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Review Article

MANAGEMENT OF RHEUMATOID ARTHRITIS: SPECIAL CONSIDERATION FOR BIOLOGIC DISEASE-MODIFYING ANTIRHEUMATIC DRUGS

SALMI ABDUL RAZAK, MOHD MAKMOR-BAKRY, ADYANI MD-REDZUAN*

Faculty of Pharmacy, Universiti Kebangsaan Malaysia, Jalan Raja Muda Abdul Aziz, 50300 Kuala Lumpur, Federal Territory of Kuala Lumpur. Email: adyani@ukm.edu.my

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ABSTRACT

Rheumatoid arthritis (RA) is a progressive chronic inflammatory disease affecting 0.5–1.0% of the adult population worldwide. Due to the damages caused by this autoimmune disease, new biologic therapies, particularly the biologic disease-modifying antirheumatic drugs (bDMARDs), are now being the treatment of choice in the management of RA. However, special precaution and prescreening before the usage of bDMARDs are needed to ensure better clinical response and avoiding risk of adverse event during treatment with the selected bDMARDs. In this review paper, we will provide overview on the incidence and pathogenesis of the disease, available pharmacological treatment and emphasizing special consideration in need on initiation of bDMARDs among RA patients. A literature review was performed by searching for relevant articles in Medline database through PubMed using medical subject headings terms and keywords: RA, bDMARDs, special consideration, tumor necrosis factor inhibitor, and non-tumor necrosis factor inhibitor. All papers reviewed were from 1999 to 2017 and were written in English. In this article, use of conventional synthetic DMARDs (csDMARDs), bDMARDs and special consideration to be taken upon initiation of biologic therapies in RA will be reviewed.

Keywords: Biologic therapy, Non-tumor necrosis factor inhibitors, Precaution, Prescreening, Rheumatoid arthritis, Tumor necrosis factor inhibitor.

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INTRODUCTION

Rheumatoid arthritis (RA) is a progressive chronic inflammatory disease with which, if left untreated, 20–30% of patients would become permanently work disabled within 3 years of diagnosis. It is known to affect 0.5–1.0% of the adult population worldwide, and the overall prevalence of the disease for the adult population of Asia is reported between 0.2 and 0.3% [1-3]. This inflammatory autoimmune disease is chronic progressive symmetrical polyarticular joint disease, characterized by progressive destructions of the articular cartilage, bone, and non-articular muscular structures that can cause joint deformities. After a mean follow-up of 3.9 years, 47.5% of RA patients experienced at least one extra-articular or systemic manifestation. New treatment modalities by the initiation of targeted biologic therapies are recommended to for disease control, damage prevention, persevering affected joint function, increase in patients' quality of life, and increase the possibilities to achieve complete remission of the disease [4]. The biologic disease-modifying antirheumatic drugs (bDMARDs) or known as the monoclonal antibody (mAb) therapies, which target directly to the specific cytokines cells and molecules of the disease pathophysiology, can be initiated either alone as monotherapy or as combination therapy with the conventional synthetic DMARDs (csDMARDs) therapy within the first 3 months of early RA diagnosis [5-7]. This review will provide an overview of the RA disease, the use of new mAb therapies in addition to the csDMARDs used in the management of RA, as well as suggestive prescreening test based on disease history or concurrent condition on selection of biologic treatment initiation in RA patient.

METHODOLOGY

Relevant articles were searched in Medline database through PubMed using medical subject headings terms and keywords: RA, bDMARDs, special consideration, tumor necrosis factor inhibitor, and non-tumor necrosis factor inhibitor. All papers reviewed were written in English, from 1999 to 2017. The articles focused on descriptive information on RA disease, treatment used in the management of RA including biologic mAb and prescreening on biologic treatment initiation.

OVERVIEW ON INCIDENCE OF RA

RA is a chronic autoimmune disease causing permanent disability that reduces patients' quality of life overtime of the disease progression. RA is known to affect 0.5–1.0% of the adult population worldwide [1]. RA is more prevalent in females than males with female-to-male ratio of 3:1 and with increasing age [8]. Studies have shown that the incidence of RA remained stable or increased over time, and the prevalence of RA is high in the general population [9]. Known as a multifactorial heterogeneous disease, RA has different incidence rate and prevalence across different populations and geographical area [2,3]. Studies on prevalence and incidence rates of RA in population of Asia consisting countries from Japan, China, Taiwan, Indonesia, and Philippine reported a prevalence of the disease between 0.2 and 0.3% [2]. It was observed that the prevalence of RA varies widely from population to population with the highest rate found among Pima Indians (5.3%) and Chippewa Indians (6.8%) and lowest rate in Asian countries. Prevalence among population from China and Japan is 0.2–0.3% [10]. The regional variation of RA prevalence may suggest role of genetic factor underlying susceptibility to the disease. In Malaysia, according to the Arthritis Foundation Malaysia 2007, RA affects 5 in 1000 Malaysians. The Rochester Epidemiology Project provides the most recent US data on the incidence of RA. It is observed that in a period of time from 1995 to 2007, it was estimated 1.5 million of the United States (US) adults age more than 18 years old had RA and the RA incidence increased among women compared to men [8]. Published data showed that prevalence rate of RA is generally 2–3 times higher in female than male, and the prevalence increases with increasing age up to about eighth decade of life and peaks at around age of sixties. The incidence peaked earlier for women than men at about ages 55–64 years for women, compared with 75–84 years for men [11,12].

Pathogenesis and extra-articular manifestation of RA

Basically, the first affected joint structure in RA is the synovium. Synovium is the synovial membrane lines within the joint capsule and produces the synovial fluid. The inner layer of the synovial membrane consists of two synoviocytes which are the macrophage-like

synoviocytes and fibroblast-like synoviocytes, and both are capable of expressing cytokines and degenerative enzymes. In the case of joint inflammation, the inflammatory arthritis leukocytes migrate from the blood vessels into the synovial lining and trigger release of inflammatory mediators and enzymes by cellular interactions. This synovial immunologic process and inflammation will lead to synovitis, irreversible damage to the cartilage and bone and contributes to systemic consequences of the disease [1,13].

It is suggestive that the development of RA is related to trauma, degeneration, abnormalities in biochemical pathways, autoimmunity, inflammation, and genetic polymorphisms. Environmental factors were found to trigger the disease, as well as social factors [13]. The interaction of genetics and environmental factors such as cigarette smoking, infection, or trauma can cause a breakdown of immune tolerance and synovial inflammation in a characteristic symmetric pattern [10]. The T-cells, B-cells, and coordinated interaction of pro-inflammatory cytokines play important roles in the pathophysiology of RA. CD4 T-cells are activated to secrete interleukin (IL)-2 and interferon gamma (tumor necrosis factor [TNF]-γ) for infiltration into the synovial membrane. These cells later activate synovial macrophages and fibroblasts and hence lose responsiveness to T-cell activities in the course of RA. The B-cells may serve as antigen- presenting cells, together with the production of autoantibodies such as rheumatoid factors. Autoantibodies can form larger immune complexes that can further stimulate pro-inflammatory cytokines, TNF-α through complement, and Fc-receptor activation [14].

Cells of innate immune system including macrophages, neutrophils, and mast cells also play a pivotal role in pathophysiology of synovial inflammation in RA. Neutrophils that present in synovial fluid will synthesize inflammatory prostaglandins, proteases, and reactive oxygen intermediates. Besides macrophages involvement in osteoclastogenesis, macrophages also secrete pro-inflammatory cytokines such as TNF-α, IL-1, and IL-6. These cytokines are key mediators of cell migration and inflammation in RA. TNF-α activates cytokines, chemokine expression, endothelial cell adhesion molecules, protects fibroblast, promotes angiogenesis, and suppresses regulatory T-cells. Whereas, IL-6 promotes leukocyte activation, autoantibody production, contributes to anemia, and dysregulation of lipid metabolism. Both TNF-α and IL-6 will amplify osteoclast activation and differentiation [10].

Although RA primarily affects the joints, the disease process can involve other organ systems. Involvement of other organ systems is defined as extra-articular manifestation involving systemic effects or all conditions and symptoms which are not directly related to the locomotor system [13,15]. A retrospective analysis done by Hochberg *et al*. on the incidence and prevalence of extra-articular and systemic manifestations in a cohort of newly diagnosed patients with RA in the US, 47.5% of 16,752 patients with RA experienced at least one extra-articular or systemic manifestation with a mean follow-up of 3.9 years diagnosis [16]. Extra-articular manifestations identified were rheumatoid nodules, vasculitis, pericarditis, keratoconjunctivitis sicca, uveitis, Felty's syndrome, scleritis, pericarditis, and rheumatoid lung disease [17]. Whereas, for systemic manifestations identified include non-specific features such as asthenia, fatigue, muscle weakness, fever, anorexia, anemia, osteoporosis, weight loss, acute-phase protein production, cardiovascular disease (CVD), and depression [18].

Epidemiologic studies of comorbidities and extra-articular manifestations in RA patients have emphasized that both were associations and predictors to increased morbidity and premature mortality in RA patients [19-21]. A cross-sectional, international, and multicenter study, COMORA (Comorbidities in RA) of 3920 RA patients recruited from 17 countries on five different continents, revealed high prevalence associated comorbidities were psychiatric disorder, mainly depression, gastrointestinal diseases, pulmonary diseases, especially chronic obstructive pulmonary disease (COPD) and asthma, ischemic CVD, hepatitis B, and hepatitis C infections, and solid malignancies, excluding basal cell carcinoma [22]. When compared to RA patients without extra-articular manifestation, the RA patients with extra-articular manifestation had higher mortality rates of 2.5 (95% CI: 1.4–4.0) [23]. A study by Norton *et al*. have shown on average, RA patients had 0.9% comorbidities at baseline (95% CI 0.8–1.0%), and after 5 years from diagnosis increases to 1.8 (95% CI 1.6, 1.9) and 2.3 (95% CI 2.1, 2.5) after 10 years. With the increasing comorbidities in RA patients, this study has found that comorbidity impacts on mortality, functional and work disability, but not on structural damage or disease activity of RA patients [24].

OVERVIEW OF TREATMENT IN RA

According to the European League Against Rheumatism (EULAR) recommendations for the management of RA with synthetic and bDMARDs on the 2016 updates, on classifying the DMARDs, the task force adhered to the previously proposed new nomenclature of DMARDs as tabulated in Table 1 [5,25]. The new nomenclature of the DMARDs provides mechanistic distinction based on the drugs mechanism of action. The chemical compounds of the conventional synthetic DMARDs (csDMARDs), are small molecules that can enter the cell and interact

Table 1: The nomenclature types of treatments for RA

DMARDs			
sDMARDs		bDMARDs	
csDMARDs	Targeted sDMARDs	Biological originator DMARDs	Biological biosimilar DMARDs
Methotrexate	Tofacitinib	TNF-TNFi	
		Adalimumab	
		Certolizumab	
		Etanercept	
		Golimumab	
		Infliximab	
Leflunomide	Baricitinib	Costimulation inhibitor	
		Abatacept	
Sulfasalazine		IL-6 receptor inhibitor	
		Tocilizumab	
		Sarilumab	
		Clazakizumab	
		Sirukumab	
Hydroxychloroquine		Anti-B-cell agent	
Gold salts		Rituximab	

DMRDs: Disease-modifying antirheumatic drugs, RA: Rheumatoid arthritis, TNF: Tumor necrosis factor, TNFi: Tumor necrosis factor inhibitors, csDMARDs: Conventional synthetic disease-modifying antirheumatic drugs, sDMARDs: Synthetic disease-modifying antirheumatic drugs, bDMARDs: Biologic disease-modifying antirheumatic drugs, IL-6: Interleukin-6

with the intracellular structures. Whereas, the targeted biological agents, either the targeted synthetic DMARDs (tsDMARDs) or the Biological Originator DMARDs and Biosimilar DMARDs, are engineered to target specifically well-defined functional moiety either as inhibitor of a signal transduction pathways or activate sites on extracellular or cell membrane molecules [25].

csDMARDs therapies in RA

The goal of therapy in managing RA is mainly to control disease activity, reduce joint damage, and improve patients' quality of life. Earlier treatment modalities for RA, in the 1980s, start with giving support through physical therapy and non-pharmacological interventions. Later, pharmacological interventions are initiated with the use of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) for symptomatic control, followed with a single antirheumatic agent or the DMARDs [26]. However, in the 1990s, it was found that after 1 year early intervention with DMARDs, treatment and management of RA was more effective in terms of slowing down disease progression as compared to treatment with NSAID alone [27]. DMARDs were then known as an agent that was able to suppress the acute phase responses, inhibit joint destruction, and reduce autoantibody levels in RA. Inverting the therapeutic pyramid in managing RA was proposed as the new approach at that time to start using DMARDs as early as possible or at a disease duration of <6 months. The first 6 months of RA disease is established as a window of opportunity for treatment given to benefit and effective in controlling disease progression at long term [28,29].

Better clinical outcomes are achieved with suppressing disease progression with early DMARD intervention rather than following the previous pyramid approach [30]. The treatment approach used in RA patient was maintained for long periods of time [4,26,31]. Available csDMARDs are gold salts, methotrexate (MTX), sulfasalazine, chloroquine, hydroxychloroquine (HCQ), leflunomide (LEF), cyclosporine-A, azathioprine, d-penicillamine, and minocycline. DMARDs were previously termed as slowly acting antirheumatic drugs due to their relatively long treatment effect or lag time that occurs only after 3–6 months on starting the medication [32]. To overcome lag time of DMARD to take effect, glucocorticoid, a strong anti-inflammatory agent or an analgesic medication is required as a bridging therapy for at least 4–6 weeks duration, to rapidly control inflammation, pain, and associated symptoms during RA disease flares [33].

Apart from the inversion of the pyramid for the treatment management of RA, combination of DMARDs is one of the recommendations for patients with symptomatic early RA suggested in the American College of Rheumatology (ACR) guideline for the treatment of rheumatoid arthritis [34]. Combination therapy was long discussed in the late 1990s due to evidence in long-term failure of using single-drug therapy despite early intervention with DMARDs in RA. The purpose of combination therapy is mainly to increase drug efficacy and minimize risk of drug toxicities using DMARDs targeting different site and mechanism of action. Selection of doses in combining therapy either in double or triple therapy depends either to decrease drug toxicity using lower doses of toxic DMARD drugs or using higher doses of toxic DMARDs or drugs to diminish active RA disease [31]. Combination of DMARDs either as a double or triple therapy most commonly includes MTX as the dominant or anchor DMARD that shows good efficacy with tolerable toxicity [35], slow down radiological damage, and reduce RA mortality [26]. According to the 2015 update of the 2008 ACR recommendations for the use of DMARDs and biologic agents in the treatment of RA, examples of double therapy are MTX + HCQ, MTX + LEF, MTX + sulfasalazine (SSZ), and SSZ + HCQ. Whereas, for triple therapy of csDMARDs is MTX + HCQ + SSZ [36]. These combinations of DMARDs are recommended for early RA patients with moderate or high disease activity accompanied with poor prognosis features, as well as the established RA patients with low or moderate to high disease activity with poor prognosis features to achieve complete remission. Recent updates in the management of early RA and established RA permit the combination with a biologic therapy either a TNF inhibitors (TNFi) or a non-TNFi, either with or without MTX based on the agreement of the expert panels on the superior efficacy of treatment combination over a biologic monotherapy [25,34]. MTX in known to exhibit synergistic effect when used in combination with other csDMARDs or bDMARDs specifically the TNFi and IL-6 inhibitor which also suggests reduced of immunogenicity effect of the biologic therapy [37-39].

bDMARDs therapies in RA

The emergence of biologic targeted therapies in the management of RA has shift the current practice of RA managed care for tight control and treat-to-target approach. bDMARDs have shown evidence in improving signs and symptoms of the disease, positive radiological progression, improve patient-reported outcomes in terms of gaining higher quality of life, and achieving disease remission or low disease activity [29,40]. However, RA in acknowledge as a disease that acquires high cost in terms of medication procurement and availability when biologic therapies or new treatment modalities are added to patients' treatment regimen. Therefore, in accordance to the latest 2016 updates in the EULAR recommendation for the management of RA, treatment of RA patient should aim at the best care and based on shared decision between the patient and health-care practitioner, specifically the rheumatologist. Selection of treatment in managing RA should be based on disease activity, progression of structural damage, comorbidities, and safety issues [25].

Biologics are large molecule, protein-based drugs targeting and identifying the cell subsets, and cytokines causing inflammatory and destructive components in RA. Cytokines modulation of rheumatoid synovitis is either the inhibition of the dominant pro-inflammatory cytokines such as the TNF-α, IL-1, IL-6, and IL-15 or the augmentation of the inadequate anti-inflammatory activity of certain cytokines or naturally occurring cytokines inhibitors. Currently, there are several types of biologic approved for RA. The classification of these biologics depends on which target molecules in their mechanism of actions as listed in Table 2.

TNFi

The TNF-α is one of the proinflammatory cytokines which is the mediators of inflammation in RA. It is produced by macrophages, T-cells, mast cell, the natural killer cells, fibroblast, adipocyte, and the dendritic cells. It is usually inactive but can be induced by bacteria, viruses, tumor cells, trauma, and other exogenous stimuli through posttranscriptional regulation of gene expressions. When in high concentrations of TNF-α, it may lead to inflammation and organ injury [41]. The TNF-α is a trimeric molecule with two bioactive forms, membrane-bound TNF-α and soluble TNF-α. It is mediated through two types of receptors which are the TNF receptor 1 (TNFR1) and TNFR2. TNFR1 is expressed on most cells except the endothelial and hematopoiesis cells which are expressed by the TNFR2. The TNF-α or known as the soluble TNF (sTNF) activation is mediated through two pathways either by the activation of nuclear factor-kappa B (NF-kB) cells or the caspase-8-dependent apoptosis or the caspase-3-dependent apoptosis. The activation of the NF-kB acts as the transcriptional activators and induces the transcription factors can induce other inflammatory cytokines, namely the IL-6, IL-8, synergize with interferons, and T-cells activation causing inflammation [41,42]. Blockade of the excessive cytokines TNF-α is beneficial to halt inflammation and prevent immune activation in RA disease.

Currently, there are five TNFi for the treatment of RA, approved by the Food and Drug Administration and the European Medicines Agency. The TNFi are the infliximab, adalimumab, etanercept, golimumab, and certolizumab [43]. Infliximab is a chimeric mAb with the variable region or fragment antigen binding (Fab') of mouse origin and the Fc region of human origin. Whereas, adalimumab and golimumab are fully humanized IgG1 TNFi mAbs. Infliximab, adalimumab, and golimumab are IgG1 antibodies that are capable for complement fixation and receptor binding at constant region (Fc). The three biologic agents bind both the transmembrane TNF (tmTNF) and the sTNF. Certolizumab which is a humanized Fab' fragment bound to polyethylene glycol (PEG) without the Fc region and has higher binding affinity for TNF-α. The PEG component reduces immunogenicity, not causing antibody-dependent cell-mediated cytotoxicity, and prolongs its pharmacological availability in the system [42,44]. Etanercept is a

fusion protein composed of human TNFR2 fused to the Fc region of the human IgG1. It is the only TNFi that can bind and neutralize both TNF-α and a ligand of the lymphotoxin family. Etanercept binds and inactivates sTNF but not the tmTNF [41,42,44]. Pharmacokinetic characterization for TNFi is presented in Table 3.

Non-TNFi

The 2013 update of the EULAR recommended the use of non-TNFi bDMARDs, in cases of RA patients responding insufficiently to MTX and/or other csDMARD strategies, with or without glucocorticoids or the TNFi bDMARDs, and should be commenced with MTX to reduce

Table 2: Biologic therapies used in the treatment of RA

Biologic agent	Type	Mechanism of action	Available route	Suggested dose
Infliximab	Chimeric antibody Fab' domain mouse origin, Fc domain human origin	Inhibit TNF-α	Intravenous (IV)	3 mg/kg, infusion at week 0, 2, 6, then every 8 weeks
Adalimumab	mAb fully human igG1 antibodies	Inhibit TNF-α	Subcutaneous (SC)	SC 40 mg every 2 weeks (fortnightly)
Golimumab	mAb fully human IgG1 antibodies	Inhibit TNF-α	Subcutaneous (SC)/ intravenous (IV)	SC 50 mg monthly or 4 weekly
Certolizumab pegol	mAb humanized Fab' fragment bound to PEG	Inhibit TNF-α	Subcutaneous (SC)	Loading dose SC 400 mg at week 0, 2, and 4, maintenance dose SC 200 mg every 2 weeks or SC 400 mg every 4 weeks
Etanercept	Recombinant protein (TNF receptor p75-Ig) fusion protein between human IgG1 Fc tail and TNF receptor	Inhibit TNF-α	Subcutaneous (SC)	SC 50 mg weekly
Tocilizumab	Humanized anti-IL receptor antibody	IL-6 receptor blocker	Intravenous (IV)/ subcutaneous (SC)	IV infusion 4 mg/kg every 4 weeks followed by an increase to 8 mg/kg every 4 weeks SC 162 mg given once weekly
Sarilumab	mAb	IL-6 receptor blocker	Subcutaneous (SC)	SC 200 mg once every 2 weeks or fortnightly
Rituximab	Anti-CD20 mAb	Block CD20 B-cell, depletes B-cells but not plasma cells up to 6–12 months	Intravenous	IV infusion 1 g at day 0 and day 14 given 6–12 months Confirmed in RA seropositive for RF and/or anti-CCP antibodies
Abatacept	Recombinant protein - cytotoxic T lymphocyte antigen 4 immunoglobulin (CTLA4-Ig)	T-cell costimulation blocker Block interaction between CD80 and CD86 on antigen-presenting cells and CD28 ligands on T-cells	Intravenous (IV)/ subcutaneous (SC)	IV infusion initial dose give at 2 and 4 weeks, then every 4 weeks IV dose based on weight: <60 kg=500 mg 60–100 kg=750 mg More than 100 kg=1000 mg SC 125 mg weekly
Anakinra	Recombinant protein, non-glycosylated human IL-1-receptor antagonist (IL-1ra)	IL-1 receptor inhibitors	Subcutaneous (SC)	SC 100 mg once daily (OD)
Tofacitinib	JAK inhibitors	JAK1 and JAK 3 inhibitor, interfering with the JAK-STAT signaling pathway	Oral (PO)	PO 5 mg twice daily (BD)
Baricitinib	JAK inhibitors	Selective JAK1 and JAK2 enzymes inhibitor, interfering with the JAK-STAT signaling pathway	Oral (PO)	PO 4 mg once daily (OD)

Table 3: Characterization of TNFi

TNFi	Infliximab	Adalimumab	Golimumab	Certolizumab	Etanercept
Abbreviation	**IFX**	**ADA**	**GOL**	**CER**	**ETA**
Type of agent	Immunosuppressive agents				
Structure	Chimeric Mab Fab' domain of mouse origin and Fc region of human origin	Fully Human	Fully Human	Humanized Fab' fragment PEGylated	Fusion protein between human IgG1 at Fc region and TNFR2
Binding site	Specifically bind TNF-α				Binds both TNF-α and TNF-β (lymphotoxin)
Peak plasma concentration		5–6 days	2–7 days	2–6 days	1–2 days
Half-life	Intravenous (IV) infusion: 7–10 days	Subcutaneous (SC): 15–19 days	Subcutaneous (SC): 14 days	Subcutaneous (SC): 11 days	Subcutaneous (SC): 3–5 days (68 h)

TNF: Tumor necrosis factor, Mab: Monoclonal antibody, Fab': Fragment antigen-binding, IgG1: Immunoglobulin G1, TNFR2: Tumor necrosis factor receptor 2, IV: Intravenous, SC: Subcutaneous

Table 4: List of screening based on disease history or concurrent condition on biologic treatment selection or initiation for RA patient

Disease history or concurrent condition	Laboratory test/suggestion on vaccination		Advice on treatment selection
TBC signs and symptoms	Tuberculin skin test/Mantoux test interferon-gamma release assays (IGRAs) test		Provide TBC (TB) treatment on confirmation of active TB
Latent TBC infection	Tuberculin skin test/Mantoux test Interferon-gamma release assays (IGRAs) test		Provide TB prophylactic treatment with isoniazid on suspected latent TBC infection
History of malignancy	Duration of disease more or equal to 5 years		Initiate biologic if solid malignancies or NMSCs have been treated for more than 5 years Caution needed if malignant disease has been treated within 5 years
Human immunodeficiency virus (HIV) test	Close monitoring of viral load and cluster of differentiation antigen 4 (CD4) count		Tumor necrosis factor inhibitor (TNFi) should be used after weighing the benefit to risk ratio for HIV-positive patients Non-TNFi to be used cautiously
Varicella zoster or Herpes zoster	Varicella zoster virus antibody test		Contraindicated in active zoster infection
Vaccination history	Killed vaccines	Pneumococcal vaccination: Pneumococcal vaccine (13-valent) Pneumococcal vaccine (23-valent)	Recommended before initiating biologic therapy or currently on biologic therapy
		Influenza vaccination	Recommended before initiating biologic therapy or currently on biologic therapy Annual vaccination
		Hepatitis B vaccination	Recommended in high risk of hepatitis presented (intravenous drug abuse, multiple sex partners in previous 6 months, health-care personnel)
	Recombinant vaccine	Human papillomavirus (HPV) vaccination	Recommended before initiating biologic therapy or currently on biologic therapy
	Live attenuated vaccine	Herpes zoster vaccination	Recommended before initiating biologic therapy. Not recommended for TNFi and non-TNFi biologics currently on biologic therapy
Pregnancy (women of child-bearing age)	Pregnancy test		Teratogenic risk: Data insufficient to claim safety Limited human data Animal data suggest low risk Contraindicated if use in combination with MTX
Heart failure symptoms	Electrocardiography (ECG)		TNFi contraindicated in congestive heart failure or in moderate-to-severe heart failure (NYHA class III-IV, EF<50%)
Demyelinating disorder	Example of disorders: Multiple sclerosis Optic neuritis Transverse myelitis Guillain-Barre' syndrome (GBS)		TNFi contraindicated
Hepatitis B	Hepatitis B surface antigen (HBsAg) Antibody to hepatitis B surface antigen (anti-HBs) Antibody to hepatitis B core antigen (anti-HBc)		Continue immunosuppressive treatment as recommended in patients without this condition Safe to use in combination with effective antiviral therapy or prophylactic antiviral therapy
Transaminitis	Liver function test (LFT)		Close monitoring in elevated aminotransferase three times the upper limit of normal (ULN) Discontinue if aminotransferase increased 5 times the ULN
Baseline inflammatory markers	Erythrocyte sedimentation rate (ESR) C-reactive protein (CRP)		On treatment initiation and every follow-up visit
Other baseline laboratory tests	Full blood count (FBC) Fasting blood sugar (FBS) Renal profile Lipid profile		Before and during TNFi treatment within 1st month of treatment initiation and repeated 2 to 3 months during treatment. To perform on each infusion, infliximab-treated patients.

IGRA: Interferon-gamma release assays, TB: Tuberculosis, CD4: Cluster of differentiation antigen 4, TNFi: Tumor necrosis factor inhibitor, HIV: Human immunodeficiency virus, HPV: Human papillomavirus, MTX: Methotrexate, ECG: Electrocardiography, NYHA class: New York Heart Association Functional Classification, EF: Ejection fraction, HBsAg: Hepatitis B surface antigen, Anti-HBs: Antibody to Hepatitis B surface antigen, Anti-HBc: Antibody to Hepatitis B core antigen, LFT: Liver function test, ULN: Upper limit of normal, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, FBC: Full blood count, FBS: Fasting blood sugar

treatment failure due to immunogenicity issues [5]. Non-TNFi when given in combination with MTX had shown improvements in RA signs and symptoms, physical function, health status, and progression of joint damage, therefore, are useful alternatives in patients with long-standing RA who have an inadequate response to TNFi [39]. The non-TNFi approved for the treatment of RA include abatacept, a T-cell inhibitor,

tocilizumab, an IL-6 inhibitor, rituximab, a B-cell indicator, anakinra, an IL-1 inhibitor, tofacitinib, janus kinase inhibitor, and secukinumab, a fully human antihuman IL-17A mAb.

SPECIAL CONSIDERATION IN USING BDMARDS THERAPIES

Reactivation of latent tuberculosis (TBC) is a well-known fact in TNFi usage. The occurrence of latent TBC or the incidence rate ratio is higher in infliximab-treated patient, followed by adalimumab-treated patient as compared to etanercept-treated patient. Proportionate to the incidence of latent TBC per event per 1000 patient-years was reported as 1.5, 0.9, and 0.5 events for infliximab, adalimumab, and etanercept, respectively [45]. The mean onset for the development of TBC was found much more earlier in infliximab which is 12 weeks after initiation, 30 weeks for adalimumab, and a total of 46 weeks for etanercept [46]. All patients in TNFi should be monitored for incidence of latent TBC at least for an annual screening despite initial screening done on initiation of TNFi treatment [47].

Based on the observational databases available for incidence of malignancy or cancer in RA patient treated with biologic TNFi, lymphoma and non-melanoma skin cancers (NMSCs) were found to have increased risk and risk of frequent incidence in RA patients compared to the general population [41]. A study by Elandt and Aletaha [48] suggested a generic stepwise approach for the management of patients with a rheumatic condition requiring immunosuppressive treatment in the context of a current or past malignancy. At least a minimum of 2 years for a complete remission of a low-risk malignant disease is required before decision on type of immunosuppressive drug to be used in patients with a history of cancer. Whereas, for lymphomas, carcinomas of the breast, prostate, or colon or large symptomatic renal carcinomas of more than 5 cm, 5 years duration of complete remission of the malignancy disease is desirable. Common immunosuppressive drug used in rheumatic patient with a history of cancer are MTX, sulfasalazine, chloroquine, HCQ, cyclosporine, and mycophenolate mofetil. Whereas for biologic therapy, the TNFi are used, but caution is needed with close monitoring of risk of cancer development for all immunosuppressive agents selected [48-50].

Stringent patient screening before initiating a bDMARD is required and necessary to the best of effort in avoiding possible infectious complication or malignancy development [51,52]. List of screening based on disease history or concurrent condition and summary on advice, caution to be considered, and recommendation on treatment selection or initiation is simplified as in Table 4. Biologic therapy is large molecular protein structures that can provoke the development of antidrug antibodies (ADAbs) which associated to immunogenicity that can cause loss of response or reduced efficacy of the biologic treatment. Immunogenicity is the development of unwanted immune response against foreign protein introduced to the body system [43,53]. Studies have demonstrated that comedication of a biologic with MTX reduces immunogenicity. As an example, by concomitant MTX therapy in the treatment regimen of infliximab, it decreased the development of antibodies against infliximab which delayed reduction of serum infliximab concentrations as well as reducing the incidence of infusion reactions [54-56]. In a study among RA patient, the cumulative incidence of antibody formation was 6% and 12 patients treated with only adalimumab was found having antibody positive against adalimumab compared to patients with comedication with MTX. Similar to golimumab, without adding MTX to the treatment regimen, 30% reduction of golimumab serum concentration were found compared to patient received MTX combination with golimumab [57,58].

CONCLUSION

Emergence of new treatments in managing RA is evidently improved the patients' quality of life and reduced burden or social impact caused by the autoimmune disease. Selection of treatment either using the conventional or bDMARDs should be done appropriately to prevent further progression of bone destruction in patient, achieving remission state with tolerable side effects while on treatment. For long-term safety, risk-benefit evaluation should be done thoroughly before initiation of bDMARD, and frequent monitoring is compulsory to reduce risk of infection and malignancy during commencement of treatment with bDMARDs. In view of the development of immunogenicity or formation of antibodies while on bDMARDs that can cause loss of response or ineffectiveness of treatment, identifying the factors contributing this issue may assist in personalizing bDMARDs selection for each individual RA patient. Incorporating pharmacokinetic measurement of bDMARD trough levels and the ADAb level may suggest a clear treatment strategy or algorithm to overcome issues of bDMARDs non-responsiveness among affected primary and secondary non-responders' RA patients.

AUTHORS' CONTRIBUTION

Salmi Abdul Razak performed the literature search, synthesized the data, and prepared the manuscript. Assoc. Prof. Dr. Mohd Makmor Bakry and Dr. Adyani Md Redzuan contributed toward revising the article for intellectual content. The manuscript has been read and approved by all the authors.

CONFLICTS OF INTEREST

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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