CK (* = pre-HDIC)

	Urine protein (g)	Prednisone (mg)	Immunosuppressive
8/24/98*	2.688	40	+
11/19/98	2.033	25	0
2/18/99	1.427	10	0
4/29/99	0.493	5	0

Conclusion: HDIC can lead to durable, complete remission of SLE in pts who have failed all other immunosuppressive therapies, including monthly IV cyclophosphamide. 50% of pts with renal lupus refractory to all other therapies responded. There have been no cases of infertility to date. HDIC offers an alternative to stem cell rescue in refractory to SLE pts at 1/5 the cost of stem cell transplantation.

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rHUIL-10 (TENOVIL) PLUS METHOTREXATE (MTX) IN ACTIVE RHEUMATOID ARTHRITIS (RA): A PHASE I/II STUDY. Michael E Weinblatt, E William St Clair, Ferdinand C Breedveld, Larry W Moreland, Edward C Keystone, Sicy H Lee, Lowell B Robison, Daniel E Furst, Ken J Bulpitt, Eric M Veys, Thomas Haverty, Paul Grint, Janice C Wherry

rHUIL-10 (rIL-10, TENOVIL) is an anti-inflammatory cytokine which inhibits proinflammatory cytokines and is effective in animal models of arthritis. Trends towards improvement in RA have been seen in early clinical studies of rIL-10 alone.

This study evaluated the effects of adding rIL-10 to chronic MTX in patients with active RA.The study was a multicenter, randomized, placebo-controlled dose-escalating-study of rIL-10 (1, 4 or 8 μ g/kg qD or 8 or 20 μg/kg TIW)SC or placebo SC plus MTX (12.5-25 mg/week PO, SC or IM) in 50 pts with active RA treated for 4 weeks along with their stable dose of MTX.

ACR 20% response criteria was observed in 50% of pts receiving IL-10 at a dose of 8 μg/kg qd, 50% of patients receiving the 8μg/kg TIW dose and 63% at 20 μg/kg TIW dose vs 10% with placebo. ACR 50% response criteria was observed in 13% of pts receiving IL-10 at a dose of 8 μg/kg qd, 25% of patients receiving the 8μg/kg TIW dose and 13% at 20 μg/kg TIW dose vs 10% with placebo. Increases in serum TNF p55 and p75 soluble receptors were seen with rIL-10 therapy.

rIL-10 was clinically well tolerated and no anti-IL-10 antibodies were found. A dose-dependent decrease in platelets and hemoglobin were seen (with the highest doses of rIL-10, ~25% of subjects experienced a >40% decrease in platelets or a > 2g/dL decrease in hemoglobin) with rapid full recovery following cessation of rIL-10. 50-70% of subjects treated with 8 or 20 μg/kg TIW are continuing therapy with rIL-10 for >12 months in an extension protocol.

In this study rIL-10 therapy was well tolerated and safe and trends towards improvement in RA activity were seen. For future studies, the rIL-10 doses that maximize the safety and efficacy profile are 8 and 20 μg/kg TIW.

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A PILOT STUDY OF ISIS 2302, AN ANTISENSE OLIGODEOXYNUCLEOTIDE, IN PATIENTS WITH ACTIVE RHEUMATOID ARTHRITIS. Walter Maksymowych, Warren Blackburn, Edna Hutchings, Lucille Williams, Joseph Tami, Kathleen Wagner, William Shanahan Edmonton, Canada, Birmingham, AL, Carlsbad, CA

Forty-three patients were enrolled in a double-masked, randomized (3:1; ISIS 2302:placebo [PBO]), dose-escalation, PBO-controlled pilot study. ISIS 2302 is a 20-base phosphorothioate oligodeoxynucleotide (ODN) that downregulates human intercellular adhesion molecule 1 (ICAM-1) through an antisense mechanism.

Patients had to meet criteria for active disease (≥10 swollen joints and other criteria) despite adequate NSAID background therapy ± approved 2nd line agents ± low dose (≤10 mg/d)corticosteroids. Patients were administered thirteen 2 hour intravenous infusions over 26 days of ISIS 2302 at doses of 0.5 (10 pts.), 1.0 (3 pts.) or 2.0 (19 pts.) mg/kg, or normal saline PBO (11 pts.), and were followed for a total of 6 months.

By Paulus 20% criteria, responses were similar in the ISIS 2302 and PBO-treated patients over the first 3 months, but differentiated thereafter, with the greatest response observed in the 0.5 mg/kg patients. Over Months 4-6, the proportion of patients achieving Paulus 20% responses averaged 37%, 33%, 18% and 10% for the 0.5, 1.0, 2.0 mg/kg and PBO groups, respectively. Transient Paulus 50% responses, occurring sometime between Days 60-180, were observed in 10%, 33%, 21%, and 0% of patients in the 0.5, 1.0, 2.0 mg/kg, and PBO groups, respectively. Administration of ISIS 2302 was well tolerated. The only apparent drug-related adverse effect was an anticipated, transient (2-4 hours post dose), and dose-related increase in aPTT (~7 seconds at 2 mg/kg), due to inhibition of intrinsic tenase complex activity, a class effect of phosphorothioate ODNs.

Although these results suggest that ISIS 2302 is effective and well tolerated in the treatment of rheumatoid arthritis, the delayed response suggests that chronic dosing may be more effective. The development of second generation antisense chemistries targeting ICAM-1 may allow for chronic oral dosing.

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RESULTS FROM THE FIRST HUMAN CLINICAL TRIAL OF GENE THERAPY FOR ARTHRITIS. C H Evans, P D Robbins, S C Ghivizzani, J H Herndon, M C Wasko, M Tomaino, T A Muzzonigro, H I Georgescu, E Elders, T Whiteside, S C Watkins, R Kang Pittsburgh, PA

PURPOSE To determine whether it is possible to transfer safely IL-1Ra cDNA to the joints of patients with RA, and to express that DNA intraarticularly.

METHODS Nine postmenopausal women were recruited to the study. Eligibility criteria included the need for total joint replacement surgery of the MCP joints 2-5 and surgery on at least one other joint. Autologous synovium was recovered at the time of the latter surgery and used as a source of synovial fibroblasts, which were then expanded in culture. Cultures were divided in two. One was stably transduced with a retrovirus carrying the IL-1Ra cDNA and the other remained as an untransduced, control cell population.

Cells were tested for a variety of adventitious agents prior to injection into the MCP joints destined for surgical replacement. In a double blinded fashion, two joints received transduced cells and two received control cells. Patients were treated in a dose escalation manner. One week after gene transfer, the MCP joints were surgically removed and the retrieved tissues analyzed for evidence of successful gene transfer and gene expression.

RESULTS All patients completed the protocol unproblematically and no adverse events were noted. All synovia recovered from joints receiving the transgene showed evidence of gene expression by both RT-PCR and by ELISA measurement of IL-1Ra in media conditioned by the retrieved tissues. It was also possible to confirm this conclusion by *in situ* hybridization. Interestingly, several joints receiving the control cells also gave positive RT-PCR and protein signals. The results of rigorous control experiments suggest that these are not false positives.

CONCLUSIONS It is possible to transfer genes to human rheumatoid joints and to express them intraarticularly. The first patient received her genes nearly three years ago and neither she, nor any other participant, has experienced adverse events related to the gene transfer protocol. The detection of transgene expression in control joints adjacent to those receiving the gene remains an unexplained observation. It may suggest the existence of communication channels between adjacent, severely diseased joints, or the ability of injected cells to migrate interarticularly.

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