Cyclophosphamide in Biologic Naïve Rheumatoid Arthritis patients Resistent to Traditional DMARDs

Thesis

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List of Contents

List of Tables

List of Tables (Cont...)

List of Figures

List of Figures (Cont...)

List of Abbreviations

Abb.	Full term
ACPA	*Anticitrullinated protein antibodies*
ACR	*American College of Rheumatology*
ALDH	*Aldehyde dehydrogenase*
AML	*Acute myeloid leukemia*
CD	*Cell of differentiation*
CDAI	*Clinical Disease Activity Index*
COX2	*Cyclo-oxygenase 2*
CRP	*C- reactive protein*
CTLA	*Cytotoxic T-lymphocyte–associated antigen*
CVD	*Cardiovascular diseases*
CYC	*Cyclophosphamide*
DAS	*Disease activity score*
DIP	*Distal interphalangeal.*
DMARDs	*Disease modifying antirheumatic drugs*
EAM	*Extra articular manifestation*
EGPA	*Eosinophillic granulomatosis with polyangiitis*
ESR	*Erythrocyte sedimrntation rate*
EULAR	*European League Against Rheumatism*
FDA	*Food and drug administration*
GCs	*Glucocorticoids*
GM-CSF	*Granulocyte / macrophagecolony-stimulating factor.*
GPA	*Granulomatosis with Polyangiitis*
HAQ	*Health assessment questionnaire*
HB	*Hemoglobin*
HCQ	*Hydrochloroquine*

List of Abbreviations (Cont...)

Abb.	Full term
HLA	*Human Leucocyte antigen*
HRCT	*High resolution computed tomography*
IC	*Immune complex*
ICAM-1	*Intercellular adhesion molecule-1*
Ig	*Immunoglobulin*
IL	*Interleukin*
ILD	*Interstitial lung disease*
IM	*Intramuscular*
JAK	*Janus kinase*
JIA	*Juvenile inflammatory arthritis*
MCP	*Metacarpophalangeal*
MI	*Myocardial infarction*
MMP	*Metalloproteinases*
MPA	*Microscopic polyangiitis*
MRI	*Magnetic resonance imaging*
MS	*Multiple sclerosis*
MTP	*metatarsophalangeal*
MTX	*Methotrexate.*
NHS	*National health service*
NICE	*The National Institute for Health and Care Excellence*
NSAIDs	*Non steroidal anti-inflammatory drugs*
OPN	*Osteopontin*
PADI	*Peptidylarginine-deiminase*
PAF	*Platelet activating factor*
PDGF	*Platelet derived growth factor*

List of Abbreviations (Cont...)

Abb.	Full term
PIP	*Proximal interphalangeal.*
PLT	*Platelets*
PRF	*Perforin 1 (pore forming protein).*
PSc	*Progressive systemic sclerosis*
PTPN22	*Protein tyrosine phosphatase non-receptor type 22*
RA	*Rheumatoid arthritis*
RANKL	*Receptor activator of nuclear factor κB.*
RF	*Rheumatoid factor*
SC	*Subcutaneous*
SD	*Standard deviation*
SDAI	*Simplified Disease Activity Index*
SE	*Shared epitope*
SIADH	*Syndrome of inappropriate antidiuretic hormone*
SJC	*Swollen joint count*
STAT	*Signal Transducer and Activator of Transcription*
SyK	*Spleen tyrosine kinase*
Th	*T helper cell*
TJC	*Tender joint count*
TNF	*Tumor necrosis factor*
TRAF	*TNF receptor-associated factor*
URT	*Upper respiratory*
VCAM-1	*Vascular cell adhesion molecule-1*

ABSTRACT

There was no significant statistical correlation between patients with positive and negative RF and different disease activity markers except for Hb level showing significant increase in patients with positive RF post-treatment with CYC (P-value=0.042), there was also no significant statistical correlation between patients with positive and negative ACCP and different disease activity markers except for Plt level showing significant decrease in patients with positive ACCP post-treatment with CYC (P-value=0.034).

Higher CRP at baseline in RA patients indicates poor response to treatment and higher VAS at study endpoint.

IV pulse CYC and methylprednisolone (MP) are of a significant benefits in induction of remission in resistant aggressive RA patients who failed to respond to traditional DMARDs.

Keywords: Non steroidal anti-inflammatory drugs - Progressive systemic sclerosis - Protein tyrosine phosphatase non-receptor type 22

INTRODUCTION

Rheumatoid arthritis (RA) is characterized by abnormal proliferation of synoviocytes, leukocyte infiltration, and angiogenesis ***(Park et al., 2014).*** Epidemiological studies show that RA affects 1% of the population worldwide ***(Rojas-Villarraga et al., 2009).***

The therapeutic array of RA includes several categories of medicinal products, of varying potential. There are several criteria for the classification of medicinal products used against this disease, one of the most important and modern of which divides such substances according to their effects on the progress of the disease: symptom-modifying antirheumatic drugs (including non-steroidal anti-inflammatory drugs and corticosteroids), disease-modifying antirheumatic drugs (including various substances, such as gold salts, antimalarials, sulfasalazine, D-penicillamine; non-specific immunosuppressive medication, such as methotrexate, cyclophosphamide, azathioprine and leflunomide) and biological therapy is a recent addition ***(Negrei et al., 2016)***.

Costs of biologics for Rheumatoid arthritis (RA) are remarkably high, which makes these agents an important target for economic evaluations ***(Joensuu et al., 2015).***

Cyclophosphamide is an immunosuppressive medicine, it has been found to be effective in treating serious complications of rheumatoid arthritis such as vasculitis. By

interrupting the immune process, cyclophosphamide reduces inflammation and slows joint damage caused by rheumatoid arthritis ***(Longo et al., 2012).***

However, by reviewing the literature there were limited studies about the use of cyclophosphamide as antirheumatic drug in patients with rheumatoid arthritis.

AIM OF THE WORK

To evaluate the efficacy of CYC and methyl prednisolone pulse therapy in induction of remission in biologic naïve RA patients resistant to conventional DMARDs and can't afford biological treatment.

Chapter 1
RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic inflammation of synovial tissue that leads to damage of cartilage and bone, resulting in irreversible joint destruction ***(Smigielska-Czepiel et al., 2014).*** More aggressive forms of RA also involve extra-articular tissues, causing lung inflammation, splenomegaly with cytopenia, skin nodules and vasculitis ***(Fleischman et al., 2012).***

Epidemiology:

The prevalence of RA is relatively constant in many populations, at 0.5-1% ***(Uhlig, 2014).*** The prevalence of RA in rural Egypt is 0.29% similar to other oriental rural populations but lower than western populations ***(Abdel Tawab et al., 2009)***.

Women are 3 times more often than men. Onset is most frequent between the ages of 40 and 50, but people of any age can be affected ***(Vollenhoven 2009)***

Mortality rates are more than twice as high in patients with RA as in the general population ***(Choy, 2012).***

Etiology of RA:

The exact cause of RA is unknown. It is the result of an environmental exposure or "trigger" in a genetically susceptible individual ***(Gibofsky, 2012).***

1. Hormonal factors:

The predominance of RA in females suggests a role for hormonal factors, estrogens stimulate the immune system, and low testosterone levels have been reported in men with RA ***(Tobon et al., 2010).*** Female sex hormones may play a protective role in RA. For example, the use of the oral contraceptives pills and pregnancy are both associated with a decreased risk ***(Alan and Jacqueline, 2012)***. One possible explanation to this finding is that hormone replacement therapy (HRT) protects against the production of anti-citrullinated protein-antibodies (ACPA) ***(Tobon et al., 2010).***

Improvement occurs for 50 to 70% of patients by the end of the first trimester and is usually sustained throughout pregnancy. However, within 3 months of delivery, relapse is observed in 90% of patients ***(Shammas et al., 2010).*** Both female subfertility and the immediate postpartum period after a first pregnancy (especially when breastfeeding) appear to increase the risk of RA ***(McInnes and Schett, 2011).***