Rheumatology's 'Difficult-to-Treat' Patients Need More Than Just Drugs

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Despite significant advancements in pathogenesis-based therapeutics and the widespread adoption of evidence-based treatment recommendations, a persistent and clinically significant subgroup of rheumatology patients continues to respond poorly to standard interventions. These individuals often experience a progressive decline in disease trajectory, posing an escalating challenge for healthcare systems. A recent Personal View in Lancet Rheumatology argues for a more structured approach to defining and managing these 'difficult-to-treat' patients, advocating for holistic, multidisciplinary care that extends beyond mere pharmacological adjustments.1

KEY TAKEAWAYS

- The Pivot: The concept of 'difficult-to-treat' in rheumatology expands beyond drug-refractory disease to include misdiagnosis, limited treatment options, and psychosocial factors.
- The Data: No single numerical endpoint, but a conceptual framework emphasizing that up to 30% of patients in some chronic diseases fall into this category.
- The Action: Clinicians should adopt a comprehensive, multidisciplinary assessment for patients not responding to standard rheumatological care, considering non-pathological contributors to disease activity.

The evolution of rheumatology has been marked by a succession of targeted therapies, from conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) to biologics and targeted synthetic DMARDs (tsDMARDs). These agents, coupled with increasingly sophisticated treatment-to-target strategies, have dramatically improved outcomes for many patients with chronic inflammatory conditions such as rheumatoid arthritis, psoriatic arthritis, and axial spondyloarthritis. But for a substantial minority, these advances have not translated into sustained remission or even adequate disease control. These are the patients who cycle through multiple lines of therapy, experience persistent symptoms, and often report a significant impact on their quality of life, despite clinicians adhering strictly to established guidelines.1

Gábor Nagy, Lilla Gunkl-Tóth, and Anna M. Dorgó, from Semmelweis University in Budapest, argue that the term 'difficult-to-treat' (DTT) needs a formal definition in rheumatology, akin to those established in other medical fields.1 They contend that the current paradigm, which often defaults to escalating or switching immunosuppressive therapy, overlooks important non-pathological factors contributing to a patient's refractory state. Their Personal View outlines a framework that acknowledges the complexity of these patients, moving beyond a simplistic view of drug failure to embrace a broader understanding of disease drivers.1

Beyond Drug Resistance: Defining 'Difficult-to-Treat'

The authors propose that the DTT state encompasses more than just a lack of response to available treatments. It is a multifactorial condition where patients exhibit persistently high disease activity, despite receiving optimal, guideline-recommended therapy.1 This definition moves beyond the narrow focus on pathology-driven, treatment-refractory disease, which has historically dominated the clinical discourse. Instead, it explicitly incorporates other significant elements: having few remaining treatment options, the possibility of misdiagnosis, and the substantial influence of coincident psychosocial factors.1

Consider a patient with rheumatoid arthritis who has failed two biologics and a JAK inhibitor. The immediate clinical instinct might be to try another biologic. But what if the persistent pain is neuropathic, or driven by severe depression, or exacerbated by an undiagnosed fibromyalgia component? What if the patient is non-adherent due to complex medication regimens or financial constraints? These scenarios, the authors stress, are not merely complications of the primary disease; they are integral to the 'difficult-to-treat' designation and demand a different therapeutic approach.1

The Broader Context of Disease Trajectory

The concept of DTT is not unique to rheumatology. Similar frameworks exist in oncology, infectious diseases, and even psychiatry, where patients with refractory depression or multidrug-resistant tuberculosis require highly specialized, often multidisciplinary, interventions.1 The authors highlight that in many chronic diseases, a subgroup of patients, sometimes as large as 30%, falls into this DTT category. This proportion emphasizes the scale of the challenge and the inadequacy of a purely pharmacological response.1

For rheumatology, the implications are profound. It means moving away from a purely biomedical model that prioritizes disease activity scores and inflammatory markers, towards one that integrates patient-reported outcomes, functional status, and mental health. The current focus on RA treatment optimisation has yielded significant gains, but it may not be sufficient for this specific cohort. The authors argue that the DTT concept provides a necessary framework to identify these patients earlier and intervene more effectively.1

Unpacking the Contributing Factors

The Personal View meticulously breaks down the various factors contributing to a DTT state. First, there is the genuine pathology-driven, treatment-refractory disease, where the underlying immune dysregulation is simply not adequately controlled by available therapies. This is the traditional understanding of 'refractory' disease. But even here, the authors suggest that a deeper dive into specific inflammatory pathways or genetic predispositions might reveal novel targets.1

Second, the issue of limited treatment options is important. While the rheumatology trial pipeline remains active, with new trials continually emerging, some patients exhaust all approved and accessible therapies. This necessitates a re-evaluation of off-label use, participation in clinical trials, or even a shift towards palliative symptom management.1 The regulatory guidelines and reimbursement policies also play a role, often restricting access to newer, potentially effective, but expensive treatments.1

Third, misdiagnosis or overlapping conditions can masquerade as treatment resistance. A patient initially diagnosed with rheumatoid arthritis might, in fact, have seronegative spondyloarthritis, or a complex pain syndrome like fibromyalgia, or even a rare autoinflammatory disease. The initial diagnosis, even if correct, might not capture the full spectrum of their pathology. The authors emphasize the importance of re-evaluating the diagnosis in DTT patients, perhaps through advanced imaging, genetic testing, or expert second opinions.1

Finally, and perhaps most overlooked, are the psychosocial factors. Chronic pain, fatigue, and disability take a heavy toll on mental health, often leading to depression, anxiety, and sleep disturbances. These, in turn, can amplify pain perception, reduce treatment adherence, and impair overall function, creating a vicious cycle that perpetuates the DTT state.1 Financial stress, lack of social support, and health literacy barriers also contribute. For a comprehensive approach to managing these patients, a clinician might find the Oxford Handbook of Rheumatology a useful quick reference for diagnostic criteria and management strategies.

The Call for Holistic, Multidisciplinary Care

The core argument of Nagy, Gunkl-Tóth, and Dorgó is that the DTT state demands a comprehensive, holistic, multidisciplinary approach. This is not merely a suggestion; it is presented as a necessity. Such an approach would involve a team of specialists, potentially including rheumatologists, pain specialists, physical therapists, occupational therapists, psychologists, social workers, and dietitians.1 Each member would address a specific facet of the patient's complex presentation, moving beyond the traditional siloed approach to care.1

For example, a patient struggling with chronic pain and fatigue might benefit from cognitive behavioral therapy (CBT) alongside pharmacological interventions. A patient with poor adherence due to polypharmacy could benefit from a medication review by a clinical pharmacist and a simplified regimen, perhaps aided by a 7-Day Weekly Pill Organiser. Addressing the oral-systemic link, for instance, might involve dental care for periodontitis, which can exacerbate systemic inflammation.1

The authors propose that incorporating the DTT concept more widely in rheumatological treatment strategies would have several advantages. It would standardize the identification of these patients, facilitate targeted research into their specific needs, and ultimately lead to more personalized and effective care plans.1 This framework would also encourage a shift in clinical trial design, moving beyond efficacy in broad populations to focus on interventions tailored for DTT subgroups.1

Challenges and Future Directions

Implementing a truly holistic, multidisciplinary approach faces significant hurdles. Healthcare systems are often not structured to support such integrated care, with funding models and referral pathways favoring specialist silos. Training for rheumatologists often emphasizes pharmacological management, with less focus on the psychosocial aspects of chronic disease.1 The time and resources required for comprehensive assessments and coordinated care plans are substantial, posing a challenge in busy clinical settings.

Still, the authors contend that the long-term costs of failing to address DTT patients effectively, including repeated hospitalizations, escalating drug costs, and significant disability, far outweigh the investment in a more integrated approach.1 They call for the development of consensus definitions for DTT in specific rheumatological diseases, such as rheumatoid arthritis and psoriatic arthritis, to guide both clinical practice and research. This would allow for better stratification of patients and the development of tailored interventions.1

The paper does not present new data from a clinical trial; rather, it offers a conceptual framework and a call to action. The strength of the argument lies in its comprehensive synthesis of existing challenges and its pragmatic proposals for moving forward. It serves as a reminder that even with the most advanced therapies, medicine remains as much an art of holistic patient management as it is a science of molecular pathways. The ongoing discussions around JAK inhibitor

safety and the need for updated EULAR safety guidance further underscore the complexity of managing these powerful but sometimes problematic therapies, especially in patients who are already struggling.1

The next step, according to Nagy and colleagues, involves developing specific criteria for identifying DTT patients within each rheumatological condition, followed by the creation of evidence-based multidisciplinary care pathways.1 Without such a structured approach, a significant proportion of patients will continue to suffer, despite the best intentions and the most advanced drugs.1

CLINICAL IMPLICATIONS

The concept of 'difficult-to-treat' patients in rheumatology is not new, but this paper formalizes the argument that we have been looking at the problem too narrowly. Simply escalating or switching immunosuppressants for every patient who fails to achieve remission is often an exercise in futility, incurring significant costs and exposing patients to unnecessary risks without addressing the root causes of their persistent symptoms.

Clinicians must adopt a more expansive diagnostic mindset. When a patient is not responding as expected, the first thought should not always be 'what's the next drug?' but rather 'is the diagnosis correct?' or 'what other factors are at play?' This requires a willingness to revisit established diagnoses and consider comorbidities, including psychosocial elements, that are often dismissed as secondary.

For healthcare systems, the implication is clear: invest in multidisciplinary teams. Rheumatology clinics cannot operate as isolated silos focused solely on prescriptions. Integrating pain specialists, psychologists, and social workers into the care pathway for DTT patients will likely yield better outcomes and, in the long run, prove more cost-effective than endlessly cycling through expensive biologics.

The pharmaceutical industry also has a role. While developing novel pathogenesis-based therapies is vital, there is an unmet need for interventions that address the non-pathological drivers of the DTT state. This could include digital health solutions for adherence, targeted pain management strategies, or even integrated care models that support a holistic approach.

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REFERENCES

1. 1. Nagy G, Gunkl-Tóth L, Dorgó AM. The concept of difficult-to-treat disease in rheumatology: where next? Lancet Rheumatol 2025.

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