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Medical Guidelines

Diagnosis, Monitoring and Management of Rheumatoid Arthritis

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Introduction

Rheumatoid Arthritis (RA) is a major health problem that is affecting life quality and lot of healthcare resources are utilised in the treatment and management, especially in countries with low GDP such as Pakistan[1,2]. Rheumatoid arthritis (RA) is a chronic immune mediated disease of unknown etiology that is affecting nearly 1% of the world population[3]. The major features of this disease are swelling, pain and stiffness and if left untreaded leads to permanent joint damge resulting in high rates of morbidity and mortality. RA is associated with work loss leading to augmented financial problem, amplified psychological stress, depression and, ultimately leading to decreased quality of life[4].

Need for RA recommendations in Pakistan:

As the international RA treatment guidelines are based on the data mostly collected from the research on Caucasian people, so these guidelines can not be implicated on RA patients in Pakistan[5]. The data shows that there are some infections which are very much prevalent Asian counties including Pakistan, such as tuberculosis, hepatitis B and C infection, Epstein–Barr virus infection and certain malignancies (such as T-cell and NK-cell lymphomas). Thus, there is a dire need to make country-specific treatment guidelines for RA in accordance with the local issues[4].

Due to the shortage of rheumatologists in Pakistan, RA patients are often managed by general practitioners and medical specialist along with rheumatologists. Accordingly, there is no standardized treatment guidelines for the treatment of RA. Moreover, the data is very limited to formulate evidence-based treatment guidelines in Pakistan.

Signs and symptoms of RA:

Many different diseases present with the symptom of Joint pains. In rheumatoid arthritis, symptoms are developing slowly over a span of weeks to months.

Joint symptoms may include[6]:

- Other Painful, swollen, tender, stiff joints. The same joints on both sides of the body (symmetrical) are usually affected, especially the hands, wrists, elbows, feet, ankles, knees, or neck.
- Morning stiffness: Joint stiffness may develop after long periods of sleeping or sitting. It lasts at least 60 minutes and often up to several hours.
- Bumps (nodules): Rheumatoid nodules ranging in size from a pea to a mothball develop in nearly one-third of people who have rheumatoid arthritis. Nodules usually form over pressure points in the body such as the elbows, knuckles, spine, and lower leg bones.

In addition to specific joint symptoms, rheumatoid arthritis can cause symptoms throughout the body (systemic). These include:

- Fatigue
- A loss of appetite
- Weight loss
- Low grade fever

Diagnosis of RA:

The 2010 American College of Rheumatology/ European League Against Rheumatism classification criteria for rheumatoid arthritis [6,7,8]:

Target population (Who should be tested?): Patients who
1) have at least 1 joint with definite clinical synovitis (swelling)
2) with the synovitis not better explained by another disease

Classification criteria for RA (score -based algorithm: add score of categories A –D; a score of 6/10 is needed for classification of a patient as having definite RA)

Criteria	Score
A. Joint involvement:	
• 1 large joint	0
• 2-10 large joints 1	1
• 1-3 small joints (with or without involvement of large joints)	2
• 4-10 small joints (with or without involvement of large joints)	3
• 10 joints (at least 1 small joint)	5
B. Serology (at least 1 test result is needed for classification)	
• Negative RF and negative ACPA	0
• Low-positive RF or low-positive ACPA	2
• High-positive RF or high-positive ACPA	3
C. Acute-phase reactants (at least 1 test result is needed for classification)	
• Normal CRP and normal ESR 0	0
• Abnormal CRP or abnormal ESR	1
D. Duration of symptoms	
• Less than 6 weeks	0
• More than 6 weeks	1

The presence of autoantibodies, such as rheumatoid factor (RF) and anti–citrullinated protein antibody (ACPA) (tested as anti–cyclic citrullinated peptide [anti CCP]), which can precede the clinical manifestation of RA by many years, RA is considered an autoimmune disease. Autoimmunity and the overall systemic and articular inflammatory load fuel the destructive course of the disease. However, although structural changes, which can be visualized by conventional radiography or other imaging modalities, best differentiate RA from other arthritic disorders, joint damage is seldom appreciable in the preliminary stages of disease, instead, they build up consistently over time.

Treatment Guidelines for RA:

Rheumatologists and all other medical professionals who deal with RA are part of the document's intended target audience. Its primary emphasis is on suggestions for the pharmacological therapy of RA. The document includes recommendations across the following RA treatment domains (7-10):

A) General approaches to treat RA;
B) The utility of non-steroidal anti-inflammatory drugs (NSAIDs), such as: cyclooxygenase-2 (COX-2) inhibitors;
C) The role of corticosteroids;
D) The role of conventional DMARDs (cDMARDS); and
E) The role of bDMARD agents.

A) General RA treatment strategies

1. Treatment of RA should aim to maintain physical function and good quality of life, achieving a state of long-term remission or low disease activity when remission is not an achievable goal.
2. Treatment of RA is a joint decision between doctor and patient and should be initiated as soon as the diagnosis is made.
3. The choice of treatment depends on the active disease and/or poor prognosis and comorbidities.
4. Poor prognostic factors include positivity for ACPA or RF, elevated ESR or CRP, and radiological signs of erosion or worsening of erosions.
5. All patients with newly diagnosed RA or active disease should be monitored for disease activity every 1 to 3 months.
6. Appropriate and practically standardized measurement of disease activity should be performed regularly to assess the patient's response to treatment.
7. Safety monitoring is also recommended for patients receiving bDMARD therapy.
8. All patients should be clinically evaluated when they present, for extra-articular disease manifestations, comorbidities, and infections such as TB and hepatitis. Information on vaccination status and special situations such as pregnancy and breastfeeding should be obtained.
9. If patients are in remission for 6 months, corticosteroids and NSAIDs can be gradually reduced to eventually discontinue treatment.
10. If a patient is in sustained remission for more than 6–12 months after discontinuation of NSAIDs, corticosteroids, and bDMARDs, careful tapering of cDMARDs may be attempted as a joint patient-physician decision.

B) Role of NSAIDs (including COX-2 inhibitors)

1. NSAIDs and COX-2 inhibitors should be used at a minimum effective dose for the shortest possible time

C) Role of corticosteroids

1. Monotherapy with oral corticosteroids is not recommended.
2. Oral corticosteroids can be considered to control active RA in combination with cDMARDs.
3. In the early stages of RA, the addition of corticosteroids (prednisolone ≤7.5 mg/day) to cDMARDs leads to a reduction in radiographic progression.
4. Corticosteroids should be used at the lowest possible dose with a rapid taper according to clinical feasibility.

D) Role of conventional DMARDs

1. Treatment with cDMARDs as monotherapy or

in combination should be started as soon as the diagnosis of RA is established.

2. Methotrexate is the first-line cDMARD for RA patients, and is considered as the "anchor drug".
3. Patients who are unable to tolerate methotrexate may be prescribed other cDMARDs such as leflunomide, sulfasalazine and hydroxychloroquine as first-line therapy.
4. Pre-requisite investigations for treatment: complete blood count, liver function and renal function tests, viral hepatitis serology and chest radiograph should be ordered ahead of initiating methotrexate therapy.
5. In active RA, combination therapy with cDMARDs should be considered patients, especially those with poor prognostic factors
6. Combination cDMARD therapy should include methotrexate as the anchor drug unless methotrexate is contraindicated.
7. Triple therapy with cDMARDs is another potent option in patients who have an insufficient response to methotrexate monotherapy.
8. Patients should be evaluated every 1 to 3 months after the initial treatment or change of regimen until the disease has achieved sability, is in remission or a state of low disease activity
9. For Patients whose condition has stabilized or who are in remission or have low disease activity, monitoring can be done every 3 to 6 months.
10. Definition of treatment failure: Inadequate response with cDMARDs is defined as failure to achieve remission or low disease activity after a therapeutic trial of at least two standard cDMARDs in combination at optimal doses for 6 months. One of the failed cDMARDs must be methotrexate unless methotrexate is contraindicated.

E) Role of bDMARDs

In the Southeast Asia region, there may be some circumstances in which remission or even low disease activity may not be attainable. For example, patients with advanced disease at first presentation and often severe joint deformity. The use of bDMARDs is crucial in order for these patients to achieve remission, but the irony is the non-affordability of drugs for the majority of them. Furthermore, another factor for the remission to be rendered unachievable is the involvement of the patients in jobs requiring strenuous physical labor leading to aggravation of their signs and symptoms. Thus, for many RA patients in the region, we recommend counselling to ensure compliance, and an agreement on treatment aims, maintaining symptom control and workability, to be reached upon between the clinician and the patient [7-10].

1. A bDMARD can be prescribed in patients who have inadequate response or intolerance to cDMARDs.
2. An earlier use of bDMARD can be considered in patients who have an active disease with poor prognostic factors.
3. Before initiating treatment with bDMARDs, a history regarding active or current infections, comorbidities including tumours and malignancies, vaccinations, pregnancy, and possible contraindications should be obtained in all patients.
4. Prior to ensuing treatment with bDMARDs, all patients should be screened for Tnd HBV and HCV infections.
5. Live vaccines should be given at least 4 weeks before bDMARD administration.
6. Monotherapy or combination with methotrexate/ cDMARDs: bDMARDs are most fruitful when combined with methotrexate.
7. In patients with RA who are candidates for bDMARD therapy, the therapeutic options encompass TNF antagonists, abatacept, rituximab and tocilizumab.
8. Patients who have not achieved remission or a decreased disease activity after 6 months of bDMARD therapy are recommended to change over to another bDMARD agent.

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