EDITORIAL

32. Putting the spotlight on a backbencher: psychosocial aspects of rheumatologic diseases
   Nakitare S

RESEARCH ARTICLES

34. Prevalence and pattern of knee osteoarthritis in patients presenting at a rheumatology clinic of a tertiary hospital in north east Nigeria
   Yerima A, Adelowo O, Mustapha SK

41. Antinuclear antibodies staining patterns and their clinical association in systemic lupus erythematosus: a cohort of 126 Libyan patients
   Basma E

44. Cutaneous manifestations in systemic lupus erythematosus patients attending a tertiary hospital in Nigeria
   Ayanlowo O, Ima-Edomwonyi U, Adelowo O, Anigbo AE

50. Barriers to the use of methotrexate in Ethiopia for rheumatic diseases: Insights from pharmacy providers
   Hitchon CA, De Jong Y, Melkie A, Meltzer M, Scuccimarri R5, Tadese Y, Colmegna I

56. Guidelines to authors

57. Arthrheuma Society of Kenya consensus report: Recommendations for the management of rheumatoid arthritis
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THEME: RHEUMATOLOGY IN THE FAST LANE: RACING TOWARDS THE GOAL

SUB-THEMES
> Insights into Rheumatoid arthritis
> Connective tissue diseases in clinical practice
> Crystal arthropathies
> Osteoarthritis
> Diagnostic evaluation of rheumatic diseases
> Surgery in rheumatology
> Allied health workers in musculoskeletal health and rehabilitation
> Paediatric rheumatology
> Biologics in Kenya
> Research papers on rheumatic diseases

DEADLINE FOR SUBMISSION OF ABSTRACTS: 30th June 2018

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Students / Residents | 5,000 | 5,000
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More than one hundred and fifty rheumatologic diseases and/or syndromes have been described, each with a variety of clinical manifestations. As they often cause musculoskeletal symptoms, including articular pain, rheumatologic diseases are recognized as one of the leading causes of disability globally\(^1\). While healthcare providers focus on providing solutions to the physical and biological aspects of these diseases, the psychosocial aspects may remain unrecognized, yet their impact on treatment outcome is significant.

The relationship between disease processes and psycho-social wellbeing is complex. Chronic diseases affect the general functioning and wellbeing of an individual. At the same time, social, psychological and physiological factors have a strong influence on both the disease process and the general functioning and wellbeing of an individual. This relationship is a potentially vicious, bilateral cycle, where poor functioning in one dimension upsets functioning in other dimensions.

Biomedical and biopsychosocial models attempt to explain the role of the biologic disease process and individual characteristics in manifestation of disease processes\(^2\). The hypothalamic-pituitary axis and sympathetic nervous system are susceptible to the effects of cytokines and stress hormones (cortisol and catecholamines), which are all possible causes or end-products of inflammation. In addition, persons with chronic diseases have a tendency towards low self-esteem and neuroticism. When these factors combine, they may change an individual’s perception of disease and affect how they cope.

Negative psychosocial factors such as mood disorders (depression and anxiety), learned helplessness, external stressors, sleep disturbance and fatigue are common in patients with rheumatologic diseases, and negatively impact treatment outcomes. In one series of cross-sectional multi-country population studies, mood disorders were up to twice as likely to be present in patients with arthritis, than with those without\(^1\). Approximately 25% of patients with osteoarthritis and ankylosing spondylitis have been reported to have depression and anxiety. The prevalence is even higher in patients with rheumatoid arthritis and fibromyalgia where numbers as high as 42% and 71% respectively have been reported\(^2-8\). Additional psychosocial factors with negative impact include a personal history of psychiatric disorders and history of abuse.

It is worth our time as health care providers to actively identify and address negative psychosocial factors in our patients. These factors have consequences on the course and outcome of rheumatic diseases. Patients with depression and anxiety may have higher levels of pain, higher painful joint counts, reduced functional ability and mortality. They may spend more time in bed, and pay more visits to the physician, which both have economic and health system consequences\(^2-8\).

Interventions to address negative psychosocial factors include patient education and cognitive behavioural therapy. Patient education provides the patient with credible rationale that alters negative perceptions and gives the patient confidence that coping skills can be learned. Cognitive Behavioural Therapy (CBT) is a goal-oriented systematic intervention that employs a variety of techniques which help patients to develop sustainable strategies to cope with pain and manage negative factors. Mindfulness Based Stress Reduction (MBSR) therapy is a related technique that may also be applied. The ultimate goal of these interventions is to increase positive psychosocial factors in the patient, including self-efficacy, optimism, acceptance, and coping skills. Addressing negative psychosocial factors reduces displays of pain behaviour, improves psychological functioning and has a positive impact on disease activity scores by changing joint counts and patient self-assessment scores. Results of these interventions vary. While some
studies report at least short term gains, others such as patient education and lay-led self-management programs fail to show long term benefits. There are also few studies addressing the aspect of patient adherence to medication\(^8\)\(^{-\text{11}}\).

Psychosocial evaluation and interventions should be integrated into our ambulatory clinics. In our African setting, simple, inexpensive strategies should be considered. The 2-question screen\(^\text{12}\) can be applied at triage or during patient registration; it takes almost no time but provides useful information. Rheumatologic units may choose to adopt one of the many available validated psychosocial screening tools, including the PHQ-9 (Patient Health Questionnaire) or the HADS questionnaire (Hospital Anxiety and Depression Score) among others. Decision makers in units may choose to design structured ways to periodically assess the psychosocial dimensions of their patients, for example, detailed questionnaires may be applied to all new patients and periodically thereafter (6-monthly perhaps) according to the resources available. Time-saving strategies such as patient self-administration of questionnaires in waiting rooms can be considered. Patient educational materials should be on display and accessible in units, and where possible, health talks should be provided in waiting rooms. Cognitive behavioural therapy requires investment in both human resources and capacity. Large units with access to multi-disciplinary teams may find it easier to link patients to mental health units with these services. We suggest that arthritis self-management programs and patient peer support groups would greatly benefit the often resource limited African setting in addressing psychosocial problems.

Negative psychosocial factors in our patients may pass unnoticed and fail to be addressed. There is evidence that these factors influence treatment outcomes. The cost impact of screening our patients for these factors is low, yet identifying and addressing them may go a long way in cutting treatment costs and reducing morbidity and mortality. Rheumatologic units in the African setting should identify the low-hanging fruits and implement cost-effective strategies to address the psychological and social factors in our patients, and generate supportive scientific evidence relevant to our setting.

References

Research article

Prevalence and pattern of knee osteoarthritis in patients presenting at a rheumatology clinic of a tertiary hospital in north east Nigeria

Yerima A1, Adelowo O2, Mustapha SK1

Abstract

Background: Osteoarthritis (OA) is the most common joint disease in the world and a major cause of morbidity and activity limitation. It is among the top 5 causes of disability especially in people aged 45 years and above.

Objectives: This study aimed to determine the pattern and radiographic features of knee OA and its association with pain, age and BMI in patients presenting at the rheumatology clinic of the University of Maiduguri Teaching Hospital, Nigeria.

Method: This was a descriptive cross-sectional hospital-based study. Consecutively presenting adults satisfying the 1986 American College of Rheumatology criteria for knee OA were recruited from March to October 2015. Detailed history, physical examination of the knee and anthropometric measurements were obtained. Pain and functional status were assessed using Visual Analogue Score (VAS) and Steinbrocker’s criteria respectively. Blood samples for biochemical profiles were obtained. Standard radiographs of the knee in both anteroposterior and lateral views were taken.

Results: Four hundred and fifty-one patients with rheumatic complaints were seen at the clinic, out of whom 244 (54.1%) had knee OA. There were 63 (25.8%) males and 181 (74.2%) females with a male to female ratio of 1:2.9. The median age was 50 years (IQ range 45-57). All (100%) patients reported knee pain with a median duration of pain of 24 months (IQ range 12 -48) and mean VAS score 8.59±1.14. Two hundred (82%) had bilateral knee OA. The mean BMI was 32.20±5.95Kg/m². Two hundred and four (83.6%) were in functional class II and III. The median ESR was 13 (IQ range 5 - 29.5). One hundred and seventy-four (71.4%) patients’ radiographs showed KL grade III (48.4%) and grade IV (23%). The combined medial and patella femoral compartment OA was observed in 93 (38%) patients. There was a significant association between age, BMI, functional class, pain severity and the KL grading.

Conclusions: Knee osteoarthritis is the most common rheumatic disease in our clinic. The commonest radiographic pattern is the combined medial and patellofemoral compartments. There is significant correlation between age, pain severity and BMI with KL grading of the knee.

Key words: Knee osteoarthritis, Prevalence, Pain, Kellgren-Lawrence grade.

Introduction

Osteoarthritis (OA) is the most common joint disease in the world, with an age-associated increase in both incidence and prevalence1. It is a major cause of morbidity, activity limitation, physical disability, excess health care utilization and reduced health-related quality of life and ranks among the top 5 causes of disability especially in people aged 45 years and above1.

Diagnosis of OA is based on the combination of clinical findings and radiographic changes. Age is the strongest risk factor for knee OA. Other major risk factors for osteoarthritis are female sex, obesity, diabetes, geographic factors, occupational knee-bending, physical labour, genetic factors, race and joint trauma2,3.

Although osteoarthritis occurs worldwide, both its pattern and prevalence vary among populations, and from place to place4. Knee joint is the commonest site affected by OA in Nigerians5-8, with the prevalence of symptomatic knee OA ranging from 16.3 to 61.2%.

A study comparing radiographic features of knee OA in Beijing to the Framingham study showed gender difference in prevalence, with 42.8% in women and 21.5% in men in Beijing compared to 34% in women and 31%
in men in the Framingham cohort\(^6\). Osteoarthritis of the knee has significant functional impact and is associated with considerable medical costs. In the United States for instance, it accounted for 97% of the 455,000 total knee replacements for arthritis in 2004\(^10\). The burden tends to be higher in developing countries including Nigeria, due to delay in diagnosis and lack of access to specific interventions such as arthroplasty, joint replacement, and rehabilitation, among others\(^11\).

Despite the global distribution of OA, there exists some geographic variation in occurrence and/or pattern of the disease. These variations can be exploited for a better understanding of the risk factors, aetiology and pathogenesis of the disease\(^12\). There are few epidemiological studies on the pattern of knee OA in Nigeria, and the sub-Saharan Africa. We performed a cross sectional study to determine the clinical, radiographic and biochemical profiles of patients with knee OA in a rheumatology clinic at a tertiary hospital in Nigeria.

**Materials and Methods**

*The study area:* The study was conducted at the Rheumatology Clinic of the University of Maiduguri Teaching Hospital (UMTH).

Ethical approval was obtained from the hospital ethics and research committee, and the HELSINKI declaration was adhered to. Informed written consent was obtained from each patient.

*Study design:* A cross sectional, descriptive hospital based study was conducted in consecutive adults presenting with clinical and/or radiological features satisfying the ACR criteria for knee OA\(^13\) from March through October 2015. Inflammatory arthritis, previous knee surgery, congenital abnormalities of the knee and hip, traumatic injury to the knee, crippling arthritis and refusal of consent served as exclusion criteria. A sample size of 224 was arrived at using a community prevalence of 16.3% for knee OA\(^14,15\).

*Study procedure:* Two hundred and forty-four patients satisfying the inclusion criteria were consecutively recruited. Information including biodata, medical history and clinical examination findings, laboratory parameters, and radiographic findings was collected using a pre-tested, interviewer-administered questionnaire. History of the presenting knee pain as well as its severity and duration, were obtained and the patient’s functional status determined. Severity of pain was assessed using visual analogue scale of 0 to 10, with 10 being maximum pain experienced while 0 is no pain. Scores of \(\leq 4\), 5 to 7, and \(\geq 8\) were considered mild, moderate and severe respectively. Functional disability was assessed using Steinbrocker’s criteria\(^6\). Blood pressure and anthropometric variables were measured using standard procedures, and Body Mass Index (BMI) in Kg/m\(^2\) determined.

Each knee was examined separately for varus or valgus deformity, effusion, joint line tenderness and crepitus. The Range of Motion (ROM) and alignment of the knee joint was measured using an International Standard Goniometer. Quadriceps strength was graded using the medical research council grading scale. Blood samples were obtained for measurements of haematocrit, ESR and other biochemical parameters.

All patients had standard anteroposterior (AP) and lateral semi-flexed radiographs of their knees in weight bearing position taken by qualified radiographers. The radiographs were independently interpreted and graded by a radiologist and the first author using the Kellgren and Lawrence Criteria\(^17\), and both agreed on the different grades. Grades 2 to 4 were considered diagnostic of radiographic OA while grades 0 and 1(with appropriate clinical features) were considered clinical OA.

*Statistical analysis:* Data was analyzed using SPSS version 22.0 software (SPSS Inc., Chicago, IL, USA). Normality of continuous variable was assessed using the Kolmogorov- Smirnov test. Normally distributed variables were expressed as mean ±SD while skewed variables were expressed as median and inter-quartile. Independent t-test was used in comparing means of continuous variables and Mann-Whitney test was used in comparing medians of skewed variables. Categorical variables were presented as percentages and compared using Fisher’s exact Chi-square test of association. Spearman’s \(\rho\) (rho) correlation coefficient was used in computing associations between age and BMI with various categories of KL grades. Kendall’s \(\tau\) (tau) was used in correlating various categories of functional class and pain score with various categories of KL grades. A p value of <0.05 was considered statistically significant.

*Results*

*Demographics:* During the study period, 451 rheumatological cases were seen at the rheumatology clinic of UMTH, out of whom 244 (54.1%) met the ACR clinical and/or radiological criteria for knee OA. There were 63 males and 181 females with male to female ratio of 1:2.9. The baseline demographic and clinical characteristic of the patients is presented in Table 1.
Table 1: Demographic characteristic of patient with knee OA

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>18 – 24</td>
<td>5 (2.0)</td>
</tr>
<tr>
<td>25 -34</td>
<td>35 (14.3)</td>
</tr>
<tr>
<td>35 - 44</td>
<td>95 (38.9)</td>
</tr>
<tr>
<td>45 – 54</td>
<td>78 (32.0)</td>
</tr>
<tr>
<td>55 – 64</td>
<td>30 (12.3)</td>
</tr>
<tr>
<td>≥ 65</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>181 (74.2)</td>
</tr>
<tr>
<td>Female</td>
<td>63 (25.8)</td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
</tr>
<tr>
<td>Civil servant</td>
<td>10 (4.1)</td>
</tr>
<tr>
<td>Teaching</td>
<td>6 (2.5)</td>
</tr>
<tr>
<td>Farming</td>
<td>82 (33.6)</td>
</tr>
<tr>
<td>Private skill workers</td>
<td>86 (35.2)</td>
</tr>
<tr>
<td>Unemployed</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Characteristic of pain according to gender of the study population

<table>
<thead>
<tr>
<th>Duration of pain (median month)</th>
<th>Male n=63</th>
<th>Female n=181</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to develop pain after walking (median time in minutes)</td>
<td>24</td>
<td>33</td>
<td>0.167*</td>
</tr>
<tr>
<td>Pain at rest, n (%)</td>
<td>28 (43.8)</td>
<td>118 (65.6)</td>
<td>0.047*</td>
</tr>
<tr>
<td>Pain on standing &gt; 30min, n (%)</td>
<td>46 (71.9)</td>
<td>154 (85.6)</td>
<td>0.474*</td>
</tr>
<tr>
<td>Pain on sitting &gt; 2 hours, n (%)</td>
<td>56 (87.6)</td>
<td>172 (95.6)</td>
<td></td>
</tr>
<tr>
<td>Visual analogue score for pain</td>
<td>3 (2.0)</td>
<td>2 (1.1)</td>
<td>0.085*</td>
</tr>
<tr>
<td>≤ 4, n (%)</td>
<td>2 (3.1)</td>
<td>2 (1.1)</td>
<td></td>
</tr>
<tr>
<td>5 - 7, n (%)</td>
<td>35 (56.2)</td>
<td>81 (44.4)</td>
<td></td>
</tr>
<tr>
<td>≥ 8, n (%)</td>
<td>26 (40.6)</td>
<td>98 (54.4)</td>
<td></td>
</tr>
</tbody>
</table>

*K Mann–Whitney U test, + Chi square n = number

The median age at presentation was 50 (IQ range 45 -57). The median duration of pain reported was 24 months (IQ range 12-48). Two hundred (82%) patients reported bilateral knee pain, while 44 (18%) had pain in either knee. Scores of ≥ 8 on VAS was reported by 124 (50.8%) patients. The characteristic of pain based on gender is shown in Table 2.

Table 3: Signs of knee OA amongst the patients examined

<table>
<thead>
<tr>
<th>Sign</th>
<th>Right knee n (%)</th>
<th>Left knee n (%)</th>
<th>Both knees n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varus deformity</td>
<td>82 (33.6)</td>
<td>69 (26.2)</td>
<td>58 (23.7)</td>
</tr>
<tr>
<td>Valgus deformity</td>
<td>68 (27.9)</td>
<td>20 (8.2)</td>
<td>53 (21.7)</td>
</tr>
<tr>
<td>Flexion contraction</td>
<td>58 (23.7)</td>
<td>16 (6.6)</td>
<td>54 (22.1)</td>
</tr>
<tr>
<td>Hyperextension</td>
<td>17 (7.0)</td>
<td>14 (5.7)</td>
<td>11 (4.5)</td>
</tr>
<tr>
<td>Knee effusion</td>
<td>46 (18.9)</td>
<td>29 (11.5)</td>
<td>23 (9.4)</td>
</tr>
<tr>
<td>Tenderness</td>
<td>153 (62.3)</td>
<td>46 (18.9)</td>
<td>136 (55.7)</td>
</tr>
<tr>
<td>Crepitus</td>
<td>222 (91)</td>
<td>220 (90.2)</td>
<td>198 (81)</td>
</tr>
<tr>
<td>Ligament instability</td>
<td>12 (4.9)</td>
<td>8 (3.3)</td>
<td>5 (2.0)</td>
</tr>
<tr>
<td>Quadriceps strength</td>
<td>100 (41)</td>
<td>92 (37.9)</td>
<td>83 (34)</td>
</tr>
</tbody>
</table>

*medical research council grading of power

Radiological features of knee OA: Table 4 shows the various Kellgren-Lawrence (KL) grades and the knee compartments affected. Four hundred and seventy knees (97.5%) were KL grade II and above, while 12 (2.5%) were of grade I and below (clinical OA). The most common compartment affected by OA in both knees was the combined medial and patellofemoral compartments (37.7% on the right and 38.1% on the left). Pure lateral compartment was the least, observed in eight (1.6%) patients of which Six (9.5%) were males and two (1.1%) were females.
There was a significant, albeit weak correlation between age and various KL grades (r =0.16, p=0.012, and r = -0.21, p=0.004, for the right and left knee respectively). BMI was significantly correlated with KL grades (r=0.244, p<0.001, and r=0.237, p<0.001, for right and left respectively). A positive correlation was seen when pain severity was compared to KL grades (r =0.128, p=0.035, and r=0.117, p=0.006, for right and left knees, respectively). Similarly, the functional status was significantly correlated to the KL grades (r = 0.278, p<0.001, and r = 0.22 p=0.001, for right and left knee, respectively).

**Discussion**

Osteoarthritis constitutes 54.1% of all the rheumatic diseases seen during the study period, signifying that, it is the commonest rheumatological disorder necessitating hospital visit. This study also shows that it commonly affects middle age, obese patients and is associated with marked limitation of physical activity.

Most of the patients presented late, probably because of the dissociation between joint damage and pain which is the commonest clinical symptom. These findings are consistent with what has been reported by other researchers.

The median age of 50 years at presentation in our study is similar to that observed in Ibadan by Ebong (66.7%) and Adebajo (77.9%)8. Our male to female ratio of 1:2.9 is similar to, but slightly lower than the 1:4.6 reported by Adelowo7. Similar observations were made by Adebajo8 and among the Framingham cohort21. Occupations associated with repetitive movements coupled with excessive joint loading e.g. mining, farming and female housekeepers, have long been associated with OA.

Pain on activity is the most consistent presenting symptom in our patients, like what was reported in Ibadan. The median duration of pain observed in our study is similar to that reported in Cameroon and other parts of Africa, with more than 50% of the subjects presenting with a pain score of greater than 7.7,7,20,25. The significantly higher pain score in our female cohorts compared to the males appears intriguing. However, depression, disturbed sleep and other psychosocial factors that impact on perception of pain are more prevalent among women, and may perhaps be responsible for the discrepancy in pain score 26,27. Few patients had sensation of their knee “giving way” or locking, but we did not identify falls due to these symptoms as reported by others28 probably due to our exclusion of patients with crippling arthritis.

More than 75% of our patients were in Steinbrocker’s functional class I and II while a third were in class III. A study from Zaria, Nigeria revealed self-reported functional disability in up to 89.3% of their patients28. The study also showed that self-reported disability correlates strongly and independently with self-reported pain, body mass index, comorbidity and radiographic severity. There was no comparison between genders in their study.

About half (48.4%) of our patients had family history of OA of the knee with most (64.4%) reporting their mothers having had OA. Twin studies suggest that knee OA in women has a heritability rate of 39 to 65%, their mothers having had OA. Twin studies suggest that knee OA in women has a heritability rate of 39 to 65%, with a concordance rate in monozygotic twins of 0.6429. In our study, genetic influences was inferred from history of OA of the knee with most (64.4%) reporting their mothers having had OA.

The predominance of females (74.2%) in our study is similar to that observed in Ibadan by Ebong (66.7%) and Adebajo (77.9%)8. Our male to female ratio of 1:2.9 is similar to, but slightly lower than the 1:4.6 reported by Adelowo et al30. Although postmenopausal women often have a higher incidence of OA due to the lack of the protective effect of oestrogen29, only a few of our patients (29%) were postmenopausal. The higher number of premenopausal females may be attributed to other confounding factors like obesity.

The high rate of OA observed may be related to some prevailing common practices. The major ethnic groups in Maiduguri share a common culture of habitual knee bending during greetings, prayers and when carrying out domestic work. Additionally, most households use mats and carpets for relaxation with knees folded at most times. Adelowo7 reported an association between knee OA and the habit of sitting on low stools, about a foot off the grounds with knee in extreme flexion among women traders. Similar observations were made by Adebajo8 and among the Framingham cohort21. Occupations associated with repetitive movements coupled with excessive joint loading e.g. mining, farming and female housekeepers, have long been associated with OA.

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Klußmann et al30 reported that in both genders, knee OA within parents, brothers, or sisters was a significant predictor for symptomatic knee OA. The prevalence of Diabetes Mellitus (DM) among our patients was 16.4%, in contrast to 9% seen in Cameroon22. In a recent systematic review and meta-analysis involving 645,089 patients with OA, the prevalence of DM was 14.4±0.1%.31 There are no local data in Nigeria regarding the prevalence of DM in knee OA patients.

Several epidemiological studies have now shown that OA is more frequent in people with hypertension12,33. In this study 59% had hypertension with a median duration of 60 months, in contrast to the 23.4% reported by Adebajo et al in Ibadan. This may be explained by the difference in the definition of hypertension.

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**Table 4: Radiological findings of knee OA**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Category</th>
<th>Right knee n (%)</th>
<th>Left knee n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KL grade</td>
<td>Grade 0</td>
<td>8 (3.1)</td>
<td>8 (3.3)</td>
</tr>
<tr>
<td></td>
<td>Grade 1</td>
<td>6 (2.4)</td>
<td>6 (2.5)</td>
</tr>
<tr>
<td></td>
<td>Grade II</td>
<td>50 (19.7)</td>
<td>56 (22.9)</td>
</tr>
<tr>
<td></td>
<td>Grade III</td>
<td>110 (43.3)</td>
<td>118 (48.4)</td>
</tr>
<tr>
<td></td>
<td>Grade IV</td>
<td>80 (31.5)</td>
<td>56 (22.9)</td>
</tr>
<tr>
<td>Knee compartment</td>
<td>Medial (M)</td>
<td>78 (32.0)</td>
<td>84 (24.4)</td>
</tr>
<tr>
<td></td>
<td>Lateral (L)</td>
<td>4 (1.6)</td>
<td>4 (1.6)</td>
</tr>
<tr>
<td></td>
<td>Patellofemoral (PTF)</td>
<td>10 (4.1)</td>
<td>6 (2.5)</td>
</tr>
<tr>
<td></td>
<td>Medial and lateral</td>
<td>2 (0.8)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td></td>
<td>Medial and PTF</td>
<td>92 (37.7)</td>
<td>93 (38.1)</td>
</tr>
<tr>
<td></td>
<td>Lateral and PTF</td>
<td>2 (0.8)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td></td>
<td>M, L and PTF</td>
<td>44 (18.0)</td>
<td>40 (16.4)</td>
</tr>
</tbody>
</table>
Anthropometric measures such as height, weight, waist circumference and BMI have a significant relationship with the severity of osteoarthritis of knee in non-obese subjects. Sanghi et al\textsuperscript{44} showed that BMI and other anthropometric measures have a significant association with knee OA. Contrary to common belief; peripheral fat in males and central fat in females were more strongly associated with knee OA in comparison to heuristic body weight\textsuperscript{33}.

In our study, the prevalence of obesity, defined as BMI of 30 Kg/m\textsuperscript{2} and above was 64.7%. This trend was reported by researchers in Cameroon\textsuperscript{25}. Previous studies from Ibadan used percentage increase in body weight to assess obesity, making it difficult for comparison with our study.\textsuperscript{5,6,8} We found a correlation between BMI and KL grading in both knees. Our subjects in the overweight and obese category had higher KL grading (III and IV), similar to what was reported in other studies\textsuperscript{17,21,22,35}. Obesity is the strongest modifiable risk factor for OA, possibly due to the high mechanical stress imposed on the joint\textsuperscript{36}. It is a stronger risk factor in women than in men, and is more strongly related with bilateral than unilateral knee OA\textsuperscript{36,37}. Obesity can also cause OA through its metabolic effects. There is a close relationship between BMI and central obesity, a component of metabolic syndrome. Studies on the relationship between knee OA and metabolic syndrome have revealed conflicting results. In a meta-analysis by Wang et al\textsuperscript{38} a pooled adjusted OR of 1.05 (p<0.00001) supports that metabolic syndrome increases the risk of knee OA. However, Niu et al\textsuperscript{39} showed that after adjustment for BMI neither metabolic syndrome nor its component were associated with increased incidence of knee OA. A Nigerian study by Yerima et al\textsuperscript{40} revealed that 59.8% of patients with knee OA had metabolic syndrome. Our current study was not designed to look at the metabolic effect on knee OA.

Knee deformities are either consequences or causes of knee OA. Studies have shown that valgus and varus alignment result in increased risk of tibiofemoral OA progression, after controlling for age, sex, and BMI\textsuperscript{41}. A third (33.6%) of our patients had bilateral varus, with similar percentage having valgus deformity. Eбong et al\textsuperscript{42} reported 19.8% with valgus and varus deformity at Ibadan, Nigeria.

Slemenda et al\textsuperscript{43} showed that, after adjusting for body weight, quadricep weakness preceded radiographic knee OA in women. We found more females with decreased quadriceps strength than men (72 females vs 11 males) but the cross sectional nature of our study limited our ability to determine whether the weakness preceded the knee OA or it was the other way round.

Almost all (97.5%) of our patients were found to have radiographic KL grade II and above in addition to clinical symptoms of OA, thus most of the patients had symptomatic OA. The commonest compartment affected is the combined medial and patellofemoral knee OA (37.7%) supporting other studies\textsuperscript{43}. A third (32%) had only medial compartment affected by knee OA in contrast to 25% reported from Cameroon\textsuperscript{25} and 55% by Adeabajo et al\textsuperscript{8}. Tri-compartmental disease was seen in less than a quarter (18%) of our patients compared to 40% reported by Duncan et al\textsuperscript{44}. Wise et al\textsuperscript{45} revealed that women had a higher prevalence of lateral compartment OA than men in both African Americans and whites, although the difference did not reach significance among African Americans. This may probably explain why we had more men than women in our study with only lateral compartment OA (6 men versus 2 women). Isolated patellofemoral joints (PFJ) OA is considered to be rare in spite of the fact that patellofemoral joint (PFJ) is one of the most commonly affected compartments in combination with other compartments\textsuperscript{46}. We found only 16 (4.1%) with isolated PTJ OA compared to 24% seen by Duncan et al\textsuperscript{44}. Overall, we found that women were in higher proportion than men irrespective of the knee and the compartment involved except for lateral compartment OA.

Knee OA is often not accompanied by elevation in ESR. The ACR recommended ESR of less than 20mm in the first hour in the diagnosis of knee OA. Our finding of a median ESR of 13 is in keeping with that. The wide range noted in our study (1-80) was due to few outliers which can probably be explained by the relatively high age of the subjects and infections /infestations due to being residents in the tropics. Adelowo\textsuperscript{6,7} and Adebajo\textsuperscript{8} found a mean of 31 and 35.6 mm/hour, respectively in their study.

Our study has shown significant positive correlation between age and severity of radiographic knee OA. Aging being a strong risk factor in combination with late presentation of our subjects might be the reason. Most studies revealed poor association between severity of pain and radiographic features of OA with less than 50% reporting pain\textsuperscript{18}. We also found no significant association between severity of pain based on visual analogue scale (VAS) score and KL grading in both knees. However, Avasthi et al\textsuperscript{47}, compared three clinical scoring system (VAS score, WOMAC score and Lequesne) and concluded that WOMAC is the best for assessing severity of disease\textsuperscript{39}.

In addition to pain we observed that there is a significant association between functional status and KL grading. Patients with higher KL grade had marked limitation of activities of daily living. Majority (84%) of our subjects were in class II to IV. High disability level (56.2%) was also reported elsewhere in Nigeria by Ebong\textsuperscript{4}, Adelowo et al (90%)\textsuperscript{4}, Akinpelu et al (90.2%)\textsuperscript{44} and Umar (89.3%)\textsuperscript{28}. In a community which relies heavily on physical activity for sociocultural and occupational activities, this high level of disability places a lot of burden and challenge.

Conclusion

We found that knee OA is the commonest rheumatic disorder in our clinic. The pattern is similar to that seen in
developed countries and males have higher rate of lateral knee OA. We also found a significant association between pain and higher KL grade.

**Acknowledgments**

We acknowledge the contributions of the Medical laboratory scientist of the pathology department of the University of Maiduguri Teaching Hospital for the biochemical and haematological analysis.

We are also grateful to the radiologist and the radiographers who assisted in interpreting the radiographs and taking the X-rays respectively.

**Disclosure:** Authors declare no conflict of interest.

**References**


Antinuclear antibodies staining patterns and their clinical association in systemic lupus erythematosus: a cohort of 126 Libyan patients

Basma E

Abstract

Background: Nuclear constituent such as histone protein, double stranded (ds) DNA, DNA/histone complexes (nucleosomes), various nuclear enzymes and other protein/ribonucleoproteins are common target antigens for antinuclear antibodies (ANA). On this base, different intranuclear immunofluorescent ANA staining patterns can be detected in SLE.

Objective: To study a different ANA patterns in our patients with SLE and to detect the associations between ANA patterns and clinical manifestations of SLE in our patients.

Methods: The study included 126 SLE patients who were registered in rheumatology out patient’s clinic in Tripoli Medical Center in Libya in the period from January 2015 to January 2018. All patients met ≥ 4/11 of the 1982 American College of Rheumatology (ACR-82) criteria. Age, sex and clinical manifestations of their illness at diagnosis were recorded. ANA analysis by immunofluorescence (IF) microscopy (HEP-2cells) was sent to Bioscientia laboratory Ingelheim, Germany for all patients. Anti double stranded DNA (crithidia luciliae) analysis was also sent to the same laboratory for all patients.

Results: One hundred and twenty six patients (124 females and 2 males) were included in the study. Their mean age was 32.46 years. The most common ANA pattern in our patients was combined homogenous and fine speckled (HS-ANA) which present in 50/126 (39.7%) of patients followed by speckled pattern (S-ANA) in 37/126 (29.4%) of patients. The classical homogenous pattern (H-ANA) was present in only 13/126 (10.3%) of our patients. Nucleolar pattern (N-ANA) ± other patterns were recorded in 14/126 (11.1%) of patients.

Conclusion: Combined homogenous and fine speckled (HS-ANA) is the dominant immunofluorescent antinuclear antibody pattern among Libyan patients with SLE which was more associated with renal disorders and positive anti dsDNA antibodies than other patterns. Nucleolar pattern ± other patterns were recorded in 11.1% of our patients and associated with least renal disorders and positive anti dsDNA antibodies.

Key words: Antinuclear antibodies, Systemic Lupus Erythematosus, Antids DNA antibodies.

Introduction

Systemic Lupus Erythematosus (SLE) is multisystemic, relapsing and remitting disease that involves multiple organs. Mucocutaneous, arthritis, serositis, haematological, renal, neurological and immunological disorders are the most common features which present in ACR82 criteria of SLE. Nuclear constituent such as histone protein, double stranded (ds) DNA, DNA/histone complexes (nucleosomes), various nuclear enzymes and other protein/ribonucleoproteins are common target antigens for antinuclear antibodies (ANA). On the basis of their different intranuclear distribution, immunofluorescent ANA staining patterns can be subdivided into homogenous / chromosomal (H-ANA), centromeric (C-ANA), speckled /extrachromosomal (S-ANA), nucleolar (N-ANA), nuclear membrane, nuclear dots and other defined patterns. The use of immunofluorescent microscopy to identify ANAs was introduced by Holman, Kunkel and Friou already in the 1950s, and still remain the gold standard for ANA diagnostics.
ANA presence, its titer and pattern is very important for diagnosis of SLE and it is one of its criteria. But it is not related to SLE activity. Anti ds DNA antibody is also considered in ACR82 criteria of SLE and it is related to SLE activity.

Materials and Methods

The study included 126 SLE patients who were registered in rheumatology outpatient’s clinic in Tripoli Medical Center in Libya in the period from January 2015 to January 2018.

All patients met ≥ 4/11 of the 1982 American College of Rheumatology (ACR-82) criteria. Age, sex and clinical manifestations of their illness at diagnosis were recorded. ANA analysis by immunofluorescence (IF) microscopy (HEP-2 cells) was sent to Bioscientia laboratory Ingelheim, Germany for all patients. Anti double stranded DNA (crithidia luciliae) analysis was also sent to the same laboratory for all patients.

Statistical analysis: The mean age of patients and frequencies of different IF-ANA patterns were measured. Clinical and laboratory features frequencies for each ANA pattern groups were noticed. Differences in distribution of different staining patterns regarding clinical and laboratory features were analysed using Chi-square tests. All statistics were performed using SPSS V.20.0. For each statistical test, exact p values were reported.

Results

One hundred and twenty six patients (124 females and 2 males) were included in the study. Their mean age was 32.46 years. The most common ANA pattern in our patients was combined homogenous and fine speckled (HS-ANA) which present in 50/126 (39.7%) of patients followed by speckled pattern (S-ANA) in 37/126 (29.4%) of patients. The classical homogenous pattern (H-ANA) pattern was present in only 13/126 (10.3%) of our patients. Nucleolar pattern (N-ANA) ± other patterns were recorded in 14/126 (11.1%). Other rare patterns as nuclear membrane and nucleolar dots were present in 5/126 (4.8%) of patients. The first four pattern groups (HS-ANA, S-ANA, H-ANA & N-ANA) were considered large enough for statistical comparisons regarding different clinical features. Clinical manifestations as renal disorder was associated with HS-ANA, H-ANA, and S-ANA patterns more than N-ANA± other pattern (p<0.0001). Arthritis was less associated with S-ANA pattern than other patterns (p-value=0.0049). Haematological disorders occurred more in H-ANA pattern than other patterns (p<0.00001). Positive anti dsDNA analysis was associated more with HS-ANA and H-ANA than N-ANA± other pattern and S-ANA (p<0.0001).

Other clinical features (mucocutaneous, neurological disorder and serositis), no significant differences between the four groups was present (p=0.83, 0.40, 0.07) respectively.

Table 1 shows the most common four ANA pattern groups and their clinical features frequencies. The differences in clinical features between different ANA pattern groups were analysed using Chi-square test and p- values were measured.

Discussion

In our study, we made a comparison between the four common ANA patterns (HS-ANA, S-ANA, H-ANA and N-ANA) and we found a significant difference between them regarding arthritis, haematological, renal and positive anti dsDNA antibodies (p<0.05). No differences were found in other features (Serositis, mucocutaneous and neurological) p>0.05.

In a Swedish study by Frodlund et al1, the most common ANA pattern was classical (homogenous) type followed by speckled (S-ANA), HS-ANA and N-ANA respectively.

They found a significant differences between the four groups regarding arthritis (p=0.02), neurological disorders (p=0.04) and positive anti dsDNA antibodies (p=0.001). No differences were found between other features (Serositis, mucocutaneous, haematological and renal disorders) p>0.05. These differences between our study and the Swedish study calls for further studies.

Nucleolar staining of antinuclear antibodies is not exclusive to patients suffering systemic sclerosis since it can occur in other autoimmune diseases, such as SLE7. The nucleolar ANA patterns present a low incidence in patients with SLE, with less than 9% reported in some studies7. The significant of nucleolar staining and antinuclear antibodies in SLE is still unknown7.

In our study, N-ANA pattern ± other patterns were present in 11.1% of patients and were associated with less renal disorders and positive anti dsDNA antibodies. But these results need more studies with larger group of N-ANA pattern.

Conclusion

Combined homogenous and fine speckled (HS-ANA) is the dominant immunofluorescent antinuclear antibody pattern among Libyan patients with SLE which was more
associated with renal disorders and positive anti dsDNA antibodies than other patterns.

Nucleolar pattern ± other patterns were recorded in 11.1% of our patients and associated with least renal disorders and positive anti dsDNA antibodies.

References

Abstract

**Background:** Systemic Lupus Erythematosus (SLE) is a systemic autoimmune connective tissue disorder. The clinical presentation is protean and it affects the skin, joints and other internal organs. The American College of Rheumatology criteria for diagnosis has four cutaneous signs out of the eleven. SLE can be diagnosed in patients who present with only skin features, in the presence of a serological marker according to the Systemic Lupus International Collaborating Clinics (SLICC) criteria.

**Objective:** This study aimed to document the cutaneous findings in SLE patients who presented at the Lagos University Teaching Hospital (LUTH).

**Methods:** This was a retrospective study of SLE patients who presented to the Rheumatology/Dermatology clinics of LUTH. Data was obtained from the clinic register and patients’ case record files.

**Results:** Systemic lupus erythematosus was diagnosed in 90 (23.9%) of the 377 patients with rheumatologic conditions. Fifty (55.6%) of these patients had cutaneous lesions. Twenty eight patients (48.9%) had acute cutaneous LE, 10 (21.3%) had sub-acute cutaneous LE; while 14 (29.8%) had chronic cutaneous LE. There was a female preponderance with the male to female ratio of 1: 14.7. The mean age of presentation was 33.5 ± 14.3 (range was 9 - 68 years). The mean duration of symptoms was 28.4 ± 38.8 months. Other cutaneous lesions were alopecia, photosensitivity, oral ulcers and malar rash.

**Conclusions:** Skin lesions are common presentation of SLE, yielding valuable diagnostic information essential for early diagnosis, prompt management, and reduction in frequency of flares and complications.

**Key words:** Lupus, Connective tissue diseases, Cutaneous clues to systemic diseases

Introduction

Systemic Lupus Erythematosus (SLE) is a systemic autoimmune connective tissue disorder. The term was first coined by Sir William Osler in 1895 when he reported some cardiac, pulmonary, renal and cutaneous features of the condition. The modern concept of SLE was described in 1948 with discovery of LE cells by Hargraves and his colleagues1,2. It has a worldwide prevalence and is reported to be about four times more prevalent in blacks than whites, and a female preponderance. Until recently, it was thought to be rare in Africans as a result of paucity of data. The clinical presentation is protean ranging from cutaneous only to affection of joints and other organs of the body3.

The skin because of its visibility provides an early marker for SLE. While cutaneous lupus on its own does not cause severe morbidity or mortality, it is a pointer enabling early diagnosis of other life threatening features of SLE such as haematologic, renal and neurological manifestation. Cutaneous lupus has also been noted to severely impair the quality of life of individuals with lupus comparable to some common cutaneous and chronic systemic disorders4. The American College of Rheumatology (ACR) in 1997 developed a set of criteria for the diagnosis of SLE based on the specific findings of patients5. The importance of cutaneous manifestations in making a diagnosis of lupus is highlighted by the American College of Rheumatology criteria for diagnosis of SLE which includes 4 cutaneous criteria out of 11. The skin findings may be the initial presentation predating other systemic features; and SLE can be diagnosed in patients who present with only skin features, in the presence of a serological marker according to the more recent Systemic Lupus International Collaborating Clinics (SLICC) criteria6.
Cutaneous changes of SLE are divided into two categories; lupus erythematosus specific (acute, subacute and chronic) and the lupus erythematosus non-specific skin lesions such as photosensitivity, Raynaud’s phenomenon, vasculitis and hair changes. These lupus specific cutaneous features are captured in the 2010 SLICC classification criteria of SLE, but not in the ACR criteria.

Treatment options depend on the severity of symptoms and specific organ involvement. For mild diseases with predominantly skin and joint affectations, the disease modifying anti rheumatic drug hydroxychloroquine and low dose systemic steroids often control the symptoms while severe diseases are treated according to either the European League Against Rheumatologist (EULAR) or the ACR guidelines which involves the use of immune suppressants such as azathioprine, mycophenolate mofetil, dapsone, thalidomide and biologics that target specific cytokines.

Cutaneous manifestations of SLE have significant impact on the quality of lives of patients. On the background of the often documented late diagnoses of SLE, understanding the variability of the cutaneous findings of SLE creates an index of suspicion allowing early recognition and initiation of appropriate therapy. There are few reports on cutaneous manifestations of SLE amongst African blacks and Nigerians. This study will provide a baseline for further researches on SLE and cutaneous LE.

This study therefore aims to document the cutaneous findings in SLE patients who presented at the Lagos University Teaching Hospital (LUTH) Rheumatology/Dermatology clinics between January 2012 and July 2016.

Materials and Methods

This is a retrospective study of SLE patients who presented at the Rheumatology clinic of Lagos University Teaching Hospital between January 2012 and July 2016. Rheumatology clinic of LUTH was started in January 2012 as part of the dermatology unit with the employment of the rheumatologist and training of specialist residents in rheumatology. All patients with SLE were seen by the rheumatologists; and individuals with cutaneous lesions were assessed and managed by the dermatologists. Diagnosis of skin lesions were confirmed by histology. Data of all patients presenting with SLE was obtained from the clinic records and patients’ case record files.

Inclusion criteria were individuals who met the 1997 ACR criteria for diagnosis of SLE and or 2010 SLICC criteria. Individuals with inconclusive diagnosis; those who did not meet the ACR and or SLICC criteria; and those with purely cutaneous LE with no systemic findings and negative serology, were excluded. Approval from the Health Research and Ethics Committee was obtained. Information extracted from the case record files included age, sex, specific cutaneous LE (CLE) diagnoses and classification, other skin lesions, duration of disease and systemic findings. Investigation results such as Erythrocyte Sedimentation Rate (ESR), Antinuclear Antibody Titre (ANA), anti-Double Stranded Antibody (anti-dsDNA), medications used and management outcome were also included in the data.

Gilliam’s classification of cutaneous LE lesions was used and these include: Acute CLE: localized (malar rash, butterfly rash), generalized (morbilliform eruption), and toxic epidermal necrolysis-like lesion. Subacute cutaneous LE includes annular lesion, papulosquamous/psoriasiform eruptions, vesiculobuluous eruption and toxic epidermal necrolysis-like lesion. Chronic cutaneous LE: Discoid LE, hypertrophic/verrucous LE, LE profundus/panniculitis, LE tumidus/papulomucinous LE, mucosal LE (oral, nasal, conjunctival, genital), chilblain LE and lichenoid LE.

Data was captured on Microsoft excel spreadsheet and analyzed with IBM SPSS Statistics 21 (SPSS Inc., Chicago, IL., USA). Descriptive statistics were used; with tables and charts to summarize the data. Absolute and relative frequencies were calculated for qualitative variables; while quantitative data was documented with means and standard deviation. For comparison of variables, Pearson chi square was used and level of significance p value was put at <0.05.

Results

Ninety (23.9%) of the total number of patients with rheumatologic conditions (377) seen during the study period, were diagnosed as SLE. Fifty (55.6%) of the 90 patients with SLE had cutaneous lesions. Data extracted from records of forty seven patients were analyzed; data of 3 patients were excluded because they were incomplete. Twenty eight (48.9%) out of the 47 patients had acute cutaneous LE; 10 patients (21.3%) had subacute cutaneous LE; while 14 patients (29.8%) had Chronic Cutaneous Lupus Erythematosus (CCLE) (Table 1). There was a female preponderance with the male to female ratio of 1:4.7. The mean age at presentation was 33.5 ± 14.3 years (range was 9 to 68). The peak age of presentation was in the 3rd decade of life (40.4%) followed by the 4th decade (33.5%)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Frequency (%)</th>
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</thead>
<tbody>
<tr>
<td>Total number of SLE patients seen</td>
<td>377 (100)</td>
</tr>
<tr>
<td>Total number of SLE patients</td>
<td>90 (23.9)</td>
</tr>
<tr>
<td>Number of SLE patients with skin findings</td>
<td>50 (55.6)</td>
</tr>
<tr>
<td>No of records included in analysis</td>
<td>47</td>
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<tr>
<td>Sex distribution: n=47</td>
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</tr>
<tr>
<td>Males:</td>
<td>3 (6.4)</td>
</tr>
<tr>
<td>Females:</td>
<td>44 (93.6)</td>
</tr>
<tr>
<td>Male: female ratio</td>
<td>1:14.7</td>
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<tr>
<td>Age range</td>
<td>9 - 68 years</td>
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<tr>
<td>Mean age ± SD</td>
<td>33.51 ± 14.3</td>
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<tr>
<td>Age (years) of SLE patients with skin feature</td>
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<td>&lt;20</td>
<td>7 (14.9)</td>
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<tr>
<td>20 – 29</td>
<td>19 (40.4)</td>
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<tr>
<td>30 – 39</td>
<td>10 (21.3)</td>
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<tr>
<td>40 – 49</td>
<td>3 (6.4)</td>
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<td>50 – 59</td>
<td>5 (10.6)</td>
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<tr>
<td>&gt;/= 60</td>
<td>3 (6.4)</td>
</tr>
</tbody>
</table>

Table 1: Demographics of SLE patients with cutaneous diseases
Acute cutaneous LE was the most common LE specific cutaneous manifestation of SLE affecting 48.9% of patients. Figure 1 revealed Exanthematous eruption on the abdomen and extensor surface of the arm in acute cutaneous LE. Specific skin lesions include alopecia (scarring and non-scarring) in 48.8%, photosensitivity in 40.4%, oral ulcers in 40.4% and malar rash in 36.2%. Findings in other systems include anaemia in 59.6% of patients, fever in 57.4%, renal manifestation in 46.8%, and neuropsychiatric manifestation in 14.9% (Table 2). Figures 2 and 3 shows extensive scarring alopecia and depigmented atrophic patches which are features of chronic cutaneous LE. The mean duration of symptoms was $28.4 \pm 38.8$ (months). The mean duration of presentation at the rheumatology clinic was 28.4 (SD 38.8) months; and only 35.6% of patients presented within the first six months of onset (Table 3). Raised ESR was documented in 85.1% of patients; and the mean $\pm$ SD was 82.08 $\pm$ 48.3. Antinuclear antibodies and anti-dsDNA were raised in 68.1% and 72.4% of patients respectively.

Table 2: Clinical findings in SLE patients with cutaneous lesions

<table>
<thead>
<tr>
<th>Clinical findings</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classification of cutaneous LE: n=47</td>
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<tr>
<td>Acute cutaneous lupus</td>
<td>23</td>
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<tr>
<td>Subacute cutaneous lupus</td>
<td>10</td>
</tr>
<tr>
<td>Chronic cutaneous lupus</td>
<td>14</td>
</tr>
<tr>
<td>Specific skin findings n=47</td>
<td></td>
</tr>
<tr>
<td>Alopecia (non scarring-19; scarring 4)</td>
<td>23</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>19</td>
</tr>
<tr>
<td>Oral ulcers</td>
<td>19</td>
</tr>
<tr>
<td>Malar lesion</td>
<td>17</td>
</tr>
<tr>
<td>Discoid lesion</td>
<td>11</td>
</tr>
<tr>
<td>Bullous eruption</td>
<td>1</td>
</tr>
<tr>
<td>Systemic findings n=47</td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>33</td>
</tr>
<tr>
<td>Arthritis</td>
<td>28</td>
</tr>
<tr>
<td>Fever</td>
<td>27</td>
</tr>
<tr>
<td>Renal</td>
<td>22</td>
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<tr>
<td>Neuropsychiatric features</td>
<td>7</td>
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<tr>
<td>Leucopenia</td>
<td>4</td>
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<tr>
<td>Thrombocytopenia</td>
<td>4</td>
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<tr>
<td>Serositis</td>
<td>4</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>3</td>
</tr>
<tr>
<td>Raised ESR (n=47)</td>
<td>40</td>
</tr>
<tr>
<td>Mean ESR $\pm$ SD</td>
<td>82.08 $\pm$ 48.3</td>
</tr>
<tr>
<td>Positive ANA (n=47)</td>
<td>32</td>
</tr>
<tr>
<td>Positive dsDNA (n=29)</td>
<td>21</td>
</tr>
<tr>
<td>ENA (n=7)</td>
<td>6 positives</td>
</tr>
</tbody>
</table>

Table 3: Duration of symptoms in SLE patients with cutaneous disorders

<table>
<thead>
<tr>
<th>Duration of symptoms (in months)</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-6</td>
<td>16 (35.6)</td>
</tr>
<tr>
<td>7-12</td>
<td>9 (20.0)</td>
</tr>
<tr>
<td>13-18</td>
<td>1 (2.2)</td>
</tr>
<tr>
<td>19-24</td>
<td>9 (20.0)</td>
</tr>
<tr>
<td>&gt;24</td>
<td>10 (22.2)</td>
</tr>
<tr>
<td>Mean Duration (months) $\pm$ Standard Deviation</td>
<td>28.4 $\pm$ 38.8</td>
</tr>
</tbody>
</table>
The most commonly used medication was hydroxychloroquine in 45 patients (95.7%) followed by prednisolone in 42 (89.5%), azathioprine 18 (38.3%), steroid cream 17 (36.2%), non steroidal anti inflammatory drugs 6 (12.8%), cyclophosphamide 4 (8.5%), and methotrexate 3(6.7%) in descending order. Twenty patients (42.5%) had improvement in clinical findings; 14 (29.8%) had remission; 11 (23.4%) defaulted while 2 (4.3%) had worsening of symptoms. Part of the management of cutaneous LE included minimizing sun exposure and photoprotection with the use of sunscreen with SPF >50+ to prevent further UV induced skin lesions.

Discussion

The skin has been regarded as the window of the body and is the pointer to many systemic disorders including connective tissue disorders5. Systemic Lupus Erythematosus (SLE) may be diagnosed in the presence of cutaneous signs and positive serology6. The skin is one of the most common organ manifesting symptoms of SLE7. Cutaneous lesions were seen in 55.6% of all patients who presented with SLE during the study period. Adelowo et al10 found a lower figure, in which 45% of their series presented with hair loss and 43.9 with discoid lesions10. Similar hospital based studies done in Malaysia, Pakistan and India revealed the frequencies of cutaneous lesions in the SLE patients to be 62%, 70% and 100% respectively11-13. A recent study in the US revealed the incidence of cutaneous LE to be 4.0/100,000 population similar to that done in Sweden14,15. There are few reports on cutaneous manifestation of SLE in African blacks and population studies are yet to be done on both SLE and cutaneous LE in Nigerians.

There is variable relationship between cutaneous LE and SLE. Individuals can present with cutaneous LE without systemic diseases; systemic diseases without skin manifestations; cutaneous flare independent of the internal organs; and the drugs used for cutaneous disorders may not be effective on systemic diseases16. All these suggest possibility that different pathophysiologic mechanisms may exist for the different presentations and courses of cutaneous LE. Trigger factors identified for cutaneous lupus erythematosus include Ultraviolet Light (UV), medications, hormones, stress, viruses and skin trauma16.

Ultraviolet light has been found to induce release of pro-inflammatory cytokines, chemokines and adhesion molecules. Ultraviolet radiation also induce apoptotic bodies which bind with autoantibodies leading to the upregulation of the p53 protein expression, induction of cellular cytotoxicity, DNA damage and cytokine synthesis (such as IL1, IL6, IL8, IL10 and TNF)16. Subsequently there may be homing of inflammatory cells to the skin and upregulation of nitric oxide in the endothelial cells16. Specifically discoid LE has been associated with smoking, and subacute LE with medications and phototoxicity16,17.

This study corroborates other studies that SLE is a disease found amongst females of childbearing age. The male to female ratio was 1:14.7; with 61.4% of the patients aged between 20 and 39 years; and a mean age of presentation of 33.51 ± 14.3, similar to work done by Adelowo et al10. The female predilection is thought to be due to both hormonal and genetic factors. The teen age to early forties, the age group most affected by SLE in females has been noted to correspond to the age of greatest hormonal instability18. The mean age found in this study is lower than that reported in other series where patients with cutaneous lupus are predominantly Caucasians. A multicenter study done in Europe reported the mean age of 43.0 + 15.7 (SD)19. The mean age for the cohort in Sweden was 54 years and Minnesota US 47.6 years14,15. Deligny et al20 found lower age of presentation in their patients with African descent compared to the Caucasians counterpart in French Guiana in South America.

Cutaneous features of SLE in themselves, though sometimes painful, are not life threatening, but may impair the quality of life of the affected individuals. Facial lesions such as malar rash, discoid lesions; hair loss and hyperpigmentation from photosensitivity are of immense cosmetic significance. Studies show that cutaneous lupus erythematosus have severe effects on the quality of life, worse than skin conditions such as acne vulgaris, non melanoma skin cancers and alopecia; and comparable or worse mental health scores than systemic disorders such as hypertension, diabetes mellitus and congestive cardiac failure21.

Systemic lupus erythematosus has been associated with late presentation in African Americans and Africans7,10. In this series, only about a third of the patients presented within 6 months of onset of symptoms; and the mean duration of symptoms was 28.4 months (2.3 years) which is comparable to an earlier study in Nigeria which reported 2.6 years10. One of the reasons suggested for this late diagnosis include low index of suspicion by the primary and the secondary health care givers, against the background of the previous belief that lupus is rare in Africans3,22. Good knowledge of the cutaneous features of SLE affords the patients and clinicians the benefit of early diagnosis and prompt management.

Our patients are managed using the American College of Rheumatology and the European League Against Rheumatologist (EULAR) recommendations8,23. One of the major constraints to management is paucity of funds as the health insurance scheme is not established in Nigeria and often does not include management of chronic illnesses like SLE, hence most patients pay out of pocket. This may be one of the factors implicated in the high rate of default and complications seen by African specialists10,24,25. Furthermore our patients also seek alternative therapy especially when there are no dramatic improvement. About a quarter of patients in this series defaulted treatment.
In accordance with the current understanding of lupus management, hydroxychloroquine was the most prescribed medication used in 95.7% of patients in this study. Ekwom et al. and Genga et al. reported the use of hydroxychloroquine in 77% and 92% of their patients respectively. The medication use in 95.7% of patients in this study. Ekwom and Genga reported the use of hydroxychloroquine in 77% and 92% of their patients respectively. Hydroxychloroquine use has been found to prevent flares, reduce damage to organs, reduce renal damage and improve survival rate, hence it is indicated in all lupus management. Hydroxychloroquine use also improves lipid profile, prevents thrombotic events and reduces occurrence of congenital heart blocks in offspring of mothers who have lupus. Hydroxychloroquine use also improves lipid profile, prevents thrombotic events and reduces occurrence of congenital heart blocks in offspring of mothers who have lupus. Apart from the medications, management of cutaneous LE includes minimizing sun exposure and photoprotection with the use of sunscreen and photoprotection with the use of sunscreen with SPF >50+ to prevent further UV induced skin lesions.

Systemic lupus erythematosus is a multi organ disorder, although cutaneous disease may be the only presentation. Acute cutaneous LE is the most common presentation in this study. This is comparable to the findings from an English hospital which reported 51% acute cutaneous LE. Cutaneous lesions are pointers and may help in the early diagnosis of the severe life threatening features of SLE such as renal, cardiopulmonary and neuropsychiatric symptoms. In this series, anaemia was seen in 70.2%, arthritis in 59.6%, fever in 57% and renal disease in 46.8% of patients with cutaneous LE. It is advised that all patients with cutaneous lupus be screened for SLE.

The limitations of this study include the fact that this is a retrospective study and many less prominent cutaneous signs may not have been documented. Also in the setting of a severe flare which involves other organs, cutaneous lesions may not be documented. This is a hospital based study and patients seen will usually come with a flare; this study excludes cutaneous findings in patients who did not have a flare or significant/bothersome skin lesions or health challenges necessitating their visits to the clinic.

In conclusion, skin lesions in patients with SLE can yield valuable diagnostic as well as prognostic information essential for early diagnosis; prompt and efficient management; and in the long term reduction in the frequency of flares and complications. In view of this, educating primary care physicians, non-rheumatologists and non-dermatologists will aid early identification and referral, rather than administration of arbitrary topical therapies that will delay access to appropriate treatment.

Conflict of Interest: None to declare

References


Barriers to the use of methotrexate in Ethiopia for rheumatic diseases: Insights from pharmacy providers

Hitchon CA¹, De Jong Y², Melkie A³, Meltzer M⁴, Scuccimarri R⁵, Tadese Y³, Colmegna I⁶

Abstract

Objectives: African countries with a Low Human Development Index (LHDI) face competing social, economic, and health priorities that distract from the treatment of chronic conditions like Rheumatoid Arthritis (RA). Methotrexate (MTX) is standard of care for RA. We sought to determine MTX availability and dispensing practices of Pharmacy Providers (PP) in Ethiopia, an LHDI country.

Methods: Pharmacy Providers (PP) from across Ethiopia completed a survey regarding their experience with dispensing MTX for the treatment of rheumatic conditions. In addition, a semi-structured interview was conducted with two pharmacists serving the country’s sole public rheumatology clinic. We report descriptive statistics from the survey and thematic analysis of the interview.

Results: Twenty-three PP working in hospital and community pharmacies completed the survey. Oral MTX was available in 13% of pharmacies and dispensed by two PP for rheumatic conditions. Only three PP felt comfortable educating patients taking MTX. Interviewed pharmacists identified barriers to MTX use including inconsistent availability for rheumatic diseases, and sub-optimal patient acceptance due to low health literacy combined with social and cultural determinants of non-adherence. Identified needs included specialty-specific tools and recommendations for prescribing, monitoring, and counselling patients regarding MTX that are appropriate to the local health and social environment.

Conclusion: We identified key factors limiting the use of MTX among Ethiopian patients with rheumatic conditions including drug availability, confidence of pharmacists counselling on MTX, and patient confidence in the drug. Enhancing access to MTX and promoting training of health care professionals in patient counselling could optimize the treatment of rheumatic patients in LHDI.

Key words: Methotrexate, Pharmacists, Low Human Development Index, Africa, ILAR, Rheumatoid arthritis

Introduction

African countries with a Low Human Development Index (LHDI) based on life expectancy, education and income per capita, face competing social, economic, health and poverty related issues that distract from the treatment of chronic conditions such as Rheumatoid Arthritis (RA)¹⁻³. Methotrexate (MTX) is standard of care for RA and used for many other rheumatic diseases⁴. When used and monitored appropriately, it is well-tolerated and effective in reducing morbidity and mortality associated with rheumatic conditions⁵⁻⁷. Safe and effective use of MTX requires input from multiple health care providers including dispensing pharmacists. Pharmacists are medication experts with a key role in collaborative care models of chronic disease management⁸ and are well positioned to assist with medication use and general management of RA (i.e. reminding and encouraging patients about regular blood-work monitoring)⁹.

Ethiopia, with over 102 million inhabitants (45% below the poverty line), is the most populated landlocked country in the world and the second-most populated nation on the African continent¹⁰. Ethiopia’s health status is poor, even when related to other low-income countries including those in sub-Saharan Africa. Ethiopia’s main health priorities are communicable diseases which are linked to poverty, poor sanitation facilities, lack of access to safe drinking water, malnutrition, and high migration rates⁴. Health care resources in Ethiopia are limited, and gross inequalities exist in access to health services amongst different regions of the country¹. The limited number of health institutions, the poor distribution of medical supplies among regions and the disparity between urban and rural areas contribute to the inaccessibility of health care services to the population.
Rheumatology care in Ethiopia is challenging as there is no full time practicing rheumatologist in the country. The single public rheumatology clinic at Tikur Anbessa Specialized Hospital (TASH) in Addis Ababa is attended by rotating non-rheumatologists with limited expertise in prescribing or optimizing doses of methotrexate. In that clinic, the opportunity for patient counselling is limited due to the large number of patients requiring care, and the limited number of care providers (staff physicians and residents)\(^1\). In this setting, dispensing pharmacists could play a fundamental role to reinforce the safe use of MTX. Using a mixed methods qualitative study design, we sought to determine MTX availability and MTX dispensing practices of Pharmacy Providers (PP) in Ethiopia. This work will inform the development of culturally appropriate strategies to facilitate safe and effective use of MTX to treat rheumatic diseases.

**Materials and Methods**

**Pharmacy providers survey:** The Ethiopian Catholic Church– Social and Development Commission (ECC-SDCO) Health Department, a member of The Ecumenical Pharmaceutical Network (EPN), is the second largest health institution in Ethiopia after the public health system. The ECC-SDCO oversees 83 health institutions (5 hospitals, 16 health centres, 2 specialty centres, 60 clinics), 18 hospice centers providing palliative care for terminally ill persons and 5 HIV/AIDS counselling and social service centres. Fifty-two of these centres have a pharmacy department (4 hospitals, 16 health centers and 32 clinics). In September 2016, 23 pharmacists and pharmacy technicians (hereafter referred to as Pharmacy Providers PP) attended the Essentials of Pharmacy Practice course provided by the ECC-SDCO and EPN. Course invitations were based on the population serviced by the different hospitals and health centres and included a random sample of other clinics. All attendees were invited to complete an anonymous written questionnaire regarding their experience with dispensing methotrexate for the treatment of rheumatic conditions. Areas addressed by the questionnaire included local drug availability, MTX counselling practices and personal confidence with counselling patients taking MTX. Descriptive statistics are reported as obtained using SPSS 24 (IBM Software).

**Semi-structured interview:** To learn about the experience of dispensing MTX pharmacists (n=2) working at the country’s sole public hospital with a rheumatology clinic (TASH), we conducted a 45-minute semi-structured interview. TASH is a teaching hospital under Addis Ababa University, College of Health Sciences. In TASH there are approximately 73 PP and 13 dispensaries supplying the emergency department, intensive care units, inpatient wards and outpatient clinics. Both PP had experience working in the inpatient wards and outpatient clinics at TASH and provided written informed consent. Both rheumatologists conducting the interview were familiar with the inpatient medicine wards and the rheumatology clinic at TASH. Interviews were audio recorded and transcribed verbatim. After defining relevant thematic codes, transcripts were reviewed and coded for themes separately by the two rheumatologists who conducted the interviews. Discrepancies usually due to elements fitting more than one theme, were resolved by consensus. Themes related to MTX dispensing patterns and barriers to dispensing were identified. The content of each theme was summarized qualitatively and informative quotations highlighted.

**Ethics:** The study was approved by the Institutional Review Boards of participating universities. Participants provided informed consent.

**Results**

**Pharmacy providers survey:** Twenty-three PP (18 pharmacy technicians; 5 pharmacists; 65% male) from hospitals and health centers of 9 regional states and 2 chartered cities of Ethiopia completed the survey [18/23 (78%) were located outside Addis Ababa]. Seven PP (30%) worked in a hospital-based pharmacy, 12 (52%) in a health center pharmacy and 4 (17%) in other areas (i.e. clinic pharmacy). The number of years of practice [median (range)] was less for pharmacy technicians compared to pharmacists [4 (1-8) vs 10(6-15) p<0.0001]. MTX was available in only 3/23 (13%) pharmacies (2 were hospital pharmacies) and only as oral tablets. Five PP reported that MTX was available in the hospital pharmacy of their region. Only 2/23 (9%) PP had dispensed MTX for rheumatic conditions. Only 3(13%) PP reported feeling comfortable educating/instructing patients on how to take MTX, (2 had counseled on MTX, 1 had not). Counselling included need for blood work (n=3), folic acid supplementation (n=3) and restricted alcohol intake (n=1). No PP reported counselling on contraception.

**Semi-structured interview:** The two interviewed pharmacists worked in the nephrology and rheumatology clinics at TASH for 2-3 years. Both had experience with MTX use mainly for haematology/oncology disorders, the primary reason for prescribing MTX in Ethiopia, but also for rheumatic diseases. Four major themes were identified from the interview: (i) access to MTX for rheumatic disease patients at TASH, (ii) barriers to prescribing MTX, (iii) MTX counselling, and (iv) patient related factors affecting MTX acceptance. Themes and representative quotations are shown in Table 1.
Table 1: Themes and representative quotations from the semi-structured interview

<table>
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<tr>
<th>Access to MTX for rheumatic disease patients at TASH</th>
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<td>&quot;For patients in this hospital to access MTX the hospital has to buy this medication through open tender… So even the hospital cannot buy this medication, why, because… since [the] Ministry of Health had a mandate to buy MTX for oncology patients, the hospital doesn’t have a chance to buy this medication in the open bid or open tenders.”</td>
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| "If the department - the rheumatology, the renal/ rheumatology department - states that MTX is vital and critical for the management of … RA patients the hospital has to accept this…it is professional judgement and anyone can say this so the hospital … will buy that medication.” |

| "Last year I think … there was a catastrophe. All MTX in the country was out of stock. Most MTX available in [the] market in the community pharmacies is counterfeit or … came into the country in the black market. So we now made it a vital medication for oncology maintenance or for the rheumatologic patients but for continuity, there is a sustainability problem… So we are not sure how much or how long the patient can access the medication, even if they are oncology patients.” |

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<th>Additional barriers to prescribing MTX at TASH</th>
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<td>&quot;…since [TASH] was the only outpatient oncology centre in [the] country, patients come from all over [the] countryside and from far away so they are given a 4-6 month supply of oral MTX and so [TASH pharmacy] runs out of stock.”</td>
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<th>MTX counselling practices of PP at TASH</th>
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<td>&quot;Pregnancy is a sensitive issue. So first of all, before I try to ask about pregnancy I create a good atmosphere to make the communication easy, then it is easy to ask whether you are pregnant or plan to be.”</td>
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| "…[patients] challenge me because I make the communication easy, I tell them ‘I am a pharmacist, don’t worry, ask me anything… what you feel’. So they tell me whatever they feel.” |

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<th>Patient factors affecting MTX acceptance</th>
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<td>&quot;… most of the patients in our country …their health literacy is poor.”</td>
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| "… there is also in our country cultural and social worries …. In our country, there are adherence issues”. |

Access to MTX for rheumatic disease patients at TASH:
At the time of the interview, all medications for the country were purchased through a central national agency (Pharmaceutical Supply and Funding Agency, PSFA) and regulated by the Federal Food Medicine Health Care Administration and Control Agency. Relevant to MTX, the Ethiopian Ministry of Health has a mandate to purchase oncology medications nationally by the PSFA (including MTX) and covers 50% of their cost for oncology patients. Access to this national supply of MTX is restricted to oncology patients and only accessible in hospitals with oncology programs (6 in Ethiopia including TASH). Further, national MTX supply is often inconsistent with intermittent availability. A second route to accessing MTX exists at TASH if the drug is considered a ‘priority medication’. Recently, MTX was included as a “priority medication” primarily for oncology although rheumatology patients can sometimes access this. A third route for rheumatology patients to access MTX is through community pharmacies however, supply is often limited, not available or of uncertain quality, and more expensive.

Parenteral MTX can be prescribed when available however, due to limited experience with using parenteral MTX for rheumatic disease, oral MTX is usually prescribed. Folic acid is readily available and usually co-prescribed. In contrast to the limited availability of MTX, oral corticosteroids are readily available from community pharmacies even without prescriptions. Patients with inflammatory arthropathies can obtain and often take corticosteroids unsupervised for disease management.

Additional barriers to prescribing MTX at TASH: The pharmacists reported that the majority of patients in the rheumatology clinic are not prescribed MTX but instead receive NSAIDs and oral corticosteroids. When prescribed, because of inconsistent supplies, MTX is often only dispensed for short intervals (i.e. a few months). Refills require repeated hospital visits which are not feasible for patients travelling extended distances and/or with financial limitations. This was felt to contribute to treatment nonadherence. Those patients depend on community pharmacies many of which do not stock MTX and if stocked the cost is much higher than at TASH. Some patients resort to obtaining their MTX from unregulated sources at even higher cost.

MTX counselling practices of PP at TASH: At TASH, pharmacists participate in patient counselling and may advise prescribers at the rheumatology clinic regarding medication options. The interviewed pharmacists estimated they identify and counsel approximately 10-20% of clinic patients about MTX. They review the patient’s chart for working diagnosis, medication history, and prescribed medications, however they do not check laboratory reports. The pharmacists report that mostly low dose MTX is used however rarely doses up to 20 mg/week are prescribed (‘2.5 mg/3x per week or 7.5 mg/week up to 20mg/week’). Pharmacists discuss indications for using MTX with the prescribing physician according to the patient’s medical situation, recognizing that MTX is first line therapy for RA. The pharmacists acknowledge the limited time of the patient-physician encounter and the lack of private areas for physician counselling on MTX at TASH. They emphasized the need to consider cultural and social aspects as well as patients’ beliefs while providing MTX counselling. Further they suggest that information...
is provided in a simple, culturally appropriate way and reinforced by confirming patients’ understanding of the discussion. They indicate that when they counsel, they include a discussion of the benefits and risks of MTX compared to other drugs that patients commonly use for arthritis (i.e., steroids and NSAIDs). The MTX side effects discussed by the pharmacists include haematological myelosuppression, hepatotoxicity, skin rash, central nervous system symptoms (i.e., confusion dizziness), GI side effects and alopecia (temporary). At the same time, patients are reassured about the benefit of MTX, and are encouraged to contact the pharmacists with further questions or concerns if needed. However, in reality there is limited opportunity for follow-up counselling.

**Patient factors affecting MTX acceptance:** According to the pharmacists, the level of health literacy among the population is generally poor even for otherwise educated individuals. The clinic environment for counselling is suboptimal thus restricting effectiveness of counselling provided by physicians. Despite fear of experiencing adverse effects, patients are generally reluctant to ask questions or address their concerns regarding medications with their physician providers. These concerns, combined with inadequate counselling and lack of clinical improvement when taking MTX (e.g., related to low medication dosing), may lead to unrecognized nonadherence. Cultural and social practices also affect adherence particularly relating to religious fasting days which impact dosing schedules.

**Discussion**

The survey and interview conducted with PP identified several key aspects limiting the use of MTX for treating rheumatic diseases in Ethiopia. These include availability of the drug in hospitals and pharmacies, experience and confidence of designated pharmacists in supplying and counselling rheumatic disease patients on MTX, and patients’ social and cultural concerns related to taking the medication.

A key limiting factor for the use of MTX in Ethiopia is maintaining a consistent availability of regulated MTX for rheumatology patients. While systems are being implemented to address this supply gap for rheumatic disease patients attending TASH, improved availability in hospitals and clinics outside of TASH remains a challenge that will hopefully be improved with increased rheumatic disease awareness.

PP play a key role in counselling patients regarding medication use and monitoring and are important partners in providing medical care, particularly in settings where physician resources are limited. Even in North American rheumatology clinics, the degree to which medication risks are discussed by physicians is limited. Patients frequently desire additional information regarding their medications yet are often reluctant to discuss their concerns. This hesitation can be even greater in settings where physicians are deemed less accessible due to clinic volume, lack of privacy, or where frequent physician turnover limits the development of patient–physician alliances. The result can be medication nonadherence particularly for patients with low health literacy. Patiennt education has been identified as one means to improve poor medication adherence in patients with arthritis and other chronic diseases in Africa and globally. Pharmacists in Ethiopia recognize their role in providing accurate and appropriate counselling regarding medication use and monitoring and the openness of the TASH pharmacists to address patient concerns is fundamental as physicians are perceived to be less accessible. This pharmacist-directed education is a critical adjunct to physician-provided counselling.

Clear, balanced discussions of risk and benefit are particularly relevant when counselling patients regarding MTX. Common misconceptions often arise regarding the toxicity of low dose compared to high dose MTX. Discussions of potential MTX toxicity that are based on the degree of risk associated with high doses used for oncology create unnecessary concern for patients, families, and care providers potentially leading to nonadherence and reluctance to take the medication even at doses needed for treating rheumatic diseases. At the same time, low dose MTX does require appropriate monitoring to ensure safety as serious toxicity can occur with misuse. It is critical that pharmacists provide balanced information on the specific benefits versus toxicity and need for appropriate monitoring. Our survey of Ethiopian PP found, at least for community pharmacists, limited experience with dispensing MTX, and a low level of confidence in counselling patients who are taking or starting MTX particularly for rheumatic diseases. While the TASH pharmacists had more experience, confidence and knowledge regarding the use of low dose MTX, they also recognized the need for specialty-specific treatment recommendations to increase their confidence and that of MTX prescribers. Recommendations on pre-MTX screening and surveillance of patients on MTX, as well as a system to ensure adequate review of monitoring investigations were identified as interventions to increase the safe use of this drug among rheumatology patients.

To be effective, education and counselling methods must acknowledge and incorporate cultural beliefs and practices. This is particularly relevant in Ethiopia where there is a rich history of traditional healing practices and holistic approaches to health and wellness often linked with spirituality. The majority of the population, particularly in rural areas, seek health care from traditional healers and many prefer to use traditional remedies over “Western medicines”. This is combined with severely limited formal “Western” health care resources including infrastructure and medication access (or affordability). Importantly for rheumatology, the safety of combining a rheumatologic medication such as methotrexate with traditional therapies is under-studied and open dialogue with patients is needed to monitor for potential unexpected adverse effects.
The pharmacists acknowledged difficulty seeing patients for follow-up counselling. Ethiopia has one of the lowest density of pharmacists per population globally with less than 500 community pharmacists in the country. While individual counselling enables patient-specific information to be provided and concerns addressed, additional patient education tools could contribute to increasing acceptance and adherence to MTX. To be effective, culturally appropriate patient-oriented educational tools, suitable for environments with limited access to modern technology are needed. Strategies and education or counselling programs such as those endorsed by the World Health Organization that safely incorporate traditional practices with “Western medicine” are most likely to be successful.

The societal impact of RA and rheumatic conditions in Ethiopia is under-recognized. Musculoskeletal conditions are among the leading causes of global physical disability and the burden to individuals and society may be especially acute in LHDI countries due to increased reliance on physical labour. In southern Ethiopia, musculoskeletal disorders were the most common chronic medical conditions identified in patients attending outpatient clinics. Although epidemiological data on RA prevalence is lacking for Ethiopia, the prevalence of RA in Africa has been estimated at 0.36% of the population (thus potentially affecting several million population) but varies widely based on region. Since there is no practicing rheumatologist in Ethiopia, the number of undiagnosed (or untreated) RA patients is likely substantial. As awareness of rheumatic conditions increases, the number of individuals prescribed medications such as MTX will also increase highlighting the importance of developing strategies to facilitate optimal care delivery. Care delivery models incorporating pharmacy-physician partnerships similar to those successfully implemented in other chronic diseases are one option.

Improving outcomes for patients with rheumatic disease, particularly in resource limited settings such as Ethiopia, requires a multidisciplinary approach that includes PP. Enhancing access to MTX and promoting training of health care professionals in patient counselling are key measures to optimize the treatment of rheumatic patients in LHDI. Increasing the number of rheumatologists (or other trained clinicians) to identify and accurately diagnose rheumatic diseases, institute and monitor appropriate treatment, and importantly provide patient counselling and support would improve patient acceptance and adherence to MTX. Establishing consistent access to a regulated supply of medication is critical for the effective and safe management of rheumatic diseases. Actionable goals include the development of culturally appropriate educational resources for patients and providers. These measures may ultimately lead to improved outcomes for rheumatology patients in Ethiopia, a country with significant needs, and can potentially be adapted for use in other LHDI African countries.

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Conflict of interest: None declared

References


Guidelines to authors

The *African Journal of Rheumatology* is published biannually by the The African League of Associations for Rheumatology (AFLAR). The journal aims to publish papers on basic and clinical research in rheumatism and arthritis and be a vessel of sharing knowledge a close the globe. Original research work, reviews, case reports and other relevant understanding that the work submitted will not be under consideration in any other journal. This must be stated by the authors when submitting papers. All submitted papers will be acknowledged and are peer reviewed. The journal will strive to communicate to the authors the verdict of the reviewers within three months from date of submission. Papers should be submitted to: The Editor, African Journal of Rheumatology, P. O. Box 29727 – 00202, Nairobi, Kenya. Email: rheumatologyjournal@gmail.com

Studies on patients and volunteers require informed consent. Authors of this kind of papers must as well state the study has been cleared by the relevant ethics committee.

Submitted papers should follow the guidelines below;

1. Original research papers should follow the IMRAD format and the abstract should be structured and not more than 30 references. The paper should not exceed 3000 words. Reviews should have an abstract, introduction and the rest of the review should have the necessary sub-headings with no more than 50 references. The review should have no more than 4500 words.

2. Case reports should have a background, introduction followed by the discussion with not more than 20 references. The word count should not exceed 2000 words. prose form and should not exceed 1500 words.

3. References should be numbered in order of appearance (Vancouver style) and only those cited should appear in the reference list.
Arthrheuma Society of Kenya consensus report: Recommendations for the management of rheumatoid arthritis

Oyoo GO1, Simani P2, Otieno FO3, Genga EK1, Syokau C1, Etau P4, Ganda B5, Mumo N6, Nakitare S8, Owino LO1, Migowa A3, Odhiambo J7, Komu R7, Odhiambo F3, Nkirote G4, Abunge D4, Mpinda B5, Biomdo I8, Omondi E1

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-pharmacologic 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 most 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. Most patients experience a chronic fluctuating course of disease that, despite therapy, may result in progressive joint destruction, deformity, disability, and even premature death. RA results in more than 9 million physician visits and more than 250,000 hospitalizations per year in the United States of America. 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. 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. 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. 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.

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 diabetes10-14. RA is also a cause of gender inequality as it predominantly affects woman. The prevention and management of RA could help reduce other NCDs by reducing shared risk factors and prevalence of systemic manifestations15. 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
- Articulargia- joint pain with absence of swelling
- Arthritis- 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
disease course, and patient demographics.

Inflammation, distribution, extra articular manifestations, investigation of six clinical factors: disease chronology, the differential diagnosis can be narrowed through 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. 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. 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).

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.

Morning stiffness lasting longer than one hour suggests inflammatory rather than mechanical etiology. 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. 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.

- 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. 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.
- Spondyloarthopathies 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 gout1,17,18.

![Figure 1: Symmetrical and asymmetrical disease](image)

<table>
<thead>
<tr>
<th>Systemic Involvement</th>
<th>Lymphatics Involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>Felty’s syndrome</td>
</tr>
<tr>
<td>Weight loss fatigue</td>
<td>Splenomegally</td>
</tr>
<tr>
<td>Susceptibility to infections</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Musculoskeletal Involvement</th>
<th>Ocula Involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle wasting</td>
<td>Keratoconjunctivitis Episcleritis</td>
</tr>
<tr>
<td>Tenosynovitis</td>
<td>Scleritis</td>
</tr>
<tr>
<td>Bursitis</td>
<td>Scleromalacia</td>
</tr>
<tr>
<td></td>
<td>Osteoporosis</td>
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</table>

<table>
<thead>
<tr>
<th>Haematological Involvement</th>
<th>Pulmonary Involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaemia</td>
<td>Eosinophilia</td>
</tr>
<tr>
<td>Thrombocytosis</td>
<td>Nodules</td>
</tr>
<tr>
<td>Lung fibrosis</td>
<td>Pleural effusions</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiovascular Involvement</th>
<th>Other Involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td>Rheumatoid nodules</td>
</tr>
<tr>
<td>Asymptomatic IHD</td>
<td>Simuses</td>
</tr>
<tr>
<td></td>
<td>Fistulae</td>
</tr>
<tr>
<td></td>
<td>Peripheral neuropathy (mononeuritis multiplex)</td>
</tr>
</tbody>
</table>

2.2.4 Disease Course

2.2.4.1 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 diagnosis8,19.

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 location17. 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 arthritis4,16. 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 arthritis4,16. The American Rheumatology Association’s revised diagnostic criteria for rheumatoid arthritis use findings from the history, physical examination, and laboratory tests4. These criteria, which have been shown to be 91 to 94% sensitive and 89% specific, are useful for establishing a diagnosis of rheumatoid arthritis4,16.

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 caution4,6. Given the high sensitivity of the currently used substrate for testing, a negative ANA test essentially rules out systemic lupus erythematosus1,5.

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 mm³ (2 x 10⁹ per L) suggests inflammation, whereas a count higher than 50,000 per mm³ (50x10⁹ per L) typically indicates synovial infection. 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.

| 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. 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

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

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. Common symptoms include joint pain and stiffness. When prolonged the disease is associated with psychological problems such as depression\(^7\). The cause of onset is currently unknown, but a genetic susceptibility to an environmental trigger seems the most plausible aetiology. Various bacteria and viruses have been suggested as the initial trigger; with a form of molecular mimicry 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. Specific manifestations may include: lymphadenopathy, rheumatoid nodules, peripheral neuropathy, pleural and pericardial effusions, fibrosing alveolitis, 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 threatening conditions.\(^\text{10}\)

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 as the initial trigger; with a form of molecular mimicry activating an immune response against the host’s own cells.

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. Total the number of swollen and tender joints.

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 of involvement of all joints is required. Figure 4 shows the homonymous suggested for documentation of joint involvement to aid in disease activity assessment.
4.0 RECOMMENDATIONS BY THE ARTHRHEUMA SOCIETY OF KENYA ON THE TREATMENT OF RA

Table 5: Recommendations for RA treatment

<table>
<thead>
<tr>
<th>PRINCIPLES OF MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>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</td>
</tr>
<tr>
<td>B. Rheumatologists are the specialists who should primarily care for RA patients</td>
</tr>
<tr>
<td>C. RA incurs high individual, societal and medical costs, all of which should be considered in its management by the treating rheumatologist</td>
</tr>
<tr>
<td>D. Patient education should form an integral part of the management of rheumatoid arthritis</td>
</tr>
</tbody>
</table>

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

[Flowchart diagram]

Failure of phase 1. Go to phase 2

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

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

[Flowchart diagram]
Figure 5b: Flow chart on RA treatment – phase 2 & 3

Table 5: List of conventional DMARDs used in RA

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Dose</th>
<th>Side effect</th>
<th>Monitoring</th>
<th>Contra-indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTX</td>
<td>First choice DMARD as monotherapy or combination therapy</td>
<td>7.5-25mg weekly orally or subcutaneously</td>
<td>Common: nausea, vomiting, mucositis, alopecia, elevated liver enzymes, neutropenia, anemia</td>
<td>Baseline CXR, Full blood count and liver transaminases within the first month of starting treatment and thereafter every 3-6 months</td>
<td>Pregnancy, breastfeeding, alcoholism, liver disorders, renal disorders, bone marrow suppression, intestinal lung disease.</td>
</tr>
<tr>
<td>HCQ</td>
<td>Mild RA or part of combination therapy</td>
<td>400mg/day (generally 200mg 3 times per week) orally</td>
<td>Common: gastrointestinal intolerance, skin hypopigmentation, headaches, dizziness</td>
<td>Less frequent: Retinopathy and myopathy</td>
<td>Caution in HIV positive patients</td>
</tr>
<tr>
<td>SSZ</td>
<td>Monotherapy if MTX contraindicated or not tolerated, or combination therapy</td>
<td>1-3g/day orally</td>
<td>Common: GI intolerance (anorexia, nausea, vomiting), skin rash, elevated liver enzymes, myelosuppression</td>
<td>Full blood count and liver transaminases within the first month of starting treatment and thereafter every 3-6 months</td>
<td></td>
</tr>
<tr>
<td>Leflunomide</td>
<td>Monotherapy or in combination with MTX</td>
<td>20mg daily</td>
<td>Nausea, vomiting, abdominal pain, diarrhea, alopecia, elevated liver enzymes, skin rash</td>
<td>Full blood count and liver transaminases within the first month of starting treatment and thereafter every 3-6 months</td>
<td>Pregnancy and breastfeeding: suspension recommended at least 2 years before possible pregnancy, alternatively cholestyramine wash out</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Dose</th>
<th>Side effect</th>
<th>Monitoring</th>
<th>Contra-indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Certolizumab</td>
<td>40mg SC week 0, 2, 4 then every 4 weeks.</td>
<td>Pegylated Fab fragment of humanized anti-TNF monoclonal antibody</td>
<td>Pyrexia, fatigue, back pain, arthralgia, serious infections, seizures, aplastic anemia, photosensitivity, optic neuritis, demyelinating CNS disease, lupus, bronchitis, dizziness, sinusitis, elevated liver enzymes, poriiasis exacerbation.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Golimumab</td>
<td>50mg SC every month.</td>
<td>Fully human anti-TNF IgG monoclonal antibody</td>
<td>Fevers and rigors within 2 hours of therapy, rash, pruritus, dyspnea, bronchospasm, flushing, angioedema, hypotension.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rituximab</td>
<td>100mg IV every 2 weeks X 2 doses.</td>
<td>Chimeric anti-CD20 monoclonal antibody</td>
<td>Fevers and rigors within 2 hours of therapy, rash, pruritus, dyspnea, bronchospasm, flushing, angioedema, hypotension.</td>
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<td></td>
</tr>
<tr>
<td>Abatacept</td>
<td>Dosed on body weight starting 500mg (&lt;60kg) to 1000mg (&gt;60kg) IV week 0, 2, 4 then every 4 weeks.</td>
<td>Fusion protein with an extracellular domain of human cytotoxic T-lymphocyte-associated antigen and modified Fe domain of human IgG1</td>
<td>Haedache, nausseropathy, hypertension, dyspepsia, UTI, diarrhea, pyrexia, abdominal rash, extremity pain, serious infections. More serious: LS, Pneumonia, cellulitis, acute pyelonephritis, anaphylactic and hypersensitivity reactions.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>4mg/kg IV every 4 weeks, increase to 8mg/kg</td>
<td>Humanized anti-IL-6 monoclonal antibody</td>
<td>Same as abactept; as well as GI perforation, neutropenia, demyelinating CNS disease, elevated liver enzymes.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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. 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.

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. 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. 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. The ACR, EULAR and ARHSK have developed recommendations for the use of these agents. 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). 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.

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. 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.

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. 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. 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. 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).

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. 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. 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. Concomitant corticosteroid use and monoclonal rather than soluble anti-TNF drugs has been shown to confer a higher risk for TB.

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.
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. 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 LTBI patients. This is the current practice has been shown to be effective in high-risk patients in Germany, Algeria and Morocco.

6.1.2 Other infections

There is an increased risk of infection amongst RA patients, particularly in patients treated with biologic therapy. 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.
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.

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 (\(\geq 10\)-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 multifactorial. 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 therapy53. 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 therapies56.

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 pregnancy57.

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 appropriate58.
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 society58. 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. EULAR recommendations have showed that the merits of effective control of RA outweigh the costs of therapy. If these fail, treatment escalations with biologic therapy are cost-effective, provided standard dosing 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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