ASSESSMENT OF CLINICAL OUTCOMES AND SAFETY PROFILE OF BIOLOGIC AND TARGETED DISEASE MODIFYING ANTI-RHEUMATIC DRUGS (DMARDS) FOR RHEUMATOID ARTHRITIS MANAGEMENT IN MALAYSIAN POPULATION

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by

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LIST OF ABBREVIATIONS

ACPA	Anti-Citrullinated Peptide Antibodies
ACR	American College of Rheumatology
ADA	Adenosine Deaminase
ADR	Adverse Drug Reaction
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
ANTI-CCP	Anti-Cyclic Citrullinated Peptides
ANTI-IL-6	Anti-Interleukin 6
APCS	Antigen-Presenting Cells
APR	Acute Phase Reactant
AST	Aspartate Aminotransferase
bDMARD	Biologic Disease Modifying Anti Rheumatic Drug
BID	Twice Daily
BMI	Body Mass Index
BSRBR	British Society for Rheumatology Biologics Register
CCB	Calcium Channel Blocker
CDAI	Clinical Disease Activity Index
CSDMARD	Conventional Synthetic Disease-Modifying Antirheumatic Drugs
CI	Confidence Intervals
COPD	Chronic Pulmonary Disease
CRP	C-Reactive Protein
CVD	Cardiovascular Diseases
DAS	Disease Activity Score

DCF	Data Collection Form
DM	Diabetes Mellitus
DMARD	Disease-Modifying Antirheumatic Drugs
EMR	Electronic Medical Records
ESR	Erythrocyte Sedimentation Rate
EULAR	European League Against Rheumatism
FDA	Food And Drug Administration
GC	Glucocorticoids
GM-CSF	granulocyte-macrophage-colony stimulating factor
HCQ	Hydroxychloroquine
HDL	High Density Lipoprotein
HLA-DR	Human Leukocyte Antigen – DR isotype
DRB1	Human Leukocyte Antigen – DR isotype Beta 1
HR	Hazard Ratio
IFN-γ	interferon-γ
IGG	Immunoglobulin G.
IL-2	Interleukin-2
ILD	Interstitial Lung Disease
IM	Intramuscular
IGG1	Immunoglobulin G1
IQR	Interquartile
IRR	Incidence Rate Ratio
IV	Intravenous
JAK	Janus Kinases
JAK-STAT	Janus Kinase/Signal Transducers and Activators of Transcription
LDA	Low Disease Activity

LDL	Low Density Lipoprotein
LEF	Leflunomide
MCP	Metacarpophalangeal
MI	Myocardial Infarction
MIL-6R	Transmembrane Interleukin 6 Receptor
MMPs	Matrix Metalloproteinase
MRCI	Medication Regimen Complexity Index
MREC	Medical Research and Ethics Committee
MTP	Metatarsophalangeal
MTX	Methotrexate
NIAR	National Inflammatory Arthritis Registry
NMRR	National Medical Research Register
NSAIDS	Non-Steroidal Anti-Inflammatory Drugs
OD	Once Daily
OMERACT	Outcome Measures in Rheumatology
OR	Odds Ratio
PGA	Patient's Global Assessment
PIP	Proximal Inter-Phalangeal
PO	Oral Administration
PTPN22	Protein- Tyrosine-Phosphatase Non-Receptor Type 22
PUD	Peptic Ulcer Disease
QW	Every Week
RA	Rheumatoid Arthritis
RCT	Randomised Controlled Trials
RDCI	Rheumatic Disease Comorbidity Index
RF	Rheumatoid Factor
SC	Subcutaneous

SD	Standard Deviation
SE	Shared Epitope
SIL-6R	Soluble Interleukin 6 Receptor
SJC	Swollen Joint Count
SPSS	Statistical Package for Social Sciences
SSZ	Sulfasalazine
tDMARD	Targeted Disease Modifying Anti-Rheumatic Drug
TG	Triglyceride
THIS	Total Hospital Information System
TIA	Transient Ischemic Accident
TJC	Tender Joint Count
TNF	Tumour Necrosis Factor
TYK2	Non-Receptor Tyrosine-Protein Kinase
UK	United Kingdom
URTI	Upper Respiratory Tract Infection
VAS	Visual Analogue Scale
WHO	World Health Organization

LIST OF APPENDICES

PENILAIAN HASIL KLINIKAL DAN PROFIL KESELAMATAN UBAT ANTI-REUMATIK BIOLOGI (DMARDS) DAN PENGUBAH PENYAKIT BERSASAR BAGI PENGURUSAN ARTRITIS REUMATOID DALAM POPULASI MALAYSIA

ABSTRAK

Artritis Rheumatoid (RA) merupakan gangguan autoimun kronik yang dicirikan oleh keradangan tisu sinovial dalam sendi, menyebabkan kerosakan sendi dan kecacatan fizikal yang berikutnya. Dalam beberapa tahun terakhir, terdapat kemajuan penting dalam rawatan RA, terutamanya disebabkan oleh pengenalan ubat biologi dan pengubahan sintetik berpendahuluan penyakit pengubah antirheumatik (DMARDs). Walau bagaimanapun, walaupun keberkesanan mereka, mereka mempunyai konsekuensi klinikal yang tidak menyenangkan. Tujuan tesis ini adalah untuk menilai keberkesanan dan keselamatan terapi DMARDs biologi dan sintetik bersasarkan dalam hasil klinikal individu Malaysia dengan RA. Untuk mencapai objektif tesis, kajian retrospektif dan prospektif, longitudinal dilakukan di Hospital Putrajaya dan Hospital Serdang, Malaysia. Pesakit RA berumur 18 tahun ke atas dengan terapi DMARDs biologi dan sintetik berpendahuluan disaring dan dimasukkan dalam kajian. Borang pengumpulan data yang direka khusus digunakan untuk mendapatkan maklumat yang diperlukan. Data yang diperolehi dianalisis dengan menggunakan Perisian Pakej Statistik untuk Sains Sosial (SPSS versi 26). Daripada 270 pesakit dengan terapi DMARDs biologi dan sintetik berpendahuluan yang dimasukkan dalam kajian, majoriti populasi kajian terdiri daripada perempuan (70.7%) dan 51.1% Melayu. Lebih separuh daripada pesakit adalah tidak pernah mendapat rawatan secara cara biologi (54.8%), dan 55.9% menerima monoterapi. Semasa

pemantauan 12 bulan, pengurangan yang signifikan secara statistik dalam skor aktiviti penyakit (DAS28) telah diperhatikan ($F (2.97, 701.48) = 255.91$, $p < 0.001$). Penilaian telah menunjukkan peningkatan dalam peratusan individu yang mengalami keadaan penyakit yang berkurangan, LDA, dan respons sederhana hingga baik. Selain itu, 9.3% daripada pesakit mengalami kembali penyakit dalam tempoh 12 bulan di mana komponen DAS 28 berkaitan dengan kembalinya penyakit bagaimanapun, hanya VAS yang merupakan penentu negatif bagi kembali penyakit (HR: .099, p=.012). Pelbagai faktor peramal termasuk jumlah biologis sebelumnya, jenis DMARDs, csDMARDs sejajar, umur, DAS28, ESR, RF, merokok, pemilihan ubat telah dikenal pasti untuk mencapai respons terapeutik yang lebih baik. Di antara 57.8% pesakit RA dengan polifarmasi, pengurangan signifikan sebanyak 17% dalam peluang mencapai LDA/remisi pada 12 bulan telah diperhatikan (OR: .83, 95% CI: .41, 1.67, p= .001). Kegagalan rawatan disebabkan oleh ketidakefektifan dan ADR diperhatikan di kalangan 12.9% semasa pemantauan. Keputusan menunjukkan bahawa DMARDs sintetik yang sasarkan adalah penentu negatif terhadap penghentian rawatan (HR: .27, 95% CI: .07, .92, $p < .001$). 60.4% daripada jumlah pesakit mengalami ADR dan Umur ≥60 tahun berkaitan dengan peningkatan risiko ADR (OR: 1.67, 95% CI: .93, 2.98, p= .043). Pesakit RA dengan komorbiditi penyakit diabetes mellitus dan menerima DMARDs biologi berkaitan dengan peningkatan risiko jangkitan (HR: 1.99, 95% CI: .038, 3.29, p .007; HR: 2.13, 95% CI: .97, 4.69, p .049). Walau bagaimanapun, DMARDs sintetik bersasarkan menunjukkan perkaitan negatif dengan risiko jangkitan (HR: .55, 95% CI: .22, 1.38, p .008). Penemuan kajian menunjukkan bahawa terapi DMARDs biologi dan sintetik bersasarkan mengurangkan secara signifikan aktiviti penyakit dan meningkatkan respons terapeutik dalam tempoh 12 bulan. Strategi rawatan escara individual berdasarkan ciri-ciri individu seperti umur, positiviti RF,

tahap ESR, dan polifarmasi dapat mengoptimalkan hasil dan meminimalkan risiko. Kajian ini juga menekankan kepentingan mempertimbangkan pilihan kelas DMARD dalam mengurangkan risiko tindak balas ubat yang tidak diingini dan kegagalan rawatan, menekankan kepentingan penilaian teliti dan penyesuaian regimen rawatan untuk menguruskan RA dengan berkesan.

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ABSTRACT

Rheumatoid Arthritis (RA) is a chronic autoimmune disorder characterized by inflammation of the synovial tissue in the joints, resulting in joint damage and subsequent physical disability. In recent years, significant advancements in the treatment of RA have been witnessed, primarily due to the introduction of biologic and targeted synthetic disease-modifying antirheumatic drugs (DMARDs). However, despite their effectiveness, they possess clinically unfavourable consequences. The aim of this thesis is to assess the efficacy and safety of biologic and targeted synthetic DMARDs therapy on the clinical outcomes of Malaysian individuals with RA. To meet the objective of the thesis, retrospective and prospective, longitudinal study was conducted at Hospital Putrajaya and Hospital Serdang, Malaysia. RA patients 18 years old and above with biologic and targeted synthetic DMARDs therapy were screened and enrolled. The specifically designed data collection form was used to obtain required information. Obtained data were analysed by using Statistical Package for Social Sciences (SPSS version 26). Out of 270 patients with biologic and targeted synthetic DMARDs therapy included in the study, female comprises the majority of study population (70.7%) and 51.1 % Malay. More than half of the patients were biologic naïve (54.8%), and 55.9% received monotherapy. During 12 months follow up, statistically significant reduction of disease activity score (DAS28) was observed ($F (2.97, 701.48) = 255.91$, $p < 0.001$). The assessments have indicated a rise in the percentage of individuals experiencing remission, LDA, and moderate to good

response. Furthermore, 9.3% of patients experienced disease flares within 12 months in which DAS 28 component were correlated with disease flares however, only VAS was a negative predictor of flares (HR:.099, p=.012). Different predictor factors including number of previous biologics, DMARDs type, concomitant csDMARDs, age, DAS28, ESR, RF, smoking, selection of medicine was identified to better achieving therapeutic response. Among 57.8% RA patients with polypharmacy, a significant 17% reduction in odds of achieving LDA/remission at 12 months was observed (OR: .83, 95% CI: .41, 1.67, p= .001). Treatment failure due to inefficacy and ADRs were observed among 12.9% during follow up. Results indicated that targeted synthetic DMARDs are negative predictor of treatment discontinuation (HR: .27, 95% CI: .07, .92, p < .001). 60.4% of total patients experienced ADRs and Age ≥60 years was associated with increased risk of ADRs (OR: 1.67, 95% CI: .93, 2.98, p= .043). RA patients with comorbid diabetes mellitus and receiving biologic DMARDs were associated with increased risk of infection (HR: 1.99, 95% CI: .038, 3.29, p .007; HR: 2.13, 95% CI: .97, 4.69, p .049 respectively). However, targeted synthetic DMARDs showed to have negative association with infection risk (HR: .55, 95% CI: .22, 1.38, p .008). The study findings suggest that biologic and targeted synthetic DMARDs therapy significantly reduced disease activity and improved therapeutic response in 12 months. Personalized treatment strategies based on individual characteristics like age, RF positivity, ESR levels, and polypharmacy can optimize outcomes and minimize risks. The study also highlights the importance of considering the choice of DMARD class in reducing the risk of adverse drug reactions and treatment failure, underscoring the importance of careful assessment and tailoring of treatment regimens to manage RA effectively.

CHAPTER 1

INTRODUCTION

1.1 Rheumatoid arthritis (RA)

Rheumatoid arthritis (RA) is known to be a systemic inflammatory autoimmune disorder that is chronic. It has an unclear etiology which has the potential to contribute to gradual joint destruction, physical handicaps, and extra-articular complications [1]. As a systemic condition, RA affects multiple organs and is linked to elevated rates of other conditions such as malignancy, infections, and cardiovascular illnesses [2].

RA patients suffer from persistent pain that may be restricted to a specific part of the body, like the knees, or maybe throughout the entire body. The tissues surrounding the joints, in addition to other body organs, will be affected by the inflammation resulting from the disease [3]. Healthy tissues in the RA patient's body will be attacked by the immune system through the use of antibodies to eradicate infections caused by invaded pathogens. As a result of the autoimmune phenomenon, patients diagnosed with RA always possess antibodies in their blood circulation that target the body's tissues, therefore causing joint inflammation. Joint deformations take place due to the destruction of the bones, cartilage, and ligaments caused by the chronic inflammation of the illness.

1.2 Epidemiology

The prevalence of RA in Malaysia is 0.5% [4], 0.4% in Southeast Asia [5], and 1% in the United States [6]. Moreover, the worldwide prevalence of RA is known to be 0.4% to 1.3% [1]. RA has been related to a remarkable regional variation. It was

observed that the prevalence of RA in southern European countries is lower compared to Northern Europe, whereas in other reports, RA is believed to be higher in North America [7]. Moreover, in some ethnic groups of the native Americas, approximately 5% of their population is affected, whereas in a few regions of rural Africa, this disease is absent.

RA can be developed at any age. However, most of the patients are affected in the third to sixth decades of their lives. The prevalence of RA increases with age and is more common in women over the age of 65. An increase in age showed a direct relationship with the prevalence rate. The prevalence of this autoimmune disease, based on gender, was indicated to be three times higher in women compared to men and increases with age [8-10]. This is believed to arise because of epigenetics, immune system activity variation, and unsimilar sex hormones [11].

1.3 Etiology, pathophysiology, and risk factors

RA, as an autoimmune disorder, involves the innate and adaptive immune systems [12]. The etiology of RA is yet unknown, despite comprehensive research [12]. However, similar to other autoimmune disorders, multiple factors have been identified to initiate the autoimmune response and cause RA [13]. Identified risk factors such as environmental, genetic, and hormonal, as well as evidence of interactions among them, make RA etiology difficult to explain and, until now, inadequately known [12].

According to the hypothesis of autoimmune disorders, the RA primary formation phase necessitates two individual phenomena: first, the genetic tendency of the patient, which leads to the production of autoreactive T and B cells; and second,

trigger incidence, like infection caused by bacteria, viruses, or tissue damage, which can enable the activated antigen-presenting cells (APCs) to activate the lymphocyte that was formerly produced, thereby causing tolerance disruption and further destruction of tissue and organs. Thus, patients with genetic predisposition tend to develop RA due to a combination of genetic differences, epigenetic alteration, and environmental factors induced by accidental events such as injury or infection [14].

1.3.1 Early innate and adaptive immune responses

As the exact cause of RA is still unclear, in a genetically susceptible individual, an infectious agent or another external factor attaches to toll-like receptors located on peripheral dendritic cells and macrophages. Therefore, the innate immune system reacts promptly, causing the release of cytokines, complements, and inflammatory mediators while also activating natural killer cells and neutrophils [15]. The migration of dendritic cells towards lymph nodes enables them to act as antigen-presenting cells. They present antigens that are bound to major histocompatibility-complexes to the T cell receptor, which activates T cells. This activation initiates the adaptive immune response, leading to cell proliferation and migration towards the joint synovial membrane. Within the synovium, T cells are activated through interaction with other antigen-presenting cells, such as macrophages and B cells [16] (Figure 1).

1.3.2 Cytokine production and inflammatory mediators

Activated T cells secrete various cytokines, including interleukin-2 (IL-2), interferon-γ (IFN-γ), tumour necrosis factor alpha (TNF-α), and granulocyte-macrophage-colony stimulating factor (GM-CSF). These cytokines play a crucial role in stimulating the activity of monocytes, macrophages, fibroblasts, chondrocytes, and osteoclasts [17]. Macrophages and fibroblasts that have been activated in the synovium

secrete additional proinflammatory cytokines such as TNF-α, IL-1, and IL-6. The production of various inflammatory mediators, such as chemokines, matrix metalloproteinases (MMPs), co-stimulatory and adhesion molecules, and growth factors (such as fibroblast growth factor-2 and vascular endothelial growth factor), is stimulated by these cytokines. This stimulation further amplifies the inflammatory process [16, 18].

The production of cytokines and mediators with inflammatory characteristics is significantly important in the progression of RA. Cytokines with inflammatory characteristics, including tumour necrosis factor (TNF)-α, interleukin (IL)-1, IL-6, and IL-17, as well as ensuing mediators, stimulate inflammation within the joints and result in the deterioration of cartilage and bone, ultimately resulting in RA [19-21]. The stimulation of synovial tissue by these cytokines leads to joint damage through hypertrophy, the expression of inflammatory cytokines, and the recruitment of inflammatory cells [22]. The comprehension of these mechanisms has advanced the progress of specialized, targeted treatments for RA. Current therapeutic strategies involve monoclonal antibodies, fusion proteins, or antagonists aimed at pro-inflammatory cytokines like TNF-α, IL-1, and IL-6 [19, 22].

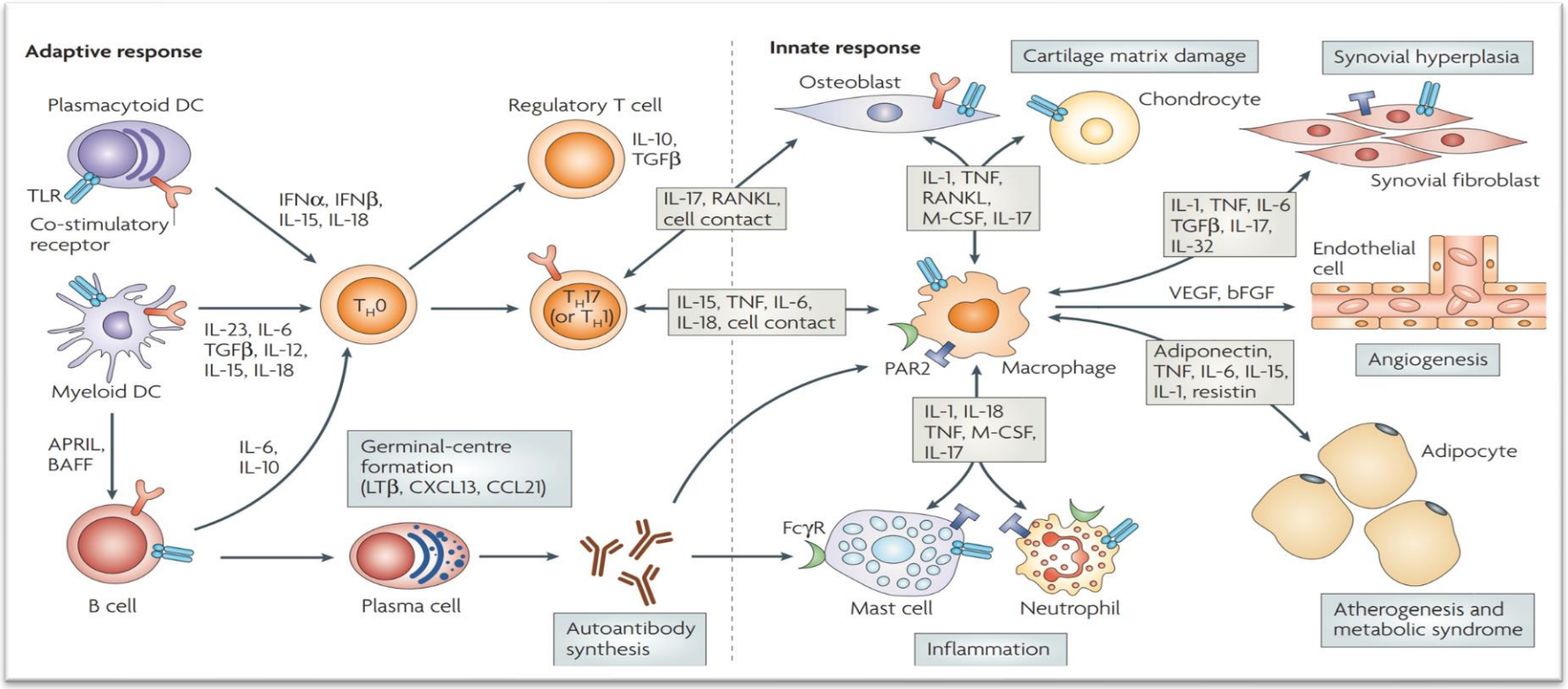

Figure 1.1 Compartments of the inflammatory response.

This figure represents the innate and adaptive divisions of the inflammatory response in RA The stimulation of dendritic cells, T cells, B cells, and macrophages, along with the dysregulated manifestation of cytokines, incite the activation of neutrophils, mast cells, endothelial cells, and synovial fibroblasts [23].

1.3.3 Genetic risk factors

Hereditary factors in RA etiology were detected many years ago, when research indicated a greater incidence of RA in first-degree family members of RA patients compared to the general population [24]. According to estimation, RA heredity was found to be around sixty percent [25, 26]. Currently, over a hundred loci have been linked to RA risk [26, 27].

The HLA DRB1 alleles, known as shared epitope (SE), were detected to be the first and the greatest genetic factor for RA development [28]. Patients with rheumatoid factor (RF) antibodies were later identified as having a link between RA and SE [29]. Moreover, having antibodies against citrullinated peptides (ACPA) RA patients was detected as well [30]. Protein- tyrosine-phosphatase non-receptor type 22 (PTPN22) was found to be the second genetic factor among RA patients [31]. In the term of SE, PTPN22 is related to ACPA-positive RA [32].

In particular, variations in the HLA-DRB1 gene have been implicated as a potential risk factor for RA. More specifically, the presence of the shared epitope alleles, a group of closely related genetic variants, has been associated with an increased susceptibility to RA. The findings suggest that genetic factors may play a critical role in the onset and progression of RA [33-35]. Other genetic factors, such as variations in gene-encoding cytokines, chemokines, and other immune-related molecules, may also contribute to the development of the disease. These molecules are responsible for regulating the immune system, and their dysfunction can lead to an abnormal immune response, which can trigger the onset of the disease. Therefore, studying the genetic factors that contribute to the development of a disease can provide

valuable insights into its pathogenesis and pave the way for the development of targeted therapies [34, 36-38].

While the exact cause of RA is unknown, research has shown that certain genetic factors can play a significant role in the development and severity of the disease. One such genetic factor is the presence of specific HLA-DRB1 alleles. These alleles are part of the human leukocyte antigen (HLA) system, which plays a crucial role in the body's immune response. Studies have shown that individuals with certain HLA-DRB1 alleles have a higher risk of developing RA and experiencing more severe symptoms. Moreover, the presence of these genetic factors may also influence an individual's response to treatment with biologic and targeted synthetic DMARDs. Since these medications work by targeting specific immune cells and pathways, the genetic makeup of a patient can impact the effectiveness of the treatment [33, 39].

In addition, it has been observed that the possibility of experiencing a flare-up while undergoing treatment with biologic and targeted synthetic DMARDs for RA may be influenced by genetic factors. In other words, certain genetic characteristics may make some patients more susceptible to experiencing a flare while undergoing this form of treatment [40, 41].

Furthermore, polypharmacy, a common practice in treating RA patients, involves the simultaneous use of multiple medications to manage the condition. However, the use of multiple medications may increase the risk of drug interactions, which can pose a challenge for patients undergoing treatment with biologic and targeted synthetic DMARDs. This is particularly significant since biologic and targeted synthetic DMARDs are designed to target specific pathways in the immune system, which may be influenced by genetic factors. Therefore, it is essential to

consider the potential impact of polypharmacy and genetic factors on the efficacy and safety of biologic and targeted synthetic DMARDs in RA patients [42].

Moreover, research suggests that the safety of biologic and targeted synthetic DMARDs in patients with RA might be impacted by their genetic factors. This means that certain genetic factors might affect how well a patient responds to these medications and how likely they are to experience ADRs. Understanding these genetic factors could help healthcare providers personalize treatment plans for patients with RA, potentially improving their outcomes and reducing the risk of ADRs [41, 43].

1.3.4 Environmental risk factors

RA is known to be a complex disease [44], which has been linked with several environmental, diet and style of living components [45] that contribute to disease occurrence [44]. Among multiple identified environmental factors, smoking was found to be the most strong and prominent cause of disease enhancement risk in RA [46], in which the proportion of tobacco dose [47] and duration of smoking play a significant role in occurrence of disease [48]. Based on the observation of several studies, the odds ratio of the relationship between tobacco smoking and RA was found to be more than two, and according to estimations, tobacco exposure is reported to be between 20 and 30 percent of environmental risk factors [49]. Multiple important factors in the association between tobacco smoking and RA that may interpose the enhanced chance of RA development. Initially, Tobacco smoking and RA development relation is mainly observed in RF Positive RA [47, 49, 50] and ACPA-positive RA [49]. Additionally, association of tobacco smoking and RA was found to be linked with RF even if RF is not present in RA [51], whereas the association of smoking has been shown to be weak in patients with seronegative RA [52]. Moreover, it has been

demonstrated that patients with RA who continue smoking after RA diagnosis have a worse prognosis with a considerable higher risk of radiographic progression, and the response to anti-rheumatic medications is worse as well [53-55].

Dust inhalation has been found to be another environmental risk factor contributing to the development of RA [55-60]. Besides exposure to tobacco smoke, several studies have shown a relation between exposure to occupational silica and dust [56], specifically in ACPA-positive RA [57-60]. In addition, textile dust exposure has also been shown to increase the risk of RA. Although this risk factor was observed to be associated with the development of both ACPA-positive RA and ACPA-negative RA [61].

Beyond smoking and dust inhalation, various dietary and alternative factors like medicines and supplements have been indicated to be related to increasing the risk of RA development. As a case in point, low consumption of vitamin D and antioxidant dietary products and high levels of sodium, iron, protein, red meats, and sugar consumption have been observed to be related to elevation in RA risk [62-68]. In addition, based on the conclusions of various studies, it has been indicated that high levels of omega-3 fatty acids and fish consumption have been associated with a lower risk for RA in a range of different studies, containing research indicating that dietary information was gathered before the occurrence of RA [69-73].

1.3.5 Hormonal risk factors

The frequency of RA in females aged less than 50 years old was found to be 4 times higher than in males and 2 times higher in patients older than 60 years old. According to this ratio, it has been indicated that the pathogenesis of RA is affected

by hormonal factors implications, however, the function of these hormonal factors left to be contentious. [74].

1.3.6 Microbiota

For a long period of time, it has been indicated that microbes can have a role in RA development [75]. The occurrence of RA rises in patients with Periodontal illness [76]. This condition was found to enhance disease activity in RA patients as well [77]. Based on the reports, it has been indicated that oral microbiota mediates the enhancement of risk to a certain extent, particularly bacteria such as ggregatibacter actinomycetemcomitans and Porphyromonas gingivalis that are capable of citrullinating peptides. Moreover, the microbiota of the gut in RA showed to be different from the general population, on the other hand, the microbiota alters with disease duration and treatment of RA [78].

1.4 Clinical features and manifestations

The onset of disease, signs and symptoms, and duration of RA are different among patients. For instance, it has been observed that some patients had an acute onset of disease with dramatic and systemic symptoms such as loss of weight, fever, polyarthritis, and extra-articular manifestation, whereas other patients showed an insidious onset, which is more common [79, 80]. It is common that small to medium-sized joints of the body are always symmetrically affected in RA; however, larger joint sizes can be affected as well [81-83]. Swelling, pain, prolonged morning stiffness lasting more than 30 minutes and a decrease in movement are the results of joint inflammation [79-81, 83]. Moreover, upon extra examination of patients with RA,

elevation of inflammatory markers, including C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), has been clearly found [10, 84-86].

Although RA's early clinical features are not specific, it is crucial to diagnose the condition prior to the appearance of further typical characteristics of disease progression, such as mechanical dysfunction and deformation of joints [84, 87]. Typically, up to 40% of RA patients experience extra-articular symptoms of the disease, which are frequently related to prolonged disease duration [10, 88, 89]. The most common extra-articular manifestation of RA is known to be Subcutaneous rheumatoid nodules, which can affect approximately one-third of RA patients [2, 90, 91]. These nodules are painless and usually appear on extensor surfaces. However, they may turn out to be ulcerated, particularly at sites of pressure. Furthermore, these nodules may appear extracutaneous, especially on the lungs or heart. Typically, RA patients with positive antibody (seropositive RA) develop these nodules, and its occurrence is infrequent in seronegative RA patients [92]. In addition, nodule development found to be related to smoking as well [81, 92]. Up to 1% of patients with RA develop Episcleritis that is generally mild and self-limiting condition. Episcleritis in RA patients is well described as being extremely painful and aggressive and can be accompanied by corneal ulceration [92, 93].

Another manifestation of RA disease is systemic or cutaneous vasculitis. Patients with cutaneous vasculitis usually suffer from splinter haemorrhages, digital and periungual infarcts, leg ulcers, and pyoderma gangrenosum. Whereas in patients with systemic vasculitis, other organs such as the lungs, kidneys, peripheral nerves, and mesentery can be affected [92, 94]. Interstitial lung disease (ILD) represents a common extra-articular feature of RA, which is usually characterised by diffuse interstitial pulmonary fibrosis. Pleural effusions can arise too. RA cardiac events

include accelerated atherosclerosis, myocarditis, and pericarditis. Valvular heart disease is caused by the existence of rheumatoid nodules which are located on or close to the heart valves [92, 95-99].

RA patients usually experience haematological disorders and normocytic normochromic anaemia was found to be the most common haematological abnormality, however, thrombocytosis and thrombocytopenia tended to be less common, respectively [81, 92, 100]. Extra-articular features of RA possess a significant value since they are able to be used for the prediction of more severe illness [92, 101].

1.5 Comorbidity

Beside the extra-articular manifestations of RA that may appear in patients, the inflammation stimulates other conditions and illnesses as well. RA patients possess a higher risk of developing cardiovascular diseases (CVD) [102-105].

According to the findings of one study conducted in Denmark regarding myocardial infarction (MI), it has been indicated that the total incidence rate ratio (IRR) of MI in patients with RA tends to be 1.7 (95% CI: 1.5 to 1.9) in comparison with the general population [106]. Furthermore, other studies have demonstrated a thirty percent higher risk of stroke in RA patients in comparison to the overall population [107]. Systemic inflammations as a mechanism of RA disease are considered to stimulate atherosclerosis, which may result in CVD [108]. However, alternative risk factors for CVD, such as diabetes mellitus (DM), smoking, and/or a reduced level of HDL cholesterol, turned out to be more common in RA patients [109-111].

It has been observed that the higher risk of CVD in RA patients is mostly caused by systemic inflammation and an increase in the rate of classic risk factors. Patients with RA were found to have a higher risk of developing osteoporosis [112-114]. Aside from corticosteroid medications in the RA patient's therapeutic regimen, the systemic impact and functional disorder of the illness itself can lead to osteoporosis in this population. Hyperthyroidism [115], peptic ulcer disease (PUD), dementia, chronic pulmonary disease (COPD), and congestive heart failure are known to be other disorders among RA patients [116].

According to the findings, it has been observed that in patients diagnosed with RA within the first 5 years, approximately 41% developed minimum one new comorbidity. This study indicated that hypertension (15.1%), malignancy (7.6%), stroke/transient ischemic accident (TIA) (5.1%), myocardial infarction (MI) (4.3%), and osteoporosis (3.7%) found to be the most common comorbidities among RA patients [110].

1.6 Extra-articular features and systemic involvements of Rheumatoid arthritis

Although the number varies according to the sources, extra-articular findings can be seen in approximately 40% of individuals with RA at some point in their lives. Smoking, RF positivity, and some alleles of the HLA-DR gene are thought to predispose to extra-articular findings in RA [117].

1.7 Diagnosis and classification of RA

RA diagnosis is a medical and clinical chore in which symptoms of joints, clinical investigation result items, acute phase stimulant assessment, rheumatoid factor (RF), and Anti-cyclic citrullinated peptides (anti-CCP) examination, as well as x-ray are taken into account. RA criteria for identification and categorisation purpose turned out to be used since 1956. In 1987, the American college of rheumatology (ACR) had established a set of categorisation criteria systems [118], which has been practiced until 2010. Thereafter, these criteria were exchanged with new categorisation criteria system by the partnership with the ACR and the European league against rheumatism (EULAR) [119]. Revised RA categorization measures by ACR in 2010 was done in order to include the requirements for early diagnosis of RA [119]. The goal of the approved new criteria (Table 2.1) is to detect and diagnose RA earlier, compared to conventional criteria (Table 2.2). The new criteria incorporate auto-antibodies such as RF and ACPA. The criteria, however, omit the radiological changes examination of RA patients. It has been indicated that the new classification criteria have a critical rolethe in the research area and as a reference for physicians as well [120, 121].

Table 1.1 Classification criteria for RA diagnosis (2010 ACR/EULAR).

A: Joint involvement	
1 large joint	0
2–10 large joints	1
1–3 small joints	2
4–10 small joints	3
>10 joints	5
B: Serology	
Negative RF and negative ACPA	0
Low-positive RF or low-positive ACPA	2
High-positive RF or high-positive ACPA	3
C: Acute-phase reactants	
Normal CRP and normal ESR	0
Abnormal CRP or Abnormal ESR	1
D: Duration of symptoms	
<6 weeks	0
≥6 weeks	1

According to the 1987 RA classification criteria, at least 4 of these 7 criteria had to be satisfied for a patient to be classified as having RA. Furthermore, criteria 1-4 had to be present for at least 6 weeks [118].

In RA patients in the early illness development stage, only one or a few joints might be affected. Concurrently or before the commencement of the disease, tenosynovitis might develop, which is inflammation of the tendon. Detection of tenosynovitis can be done by imaging Doppler's colour sonography or by magnetic resonance imaging with Gadolinium-enhanced imagery, which shows soft tissue intra-articular extension or synovial membrane hypervascularization [122].

In order to classify RA, the existence of minimum one swollen joint and minimum score of six out of ten from the scoring system are essential [119].

Involvement of the joint in accordance with a physical check-up, or ultrasound imaging or imaging by magnetic resonance provides five scores; elevation in the levels of RF or ACPAs, or even both, gives two extra scores or three scores if the levels are elevated 3 times more than the normal range; and elevation in the acute phase reactant (APR) response, like an elevated level of CRP or ESR, and symptoms duration (more than six weeks), gives one extra score individually [121].

Table 1.2 The 1987 RA classification criteria.

Criterion	Definition
Morning stiffness	Morning stiffness in and around the joints, lasting at least 1 hour before maximal improvement.
Arthritis of 3 or more joint areas	At least 3 joint areas simultaneously have had soft tissue swelling or fluid (not body overgrow alone) observed by a physician. The 14 possible areas are right or left PIP, MCP, wrist, elbow, knee, ankle and MTP joints.
Arthritis of hand joints	At least 1 area swollen (as defined above) in a wrist, MCP or PIP joint
Symmetric Arthritis	Simultaneous involvement of the same joint areas (as defined in 2) on both sides of the body (bilateral involvement of PIPs, MCPs or MTPs is acceptable without absolute symmetry).
Rheumatoid Nodules	Subcutaneous nodules over bony prominences or extensor surfaces, or in juxta articular regions, observed by a physician
Serum rheumatoid factor	Demonstration of abnormal amounts of serum RF by any method for which the result has been positive in <5% of normal control subjects
Radiographic Changes	Radiographic changes typical of RA on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints (osteoarthritic changes alone do not qualify)

While early diagnosis and initiation of therapy avoids disease progression and joint deterioration in up to 90% of patients in the early stages [123], it is critical to diagnose RA patients at the earliest possible time. Particular signs of suspected RA

involve joint pain and swelling of metatarsophalangeal joints or metacarpophalangeal joints, or even both; finger joints morning stiffness that persists for more than 30 minutes; and positive autoantibody [124].

1.8 Problem statement

To the best of our knowledge, this is the first study in Malaysia that included all the available biologic and targeted synthetic DMARDs medications for comparative detection of clinical outcomes among the RA population. The study includes 3 main considerable parts, including efficacy, adverse drug reactions, and flares.

The first part includes an examination of the therapeutic efficacy of all medications. A comparative examination of all available biologic and targeted synthetic DMARDs efficacy and their predictors has not yet been studied among Malaysian RA patients. The available data did not include all available medications in the classification.

The second part is when RA flares. It is crucial to minimize the frequency and severity of disease flares. However, despite their common occurrence, flares have received limited attention the in literature. There are only a few studies that have investigated the frequency of flare events in patients with low disease activity and examined the impact of flares on clinical outcomes [125, 126]. Furthermore, in the Malaysian population, there is only one study that has explored the prevalence and predictor of flares in RA, but it was focused specifically on flares following COVID-19 vaccination and included patients receiving conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) therapy only [127].

The third part is the safety of biologic and targeted synthetic DMARDs therapy among Malaysian RA patients. In this section, we have focused on the prevalence and predictors of adverse drug reactions (ADRs) associated with biologic and targeted synthetic DMARDs as well as treatment failure, which is explained by discontinuation of therapy due to inefficacy or adverse drug reactions and necessitating change of therapy. Extensive efforts have been made to identify RA patients who are more susceptible to treatment failure. However, there are significant gaps in the current literature, particularly regarding the impact of age, comorbidity, and polypharmacy. Although the efficacy and safety of biologics have been investigated in older adults, the findings are inconclusive. Some studies have reported reduced efficacy [128, 129], while others have not found any association [130, 131]. Additionally, Polypharmacy, the concurrent use of multiple medications by an individual, is becoming increasingly prevalent due to an aging population with multiple comorbidities and advancements in therapeutics that advocate combination therapies. However, the role of polypharmacy in RA and its potential association with treatment failure have yet to be explored. Therefore, the detection of the efficacy and safety of these agents in RA patients is important to support the treatment safety and also optimize pharmacotherapy management of the disease in these patients.

1.9 Aims and objectives

This study aims to evaluate the various impacts of biologic and targeted synthetic DMARDs therapy on the clinical outcomes and occurrence of ADRs among RA-treated patients at multi-center Malaysian hospitals.

1.9.1 Specific objectives

In order to achieve the aim, the objectives of this study are as follows:

1. To evaluate the impact of biologic and targeted synthetic DMARDs on reducing disease severity (DAS28) and identify demographic and clinical predictor factors at different time intervals.
2. To identify the predictors of flares among RA patients with biologic and targeted synthetic DMARDs therapy.
3. To evaluate the impact of polypharmacy on clinical response and occurrence of adverse drug reactions.
4. To assess the association between demographic and clinical predictors and the safety of biologic and targeted synthetic DMARDs among RA patients.

1.10 Significance of study

The results of the study can be used by clinicians and pharmacists to evaluate different aspect of treatment outcomes and prevent or manage adverse drug reactions (ADRs) associated with biologic and targeted synthetic DMARDs by understanding the valuable predictors, thus improving the clinical outcomes. Furthermore, the cost of biologic and targeted synthetic DMARDs is high. Conversely, understanding the biologic and targeted synthetic DMARDs impact on modifying the disease activity and their prognostic factors could also influence and sequentially assist physician for better decision making, facilitating commencement of treatment, and choosing the most appropriate medicine for patients with RA.

CHAPTER 2

LITERATURE REVIEW

2.1 Rheumatoid arthritis

Rheumatoid Arthritis (RA) is an inflammatory joint disease that is prevalent and incurable despite significant advancements in treatment. In Malaysia, it affects around 0.5% of the population with a higher frequency in women [4]. The disease is caused by a complex interaction between genes and the environment, leading to a breakdown of immune tolerance. RA is a heterogeneous condition, with highly variable presentations and disease courses among individuals. Although clinical outcomes have improved due to advances in its management, including disease activity, joint damage, functional disability, and quality of life, the remarkable heterogeneity of RA in its presentation, natural history, and drug responsiveness makes it a challenging condition to manage and a fascinating subject of study. Being a systemic disease, RA affects many organ systems and is associated with high rates of other diseases, such as malignancies, infections, and cardiovascular diseases [92].

The management of RA has demonstrated progressive improvement in recent decades due to the introduction of biologic and targeted synthetic disease-modifying antirheumatic drugs (DMARDs) therapy, which are more particular towards inflammatory factors compared to conventional synthetic DMARDs (csDMARDs) and aim to decrease the level of disease activity, either by achieving clinical remission or attaining a state of low disease activity, by slowing down or avoiding the process of joint destruction and deformity particularly for patients who have previously failed to respond to treatment this approach has improved therapeutic outcomes and quality of life, while reducing patient morbidity and mortality [132-136]. Although in patients

with high disease activity score, biologics can be considered the first-line therapy. The initial choice of a biologic DMARDs is typically tumor necrosis factor (TNF) inhibitor agent, such as Infliximab, Adalimumab, Etanercept, and the newer Golimumab and Certolizumab [137].

The results of various investigations emphasize the advantages of biologic DMARDs when used in conjunction with csDMARDs, and in certain cases, when used alone as well. However, the combination therapy of biologic or targeted synthetic DMARD plus csDMARDs demonstrated greater effectiveness compared to biologic or targeted synthetic DMARD monotherapy [138]. According to several findings, biologic DMARDs were demonstrated to reduce inflammation of the joints and radiographic damage. Moreover, they have shown to produce clinical response in 70% to 80% of patients with RA [139]. These targeted therapies are well tolerated by the patients. However, the discomfort of intravenous (IV) administration, high cost and adverse events (AEs) related to these medications prohibit their use as the first-line therapy.

The selection and utilization of these agents are influenced by a variety of important safety considerations, as is the case with any medications. Biologic and targeted synthetic DMARDs agents have been related to an elevated incidence of overall AEs, such as the risk of infection or administration reactions, nervous system symptoms, and therefore withdrawals as a result of AEs [140].

2.2 Assessment of disease activity

Disease activity in RA cannot be effectively predicted using just one or a few parameters. As a result, a number of combination rating systems including laboratory

and clinical findings have been developed to measure disease activity. persistent assessment using a standard algorithm that has been devised enables healthcare professionals and specialists to a rapid and suitable increase in the intensity of treatment in order to attain disease remission [141]. A practical tool for assessment of disease activity is the modified Disease Activity Score (DAS28) that contains 28-joint counts of swollen and tender joints. The modified DAS28 was evolved from the DAS that utilised forty-four joints. Moreover, by decreasing the number of joints involved in this assessment system, the utility of the modified DAS28 even beyond the formal study has been increased without affecting its validation. The modified DAS28 indicator shows a strong correlation with the main DAS indicator as well as with evaluations of disability and functional status. Furthermore, the patient's global assessment (PGA), and CRP or and ESR are included as well.

The DAS28 calculates disease activity on unremitting and continuing values from 0 to 9.4 and divides disease activity into low, moderate, and high levels with the following scales (DAS28 $\leq$ 3.2), (DAS28 > 3.2 but $\leq$ 5.1), or high (DAS28 > 5.1) respectively [142].

2.3 Assessment of therapeutic response

The alteration in the DAS28 measurements during time could be used to evaluate the responsiveness to the efficacy of treatment and therapeutic intervention. The EULAR established response criteria that are computed by using disease activity level at the time of computation in combination with the modification in disease activity over the period of evaluation or since beginning treatment. To be called a "responder," a patient needs to demonstrate a serious alteration in disease activity while simultaneously attaining disease activity levels lower than predefined goals.

Response criteria are classified as good, moderate, or no response as shown in below table [142].

Table 2.1 EULAR response criteria

Improvement in DAS28 →	**> 1.2**	**> 0.6 and ≤ 1.2**	**≤ 0.6**
Present DAS28 ↓			
≤ 3.2	Good response	Moderate response	No response
>3.2 and ≤ 5.1	Moderate response	Moderate response	No response
>5.1	Moderate response	No response	No response

Furthermore, comprehensive clinical studies have confirmed the EULAR response criteria, which associate strongly with indicators of functional class and radiographic development of joint deterioration [142].

2.4 Treatment

In recent years, there has been a substantial improvement in the treatment of RA. On one hand, there has been an improvement in treatment strategies with the more effective use of existing disease-modifying drugs, and on the other hand, several new treatments have been developed [143]. There are currently 4 classes of therapies for RA and they are divided into: non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids (GC), classic non-biological DMARDs also known as conventional synthetic DMARDs, biologic and targeted synthetic DMARDs [144].

Treatment should be started particularly in the first 12 months of disease onset (initial RA), especially in the first 12 weeks (very early RA), being considered a therapeutic window of opportunity. Therefore, the initial identification of the condition and the start of treatment can result in a better prognosis for the patient while awaiting

consultation at the specialized rheumatology service [145]. The goal of treatment should focus on pain relief, suppressing the inflammatory process, inhibiting cartilage destruction, improving the feeling of well-being and preventing joint deformation [146].

2.4.1 Non-steroidal anti-inflammatory drugs (NSAIDS)

Its analgesic and anti-inflammatory properties of NSAIDs are used to reduce joint pain and swelling [147]. NSAIDs are a group of chemically heterogeneous compounds that generically share therapeutic action and adverse effects. These drugs have an anti-pyretic, analgesic, and anti-inflammatory therapeutic action. As RA is an inflammatory condition, NSAIDs and GCs are used as the first line to decrease the inflammatory response and reduce the pain [144]. These agents are commonly used as bridging therapy for DMARDs. However, they should not be used alone when RA is diagnosed, as there are no clinical data to show that they delay the clinical or radiographic progression of the disease [148].

2.4.2 Glucocorticoids (GC)

GCs are a class of steroid hormones characterized by their ability to bind cortisol receptors and trigger various biological effects. They have potent anti-inflammatory and immunosuppressive properties. It is estimated that more than 50% of patients with RA are treated with GC [144, 147]. Administration can be done orally, intramuscularly, or intra-articular. GCs act by inhibiting the release of cytokines and help to quickly relieve symptoms as well as reduce inflammation [147]. Recent studies show that, with long-term low-dose treatment, GCs can substantially decrease the rate of erosion progression in RA, in addition to their anti-inflammatory and immunosuppressive capabilities with short- and medium-term use [144]. Given the