Research article

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Arthrheuma Society of Kenya consensus report: Recommendations for the management of rheumatoid arthritis

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ABSTRACT

Objectives: This study aims to recommend Arthrheuma Society of Kenya (ARSK) proposed Rheumatoid Arthritis (RA) management and to compose a national expert opinion management of RA under guidance of current guidelines and implantation and dissemination of these international guidelines into our clinical practice.

Materials and methods: A scientific committee of nineteen experts consisting of nine rheumatologists, three rheumatology nurses and seven physicians was formed. The recommendations, systemic reviews, and meta-analysis including pharmacologic and non-pharmacologic treatment were scrutinized paying special attention with convenient key words. The draft ARSK recommendations for management of RA opinion whose roof consisted of international treatment recommendations, particularly the assessment of American College of Rheumatology (ACR)/ European League Against Rheumatism was composed. Assessment of level of agreement with opinions by task force members was established through the Delphi technique. Voting using a numerical rating scale assessed the strength of each recommendation.

Results: Panel comprised of six basic principles and recommendations including pharmacological and non-pharmacological methods. All of the recommendations had adequate strength.

Conclusion: ARSK expert opinion for the management of RA was developed based on scientific evidence. These recommendations will be updated regularly in accordance with current developments.

Key words: Arthrheuma Society of Kenya, Rheumatoid Arthritis, Management guidelines

1. INTRODUCTION

1.1 The Burden of Rheumatoid Arthritis

RA is the commonest inflammatory polyarthritis seen in clinical practice. Rheumatoid arthritis(RA) is an autoimmune disorder of unknown aetiology characterized by symmetric, erosive synovitis and, in some cases, extra-articular involvement[1]. Most patients experience a chronic fluctuating course of disease that, despite therapy, may result in progressive joint destruction, deformity, disability, and even premature death[2]. RA results in more than 9 million physician visits and more than 250,000 hospitalizations per year in the United States of America[3,4]. Disability from RA causes major economic loss and can have a profound impact on families globally. The prevalence of RA worldwide is 1% of the adult population[2]. This means that the average physician often develops little experience with its diagnosis or management. Despite this it is one of the leading causes of chronic morbidity in the developed world, but little is known about the disease burden in Africa. RA is often seen as a minor health problem and has been neglected in research and resource allocation throughout Africa despite emerging experience of severe morbidity and potentially fatal systemic manifestations in Africa as well as the rest of the world.

The long-term disabilities caused by RA can impact on quality of life, with loss of productivity due to damaged and deformed joints inhibiting fine movements of the hand[5]. This can lead to loss of career and income generation capacity, which is a particular problem in low income settings. For majority of the population, jobs in Kenya and Africa as a whole involve a level of manual labour. Due to scarcity of resources in Africa

the governments can afford only limited or no welfare support for disabled individuals[6]. Along with the increase in Non–Communicable Diseases (NCD) in developing countries, an increase in RA occurrence could stress medical services that are already struggling with a high burden of acute infectious illness to an extent that they may be unable to cope with the fast changing patterns of disease distribution seen in Africa today[7].

The importance of NCDs in low and middle income countries has recently been internationally recognized by the United Nations (UN) as a problem that perpetuates and drives poverty and is a "threat to human, social, and economic development"[8,9]. Not only does RA contribute significantly to this burden, but it also contributes by increasing the rate of cardiovascular disease, certain cancers, and possibly diabetes[10-14]. RA is also a cause of gender inequality as it predominantly affects woman[7]. The prevention and management of RA could help reduce other NCDs by reducing shared risk factors and prevalence of systemic manifestations[15]. Further, childhood onset arthritis (Juvenile Idiopathic Arthritis or JIA) may lead to great morbidity and disability causing lost school days, school dropouts, social and physical developmental delays due to failure to interact with peers and to participate in normal daily activities (Ref effects of JIA). RA (and JIA) is therefore a major threat to the attainment of sustainable development goals on alleviation of poverty, hunger, ensuring decent work and economic growth, ensuring good health and wellbeing, attaining quality education, and reducing gender and other inequalities (Ref SDPs).

1.2 Scope

These recommendations are aimed at all healthcare professionals managing RA, including rheumatologists, physicians, general practitioners, nurses and allied healthcare professionals. The ARTHRHEUMA Society of Kenya (ARHSK) adhered to the following ideologies when formulating these recommendations:

i. They are recommendations to be used by all healthcare professionals managing RA, including allied healthcare professionals, nurses, general practitioners, physicians and rheumatologists.
ii. They should be made in consultation with the stakeholders in the final consensus of the document.
iii. The guidelines should be based on scientific evidence or, if unavailable, expert consensus.
iv. These are recommendations and not a guideline. Management of RA is not cast in stone (and is subject for review in the near future) and failure to adhere to them is not incriminating or negligent. They represent what ARHSK, as a professional body, recommends and set a certain standard of care that should be aimed for, from the very basic management to the highly sophisticated. Should practitioners not be able to offer expertise where appropriate, they may consider referral to a center with appropriate expertise.
v. These recommendations should be disseminated widely throughout the country.
vi. Kenya is a multi-cultural society and thus a policy of generalizability does not apply for all practitioners and patients. These recommendations should provide a guide and insight to treating practitioners and stakeholders.
vii. There are limitations to all recommendations and they cannot cover all clinical problems. However, the recommendations should be detailed enough to cover common circumstances, yet be practical to be used by the reader. The treatment strategy is presented in the form of an algorithm (Figure 1),* and is accompanied by a more in depth discussion of key management principles. This algorithm provides a step-wise approach to treatment, to enable health authorities and practitioners to develop and support the most effective method of achieving and maintaining remission in RA patients in both public and private health sectors. The purpose is not to remove the physician's autonomy, and physicians must select the most appropriate therapeutic option, taking into consideration the patient's preferences.

1.3 Methods

For this guideline to be widely accepted, the following methodology has been followed. Evidence from the literature and from RA guidelines developed elsewhere in the world has been reviewed. A symposium was organized by the ARHSK for the pivotal stakeholders in the rheumatology field in Kenya where these recommendations were discussed and approved. Various stakeholders consulted included the Ministry of Health, pharmaceuticals, allied healthcare professionals, nurses, general practitioners, physicians, rheumatologists and patient representative bodies. The Kenya guidelines are borrowed from the ACR/EULAR and the South African rheumatoid arthritis guidelines. They have been modified to fit our local set up.

2. DIAGNOSTIC APPROACH TO POLYARTICULAR JOINT PAIN

2.1 Introduction

2.1.1 Definitions

- *Monoarticular*- affecting only one joint
- *Oligoarticular*- affecting two to four joints
- *Polyarticular*- affecting five or more joints
- *Athralgia*- joint pain with absence of swelling
- *Athritis*- inflammation of the tissues of the joint, often accompanied by pain and swelling
- *Synovitis*- inflammation of the synovial membrane lining the joint
- *Axial skeleton*- the bones that make up the vertebral column

- *Appendicular skeleton*- the bones of the limbs, including the pectoral and pelvic bones
- *Enthesitis*- inflammation the sites where tendons or ligaments insert into the bone
- *Symmetrical joint involvement* - a disease process that affects the same joints on both the right and left side of the body
- *Asymmetrical involvement*- a disease process that affects joints on the left and right in an non-uniform manner

Polyarticular joint pain (i.e. pain in more than four joints) poses a diagnostic challenge because of the many differential diagnosis. Because many rheumatologic laboratory tests lack the desired specificity, results should be interpreted in the clinical context and with caution. Tests with low specificity, such as those in arthritis panels, are frequently positive in the general population, for example rheumatoid factor. Thus some of these tests may be misleading. In the absence of definitive rheumatologic laboratory tests, the history and physical examination are key to the early diagnosis and treatment of conditions that cause polyarticular joint pain. Indeed, the differential diagnosis can be narrowed through investigation of six clinical factors: disease chronology, inflammation, distribution, extra articular manifestations, disease course, and patient demographics.

2.2 Clinical evaluation

2.2.1 Disease chronology

Acute polyarticular joint pain (pain that has been present for less than six weeks) may be the sign of a self-limited disorder or part of a chronic disease. Although chronic polyarticular arthritides more often develop insidiously, they can present abruptly. Thus, chronic conditions such as rheumatoid arthritis and systemic lupus erythematosus should be considered, at least initially, in patients who present with acute polyarticular joint pain[5-7]. To avoid treating a self-limited disorder with potentially toxic disease modifying agents, synovitis should be present for six weeks before rheumatoid arthritis is diagnosed. Viruses (e.g human parvovirus B19, hepatitis viruses), crystals, and serum sickness reactions are known causes of acute, self-limited polyarthritis[8]. Except for Neisseria gonorrhoeae, direct bacterial infections in joints seldom cause polyarthritis. Although typically oligoarticular, extra-articular bacterial infections may induce acute arthritis. It can also be seen as part of classic reactive arthritis, for example, associated with enteric infections (Salmonella, Shigella, Campylobacter, or Yersinia species) and urogenital infections (Chlamydia trachomatis). Early gout usually affects only one joint. However, gout should also be considered in patients with acute polyarticular arthritis, particularly older women who are taking diuretics and have hypertrophy and degenerative changes of the distal interphalangeal (DIP) joints (Heberden's nodes) and proximal interphalangeal (PIP) joints (Bouchard's nodes)[9].

2.2.2 Inflammation

Arthritis is joint pain with inflammation, whereas arthralgia is joint pain without inflammation. Inflammatory arthritides include

- Rheumatoid arthritis
- Infectious arthritis
- Systemic lupus erythematosus
- Gout, and
- Reactive arthritis.

The cardinal signs of inflammation include erythema, warmth, pain, and swelling. Patients with severe joint inflammation also may present with systemic symptoms of fatigue, weight loss, or fever[7].

Morning stiffness lasting longer than one hour suggests inflammatory rather than mechanical etiology[1]. Duration of morning stiffness gives a useful guide to assessing the extent of inflammation. For example, morning stiffness may last for hours in rheumatoid arthritis[10]. Palpation of multiple joints is important to look for soft tissue swelling and effusions that result in edema and influx of inflammatory cells into and around the synovium.

Palpation will help distinguish between soft tissue swelling and non-inflammatory bony hypertrophy, such as Heberden's and Bouchard's nodes, which often indicate osteoarthritis. Presence of crepitus is an indication of irregularities of the articular cartilage. This is commonly associated with osteoarthritis, injury, or previous inflammation. Because findings can be subtle, it is important to palpate each joint.

2.2.3 Distribution

2.2.3.1 Pattern

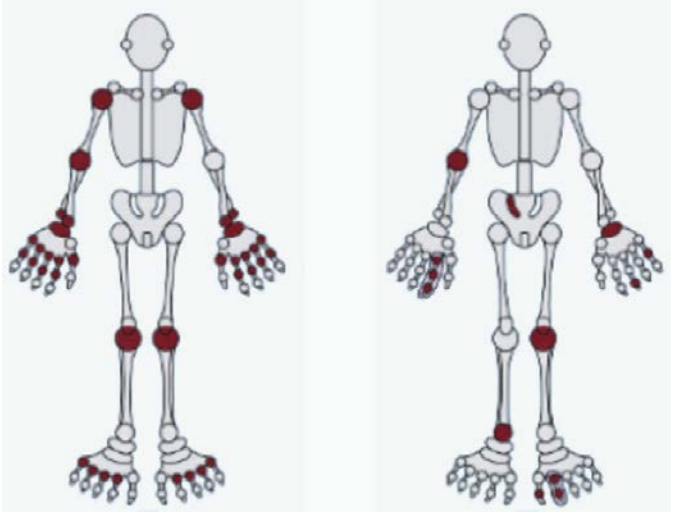
The pattern of joint involvement can help provide diagnostic clues[16].

- Rheumatoid arthritis of the hand most often affects the PIP and MCP joints, but not the DIP joints as this joint has no synovium.
- Osteoarthritis of the hand usually involves the DIP and PIP joints and not the metacarpophalangeal (MCP) joints[4,16]. Osteoarthritis tends to spare wrists, elbows, and ankles. These large joints are affected if there is a history of trauma, inflammation, or a metabolic disorder such as hemochromatosis psoriatic arthritis, crystal induced arthritis, and sarcoidosis may affect all of these joints.
- Spondyloarthropathies typically affect the joints of the spinal column, sacroiliac and larger joints of the lower extremities. They also have extra articular features like enthesitis, anterior uveitis, enteropathy, aortic regurgitation, heart blocks etc.

2.2.3.2 Symmetry

Joint involvement is more symmetric when systemic diseases are involved such as rheumatoid arthritis, systemic lupus erythematosus, viral arthritides, polymyalgia rheumatica and serum sickness reactions. Asymmetric peripheral involvement is seen more with reactive arthritis, psoriatic arthritis and gout[1,17,18].

Figure 1: Symmetrical and asymmetrical disease



a. Symmetrical joint. Involvement

b. Asymmetrical joint Involvement

Systemic	Lymphatics
• Fever	• Felty's syndrome
• Weight loss fatigue	• Splenomegally
• Susceptibility to infections	

Musculoskeletal	Occula
• Muscle wasting	•Keratoconjunctivitis Episcleritis
• Tenosinovitis	• Scleritis
• Bursitis	• Scleromalacia
	• Osteoporosis

Haematological	Pulmonary
• Anaemia	• Eosinophillia
• Thrombocytosis	• Nodules
• Lung fibrosis	• Pleural effusions

Cardiovascular	Other
• Myocardial infarction	• Rheumatoid nodules
• Asymptomatic IHD	• Sinuses
	• Fistulae
	• Peripheral neuropathy (mononeuritis multiplex)

2.2.4 Disease Course

2.2.41 Intermittent Arthritis

A patient presenting with symptoms for a short duration (a few days to a month) which resolve completely before presenting again, crystal-induced arthritis (e.g., gout, pseudogout) is the likely diagnosis. Arthrocentesis should be considered during a symptomatic flare to aide in diagnosis[9,19].

2.2.4.2 Migratory Arthritis

Migratory arthritis is characterized by rapid onset of swelling in one or two joints, with resolution over a few days. As the symptoms resolve, similar symptoms emerge in another joint, usually in an asymmetric location[17]. This pattern is commonly seen in rheumatic fever, gonococcal arthritis, systemic lupus erythematosus, sarcoidosis etc.[20].

2.3 LABORATORY INVESTIGATIONS

Many of the rheumatologic laboratory tests must be interpreted in the context of the individual patient. This should not substitute a good history and examination, but should augment in clinching the final diagnosis.

For example, rheumatoid factor testing lacks both sensitivity and specificity: the test is positive in 5 to 10% of the general population and negative in approximately 20% of persons with rheumatoid arthritis[4,16]. Therefore, both positive and negative rheumatoid factor test results must be interpreted cautiously. Rheumatoid factor testing is not useful when a patient lacks other diagnostic criteria for rheumatoid arthritis especially synovitis and should not be used as a screening tool. The CCP (cyclic citrullinated peptide) antibody is an autoantibody against citrullinated proteins (ACPA). The anti-CCP test is able to detect the autoantibodies against citrullinated proteins which have a relatively high sensitivity (reportedly between 50 and 75%) for rheumatoid arthritis and extremely high specificity (about 90%) for rheumatoid arthritis. Its high specificity is why the anti-CCP test has become an important part of the diagnostic process for rheumatoid arthritis[4,16]. The American Rheumatology Association's revised diagnostic criteria for rheumatoid arthritis use findings from the history, physical examination, and laboratory tests[4]. These criteria, which have been shown to be 91 to 94% sensitive and 89% specific, are useful for establishing a diagnosis of rheumatoid arthritis[4, 16].

Another example is antinuclear antibody (ANA) tests which are positive in 5 to 10% of the general population, a rate that increases with age. Positive ANA test results must be interpreted with caution[4-6]. Given the high sensitivity of the currently used substrate for testing, a negative ANA test essentially rules out systemic lupus erythematosus[1, 5].

A complete blood count, urinalysis, and ESR and CRP may provide more useful diagnostic clues than classic rheumatologic laboratory tests. For example, hematuria, proteinuria, a low white blood cell (WBC) count, and thrombocytopenia may indicate the presence of systemic lupus erythematosus.

Synovial fluid analysis is performed primarily to diagnose infection or a crystal-induced arthritis. A synovial fluid WBC count of at least 2,000 per mm^3 (2 $x10^9$ per L) suggests inflammation, whereas a count higher than 50,000 per mm^3 (50$x10^9$ per L) typically indicates synovial infection[9]. Fluid with a highly-elevated WBC count or a predominance of neutrophils should

be cultured to exclude infection. These features are summarized in Table 2.

	Normal	Non-inflammatory	Inflammatory	Septic	Haemorrhagic
Clarity	Transparent	Transparent	Translucent	Opaque	Bloody
Colour	Clear	Yellow	Yellow	Yellow/ dirty	Red
Viscosity	High	High	Low	Variable	Variable
WBC/ mm^3	<200	200-2,000	2,000-10,000 upto 100,000	>80,000	<200
PMNs%	<25	<25	>50	>75	50-75

Source: Agudelo CA, Wise CM: diagnosis, pathogenesis and clinical manifestations

2.4 DIAGNOSTIC IMAGING

The role of imaging in rheumatology includes diagnosis, monitoring treatment and prognostication purposes. A number of radiographic findings are characteristic of specific rheumatic disorders.

For instance:

- Sacroiliitis is indicative of ankylosing spondylitis,
- Erosions with periarticular osteopenia are typical of rheumatoid arthritis, and
- "pencil-in-cup" deformities are a sign of psoriatic arthritis.

However, these radiographic findings take months to develop; and are therefore not mandatory requirements for diagnosis of RA especially in early disease. Early in the process, radiographs may be normal or show only nonspecific changes. In early rheumatoid arthritis, magnetic resonance imaging demonstrates cartilage damage that is not evident on plain-film radiographs[18]. This damage highlights the importance of diagnosing rheumatoid arthritis early on the basis of the history and physical examination so that disease-modifying treatment can be initiated.

Joint ultrasonography is a new inexpensive imaging modality that has been approved for various indications from diagnosis to monitoring effect of treatment by ACR/ EULAR. The ARHSK also recommends its use in rheumatology.

Table 3: Differential diagnosis of Arthritis

Category	Examples
Infections	Viral (dengue, HIV, chikungunya, Hepatitis viruses, cytomegalovirus). Bacterial (Neisseria gonorrhoeae, Staphylococcus aureus) Other: Mycobacterial and fungal infections.
Spondyloarthrites	Reactive arthritis (Chlamydia, Salmonella, Shigella, Yersinia). Psoriatic arthritis, ankylosing spondylitis, enteropathic arthropathies.
Systemic rheumatic diseases	Systemic lupus erythematosus (SLE), Polymyositis, Dermatomyositis, Sjogren's syndrome, Behcet's syndrome, Polymyalgia rheumatic, systemic sclerosis, systemic vasculitides.
Microcrystal arthritides	Gout, Calcium pyrophosphate crystal deposition disease.
Endocrine disorders	Hyperthyroidism, hypothyroidism.
Neoplastic disease	Metastatic neoplastic diseases, leukemias, lymphomas, paraneoplastic syndromes.
Others	Osteoarthritis, sarcoidosis, haemochromatosis, amyloidosis, serum disease, angioedema.

Figure 2: Dactylitis, or "sausage digit," is seen in the toes of a child with psoriatic juvenile idiopathic arthritis

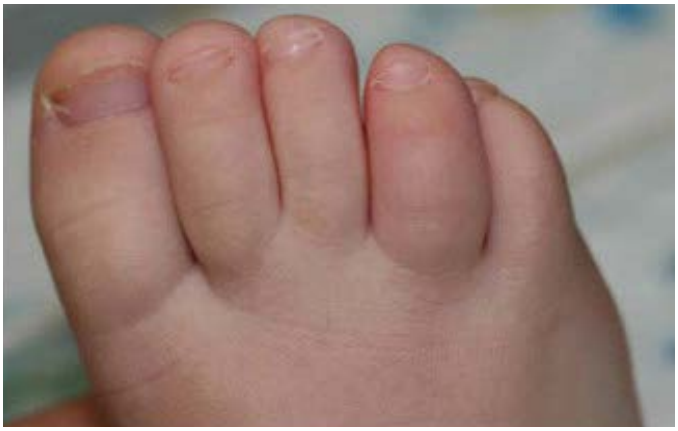
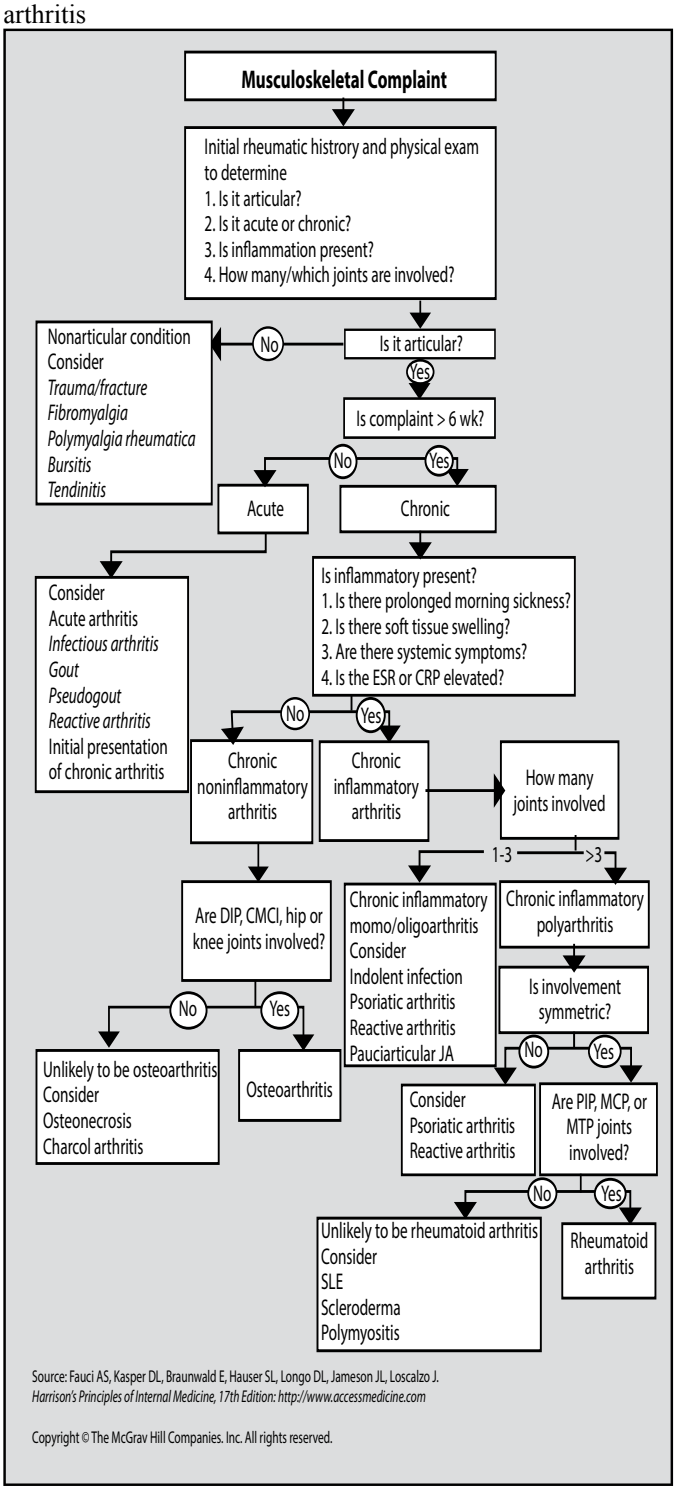


Figure 3: Summary of diagnostic approach to poly articular arthritis



3. DIAGNOSIS OF RA

3.1 Early diagnosis of RA

RA is an autoimmune disease that primarily affects the small joints of the hand, wrist, and feet. If left untreated, it can lead to extensive erosion of the cartilage, causing deformity and disability[6]. Common symptoms include joint pain and stiffness. When prolonged the disease is associated with psychological problems such as depression[6-7]. The cause of onset is currently unknown, but a genetic susceptibility to an environmental trigger seems the most plausible aetiology[21]. Various bacteria and viruses have been suggested as the initial trigger; with a form of molecular mimicry imitating human antigens activating an immune response against the host's own cells.

RA not only affects small joints but is also associated with significant extra–articular manifestations and mortality. Extra-articular manifestations affect the skin, respiratory, cardiac and visual systems[10]. Specific manifestations may include: lymphadenopathy, rheumatoid nodules, peripheral neuropathy, pleural and pericardial effusions, fibrosing alveolitis, obliterative bronchiolitis, splenomegaly, vasculitis and Raynaud's phenomenon. Since RA is an autoimmune disease, it can affect any part of the body, especially those that depend on small vessel beds or extensive nerve systems. This can contribute to the development of a whole plethora of life threating conditions[10].

The ultimate goals in managing RA are to prevent or control joint damage, prevent loss of function, and decrease pain. Table 4 summarizes the approach to the diagnosis of RA. The initial steps in the management of RA are to establish the diagnosis, perform a baseline evaluation (Figure 4), and estimate the prognosis. An evaluation by a rheumatologist is strongly recommended if the primary care provider is uncertain about any of these initial steps.

3.2 Diagnostic criteria for RA

The ACR and EULAR installed a joint working group that developed, in three phases, a new approach to classifying RA in this era of early arthritis clinics. The group focused on patients newly presenting with undifferentiated inflammatory synovitis. The Kenya guidelines are adopted from the ACR/EULAR guidelines (Table 4).

To be classified as 'definite RA' requires the confirmed presence of synovitis in at least one joint, the absence of an alternative diagnosis for the observed arthritis, and a total score of at least 6 from the individual scores in the four domains: number and site of involved joints (range 0–5), serological abnormalities (range 0–3), elevated acute-phase response (range 0–1), and symptom duration (range 0–1). Once a diagnosis of RA has been made, a comprehensive assessment and documentation on involvement of all joints is required. Figure 4 shows the homonymous suggested for documentation of joint involvement to aid in disease activity assessment.

Adopted from: The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for RA (*Ann Rheum Dis.* 2010 Sep; **69**(9):1580-8).

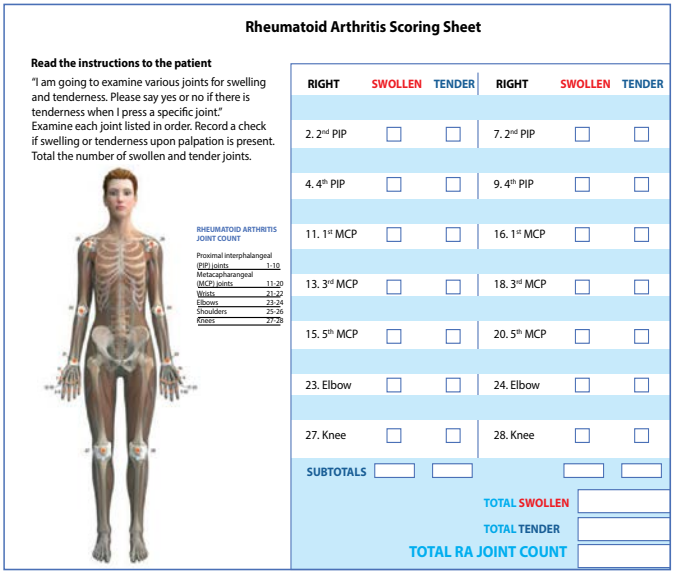
Table 4: Classification criteria for RA in newly presenting patients

Target population: Patients who have at least one joint with definite clinical synovitis and whose synovitis is not better explained by another disease.

Using the score based algorithm below, add the scores from A to D; a score of 6 or more is required for classification as RA.

Domain	Score
A. Duration of symptoms .	
Less than 6 weeks	0
6 weeks or longer	1
B. Joint involvement.	
1 large joint	0
2-10 large joints	1
1-3 small joints	2
4-10 small joints	3
More than 10 joints (at least 1 small)	
C. Acute phase reactants (at least 1 test result needed for classification)	
Normal ESR and CRP	0
Abnormal ESR or CRP	1
D. Serology (at least 1 test result needed for classification).	
Negative RF and ACCP	0
Low positive RF or ACCP	2
High positive RF or ACCP	3
Abbreviations: ACPA: Anti-citrullinated peptide antibodies; CRP: C-Reactive proteins; ESR: Erythrocyte sedimentation rate; RF: Rheumatoid factor. Definition of terms: Large joints refers to shoulders, elbows, hips, knees and ankles. Small joints refers to metacarpophalangeal joints, proximal interphalangeal joints, second to fifth metatarsophalangeal joints, thumb interphalangeal joints and wrists. Synovitis clinically refers to swelling; or pain and limitation of movement of joints. Serological abnormalities: RF and ACPA both are sensitive for the diagnosis. ACPA is more specific, RF more sensitive but has many false positives. Acute phase reactants include ESR and CRP.	

Figure 4: Rheumatoid Arthritis Scoring Sheet (Adopted image from physicianspractice.com)



To perform a standardized joint count for RA, record joint tenderness and swelling results on a scoring sheet. For each joint, enter a tick mark for each yes response for swelling or tenderness on palpation. Calculate number of tender and swollen joints separately and add them to determine the total score for RA joint count.

4.0 RECOMMENDATIONS BY THE ARTHRHEUMA SOCIETY OF KENYA ON THE TREATMENT OF RA

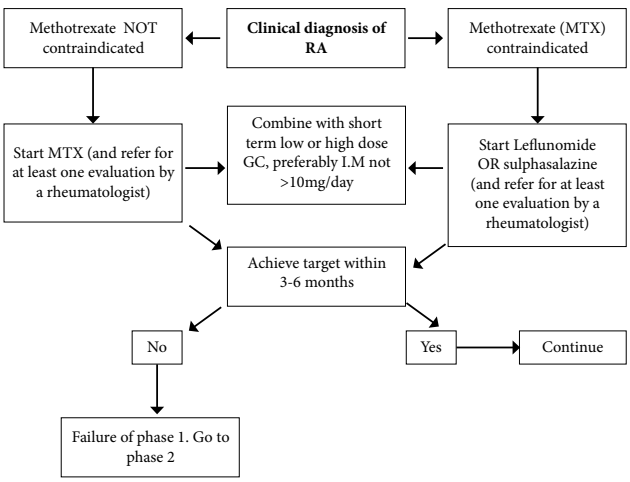
Table 5: Recommendations for RA treatment

	PRINCIPLES OF MANAGEMENT
A.	Treatment of RA patients should aim at the best care and must be based on a shared decision between the patient and the rheumatologist
B.	Rheumatologists are the specialists who should primarily care for RA patients
C.	RA incurs high individual, societal and medical costs, all of which should be considered in its management by the treating rheumatologist
D.	Patient education should form an integral part of the management of rheumatoid arthritis
	RECOMMENDATIONS
	Therapy with DMARDs should be started as soon as the diagnosis of RA is made
	Treatment should be aimed at reaching a target of remission or low disease activity in every patient
	Monitoring should be frequent in active disease (every 1–3 months); if there is no improvement by at most 3 months after the start of treatment or the target has not been reached by 6 months, therapy should be adjusted. Disease activity monitoring includes use of the CDAI, SDAI or DAS28 scores. Laboratory monitoring involves assessment of disease activity, adverse drug events and comorbidities.
	MTX should be part of the first treatment strategy in patients with active RA. If oral MTX is not tolerated, subcutaneous should be considered.
	In cases of MTX contraindications (or early intolerance), sulfasalazine or leflunomide should be considered as part of the (first) treatment strategy
	In DMARD-naïve patients, irrespective of the addition of glucocorticoids, csDMARD monotherapy or combination therapy of csDMARDs should be used
	One off intra-muscular depo steroid injection can be used as initial treatment. Short term low-dose glucocorticoids should also be considered as part of the initial treatment strategy (in combination with one or more csDMARDs) for up to 6 months, but should be tapered as rapidly as clinically feasible
	NSAIDs should be used for pain management as required, provided there are no contra-indications.
	Biologics should be considered as equal options for when using bDMARDs.
	If the treatment target is not achieved with the first DMARD strategy, in the absence of poor prognostic factors, addition of another csDMARD strategy should be considered. The doses of the csDMARDS should be incremental, until the desired clinical control is achieved. When poor prognostic factors are present, addition of a bDMARD should be considered. The threshold for considering bDMARD should be after at least 6 months of therapy with appropriate doses of combination csDMARD
	In patients responding insufficiently to MTX and/ or other csDMARD strategies, with or without glucocorticoids, bDMARDs (TNF inhibitors*, abatacept or tocilizumab, and, under certain circumstances, rituximab†) should be commenced with MTX
	If a first biologic DMARD has failed, patients should be treated with different bDMARD; if a first TNF inhibitor therapy has failed, patients may receive another TNF inhibitor* or a biological agent with a different mode of action
	If a patient is in persistent remission after having tapered glucocorticoids, one can consider tapering‡ bDMARDs§, especially if this treatment is combined with a csDMARD
	In cases of sustained long-term remission, cautious reduction of the csDMARD dose could be considered, as a shared decision between patient and physician
	When therapy needs to be adjusted, factors apart from disease activity, such as progression of structural damage, comorbidities and safety issues, should be taken into account

- *TNF inhibitors: adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, biosimilars (as approved according to a thorough approval process, such as by EMA and/or FDA).
- †The 'certain circumstances', which include history of lymphoma or a demyelinating disease, are detailed in the accompanying text.
- ‡Tapering is seen as either dose reduction or prolongation of intervals between applications.
- §Most data are available for TNF inhibitors, but it is assumed that dose reduction or interval expansion is also pertinent to biological agents with another mode of action.

Abbreviations: DMARD, disease-modifying antirheumatic drug; cs DMARDS- conventional DMARD; bDMARD- biologic DMARD ; EMA, European Medical Agency; EULAR, European League against Rheumatism; FDA, Food and Drug Administration; MTX, methotrexate; RA, rheumatoid arthritis; TNF, tumour necrosis factor

Figure 5a: Flow chart on RA treatment – phase 1



Methotraxate contraindications: pregnancy, lactation, severe liver disease, severe kidney disease, lung fibrosis, severe anaemia, thrombocytopenia, leukopenia, severe infections and known hypersensitivity to methotrexate.

Figure 5b: Flow chart on RA treatment – phase 2 & 3

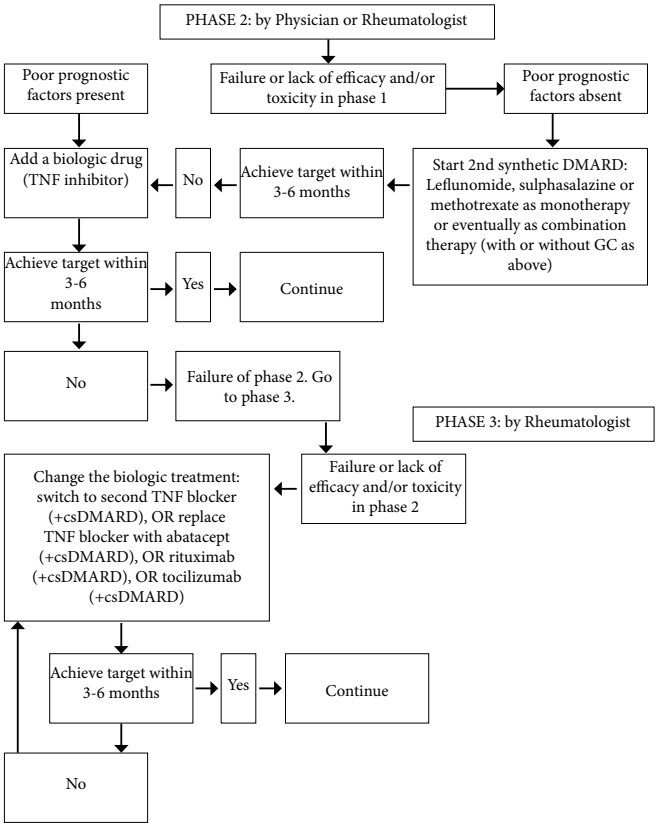


Table 5: List of conventional DMARDS used in RA

Drug	Indication	Dose	Side effect	Monitoring	Contra-indications
MTX	First choice DMARD as monotherapy or combination therapy	7.5-25mg weekly orally or subcutaneously.	Common: nausea, vomiting, mucositis, alopecia, elevated liver enzymes, neutropaenia, anaemia.	Baseline CXR, Full blood count and liver transaminases within the first month of starting treatment and thereafter every 3-6 months.	Pregnancy, breast-feeding, alcoholism, liver disorders, renal disorders, bone marrow suppression, interstitial lung disease.
	Co-prescribed with biologics	Co-prescribed with folic acid 5-10mg weekly 24 hours after MTX	Less frequent: pneumonitis, teratogenic.		Caution in HIV-positive patients.
HCQ	Mild RA or part of combination therapy.	4mg/kg/day (generally 200mg 3-5 times per week) orally	Common: gastrointestinal intolerance, skin hyperpigmentation, headaches, dizziness Less frequent: Retinopathy and myopathy.		
SSZ	Monotherapy if MTX contraindicated or not tolerated; or combination therapy.	1-3g/day orally.	Common: GI intolerance (anorexia, nausea, vomiting); skin rash, elevated liver enzymes, myelosuppression.	Full blood count and liver transaminases within the first month of starting treatment and thereafter every 3-6 months.	
Leflunomide	Monotherapy or in combination with MTX.	20mg daily BUT 20mg alternate day can be used	Nausea, vomiting, abdominal pain, diarrhea, alopecia, elevated liver enzymes, skin rash.	Full blood count and liver transaminases within the first month of starting treatment and thereafter every 3-6 months.	Pregnancy and breastfeeding; suspension recommended at least 2 years before possible pregnancy; alternatively cholestyramine wash out.
			Teratogenic in both males and females.		Appropriate contraception is indicated.

DMARDs: Disease modifying antirheumatic drugs; CXR: Chest Xray; HCQ: Hydroxychloroquine *MTX:* Methotrexate; RA: Rheumatoid arthritis; SSZ: Sulphasalazine.

Table 6: Biologic DMARDS in RA
(Biologics should be handled at the physician/rheumatologist level)

Newer TNF-Inhibitors			
Certolizub	40mg SC week 0, 2, 4 then every 4 weeks.	Pegilated Fab fragment of humanized anti-TNF monoclonal antibody	Pyrexia, fatigue, back pain, arthralgia, serious infections, seizures, aplastic anaemia, photosensitivity, optic neuritis, demyelinating CNS disease, lupus, bronchitis, dizziness, sinusitis, elevated liver enzymes, psoriasis exacerbation.
Golimumab	50mg SC every month.	Fully human anti-TNF IgG monoclonal antibody.	
B-cell agents			
Rituximab	100mg IV every 2 weeks X 2 doses.	Chimeric anti-CD20 monoclonal antibody	Fevers and rigors within 2 hours of therapy, rash, pruritus, dyspnea, bronchospasm, flushing, angioedema, hypotension. Less common: Thrombocytopaenia, leucopaenia, neutropaenia, anaemia, exacerbation of angina, heart failure. Rare: Mucocutaneous reactions.
T-Cell action			
Abatacept	Dosed on body weight starting 500mg (<60kg) to 1000mg (>100kg) IV week 0, 2, 4 then every 4 weeks.	Fusion protein with an extracellular domain of human cytotoxic T-lymhocyte associated antigen and modified Fc domain of human IgG1	Haedache, nasopharyngitis, nausea, dizziness, cough, hypertension, dyspepsia, UTI, diarrhea, pyrexia, abdominal rash, extremity pain, serious infections. More serious: LS, Pneumonia, cellulitis, acute pyelonephritis; anaphylactic and hypersensitivity reactions.
IL-6 Inhibitor			
Tocilizumab	4mg/kg IV every 4 weeks; increase to 8mg/kg	Humanized anti-IL-6 monoclonal antibody	Same as abatacept; as well as GI perforation, neutropaenia, demyelinating CNS disease, elevated liver enzymes.

CHF: Congestive heart failure; CNS: Central nervous system; DMARDs: Disease modifying antirheumatic drugs; GI: Gastrointestinal;
IgG: Immunoglobulin G; IL-6: Interleukin 6; MS: Multiple sclerosis; RA: Rheumatoid arthritis; UTI: Urine tract infection.

5. THERAPY IN RA

5.1 Synthetic DMARDs

Methotrexate (MTX) has been the most widely used DMARD and is recommended as first-line therapy in doses starting at 7.5 - 15 mg weekly. Depending on response and tolerance can be increased to a maximum of 25 mg weekly. The drug few side effects apart from mild elevation of liver enzymes, this is usually transient. It rarely is a cause of cirrhosis[22,23]. Another DMARD that can be prescribed as mono or dual therapy with MTX is leflunomide. A summary of the doses, major side-effects and recommendations for monitoring patients is presented in Table 4. The new recommendations for patients who have failed MTX monotherapy are to be treated with combination synthetic DMARDs. Hydroxychloroquine (HCQOS) is to be used in combination with MTX for moderate to severe disease. Sulphasalazine (SSZ) is

effective as monotherapy, and is particularly useful in patients in whom MTX is contraindicated, or as part of combination DMARD therapy [23].

5.2 Glucocorticoids

Glucocorticoids (GCs) rapidly reduce symptoms of RA and may inhibit development of erosions, particularly in early RA and act as a bridge when used in combination with DMARDs[23]. They may not be used as monotherapy as the side effect profile may limit their long-term use. However, they may be used in low doses as "bridge therapy" when initiating DMARDS in early RA. This is because most of the DMARDS have a long onset of action. Low-doses of oral prednisone (≤10 mg/day) are recommended[24,25]. Intra-articular GCs are useful for a mono- or oligo-articular flare of disease. Long-acting intramuscular methylprednisolone may be used as an alternative to oral prednisone.

5.3 Biologic DMARDs

The introduction of biologics has transformed the management of RA in recent years. Biologic DMARDs are proteins directed towards specific cytokines or their cell receptors. They are classified into two according to mode of action, those inhibiting tumour necrosis factor (TNF) (i.e anti-TNF), and those targeting other cytokines or cells (non-anti-TNF). The benefits of Biologic DMARDs include suppression of joint inflammation, prevention of radiographic progression, and improvement of physical function and health-related quality of life[26]. The ACR, EULAR and ARHSK have developed recommendations for the use of these agents[23,26,27]. Research has shown the work better when co prescribed with MTX as it improved efficacy and reduce production of antibodies. There is no benefit of co-prescription/ combined use of biologic DMARDs. Table 5 summarizes the biologics currently available and provides details of dose and administration. Biologic DMARDs should be initiated by a rheumatologist, and information about patients on biologic therapy entered into an ARHSK biologics registry.

5.4 Timing and choice of biologic therapy

ARHSK recommends commencement of biologic therapy after a 6-month trial of at least three synthetic DMARDs (including MTX, unless contraindicated)[28]. Indications for biologic therapy include an inadequate response to synthetic DMARD therapy, with high disease activity (SDAI >26), or moderate disease activity (SDAI 11 - 26) in the presence of poor prognostic factors (seropositivity, radiographic erosions within the first two years, extraarticular complications or functional disability). The efficacy of all currently available biologic drugs has been confirmed by clinical trials and by clinical experience, and the choice of drug depends on the safety profile and on the patient's preferred route of administration.

At present, the optimal sequence of biologics remains unclear. In future, biomarkers may assist in identifying the most appropriate biologic agent for an individual patient. In cases where biologic DMARD that has not brought an adequate clinical response after 6 months of treatment should be withdrawn and another biologic DMARD should be prescribed[29].

5.5 Analgesics and anti-inflammatory drugs

Analgesics are used in management of RA for pain control. The most effective being the Nonsteroidal anti-inflammatory drugs (NSAIDs). Their long-term use is associated with adverse reactions. Some of the side effects include NSAID-induced gastrointestinal tract events. Risk factors for this include age higher than 60 years, co-prescription with corticosteroids and aspirin. To mitigate this effect its recommended to co-administration with a proton pump inhibitor[30]. NSAIDs are associated with increased risk of thrombotic events and should be used with caution in patients with cardiovascular risk factors. They are also known to cause hypertension, renal and liver dysfunction. Ideally, NSAIDs should be used in the lowest effective dose and for the shortest duration of time and withdrawn if possible once disease activity is controlled with DMARDs[30].

5.6 Extra-articular disease

Moderate to high-dose GCs, possibly combined with other immunosuppressant drugs, are used in severe extra-articular disease including serositis, vasculitis and scleritis.

5.7 Multidisciplinary team

Management of a RA patient should occupational therapist, podiatrist, physiotherapist, clinical psychologist and social worker. There is an increasing role for a rheumatology nurse as they provide patient education and support, with positive effects on adherence to therapy and on health-related quality of life. They also advise on RA healthy lifestyle that has regular exercise, loss of weight if overweight, and discontinuation of smoking. Cigarette smoking has been associated with higher disease activity and more severe joint disease. With improved RA care, there is a declining need for joint replacements and other surgical interventions[31]. However, referral to orthopedic team should be done where appropriate.

6. COMPLICATIONS AND SAFETY ISSUES

6.1 TB

Kenya has a high tuberculous disease burden. The risk of TB is higher in RA as compared to the normal population. This partly due to the disease itself and also the drugs used to treat RA including GCs, MTX and biologic drugs, in particular anti-TNF therapy[32]. This is in part due to the pro-inflammatory cytokine TNF which helps contain mycobacterial infection in granulomas. Its inhibition may lead to reactivation of latent TB, or possibly to new TB infection within 3-6 months of initiation of anti-TNF therapy[33]. The presentation may be atypical, with over half of cases reported as extra-pulmonary, and a high proportion of disseminated TB. Before initiation of anti-TNF therapy its recommended to screen for latent TB infection (LTBI), and an assessment of the risk of TB infection/ reactivation (risk stratification)[34].

6.1.1 Screening for LTBI

The efficacy of screening for and treatment of LTBI before initiation of anti-TNF therapy has been well demonstrated, but the most appropriate test to detect LTBI is uncertain[35,36]. In a high prevalence setting such as Kenya, there is no reliable test for LTBI. The tuberculin skin test (TST) has traditionally been the primary tool for identifying LTBI, but limitations include false-negative results in immunocompromised patients (for example patients on immunosuppressive drugs such as MTX or corticosteroids and a false-positive test after BCG vaccination at birth. Other drawbacks with the TST are the logistics of return visits for evaluation, and variations in administration and interpretation of the test. Despite this, detection of LTBI by TST (defined as induration ≥5 mm) is highly effective. Recently, interferon (IFN)-γ release assays (IGRAs), which measure IFN-γ response to TB-specific antigens, have been introduced. While excellent performance and good cost effectiveness of these tests have been reported a negative IGRA does not exclude LTBI. Currently, there is little consensus on the most appropriate screening test in high-prevalence settings[36,37]. The risk of developing active TB in RA patients treated with biologic DMARDs appears to depend on the background prevalence of LTBI. Established risk factors associated with LTBI include, residence or travel in a TB-endemic area, older age, high-risk occupation (healthcare or institution worker), previous TB infection, Felty's syndrome and low socio-economic status[38,39]. Concomitant corticosteroid use and monoclonal rather than soluble anti-TNF drugs has been shown to confer a higher risk for TB[35,40].

Recommendations

1. Work up for a patient due for biologic therapy should include TST, an IGRA test (if deemed appropriate by the clinician), and a CXR.
2. An abnormal CXR suggesting active pulmonary TB clearly needs investigation, and treatment for the patient.
3. A patient with a positive TST, and a normal CXR, should be given anti-TB chemoprophylaxis. Data from studies in HIV-positive patients, chemoprophylaxis may be either isoniazid (INH) for 9 months, or rifampicin combined with INH for 3 months[41].
4. The consensus is that anti-TNF therapy can be initiated after completion of a minimum of 1 month of chemoprophylaxis.
5. Patients who are at very high risk of LTBI and who require biologic therapy need can be considered INH prophylaxis of 9months or longer regardless of TST/ IGRA result. This stratification is left to the physician's discretion, but would include healthcare workers, inmates or employees at institutions, patients who have had previous TB or who have a poor socio-economic background[42]. Despite concerns of INH toxicity and of propagating INH-resistant TB, this strategy may be valid in high-risk settings such as Kenya.
6. Non-anti-TNF drugs may be the safest choice of first-line biologic therapy in high risk LTB patients. This is the current practice has been shown to be effective in high-risk patients in Germany, Algeria and Morocco[43,44].

6.1.2 Other infections

There is an increased risk of infection amongst RA patients, particularly in patients treated with biologic therapy[45]. These include serious bacterial infections, as well as opportunistic fungal (histoplasmosis in particular), Listeria, non-tuberculous mycobacterial infections and varicella zoster infection.

Recommendations

1. Biologic drugs should be used with caution in patients with chronic infected leg ulcers, septic arthritis in the preceding 12 months, septic arthritis of prosthetic joints, recurrent urinary or respiratory tract infections, an indwelling urinary catheter, or hypogammaglobulinaemia.
2. Administration of a biologic drug should be delayed in the presence of active infection
3. MTX can be continued in patients undergoing joint replacement surgery as it does not increase the risk of sepsis or peri-operative complications[46].

4. It is recommended that patients using biologic DMARDs be discontinued prior to surgery for a period of 3 - 5 times the half-life of the drug, and resumed after good wound healing. They also carry a small risk of peri-operative infections.
5. Where possible, patients for biologics should be vaccinated before biologic therapy.

6.2 HIV infection

HIV has both diagnostic and therapeutic implications for the management of patients with concomitant inflammatory arthritis[47]. HIV infection can cause, among other musculoskeletal syndromes, inflammatory polyarthritis mimicking RA. There are several challenges in the management of RA patients who are HIV positive. Information on the safety of using immunosuppressive drugs in an HIV positive patient is limited. MTX and biologic drugs place patients at risk of opportunistic infections, and there is concern of added immunosuppression if prescribed in an HIV positive patient[48]. There are also difficulties in the assessment of disease activity in HIV positive patients due to the nonspecific increase in erythrocyte sedimentation rate (ESR) associated with HIV infection[49]. Little is known about the effect of antiretroviral therapy (ART) on RA disease, or the safety of biologic drugs in patients receiving ART. These are areas for future research.

Recommendations

1. HIV test should be offered to all patients according to the Kenya national guidelines. All HIV infected patients should be initiated on anti-retroviral therapy as per the current national guidelines.
2. MTX and biologic drugs should be used with caution in patients at risk of opportunistic infections (CD4 below 200 cells/mm^3). HCQS and SSZ may be considered as first line DMARDs in such patients.
3. Close monitoring and a multi-disciplinary approach are recommended for drug interactions and adverse events.

6.4 Viral hepatitis

Hepatitis B reactivation can occur in hepatitis B surface antigen (HBsAg)- positive patients treated with MTX or biologic therapy (particularly rituximab).

Recommendations

1. Screening for viral hepatitis should take place before starting treatment in high risk patients is recommended[50].
2. Hepatitis B vaccination should ideally be offered to non-immune patients before commencing DMARD treatment.
3. In Hepatitis C-infected patients, anti-TNF therapy and rituximab is considered safe, and possibly beneficial[51].

6.5 Recommendations on vaccination

1. Patients with RA should receive killed vaccines based on age and risk, ideally at least 14 days before commencing DMARD or biologic therapy for optimal efficacy. These might include influenza, pneumococcal, hepatitis B and human papillomavirus vaccines.
2. Live vaccines including herpes zoster and yellow fever vaccines are not recommended in RA patients on MTX or biologic therapy. It may, however, be appropriate to vaccinate a patient likely to travel to a high-risk yellow fever area, prior to commencing biologic therapy.

6.6 Cardiovascular events

RA patients have a similar cardiovascular risk profile as diabetic patients. This is due to the combination of systemic inflammation and traditional cardiovascular risk factors. The risk is higher in RA patients who are seropositive, have extra-articular or established (≥10-year disease duration), high disease activity, extra-articular disease, physical inactivity and corticosteroid use[52]. Traditional risk factors including smoking, hypertension, diabetes mellitus, and dyslipidaemia (most importantly low levels of high-density lipoprotein (HDL) cholesterol and resultant high total cholesterol to HDL ratio) need to be addressed[52]. Improved disease control with therapy, such as MTX and anti-TNF therapy, has been shown to decrease cardiovascular risk in RA patients[53].

6.7 Osteoporosis

One of the complications of long standing RA is osteoporosis. The pathogenesis is thought to be multi factorial. In early disease its more of the pro-inflammatory cytokines that act locally leading to localized, or juxta-articular, osteoporosis. There is paucity of data on whether biologic DMARDs are capable of retarding or reversing bone loss in RA. More data will be required. Other risk factors include combination of immobilization, age, menopause, GC therapy and inflammation due to RA. Control of joint inflammation with DMARD therapy will help to maintain the bone density by improving physical activity.

Recommendations

1. The ACR guidelines for the treatment of GC induced osteoporosis be used[54].

2. Calcium and vitamin D supplementations are recommended for routine use in all patients likely to receive GC therapy for longer than 6 months, irrespective of dose.

6.8 Malignancy

Patients with RA are at increased risk of lymphoma. Research has shown that the increased risk is due to uncontrolled joint inflammation rather than DMARD therapy[55]. There is currently no compelling evidence that synthetic or biologic DMARDs confer an increased risk of malignancy; nor that they increase the chance of recurrence of a malignancy, or change the prognosis of cancers that occur in patients using biologic therapies[56].

Recommendation

1. Biologic therapy be avoided in patients with a current or recent (<5 years) diagnosis of a malignancy.

6.9 Pregnancy and RA

1. RA tends to improve during pregnancy.
2. In general, because of potential risks to the fetus, some DMARDs are not recommended, and low-dose GCs may be adequate to control symptoms.
3. MTX and leflunomide are contraindicated in pregnancy and breast feeding, but SSZ and HCQ are considered relatively safe and may be useful in active disease.
4. There is sparse evidence for the safety of biologic drugs in pregnancy or lactation and formal recommendations are that anti-TNF drugs and rituximab be stopped 3 months and 12 months, respectively, before conception. However, there are recent reports of successful pregnancies in patients using anti-TNF drugs, and many experts feel that these drugs can be safely continued during conception and the first 2 trimesters of pregnancy[57].

Recommendations

1. Counsel patients in reproductive age group on birth planning, use of contraception and open communication with health care providers.
2. Prior to planned conception, leflunamide and methotrexate should be stopped at least 2 years and 3 months respectively (or washed out with cholestyramine for leflunomide).
3. Sulfasalazine and hydroxychloroquine can be continued up to positive pregnancy test, and thereafter, continued or stopped after risk-benefit analysis.

7. RECOMMENDATIONS ON MONITORING PATIENTS ON THERAPY

1. The routine follow up review of patients should include determination of disease activity, monitoring for drug toxicity, baseline tests and assessment for risk of infection.
2. Disease activity should be evaluated with an SDAI, and an intensive disease control strategy should be used with escalation of therapy if LDA or, ideally, remission is not achieved.
3. Patients with moderate or high disease activity should be assessed frequently (1-3 monthly) until an LDA state is achieved, after which less frequent visits (3 - 6 monthly) are acceptable.
4. Monitoring for toxicity of DMARD therapy is summarized in Table 4. There is no indication for 'routine' liver biopsy in patients on MTX therapy. A biopsy may be indicated in a patient with persistently elevated liver enzymes (>3 times the upper level of normal) despite DMARD discontinuation. Annual serum creatinine and cholesterol tests are appropriate[58].
5. RA patients and their physicians must remain vigilant for symptoms of infection. Patients should be advised to seek medical attention for any symptoms of possible infection, to allow for prompt assessment and treatment. Loss of weight, fever or lymphadenopathy in a patient on biologic therapy requires prompt investigation for TB, which might include a CXR, abdominal ultrasound and bone marrow aspiration.
6. Baseline bone mineral density measurements are recommended in postmenopausal women starting long-term GC therapy and should be repeated at 5-yearly intervals.

8. ECONOMIC ASPECTS OF THERAPY

The economic costs of RA treatment need to be balanced between cost of treatment (synthetic and biologic DMARDs) and complications of ensuing joint damage and disability. Majority of RA patients are in the income generating age bracket. RA can lead to loss of productivity in the home and workplace, loss of income, isolation from society and reduced recreational comforts, together with the negative psychosocial impact of the disease, have severe economic consequences for patients, their families, and to society[48]. The measures used to quantify these effects include the disability adjusted life-years (DALY) and the quality of life-years lost (QALY). The cost of treatment usually goes up when switching from non-biologic to biologic DMARDs. Studies on the cost-effectiveness of all biologics showed that the number

needed to treat NNT varied between 2.8 and 5.7.[59]. EULAR recommendations have showed that the merits of effective control of RA outweigh the costs of therapy[50]. At disease onset, synthetic DMARDs should be initiated. If these fail, treatment escalations with biologic therapy are cost-effective, provided standard dos ing schemes are used.

9. FUTURE RESEARCH AREAS

There are several areas for future research to provide answers to optimal RA management in Kenya. Epidemiological data on the prevalence and incidence of musculoskeletal diseases including RA in Kenya is unknown. The burden of RA on productivity in Kenya, and local ways of the cost effectiveness of RA treatment are areas requiring further research. With recent advances in RA therapies the most important issues revolve around TB and HIV. They include safety of biologic DMARDs and the risk factors for development of TB. Research is also needed on management of RA in HIV-positive patients. Kenya and other sub-Saharan Africa countries are at a unique position to be leaders in research in these areas due to the relatively high prevalence of HIV and TB.

In summary, the aim of treatment should be to ideally achieve remission in RA, or at least the lowest practical disease activity. Goals for effective management of RA are prompt diagnosis, early initiation of DMARD therapy, and an intensive control strategy with frequent assessments and rapid escalation of therapy is paramount. Biologic drugs should be considered in patients who have shown inadequate response to synthetic DMARDs. The ARHSK suggest that these recommendations be updated every 2 years.

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