TREATMENT OF RHEUMATIC DISEASES WITH MONOCLONAL ANTIBODIES

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**Most prayers are answered,
although usually in the negative.**

W. Allen

INTRODUCTION

Recent advances in a number of areas of biology and medicine have made it reasonable to consider the use of monoclonal antibodies in the treatment of patients with rheumatic diseases, such as rheumatoid arthritis and systemic lupus erythematosus. These include an increasing understanding of the immunopathogenesis of these conditions, development of the technology to produce large amounts of appropriate monoclonal antibodies and information from animal models of rheumatic diseases, as well as transplant patients, undergoing monoclonal antibody treatment. Because of rapid developments in each of these areas and the continued lack of safe and effective therapy for many rheumatic conditions, a number of clinical trials have been initiated to examine the effect of monoclonal antibody therapy in rheumatic diseases. Most of these trials have focused on rheumatoid arthritis, but some initiatives in other diseases have also begun.

It should be noted that most of these therapies are aimed at pathophysiologic processes, not underlying causes. If these diseases are caused by abnormalities in immunoregulation that can be influenced by monoclonal antibody mediated perturbations of the immune system, cure by correction of the immunoregulatory aberration might be feasible. However, if these diseases are caused by exogenous agents that cannot be cleared by the immune system and thereby lead to persistent inflammation, disease suppression rather than cure would be the expected result. The results of the trials should give some insight into these issues. One reason to examine the effects of monoclonal antibody treatment on rheumatic diseases, therefore, is to gain additional insight into these and other questions concerning the immunopathogenesis of these conditions. Even if the initial trials do not produce practical therapeutics, the administration of monoclonal antibodies should test hypotheses about the immunopathogenesis of the diseases. It should also be pointed out that this approach is in its infancy. No controlled trials have been done. Only patients with advanced disease unresponsive to conventional therapy have been treated. Therapy with a very limited number of monoclonal antibodies has been attempted. Although the early results have been promising and instructive, it is too early to determine whether monoclonal antibody therapy will evolve as a standard treatment for rheumatoid arthritis and other rheumatic diseases.

MONOCLONAL ANTIBODIES

Köhler and Milstein described the technique to produce monoclonal antibodies in 1975 and were awarded the Nobel Prize in Medicine in 1984 for this discovery. In essence, a monoclonal antibody is produced by immunizing a suitable host, usually a mouse, rat, or hamster with an antigen and then immortalizing the antibody-secreting B cells by fusion with a non-secreting drug-sensitive myeloma cell line. The normal antibody secreting cells cannot survive indefinitely in an *in vitro* culture system. Similarly, the tumor cell line cannot survive in selection medium (hypoxanthine, aminopterin, thymidine; HAT) because of an enzyme deficiency (hypoxanthine-guanine phosphoribosyl transferase, HGPRT). Thus, only hybridoma cells (normal B cells fused to tumor cells) will survive in this medium. If a hybridoma that produces the antibody of interest is identified and subjected to a cloning procedure that results in monoclonality (derivation of all progeny from a single cell), a monoclonal antibody of desired specificity is produced.

Köhler G and Milstein C: Continuous culture of fused cells secreting antibody of predefined specificity. Nature 256:495-497, 1975.

FACTORS DETERMINING THE EFFECTIVENESS OF TREATMENT WITH MONOCLONAL ANTIBODIES

I. Immunoglobulin heavy chain isotype

- **Complement activation**
- **Fc interactions**

II. Density of the recognized antigen

III. Specific epitope recognized

IV. Production of antibodies to the monoclonal antibody

- **Alter clearance**
- **Block function**
- **Increase activity**

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APPROACHES TO IMPROVE THE EFFECTIVENESS OF TREATMENT WITH MONOCLONAL ANTIBODIES

1. **Use of class-switch variants**
2. **Use of multiple monoclonal antibodies**
3. **Use of immunotoxins**
4. **Use of humanized antibodies**

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SIDE EFFECTS OF

MONOCLONAL ANTIBODY THERAPY

1. **Cytokine Release syndrome**
2. **Allergic manifestations**

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EVIDENCE THAT T CELLS PLAY AN IMPORTANT ROLE IN THE PATHOGENESIS OF RHEUMATOID ARTHRITIS

1. **Phenotypic analysis indicates that activated T cells play a role in the pathogenesis**
   - **presence of activated T cells in the circulation**
   - **synovial tissue is infiltrated with T cells**
   - **activated T cells in the synovial fluid and tissue**

2. **Improvement with maneuvers that deplete T cells**
   - **thoracic duct drainage**
   - **total lymphoid irradiation**
   - **lymphapheresis**

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MONOCLONAL ANTIBODIES USED TO TREAT RHEUMATOID ARTHRITIS

Monoclonal Antibody	Species	Isotype	Target	Reference
Campath 1H	humanized[2]	hu IgG1	CDw52	A
RFT2	mouse	IgG2a	CD7	B
5D2 CHH-380	chimeric[3]	?	CD7	C
H65RA[1] (CD5 Plus)	mouse	IgG1	CD5	D,E,F

1. Conjugate with ricin A chain
2. CDR engrafted
3. Murine $V_H V_L$ + human C_H

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IMMUNOSUPPRESSIVE ACTIVITIES OF MONOCLONAL ANTIBODIES TO CDw52, CD7 AND THE ANTI-CD5-RICIN IMMUNOCONJUGATE

1. **Allograft rejection**
2. **Graft versus host disease**

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SUMMARY OF THE RESULTS OF UNCONTROLLED TRIALS OF THE TREATMENT OF ADVANCED RHEUMATOID ARTHRITIS WITH VARIOUS ANTI-LYMPHOID CELL MONOCLONAL ANTIBODIES

Antibody	No. of Patients	Days of Treatment	Dose	Biologic Effect	Clinical Effect	Adverse Events	HAMA	Retreatment
RFT2	6	14	6mg/day	Yes	2	2	6	0
SDZ CHH-380	10	2	4-20mg/day	Yes	0	9	0	0
Campath 1H	1	14	2mg/day	Yes	1	0	0	0
H65 RA (CD5 Plus)	79	5	0.1-0.3mg/day	Yes	Yes	Yes	78	Yes

RESPONSE OF PATIENTS WITH SEVERE RHEUMATOID ARTHRITIS TO TREATMENT WITH H-65 RA (CD5-PLUS)

	Months						
	1	2	3	4	5	6	10
Evaluable patients	76	63	44	32	24	23	10
Patients Improved	55	24	22	20	18	14	8
Percentage of treated patients who improved	72	32	29	26	24	18	11

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ADVERSE EVENTS IN 76 PATIENTS

TREATED WITH H65-RA (CD5 PLUS)

Adverse Event	Percentage
Constitutional Symptoms	65
Rash	52
Peripheral edema	45
Myalgias, arthralgias	21
Anaphylactic reactions	4
Vasculitis	1
Myopathy	1

CD4

1. **59kDA transmembrane glycoprotein expressed by helper/inducer T cells and monocyte/macrophages.**
2. **Receptor for polymorphic determinants on class II MHC molecules (HLA-DR) and HIV.**
3. **Intracellular domain is associated with $p56^{lck}$, a lymphocyte specific tyrosine kinase.**
4. **Acts as a co-receptor with the T cell receptor/CD3 complex in the functional activation of T cells.**

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EVIDENCE THAT CD4+ T CELLS PLAY A ROLE IN THE PATHOGENESIS OF RHEUMATOID ARTHRITIS

1. **Predominance of CD4+ T cells in the rheumatoid synovial membrane**
2. **Association of rheumatoid arthritis with the expression of particular class II MHC molecules**
3. **Amelioration of disease with HIV infection**

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MECHANISMS OF ACTION OF MONOCLONAL ANTIBODIES TO CD4 IN VIVO

1. **Eliminate CD4+ T cells**
2. **Alter recirculation of CD4+ T cells**
3. **Inhibit the function of CD4+T cells**
4. **Eliminate or alter the function of CD4+ Monocyte/Macrophages**

EFFECTS OF ANTI-CD4 MONOCLONAL ANTIBODIES IN ANIMAL STUDIES

1. **Profound depletion of CD4+ T cells**
2. **Profound suppression of immune responses mediated by CD4+ T cells**
3. **Induction of immune tolerance to itself and to antigens administered during the treatment**

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2. Benjamin RJ, Cobbold SP, Clark MR, Waldmann H: Tolerance to rat monoclonal antibodies. Implications for serotherapy. J. Exp. Med. 163:1539, 1986.
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EXPERIMENTAL MODELS OF HUMAN AUTOIMMUNE DISEASE SUCCESSFULLY TREATED WITH MONOCLONAL ANTIBODIES TO CD4

1. **Experimental Allergic Encephalomyelitis**

   - mouse, rat, monkey

2. **Insulin Dependent Diabetes Mellitus**

   - mouse

3. **Systemic Lupus Erythematosus**

   - mouse

4. **Collagen-Induced Arthritis**

   - mouse

5. **Thyroiditis**

   - mouse

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administration of anti-CD4 monoclonal antibody prolongs survival in long-tailed macaques with experimental encephalomyelitis. Clin. Immunol. Immunopathol. 45:405-423, 1987.

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mechanisms in murine autoimmune thyroiditis after depletion *in vivo* of L3T4+ and Lyt2+ cells. Immunobiology (Suppl.) 3:30, 1987.

MONOCLONAL ANTIBODIES TO CD4 USED TO TREAT RHEUMATOID ARTHRITIS

Monoclonal Antibody	Species	Isotype	Target	Reference
BL4	mouse	IgG2a	CD4	A
MT151	mouse	IgG2a	CD4	B,C,D
BF5	mouse	IgG1	CD4	E,F
VIT4	mouse	IgG2a	CD4	C
16H5	mouse	IgG1	CD4	G
MT412	chimeric[1]	hu IgG1	CD4	H

1. Murine $V_H V_L$ + human C_H

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C. Herzog C, Walker C, Muller W, Rieber P, Reiter C, Reithmüller, Wassmer P, Stockinger H, Madic O and Pichler WJ: Anti-CD4 antibody treatment of patients with rheumatoid arthritis: I. Effect on clinical course and circulating T cells. J. Autoimmunity 2:627-42, 1989.

D. Wassmer P, Neidgart M, Hintermann U, Reiter C, Rieber P, Riethmuller, P, Fehr K and Wagenhauser, JF: Therapy of rheumatoid arthritis with CD4 monoclonal antibodies. Arthritis Rheum. 33:S153, 1990.

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follow-up of 13 patients with rheumatoid arthritis treated by anti-CD4 monoclonal antibodies. Br. J. Rheum: 30 (Suppl 2):88, 1991.

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SUMMARY OF THE RESULTS OF UNCONTROLLED TRIALS OF THE TREATMENT OF ADVANCED RHEUMATOID ARTHRITIS WITH VARIOUS ANTI-CD4 MONOCLONAL ANTIBODIES

Antibody	No. of Patients	Days of Treatment	Dose	Biologic Effect	Clinical Effect	Adverse Events	HAMA	Retreatment
16H5	10	7	0.3mg/kg/day	Yes	6	4	6	4
BL4	7	10	20-40mg/day	Yes	Yes	3	4	0
MT151	9	3-7	20-200mg/day	Yes	5	2	Yes	3
MT151	18	7	20mg/day	Yes	10	0	6	4
MT151	5	7	10mg/day	Yes	Yes	0	3	0
V1T4	3	7	10mg/day	Yes	Yes	0	3	0
BF5	10	10	10-20mg/day	Yes	Yes	1	2	1
MT412	25	1-7	10-200mg	Yes	11	Yes	?	0
Total	87			Yes	32/62	10/62	24/53	12

SUMMARY OF THE EFFECTS OF TREATMENT OF ADVANCED RHEUMATOID ARTHRITIS WITH ANTI-CD4 MONOCLONAL ANTIBODIES

1. **Biologic effect is uniformly observed**
    a. **Decrease in circulating CD4+ T cells**
    b. **Decrease in T cell function**

2. **Transient clinical response in about 50%**
    - **prolonged response in few**
    - **remission in none**

3. **Adverse events are infrequent and mild**

4. **No sustained clinically significant immunosuppression**

5. **Immunization to mouse immunoglobulin in about 50%**

6. **Retreatment is comparably effective**

THE USE OF ANTI-CD4 MONOCLONAL ANTIBODIES IN OTHER HUMAN DISEASES

1. Multiple sclerosis

1. Hafler DA, Weiner HL: Immunosuppression with monoclonal antibodies in multiple sclerosis. Neurology 38 (suppl 2):42-47, 1988.
2. Hafler DA, Ritz J, Schlossman SF, Weiner HL: Anti-CD4 and anti-CD2 monoclonal antibody infusions in subjects with multiple sclerosis. J. Immunol. 141:131-138, 1988.
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IMMUNOSUPPRESSIVE ACTIVITIES OF MONOCLONAL ANTIBODIES TO THE INTERLEUKIN 2 RECEPTOR

1. **Murine insulin dependent diabetes mellitus**
2. **Murine lupus**
3. **Allograft rejection**

1. Kelley VE, Gaulton GN, Hattori M, Ikegami H, Eisenbarth G, Strom TB: Anti-interleukin 2 receptor antibody suppresses murine diabetic insulitis and lupus nephritis. J. Immunol. 140:59, 1988.
2. Tighe H, Friend PJ, Collier St. J, Decurtins M, Lim S, Cobbold, SP, Thiru S, Calne RY and Waldmann H: Delayed allograft rejection in primates treated with IL-2 receptor monoclonal antibody, Campath 6. Transplantation 45:226, 1988.
3. Reed MH, Shapiro ME, Strom TB, Milford EL, Carpenter CB, Weinberg DS, Reimann KA, Letvin NL, Waldmann TA and Kirkman RL: Prolongation of primate renal allograft survival by anti-Tac, an antihuman IL2 receptor monoclonal antibody. Transplantation 47:55, 1989.

TREATMENT OF RHEUMATOID ARTHRITIS WITH MONOCLONAL ANTIBODIES TO THE THE INTERLEUKIN 2 RECEPTOR

Monoclonal Antibody	Species	Isotype	Target	Reference
Campath 6	rat	IgG2b	CD25 (IL2R)	A

A. Kyle V, Coughlan RJ, Tighe H, Waldmann H and Hazleman BL: Beneficial effect of monoclonal antibody to interleukin 2 receptor or activated T cells in rheumatoid arthritis. Ann. Rheum. Dis. 48:428-429, 1989.

TREATMENT OF ADVANCED RHEUMATOID ARTHRITIS WITH MONOCLONAL ANTIBODY TO THE INTERLEUKIN 2 RECEPTOR

Monoclonal Antibody:	Campath 6
Number of patients:	3
Days of Treatment:	10
Dose:	25mg/day
Biologic effect:	Not apparent
Clinical effect:	2
Adverse events:	2

OTHER TARGETS OF MONOCLONAL ANTIBODY THERAPY

1. **Class II MHC Molecules**
2. **Adhesion Molecules**

EXPERIMENTAL MODELS OF HUMAN AUTOIMMUNE DISEASE SUCCESSFULLY TREATED WITH MONOCLONAL ANTIBODIES TO CLASS II MHC MOLECULES

1. **Experimental Allergic Encephalomyelitis**
2. **Myasthenia Gravis**
3. **Murine Lupus**
4. **Thyroiditis**
5. **Insulin dependent diabetes mellitus**

1a. Steinman L, Rosenbaum JT, Sriram S, McDevitt HO: *In vivo* protective effects of antibodies to immune response gene products: prevention of experimental allergic encephalitis. Proc. Natl. Acad. Sci. USA 78:7111, 1981.

b. Waldor M, Sriram S, McDevitt HO, Steinmann HL: In vivo therapy with monoclonal anti-I-A antibody suppresses immune responses to acetylcholine receptor. Proc. Natl. Acad. Sci. USA 80:2713, 1983.

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3. Adelman NE, Watling DL, McDevitt HO: Treatment of NZB/NZW disease with anti-IA monoclonal antibodies. J. Exp. Med. 158:1350, 1983.

4. Vladiutu AO, Steinmann L: Inhibition of experimental autoimmune thyroiditis in mice by anti-IA antibodies. Cell. Immunol. 109:169, 1987.

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IMMUNOSUPPRESSIVE ACTIVITIES OF MONOCLONAL ANTIBODIES TO ADHESION MOLECULES

1. **Allograft rejection**
2. **Antigen-induced arthritis**

1. Cosimi AB, Conti D, Delmonico FL, Preffer FL, Wee S-L, Rothlein R, Faanes R and Colvin RB: In vivo effects of monoclonal antibodies to ICAM-1 (CD54) in non-human primates with renal allograft. J. Immunol. 144:4604-4612, 1990.
2. Fischer A, Griscelli C, Blanche S, LeDeist F, Verber F, Lopez M, Delaage M, Oliver D, Mawas C and Janossy G: Prevention of graft failure by an anti-LFA-1 monoclonal antibody in HLA-mismatched bone marrow transplantation. Lancet 2:1058, 1986.
3. Jasin HE, Lightfoot E, Kavanaugh A, Rothlein R, Faanes RB and Lipsky PE: Successful treatment of chronic antigen-induced arthritis in rabbits with monoclonal antibodies to leukocyte adhesion molecules. Arthritis Rheum. 39:S34, 1990.

SUMMARY OF MONOCLONAL ANTIBODY THERAPY IN RHEUMATOID ARTHRITIS

1. **Phase I/II trials suggest efficacy in patients with advanced disease**
2. **Retreatment seems possible**
3. **Toxicity is acceptable**
4. **Effectiveness in early disease is unknown**
5. **Mechanisms of action are unclear**

SUMMARY

1. **Preliminary trials of monoclonal antibody treatment of patients with rheumatoid arthritis have shown promise of efficacy.**
2. **These studies have clearly confirmed that T cells and particularly CD4+ T cells play a role in rheumatoid arthritis.**
3. **Additional controlled studies will be necessary to determine whether these monoclonal antibodies will be effective and practical therapy for rheumatoid arthritis.**