THE ROLE OF BIOLOGIC AGENTS IN THE MANAGEMENT OF RHEUMATOLOGICAL DISEASES

ESSAY

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Abstract

Biologic drugs are now available for the treatment of some rheumatic diseases. **Etanercept** (Enbrel) is a soluble receptor fusion protein that binds to soluble TNF neutralizing its biologic activities. **Infliximab** (Remicade) is a chimeric monoclonal antibody that binds to both soluble and membrane bound TNF, whereas **adalimumab** (Humira) is a fully human monoclonal antibody with binding properties similar to Infiximab. **Anakinra** is a human recombinant interleukin-1 receptor antagonist. Newer drugs include, Abatacept, Rituximab and Tocilizumab. **Abatacept** (Orencia) modulates T cell activation. **Rituximab** (Mabthera) is a chimeric anti-CD20 monoclonal antibody. **Tocilizumab** (Actemra) is an interleukin-6 receptor antagonist

Key words: Biologics; Etanercept, Infliximab, adalimumab, Abatacept, Rituximab ,Tocilizumab

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Introduction

Rheumatoid arthritis (RA) is the most common inflammatory arthritis, affecting, from 0.5 to 1% of general population worldwide ***(Firestein, 2005).***

The etiology of RA remains poorly understood. However, evidence supports an immune-mediated process that leads to joint inflammation and destruction. Genetic studies have demonstrated links to major histocompatibility class II molecules. in particular HLA-DRB I. RA is characterized by synovial inflammation with hyperplasia and increased vascularity (pannus formation) in addition to leukocytic infiltration. Several cytokines, including IL-1, IL-6 and TNF-alpha, have been found to be associated with inflammatory cascade and provide targets for anti-inflammatory therapy ***(Choy and Panayi, 2001).***

TNF- alpha and IL-1are considered to exert pivotal roles in the pathogenesis of RA both are present in synovial fluid and synovial tissue.

TNF-alpha has been identified in approximately 40% of lining cells and 5-10% of sub lining cells. While IL-1 is found in 20% of lining cells and 25% of sub lining cells. Double- staining immunochemical experiments have demonstrated that cells expressing macrophage surface markers, in particular produce these tow cytokines ***(Moreland et al., 1997).*** TNF-alpha and IL1stimulate the development of a pro-inflammatory phenotype on responding cells, this gives rise to positive effects on chemotaxis, angiogenesis,

vessel permeability, matrix metalloproteinase production (responsible for matrix degradation), and T- and-B-cell recruitment and activation ***(Vassalli, 1992).*** IL-1and TNF-alpha have been shown to exert a synergistic effect, the addition of both factors resulting in even greater effector stimulus ***(Buch and Emery, 2002)***.

Meanwhile a revolution occurred in the therapy of rheumatoid arthritis with the realization that the pro inflammatory cytokine tumor necrosis factor alpha played a central and hierarchical part in the pathogenesis of the disease, and that its blockade would lead to major improvement in symptoms and signs ***(Feldmann and manini, 2003).*** TNF-alpha antagonists include, infliximab (Remicade), etanercept (enbrel), adalimumab (humira). Anakinra is a human recombinant interlukin-1 receptor antagonist. New biological treatment of AR includes CTLA4IG or abatacept (orencia), rituximab (mabthera) and tocilizumab.

The availability of TNF-alpha antagonist (both monoclonal antibodies and a receptor fusion protein) led to landmark studies, which showed that these agents where remarkably effective in patients who has not responded to disease modifying antirhematic drugs including methotrexete ***(Manini et al., 1999 & Weinblatt et al., 1999).***

Aim of Work

The goals of treatment of rheumatological diseases are to alleviate pain, control inflammation, preserve and improve activities of daily living and prevent progressive joint destruction.

DMARDs can slow or arrest the progression of some rheumatological diseases. Many of the DMARDs have significant potential toxicities and may take several months to attain optimal clinical benefit.

Patients who are refractory to traditional DMARDs are candidates for the use of biological agents.

The aim of this study was to highlight the use of biologic agent in the management of some rheumatic diseases through discussing recent published researches concerning this issue.

LIST OF ABBREVIATIONS

AAV	**:** Antineutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitides
ACR-20	**:** American College of Rheumatology-20 clinical response criteria
ADCC	**:** Antibody Dependent Cellular Cytotoxicity
AIDS	**:** Acquired Immune Deficiency Syndrome
AIM	**:** Abatacept in Inadequate Responders to Methotrexate trial.
ALT	**:** Alanine Transminase
AMBITION	**:** Actemra versus Methotrexate double-Blind Investigative Trial In mONotherapy
ANA	**:** Anti Nuclear Antibodies
ANCA	**:** Antineutrophil Cytoplasmic Antibody
anti-ENA	**:** Antibody to soluble Extractable Nuclear Antigen
APCs	**:** Antigen-Presenting Cells
AS	**:** Ankylosing Spondylitis
ASAS	**:** ASsessments in Ankylosing Spondylitis
ASSURE	**:** Abatacept Study of Safety in Use with other RA therapies.
ASPIRE	**:** Active-Controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset .
AST	**:** Aspartate Transminase
ATLAS	**:** Adalimumab Trial evaluating its Long-term efficacy and safety in Ankylosing Spondylitis.
ATTAIN	**:** Abatacept Trial in Treatment of Anti-TNF Inadequate Responders

ATTEST **:** Abatacept or infliximab versus placebo, a Trial for Tolerability, Efficacy and Safety in Treating RA

ATTRACT **:** Anti-TNF Trial in Rheumatoid Arthritis with Concomitant Therapy trial

BAFF **:** B cell activating factor

BASDAI **:** Bath Ankylosing Spondylitis Disease Activity Index .

BASFI **:** Bath Ankylosing Spondylitis Functional Index.

BASMI **:** Bath Ankylosing Spondylitis Metrology Index.

BCG **:** Bacille Calmette-Guérin.

CD **:** Cluster of Differentiation

CD **:** Crohn's Disease

CDC **:** Complement Dependent Cytotoxicity

CHARISMA **:** Chugai Humanized Anti-Human Recombinant Interleukin-6 Monoclonal Antibody

CHF **:** Congestive Heart Failure

CMV **:** CytoMegaloVirus

COPD **:** Chronic Obstructive Pulmonary Disease

CRP **:** C-Reactive Protein

CTLA-4 **:** Cytotoxic T Lymphocyte Antigen-4.

DANCER **:** Dose-ranging Assessment: International Clinical Evaluation of Rituximab in RA trial

DAS **:** Disease Activity Score.

DM **:** DermatoMyositis

DMARD **:** Disease Modifying Anti rheumatic Drugs

DNA **:** DeoxyriboNucleic Acid.

dsDNA **:** Double stranded DeoxyriboNucleic Acid.

EBV **:** Epstein-Barr Virus

EMEA **:** European Medicines Evaluation Agency

ENT **:** Ear, Nose and Throat

ESR **:** Erythrocyte Sedimentation Rate

EULAR response : European League Against Rheumatism.

Fc **:** Constant (crystallizable) Fragment

FDA **:** Food and Drug Administration

GM-CSF **:** Granulocyte-Macrophage Colony-Stimulating Factor.

HACA **:** Human Anti-Chimeric Antibodies

HAQ **:** Health Assessment Questionnaire

HBV **:** Hepatitis B Virus

HCV **:** Hepatitis C Virus

HDL-C **:** High Density Lipoprotein Cholesterol

HIV **:** Human Immunodeficiency Virus

HLA **:** Human Leukocyte Antigen;

HRQOL **:** Health-Related Quality Of Life

ICAM-1 **:** InterCellular Adhesion Molecule-1

Ig **:** ImmunoGlobulin

IgG1 **:** Human ImmunoGlobulin type 1

IL-1 **:** Interleukin 1

IL-1AcP **:** Interleukin -1 Accessory Protein.

IL-1Ra **:** IL-1 Receptor antagonist.

IL-1RI **:** Interleukin -1 receptor I.

IL-1β **:** Interleukin-1 Beta.

IMPACT **:** Infliximab Multinational Psoriatic Arthritis Controlled Trial.

INF-γ **:** Interferon γ

ISRs **:** Injection Site Reactions.

IV **:** IntraVenous.

JIA **:** Juvenile Idiopathic Arthritis

LCV **:** LeukoCytoclastic Vasculitis

LDAS **:** low Disease Activity Score

LDL-C **:** Low-Density Lipoprotein Cholesterol

LITHE : tociLIzumab safety and THE prevention of structural joint damage

LLN : lower Limit of Normal

LON : Late-Onset Neutropenia

LPS : LipoPolySaccharide

LT-α : LymphoToxin-alpha

LTE : Long Term Extension

MHC : Major Histocompatibility Complex

mIL-6R : Membrane IL-6 Receptors

MMP-3 : Matrix MetalloProteinase- 3

MRI : Magnetic Resonance Imaging.

MS : Multiple Sclerosis

MTX : Methotrexate

NHL : Non-Hodgkin's Lymphoma

NK : Natural Killer

NSAIDs : Non-Steroidal Anti-inflammatory Drugs .

NYHA : New York Heart Association

OPTION : tOcilizumab Pivotal Trial in methotrexate Inadequate respONders

PASI : Psoriasis Activity Severity Index.

PGE2 : ProstaGlandin E 2.

PM : PolyMyositis

PML : Progressive Multifocal Leukoencephalopathy

PsA : Psoriatic Arthritis

PsARC : Psoriatic Arthritis Response Criteria.

Pss : Primary Sjogren's Syndrome

QOL : Quality Of Life.

RA : Rheumatoid Arthritis

RADIATE : RheumAtoiD arthritis study in Anti-TNF-failurEs

RCTs : Randomized Controlled Trials

REFLEX : Randomized Evaluation of Long-term Efficacy of Rituximab in RA

RNA : RiboNucleic Acid.

RTX : Rituximab

SAMURAI : Study of Active controlled Monotherapy Used for Rheumatoid Arthritis, an IL-6 Inhibitor trial

SATORI : Study of Active-controlled TOcilizumab monotherapy for Rheumatoid arthritis patients with Inadequate response to methotrexate

SIEs : Serious Infectious Events

sIL-6R : soluble IL-6 receptor

SLE : Systemic Lupus Erythematosus.

SS : Sjogren Syndrome

sTNF : soluble Tumor Necrosis Factor

STREAM : Acronym not defined

SC : SubCutaneous

t½ : Half-life

TACE : Tumor Necrosis Factor Alpha Converting Enzyme

TB : Tuberculosis

TCR : T-cell receptor

TEMPO : The Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes

Th : T helper cell

tmTNF : transmembrane TNF

TNF : Tumor Necrosis Factor

TNFR I : Tumor Necrosis Factor Receptor 1

TNFRII : Tumor Necrosis Factor Receptor 2

TNF-α : Tumor Necrosis Factor -Alpha

TNF-β : Tumor Necrosis Factor -Beta