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Review

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Review

Difficult-to-treat rheumatoid arthritis: what have we learned and what do we still need to learn?

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Abstract

Difficult-to-treat RA (D2T RA) is an area of high unmet need. The prevalence reported in the first D2T RA cohort studies ranged from 5.5% to 27.5%. Key to the definition is a conviction by the patient and/or rheumatologist that disease management has become problematic and failure of at least two biological or targeted synthetic DMARDs. D2T RA is a multifactorial disease state which was reflected in data from D2T RA cohort studies: these pointed towards high prevalence of comorbidities and/or lower socioeconomic status in D2T RA subgroups, while others had persistent symptoms without these factors being present. A holistic approach is necessary to identify the root problems underlying D2T RA in individual patients. In this review, biological and non-biological drivers that should be considered to be optimized will be discussed in view of what we have learned from patient data emerging from the first D2T RA cohort studies.

Keywords: difficult-to-treat RA, D2T RA, rheumatoid arthritis, patient management.

Rheumatology key messages

- Difficult-to-treat RA (D2T RA) is a prevalent disease state with high unmet needs.
- D2T RA is multifactorial, a holistic view is warranted in patient management.
- D2T RA may be reversed but better understanding in how to reach remission is needed.

Introduction

RA is the most common inflammatory joint disease, having a major impact on a patient's quality of life and ability to participate in society [1]. Several changes in the landscape of RA management have been made since the beginning of this century, including treat-to-target treatment strategies aiming at achieving remission or low disease activity as early as possible, strict monitoring of disease activity and the introduction of biological/targeted synthetic DMARDs (b/tsDMARDs) [1, 2]. Cycling of b/tsDMARDs in those not responding sufficiently to first-line treatment with conventional synthetic DMARDs (csDMARDs) is the norm, but treatment goals are not achieved in a significant proportion of patients [2–5]. Until recently, the absence of uniform terminology and criteria has hampered progress in the field. The formation of a dedicated EULAR Taskforce has led to a definition for difficult-to-treat (D2T) RA [6]. The identified contributing factors and proposed points to consider for patient management will be discussed in this narrative review, followed by an in-depth discussion of real-world evidence from cohorts based on the EULAR D2T RA definition.

Defining D2T RA

A first step in improving care in these RA patients with unmet needs is addressing the problem with uniform terminology.

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With this goal in mind, a EULAR task force was established in 2018. The term 'difficult-to-treat' (D2T) was unanimously agreed upon as it is broad enough to comprise the intended population and is already in use in several other medical specialties [6, 7]. D2T RA is an umbrella term for a heterogeneous disease state, in which multiple factors—e.g. comorbidities, low socioeconomic status (SES), altered pain processing and biological factors—can underly current symptoms (Fig. 1).

The definition consists of three criteria that all need to be present in D2T RA, comprising treatment failure, signs of active/progressive disease and the notion that disease management has become problematic (Table 1) [6]. Included within the definition are patients with low disease activity based on validated measurement tools but still having symptoms that are causing a reduction in quality of life. Cycling of DMARDs might not be an appropriate management strategy in these patients, yet their symptoms still need to be addressed. Other terminology for this subgroup includes non-inflammatory refractory RA [3] or refractory inflammatory arthritis with persistent symptoms (rather than persistent inflammation), but their use often is ill-defined and not based on international consensus [8].

Comorbidities and SES in D2T RA

It has been well documented that the proportion of RA patients with extra-articular manifestations—such as nodules, concomitant Sjögren's disease, pyoderma gangrenosum and vasculitis—has declined over time as a reflection of patients' improved outcomes with new effective treatment strategies. [1] In this day and age, RA patients are still at increased risk of accruing comorbidities, something that is especially pronounced in D2T [9–11]. These predominantly include infections, osteoporosis, lung disease, diabetes and depression, and can partially be ascribed to the use of immunosuppressive medication including glucocorticoids [9, 10]. Additionally, D2T RA patients are at increased risk of developing comorbidities secondary to uncontrolled inflammation such as cardiovascular disease [9, 10]. The presence of comorbidities may already warrant caution prior to D2T RA diagnosis as they predict poorer disease outcome [12]. Although we often fail to address this topic with our patients, lower SES is associated with functional decline [13]. Worse outcomes were seen in patients with low SES independently of comorbidities [14]. As part of management and risk assessment approach in RA, both a patient's medical and social context should be considered.

Pain and pain processing as a factor complicating D2T RA

Pain in RA is a complex sensation comprising nociceptive pain from joint damage and inflammation [15]. Exacerbated pain sensitization may be brought up by fatigue and

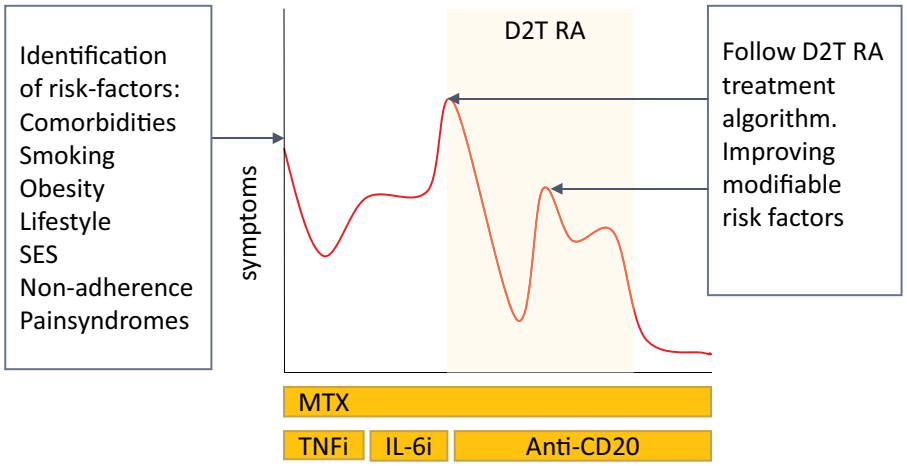

Figure 1. Factors contributing to difficult-to-treat RA

Table 1. Definition of D2T RA

All three criteria need to be present in D2T RA:
(i) Treatment according to EULAR recommendations and failure of ≥2 b/tsDMARDs (with different mechanisms of action)[a] after failing csDMARD therapy (unless contraindicated)[b]
(ii) Signs suggestive of active/progressive disease, defined as ≥1 of:
(a) At least moderate disease activity (according to validated composite measures including joint counts e.g. DAS28-ESR >3.2 or CDAI >10)
(b) Signs (including acute phase reactants and imaging) and/or symptoms suggestive of active disease (joint related or other)
(c) Inability to taper glucocorticoid treatment (below 7.5 mg/day prednisone or equivalent)
(d) Rapid radiographic progression (with or without signs of active disease)[c]
(e) Well-controlled disease according to above standards, but still having RA symptoms that are causing a reduction in quality of life
(iii) The management of signs and/or symptoms is perceived as problematic by the rheumatologist and/or the patient

[a] Unless restricted by access to treatment due to socioeconomic factors.
[b] If csDMARD treatment is contraindicated, failure of two or more b/tsDMARDs with different mechanisms of action is sufficient.
[c] Rapid radiographic progression: change in van der Heijde-modified Sharp score ≥5 points at 1 year. D2T DA: difficult-to-treat RA; b: biological; CDAI: clinical disease activity index; cs: conventional synthetic; DAS28-ESR: disease activity score assessing 28 joints using ESR; ts: targeted synthetic.

depression, which are highly prevalent in RA [10, 15, 16]. Pain processing is still mostly uncharted territory. Functional MRI studies recognized areas in the brain of RA patients associated with fatigue [17, 18] and even with response to b/tsDMARD treatment [17–20]. Moreover, non-response to DMARDs was associated with dysregulated central pain processing [17]. Inflammatory and non-inflammatory pain management require a different approach. Treatment of the latter should be focused on non-pharmacologic interventions based on a patient's individual needs such as physiotherapy, psychological or social intervention, ergotherapy or weight reduction [21]. Cycling of b/tsDMARD should be avoided in the absence of inflammation, which is strongly emphasized in the treatment algorithm of the EULAR points to consider for D2T RA (Fig. 2).

Biological factors contributing to ongoing inflammation in D2T RA

The patient population encompassed by the D2T RA definition is heterogenic and includes RA patients with ongoing inflammation regardless of treatment with multiple DMARD lines. In literature this subgroup is sometimes referred to as 'persistent inflammatory refractory RA' or 'true refractory RA' [3, 8]. Recent technological breakthroughs in synovial tissue mapping has provided a biological underpinning for the assumption of RA as a pathophysiological heterogeneous disease. Distinct cell-type subsets, explained as cell-type abundance phenotypes (CTAPs), were recognized in RA, combining single-cell RNA sequencing, surface proteins and histological data [22]. An additional study in this novel cohort suggested that CTAPs are influenced by pharmacological treatment [23]. B-lymphocytes were more abundant in patients treated with csDMARDs alone, and the endothelial–fibroblast–myeloid CTAP was overrepresented in patients treated with b/tsDMARD [23]. CTAP classification could be made in bulk RNA data from the R4RA trial [22, 24]. In the R4RA trial, responsiveness to rituximab and tocilizumab in RA patients not responding to treatment with csDMARDs and TNF inhibitors was prospectively studied. Superiority of tocilizumab *vs* rituximab in those with low B-cell signatures was demonstrated, while no difference was found in those with high B-cell signatures [24, 25]. Non-response to both tocilizumab and rituximab was associated with the fibroblast CTAP [22]. The findings from these landmark studies echo earlier work from different investigators. Based on immune histochemistry, different cellular subsets were found [26]. A pauci-immune subset was associated with non-response to TNF-α blockade [26]. The latter group is of particular interest in the context of D2T RA patients with ongoing inflammation, as patients with pauci-immune synovitis consistently respond less favourably to bDMARDs.

Further studies are needed to determine whether indeed the pauci-immune phenotype or fibroblast CTAP is more prevalent in D2T RA patients with ongoing inflammation and if this disease state is driven by pro-inflammatory fibroblasts rather than immune cells [27].

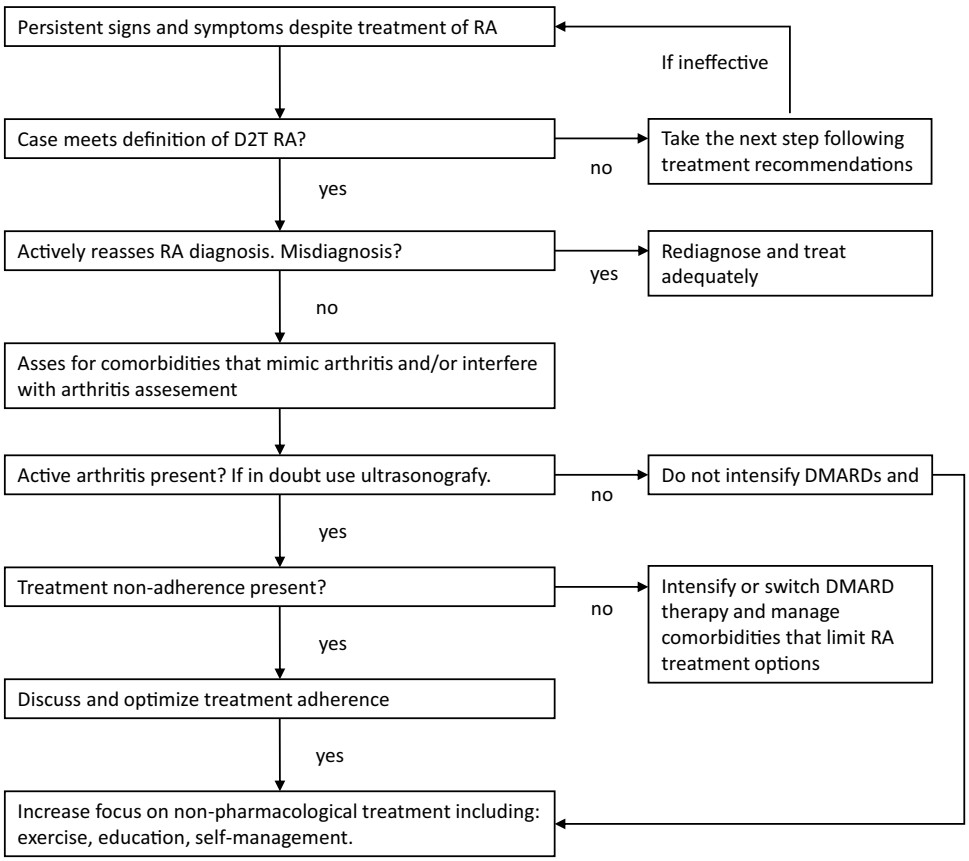

Figure 2. Treatment algorithm for difficult-to-treat RA as based on the EULAR point to consider for the treatment of RA. [a]Adapted figure from. Nagy *et al.* [32]

Management of D2T RA

A busy clinic rarely is the best setting for a clinician to reflect on the often multiple needs of a patient in pain, let alone a patient with highly complex D2T RA. Yet allocating extra time to review a suspected case of D2T RA is essential to decrease its burden. Not only to improve our patients' quality of life but also to decrease the societal impact of D2T, as a cost-of-illness study found the mean annual costs of D2T RA to be twice as high as non-D2T RA (€37 605 *vs* €19 217) [28].

The management of D2T RA includes the need to review the diagnosis of RA, address non-adherence to treatment, improve comorbidities where possible, and explore non-pharmacological interventions and self-management programs [21, 29]. Additional tests in case of discrepancy between signs and symptoms should be requested to prevent both over- and undertreatment [30, 31]. Complementing the 2019 EULAR recommendations for the management of RA a treatment algorithm was drawn up in the EULAR points to consider for D2T RA (Fig. 2) [32]. Given the fact that many such interventions take time to alter disease course, patients should be engaged in clinical decision-making and setting of treatment goals.

Ultimately, we want to prevent D2T RA, or delay reaching a diagnosis of D2T disease, which negatively impacts on the patient, also in the longer-term. A holistic approach should be part of standard patient care in RA. In reality, however, time and resources are limited and tools to predict D2T RA would be of great help to decide who needs early intervention and close monitoring. First efforts to identify predictive factors have been made [33, 34] but a validated predication model is yet to be developed.

Real-world evidence from D2T RA patient cohorts

Based on the definition of D2T RA, several studies have been conducted (search strategy in Supplementary Fig. S1, available at *Rheumatology* online). Most data were collected retrospectively and not all researchers were able to include patients based on the more subjective D2T RA criteria (e.g. Table 1, criteria 2e and 3, Supplementary Table S1, available at *Rheumatology* online, for criteria used), which should be kept in mind. We will discuss findings described in eleven cohorts from Japan, the Netherlands, Spain, Italy, South Korea and Argentina. An overview of study results can be found in Table 2, two studies were not included in this table as no comparison was made between D2T RA an non-D2T RA.

D2T RA is highly prevalent

When looking at these study results, the extent of the problem becomes apparent with a D2T RA prevalence ranging from 5.5% [34] to 27.5% [35]. Differences in prevalence are not clearly explained; possible overrepresentation in tertiary centre–based cohorts can be considered, although the highest prevalence was found in a secondary centre. Moreover, in two studies by Jung *et al.* and Yoshii *et al.* only patients on b/tsDMARDs were included, they showed a D2T RA prevalence of 10% and 22%, respectively [36, 37]. Even when using uniform terminology for D2T RA, the context in which study populations exist worldwide is expected to vary greatly. Yet, the prevalence of D2T RA appears to exceed previous estimates [38, 39], stressing the need for improvement in this challenging population.

D2T RA patients have more comorbidities

Despite differences in study design, similarities among the D2T RA populations seem to emerge. General patient characteristics were mostly similar, including age and gender. Only in the study by Takanashi *et al.* were D2T RA patients female dominant (90% *vs* 83%) [40]. D2T RA patients were not older compared with non-D2T RA (Table 2). In the three studies that did find age differences, D2T RA patients were either younger (Yoshii *et al.*, 62 *vs* 67 years; Roodenrijs *et al.*, 60 *vs* 65 years) or had their initial RA diagnosis at a younger age (Roodenrijs *et al.*, 42 *vs* 48 years; Leon *et al.*, 46 *vs* 56 years) [34, 37, 41].

Comorbidities were more common in all but one of D2T RA cohorts. D2T RA patients in the Roodenrijs study had more often interstitial lung disease (10 *vs* 2%), infections (54% *vs* 15%), osteoporosis (37% *vs* 17%), gastrointestinal disease (19% *vs* 7%), ILD (10% *vs* 2%) and FM (38% *vs* 9%) [41]. Takanashi *et al.* reported more hospital admissions due to infection (22% *vs* 5%) and more often lung comorbidities (23% *vs* 12%). Moreover, D2T RA patients had a higher rheumatic disease comorbidity index (RDCI 1.1 *vs* 0.8) same was reported by Yoshii *et al.* (RDCI 4.4 *vs* 3.5) [37, 40]. In the Hecquet cohort, D2T RA patients were more likely to have diabetes (14% *vs* 6%) and ILD (24% *vs* 7%). Garcia-Salinas *et al.* reported more frequent anaemia (26% *vs* 15%) and Jung *et al.* more cardiovascular disease (33% *vs* 26%) more frequent rheumatoid nodules (4.4% *vs* 2.1%) [35, 36, 42].

The studies by Watanabe *et al.* and Leon *et al.* both aimed to identify risk factors for development into D2T RA—data on comorbidities were collected at the first recorded visit which was prior to D2T RA diagnosis [34, 43]. Patients that would eventually progress to D2T RA more often had lung (34% *vs* 19%) or neurological (9% *vs* 3%) comorbidities in the Watanabe cohort and dyslipidaemia (29% *vs* 14%) and liver disease (6% *vs* 1%) in the Leon cohort [34, 43].

Regarding mental comorbidities, Roodenrijs *et al.* found higher rates of depression (15% *vs* 4%) and anxiety (7% *vs* 4%) [41]. Novella-Navarro *et al.* made no direct comparison between D2T RA and non-D2T RA but separated patients in three groups, namely D2T RA patients that (i) required b/tsDMARD switch due to inefficacy; (ii) due to other reasons such as comorbidities, side effects and non-adherence; and (iii) non-D2T RA in disease remission for at least 5 years after using one b/tsDMARD [44]. Anxiety and depression were highly prevalent in D2T RA (group 1, 29%; group 2, 28%; group 3, 16%) [44]. Giollo *et al.* found no statistically significant difference in depression and anxiety (6.3% *vs* 6.6%), as did Takahashi *et al.* for depression (2.3% *vs* 1.2%) [33, 40]. Leon *et al.* reported a trend to more frequent depression in D2T RA patients at RA diagnosis but this difference did not meet statistical significance (11% *vs* 5%) [34]. D2T RA patients with predominant comorbidities were discussed in the Roodenrijs [41], Takanashi [40] and Novella-Navarro [44] studies. Although the reported comorbidities varied strongly, they are a well-recognized factor complicating RA management and, through various mechanisms, contribute to D2T RA status. Optimizing comorbidities where possible is recommended in disease management of D2T RA [32].

Table 2. Clinical characteristics in D2T RA compared with non-difficult to treat controls

	Roodenrijs	Watanabe	Takanashi	Yoshii	Leon	Hecquet	Giollo	Garcia-Salinas	Jung
D2T RA, *n* (%)	52 (n/a)	53 (7.9)	173 (10.1)	71 (21.5)	35 (5.5)	76 (26)	48 (24)	76 (27.5)	271 (10.7)
Median b/ts DMARD in D2T RA/non-D2T RA	3 [e]/0	n/a	2.1/1	n/a	n/a	4.5/1.1	3/2	2.2/n/a	2/0
Female sex	=	=	↑	=	=	=	=	=	=
BMI/weight	=	=[f]	↓	n/a	n/a	=	n/a	=	=
Age	↓	n/a	=	↓	n/a	=	=	=	=
Age at disease onset	↓	=	=	n/a	↓	n/a	=	n/a	n/a
Smoking	=	=[f]	=	n/a	n/a	=	n/a	=	=
Socioeconomic status	↓[a]	n/a	↓[c]	n/a	n/a	↓	n/a	n/a	n/a
Any comorbidities	↑	↑[f]	↑	↑	↑[f]	↑	=	↑	↑
Depression/anxiety	↑	n/a	=	n/a	=[f]	n/a	=	n/a	n/a
FM	↑	n/a	n/a	n/a	n/a	n/a	=	n/a	n/a
MTX use or dose	↓	=	↓[b]	↓[d]	n/a	=	↓	↑	↓
GC use or dose	↑	↑	↑	↑	n/a	↑	↑	=	=
RF titre or % positive	=	↑[f]	↑	↑	↑[f]	↑	=	↑	=
ACPA titer or % positive	=	=[f]	↑	↑	=[f]	n/a	=	↑	=
DAS28-CRP at RA diagnosis	n/a	↑	n/a	n/a	=	n/a	=	n/a	↑
CRP	=	=[f]	↑	n/a	n/a	=	↑	=	↑
ESR	=	=[f]	↑	n/a	n/a	n/a	=	=	=
Erosions X-ray	=	n/a	n/a	n/a	n/a	n/a	=	↑	=
Non-adherence	↑[g]	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

Green shading with ↑ indicates higher/more prevalent, red shading with ↓ lower/less, and blue shading with = indicates no difference.
[a] Lower socioeconomic status at RA diagnosis was a risk factor for D2T RA.
[b] More intolerance or contra-indications to MTX.
[c] Lower socioeconomic status resulted in D2R RA because limited access to b/ts/DMARD.
[d] D2T RA patients that failed their next treatment in this study used lower MTX doses. Overall use or MTX dose did not differ.
[e] Failed b/tsDMARDs with different mechanism of action.
[f] At RA diagnosis.
[g] Discrepancy between prescribed and delivered drugs. D2T DA: difficult-to-treat RA; b: biological; ts: targeted synthetic; MTX: methotrexate; GC: glucocorticoids; DAS28-ESR: disease activity score assessing 28 joints using ESR.

D2T RA patients may receive suboptimal treatment with csDMARDs

Concomitant use of csDMARDs during b/tsDMARDs treatment is recommended in RA management recommendations, as multiple studies confirmed beneficial effects of combined use [45]. However, three studies by Roodenrijs *et al.*, Giollo *et al.* and Jung *et al.* observed that D2T RA patients used less often csDMARDs as concomitant treatment (71% *vs* 86%; 43% *vs* 60%; 74% *vs* 82%) [33, 36, 41]. Moreover, Jung reported less use of csDMARDs prior to start of b/tsDMARDs in D2T RA (86% *vs* 95% MTX; 30% and 40% SSZ; and 12% and 28% LEF) [36].

Two studies reported on MTX delay at RA diagnosis. In the Giollo cohort, D2T RA patients more often had a delayed start of MTX of >3 months (84% *vs* 66%) [33]. This finding was not observed by Leon *et al.*, who found no difference in time to treatment with csDMARDs at RA diagnosis [33]. Use of csDMARDs at D2T RA diagnosis was not reported [33].

Not all D2T RA cohort studies observed less csDMARD use in D2T RA. Hecquet *et al.* and Watanabe *et al.* found no differences [42, 43]. Garcia-Salinas *et al.* reported a higher average MTX dose (15 *vs* 13 mg) in D2T RA and Novella-Navarro *et al.* and Ochi *et al.* did not reported on this [35, 44, 46].

Yoshii *et al.* and Takanashi *et al.* did not find differences in concomitant use of csDMARD in D2T RA either [37, 40]. However, they did observed other differences related to csDMARDs. Yoshii *et al.* only included patients that used b/tsDMARDs for >1 year and followed treatment effect over time. MTX use at first recorded visit was comparable between non-D2T RA and D2T RA. However, when comparing D2T RA patients that were going to fail their last prescribed b/tsDMARD and D2T RA patients with treatment success, the treatment failure group ($n = 49$) used statistically significantly lower doses of MTX, although differences were small with 8.6 *vs* 9.1 mg/week [37]. Takanashi *et al.* found no difference in MTX use, but reported that greater numbers of csDMARDs had been prescribed in D2T RA (2.5 *vs* 1.8) while contraindications or intolerance to MTX were more frequent (27% *vs* 16%) [40]. Especially in the subgroup of patients where comorbidities were thought to be key drivers of D2T RA status, only 29% of patients were on MTX, though this was only a small proportion of the total D2T RA population [$n = 17$ (10%)] [40]. Vice versa, Novella-Navarro reported concomitant use of MTX in 86% of D2T RA patients categorized as 'treatment inefficacy' which was higher than patients with D2T RA due to 'other' reason including comorbidities and side-effects (76%), however this difference did not reach statistical significance ($P = 0.28$) [44].

It is very likely that suboptimal csDMARD treatment hampers b/tsDMARD efficacy, as csDMARD are also the cornerstone in D2T RA treatment when following treat-to-target strategies. Future studies are needed to bring to light the effect of csDMARDs to b/tsDMARD inefficacy in the D2T RA population.

Lower SES contributes to D2T RA

The association between lower SES and worse disease outcome was confirmed in all three D2T RA studies that reported on SES. First, Roodenrijs found lower SES at RA diagnosis to be an independent risk factor of development to

D2T RA [41]. Second, Hecquet reported an overrepresentation of lower-income status in D2T RA based on profession (60% *vs* 47%) [42]. Third, Takanashi *et al.* observed that lower SES status in D2T RA hampered treatment intensification [40]. Fewer b/tsDMARDs were prescribed in a subgroup of D2T RA patients where SES was deemed to be at the base of D2T RA diagnosis according to the investigators. In line with this observation, Ochi *et al.* reported 'economic reasons' as cause of b/tsDMARD treatment cessation in 38% of RA patients that prematurely stopped treatment [46]. To put this in perspective, adverse events accounted for only 20% of patients discontinuing antirheumatic treatment [46]. Despite the presence of a well-funded healthcare system in these two cohorts, b/tsDMARDs were apparently less available to low SES patients [40]. Important to note, although not represented in the studies reviewed here, is the extensive group of RA patients in low-income countries with uncontrolled symptoms due to lack of financial support to get treated with b/tsDMARDs.

Not all studies reported on SES and we still need to learn what elements of SES increase risk of developing D2T RA [13]. Filling in the needs where present is warranted, these may be educational, focused on lifestyle improvement, addressing comorbidities or financial issues.

Possible true refractory D2T RA remains hard to characterize

Several D2T RA cohort studies reported on a subgroup of patients needing to switch between classes of b/tsDMARD because of inefficacy rather than side effects, probably including. D2T RA patients with ongoing inflammation, reflecting true refractory RA.

Roodenrijs *et al.* performed a cluster analysis and identified three subgroups in their cohort of 52 D2T RA patients demonstrating heterogeneity [41]. Two subgroups displayed characteristics fitting with non-inflammatory reasons for D2T RA status, which were: patient dissatisfaction and treatment non-adherence in one subgroup ($n = 17$) and poorer coping, higher occurrences of FM, anxiety and obesity in the other subgroup ($n = 8$) [41]. In the third subgroup ($n = 27$), these characteristics were lacking. Only in this third subgroup, the rheumatologists more commonly wished to intensify treatment, compared with the other groups, while in the other two groups patients wished to intensify treatment more commonly. These findings may reflect work in early RA where discordance between patient- and clinician-reported disease predicted poorer outcome [31, 47]. Also, erosions on X-rays were numerically more frequently observed in the third subgroup, although statistical significancy was not reached (subgroup 1, 59%; subgroup 2, 57%; subgroup 3, 78%; $P = 0.33$). This latter subgroup may reflect the 'true refractory' D2T RA patient [41].

Novella-Navarro *et al.* grouped D2T RA patients based on reason for b/tsDMARD switch into 'inefficacy' ($n = 86$, 70.5%) and 'other' ($n = 36$, 29.5%; such as contra-indications, drug intolerance, non-adherence, etc.) aiming to predict D2T RA-other status [44]. The D2T RA-other patients had a longer interval between RA diagnosis and bDMARD initiation (9.5 *vs* 5 years), lower DAS28 (4.9 *vs* 5.7), less extra-articular manifestations (8.3 *vs* 26.7%) and a lower patient global health assessment (40 *vs* 54) at initiation of first b/tsDMARD compared with the D2T RA-inefficacy group [4, 44]. Whether these D2T RA-inefficacy patients had signs of ongoing inflammation was not mentioned [48].

Takanashi *et al.* reviewed all cases for their believed main driver of D2T RA status based on expert opinion. Of the 172 D2T RA patients, 59 (34%) were considered multi-drug resistant, other subgroups were characterized by comorbidities and lower SES (as mentioned before) [40]. The multi-drug resistant patients had used an average of 3.9 b/tsDMARDs and had a higher HAQ Disability Index compared with the other D2T subgroups, but not higher CRP or ESR. No further evaluation of persistent inflammation or synovitis within this population was performed [40].

Treatment inefficacy can stem from uncontrolled inflammation as well as non-inflammatory factors such as concomitant pain syndromes and depression. Ultrasonography as a tool to examine the presence of inflammation was put to the test in the Garcia-Salinas cohort. Ninety-three percent of D2T RA patients had signs of synovitis (at least grade 2 power Doppler ultrasonographic activity) [35]. However, when repeating ultrasound evaluation after 1 year, only 45% of D2T RA patients had ultrasonographic activity, this discrepancy remained unexplained [35].

Identifying D2T RA patients with ongoing inflammation, that qualify for b/tsDMARD switch, remains a challenge. It is up to the rheumatologist to review and investigate the main drivers of D2T RA status, including evaluation of the presence of persistent synovitis (Fig. 2). The EULAR D2T RA management points to consider recommend using ultrasonography when in doubt [32]. The added value of ultrasonography in D2T RA still needs to be determined in clinical studies.

D2T RA state can be reversible

It is important to note that D2T RA is, for many patients, a reversible condition. We do not know yet what proportion of the D2T RA population truly has ongoing symptoms after all DMARD options are exhausted and non-pharmacological interventions are attempted. However, response rate to b/tsDMARDs in D2T RA were reported in some cohorts.

In the study by Yoshii *et al.* [37] only patients who used b/tsDMARD for >1 year (anti-TNF, anti-IL-6, CTLA4-Ig, JAKi) were included, as the objective was to identify predictors for treatment response. The success rate after 12 months of treatment with a newly started b/ts DMARD in D2T RA was 31% compared with 63% in non-D2T RA. The success rates were significantly lower in D2T RA patients using CTLA4-Ig (25% *vs* 74%) and JAK inhibitors (38% *vs* 74%). Numerically different success rates in D2T RA were seen for treatment with anti-TNF (32% *vs* 52%) and anti-IL-6 (35% *vs* 58%), but these did not reach statistical significance [37].

Aiming to identify a preferable treatment choice in D2T RA, Ochi *et al.* retrospectively included patients from the Japan based FIRST-registry [49]. Only patients on b/tsDMARDs were included and each start or switch of a b/tsDMARD was considered as a 'case', data were analysed per case and not per patient (data not included in Table 2). Limited D2T RA criteria were used, namely, a case with a history of failure to two or more b/tsDMARDs. The highest improvement in Clinical Disease Activity Index (CDAI) was seen after JAKi treatment [49]. This result was especially pronounced in cases that were not using MTX. After 6 months of JAKi treatment, remission was reported in around 35% of D2T RA patients, comparable to the findings by Yoshii *et al.* After 1 year of JAKi treatment, remission was reported in

around 25% of D2T RA patients, which diverged to response rates to TNF inhibitor (~20%), IL-6Ri (~12%) and CTLA4-Ig (~18%) treatment [49]. An earlier analysis of the FIRST-study cohort, demonstrated that having used four or more b/tsDMARDs was a predictor for failure of a consecutive b/tsDMARD, *ergo* use of two or more b/tsDMARDs did not predict future treatment failure [46].

Hecquet reported that DAS28-ESR defined remission or low disease activity (respectively DAS28-ESR <2.6 or <3.2) in D2T RA was mostly seen after treatment with JAKi ($n = 7$, 53%) and rituximab ($n = 18$, 69%) [42]. However, despite reaching low DAS28, these patients were still considered D2T RA based on ongoing signs or symptoms of inflammation or inability to taper glucocorticoids. This demonstrates that when only limited D2T RA criteria based on DAS28 or CDAI and number of used b/tsDMARDs are used, completely different outcomes are found as to whether or not D2T RA status was reversed [42].

These early observations highlight that D2T RA can be controlled. We can only speculate on possible pharmacological treatment options as randomized controlled trials in D2T RA are lacking. Not to mention, the lack of insight on the effect of non-pharmacologic interventions. Importantly, anti-CD20 antibodies, e.g. rituximab, was not prescribed in five of the here described studies due to being off-label, limiting possible successful treatment options, especially since RF positivity was more frequent in D2T RA or higher RF titers were observed [34, 35, 37, 40, 42, 43] and seropositive patients are more likely to respond to non-TNF inhibitor bDMARDs such as rituximab [5, 50].

Conclusions and future perspectives

D2T RA refers to a heterogeneous subgroup of RA patients, whose disease has not been satisfactorily controlled with several lines of DMARDs using the treat-to-target strategy. Better understanding of the underlying factors that contribute to D2T RA is indispensable for tailoring management strategies.

The studies described above, have given valuable insights into the disease state of D2T RA, although much is still unknown. In particular, data on SES or mental comorbidities are often unreported. Data mining tools are being developed to flag up D2T RA patients from electronic healthcare records and to identify potentially modifiable comorbidities, lifestyle factors and SES in larger study populations.

Implementation of a holistic approach in D2T RA management may prevent D2T RA from progressing to end stage, irreversible tissue damage, although the clinical benefit is not yet proven in studies. Further studies are needed to identify predictive factors for D2T RA, to classify patients regarding underlying factors and, eventually, to determine effectiveness of more personalized intervention(s) in individual RA patients with or at high risk of developing D2T RA.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

No new data were generated or analysed in support of this research.

Contribution statement

Z.L.M.H. and N.R. performed a systematic review and analysed the data. Z.L.M.H., N.M.T.R. and J.M.v.L. wrote the first draft of the manuscript and contributed to additional drafts. G.N., E.N., P.M.J.W. and A.L.K. reviewed and contributed to the writing of additional drafts. Z.L.M.H. made the figures and tables in the manuscript.

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References

1. Aletaha D, Smolen JS. Diagnosis and management of rheumatoid arthritis: a review. JAMA 2018;320:1360–72. http://dx.doi.org/10.1001/jama.2018.13103
2. Smolen JS, Landewé RBM, Bergstra SA *et al.* EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. Ann Rheum Dis 2023;82:3–18. http://dx.doi.org/10.1136/ard-2022-223356
3. Buch MH, Eyre S, McGonagle D. Persistent inflammatory and non-inflammatory mechanisms in refractory rheumatoid arthritis. Nature reviews. Rheumatology 2021;17:17–33. https://www.ncbi.nlm.nih.gov/pubmed/33293696
4. Smolen JS, Landewé RBM, Bijlsma JWJ *et al.* EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Ann Rheum Dis 2020;79:685–99. http://dx.doi.org/10.1136/annrheumdis-2019-216655
5. Roodenrijs NMT, Welsing PMJ, van Roon J *et al.* Mechanisms underlying DMARD inefficacy in difficult-to-treat rheumatoid arthritis: a narrative review with systematic literature search. Rheumatology (Oxford, England) 2022;61:3552–66. https://www.ncbi.nlm.nih.gov/pubmed/35238332.
6. Nagy G, Roodenrijs NM, Welsing PM *et al.* EULAR definition of difficult-to-treat rheumatoid arthritis. Ann Rheum Dis 2021;80:31–5. http://dx.doi.org/10.1136/annrheumdis-2020-217344.
7. Roodenrijs NMT, de Hair MJH, van der Goes MC, On behalf of the whole EULAR Task Force on development of EULAR recommendations for the comprehensive management of difficult-to-treat rheumatoid arthritis *et al.* Characteristics of difficult-to-treat rheumatoid arthritis: results of an international survey. Annals of the rheumatic diseases 2018;77:1705–9. http://dx.doi.org/10.1136/annrheumdis-2018-213687
8. Chaplin H, Bosworth A, Simpson C *et al.* Refractory inflammatory arthritis definition and model generated through patient and multidisciplinary professional modified delphi process. PloS one 2023;18:e0289760. https://www.ncbi.nlm.nih.gov/pubmed/37556424.
9. Nikiphorou E, Nash P. Comorbidities in RA: bringing them to the limelight. Rheumatology (Oxford, England) 2023;62:SI235–SI236. https://search.proquest.com/docview/2881245203
10. Dey M, Nagy G, Nikiphorou E. Comorbidities and extra-articular manifestations in difficult-to-treat rheumatoid arthritis: different sides of the same coin? Rheumatology (Oxford, England) 2023;62:1773–9. https://www.ncbi.nlm.nih.gov/pubmed/36205537

11. Kronzer VL, Crowson CS, Sparks JA, Myasoedova E, Davis JM. Comorbidities as risk factors for rheumatoid arthritis and their accrual after diagnosis. Mayo Clin Proc 2019;94:2488–98. https://dx.doi.org/10.1016/j.mayocp.2019.08.010
12. Stouten V, Westhovens R, De Cock D *et al.* Having a co-morbidity predicts worse outcome in early rheumatoid arthritis despite intensive treatment: a post hoc evaluation of the pragmatic randomized controlled CareRA trial. Rheumatology (Oxford, England) 2021;60:3699–708. https://www.ncbi.nlm.nih.gov/pubmed/33434277
13. Izadi Z, Li J, Evans M *et al.* Socioeconomic disparities in functional status in a national sample of patients with rheumatoid arthritis. JAMA Net Open 2021;4:e2119400. http://dx.doi.org/10.1001/jamanetworkopen.2021.19400
14. Busby AD, Wason J, Pratt AG *et al.* Predictors of poor function in RA based on two prospective UK inception cohorts. do comorbidities matter? Rheumatology (Oxford, England) 2022;61:1563–9. https://www.ncbi.nlm.nih.gov/pubmed/34302478
15. Zhang A, Lee YC. Mechanisms for joint pain in rheumatoid arthritis (RA): from cytokines to central sensitization. Curr Osteoporos Rep 2018;16:603–10. https://link.springer.com/article/10.1007/s11914-018-0473-5
16. Stefanov K, Al-Wasity S, Parkinson JT *et al.* Brain mapping inflammatory-arthritis-related fatigue in the pursuit of novel therapeutics. Lancet Rheumatol 2023;5:e99–e109. https://dx.doi.org/10.1016/S2665-9913(23)00007-3
17. Heisler AC, Song J, Muhammad LN *et al.* Association of dysregulated central pain processing and response to Disease–Modifying antirheumatic drug therapy in rheumatoid arthritis. Arthritis & rheumatology (Hoboken, N.J) 2020;72:2017–24. https://onlinelibrary.wiley.com/doi/abs/10.1002/art.41440
18. Zheng Y, Xie L, Huang Z *et al.* Enhanced activity of the left precuneus as a predictor of visuospatial dysfunction correlates with disease activity in rheumatoid arthritis. Eur J Med Res 2023;28:276. https://www.ncbi.nlm.nih.gov/pubmed/37559139
19. Sakiyama K, Abe N, Fujieda Y *et al.* Dynamics of corticocortical brain functional connectivity relevant to therapeutic response to biologics in inflammatory arthritis. Cereb Cortex (New York, N.Y. 1991) 2023;33:8342–51. https://www.ncbi.nlm.nih.gov/pubmed/37005068
20. Dehsarvi A, Al-Wasity S, Stefanov K *et al.* Characterizing the neurobiological mechanisms of action of exercise and cognitive-behavioral interventions for rheumatoid arthritis fatigue: a magnetic resonance imaging brain study. Arthritis Rheumatol 2024;76:522–30.
21. Roodenrijs NMT, Hamar A, Kedves M *et al.* Pharmacological and non-pharmacological therapeutic strategies in difficult-to-treat rheumatoid arthritis: a systematic literature review informing the EULAR recommendations for the management of difficult-to-treat rheumatoid arthritis. Rheumatic & musculoskeletal diseases open 2021;7:e001512. http://dx.doi.org/10.1136/rmdopen-2020-001512
22. Zhang F, Jonsson AH, Nathan A, Accelerating Medicines Partnership: RA/SLE Network *et al.* Deconstruction of rheumatoid arthritis synovium defines inflammatory subtypes. Nature (London 2023;623:616–24. https://search.proquest.com/docview/2891171125
23. Weisenfeld D, Zhang F, Donlin L, Accelerating Medicines Partnership Program: RA/SLE Network *et al.* Associations between rheumatoid arthritis clinical factors with synovial cell types and states. Arth Rheumatol (Hoboken, N.J.) 2023;76:356–62. https://search.proquest.com/docview/2872804422
24. Humby F, Durez P, Buch MH, R4RA collaborative group *et al.* Rituximab versus tocilizumab in anti-TNF inadequate responder patients with rheumatoid arthritis (R4RA): 16-week outcomes of a stratified, biopsy-driven, multicentre, open-label, phase 4 randomised controlled trial. Lancet 2021;397:305–17. https://dx.doi.org/10.1016/S0140-6736(20)32341-2
25. Rivellese F, Surace AEA, Goldmann K, R4RA collaborative group *et al.* Rituximab versus tocilizumab in rheumatoid arthritis: synovial biopsy-based biomarker analysis of the phase 4 R4RA randomized trial. Nature medicine 2022;28:1256–68. https://www.ncbi.nlm.nih.gov/pubmed/35589854
26. Nerviani A, Di Cicco M, Mahto A *et al.* A pauci-immune synovial pathotype predicts inadequate response to TNFα-blockade in rheumatoid arthritis patients. Front Immunol 2020;11:845. https://www.ncbi.nlm.nih.gov/pubmed/32431716
27. Croft AP, Campos J, Jansen K *et al.* Distinct fibroblast subsets drive inflammation and damage in arthritis. Nature (London) 2019;570:246–51. https://www.ncbi.nlm.nih.gov/pubmed/31142839
28. Roodenrijs NMT, Welsing PMJ, van der Goes MC *et al.* Healthcare utilization and economic burden of difficult-to-treat rheumatoid arthritis: a cost-of-illness study. Rheumatology (Oxford, England) 2021;60:4681–90. https://www.ncbi.nlm.nih.gov/pubmed/33502493
29. Roodenrijs NMT, van der Goes MC, Welsing PMJ *et al.* Non-adherence in difficult-to-treat rheumatoid arthritis from the perspectives of patients and rheumatologists: a concept mapping study. Rheumatology (Oxford, England) 2021;60:5105–16. https://www.ncbi.nlm.nih.gov/pubmed/33560301
30. Roodenrijs NMT, Kedves M, Hamar A *et al.* Diagnostic issues in difficult-to-treat rheumatoid arthritis: a systematic literature review informing the EULAR recommendations for the management of difficult-to-treat rheumatoid arthritis. Rheum Musculosk Dis open 2021;7:e001511. http://dx.doi.org/10.1136/rmdopen-2020-001511
31. Doumen M, Stouten V, Pazmino S *et al.* Patient–physician discordance impairs outcomes in early rheumatoid arthritis through less consistent treat-to-target implementation. Rheumatology (Oxford, England) 2023. E-pub ahead of print. https://www.ncbi.nlm.nih.gov/pubmed/38127964
32. Nagy G, Roodenrijs NMT, Welsing PMJ *et al.* EULAR points to consider for the management of difficult-to-treat rheumatoid arthritis. Ann Rheum Dis 2022;81:20–33. http://dx.doi.org/10.1136/annrheumdis-2021-220973
33. Giollo A, Zen M, Larosa M *et al.* Early characterization of difficult-to-treat rheumatoid arthritis by suboptimal initial management: a multicentre cohort study. Rheumatology (Oxford, England) 2023;62:2083–9. https://www.ncbi.nlm.nih.gov/pubmed/36190344
34. Leon L, Madrid-Garcia A, Lopez-Viejo P *et al.* Difficult-to-treat rheumatoid arthritis (D2T RA): clinical issues at early stages of disease. RMD Open 2023;9:e002842. doi: 10.1136/rmdopen-2022-002842
35. Garcia-Salinas R, Sanchez-Prado E, Mareco J *et al.* Difficult to treat rheumatoid arthritis in a comprehensive evaluation program: frequency according to different objective evaluations. Rheumatol Int 2023;43:1821–8. https://link.springer.com/article/10.1007/s00296-023-05349-8
36. Jung J, Lee E, Kim J *et al.* Unveiling difficult-to-treat rheumatoid arthritis: long-term impact of biologic or targeted synthetic DMARDs from the KOBIO registry. Arthr Res Ther 2023;25:1–174. https://search.proquest.com/docview/2877504226
37. Yoshii I, Sawada N, Chijiwa T. Clinical characteristics and variants that predict prognosis of difficult-to-treat rheumatoid arthritis. Rheumatol Int 2022;42:1947–54. https://link.springer.com/article/10.1007/s00296-022-05124-1
38. de Hair MJH, Jacobs JWG, Schoneveld JLM, van Laar JM. Difficult-to-treat rheumatoid arthritis: an area of unmet clinical need. Rheumatology (Oxford, England) 2018;57:1135–44. https://www.ncbi.nlm.nih.gov/pubmed/29029308
39. Kearsley-Fleet L, Davies R, De Cock D *et al.* Biologic refractory disease in rheumatoid arthritis: results from the british society for rheumatology biologics register for rheumatoid arthritis. Ann Rheum Dis 2018;77:1405–12. http://dx.doi.org/10.1136/annrheumdis-2018-213378
40. Takanashi S, Kaneko Y, Takeuchi T. Characteristics of patients with difficult-to-treat rheumatoid arthritis in clinical practice. Rheumatology (Oxford, England) 2021;60:5247–56. https://www.ncbi.nlm.nih.gov/pubmed/33682890

41. Roodenrijs NMT, van der Goes MC, Welsing PMJ *et al.* Difficult-to-treat rheumatoid arthritis: contributing factors and burden of disease. Rheumatology (Oxford, England) 2021;60:3778–88. https://www.ncbi.nlm.nih.gov/pubmed/33331946
42. Hecquet S, Combier A, Steelandt A *et al.* Characteristics of patients with difficult-to-treat rheumatoid arthritis in a french single-centre hospital. Rheumatology (Oxford, England) 2023;62:3866–74. https://www.ncbi.nlm.nih.gov/pubmed/36961324
43. Watanabe R, Hashimoto M, Murata K *et al.* Prevalence and predictive factors of difficult-to-treat rheumatoid arthritis: the KURAMA cohort. Immunological medicine 2022;45:35–44. https://www.tandfonline.com/doi/abs/10.1080/25785826.2021.1928383
44. Novella-Navarro M, Ruiz-Esquide V, Torres-Ortiz G *et al.* A paradigm of difficult-to-treat rheumatoid arthritis: subtypes and early identification. Clin Exp Rheumatol 2023;41:1114–9. https://www.ncbi.nlm.nih.gov/pubmed/36377568
45. Kerschbaumer A, Sepriano A, Bergstra SA *et al.* Efficacy of synthetic and biological DMARDs: a systematic literature review informing the 2022 update of the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis 2023;82:95–106. http://dx.doi.org/10.1136/ard-2022-223365
46. Ochi S, Mizoguchi F, Nakano K, Tanaka Y. Difficult-to-treat rheumatoid arthritis with respect to responsiveness to biologic/targeted synthetic DMARDs: a retrospective cohort study from the FIRST registry. Clinical and Experimental Rheumatology 2022;40:86–96. https://www.ncbi.nlm.nih.gov/pubmed/33635223
47. Pazmino S, Lovik A, Boonen A *et al.* New indicator for discordance between patient-reported and traditional disease activity outcomes in patients with early rheumatoid arthritis. Rheumatology (Oxford, England) 2022;62:108–15. https://www.ncbi.nlm.nih.gov/pubmed/35416951
48. Novella-Navarro M, Cabrera-Alarcón J, López-Juanes N *et al.* Patient and physician assessment in difficult-to-treat rheumatoid arthritis: patterns of subjective perception at early stages of b/tsDMARD treatment. RMD Open 2023;9:e003382. https://search.proquest.com/docview/2870991086
49. Ochi S, Sonomoto K, Nakayamada S, Tanaka Y. Preferable outcome of janus kinase inhibitors for a group of difficult-to-treat rheumatoid arthritis patients: from the FIRST registry. Arth Res Ther 2022;24:61. https://www.ncbi.nlm.nih.gov/pubmed/35232462
50. Courvoisier DS, Chatzidionysiou K, Mongin D *et al.* The impact of seropositivity on the effectiveness of biologic anti-rheumatic agents: results from a collaboration of 16 registries. Rheumatology 2021;60:820–8. https://www.ncbi.nlm.nih.gov/pubmed/32810263

Rheumatology, 2024, 64, 65–73
https://doi.org/10.1093/rheumatology/keae544
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