Difficult to treat rheumatoid arthritis: a review and relevance to Africa

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Abstract

Background: Rheumatologists are sometimes confronted with rheumatoid arthritis patients, who despite adequate management are unable to achieve a remission or low disease activity; of recent, the terminology 'Difficult-to-Treat Rheumatoid Arthritis' has been adopted.
Objective: To identify the definition, causes, and management of these patients. The peculiar factors causing 'Difficult-to-Treat RA' in African patients are also identified.
Data source: These were obtained from literature search on this subject as stated in the references and on Pubmed search
Conclusions: Difficult-to-Treat RA constitutes a large group of patients in rheumatology practice. The causes are multifactorial. It is important to identify the factors responsible in the patients and institute appropriate measures. Since the definition factors the use of Biologics or JAK inhibitors, rheumatologists in Africa need to do further research on this subject while also providing the definition and management of this condition.

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Introduction

There have been a lot of development in the management of rheumatoid arthritis, beginning with numerous NSAIDs; glucocorticoids; early synthetic DMARDs such as D- penicillamine, Gold salts; newer synthetic DMARDs such as methotrexate, sulfasalazine, leflunomide, and hydroxychloroquine.

There are now numerous Biologic DMARDs which have revolutionized the management of RA. The latter have been followed very closely with the oral targeted therapy such as the Janus kinase inhibitors. At every stage of the evolution of these medications, the primary objective has been to achieve a remission and low disease activity, especially since a cure may be unachievable. There has also been evolution of various tools to measure in quantifiable numbers achievement of such remission with an option of low disease activity if the former is unachievable. The goals of remission and low disease activity are set up to minimize chronic pain, deformities, disabilities, other morbidities, and even deaths. Treatment to target enables us to set achievable goals. Despite all these medications, remission is not achievable in many patients and these have come to be classified in recent times as "Difficult-To-Treat Rheumatoid Arthritis" (D2T RA)[1] a nomenclature borrowed and adapted from similar concepts as used in medical specialties such as asthma, psychiatry and hypertension respectively[2-4]. When this term is used by rheumatologists, we are assuming that the patient is taking the medications as prescribed by a knowledgeable rheumatologist. We assume that the patient is not stopping the medications because of tolerability or affordability issues.

Definitions

Many attempts have been made to arrive at the definition of the term 'difficult-to-Treat RA'

The Task Force in charge of the 'Development of EULAR recommendations for the comprehensive management of difficult to treat rheumatoid arthritis' ruminated over this and had proposed different terms to describe this population, such as 'severe', 'refractory' 'resistant to multiple drugs or treatments' Eventually the term 'Difficult-to- treat RA' was chosen[1].

There are two major definitions:-

1. "Persistency of signs and/or symptoms suggestive of inflammatory RA disease activity despite prior treatment with csDMARDs and at least two bDMARDs" [5].
2. EULAR criteria which are fuller and more explanatory[1]. These criteria have been further expanded by van Laar at the 2022 Eular Congress as cited by Jason Liebowitz[6].

(i) Treatment according to EULAR recommendations of management of RA and failure of ≥ 2 biologic

DMARDs / targeted synthetic DMARDs (with different mechanisms of action) after failing csDMARD therapy.

(ii) Presence of at least one of the following: signs and/or symptoms suggestive of active or progressive disease. The latter is characterized by such features as moderate disease activity as assessed by Clinical Disease Activity Index (CDAI) or other tools; active synovitis on examination; elevated inflammatory markers; new erosive disease on imaging. Inability to taper glucocorticoid treatment to less than 7.5mg of prednisolone daily also qualifies as well as rapid radiographic progression. RA symptoms that are causing a reduction in quality of life are also factored as difficult to treat, as well as: -

(iii) The management of signs and/or symptoms is perceived as problematic by the rheumatologist and/or the patient.

The EULAR criteria for D2T RA were developed based on the data from a previous international survey; though this survey did not include African countries, as may be obvious in the emphasis on biologics, which are mostly unavailable or unaffordable. There are however some clarifications. For instance, a footnote on these set of criteria admits that 'socioeconomic factors may limit the access to expensive DMARDs (e.g., in low-income countries). As such a clause was added to the criteria to recognize this limitation. A previous study has identified lower socioeconomic status at onset of RA as an independent risk factor for the development of difficult-to-treat disease[7].

Why we should worry about "Difficult- to- treat RA patients"

High disease activity is normally associated with D2T RA thus leading to challenges with the following: - (a) social life (b) work ability (c) quality of life (d) psychological well-being (e) comorbidities (f) mortality (g) health care utilization, hospitals budgets and (h) society cost. All these will be particularly applicable to African countries. Studies have shown that "Difficult-to-treat" cases may be present in 5-20% of all patients with RA[1]

Factors contributing to "Difficult-To-Treat RA"

There are many factors, including delay in diagnosis, contributing to refractory or "difficult-to-treat RA"[8,9].

Determinants of drug loss of efficacy and "Difficult-to-treat RA"

1. Smoking[10]

a) Associated with immunologic mechanism in production of RF, ACPA.
b) Increased production of pro-inflammatory cytokines and T- cells with a resultant enhancement of systemic inflammation.
c) Smokers are shown to require higher doses of DMARDs, with the potentiality of resultant adverse effects.
d) However, studies (CORONA registry and BARFOT study) have not shown that cessation of smoking can influence disease activity[11].

2. Immunologic mechanisms[12,13]

a) The response to medications varies in patients because of the variable biology of underlying immunologic processes and pathways.
b) Variable synovial expression of TNF and presence of lymphocyte aggregates at the initiation of treatment with infliximab, for example, correlates with disease activity.
c) Variable treatment response to factors such as CD 68 positive macrophages and plasma cells.
d) Synovial fibroblast differences with resultant variable secretion of pro-inflammatory cytokines.
e) Different biomarkers reflecting exact molecular mechanism of inflammation are variable in individual patients.
f) It has also been shown that in patients with D2T RA, the persistent synovitis is regulated by stromal cell activities which are not affected by the medications used in the treatment of RA.

3. Pharmacogenetics[5]

a) This may explain the ineffectiveness of anti-rheumatic drugs and adverse drug reactions in patients. Different genetic make-up will result in variable responses and adverse effects.
b) For a drug like methotrexate, for example, folate antagonism also targets other related pathways – including homocysteine – methionine – polyamine pathway and purine metabolism. Thus, variants cause different effectiveness and toxicity.
c) Several polymorphisms of Anti TNF as seen in RA will result in variable responses.

4. Immunogenicity of biologic DMARD[14,15].

a) It is well known that 20-30% of RA patients may not respond to first bDMARD especially anti-TNFs
b) Within 2-3 years of initiating bDMARDs, 20% have secondary ineffectiveness.
c) Anti–drug antibodies (ADAs) play a big role, both neutralizing and non-neutralizing. This is more so with anti –TNFs, leading to loss of efficacy and adverse drug reactions (ADR),
d) Risk of ADAs is however reduced by 74% when there is concurrent administration of methotrexate.
e) Biologic DMARDs with low immunogenicity include rituximab, tocilizumab, and abatacept,

5. Recurrent drug reactions[5]

a) This can affect drug dosing, drug compliance, and subsequent treatment steps.
b) About 66% of all bDMARDs are discontinued over time due to adverse drug effects- 46% and loss of efficacy – 41%.

c) Increasing age increases adverse drug reactions.
d) High ESR, and CRP is associated with ADRs.
e) Patients generally report more ADRs than their physicians.
f) However, not all reported ADRs are due to the DMARDs as they may be due to other medications or co-morbidities.

6. Negative disease outcomes:

a) Over time, patients begin to doubt if they will ever get better. Psychological tiredness and frustration normally associated with chronic painful conditions.
b) Fibromyalgia and joint damage- frustration and negative disease outcomes as well as exaggeration of pain and adverse effects[16].
c) Secondary Sjogren's syndrome is associated with increasing pain.

7. Comorbidities

a) Obesity in particular can worsen the subjective measures of disease activity, reduce the likelihood of establishing remission, and can also reduce efficacy of drugs used. It may also reduce the probability of sustained remission.
b) ESR is higher in obese patients with tendency to over-treatment and adverse effects resulting in a vicious circle of pain, frustration, and poor drug compliance.
c) Certain medical comorbidities may cause DMARDs to be less effective. They can also facilitate adverse effects and may end up making it more difficult to grade the patient's disease severity and often leading to inappropriate treatment. An example is fibromyalgia which is commonly associated with RA.

8. Medication compliance

a) Compliance in rheumatic disease may vary between 30 - 99%.
b) Compliance in other chronic diseases generally may be up to 50%.
c) Multiple factors- the disease itself, adverse effects, pill overload, treatment characteristics (tablets, injections, infusions) characteristics of health care system – patients with HMO for instance do better than patients paying out of pocket.
d) Psychological state of a patient to the illness which may be one of optimism, pessimism, or nonchalance.
e) Associated psychological disorder – There is a well-recognized high prevalence of anxiety, depression, and alcohol use in patients with D2T RA.

9. Inappropriate medication responses

a) Poor drug storage. Electricity may not be available and as such biologics will lose their efficacy.
b) Poor communication with the rheumatologist or assistant.
c) Hearing difficulties, especially with elderly patients.

Peculiar factors contributing to "Difficult -To -Treat RA" in Africans

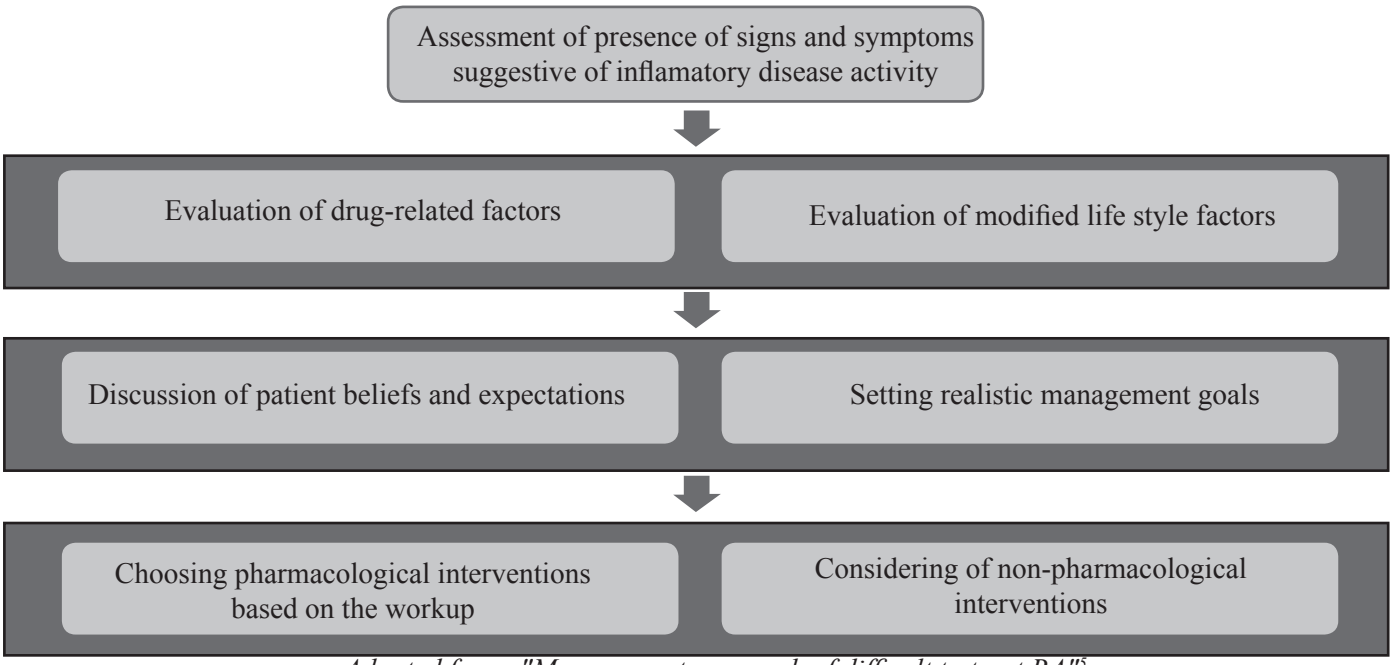
There are certain peculiar factors in African countries that may result in the inability of RA patients to achieve remission thus causing characterization as D2T RA.

i) Basic belief that RA is due to a 'Spiritual attack' or some evil spirits thus patient may stop taking DMARDs.
ii) Tendency to seek 'cheaper' treatment such as herbs because of the cost of DMARDs. We do not know what the drug-drug interaction will be in such cases.
iii) Poor education.
iv) Assumption that RA can be cured and thus patients tend to stop medications when pain appears less.
v) Ready availability of prednisolone over the counter. Patients indulge in them with attendant adverse effects and loss of drug efficacy.
vi) Lack of electricity and thus loss of efficacy of cold chain product as well as resultant possible adverse effects.
vii) Delay in presentation to a rheumatologist, averagely 3-4 years. Resultant high disease activity. Synthetic DMARDs may thus not work effectively.
viii) It is presently not possible for most African countries to apply 'Difficult-To-Treat' concept as enunciated by EULAR because of the non-availability or non-affordability of biologics and JAK inhibitors.

1. Education – Rheumatologists must work with, and on patients.
2. Psychological interventions such as cognitive behaviour therapy, mindfulness, relaxation techniques, hypnotherapy[2].
3. Physical therapy- Ultrasound, laser therapy, balneotherapy, electrotherapy, aerobic exercises, muscle strengthening, mobilisation, orthoses[2].
4. Special sports activities, dancing, tai-chi[2].
5. Diet.
6. Acupuncture.
7. Mimics of RA such as polyarticular gout and CDPD disease should be excluded.
8. Evaluation of drug related factors. Choosing a more appropriate bDMARDs for each patient based on the genomics.
9. Distinguish symptoms of ADRs from those caused by RA. May withhold medications for some time or lower the dose.
10. Factors such as non- compliance and inappropriate storage of bDMARDs to be identified.
11. Evaluation of modifiable lifestyle factors such as obesity, smoking cessation.
12. Setting realistic goals. Low disease activity if remission is not achievable.
13. Consideration of non-pharmacological interventions – Orthopaedic surgeon, pain physician, physiotherapy.
14. Careful choice of pharmacological agents.

Management

Figure 1: Schema showing outline of approach to management of "Difficult-To-Treat RA"



Adapted from; "Management approach of difficult to treat RA"[5]

Questions to ask ourselves as rheumatologists

1. Are we setting too high a target we want to achieve? Will moderate disease activity be sufficient in certain patients?
2. Will these patients do better when referred to another rheumatologist?
3. As more effective molecules are approved, will we still have difficult to treat RA in 10 years? Will our definition change?
4. Can African rheumatologists define their own 'Difficult to Treat' cases based on drugs available to them?
5. Can we change the order of our management? Can we for instance start with Biologics or JAK inhibitors?
6. Can we combine Biologics and JAK inhibitors?

Conclusions

The concept of "Difficult-to-Treat RA" is recent but it clearly identifies many cases of RA that do not reach target marks in diseases evaluation on treatment. The definitions based on poor response to Biologics and JAK inhibitors identifies that the patients are on optimal management regimens. Factors contributing to this poor response both globally and in African populations have been identified. It is important that African rheumatologists identify the factors contributing to "Difficult-To-Treat RA" and provide guidelines to its management taking into cognizance the poor penetration of Biologics and JAK inhibitors in most African countries.

Declaration: The article has been adapted from Janssen Virtual lecture "Rheumatology masterclass for sub-Saharan Africa: difficult to treat rheumatoid arthritis. What to do?" Adelowo OO. October 25, 2022

References

1. Nagy G, Roodenrijs NMT, Welsing PMJ, *et al.* Eular definition of difficult to treat Rheumatoid arthritis. *Ann Rheum Dis.* 2021; **80**:31–35.
2. Robinson DS, Campbell DA, Durham SR, *et al.* Systematic assessment of difficult–to–treat asthma. *Eur Respir J.* 2003; **22**:478-483.
3. Thase ME. Therapeutic alternatives for difficult-to-treat depression: a narrative review of the state of the evidence. *CNS Spectr.* 2004; **9**:808-821.
4. Papademetriou V, Tsioufis C, Gradman A, *et al.* Difficult-To-Treat or resistant hypertension: etiology, pathophysiology, and innovative therapies. *Int J Hypertens.* 2011; **2011**:1-4.
5. De Hair MJH, Jacobs JWG, Schoneveld JLM, *et al.* Difficult-To-Treat rheumatoid arthritis: an area of unmet clinical need. *Rheumatology.* 2018; **57**:1135–44.
6. Liebowitz J. Not your average case: Difficult-to-treat rheumatoid arthritis. *The Rheumatologist.* 2022; **18**(9):23.
7. Roodenrijs NMT, van der Goes MC, Welsin PMJ, *et al.* Difficult-to-treat rheumatoid arthritis: Contributing factors and burden of disease. *Rheumatology* (Oxford). 2021; **60**(8):3778-88.

8. Anderson JJ, Wells G, Verhoeven AC, Felson DT. Factors predicting response to treatment in rheumatoid arthritis: the importance of disease duration. *Arthritis Rheum.* 2000; **43**:22-29.
9. Unger M, Alasti F, Supp G, Smolen JS, Aletaha D. The good, the bad and the ugly refractory rheumatoid arthritis in 2016. *Arthritis Rheumatol.* 2016; **68**(Suppl 10): Abstract No.3015.
10. Fisher MC, Hochberg MC, El-Taha M, *et al.* Smoking, smoking cessation, and disease activity in a large cohort of patients with rheumatoid arthritis. *J Rheumatol.* 2012; **39**:904-909.
11. Andersson ML, Bergman S, Soderlin MK. The effect of stopping smoking on disease activity in rheumatoid arthritis (RA). Data from BARFOT, a multicenter study of early RA. *Open Rheumatol J.* 2012; **6**:303-399.
12. Haringman JJ, Gerlag DM, Zwinderman AH, *et al.* Synovial tissue macrophages: a sensitive biomarker for response to treatment in patients with rheumatoid arthritis. *Ann Rheum Dis.* 2005; **64**:834-838.
13. Thurlings RM, Vos K, Wijbrandts CA, *et al.* Synovial tissue response to rituximab: mechanism of action and identification of biomarkers of response. *Ann Rheum Dis.* 2008; **67**:917-925.
14. Schaeverbeke T, Truchetet ME, Kostine M, *et al.* Immunogenicity of biologic agents in rheumatoid arthritis patients: lessons for clinical practice. *Rheumatology.* 2016; **55**:210-220.
15. Leon L, Rodriguez-Rodriguez L, Rosales Z, *et al.* Longterm drug survival of biological agents in patients with rheumatoid arthritis in clinical practice. *Scand J Rheumatol.* 2016; **45**:1-5.
16. Pollard LC, Kingsley GH, Choy EH, Scott DL. Fibromyalgic rheumatoid arthritis and disease assessment. *Rheumatology* (Oxford). 2010; **49**(5):924-928.