Difficult-to-treat rheumatoid arthritis (D2T RA)

Dr İsmihan SUNAR

Ankara Üniversitesi FTR Romatoloji Kliniği

D2T RA neden önemli?

- ‘difficult to treat’, ‘treatment-resistant’, ‘refractory’ RA
- Kontrol edilemeyen orta/yüksek hastalık aktivitesi, azalmış QoL, direkt/indirekt ekonomik yük
- %10-20..
- British Society of Rheumatology Biologics Register for RA; %6 (n: 13502)

«csDMARD ve en az 2 bDMARDA’a rağmen persistan inflamatuar RA aktivitesi»

*Maria J H de Hair et al, Difficult-to-treat rheumatoid arthritis: an area of unmet clinical need, *Rheumatology*, Volume 57, Issue 7, July 2018, Pages 1135–1144
Bécède, M. et al. Risk profiling for a refractory course of rheumatoid arthritis. Semin. Arthritis Rheum. 49, 211–217 (2019).

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EULAR definition of difficult-to-treat rheumatoid arthritis

György Nagy ,[1,2] Nadia MT Roodenrijs ,[3] Paco MJ Welsing,[3] Melinda Kedves ,[4] Attila Hamar,[5] Marlies C van der Goes,[3,6] Alison Kent,[7] Margot Bakkers,[8] Etienne Blaas,[3] Ladislav Senolt,[9] Zoltan Szekanecz ,[5] Ernest Choy,[10] Maxime Dougados,[11] Johannes WG Jacobs ,[3] Rinie Geenen,[12] Hans WJ Bijlsma,[3] Angela Zink,[13] Daniel Aletaha ,[14] Leonard Schoneveld,[15] Piet van Riel,[16] Loriane Gutermann,[17] Yeliz Prior,[18] Elena Nikiphorou ,[19] Gianfranco Ferraccioli ,[20] Georg Schett ,[21] Kimme L Hyrich,[22,23] Ulf Mueller-Ladner,[24] Maya H Buch ,[22,23,25] Iain B McInnes,[26] Désirée van der Heijde ,[27] Jacob M van Laar[3]

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For numbered affiliations see end of article.

Correspondence to
Professor György Nagy, Department of Rheumatology, Semmelweis University, Budapest, Árpád fejedelem útja 7., 1023, Hungary; nagy.gyorgy2@med.semmelweis-univ.hu

DvdH and JMvL contributed equally.

DvdH and JMvL are joint senior authors.

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ABSTRACT

Background Despite treatment according to the current management recommendations, a significant proportion of patients with rheumatoid arthritis (RA) remain symptomatic. These patients can be considered to have 'difficult-to-treat RA'. However, uniform terminology and an appropriate definition are lacking.

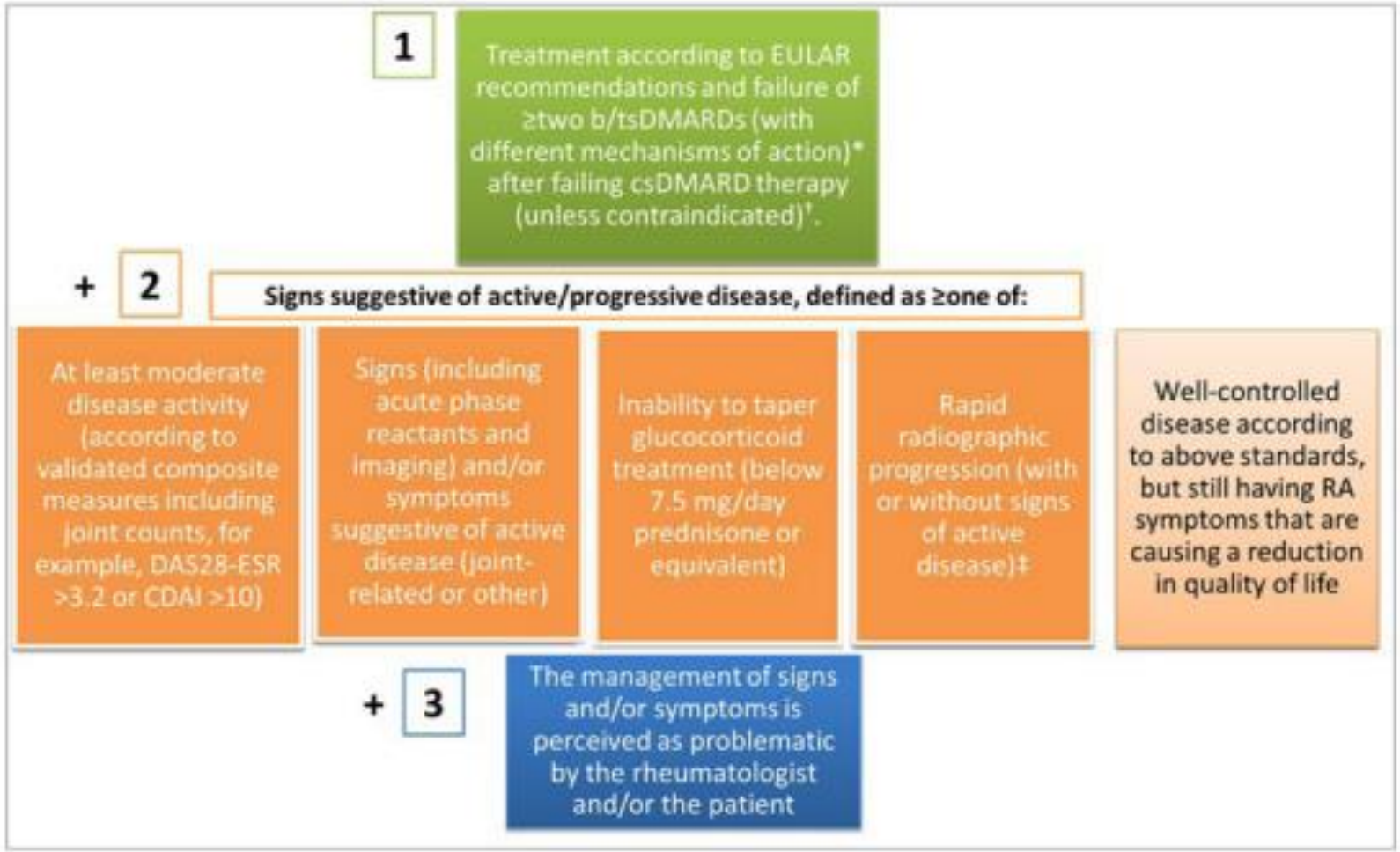
Objective The Task Force in charge of the "Development of EULAR recommendations for the comprehensive management of difficult-to-treat rheumatoid arthritis" aims to create recommendations for this underserved patient group. Herein, we present the definition of difficult-to-treat RA, as the first step.

Methods The Steering Committee drafted a definition with suggested terminology based on an international survey among rheumatologists. This was discussed and amended by the Task Force, including rheumatologists, nurses, health professionals and patients, at a face-to-face meeting until sufficient agreement was reached (assessed through voting).

Results The following three criteria were agreed by all Task Force members as mandatory elements of the definition of difficult-to-treat RA: (1) Treatment according to European League Against Rheumatism (EULAR) recommendation and failure of ≥2 biological disease-modifying antirheumatic drugs (DMARDs)/targeted synthetic DMARDs (with different mechanisms of action) after failing conventional synthetic DMARD therapy (unless contraindicated); (2) presence of at least one of the following: at least moderate disease activity; signs and/or symptoms suggestive of active disease; inability to taper glucocorticoid treatment; rapid radiographic

direct the management of rheumatoid arthritis (RA). The treat-to-target (T2T) strategy advises an agreed disease activity target, remission or at least low disease activity, that can in turn inform responsive treatment escalation.[1–3] However, a number of patients remain symptomatic despite recommended treatment changes reflecting the complex interplay of disease and wider patient and clinical factors that leads to the increasingly recognised term of 'difficult-to-treat RA'.[4–7]

A recent international survey of rheumatologists highlighted the perceived management problems and features in this patient category; the results of which confirmed the unmet need of this subpopulation of RA patients.[8] The survey indicated that in addition to new drugs, new management approaches are also needed for the optimal treatment of these patients. Consequently, a EULAR Task Force was established to derive comprehensive recommendations addressing unmet needs in the management of difficult-to-treat (D2T) RA. Uniform terminology and a clear definition for this patient group are lacking. In the current literature, different terms are used to describe this subpopulation of RA patients, for example, severe, refractory, resistant to multiple drugs or treatments, established and difficult-to-treat.[4–7] As an initial step in the development of the management recommendations for D2T RA, terminology and a definition of this complicated RA patient group was established by the Task Force, guided by the results of the survey.[8]



All three of the criteria need to be present to qualify as D2T RA

b/tsDMARDs, biological and targeted synthetic disease-modifying anti-rheumatic drugs; CDAI, Clinical Disease Activity Index; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; D2T, difficult-to-treat; DAS28-ESR, Disease Activity Score assessing 28 joints using erythrocyte sedimentation rate; RA, rheumatoid arthritis.
* Unless restricted by access to treatment due to socioeconomic factors.
† If csDMARD treatment is contraindicated, failure of ≥two b/tsDMARDs with different mechanisms of action is sufficient.
‡ Rapid radiographic progression: change in van der Heijde-Modified Sharp Score ≥5 points in 1 year or a similar progression in another validated scoring method.

Figure 1 EULAR definition of difficult-to-treat rheumatoid arthritis (D2T-RA). EULAR, European Alliance of Associations for Rheumatology.

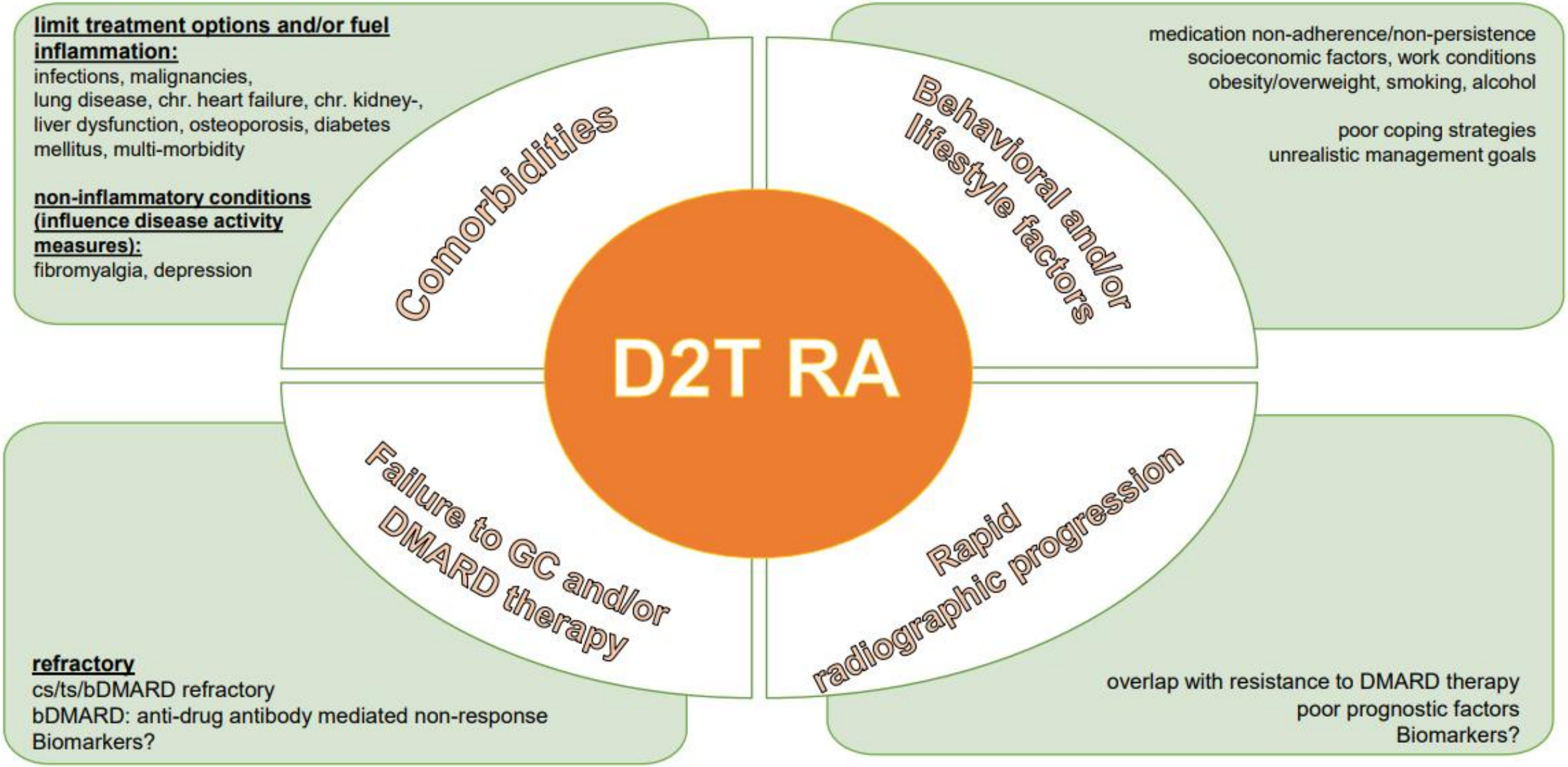
'Difficult to treat' rheumatoid arthritis: current position and considerations for next steps. Yvonne Tan, Maya H Buch

D2T RA

- DMARD yanıtsızlığı ve D2T RA nedenleri net olarak aydınlatılamamış olsa da, etyopatogenezde epigenetik modifikasyonların (metilasyon, microRNAs, long non-coding RNAs) rol oynadığı düşünülmektedir.
- Epigenetik değişiklikler ageing, tedaviler veya çevresel faktörler etkisi ile oluşabilir ve RA seyrini etkileyerek refraktör RA için temel teşkil edebilirler.
- İnflamasyon ve epigenetik değişiklikler çift-yönlü ilişkiye sahiptir.

- Prediktörler: tedavi başlangıcında gecikme, kadın cinsiyet, yüksek hastalık aktivite skorları, sigara, obezite, düşük sosyoekonomik durum, GK kullanımı..

Melville AR, Kearsley-Fleet L, Buch MH, Hyrich KL. Understanding Refractory Rheumatoid Arthritis: Implications for a Therapeutic Approach. Drugs. 2020 Jun;80(9):849-857.
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. doi: 10.1007/s00296-022-05124-1


limit treatment options and/or fuel inflammation:
infections, malignancies,
lung disease, chr. heart failure, chr. kidney-,
liver dysfunction, osteoporosis, diabetes
mellitus, multi-morbidity
non-inflammatory conditions (influence disease activity measures):
fibromyalgia, depression
Comorbidities
medication non-adherence/non-persistence
socioeconomic factors, work conditions
obesity/overweight, smoking, alcohol
poor coping strategies
unrealistic management goals
Behavioral and/or lifestyle factors
D2T RA
Failure to GC and/or DMARD therapy
refractory
cs/ts/bDMARD refractory
bDMARD: anti-drug antibody mediated non-response
Biomarkers?
Rapid radiographic progression
overlap with resistance to DMARD therapy
poor prognostic factors
Biomarkers?

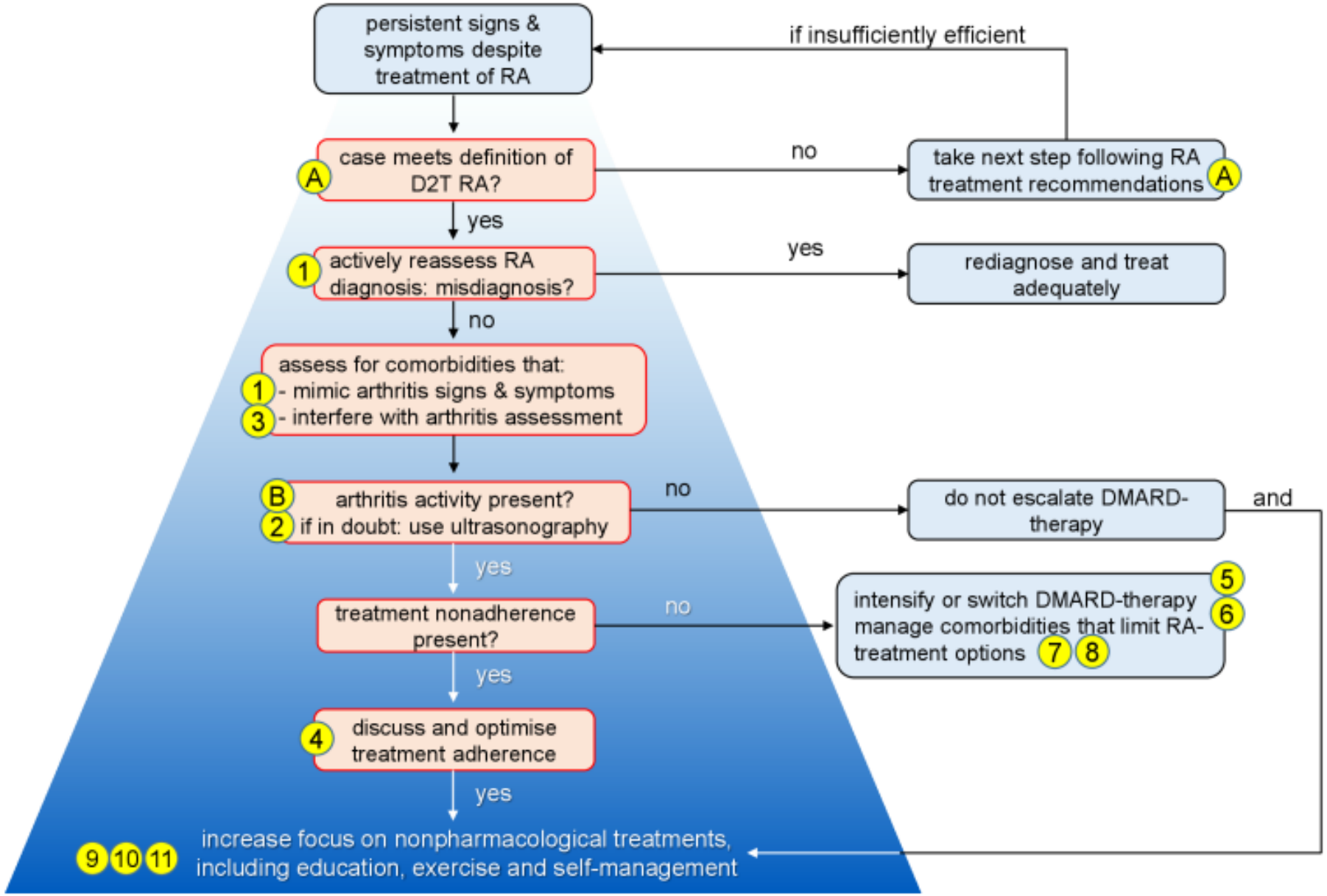


Figure 1 Algorithm based on the EULAR PtCs for the management of D2T RA. The pyramid background with increasing intensity of blue colour indicates non-pharmacological approaches and treatments, which are important throughout all phases of RA, but especially so if pharmacological treatment options are limited. The letters and numbers indicate the corresponding overarching principles and PtCs, respectively; see table 1. D2T, difficult-to-treat; DMARD, disease-modifying antirheumatic drug; EULAR, European Alliance of Associations for Rheumatology; PtCs, points to consider; RA, rheumatoid arthritis.

D2T RA EULAR Önerileri

1. Tanıyı gözden geçir/ taklitçi hastalıkları dışla..
2. İnflamatuar aktivite ile ilgili şüphe varsa görüntüleme (US) düşünülmelidir.
3. Komorbid durumlar ve özellikle *obezite/ fibromiyalji* durumunda kompozit ölçek sonuçları dikkatle yorumlanmalıdır.
4. *Tedavi uyumu* gözden geçirilmeli ve optimize edilmelidir.
5. İki TNFi başarısızlığı varsa *farklı etki mekanizmalı* ajana geçilmelidir.
6. Üçüncü b/tsDMARD düşünüldüğünde, etkin ve güvenli olan *maksimum doz* uygulanmalıdır.

D2T RA EULAR Önerileri

7. Hayat kalitesini veya RA tedavisini etkileyen *komorbiditeler* gözönünde bulundurulmalı ve bunlarla mücadele edilmelidir.

8. HBV/HCV infeksiyon durumunda b/tsDMARDs kullanılabilir, hepatologist ile antiviral profilaksi ve tedavi açısından yakın iş birliği gerekir.

9. *Non-farmakolojik* öneriler dizabilite, ağrı ve yorgunluk yönetiminde önemlidir.. (egzersiz, eğitim, psikososyal iyileştirme..)

10. Tedavi seçimi ve amacı konusunda bilgilendirmek üzere hastalara uygun *eğitim ve destek* sunulmalıdır.

11. *Self-management* programları, psikososyal müdahaleler ve eğitim verilerek hastaların kendilerinden emin şekilde hastalıklarını yönetme yeteneği optimize edilmelidir (*self-efficacy*).

Yanlış tanı/ taklitçi hastalıklar?

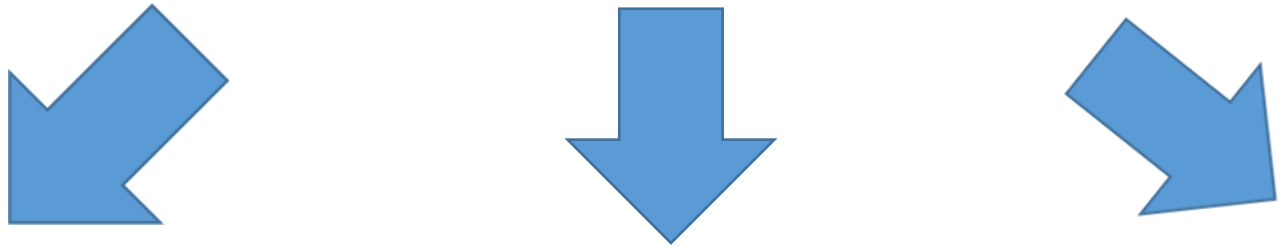
- Kristal artropatiler
- Polimyaljia romatika,
- Psoriatik artrit
- Spondiloartrit
- Still hastalığı,
- SLE,
- Rhupus
- Vaskülit
- İdyopatik inflamatuar myopati,
- RS3PE,
- Reaktif artrit (eg, parvo B19, Rubella, Whipple’s disease, HBV ve HCV),
- Paraneoplastik sendromlar,
- Osteoartrit
- Fibromyalji

Komorbiditeler/tedaviyi kısıtlayıcı klinik durumlar

- HIV,
- Gastrointestinal hastalıklar,
- Latent tbc
- Malignite
- VTE
- HBV, HCV
- Kardiyovasküler hastalık
- Gebelik/laktasyon

- Extra-artiküler tutulumlar,
- Hepatik hastalık
- Osteoporoz,
- Psikolojik distress,
- Pulmoner hastalık
- Renal hastalık

D2T RA subtipler?



- ‘Uyumsuz/ tatminsiz hasta’
- ‘Ağrı sendromları veya obezitesi olan hasta’
- ‘Gerçek refraktör RA’

D2T RA subtipler?

- ‘Uyumsuz/ tatminsiz hasta’
- ‘Ağrı sendromları veya obezitesi olan hasta’
- ‘Gerçek refraktör RA’

USG
CRP
ESR

Non-farmakolojik yaklaşımlar;
Hasta eğitimi/self-management/psikososyal müdahaleler

Check for updates

Persistent inflammatory and non-inflammatory mechanisms in refractory rheumatoid arthritis

Maya H. Buch[1,2,3]✉, *Stephen Eyre*[1,2] *and Dennis McGonagle*[3,4]

Abstract | Despite nearly three decades of advances in the management of rheumatoid arthritis (RA), a substantial minority of patients are exposed to multiple DMARDs without necessarily benefitting from them; a group of patients variously designated as having 'difficult to treat', 'treatment-resistant' or 'refractory' RA. This Review of refractory RA focuses on two types of patients: those for whom multiple targeted therapies lack efficacy and who have persistent inflammatory pathology, which we designate as persistent inflammatory refractory RA (PIRRA); and those with supposed refractory RA who have continued disease activity that is predominantly independent of objective evidence of inflammation, which we designate as non-inflammatory refractory RA (NIRRA). These two types of disease are not mutually exclusive, but identifying those individuals with predominant PIRRA or NIRRA is important, as it informs distinct treatment and management approaches. This Review outlines the clinical differences between PIRRA and NIRRA, the genetic and epigenetic mechanisms and immune pathways that might contribute to the immunopathogenesis of recalcitrant synovitis in PIRRA, and a possible basis for non-inflammatory symptomatology in NIRRA. Future approaches towards the definition of refractory RA and the application of single-cell and integrated omics technologies to the identification of refractory RA endotypes are also discussed.

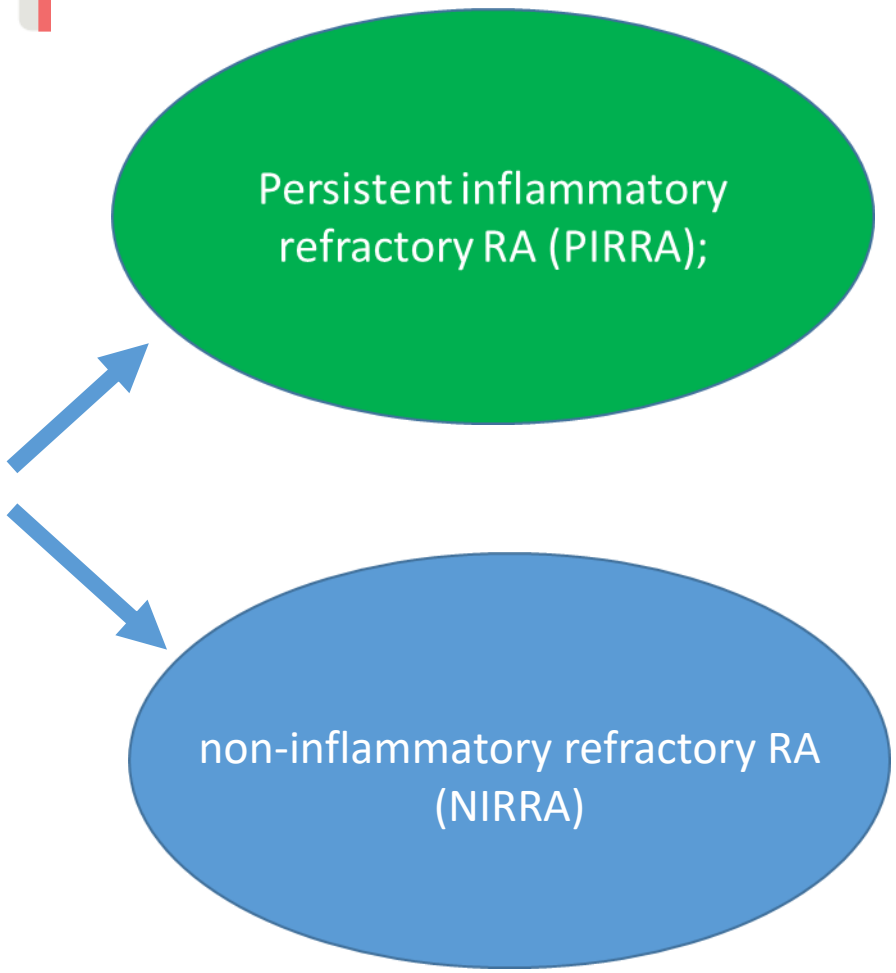
[1]*Centre for Musculoskeletal Research, School of Biological Sciences, Faculty of Biology, Medicine & Health, University of Manchester, Manchester, UK.*

[2]*NIHR Manchester Biomedical Research Centre, Manchester Academic Health Science Centre, Manchester*

Despite advances in the management of rheumatoid arthritis (RA) that have been made over the past 30 years and the availability of effective targeted synthetic DMARDs (tsDMARDs) and biologic DMARDs (bDMARDs), treatment non-response remains an ongoing clinical challenge that can result in treatment-resistant RA[1]. The goal of treatment with existing conventional synthetic DMARDs, tsDMARDs and bDMARDs in RA is the complete abrogation of inflammation. The inability to achieve this goal leads to successive cycling of therapies (BOX 1). Increasingly, the term 'refractory' RA is being used to describe disease that is

and potential somatic mutations, that could contribute to the persistence or evolution of immune responses and ongoing inflammation in individuals with persistent synovitis. We also discuss how perturbations in the joint microenvironment and subtle emergent immune mechanisms linked to pain might contribute to ongoing symptomatology in individuals with little or no discernible inflammation. Finally, we provide some thoughts on how the challenges surrounding refractory RA might be addressed in the future.

Defining refractory RA



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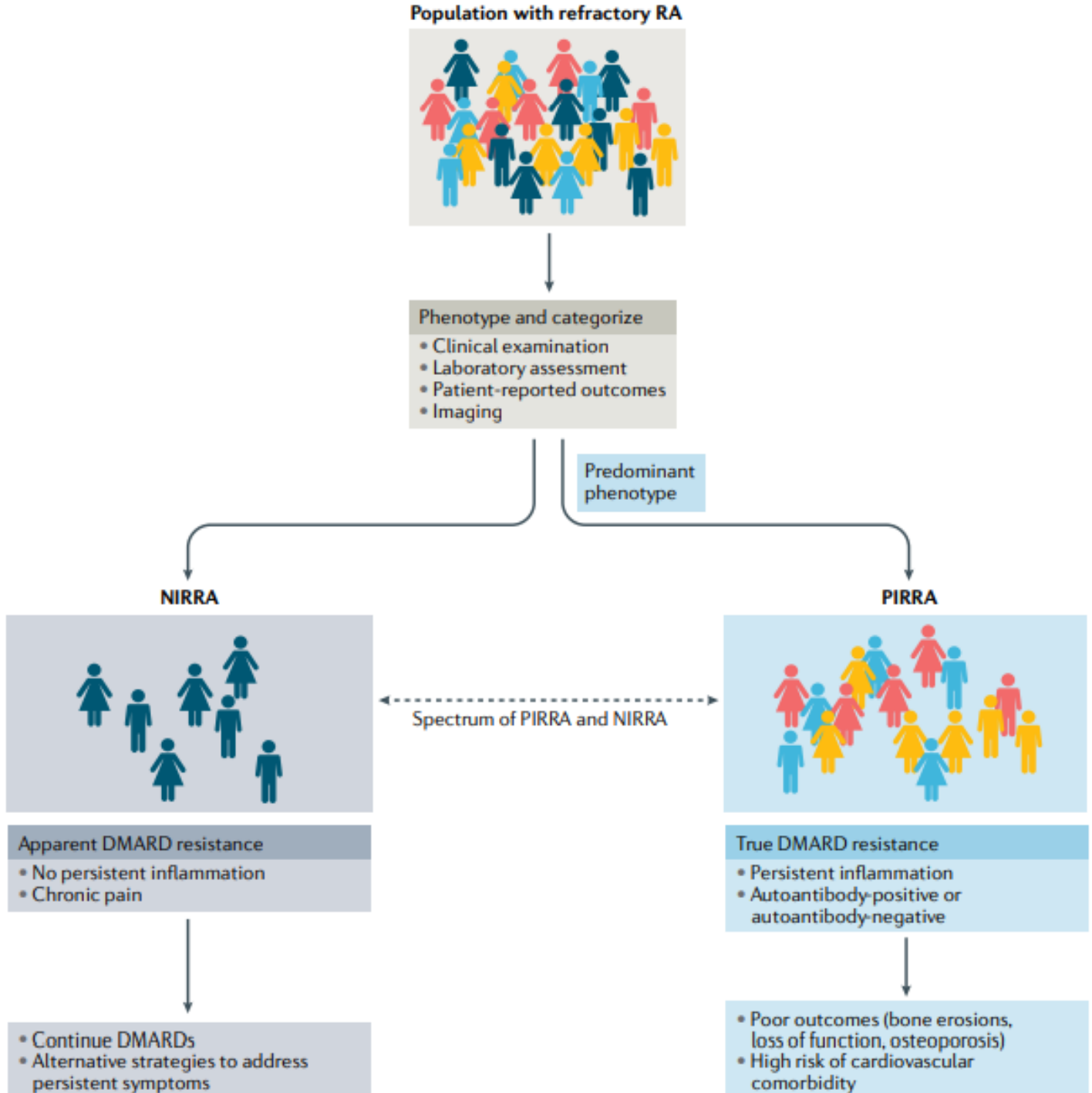

Persistent inflammatory and non-inflammatory mechanisms in refractory rheumatoid arthritis
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2 major (& örtüşen) sub-kategori

- PIRRA kategorisinde serolojik durum ve HLA ilişkilerinin belirlenmesi potansiyel tedaviler için tabakalandırma sağlayabilir

HLA ilişkili, Antikor(+) RA

Seronegatif, HLA ilişkili RA

HLA ilişkisiz, Seronegatif RA

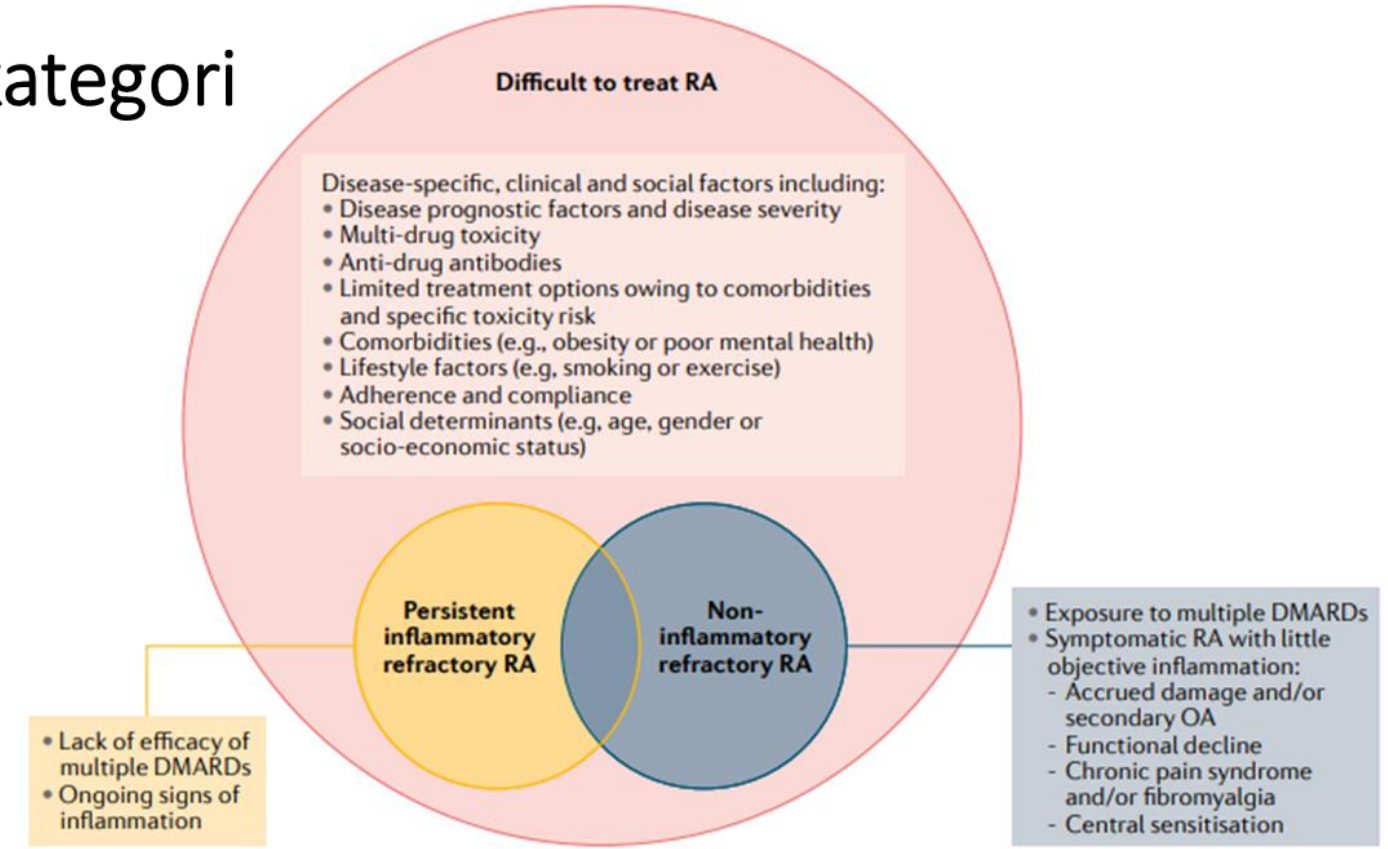
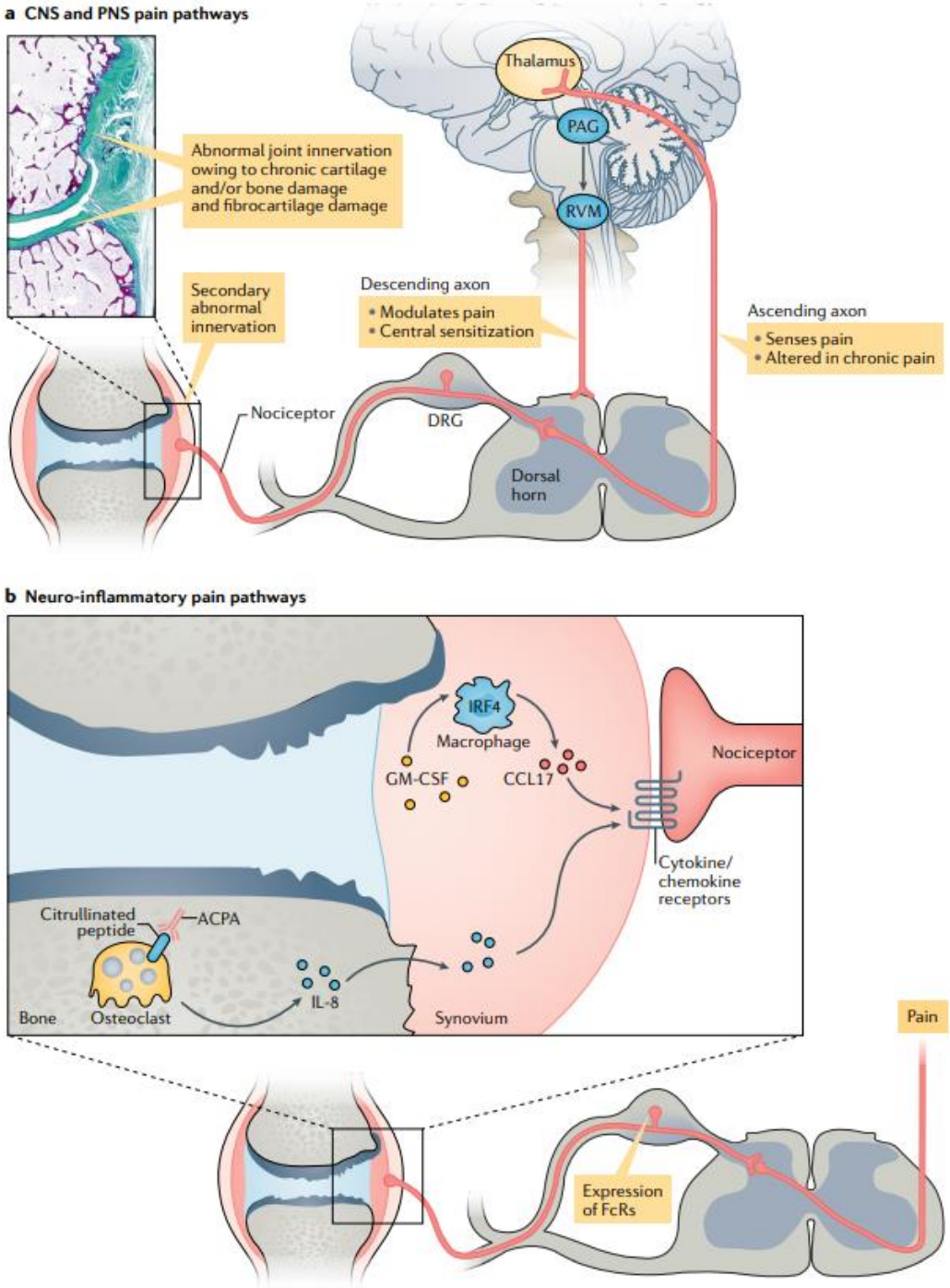


Fig. 1 | **Refractory RA subgroups within the wider context of 'difficult-to-treat' RA.** The term 'difficult-to-treat' rheumatoid arthritis (RA) is often used to describe disease in patients who are exposed to multiple biologic DMARDs and/or targeted synthetic DMARDs, but not necessarily in those for whom they lack efficacy. This group of patients encompasses those with comorbidities that preclude the use of certain therapies, repeated drug toxicity, anti-drug antibody development leading to drug inefficacy, and medication non-adherence and non-compliance. Lifestyle and social determinants might also contribute to lack of treatment efficacy in this group. We propose that the term 'refractory' RA could be defined by the inefficacy (not toxicity) of multiple types of DMARDs. Some individuals in this group will have persistent inflammation in the joints (and potentially systemic inflammation) and would be classified as having persistent inflammatory refractory RA. Other individuals will have symptomatic RA with little objective evidence of ongoing inflammation that can be modulated by DMARDs that principally target innate and adaptive immune system-mediated inflammation. Misdiagnosis of ongoing symptomatology as joint inflammation can lead to individuals in this group cycling though several therapies; such individuals would be classified as having non-inflammatory refractory RA. Importantly, all three groupings can exist in their own right and/or coexist to differing degrees, this latter scenario being the most likely. Although the definitions and terminology suggested here are preliminary, it is clear that the two subtypes of refractory RA would need distinct therapeutic approaches. OA, osteoarthritis.



- NIRRA'da rezidüel ağrının bir kısmı persistan santral sensitizasyona atfedilebilir.
- Kronik inflamasyon, malalignment ve kartilaj/kemik/kapsül hasarı sekonder anormal eklem innervasyonuna ve buna bağlı maladaptif ağrı işlenmesine yol açabilir.
- CC-chemokine ligand 17 (CCL17) gibi bazı inflamatuar mediyatörler de nosiseptif ağrı üzerinde santral etkilere sahip olabilir.

RHEUMATOLOGY

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Original article

Characteristics of patients with difficult-to-treat rheumatoid arthritis in clinical practice

Satoshi Takanashi [1], **Yuko Kaneko**[1] and **Tsutomu Takeuchi**[1]

Abstract

Objectives. The aim of this study was to investigate the clinical characteristics of patients with difficult-to-treat RA (D2T RA) and the usefulness of switching to drugs with different modes of action in real-world.

Methods. We reviewed all consecutive patients with RA treated at Keio University Hospital between 2016 and 2017 with a definition of D2T RA. We analysed clinical characteristics and evaluated the usefulness of changing drugs according to mode of action.

Results. Among 1709 patients with RA, 173 (10.1%) were D2T RA. The reason for the D2T RA was multi-drug resistance in 59 patients (34.1%), comorbidity in 17 (9.8%), and socio-economic reasons in 97 (56.1%). The multi-drug-resistance group had significantly higher tender joint count and evaluator global assessment than the other groups, despite receiving the most intensive treatment. The comorbidity group showed a significantly older age and higher rheumatic disease comorbidity index. Although changing the drug to another with a different mode of action was useful, the proportion of patients who achieved remission or low disease activity decreased as the number of switches increased.

Conclusion. Of the patients with RA, 10.1% were still difficult to treat in clinical practice, despite intensive treatment. Their characteristics were distinct by the reasons of D2T RA, which suggests the need for a personalized approach to D2T RA.

Key words: rheumatoid arthritis, difficult-to-treat rheumatoid arthritis, synovitis, switching mode of action, epidemiology

RHEUMATOLOGY

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TABLE 1 Comparison of clinical characteristics of patients who have difficult-to-treat RA (D2T RA) *vs* non-D2T RA

	All $N = 1709$	D2T RA $N = 173$	Non-D2T RA $N = 1536$	*P* value
Female	1423 (83.3)	155 (89.6)	1268 (82.6)	0.02
Age at diagnosis, years	52.0 (15.3)	50.8 (14.0)	52.1 (15.5)	0.27
Age at last visit, years	63.8 (14.6)	65.5 (13.3)	63.4 (1.7)	0.10
Disease duration, years	11.8 (8.7)	14.7 (9.7)	11.5 (8.5)	<0.001
Diagnosis to treatment initiation with bDMARD or JAKi, years, $n = 1117$	5.4 (7.6)	7.4 (8.8)	5.1 (7.4)	0.002
Smoking history, $n = 1503$	375 (25.0)	43/162 (26.5)	332/1341 (24.8)	0.63
Family history of RA, $n = 1500$	142 (9.5)	18/162 (11.1)	124/1338 (9.3)	0.48
Height, cm, $n = 1400$	157.6 (8.1)	155.7 (7.)2	157.8 (8.1)	0.002
Body weight, kg, $n = 1400$	53.9 (10.3)	52.3 (10.5)	54.2 (10.3)	0.03
BMI, $n = 1400$	21.6 (3.4)	21.5 (3.8)	21.7 (3.3)	0.60
Serology				
Anti-CCP/RF negative, $n = 1685$	296 (17.6)	17/173 (9.8)	279/1512 (18.5)	0.004
Anti-CCP positive, $n = 1685$	1262 (74.9)	150/173 (86.7)	1112/1512 (73.5)	<0.001
RF positive	1315 (76.9)	145 (83.8)	1170 (76.2)	0.02
Anti-CCP/RF positive, $n = 1685$	1167 (69.3)	139/173 (80.3)	1028/1512 (68.0)	0.001
Current treatment				
csDMARDs alone	630 (36.9)	52 (30.1)	578 (37.6)	0.06
MTX user	1061 (62.1)	105 (60.7)	956 (62.2)	0.74
Contraindication or intolerance to MTX	287 (16.8)	46 (26.6)	241 (15.7)	<0.001
PSL user	212 (12.4)	51 (29.4)	161 (10.5)	<0.001
Dose of PSL, mg/day	3.8 (2.1)	4.2 (2.4)	3.6 (1.9)	0.23
bDMARDs/JAKis	971 (56.8)	117 (67.6)	854 (55.6)	0.003
History of treatment				
Number of used csDMARDs	1.8 (1.2)	2.5 (1.6)	1.8 (1.1)	<0.001
Number of used bDMARDs/JAKis	1.1 (1.2)	2.1 (1.7)	1.0 (1.1)	<0.001
Number of used mode of action	1.4 (0.7)	2.1 (0.8)	1.3 (0.6)	<0.001
TNFi	807 (47.2)	115 (66.5)	692 (45.1)	<0.001
IL-6i	522 (30.5)	89 (51.4)	433 (28.2)	<0.001
CTLA-4Ig	206 (12.1)	46 (26.6)	160 (10.4)	<0.001
JAKi	53 (3.1)	25 (14.5)	28 (1.8)	<0.001
Comorbidity				
Admission due to infection	113 (6.6)	38 (22.0)	75 (4.9)	<0.001
eGFR, ml/min/1.73 m^2	71.2 (17.7)	72.5 (21.2)	71.1 (17.3)	0.31
eGFR < 60 ml/min/1.73 m^2	415 (24.3)	46 (26.6)	369 (24.0)	0.46
RDCI	0.8 (1.2)	1.1 (1.2)	0.8 (1.1)	0.002
Hypertension	279 (16.3)	32 (18.5)	247 (16.1)	0.45
Ischemic heart disease	51 (3.0)	4 (2.3)	47 (3.1)	0.81
Stroke	42 (2.5)	3 (1.7)	39 (2.5)	0.79
Diabetes mellitus	121 (7.1)	12 (6.9)	109 (7.1)	1.00
Liver	118 (6.9)	13 (7.5)	105 (6.8)	0.75
Lung	225 (13.2)	40 (23.1)	185 (12.0)	<0.001
Depression	22 (1.3)	4 (2.3)	18 (1.2)	0.27
Fracture	90 (5.2)	13 (7.5)	77 (5.0)	0.15
Gastrointestinal ulcer	38 (2.2)	3 (1.7)	35 (2.3)	1.00
Other stomach	32 (1.9)	5 (2.9)	27 (1.8)	0.38
Disease activity				
DAS28-ESR	2.3 (4.7)	4.0 (0.9)	2.2 (0.8)	<0.001
CDAI	3.1 (4.5)	11.7 (7.6)	2.2 (2.6)	<0.001
SDAI	3.3 (4.7)	12.2 (7.9)	2.3 (2.7)	<0.001
TJC (0–28)	0.5 (1.4)	2.5 (3.4)	0.2 (0.7)	<0.001
SJC (0–28)	0.6 (1.5)	3.1 (3.1)	0.3 (0.8)	<0.001
EGA, mm	4.6 (8.7)	19.1 (16.1)	3.0 (5.4)	<0.001
PGA, mm	16.5 (20.4)	42.1 (26.0)	13.6 (17.4)	<0.001
HAQ-DI	0.5 (0.7)	1.1 (0.9)	0.4 (0.3)	<0.001
CRP, mg/dl	0.2 (0.6)	0.7 (1.3)	0.2 (0.4)	<0.001
ESR, mm/h	21.1 (19.8)	39.4 (29.6)	19.1 (17.1)	<0.001
MMP-3, mg/dl	62.5 (74.2)	108.5 (135.3)	57.3 (61.8)	<0.001

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Clinical science

Early characterization of difficult-to-treat rheumatoid arthritis by suboptimal initial management: a multicentre cohort study

Alessandro Giollo [1,*], Margherita Zen [1], Maddalena Larosa[1,2], Davide Astorri[3], Mariangela Salvato[1], Antonia Calligaro[1], Konstantinos Botsios[1], Cristina Bernardi[3], Gerolamo Bianchi[2], Andrea Doria [1]

[1]Rheumatology Unit, Department of Medicine, University of Padova, Padova, Italy
[2]Rheumatology Unit, Department of Medical Specialties, ASL3, Genoa, Italy
[3]Rheumatology Unit, Department of Medicine, SS: Giovanni e Paolo Hospital, Venice, Italy

*Correspondence to: Alessandro Giollo, Rheumatology Unit, University of Padova, Policlinico, via Giustiniani 2, 35128 Padova, Italy.
E-mail: alessandro.giollo@unipd.it

Abstract

Objectives: To demonstrate that unsuccessful treatment optimization in early disease is associated with difficult-to-treat RA (D2T-RA).

Methods: In this retrospective multicentre cohort study conducted from 09/2021–03/2022, we enrolled individuals fulfilling the 2010 ACR/EULAR RA criteria diagnosed 2000–2019. The outcome was D2T-RA by the EULAR definition. We used robust regression to examine the associations with delay, dose, duration of methotrexate and discontinuation of glucocorticoids. We tested through multinomial regression which factors were associated with persistent inflammatory refractory RA (PIRRA) or non-inflammatory refractory RA (NIRRA). Sensitivity analysis included a case-control study matching the year of diagnosis.

Results: We enrolled 48 D2T-RA patients and 145 non-D2T-RA controls. Methotrexate was started within 3 months in 16.7% of D2T-RA *vs* 33.1% of non-D2T-RA ($P = 0.011$). Adequate duration of methotrexate was obtained in significantly fewer D2T-RA patients (70.8% *vs* 85.5%). Glucocorticoids were continued beyond 6 months in a higher proportion of D2T-RA patients (70.8% *vs* 33.8%, $P < 0.001$). In multiple regression, treatment delay beyond 3 months (OR 0.3; 95% CI 0.1, 0.9) and non-discontinuation of glucocorticoids after 6 months (OR 4.6; 95% CI 2.2, 9.5) were significantly associated with D2T-RA. Treatment delay was significantly associated with PIRRA only, while non-discontinuation of glucocorticoids was significantly associated with PIRRA and NIRRA. Results were replicated in sensitivity analyses.

Conclusion: Failure to start methotrexate within 3 months and not being off glucocorticoids within 6 months are early predictive features of D2T-RA.

Keywords: RA, difficult-to-treat, D2T, therapy, treatment, refractory, biologics, DMARDs, MTX, delay, glucocorticoids, prednisolone, steroids

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Abstract

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Table 1. Comparison of D2T and non-D2T RA patients according to their characteristics at baseline and at the current evaluation

Baseline	D2T-RA patients ($n = 48$)	Unmatched non-D2T-RA patients ($n = 145$)	*P*-value	Matched non-D2T-RA patients ($n = 48$)	*P*-value
Age at onset, years	46.0 (41.3, 53.0)	50.0 (38.0, 60.0)	0.069	47.5 (37.3, 58.5)	0.695
Year of diagnosis	2009 (2005, 2013)	2010 (2005, 2015)	0.278	2009 (2005, 2013)	1.000
Symptom duration, years	2.2 (1.4, 3.0)	2.1 (1.8, 2.8)	0.589	2.4 (1.8, 4.7)	0.186
Female sex %	83.3	84.8	0.804	85.4	0.779
Erosions %	75.0	66.9	0.293	64.6	0.266
RF %	75.0	72.4	0.726	66.7	0.369
ACPA %	68.8	69.7	0.906	66.7	0.827
Obesity %	16.7	13.1	0.537	12.5	0.563
DAS28-CRP	5.6 (4.6, 6.3)	5.2 (4.2, 6.2)	0.081	5.2 (4.2, 6.2)	0.216
MTX treatment delay %					
<3 months	16.3	33.8	0.011	43.8	
3–12 months	[illegible]	41.7		[illegible]	0.003
>12 months	44.9	24.5		16.7	
Adequate MTX dose %	[illegible]	66.2	0.134	[illegible]	0.210
Adequate MTX duration[a] %	[illegible]	85.5	0.022	[illegible]	[illegible]
Glucocorticoids > 6 months %	70.8	33.8	<0.001	41.7	0.004
Fulfilment of the EULAR DT2-RA definition					
1. Treatment according to EULAR recommendations	100.0	100.0	0.999	100.0	0.999
2. Signs suggestive of active/progressive disease, defined as ≥1 of					
– Failure of two b/tsDMARDs with different mechanism of action	100.0	37.2	<0.001	43.8	<0.001
– Moderate or severe disease activity	97.9	52.4	<0.001	64.6	<0.001
– Signs or symptoms suggestive of active disease	50.0	7.6	<0.001	8.3	<0.001
– Inability to taper glucocorticoids <7.5 mg daily	22.9	5.5	0.001	12.5	0.181
– Rapid radiographic progression	9.3	2.2	0.057	6.7	0.710
– Reduction in quality of life	7.9	2.3	0.132	5.0	0.671
3. Problematic management by the rheumatologist and/or the patient	100.0	9.0	<0.001	6.3	<0.001
Current assessment					
DAS28-CRP	4.2 (3.6, 4.9)	2.6 (1.9, 3.5)	<0.001	3.0 (2.2, 3.9)	<0.001
DAS28-ESR	4.8 (3.9, 5.4)	3.1 (2.4, 4.1)	<0.001	3.4 (2.7, 4.5)	<0.001
CDAI	15 (10, 25)	6 (2, 11)	<0.001	9 (4, 14)	<0.001
CRP	9.4 (4.0, 19.0)	4.0 (1.3, 13.0)	0.006	3.7 (1.3, 11.9)	0.004
ESR	27 (17, 49)	24 (11, 42)	0.181	26 (12, 42)	0.479
Current therapy					
Prednisone dose, mg daily	5 (4.4, 8.1)	5 (2.5, 5.0)	0.033	5 (2.5, 9.4)	0.463
b/tsDMARDs	89.6	73.1	0.018	83.3	0.371
Number of prior b/tsDMARDs	3 (2, 5)	2 (1, 3)	<0.001	2 (1, 4)	<0.001
csDMARDs	43.8	59.6	0.073	60.4	0.102
Opioids	10.4	2.8	0.044	2.1	0.204
NSAIDs	27.1	9.0	0.001	16.7	0.217
Comorbidities					
Fibromyalgia	2.0	2.6	0.999	6.3	0.617
Anxiety or depression	6.3	6.6	0.999	6.3	0.999
Dyslipidaemia	10.2	12.6	0.803	16.7	0.217
Arterial hypertension	26.5	23.2	0.701	22.9	0.811
Osteoporosis	18.4	19.9	0.818	14.6	0.584
Diabetes mellitus	4.1	6.6	0.734	2.1	0.999
Non-alcoholic fatty liver	6.3	5.5	0.999	2.1	0.617
Lung diseases					
COPD or asthma	2.0	4.0	0.999	6.3	0.617
Interstitial lung disease	4.1	4.0	0.999	2.1	0.999
Cardiovascular diseases					
Cerebrovascular accidents	2.0	3.3	0.999	2.1	0.999
Ischemic heart disease	0.0	3.3	0.337	2.1	0.999
Congestive heart failure	2.0	4.0	0.999	4.2	0.495
Thromboembolism	2,1	0,7	0.437	0.0	0.999
Thyroid diseases	6.1	6.6	0.999	8.3	0.999
Cancer or lymphoma	2.1	9.0	0.195	6.3	0.617

Difficult-to-treat rheumatoid arthritis with respect to responsiveness to biologic/targeted synthetic DMARDs: a retrospective cohort study from the FIRST registry

S. Ochi[1,2], F. Mizoguchi[3], K. Nakano[2], Y. Tanaka[2]

[1]Department of Laboratory Medicine, Jikei University School of Medicine, Tokyo, Japan;
[2]The First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan;
[3]Department of Rheumatology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan.

Abstract

Objective

Difficult-to-treat rheumatoid arthritis (dt-RA) is an emerging concept defined as persistency of signs and/or symptoms despite prior treatment. However, whether this refractoriness affects effectiveness and tolerance to next treatment is not fully understood. This study aimed to find cut-off values for a definition of dt-RA with respect to responsiveness to newly used biologic and targeted synthetic disease-modifying anti-rheumatic drugs (b/tsDMARDs).

Difficult-to-treat rheumatoid arthritis with respect to responsiveness to biologic/targeted synthetic DMARDs: a retrospective cohort study from the FIRST registry

Table III. Analysis of factors affected by treatment failure to DMARDs.
Δvalue (value at week 0 – value at week 22) was compared between above- and below- cut-off values for variables associated with disease activity using mixed-effect regression and inverse-probability score-based weighted methods (IPW), respectively.

		Mixed-effect regression				IPW			
		Average Δvalue	95% C.I.		*p*	Average effect	95% CI		*p*
Treatment failure to ≥2 csDMARDs	TJC	0.58	-0.95	2.10	0.46	0.57	-0.12	1.26	0.10
	SJC	-0.28	-0.30	-0.26	<0.01	-0.08	-0.57	0.40	0.74
	Pt-VAS	-1.91	-2.37	-1.45	<0.01	0.09	-2.78	2.97	0.95
	Dr-VAS	-2.65	-3.32	-1.97	<0.01	-1.66	-3.78	0.46	0.12
	CRP (mg/dL)	-0.23	-0.40	-0.05	0.01	-0.07	-0.19	0.06	0.29
	ESR (mm/1h)	-3.88	-5.10	-2.67	<0.01	-3.35	-6.08	-0.62	0.02
	HAQ	-0.01	-0.04	0.01	0.32	0.01	-0.05	0.08	0.71
	GH (mm)	-3.50	-4.88	-2.13	<0.01	-1.49	-4.22	1.24	0.29
Treatment failure to ≥4 bDMARDs	TJC	-0.15	-2.76	2.47	0.91	-1.24	-3.52	1.03	0.28
	SJC	-0.57	-1.10	-0.04	0.03	-0.70	-2.52	1.13	0.46
	Pt-VAS	-5.93	-11.03	-0.83	0.02	-5.59	-13.07	1.88	0.14
	Dr-VAS	-4.14	-5.90	-2.37	<0.01	-3.01	-8.24	2.22	0.26
	CRP (mg/dL)	-0.60	-0.86	-0.35	<0.01	-0.02	-0.65	0.62	0.96
	ESR (mm/1h)	-6.07	-6.95	-5.19	<0.01	-9.98	-15.59	-4.37	<0.01
	HAQ	-0.16	-0.30	-0.03	0.02	-0.12	-0.33	0.09	0.26
	GH (mm)	-11.86	-18.21	-5.51	<0.01	-9.05	-18.04	-0.06	0.05
≥3mg/day of glucocorticoid use at week 0	TJC	-1.21	-2.34	-0.08	0.04	-1.08	-1.94	-0.21	0.02
	SJC	0.40	-0.10	0.90	0.11	0.22	-0.42	0.86	0.50
	Pt-VAS	-5.98	-8.49	-3.47	<0.01	-7.14	-10.76	-3.52	<0.01
	Dr-VAS	-2.20	-2.30	-2.10	<0.01	-2.86	-5.77	0.05	0.05
	CRP (mg/dL)	0.49	0.37	0.61	<0.01	-0.25	-0.46	-0.03	0.02
	ESR (mm/1h)	-0.51	-6.28	5.27	0.86	-3.12	-6.52	0.28	0.07
	HAQ	-0.03	-0.13	0.08	0.64	-0.07	-0.15	0.01	0.11
	GH (mm)	-3.31	-10.87	4.26	0.39	-4.18	-7.64	-0.72	0.02

Difficult-to-treat rheumatoid arthritis with respect to responsiveness to biologic/targeted synthetic DMARDs: a retrospective cohort study from the FIRST registry

Table III. Analysis of factors affected by treatment failure to DMARDs.
Δvalue (value at week 0 – value at week 22) was compared between above- and below- cut-off values for variables associated with disease activity using mixed-effect regression and inverse-probability score-based weighted methods (IPW), respectively.

		Mixed-effect regression				IPW			
		Average Δvalue	95% C.I.		*p*	Average effect	95% CI		*p*
Treatment failure to ≥2 csDMARDs	TJC	0.58	-0.95	2.10	0.46	0.57	-0.12	1.26	0.10
	SJC	-0.28	-0.30	-0.26	<0.01	-0.08	-0.57	0.40	0.74
	Pt-VAS	-1.91	-2.37	-1.45	<0.01	0.09	-2.78	2.97	0.95
	Dr-VAS	-2.65	-3.32	-1.97	<0.01	-1.66	-3.78	0.46	0.12
	CRP (mg/dL)	-0.23	-0.40	-0.05	0.01	-0.07	-0.19	0.06	0.29
	ESR (mm/1h)	-3.88	-5.10	-2.67	<0.01	-3.35	-6.08	-0.62	0.02
	HAQ	-0.01	-0.04	0.01	0.32	0.01	-0.05	0.08	0.71
	GH (mm)	[illegible]	[illegible]	[illegible]	<0.01	-1.49	-4.22	1.24	0.29
					0.91	-1.24	-3.52	1.03	0.28
					0.03	-0.70	-2.52	1.13	0.46
					0.02	-5.59	-13.07	1.88	0.14
					<0.01	-3.01	-8.24	2.22	0.26
					<0.01	-0.02	-0.65	0.62	0.96
					<0.01	-9.98	-15.59	-4.37	<0.01
					0.02	-0.12	-0.33	0.09	0.26
					<0.01	-9.05	-18.04	-0.06	0.05
≥3mg/day of glucocorticoid use at week 0	TJC	-1.21	-2.34	-0.08	0.04	-1.08	-1.94	-0.21	0.02
	SJC	0.40	-0.10	0.90	0.11	0.22	-0.42	0.86	0.50
	Pt-VAS	-5.98	-8.49	-3.47	<0.01	-7.14	-10.76	-3.52	<0.01
	Dr-VAS	-2.20	-2.30	-2.10	<0.01	-2.86	-5.77	0.05	0.05
	CRP (mg/dL)	0.49	0.37	0.61	<0.01	-0.25	-0.46	-0.03	0.02
	ESR (mm/1h)	-0.51	-6.28	5.27	0.86	-3.12	-6.52	0.28	0.07
	HAQ	-0.03	-0.13	0.08	0.64	-0.07	-0.15	0.01	0.11
	GH (mm)	-3.31	-10.87	4.26	0.39	-4.18	-7.64	-0.72	0.02

Sonraki b/tsDMARD'a yanıtsızlık açısından bağımsız prediktörler :

- ≥2 csDMARD ve
- ≥4 b/tsDMARD yanıtsızlığı
- ≥3mg/gün GK

A paradigm of difficult-to-treat rheumatoid arthritis: subtypes and early identification

M. Novella-Navarro[1,2], V. Ruiz-Esquide[3], G. Torres-Ortiz[1], C.A. Chacur[3], C. Tornero[1,2], E. Fernández-Fernandez[1,2], I. Monjo[1,2], R. Sanmartí[3], C. Plasencia-Rodríguez[1,2], A. Balsa[1,2]

[1]Rheumatology Department, Hospital Universitario La Paz, Madrid; [2]Inmuno-Rheumatology Research Group, Hospital La Paz, Institute for Health Research - IdiPAZ, Madrid; [3]Rheumatology Department, Hospital Clínic, Barcelona, Spain.

Abstract

Objective

Multiple failures to biologic or targeted specific disease-modifying anti-rheumatic drugs (b/tsDMARDs) that lead to difficult-to-treat rheumatoid arthritis (D2TRA) may be the result of multi-drug inefficacy or reflect treatment problems related to adverse events, comorbidities, and/or poor adherence. We aimed to characterise a cohort of D2TRA patients in clinical practice, to analyse the differences between D2TRA due to inefficacy versus D2TRA from other causes, and to compare them with non-D2TRA.

Methods

The D2TRA group included patients who were receiving ≥2b/tsDMARDs due to inefficacy (D2TRA-inefficacy) or because of adverse events, poor adherence, contraindications, comorbidities, drug-intolerance, etc. (D2TRA-other). Patients who achieved low disease activity or remission with the first bDMARD were classified as non-D2TRA patients. For all patients, demographic, clinical characteristics and laboratory parameters were assessed prior to starting the first b/tsDMARD. Descriptive analysis was performed and bivariate logistic regression models were assembled.

Results

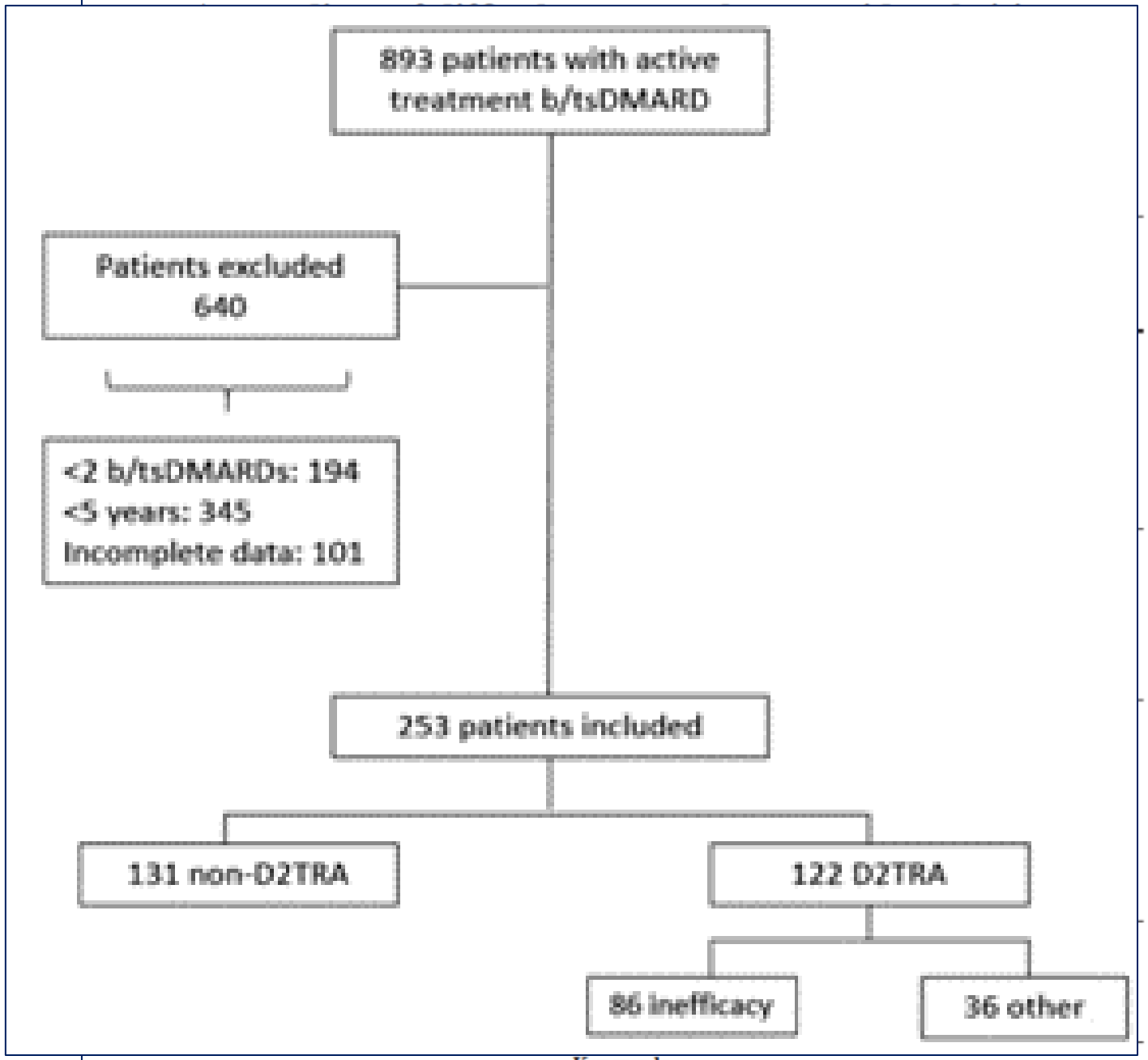
In total, 253 patients were included: 131 non-D2TRA and 122 D2TRA [86 (70.5%) D2TRA-inefficacy and 36 (29.5%) D2TRA-other]. Comparison of the two groups of D2TRA patients: no differences in gender, age at start of b/tsDMARD or age at RA diagnosis were found; this was also true of socioeconomic status, frequency of anxiety-depression and other comorbidities. Patients categorised as D2TRA-other had less extra-articular manifestations than D2TRA-inefficacy, as well as lower values of DAS28 at the start of the first b/tsDMARD. Comparisons of Non-D2TRA patients versus D2TRA-other resulted in the following observations: no differences in sociodemographic characteristics were evident nor were there any differences in terms of disease activity.

Conclusion

Patients with D2TRA-other are indistinguishable from non-D2TRA patients at baseline, indicating the former cohort does not appear to have any predictive value during the early stages of b/tsDMARD treatment, unlike what occurs in patients with D2TRA-inefficacy.

Key words

difficult-to-treat rheumatoid arthritis, biologic and targeted disease-modifying anti-rheumatic drugs, established rheumatoid arthritis



Key words

difficult-to-treat rheumatoid arthritis, biologic and targeted disease-modifying anti-rheumatic drugs, established rheumatoid arthritis

Table 1. Clinical characteristics and comparison between D2TRA patients (due to inefficacy and other causes) and D2TRA-other and non-D2TRA.

Variables	D2TRA-patients (n=122)		p-value*	Non-D2TRA (n=131)	p-value‡
	D2TRA-inefficacy (n=86)	D2TRA-other (n=36)			
Age mean (SD)					
current	61.5 (12.6)	60.1 (12.8)	0.60	65.0 (12.5)	0.05
at diagnosis	43.9 (13.1)	40.1 (12.1)	0.14	46.0 (12.6)	**0.01**
at start b/tsDMARD	49.5 (12.0)	50.2 (11.5)	0.76	54.1 (11.9)	0.08
Sex (fem) n (%)	74 (86.1)	31 (86.0)	0.61	114 (87.0)	0.53
BMI mean (SD)	26.4 (5.4)	26.8 (6.1)	0.73	25.5 (5.5)	0.18
Smoking habit n (%)					
smokers	24 (27.9)	9 (25.0)		25 (19.1)	
ex smokers	17 (18.7)	7 (19.4)	0.93	32 (24.4)	0.68
never smokers	45 (52.3)	20 (55.6)		72 (55.0)	
Comorbidities mean (SD)	1.1 (1.0)	1.2 (1.0)	0.23	0.9 (1.1)	0.11
Anxiety-depression n (%)	25 (29.1)	10 (27.8)	0.53	21 (16.0)	0.14
Fibromyalgia n (%)	16 (18.6)	9 (25.0)	0.28	20 (15.2)	0.21
Previous csDMARDs	2 (2-3)	2 (2-3)	0.79	2 (1-3)	**<0.01**
Erosions n (%)	48 (55.8)	17 (47.2)	0.25	44 (33.8)	0.17
Extraarticular manifestations n (%)	23 (26.7)	3 (8.3)	0.02	17 (13.0)	0.32
Time between diagnosis and starting bDMARD mean (SD)	5. 0 (5.6)	9.5 (9.1)	**0.01**	7.5 (7.0)	0.16
Current CE n (%)	81 (94.2)	33 (91.7)	0.22	115 (87.8)	0.49
Current MTX n (%)	74 (86.0)	28 (76.8)	0.28	99 (75.6)	0.48
1st bDMARD n (%)					
TNFi	76 (88.4)	33 (91.7)	0.63	98 (74.8)	0.06
Non TNFi	10 (11.6)	3 (8.3)	0.51	33 (25.2)	
Immunological parameters n (%)					
RF positive	72 (83.7)	30 (82.3)	0.49	106 (80.2)	0.52
ACPA positive	72 (83.7)	27 (75.3)	0.19	110 (84.0)	0.13
TJC mean (SD)	10.5 (7.0)	6.9 (6.2)	**0.02**	7.9 (5.7)	0.74
SJC mean (SD)	8.9 (5.6)	6.5 (4.5)	**<0.01**	6.7 (3.5)	0.34
CRP mean (SD)	10.0 (3.2-28.2)	4.5 (0.6-11)	**<0.01**	6.4 (2.5-18.8)	0.66
ESR mean (SD)	38.8 (26.3)	27.2 (21.3)	**0.01**	30.2 (20.2)	0.52
VAS mean (SD)	61.2 (20.9)	54.4 (24.6)	0.12	54.8 (20.6)	0.91
PGA mean (SD)	53.7 (24.4)	40.1 (22.3)	**0.03**	48.1 (21.5)	0.12
DAS28 mean (SD)	5.7 (1.2)	4.9 (1.4)	**0.01**	5.1 (1.0)	0.33
HAQ mean (SD)	10.3 (6.2)	9.0 (5.9)	0.32	7.9 (5.1)	0.37

TEDAVİ

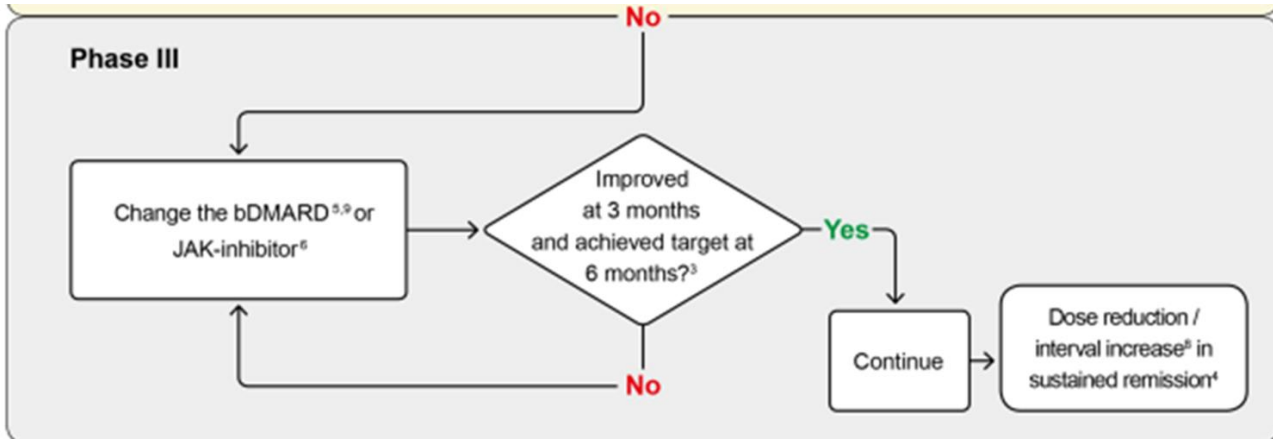
TEDAVİ

- ✓Tedavi kararında;
- hasta-hekim *ortak kararı*,
- Hasta *uyumu*,
- Hastanın *inanç ve beklentileri* göz önüne alınarak **gerçekçi** hedefler belirlenmelidir.
- ✓Sonraki basamakta hangi tedavinin seçilmesine ilişkin net öneri yoktur.
- ✓Çalışmalar heterojen, bazıları 1 bDMARD rezistan, bazısı 2, bazısı ≥3 bDMARD yanıtsız popülasyonda yapılmış..

Recommendation

EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update

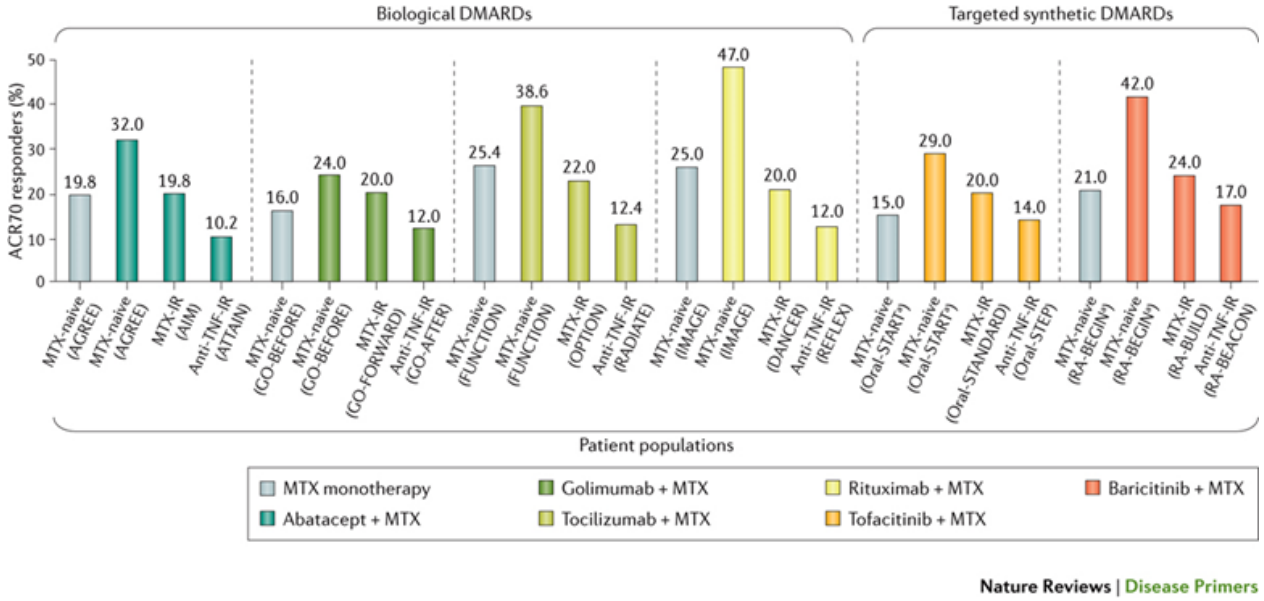
Josef S Smolen [1], Robert B M Landewé [2], Sytske Anne Bergstra [3], Andreas Kerschbaumer [1], Alexandre Sepriano [4], Daniel Aletaha [1], Roberto Caporali,[5] Christopher John Edwards,[6] Kimme L Hyrich [7], Janet E Pope [8], Savia de Souza [9], Tanja A Stamm [10], Tsutomu Takeuchi [11], Patrick Verschueren [12], Kevin L Winthrop [13], Alejandro Balsa [14], Joan M Bathon,[15] Maya H Buch [16], Gerd R Burmester [17], Frank Buttgereit [17], Mario Humberto Cardiel,[18] Katerina Chatzidionysiou [19], Catalin Codreanu,[20] Maurizio Cutolo [21], Alfons A den Broeder,[22] Khadija El Aoufy,[23] Axel Finckh [24], João Eurico Fonseca [25], Jacques-Eric Gottenberg [26], Espen A Haavardsholm,[27] Annamaria Iagnocco [28], Kim Lauper [24], Zhanguo Li,[29] Iain B McInnes,[30] Eduardo F Mysler,[31] Peter Nash [32], Gyula Poor,[33] Gorica G Ristic,[34] Felice Rivellese [35], Andrea Rubbert-Roth [36], Hendrik Schulze-Koops [37], Nikolay Stoilov,[38] Anja Strangfeld [19,39], Annette van der Helm-van Mil,[3] Elsa van Duuren,[40] Theodora P M Vliet Vlieland [41], René Westhovens [12], Désirée van der Heijde [3]



Humby F, Durez P, Buch MH, et al. Rituximab versus tocilizumab and B-cell status in TNF-alpha inadequate-responder rheumatoid arthritis patients: the R4-RA RCT. Southampton (UK): National Institute for Health and Care Research; 2022 Aug. (Efficacy and Mechanism Evaluation, No. 9.7.) Available from: https://www.ncbi.nlm.nih.gov/books/NBK583211/

TEDAVİ

- RA hastalarının yaklaşık yarısında (40%) ACR20 yanıtı mevcut değil..
- Sonraki biyolojik tedavide ACR 50 yanıt oranı %30'a düşüyor
- Bir ajan ilk basamak tedavi olarak uygulandığında yanıt oranları 2 veya 3. basamakta kullanıldığı durumdan daha yüksek..



*Persistent inflammatory and non-inflammatory mechanisms in refractory rheumatoid arthritis Maya H. Buch et al. https://doi.org/10.1038/ s41584-020-00541-7

*Smolen, J. S. *et al.* (2018) Rheumatoid arthritis. *Nat. Rev. Dis. Primers* doi:10.1038/nrdp.2018.1

Humby F, Durez P, Buch MH, et al. Rituximab versus tocilizumab and B-cell status in TNF-alpha inadequate-responder rheumatoid arthritis patients: the R4-RA RCT. Southampton (UK): National Institute for Health and Care Research; 2022 Aug. (Efficacy and Mechanism Evaluation, No. 9.7.) Available from: https://www.ncbi.nlm.nih.gov/books/NBK583211/

Rheumatoid arthritis

OPEN ACCESS

TRANSLATIONAL SCIENCE

Pragmatic randomised controlled trial of very early etanercept and MTX versus MTX with delayed etanercept in RA: the VEDERA trial

Paul Emery [1,2] Sarah Horton,[1,3] Raluca Bianca Dumitru [1] Kamran Naraghi,[1] Désirée van der Heijde [4] Richard J Wakefield,[1,2] Elizabeth M A Hensor,[1,2] Maya H Buch [1,5,6]

- Erken RA; TNFi ±MTX eş zamanlı başlanan hastalarda MTX'i takiben 24.haftada TNFi eklenen hastalara göre daha yüksek remisyon oranları gözlenmiştir.

- «Bu durum, MTX kullanımının hastalık biyolojisinde daha refrakter hastalık yönünde bir değişime neden olduğuna işaret edebilir?»

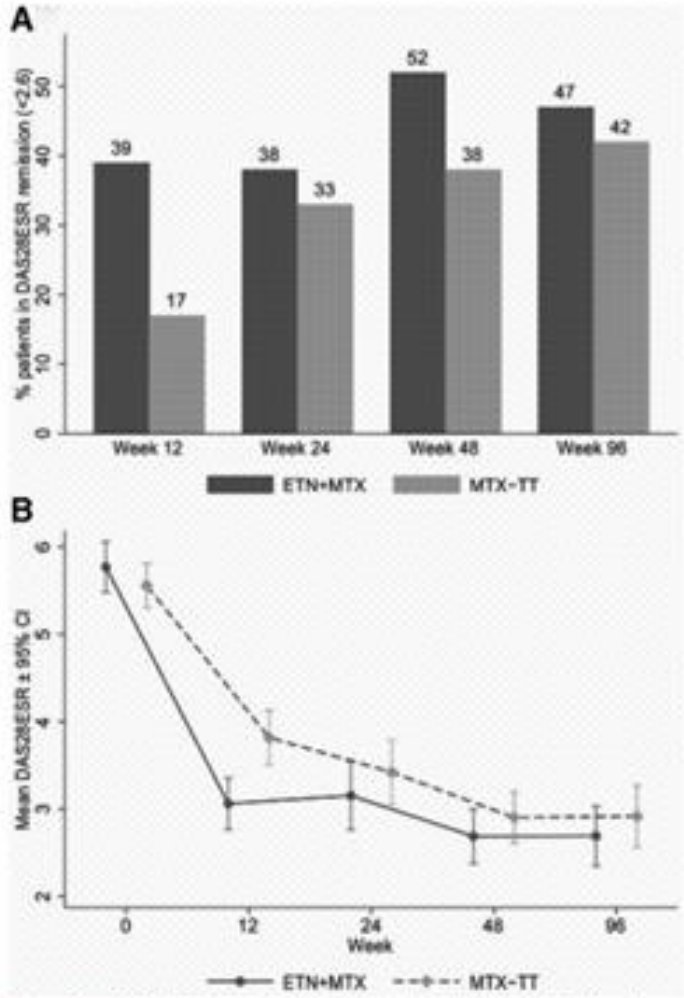


Figure 2 (A) DAS28-ESR remission rates in ETN+MTX (n=60) and MTX-TT (n=60). Percentage patient estimated via multiple imputation. (B) Individual DAS28-ESR scores over time in ETN+MTX (n=60) and MTX-TT (n=60). DAS28, Disease Activity Score 28 joint; ESR, erythrocyte sedimentation rate; ETN, etanercept; MTX, methotrexate; TT, treat-to-target.

*Emery, P. et al. A pragmatic randomised controlled trial of Very early Etanercept and MTX versus MTX with Delayed Etanercept in RA — the VEDERA trial. Ann. Rheum. Dis. 79, 464–471 (2020)

TEDAVİ

- PIRRA'daki inflamasyon;

i) predominant olarak humoral mi
ii) T hücre-aracılı mı
iii) doğal bağışıklık aracılı mı?

- Sero (+) hastalarda hücre odaklı tedaviler ve T hücre kostimulation hedefli tedaviler düşünülmelidir.

- Aksine, seronegatif refraktör RA (özellikle non-HLA-ilişkili) daha doğal bağışıklık aracılı/ otoinflamatuar orijinli olabilir (I-18 IL-1 inh).

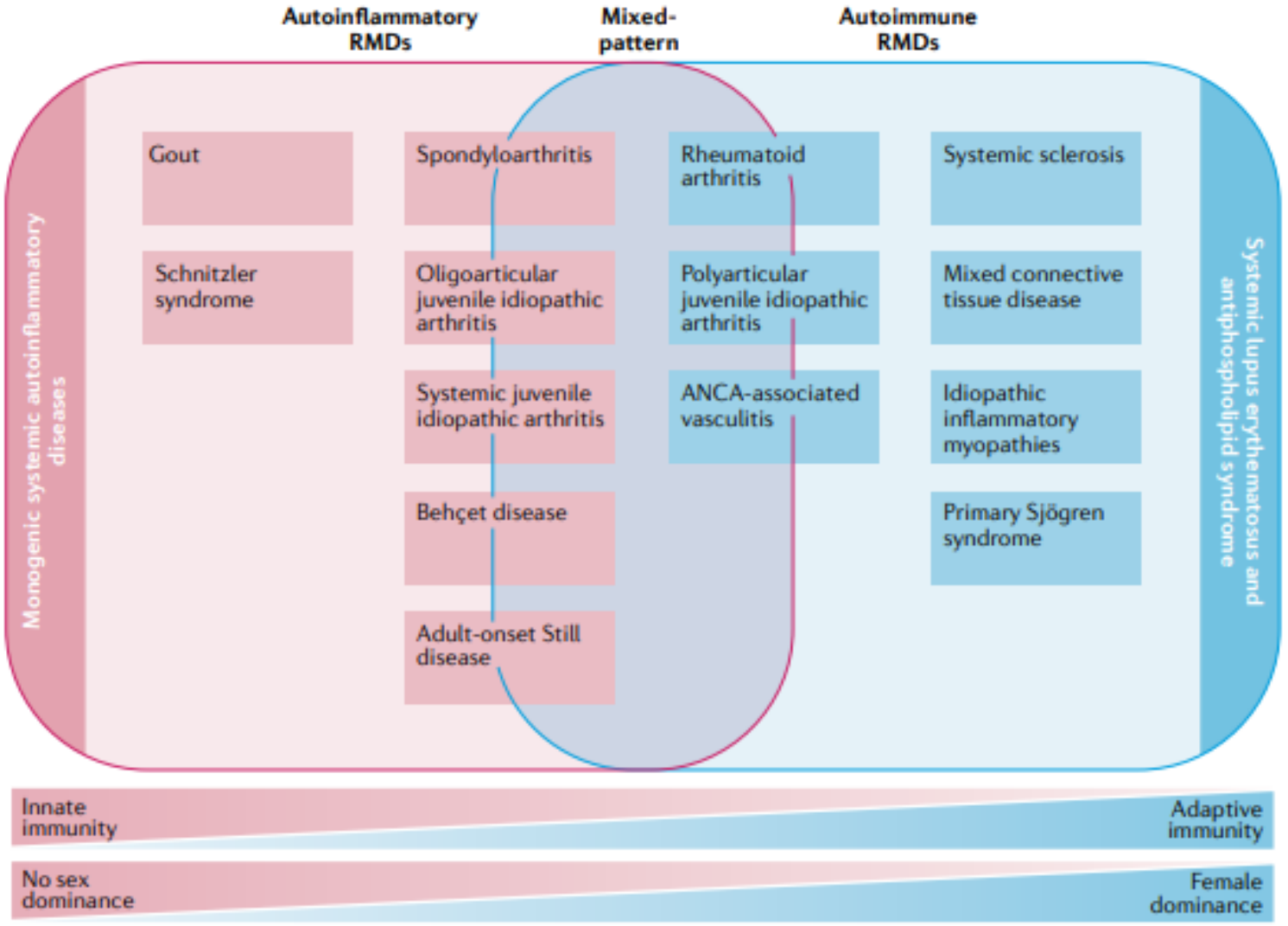


Fig. 1 | **Spectrum of autoinflammatory, mixed-pattern and autoimmune diseases.** Prototypes of a classical autoinflammatory disease are the group of monogenic systemic autoinflammatory diseases known as periodic fever syndromes (pink). Prototypes of classical autoimmune disease are systemic lupus erythematosus and antiphospholipid syndrome (blue). Diseases in the middle of the spectrum might be considered mixed-pattern rheumatic and musculoskeletal diseases (RMDs; mixed colour). Indicated by the spectra at the bottom of the figure, classical autoinflammatory conditions are characterized by a predominance of innate immunity and have no sex dominance. By contrast, classical autoimmune conditions are associated with more prominent adaptive immune responses and female dominance. ANCA, antineutrophil cytoplasmic antibody.

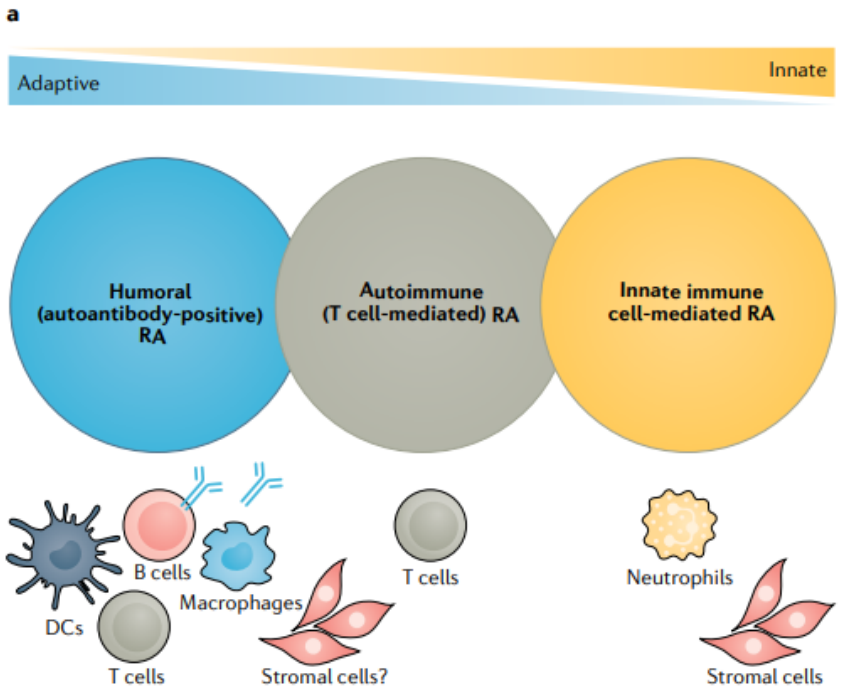
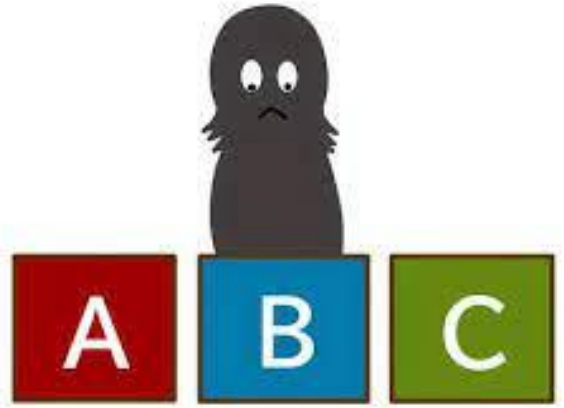


Fig. 5 | **Therapeutic approaches to targeting inflammation in refractory RA. a** | Inflammation in refractory rheumatoid arthritis (RA) can be predominantly humorally mediated, T cell-mediated or innate immune cell-mediated, or can involve a combination of all three owing to the functional integration of innate and adaptive immunity. A cellular hierarchy is likely to exist between more autoimmune RA and more innate immune cell-mediated RA. Humorally mediated disease relies on the triune axis of follicular helper T cells, dendritic cells (DCs) and B cells. Macrophages mediate much of the pathology of autoimmune RA following immune complex activation and also probably have a major role in seronegative (potentially more T cell-mediated) RA. Neutrophilic inflammation is important in innate immune cell-mediated RA. The role of stromal cells or joint fibroblasts in the pathogenesis of RA could be multifaceted and awaits elucidation in refractory RA, so we have placed stromal cells as primarily facilitating innate pathways, although speculate that they might have a role in adaptive processes via epigenetic mechanisms. **b** | Therapeutic approaches to refractory RA such as targeting B cells (rituximab), T cells (abatacept) or the IL-6 pathway affect adaptive immune cell-mediated disease, as does the use of Janus kinase (JAK) inhibitors. TNF inhibitors are effective across most of the range of RA. JAK inhibitors are beneficial in innate immune cell-mediated diseases, as are glucocorticoids, which are effective across a wide range of both innate and adaptive immune pathways. IL-1 blockade is licensed for use in RA, but has proven ineffective at a group level; however, IL-1 blockade might be beneficial in refractory RA that is innate immune cell-mediated. It remains to be seen whether some individuals with seronegative refractory RA actually have a psoriatic arthritis-type phenotype, and therefore if inhibiting the IL-23–IL-17 axis warrants consideration. **c** | Different disease activity courses can be observed over time for adaptive immune cell-mediated and innate immune cell-mediated RA. Whereas adaptive immune cell-mediated RA might typically demonstrate persistent, albeit varying, levels of disease activity, innate immune cell-mediated RA might show the episodic spikes in inflammation (disease activity) that are characteristic of autoinflammatory pathology.

the current perspective that methotrexate should be used as a generic first-line treatment for all patients.

The comparable response profiles to JAK inhibitors in patients with established RA who have previously



Persistent inflammatory and non-inflammatory mechanisms in refractory rheumatoid arthritis
Maya H. Buch et al. https://doi.org/10.1038/ s41584-020-00541-7

Ochi et al. Arthritis Research & Therapy (2022) 24:61
https://doi.org/10.1186/s13075-022-02744-7

Arthritis Research & Therapy

RESEARCH ARTICLE Open Access

Preferable outcome of Janus kinase inhibitors for a group of difficult-to-treat rheumatoid arthritis patients: from the FIRST Registry

Sae Ochi[1,2], Koshiro Sonomoto[2], Shingo Nakayamada[2] and Yoshiya Tanaka[2*]

- FiRST kayıt kütüğü, 2013 -2020 (retrospektif!)
- ≥ 2 ve ≥ 3 b/tsDMARD; D2T RA ve V-D2T
- 2128 hasta taranarak 247 D2T RA, 106 vD2T (total: 353)
- JAKi, CDAI skorlarında diğer 3 rejime göre anlamlı olarak daha iyi sonuç sağladı (D2T RA ve vD2T RA)
- JAKi üstünlüğü MTX ve GK-free hastalarda daha belirgin..

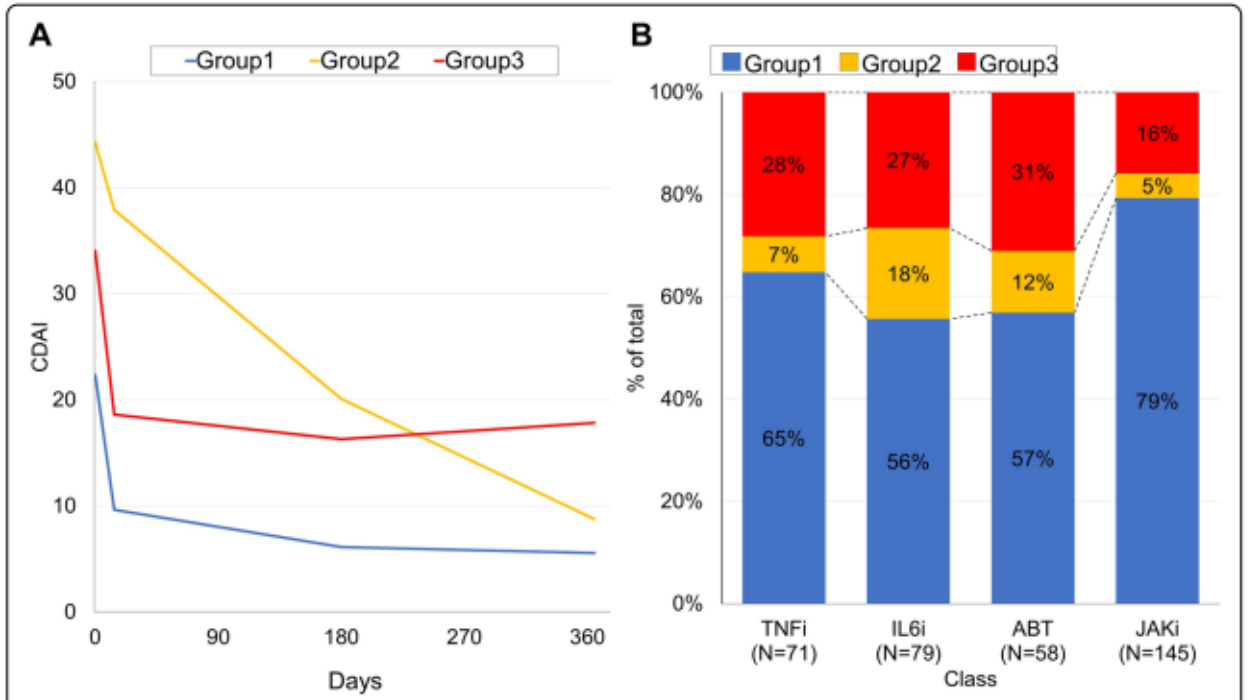


Fig. 4 Latent class analysis of patient CDAI responses in D2T RA cases. **A** Three CDAI response trajectories obtained by latent analysis. Group 1, rapid responders; group 2, slow responders; and group 3, less-responders. **B** Percentages of patients included in each group by treatment subgroups. CDAI, Clinical Disease Activity Index; D2T RA, difficult-to-treat rheumatoid arthritis; TNFi, tumour necrosis factor inhibitor; IL-6Ri, interleukin-6 receptor inhibitor; CTLA4-Ig, cytotoxic T-lymphocyte-associated antigen-4 immunoglobulin; JAKi, Janus kinase inhibitor

RHEUMATOLOGY

Rheumatology 2018;57:900–908
doi:10.1093/rheumatology/kex489
Advance Access publication 3 February 2018

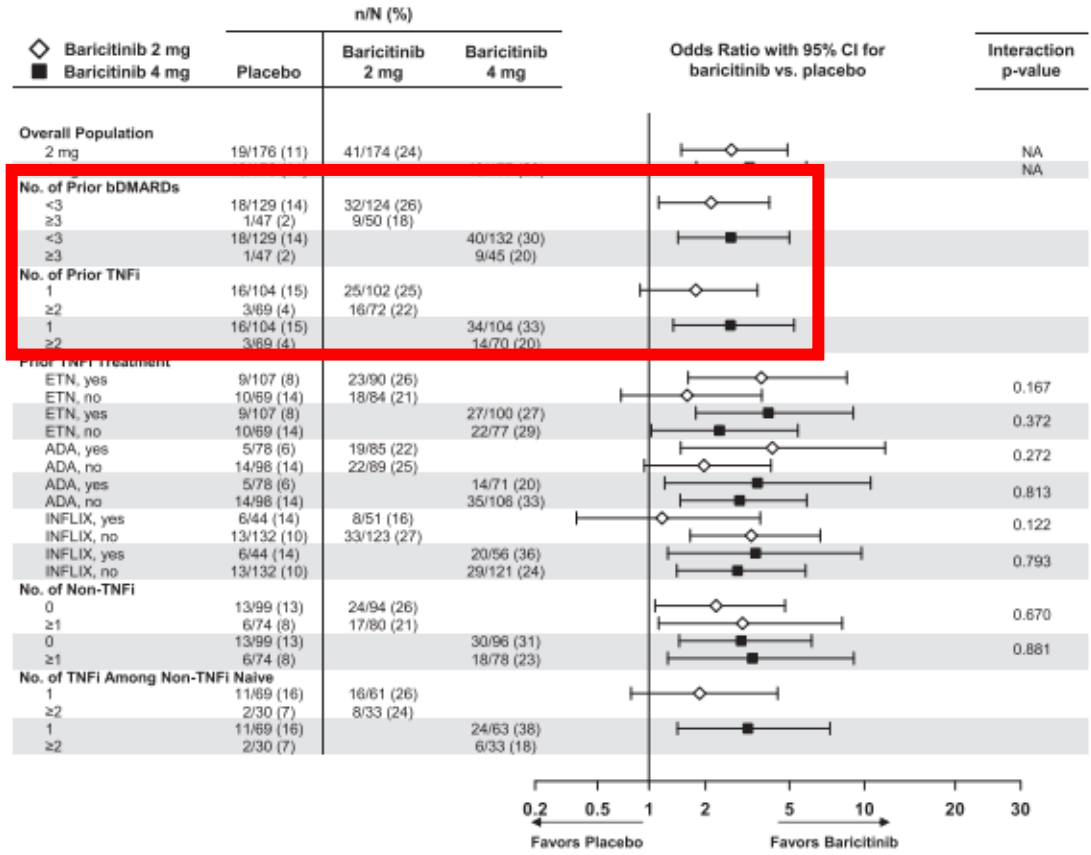
Original article

Response to baricitinib based on prior biologic use in patients with refractory rheumatoid arthritis

Mark C. Genovese[1], Joel M. Kremer[2], Cynthia E. Kartman[3], Douglas E. Schlichting[3], Li Xie[3], Tara Carmack[3], Carlos Pantojas[4], Juan Sanchez Burson[5], Hans-Peter Tony[6], William L. Macias[3], Terence P. Rooney[3] and Josef S. Smolen[7]

- 289 ≥1 TNFi yanıtsız orta/yüksek aktiviteli RA hastası plasebo ve 2/4 mg barisitinib kollarına ayrılmış (RA-BEACON faz III kohortu).
- Primer sonlanım noktası 12 ve 24. haftada ACR20 & CDAI
- Subgrup analizlerinde barisitinibin bDMARD öyküsü ve sayısından bağımsız olarak plaseboya (+cDMARDs), üstün olduğu gözlenmiş.

FIG. 4 Percentage of patients achieving CDAI ⩽10 at week 12: subgroups defined by previous bDMARD experien



AMERICAN COLLEGE of RHEUMATOLOGY
Empowering Rheumatology Professionals

Arthritis & Rheumatology
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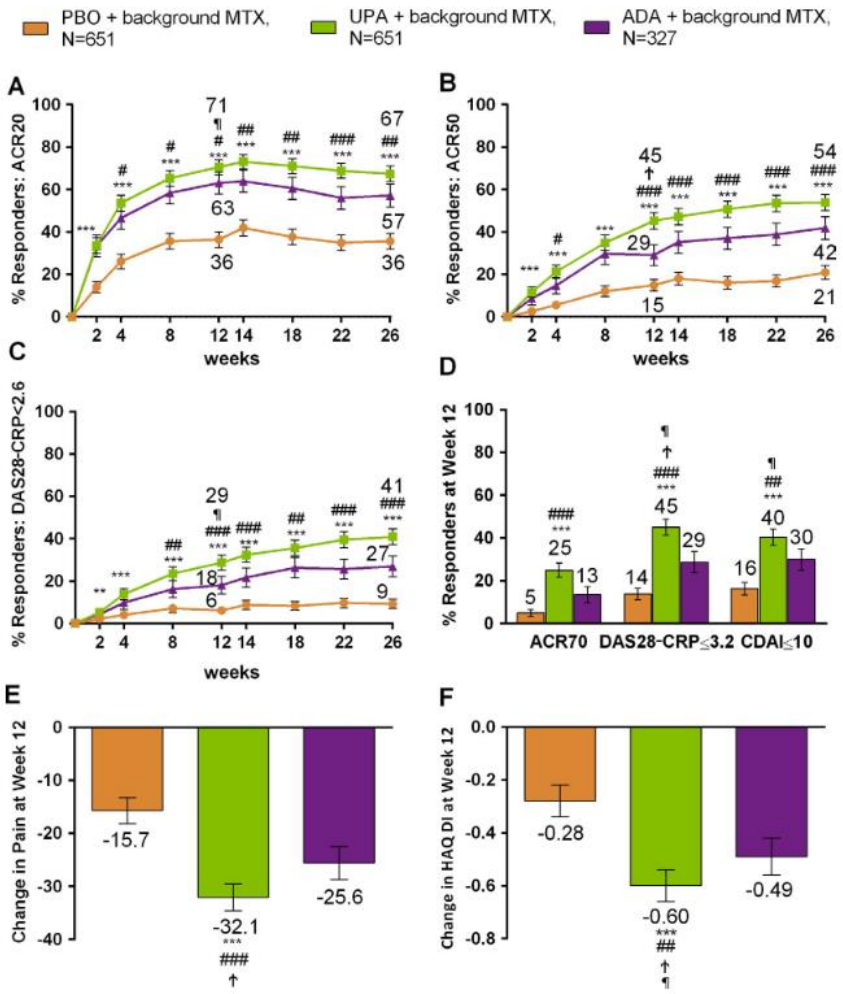
Upadacitinib Versus Placebo or Adalimumab in Patients With Rheumatoid Arthritis and an Inadequate Response to Methotrexate: Results of a Phase III, Double-Blind, Randomized Controlled Trial

Roy Fleischmann,[1] Aileen L. Pangan,[2] In-Ho Song,[2] Eduardo Mysler,[3] Louis Bessette,[4] Charles Peterfy,[5] Patrick Durez,[6] Andrew J. Ostor,[7] Yihan Li,[2] Yijie Zhou,[2] Ahmed A. Othman,[2] and Mark C. Genovese[8]

- JAKi ve TNFi arasındaki karşılaştırmalı çalışmalarda, şiş eklem sayısı, ESR, CRP ve radyografik erozyonun önlenmesi açısından benzer sonuçlar elde edilirken, JAKi'nin kompozit skorları daha fazla düşürdüğü gözlenmiş.

- JAKi'nin erken dönemde pek çok yolağı etkin olarak inhibe etmesi epigenetik değişiklikleri ve somatik mutasyonları önleyerek PIRRA gelişimini engelleyebilir?

- Yalnızca periferal inflamasyonu hedefleyen TNFi'nin aksine, JAK inhibisyonu santral ve periferal ağrı mediyatörleri üzerinde de etkiler ortaya koyuyor olabilir.



*Taylor, P. C. et al. Baricitinib versus placebo or adalimumab in rheumatoid arthritis. N. Engl. J. Med. 376, 652–662 (2017). 129.
*Fleischmann, R. et al. Upadacitinib versus placebo or adalimumab in patients with rheumatoid arthritis and an inadequate response to methotrexate: results of a phase III, double-blind, randomized controlled trial. Arthritis Rheumatol. 71, 1788–1800 (2019)

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

Frances Humby, Patrick Durez, Maya H Buch, Myles J Lewis, Hasan Rizvi, Felice Rivellese, Alessandra Nerviani, Giovanni Giorli, Arti Mahto, Carlomaurizio Montecucco, Bernard Lauwerys, Nora Ng, Pauline Ho, Michele Bombardieri, Vasco C Romão, Patrick Verschueren, Stephen Kelly, Pier Paolo Sainaghi, Nagui Gendi, Bhaskar Dasgupta, Alberto Cauli, Piero Reynolds, Juan D Cañete, Robert Moots, Peter C Taylor, Christopher J Edwards, John Isaacs, Peter Sasieni, Ernest Choy, Costantino Pitzalis, on behalf of the R4RA collaborative group

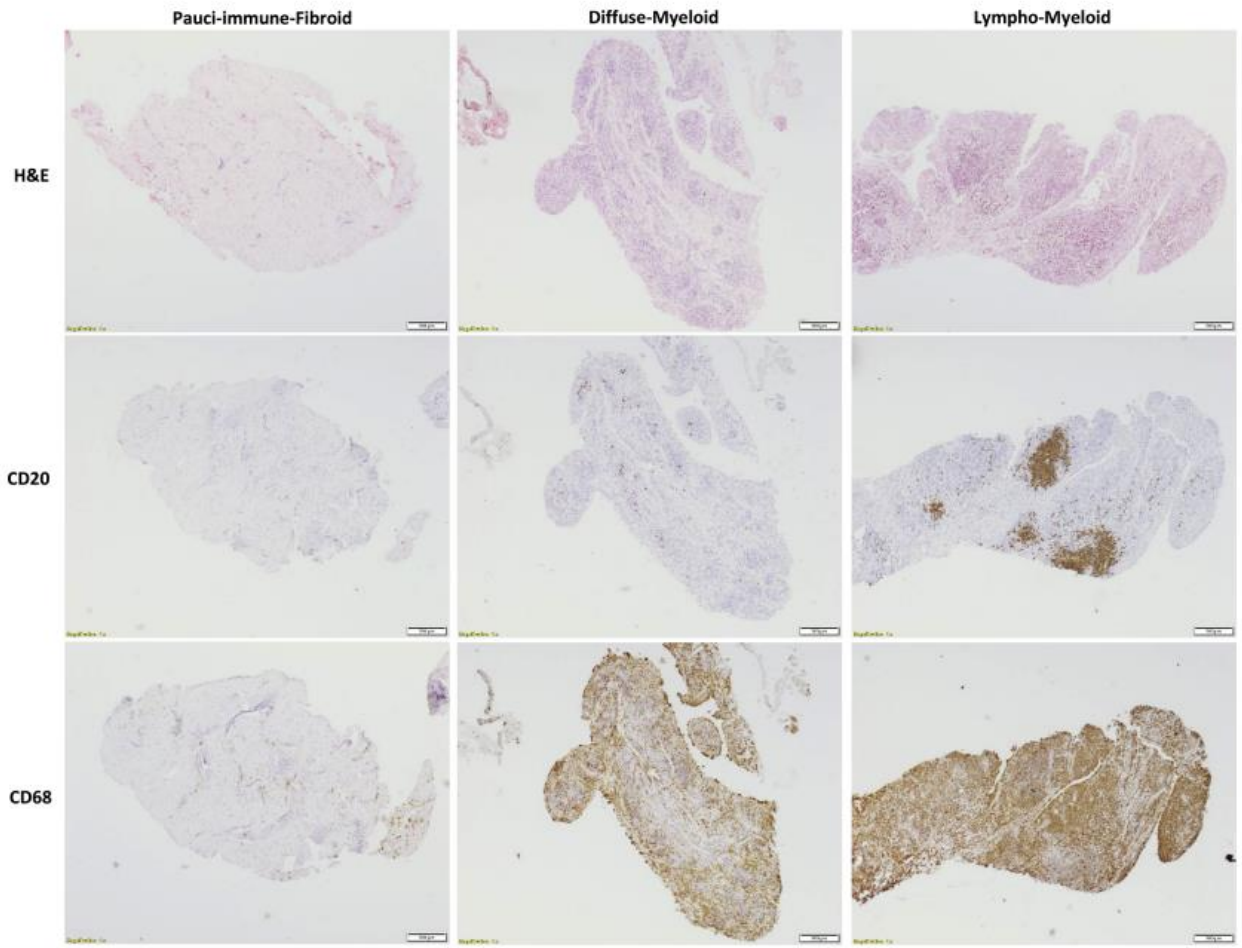
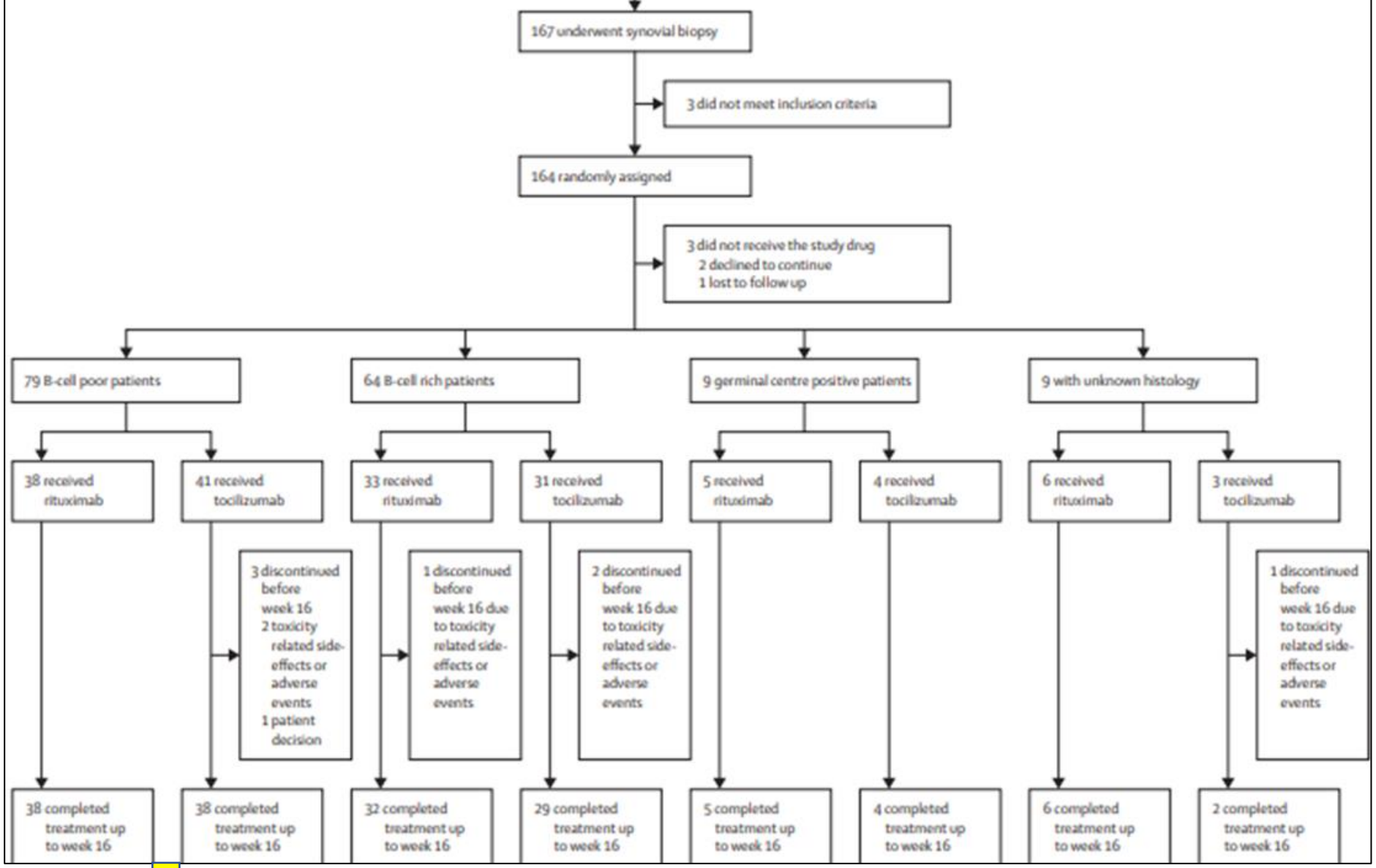


Fig. 6. Representative examples of diverse synovial tissue pathotypes in rheumatoid arthritis. Panels represent standard haematoxylin and eosin stain, and immunohistochemistry for CD20 and CD68 illustrating typical characteristics of three described pathotypes (Ref. [54,55]): pauci-immune (~20% of patients), diffuse-myeloid (~40% of patients) and lympho-myeloid (~40% of patients) prevalent cellular patterns, respectively. Courtesy of Prof. C. Pitzalis, Queen Mary University of London.

- 48 hf, açık etiketli çok-merkezli çalışma
- TNFi yanıtsız 164 hasta
- Primer sonlanım noktası 16.haftada CDAI50 yanıtı
- HİPOTEZ: sinovyal dokuda B hücre yoğunluğu az ise TOC RİT'ten daha mı etkin?
- Histolojik olarak ve RNA sekanslama ile B hücre zengin/fakir ayrımı

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 Frances Humby



Histolojik ayrım; CDAI50 yanıtında anlamlı fark yok

RNA sekanslama; rituximab 36% vs tocilizumab 63% p=0·035

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 Frances Humby, et al. Lancet 2021; 397: 305–17

Recommendation

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2021 EULAR recommendations for the implementation of self-management strategies in patients with inflammatory arthritis

Elena Nikiphorou ,[1,2] Eduardo José Ferreira Santos ,[3,4] Andrea Marques ,[3,4] Peter Böhm ,[5] Johannes WJ Bijlsma ,[6] Claire Immediato Daien,[7] Bente Appel Esbensen ,[8,9] Ricardo J O Ferreira ,[3,4] George E Fragoulis ,[10] Pat Holmes,[11] Hayley McBain ,[12] George S Metsios,[13,14] Rikke Helene Moe ,[15] Tanja A Stamm ,[16] Annette de Thurah ,[17,18] Condruta Zabalan,[19] Loreto Carmona ,[20] Ailsa Bosworth[21]

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2021 EULAR recommendations for the

Table 1 EULAR overarching principles (OAPs) and recommendations for the implementation of self-management strategies in patients with inflammatory arthritis (IA)

	LoE (1–5)	SoR (A–D)	Level of agreement (0–10)	
			Mean (SD)	% with score ≥8
OAPs				
A. Self-management implies taking an active role in learning about one's condition and in the shared decision-making process about one's health and care pathway.	n.a	n.a	9.5 (0.6)	100
B. Self-efficacy (personal confidence to carry out an activity with the aim of achieving a desired outcome) has a positive effect on various aspects of living with IA.	n.a	n.a	9.6 (0.7)	100
C. Patient organisations often provide valuable self-management resources and collaboration between healthcare professionals (HCPs) and patient organisations will therefore benefit patients.	n.a	n.a	9.4 (1.0)	88
Recommendations				
R1. HCPs should encourage patients to become active partners of the team and make them aware of HCPs and patient organisations involved in all aspects of the care pathway.	5	D	9.5 (1.1)	87
R2. Patient education should be the start point and underpin all self-management interventions.	1A	A	9.5 (0.8)	93
R3. Self-management interventions that include problem solving and goal setting and, where relevant to the individual and available, cognitive behavioural therapy should be incorporated into routine clinical practice to support patients.	1A	A	9.1 (1.4)	93
R4. HCPs should actively promote physical activity at diagnosis and throughout the disease course.	1A	A	9.9 (0.3)	100
R5. Lifestyle advice based on evidence should be given to better manage common comorbidity and patients should be guided and encouraged by their healthcare team to adopt healthy behaviours.	5	D	9.6 (0.6)	100
R6. Better emotional well-being leads to better self-management; therefore, mental health needs to be assessed periodically and appropriate intervention should be made if necessary.	5	D	9.4 (1.3)	93
R7. HCPs should invite discussion with patients about work and signpost to sources of help where appropriate or where needed.	5	D	9.6 (0.5)	100
R8. Digital healthcare can help patients to self-manage and should be considered for inclusion in supported self-management where appropriate and available.	1B	A	9.3 (1.0)	93
R9. HCPs should make themselves aware of available resources to signpost patients to, as part of optimising and supporting self-management.	5	D	8.7 (1.2)	100

EULAR, European Alliance of Associations for Rheumatology; LoE, level of evidence (1–5; 1 indicating evidence from high-quality randomised clinical trial (RCT) data and 5 indicating evidence from expert opinion without explicit critical appraisal or based on physiology, bench research or 'first principles')[11]; n.a, not applicable; SoR, strength of recommendation (A–D; A indicating consistent level 1 studies (RCTs) and D indicating level 5 evidence or troublingly inconsistent or inconclusive studies of any level).

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2021 EULAR recommendations for the

- Hastanın durumunu kabullenme ve tedavi sürecinde *aktif rol* alması, hasta eğitimi önemlidir.
- *Öz yönetim* için hedef belirleme ve problem çözmenin yanı sıra uygun bireylerde *bilişsel davranışçı tedavi* rutin klinik uygulamaya dahil edilmelidir.
- *Fiziksel aktivite* tanı aşamasında ve takiplerde teşvik edilmelidir.
- Komorbid durumları etkin yönetmek için kanıta dayalı *yaşam tarzı önerileri* sunulmalı ve sağlıklı davranışları benimsemek için yüreklendirilmelidir.
- *Duygusal iyilik hali* daha iyi öz-yönetime katkı sağlayacağından periyodik olarak *mental sağlık* değerlendirimi yapılmalıdır.
- *İş*le ilgili tartışma ve ihtiyaç halinde yardım/destek için yönlendirmeler yapılmalıdır.
- *Dijital sağlık bakımı* öz-yönetimde yardımcı olabilir.
- Sağlık bakımı sağlayıcıları öz-yönetimi optimize etmek için hastalara önerilebilecek kaynaklar hakkında haberdar olmalıdır.
- REHAB!! Ortezler, splintler, iş uğraşı terapisi, sosyal destek, psikoterapi, diyetisyen (Egz: ROM, aerobik, endurans…)

Table 1 EULAR overarching principles (OAPs) and recommendations for the implementation of self-management strategies in patients with

	f agreement	
	SD)	% with score ≥8
	)	100
	)	100
	)	88
	)	87
	)	93
	)	93
	)	100
	)	100
	)	93
	)	100
	)	93
	)	100

al trial (RCT) data and 5
licable; SoR, strength of
udies of any level).

TEŞEKKÜRLER