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The identification, goals and principles of difficult-to-treat inflammatory arthritis: a consensus statement

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Abstract

Background Despite the recent advances in the management of inflammatory arthritis, a considerable proportion of arthritis patients remain symptomatic. This cohort has recently been identified as 'difficult to treat' (D2T). In view of the limited evidence base, management of these patients has been a challenge particularly in view of its associated significant economic health burden. A better understanding of the D2T may help recognise or develop new therapeutic targets and facilitate earlier intervention in the disease course to prevent the progression of such condition.

The aim of this work is to address the unmet needs in the management of D2T arthritis and develop a comprehensive approach towards the identification and proper assessment of those patients.

Results At the completion of round 3 Delphi process, a total of 20 items were obtained and divided into 5 domains. From 88.9 to 100% of respondents agreed with the recommendations (ranks 7–9). All 20 of the clinical standards that the scientific committee identified were agreed upon in terms of wording, recommendation grade, and level of evidence (i.e. 75% of respondents strongly agreed or agreed).

Conclusion D2T inflammatory arthritis remains a relevant clinical challenge, despite the endorsement of the treat-to-target approach and the availability of a broad range of targeted arthritis medications. This study provided a comprehensive definition of the condition to facilitate the identification of this patients' group. It also highlighted the goals and principles aiming at providing an effective framework for D2T assessment, closely monitor and set up a strategy to intervene in standard clinical practice.

Keywords Difficult to treat, Rheumatoid arthritis, Synovitis, Disease-modifying drug therapy, Goals, Principles, Patient-centred care, Self-management, Shared decision making, Patient-reported outcomes

Background

The past decade has witnessed two major developments in the management of inflammatory arthritis, these are early rheumatoid arthritis classification criteria and treat-to-target management approach [1, 2]. Furthermore, since their introduction into clinical practice, biologic disease-modifying anti-rheumatic drugs have transformed the management of inflammatory arthritis

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enabling the treating rheumatologists to achieve their anticipated treatment target [3]. However, in spite of all these achievements, in standard clinical practice, all rheumatologists are familiar with a group of inflammatory arthritis patients who continue to show suboptimal response to management, with symptoms and signs suggestive of activity of the arthritic disease despite treatment with several conventional/ targeted synthetic as well as biological DMARDs (csDMARDs, tsDMARDs and bDMARDs). The underlying mechanisms of such poor response have been attributed to disease heterogeneity. Heterogeneity is not only clinical but also related to the pathogenic pathways that cause the disease in a particular patient [4]. This highlighted a gap in the current management paradigm where there are unmet needs in the management of patients living with inflammatory arthritis.

Rethinking the patient has highlighted the concept of patienthood and the need to adopt a new model of a relationship between patients living with arthritis and healthcare services, using the burden of treatment theory to understand the changing dynamics of chronic illness [5, 6]. The perceived management difficulties in patients with inflammatory arthritis were highlighted by a recent international rheumatology survey [7]. The results of the survey showed that new concepts and management strategies are required for the best treatment of this cohort of persistently active patients. This subgroup of arthritis patients has been referred to using a variety of terms, including treatment-resistant arthritis, established, severe, refractory, and difficult to treat [8–11]. The term 'difficult to treat' (D2T) has been chosen to describe this cohort of patients with inflammatory arthritis in line with other diseases in medicine. The task force recently developed terminology and a definition for this complex RA patient population in light of the survey's findings [12].

The exact prevalence of difficult-to-treat inflammatory arthritis remains unknown, but a recent audit of our local rheumatology service revealed an estimated 10% of all RA patients meet the EULAR definition. Due to a lack of knowledge about the various contributing factors of difficult-to-treat arthritis and their individual weights, treatment steps and decisions for each individual patient are based on trial and error in clinical practice. Patients will continue to suffer from symptoms that have a direct impact on their quality of life, functional ability, ability to work and general health until an effective treatment strategy or model is recommended. Aside from the personal impact, difficult-to-treat inflammatory arthritis has a negative impact on health-care resources, budgets and societal costs [9]. Based on these facts, this work was carried out to address the unmet needs of D2T arthritis and develop a comprehensive approach towards early identification and proper assessment of those patients.

Methods

Design

The evidence-based consensus concerning the D2T and unmet needs in the management of the rheumatoid/ inflammatory arthritis was developed adopting a multistep process strategy. The study followed the Clinical, Evidence-based, Guidelines (CEG) initiative protocol which was approved by the local institutional ethical committee. The manuscript conformed to the preferred reporting items for systematic reviews and meta-analyses guidelines for reporting systematic reviews [13].

Development stages

Core team

It was formed by four rheumatologists with professional experience in inflammatory arthritis management. The core team supervised and coordinated the teamwork, assisted with developing the scope of the project, developing the key clinical questions, and reaching a consensus on the key questions to include in the recommendations. The team also nominated the expert panel and drafted the manuscript.

Key questions used to develop the guideline

These recommendations are based on a list of structured key questions that define: (1) the terminology and definition of D2T, (2) the assessment of D2T or suspected D2T, (3) the goals of the management of D2T and (4) the principles of the management of D2T 5. How to put goals and principles into practice. The evidence to answer the clinical questions was gathered in the following steps: clinical questions formulation, question structuring, evidence search, evaluation and selection of evidence, results presentation, and recommendations. These questions, as shown in Table 1, served as the foundation for the systematic literature search and, as a result, the clinical care standards.

Literature review

The review of literature was conducted with the aid of a methodology expert under the supervision of an expert literature review consultant and based on the specific research questions identified to concentrate on the management of D2T inflammatory arthritis patients. The required evidence-based data was gathered through a systemic literature search using the PubMed/MEDLINE, EMBASE and Cochrane databases. After data abstraction, reviewing the published recommendations, and evaluating the quality of the evidence, a revision was made [14].

Table 1 Key Clinical Questions used to develop this recommendation

Core item	Key clinical question	Domains
4. Definition	1. How to describe this patient cohort?	1.1. Terminology & definition of D2T
		1.2. Challenges in identifying D2T
5. Characteristics	2. What are the characteristics of D2T and how to assess D2T patients?	2.1 Patient characteristics
		2.2 Illness characteristics
		2.3 Treatment history characteristics
		2.4 Assessment of D2T patients (PROMs/Lab/US)
		2.5 Comorbidities
		2.6 In what aspects is D2T different?
6. Goals	3. What are the goals of the management of D2T?	3.1 Strive for optimal symptom control
		3.2 Reduce risks and impact of flare-ups/relapse
		3.3 Optimization of HRQoL/functioning' and return to a 'meaningful life'
		3.4 Optimize treatment adherence
7. Principles	4. What are the principles of the management of D2T?	4.1 Identification of treatment goals based upon 'shared decision making' with the patient
		4.2 Implementing measurement-based care
		4.3 Enhance engagement and regular monitoring under care of the service
		4.4 Supporting self-management strategies
		4.5 Set up 'integrated service pathways'
		4.6 Frequent re-assessment and consideration of treatment direction
8. Clinical approach of tackling D2T in standard practice	5. How to put goals and principles into practice?	5.1 Treatment strategy
		5.2 Measuring treatment success

Systematic reviews, randomised controlled trials (RCTs), uncontrolled trials and observational studies including cohort, cross-sectional and case–control studies were included, while editorials, narrative/personal reviews, non-evidence-based, commentaries and conference abstracts, as well as manuscripts without English versions, were excluded.

Expert panel

The core leadership team nominated twenty people who constitute the expert panel. Their selection criteria included having professional experience in the field of rheumatology, managing inflammatory arthritis, and actively participating in scientific research on rheumatic diseases. The project's scope was developed by the expert panel which worked to refine the key clinical questions. They received recommendation statements along with the evidence report, and they voted on the recommendations.

Delphi process

The Delphi method is a forecasting process and structured communication framework based on the results of multiple rounds of questionnaires sent to a panel of experts A detailed description of the Delphi process was mentioned an a previous research [15–18].

The first round was held between July 19 and July 22, 2022 (3 days). The aspects about which respondents did not reach a consensus in this first round were revised in view of the comments and included in the second round. The second round took place on July 25–28 (lasted for 3 days), and the third round lasted for 5 days (31 July–5 August 2022).

Results

Literature research and evidence selection

A search strategy identified 1398 potentially relevant studies during the study selection process. After screening the titles and abstracts, 1284 were excluded due to duplicates. As a result, 114 relevant studies were included in the full article review, plus 3 additional studies discovered in an updated literature search. Thirty-nine studies were excluded because they did not correspond to the study design of interest. As a result, 78 studies were included in this work.

Delphi rounds

The Delphi form was sent to the expert panel ($n=20$), with 18 (90%) completing all three rounds. The first round was devoted to the key clinical questions, which included 27 items. For repetition, one item was retired. Three items were changed as a result of the expert panel's comments: one domain in characteristics and two domains in management. The expert panel's response rate for round 2 was 100% (18/18). For eight statements, wording changes were suggested. The statements have been changed and amended. A consensus was reached for all statements (80% of respondents strongly agreed or agreed). The expert panel's response rate for round 3 was 100% (18/18). For six statements, wording changes were suggested. The statements have been changed and amended. Consensus was reached for all statements (80% of respondents strongly agreed or agreed). (Table 2).

In light of those results, this document was created, which includes answers to key clinical questions as well as recommendations for the characteristics and management of D2T.

Figure 1 illustrates the algorithm for these recommendations, which involve a personalised care approach for D2T patients.

Statements: Unmet needs in the treatment of inflammatory arthritis.

1. How to describe this patient cohort?

1.1. Terminology and definition of D2T (LOE:2C GOR: C)

Definition of D2T

'Arthritis that remains persistently active [I] and/or continues to cause significant burden [II] despite standard treatment [III] as perceived by the treating rheumatologist and/or the patient [IV],

I. **Persistent joint inflammation (active/progressive disease)**: defined as ≥ one of:

a. At least moderate disease activity (according to validated composite measures including joint counts, for example, DAS28-ESR > 3.2 or CDAI > 10 for 2 readings 3 months apart).

Table 2 Breakdown of statements' level of agreement, its individual mean and SD as rated by the experts' opinion

Statements	1–3	4–6	7–9	Mean	SD
1. Terminology and definition of D2T					
1.1 Terminology and definition of D2T	0	2	16	8.17	1.17
1.2 Challenges in identifying D2T	0	1	17	8.61	0.76
2. Characteristics of D2T					
2.1 Patient characteristics	0	0	18	8.39	0.83
2.2 Illness characteristics	0	0	18	8.61	0.49
2.3 Treatment history	0	1	17	8.5	0.96
2.4 Assessment of D2T	0	0	18	8.39	0.83
2.5 Assessment of comorbidities	0	0	18	8.83	0.37
2.6 In what aspect D2T is different	1	0	17	8.39	1.83
3. Goals of management of D2T					
3.1 Goal 1: Optimum symptom control	0	1	17	8.73	0.72
3.2 Goal 2: Reduce risks of flare-up/relapse	0	1	17	8.56	1.012
3.3 Goal 3: Optimize QOL/functioning	0	0	18	8.72	0.45
3.4 Goal 4: Optimize treatment adherence	0	0	18	8.67	0.47
4. Principles of management of D2T					
4.1 Principle 1: Shared decision making	0	0	18	8.78	0.42
4.2 Principle 2: Measurement-based treatment	0	0	18	8.67	0.47
4.3 Principle 3: Enhance engagement and regular monitoring under care of the service	0	0	18	8.67	0.58
4.4 Principle 4: Adopting self-management to empower the patients	0	0	18	8.39	0.68
4.5 Principle 5: Set up 'integrated patient-centered service pathways	0	1	17	8.39	1.06
4.6 Principle 6: Frequent re-assessment and consideration of treatment direction	0	0	18	8.61	0.59
5. Tackling of D2T in standard practice					
5.1 Treatment strategy	0	0	18	8.67	0.67
5.2 Measuring treatment success	0	0	18	8.72	0.56

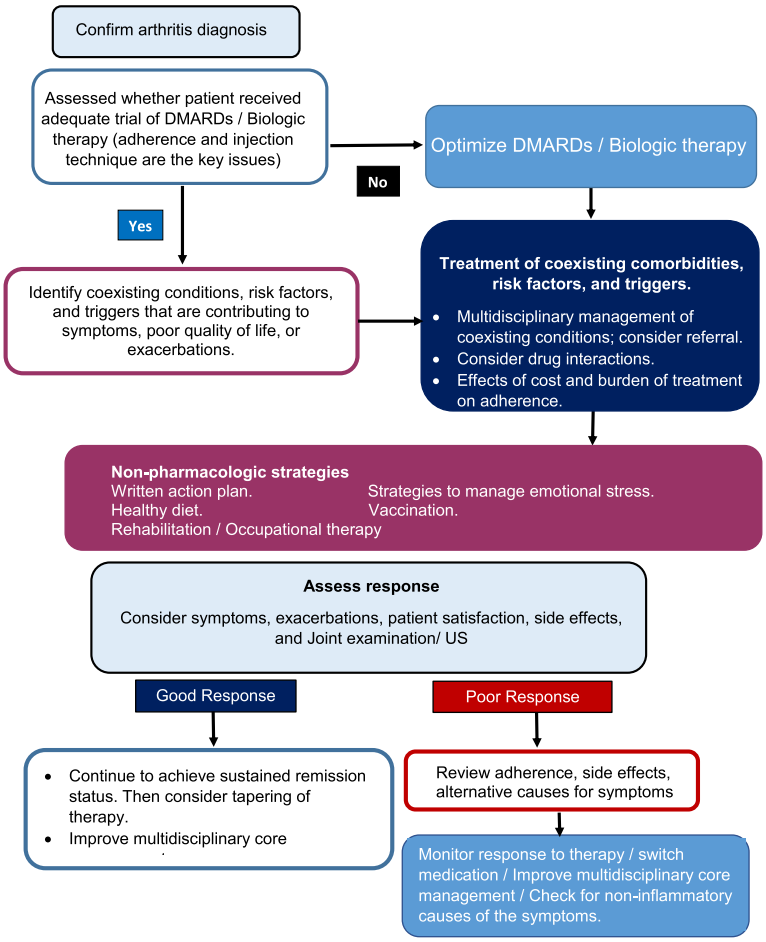

Fig. 1 Suggested treatment strategy for difficult-to-treat inflammatory arthritis

b. Ultrasound findings suggestive of persistent activity: Synovial hypertrophy, enhanced vascularity more than or equal grade 2, in 2 visits 3 months apart.
c. Progressive joint damage (with or without signs of active disease) defined as:

- Change in van der Heijde-Modified Sharp Score ≥ 5 points in 1 year.
- Progressive joint damage in the form of development of new erosions detected by musculoskeletal ultrasound (MSK-US) in 1 year.

d. Inability to taper glucocorticoid treatment (below 7.5 mg/day prednisone or equivalent).
e. Progressive deterioration of functional ability and quality of life (QoL) (deterioration more than critical difference value) despite of well-controlled disease according to the above standards, over 6 months period.

II. 'Continuous burden' is identified as having difficulties in:

– Achieving treatment target: low disease activity or remission
– Controlling disease progression.
– Sustained elevation of the acute phase response over 3 months period attributed to the inflammatory joint disease.
– Lack of functional restoration and poor quality of life despite good symptomatic control.
– Treatment compliance due to: unacceptable tolerability or non-adherence or rejection of the treatment option.

III. Standard treatment

Treatment according to guidelines: 2 cDMARDs and 2 Biologic therapy agents.

If csDMARD treatment is contraindicated, failure of ≥ two b/tsDMARDs with different mechanisms of action is sufficient.

IV. Clinical perception: Manifestations suggestive of active/progressive disease, over 3 months period, as reported by the treating rheumatologist and/or the patient include the following:

- Patient: Symptoms suggestive of progressive or persistent active disease (whether joint-related, HRQoL or other)
- Healthcare professional
  - Persistent joint swelling (> 3 joints) over 3 months period.
  - Persistent tendinitis/ tenosynovitis, development of deformities or joint subluxation.
  - Development of extra-articular manifestations, e.g. vasculitis, eye: scleritis/uveitis, heart: pericarditis, bone: osteoporosis, kidney: glomerulonephritis.

1.2. Challenges in identifying D2T (LOE:5GOR: D)

- Optimal confirmation of the diagnosis of inflammatory arthritis, particularly the inflammatory origin of the current symptoms is critical in the management of D2T patients.
- Ruling out other conditions that mimic RA, such as crystal arthritis, and lupus as part of making the RA diagnosis process.
- Presence of fibromyalgia and obesity was found to hamper proper grading of disease activity using traditional composite indices in patients with inflammatory arthritis. MSK-US can be of value to assess inflammatory arthritis activity in patients with these comorbidities.
- Secondary Sjogren syndrome (SS) in inflammatory arthritis is associated with chronic widespread pain, higher self-perceived levels of disability and deteriorated quality of life, as well as fatigue which negatively influence several measures of disease activity.
- Complications of the disease or negative disease outcomes, such as secondary fibromyalgia or joint damage (secondary OA), may lead to difficulty in interpreting and managing signs and symptoms. As they obscure clinical assessment of the inflammatory arthritis disease activity, in general giving the impression that the arthritis is more active than it really is.

2. What are the D2T characteristics? (LOE:2C GOR: C)

2.1. Patient characteristics

- Young age at onset.
- Poor socioeconomic status.
- Interfering comorbidities.
- Fatigue.
- Low motivation.
- Smoker.
- Poor treatment adherence.

2.2. Illness characteristics

- High baseline disease activity.
- Persistence of moderate disease activity measured by composite measures assessing 28 joints (> 3.2 for 3–6 months or signs suggestive of active disease.
- Progressive worsening of functional ability/HR QOL.
- Inability to taper glucocorticoid dose below 7.5 mg/day prednisone or equivalent.
- Extra-articular manifestations.
- Polypharmacy.
- High baseline anti-CCP or RF titers

2.3 Treatment history characteristics

- Long-time gap between diagnosis and onset of treatment.
- The types of medication previously used may help to decide subsequent treatment choices and give information about the degree of difficulty that might be expected in the future treatment plan.
- The adequacy of previous management should be assessed and whether the inadequacy is due to suboptimal dose or inappropriate medication use.
- Treatment failures throughout the disease management course and whether it is primary versus secondary drug failure are relevant. It is also important to consider whether the discontinuation is due to development of side effects or toxicity.
- Given the importance of remission for maximising HRQoL and minimising the risk of relapse, partial but inadequate response should also be considered a treatment failure.

- Possible causes of limited drug options should be investigated; low socioeconomic status, associated comorbidities, or fear from possible side effects.
- Identifying non- or partial-adherence is relevant to consider and possible causes of non-adherence should be investigated.
- History of intervention procedures carried out in the past and its outcomes should be taken.

2.4. Assessment of D2T patients

- Multidimensional patient-reported outcome measures (PROMs) (LOE:2C GOR: B)

It can be one of the best approaches for assessment of D2T patients. Multidimensional PROMs include assessment for:

- HRQoL: functional disability/QoL
- Pain score, morning stiffness, fatigue, patient global assessment, tender and swollen joint count, and patient motivation.
- Causes of patient's pain and disability: due to past joint structural damage, coexisting OA, or actual inadequate disease control.
- Assessment of the PROMs should be quantifiable and sensitive to change.
- Clinical assessment: signs of persistent inflammation (synovitis and/or systemic)
- Disease activity score: using validated composite measures (LOE:2B GOR: B)

- Clinical assessment: signs of persistent inflammation (synovitis and/or systemic)
- Disease activity score: using validated composite measures (LOE:2B GOR: B)

The use of disease activity indices that involve formal joint counts by trained professionals, such as the 28-joint Disease Activity Score (DAS28) [19], the Simplified Disease Activity Index (SDAI) or the Clinical Disease Activity Index (CDAI) [20], is highly recommended because they gather the most significant elements of RA in a single score.

- Imaging: US (grayscale/PD)/MRI (LOE:2B GOR: C)
- Ultrasound and MRI are superior to clinical assessment in the detection of active and subclinical joint inflammation [21–24]
- US has a greater sensitivity than other imaging techniques in the early detection of soft tissue inflammation and erosive bone process [25].
- MSUS can be used to monitor treatment response and to predict flares of RA.
- US detected typical RA findings such as joint effusion, synovial hypertrophy/proliferation, tenosynovitis, and erosion.
- MSUS assessments grayscale (GS) and power Doppler (PD) may be obtained at baseline, and at follow-up visits every 3 months.
- US may be better related to 'true' inflammatory activity in patients with D2T Arthritis in whom a doubt about the presence of inflammatory activity exists.
- Defining the number of joints and which joints should be tested is essential to accurately measuring RA activity.
- Quantitative/semi-quantitative scoring of the GS and PD changes in the inflamed joints should be recorded per each examination.

- **Laboratory tests (LOE:3B GOR: C)**

  - Elevations of the acute phase reactants such as the erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP) level are consistent with the presence of an active inflammatory state. Persistence of symptoms with normal acute phase reactants should prompt consideration of alternative diagnoses.
  - Anti-drug antibody (ADA): according to the presence or absence of ADA the refractory response can be stratified into either intrinsic refractory arthritis without ADA, pharmacokinetic refractory arthritis with ADA, or false refractory arthritis in the absence of signs of inflammation [26].
  - Although not routinely used in patient care, measuring the serum level of biologic medication in conjunction with measuring the ADA provides insight into why a patient is failing treatment and allows for personalised dosing, with potentially positive health and economic implications.

- **Assessment of the patient perspective** is becoming increasingly vital in the clinical setting. Understanding patient attitudes and expectations regarding management outcomes, as well as preferences for RA treatment administration mode are crucial to obtain better treatment response.

Table 3 Types of comorbidities and its relation to inflammatory arthritis

Type of comorbidity	Relation to RA	Example
Type I	No relationship	Trauma & certain cancers
Type II	Comorbidity increases arthritis outcome	Depression
Type III	Arthritis outcome increases comorbidity	GIT ulceration & HZ
Type IV	Arthritis causes (at least in part) the comorbidity	Myocardial infarction & lymphoma
Type V	Arthritis treatment causes or contributes to comorbidity	Steroids and infection
Type VI	A common condition leads both to arthritis and the comorbidity	Smoking, RA and lung cancer

2.5. Comorbidities

- Comorbidities affect patient compliance, treatment response, disease activity, prognosis, medication selection, adverse effects, and health care costs.
- The relationship between comorbidities and arthritis can be complicated. This might be attributed to different types of comorbidities and their pathogenesis (Table 3).
- Several factors have to be taken into consideration when measuring comorbidity; identify the morbidity, its severity and its relationship to arthritis as well as the method of gathering information about the comorbidity; self-report, hospital and pharmacy databases.
- Comorbidity indices are tools used to quantify the total burden of comorbidity contributing to the patient's overall illness. Examples: the RA comorbidity index (RACI) [27], Charlson comorbidity index [28], Elixhauser comorbidity measure [29], functional comorbidity index [30] and multimorbidity index [31].

2.6. 'In what aspects D2T is different' from treatment resistant arthritis? (LOE:2C GOR: C)

- D2T 'label' refers to a diverse group of patients.
- The proposed definition and concept of D2T are intended for clinical practice.
- D2T is different from conventional treatment-resistant arthritis (TR-RA) which focuses exclusively on failure to respond to medical treatment.
- Whilst TR-RA is unidimensional resting solely on disease activity status, D2T is multidimensional as it considers variable parameters reported by both HCP as well as patients.
- In D2T where remission cannot be obtained, the emphasis is on optimization of symptom control, minimising treatment burden and maximising function.
- In comparison to a TR-RA model, D2T conceptualises the management of arthritis somewhat differently. Although D2T sees arthritis as treatable (i.e., 'difficult' but not 'impossible'), it is still associated with difficulties that may call for extra care above and beyond the standard management protocols.

3. What are the goals of the management of D2T?

3.1. Goal 1: Optimum symptom control (LOE:4 GOR: C)

Attain optimal symptom control by implementing measurement-based care:

- The goal of 'symptomatic remission' might be difficult to achieve in this D2T group of patients as an extra Target to Treat
- The goal of 'symptom remission' might be revised to be 'optimum symptom control'.
- Standard treatment pathways or traditional approaches might not be the sole strategy for management.
- D2T patients usually have not responded to several arthritis therapy modalities, leaving them feeling helpless with a negative impact on their engagement with the treating medical team and adherence to therapy.
- Given the considerable inconsistency among this patients' cohort, their disease course, medication history and associated comorbidities; all of which might influence treatment choices in addition to patient preference. Management of this cohort of D2T patients should be tailored to the specific individual's condition and risk factors.
- External factors such as access to services, medication expenses and insurance, local medication approval status or access to treatment centres should be tackled as they may limit treatment options.
- Broad-based strategies to improve therapy engagement and adherence should be adopted these include:

- Adopting a patient-centred approach.
- Inclusion of PROMs to identify the specific patient's requirements.
- Implementing 'shared decision making' in the process of treatment selection.
- When possible, it's also advisable to involve a supportive family member in treatment decisions (such as a parent, spouse, friend, etc.).
- Managing patients' expectations is crucial in managing this D2T cohort. Restoring function to the best level possible for the individual patient is often a more realistic goal than a full return to premorbid functionality or complete remission.
- Improving the patient's quality of life also is very important to restore self-confidence and willingness to adhere to therapy.
- Support the psychological status and enhance the patient's motivation are also important. The persistence of disease activity with its negative impact on the patients may cause some degree of 'scarring'. In order to allow attention to shift to positive and significant improvements in functioning and quality of life, care should be taken to help combat pessimism about remaining deficits.

3.2. Goal 2: Reduce risk of flare-up/relapse (LOE:5 GOR: D)

– Active patients' engagement and collaboration in their own management is the cornerstone to reduce the risk of arthritis flare-ups/relapse in D2T patients.
– D2T arthritis patients are high consumers of health resources, including both inpatient and outpatient services, laboratory, radiology and high-cost medications.
– It is critical not to give up on identifying a management strategy that will work for the patient when dealing with D2T arthritis. Giving up trying by the treating doctor could instil feelings of hopelessness and lack of motivation in the patient, which by itself is a risk non-adherence to therapy.
– – It is advised to get a second opinion or consult a colleague with experience in that field if the treating physician reaches a point where it is unclear what approach to take next.
– The concept of long-term therapy, the value of maintaining adequate dosing, and the chances of developing adverse effects of arthritis therapy(ies) need to be discussed in shared decision making with the patient.
– Speaking to the patient about possible challenges with arthritis therapy (ies) may give clues regarding the need to simplify or modify the treatment regimen or convert to the patient's most preferable route of administration.
– It is of utmost importance to take into account the patient's perspectives regarding the safety as well as the efficacy of the treatment.
– Patients should be aware that stopping their arthritis medication may well be causing a relapse of their illness with a negative impact on their lives. Consequently, in such situations, careful monitoring of the patient's adherence is strongly advised.
– It is crucial to explain to the patient the time scale of response and effects of administrated DMARDs or biologic therapies.
– Targeted patient education as well as patient-centred care are the overarching principles to lessen the risk of arthritis flare-ups (Table 4)
– Checking the person's diet:

Table 4 Targeted patient education as an approach to patient-centred care of inflammatory arthritis

Patient-centered care of inflammatory arthritis: targeted patient education
• The patient is not to blame for flare-ups
• Learn about the early symptoms and how to manage them
• Recognize what factors may be causing the flare-ups
• Taking medications on time and as prescribed
• Education on how to deal with flare
• Stress management: Reduced stress levels, where possible, may aid in the management or prevention of a flare. Among the methods available are as follows:
o Meditation
o Deep breathing
o Mind–body exercises, such as yoga and tai chi
o Listening to music or doing other enjoyable activities
o Ensure having enough sleep and periods of rest

1. Implementing an anti-inflammatory diet: consuming a variety of vegetables and fruits; getting enough fibres; avoiding processed foods, refined sugars and added fats; and limiting alcohol intake.
2. Dietary supplement:

   - Some herbal supplements can aid in reducing the symptoms of arthritis flares. These include capsaicin, which is available in creams and gels for topical application, ginger, cat's claw, boswellia and curcumin.
   - Gamma linolenic acid (GLA), an omega-6 fatty acid with anti-inflammatory properties, and fish oil or omega-3.
   - Supplements with specific vitamins and minerals may also be beneficial.

3.3. Goal 3: Optimization of HRQoL/functioning' and return to a 'meaningful life' (LOE:4 GOR: C)

- Maximising functional and QoL outcomes are a key goal in the management of D2T arthritic patients.
- Poorer functional ability and quality of life are linked to poorer symptom control.
- Regular assessment of the patient's functional ability and QoL is not only important to monitor the progress of the case, but also to tackle the individual patient's specific symptoms as being linked to the impairment of his/her own health-related QoL affection.
- Identifying the minimal meaningful improvement in addition to critical improvement levels is important to record improvement of the patient's HRQoL measure.
- Sleep disturbances, depression and anxiety are the most common residual symptoms. Therefore, tackling these as part of the patient's pharmacotherapy as well as self-management and cognitive behavioural therapy can lead to obvious clinical improvement and enhance adherence to therapy.
- Fatigue is also another commonly reported symptom by the D2T patients. Fatigue self-management/energy diary can be of help significantly reduce the patients' distress caused by the symptoms.

3.4. Goal 4: Optimise treatment adherence (LOE:3C GOR: C)

- Since a patient must follow treatment instructions in order to receive an optimal drug response, poor adherence to treatment is one of the factors that may result in D2T inflammatory arthritis.
- To optimise treatment adherence, understanding non-adherence perceptions is required.
- Causes of non-adherence may be:
- Patient-related issues such as doubts about drug safety and efficacy, fear of possible side-effects, poor motivation, depression, lack of confidence on HCP and lack of communication with the treating physician and low socioeconomic status.
- Treatment-related such as unfavourable route of administration, complexity of drug regimen and development of adverse events.
- It is critical for rheumatologists to be alert about non-adherence in D2T arthritis and to understand the causes as well as potential ways to improve patients' treatment adherence.
- Strategies to enhance engagement and adherence to therapy will be planned according to the possible causes of non-adherence in Table 5.

4. What are the principles of management of D2T?

4.1. Principle 1: Shared decision making (SDM) (LOE:2B GOR: C)

- Shared decision making (SDM) is a vital component of patient-centred health care.

Table 5 Patient versus medication strategies to enhance adherence to therapy

Patient-related strategies	Medication-related strategies
-Managing patient's expectations regarding treatment outcomes	-Simplify regimen
	-Modify regimen
	-Convert to the preferred route of administration
-Beliefs about the safety and efficacy of treatment	-Recommend medication adherence apps
-Inclusion of PROMs	
-Importance of shared decision making	
-Perceived social/health care team support	

- It is a collaborative process in which rheumatologists work with patients to provide high-quality care that takes into account the best available evidence and patient values and preferences.
- SDM aids in improving patients' knowledge on treatment benefits and risks and supports communication with their clinicians with subsequent positive impact on their adherence to treatment.
- The treat-to-target approach entails selecting a shared treatment goal, assessing progress, and deciding whether to escalate treatment doses to reach a targeted improvement.
- Sometimes patients may have concerns regarding changing their current medications despite inadequate response or some fears of trying new drugs due to anticipated side effects.
- Communication between the patients and their clinicians may solve these problems and strengthen the confidence on the HCP.
- Using SDM in arthritis care helps to overcome barriers commonly faced in standard practice; e.g. different treatment targets from patients/clinician perspectives. Patients may favour pain and QoL as targets, unlike the clinicians who focus on targeting low disease activity and remission.
- - Deciding how to implement the SDM process and how to assess its effectiveness in clinical practice presents another challenge.
- -Identifying preference phenotypes, goal-sharing techniques and decision aids are examples of cutting-edge methods to promote SDM in clinical practice.

4.2. Principle 2: Measurement-based treatment (LOE:2B GOR: C)

- The patient's assessment of the disease's impact on their lives and their expectations should serve as the ideal guide for the reconceptualization of D2T perception.
- There is no standard treatment pathway because patients vary widely in terms of their disease activity levels, treatment histories and patient preferences, all of which could have an impact on the treatment options.
- Arthritis patients tend to forget how bad their arthritic symptoms were and focus on their current problem, which might not be related to the arthritic illness. Therefore, regular measurement of the treatment outcomes is vital for the management of D2T patients.
- In addition to regular disease activity score measurement, regular assessment of patient-reported outcomes can be of help to assess the patients' perception of their illness.
- – It has been reported that incorporating PROMs into routine practise can reveal crucial information that is frequently overlooked about how the disease or its treatment affects a patient's physical, emotional and social well-being.
- PROMs were reported to have a dynamic role in the standard practice and are effective in monitoring the arthritis active signs and response to treatment.
- PROMs have become a standard measure of disease activity parameters such as pain, duration of morning stiffness, patient global assessment and functional disability that are included in the American College of Rheumatology/EULAR core set variables for disease activity monitoring as well as the Outcome Measures in Rheumatoid Arthritis Clinical Trials 6 conference (OMERACT 6) [32].
- Visual feedback, a tool that allows patients to see and track changes in their disease activity parameters and reported outcome measures in real time, has been shown to significantly improve patients' adherence to their therapy and disease activity control.

4.3. Principle 3: Enhance engagement and regular monitoring under care of the service (LOE:2C GOR: B)

- In addition to routine clinical assessments, a formal case review should be carried out for D2T patients at least every 6 months or annually.
- In the regular monitoring visits, the patients' diagnosis should be revised, and individual patients should be screened for associated comorbidities.
- Residual symptoms should be considered and assessed wherever applicable.
- Monitoring of drug therapies is important to ensure that all medications have reached their therapeutic doses that are adequate for achieving the treatment target.
- If a patient has not responded to a generic drug, switching to a branded medication may be beneficial, particularly if further investigations are necessary before deciding on the next therapeutic step.
- Assessing the individual patient's symptom control is central to the formal review process. This includes also the functional and QoL levels using rating scales.

4.4. Principle 4: Adopting self-management to empower the patients (LOE:4 GOR: C)

- The learned helplessness theory is supported by conditions like inflammatory arthritis, which has an unpredictable clinical course and recurrent flare-ups. This hypothesis might help to explain why some arthritis sufferers struggle with things like health maintenance practises, medical compliance and other aspects of their wellbeing.
- People frequently experience shock, disbelief or helplessness when they learn they have arthritis. They may feel overwhelmed or irate after learning more about arthritis and its treatments. Most arthritis sufferers eventually come to terms with the fact that their condition is a reality in their lives. With this awareness, they might experience depression [33].
- Self-management programmes are recognised as an important component of quality care; however, they must be tailored to the specific needs of the patient.
- Allowing the individual patient to choose which outcome measure to modify first will make it easier for the health professional to assist the patient in dealing with his or her problems.
- Incorporating self-management and PROMs in inflammatory arthritis treatment strategies will help identify the patient's needs and establish a patient education programme that is applicable in standard clinical practice.
- The introduction of integrated self-management has paved the way toward the development of disease-specific Arthritis Self-Management Programmes such as the Joint Fitness Programme (composed of 4 components: joint learn, joint change, Joint act and joint exercise) [34].
- 'Social prescribing' may be advantageous for a variety of patients.
- Regardless of how chronic D2T is, improving a patient's capacity to manage the remaining symptoms of arthritis and making occupational or interpersonal changes to enable them to function as optimally as possible within their capacities can be crucial.
- Some patients find that using online self-management programmes and symptom rating tools to track their progress is extremely beneficial.
- Several mobile applications have been designed to offer a platform that can aid an individual in self-managing their arthritis such as RA disease education, RA lifestyle education, community connection–based apps and apps that connect users to rheumatologist providers.

4.5. Principle 5: Set up 'integrated patient-centred service pathways'

- Because of the complexity of RA symptoms and their chronic nature, effective treatment and management of RA necessitate efficient integration across the primary/secondary care interface.
- Dealing with interrelated problems faced by individuals suffering from chronic diseases or multimorbidity in a fragmented manner results in duplications in supervision, repeated evaluations, deficient or inaccurate data about the patient's health status, and multiple transaction costs.
- Between primary and secondary care, D2T patients might 'fall through the cracks.' Or in between secondary care services like hand surgery, orthopaedic surgery, physical therapy, and occupational therapy.
- In 2016, the World Health Organization (WHO) published the framework for integrated people-centred health services (IPCHS). Its vision was to encourage and guide a paradigm shift in healthcare provision towards a system that better corresponds to the needs of people with chronic diseases such as RA by combining the principles of 'integrated' and 'people-centred' care.
- The term 'people-centred' care refers to the consideration of the patient at all levels of the healthcare system. As a result, it incorporates patient-centred care principles while also considering the health of people in their communities and their contribution to influencing health policies and related medical services.

4.6. Principle 6: Frequent re-assessment and consideration of treatment direction'

- In addition to standard clinical evaluation, it is essential to review the comprehensive assessment of the patient described above on a regular basis.
- A clear decision on the course of treatment should be made. Any remaining symptoms should be addressed as soon as possible.
- Have any of the identified factors been resolved or exacerbated?
- Are there any new considerations?
- This is followed by a discussion of how treatment might progress in the future.
- Is there justification for one or more treatment trials, such as with a newly available option? Is there a case for considering a longer-term treatment, such

as joint replacement, or a strategy to address some underlying factor, in addition to current medication?
– The overarching principle is to avoid both under- and over-treatment.

5. How to manage D2T: putting goals and principles into practice?

5.1. Treatment strategy (LOE:2C GOR: B)

– Decision to be made whether to switch to a new treatment modality or augment the existing treatments.
– Care should be given to how the chosen medication(s) will be prescribed and its relation to the current patient's treatments, particularly in the event of suboptimal response or further treatment failure.
– If the patient has not received an adequate trial of DMARDs/Biologic therapy, optimising the treatment dose, method of intake, and adherence is advised.
– Coexisting comorbidities, triggers or risk factors that are contributing to the patient's symptoms, flare-up of the disease or poor quality of life should be recognised and treated.
– Patients who report improvement in symptoms but short of a substantial improvement or full remission, recorded based on assessment using the disease activity score, and/or improvement in symptoms that is more than 50% enhancement from the baseline value, are identified as having 'partial response'. Assuming there is acceptable tolerability, and to enhance the response, it is advisable to add an adjunctive therapy as well as non-pharmacologic strategies.
– For patients with poor response to previous medication, switching therapy is advised. When switching of therapies is considered, other factors should be carefully assessed. This includes (1) the degree to which the current treatment is tolerated, (2) time of the new therapy to kick in, (3) risk of flare-up on stopping the current therapy, and (4) risk of interactions with the current medications or non-compliance with a new medication regimen presents a treatment approach in standard clinical practice, considering the goals and principles of D2T management.

5.2. Measuring treatment success (LOE:2C GOR: C)

– 'Patient-centred' management approach is the bedrock of the D2T treatment strategy, as a result, the success of any new medication would be judged from the perspectives of both the treating healthcare professional and the patient.
– Assessment of the outcomes should be evaluated using quantifiable outcome measures that can be used longitudinally to guide clinical decision making.
– Disease activity should be assessed and recorded on a regular basis using a disease activity score, as well as comorbidity, ultrasound joint examination, and laboratory measures. Residual deficits should be reduced to a manageable level.
– The next steps in the management pathway should be based on shared decision making between the patient and the treating physician and should take into account the individual patient's preferences for how much invasiveness or side effects he/she is willing to accept in order to achieve greater efficacy.
– Prior to beginning therapy, the point at which treatment escalation is to be stopped, as well as the acceptable level of symptom relief/functionality expected to be achieved, should be agreed upon with the patient.

Discussion

Management of D2T inflammatory arthritis necessitates careful evaluation for the presence or absence of inflammation in order to plan pharmacological and non-pharmacological strategies. The major challenge is that D2T arthritis has been related to a variety of characteristics. These not only include the disease activity status, the patients' medical condition and adherence to therapy but also the medication regimen, approaches to assessment and associated comorbidities, as well as external circumstances that may encumber the patients' and the treating healthcare professionals' perception. These factors are manifold and rather complex and can potentially lead to non-compliance with therapy, a significant negative impact on the patients' QoL, and in some cases, unplanned hospitalisations [35]. This work was carried out to address the unmet needs and derive a comprehensive approach towards the assessment and management of the 'difficult-to-treat' inflammatory arthritis. This consensus document has been based on a formal process, the Delphi technique, and has been developed in view of best practice as evidenced in the literature review.

The current research proposed a four-pillared definition of D2T in inflammatory arthritis: 'persistent inflammation that continues to cause significant burden despite standard treatment as perceived by the treating rheumatologist and/or the patient'. The EULAR Task Force [36] has recently defined difficult-to-treat (D2T) RA as patients having persistency of symptoms and/or signs despite the failure of at least two biological or targeted

synthetic disease-modifying anti-rheumatic drugs (b/tsDMARDs) with different mechanisms of action. Whilst the definition of D2T documented in this work agrees with the recently published EULAR definition, it added another 2 factors, these are 'disease burden' and 'time frame' for the assessment of the disease activity status. A recent survey in the Netherlands reported that D2T-RA patients incurred almost twice the annual cost of direct healthcare utilisation compared with non-D2T RA [37]. In concordance, this study revealed a consensus that the time factor is vital to consider inflammatory arthritis as persistent, hence meeting the difficult-to-treat definition. Furthermore, this work endorsed the value of ultrasonography in identifying the D2T patients' cohort and ascertaining the inflammatory disease activity status. This agrees with earlier data supporting the role of ultrasonography as an additional tool in D2T RA patients [38–40]. Ultrasonography may also serve to assure the patient as well as the treating rheumatologist if a decision is made not to change the current DMARD therapy despite continuing symptoms and measured disease activity [41, 42].

The progressive nature of the disease is not limited to just clear inflammatory joint pathology, and therefore, the most effective therapeutic approaches must take into account the heterogeneity of D2T as well as the role of the diverse risk factors contributing to D2T. An international survey revealed the importance of a holistic approach for D2T patients [41]. Bearing in mind the presence of comorbidities and that most of the patients, particularly older adults are taking other medications for other medical reasons, such increasing complexity of current drug therapies affects patient adherence. While the individual patient needs to simplify a medication regimen varies from patient to patient, a straightforward approach to integrate the patients' perspective into decision making for complexity reduction is still lacking. Capturing wider contributors to treatment cycling was the cornerstone for the development of the suggested algorithm. The algorithm provides an effective framework that addresses the complexity of D2T and supports the assessment of the presence of inflammatory pathology, adherence to therapy, patient preferences and needs regarding the reduction of complexity of D2T therapies before making decisions for further treatment change. The absence or presence of inflammation should be confirmed to guide both the non-pharmacological and the pharmacological interventions [41, 43]. This clarity is essential for managing D2T RA and preventing needless DMARD therapy cycling.

The predominant principle of D2T management endorses the importance of considering the other parameters which may complicate the precise evaluation of the disease activity status. This work raised the option of the patient's diagnosis reappraisal and the importance of recognising the presence of coexistent comorbidity and/or another illness that mimics the inflammatory activity. Such an approach plays a vital role in setting up the treatment strategy of D2T cases. Bearing in mind the relatively recent perception of early arthritis diagnosis and the window of opportunity concept, a trend has developed to seek out early new diagnoses of inflammatory arthritis with consequent early treatment initiation. However, in the meantime, this might risk misdiagnosis of the disease, particularly at such early phases of the disease during which arthritis is still developing. In addition, the clinical assessment may be complicated by conditions such as polymyalgia rheumatica, fibromyalgia and osteoarthritis, which are common conditions that mimic the presentation of inflammatory arthritis. The risks of mimics and concurrent pathology apply to the entire course of a patient's illness [38, 40].

In conclusion, it is becoming increasingly apparent that D2T arthritic patients have unmet needs. However, there are numerous other variables that might make managing the condition and addressing the issue more challenging. The guiding principle for D2T management emphasises the significance of determining whether inflammatory pathology is present before making additional treatment changes. Furthermore, in addition to the several factors to be tackled and specific measures to mitigate or reduce the complexity of the condition; simple key questions could be phrased to include the patients' perspective. In summary, managing D2T advocates a more holistic approach toward the patient as opposed to viewing a patient through the lens of the index disease.

Abbreviations

b DMARDs	Biologic disease-modifying anti-rheumatic drugs
CEBM	Centre for evidence-based medicine
CEG	Clinical, evidence-based, guidelines
cs DMARDs	Conventional synthetic disease-modifying anti-rheumatic drugs
DMARDs	Disease-modifying anti-rheumatic drugs
D2T	Difficult to treat
GLA	Gamma linolenic acid
GOR	Grades of recommendations
HCP	Health care professional
HRQoL	Health-related quality of life
IPCHS	Integrated people-centred health services
LOE	Level of evidence
MSUS	Musculoskeletal ultrasound
OMERACT 6	Outcome Measures in Rheumatoid Arthritis Clinical Trials 6
PD	Power Doppler
PROMs	Patient-reported outcome measures
QoL	Quality of life
RA	Rheumatoid arthritis
RACI	Rheumatoid arthritis comorbidity index
RCTs	Randomised controlled trials
SDM	Shared decision making
ts DMARDs	Targeted synthetic disease-modifying anti-rheumatic drugs

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