BIOSIMILARS AND SMALL MOLECULE DRUGS

Essay

Submitted for partial fulfillment of Master
of science in Rheumatology

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بسم الله الرحمن الرحيم

قالوا سبحانك لا علم لنا الا ما علمتنا انك انت العليم الحكيم

سورة البقرة (أية٣٢)

Acknowledgement

First of all, thanks to **God.** Without his help, this work could not be accomplished.

I would like to present my sincere thanks and appreciation to *Prof. Dr. Dahlia Abdel Mohsen Hussein* Professor of Internal Medicine and Rheumatology, Ain Shams University, for her great help, continuous support and fruitful guidance throughout this work.

I would like to express my gratitude to *Prof. Dr. Hanan farouk* professor of Internal Medicine Faculty of Medicine, Ain Shams University, for her sincere help.

I would like to thank *Dr. Shafika Ebrahim* Lecturer of Internal Medicine Ain Shams University for her sincere help and thorough revision of every detail in this work, I am truly grateful for her.

I would like to thank *Prof. Dr. Mohammed Abd El Hafiz***,** Prof. *Dr. Magdy EL Shazly* and all my professors and colleagues in El Maadi Armed Forces Hospital for their sincere help and continuous support.

Special thanks to **my Family and my wife** for their help and continuous encouragement.

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List of Abbreviations

- **ACR** : American Collage of Rheumatology
- **A٣AR** : A٣ adenosine receptor
- **ADCC** : antibody-dependent cellular cytotoxicity
- **AEs** : adverse events
- **ANC** : absolute neutrophil count
- **ANDA** : Abbreviated New Drug Applications
- **APRIL** : a proliferation-inducing ligand
- **APC** : antigen presenting cell
- **AP-١** :Activator protein-١
- **AS** : Ankylosing spondylitis
- **ASAS** : Ankylosing Spondylitis Activity Scores
- **ATF٢** : activating transcription factor ٢
- **BASDAI** :Bath ankylosing spondylitis Disease Activity Index
- **BCR** : B-cell receptor
- **BL** : baseline
- **Btk** : Bruton tyrosine kinase
- **CCP** : Cyclic citrullinated peptide
- **CDC** : complement dependent cytotoxicity
- **CD** : Crohn's disease
- **CDAI** : Crohn's disease activity index
- **CHMP** : Committee for Medicinal Products for Human Use
- **CIN** : Chemotherapy-induced neutropenia
- **CIS** : Cytokine-inducible SH٢ protein
- **CLL** : Chronic lymphocytic leukemia

- **Cpn ١٠** :Chaperonin ١٠
- **CRP** :C-reactive protein
- **CS** : Corticosteroid
- **CTLA-٤-Ig** : cytotoxic T-lymphocyte-associated antigen ٤ immunoglobulin
- **DAS** : Disease Activity Score
- **DC** : dendritic cell
- **DMARDs** : disease modifying anti-rheumatic drugs
- **EC** : endothelial cell
- **ELK١** : Ets LiKe gene ١
- **EMEA** : European Agency for the Evaluation of Medicinal Products
- **ERK** : extracellular signal related kinase
- **ES** : erosion score
- **FDA** : Food and Drug Administration
- **FoB** : follow-on biologics
- **G-CSF** :granulocyte colony stimulating factor
- **GH** : growth hormone
- **GM-CSF** : granulocyte–macrophage colony-stimulating factor
- **HAQ** : Health Assessment Questionnaire
- **HAQ-DI** :Health Assessment Questionnaire – Disability Index
- **Hb** : hemoglobin
- **Hep** : hepatocyte
- **HLA** : Human Leucocytic Antigen
- **IBD** : Inflammatory bowel disease
- **ICAM-١** : intercellular adhesion molecule-١
- **IFN** : Interferon

- **IL** : Interleukin
- **IMIDs** : immune mediated inflammatory disease
- **INNs** :International Nonproprietary Names
- **INOS** : inducible nitric oxide synthase
- **i.v** : Intravenous
- **Jak** : Janus kinase
- **JIA** : Juvenile idiopathic arthritis
- **JNK** :Jun activated kinase
- **LITHE** : The TociLIzumab safety and THE prevention of structural joint damage
- **LMWH** : Low Molecular weight Heparine
- **LPS** : lipopolysaccharide
- **MAbs** : monoclonal antibodies
- **Mac** : macrophage
- **MAPK** : Mitogen-activated protein kinase
- **MCP-١** : monocyte chemotactic protein-١
- **MGDF** :megakaryoctye growth and development factor
- **MHC** : major histocompatibility complex
- **MIF** : Macrophage inhibition factor
- **MMP-٣** : Matrix metalloproteinase ٣
- **MS** : multiple sclerosis
- **MTX** : Methotrexate
- **NFAT** : nuclear factor of activated T cells ٤
- **NF** : Nuclear factor
- **NO** : nitric oxide
- **NSAIDs** : non steroidal anti inflammatory drugs
- **OC** : osteoclast

- **OPG** : osteoprotegerin
- **PAH** : **P**ulmonary arterial hypertension
- **PASI** : Posriatic Arthritis Activity Score Index
- **PBMCs** : Peripheral blood mononuclear cells
- **PBO** : Placebo
- **PBPCT** :Peripheral blood progenitor cell transplant
- **PD** : pharmacodynamics
- **PDGF** : platelet-derived growth factor
- **PGE٢** : prostaglandin E٢
- **PIAS** : protein inhibitor of activated STAT
- **PK** : Pharmacokinetics
- **PML** :progressive multifocal leukoencephalopathy
- **PRCA** : Pure red cell aplasia
- **PsA** : psoriatic arthritis
- **RA** : Rheumatoid arthritis
- **RANKL** : receptor activator of NF-κB ligand
- **RANTES:** Regulated upon activation, normal T cell expressed and secreted
- **RCTs** : Randomized clinical trials
- **ROI** : reactive oxygen intermediates
- **R&D** : Research and Development
- **SAMURAI** :Study of Active controlled Monotherapy Used for Rheumatoid Arthritis, an IL-٦ inhibitor
- **SATORI** : Study of Active controlled Tocilizumab monotherapy for Rheumatoid arthritis patients with an Inadequate response to Methotrexat
- **S.c** :Subcutaneous

- **SOCS** : suppressors of cytokine signaling
- **SOD** : superoxide dismutase
- **S١P** :Sphingosine-١-phosphate
- **SLE** :systemic lupus erythematosus
- **SSc** **:** systemic sclerosis
- **STAT** **:**Signal Transducer and Activator of Transcription
- **Syk** : Spleen tyrosine kinase
- **TGF** **:** Transforming growth factor
- **Th١** **:** T helper cell type ١
- **TNF** **:** Tumour necrosis factor
- **TLRs** **:** Toll-like receptors
- **Treg supp** : suppression of T regulatory cells
- **Tyk٢** : tyrosine kinase ٢
- **UC** : ulcerative colitis
- **ULN** : Upper limits of normal
- **VCAM-١** : vascular cell adhesion molecule-١
- **VEGF** : vascular endothelial growth factor

Introduction:

Biologics are a class of medications which have had a profound impact on many medical fields, primarily rheumatology and oncology, but also cardiology, dermatology, gastroenterology, neurology, and others. In most of these disciplines, biologics have added major therapeutic options for the treatment of many diseases, including some for which no effective therapies were available, and others where previously existing therapies were clearly inadequate. ***(Kerr,)***

Biosimilars are attempted copies of existing biological medicinal products, but the unique multi-dimensional structure of the proteins and in consequence their complicated mode of action are not easily reproducible. ***(Dadashzadeh,)***

Limited access for high-quality biologics due to cost of treatment constitutes an unmet medical need in the US and other regions of the world. The term "biosimilar" is used to designate a follow-on biologic that meets extremely high standards for comparability or similarity to the originator biologic drug that is approved for use in the same indications. Biosimilars can have a major impact on the affordability and availability of important biologic medicines in all markets. ***(Camish and Woollett,)***

Oral Small-Molecule Drugs are targeted immunomodulator and disease-modifying therapy for RA. They are targeting the intracellular signaling pathways that operate as hubs in the inflammatory cytokine network. ***(Rubbert-Roth and Finckh,)***

Oral Small-Molecule Drugs May be the Future of RA treatment, It appears that the next major advance in the treatment of rheumatoid arthritis will be the oral small-molecule drugs. These drugs will target different enzyme pathways, which, if left unmolested, result in the inflammation that characterizes rheumatoid arthritis. These drugs are even more precise than today's existing "biologic" drugs, ***(Borigini, .)***

Aim of the work:

The aim of this work is to review of the updates of biosimilars and small molecules drugs and their role in treatment of medical and rheumatological disorders.

Biological therapy in different medical disease

The biologic agents are specifically engineered molecules designed to block particular immunologic activation steps involved in the pathogenesis of diseases such as rheumatoid arthritis or psoriasis. These conditions involve the actions of various cellular components, including lymphocytes, macrophages and B cells, and secreted compounds, such as interleukins, tumor necrosis factor, and other cytokines. The agents themselves include monoclonal antibodies (MAbs) and fusion proteins, which are directed against proinflammatory cytokines, such as tumor necrosis factor (TNF), and the interleukin (IL)-١ receptor and selected cell surface markers on immune cells, such as cytotoxic T-lymphocyte-associated antigen ٤ immunoglobulin (CTLA-٤-Ig) and CD٢٠ (table١). ***(Gottlieb, & Scott and Kingsley, ٢٠٠٦)***

Table١. Basic information on the agents is presented in the following table:

Agent	Construct of molecule	Action(s)
Abatacept	Recombinant fusion protein	Inhibits T-lymphocyte activation by binding to CD٨٠ and CD٨٦, blocking interaction with CD-٢٨.
Adalimumab	Recombinant human MAb	Binds to TNF-α, neutralizing its activity
Alefacept	Recombinant fusion protein	Binds to CD٢ on memory T lymphocytes,preventing activation and reducing their number
Anakinra	Recombinant human IL-١ receptor antagonist	Blocks the biologic activity of IL-١ by inhibiting IL-١ binding to the IL-١ type ١ receptor.
Certolizumab	Pegylated recombinant humanized antibody Fab' fragment	Binds to TNF-α, neutralizing its activity
Etanercept	Recombinant fusion protein	Binds to TNF-α and lymphotoxin- α, neutralizing their activity
Golimumab	Recombinant human MAb	Binds to TNF-α, neutralizing its activity
Infliximab	Chimeric MAb	Binds to TNF-α, neutralizing its activity
Rituximab	Chimeric MAb	Binds to the antigen CD٢٠ on B-lymphocytes, leading to B-cell lysis
Ustekinumab	Recombinant human MAb	Binds p٤٠ subunit of IL-١٢ and IL-٢٣ cytokines and disrupts their activity

(Kuek et al., ٢٠٠٧)

Over a decade ago, investigators discovered that cytokine dysregulation was pivotal to the pathophysiology of immune mediated inflammatory disease (IMIDs). While these molecules are known to be indispensable mediators of normal immune function, an imbalance in their production can lead to chronic inflammatory conditions. Commonly, IMIDs are associated with a relative over-expression of cytokines, such as TNFα in RA, yet a relative under-expression of cytokines may be equally important in disease pathogenesis, for example interleukin ١٠ (IL١٠) deficiency in chron's disease (CD). Interestingly, cytokines may have different effects, either pro- or anti-inflammatory, depending on the stage of disease. ***(Kuek et al., ٢٠٠٧)***

Although immunoregulatory cytokines are produced by many different cell types, CD٤+ T lymphocytes are thought to be the main orchestrators of the immune response. These T helper cells are typically divided into two functionally heterogeneous subsets, Th ١ and Th ٢, on the basis of the cytokines they produce. Th ١ cells have predominantly pro-inflammatory effects and have been implicated in the immunopathogenesis of IMIDs. Th ٢ cells are thought to have anti-inflammatory or protective functions in this context (figure١) ***(Kuek et al., ٢٠٠٧)***

Because of this central role in IMIDs, modulation of T cell function has become an attractive target for intervention. Another area arousing considerable interest is the role of B lymphocytes in IMIDs. Early concepts focused on the ability of B cells to produce antibodies, however it is now known that B cells have much broader functions within the immune system,

including T cell activation, cytokine synthesis, regulation of lymphoid architecture and maintenance of tolerance. ***(Youinou et al., ٢٠٠٦)***

Emerging evidence indicates that disruption of these tightly regulated B cell processes can potentially lead to autoimmune disease. Certainly in RA loss of B cell tolerance and inappropriate autoantibody production is a key pathological process, and this has motivated investigators to attempt B cell depletion as a novel therapeutic strategy. Studies with the anti-CD٢٠ monoclonal antibody, rituximab, have now been completed for a number of IMIDs with clear evidence of efficacy. ***(Edwards et al., & Kuek et al., ٢٠٠٧)***

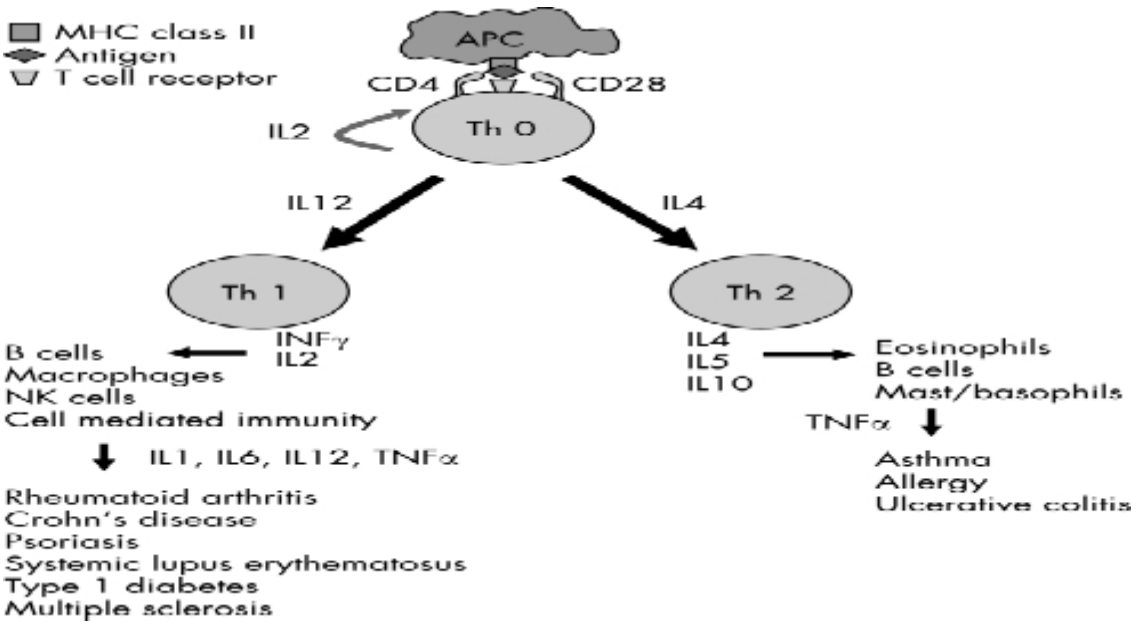

Figure ١: Th ١ and Th ٢ cell responses. APC, antigen presenting cell; IL, interleukin; MHC, major histocompatibility complex; Th, T helper cell; TNF, tumour necrosis factor.