膠原病 Journal Club
2021.02.03 by Dr.大村

Recommendation

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EULAR definition of difficult-to-treat rheumatoid arthritis

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Nagy G, et al. Ann Rheum Dis 2021;**80**:31–35.

Recommendation

EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update

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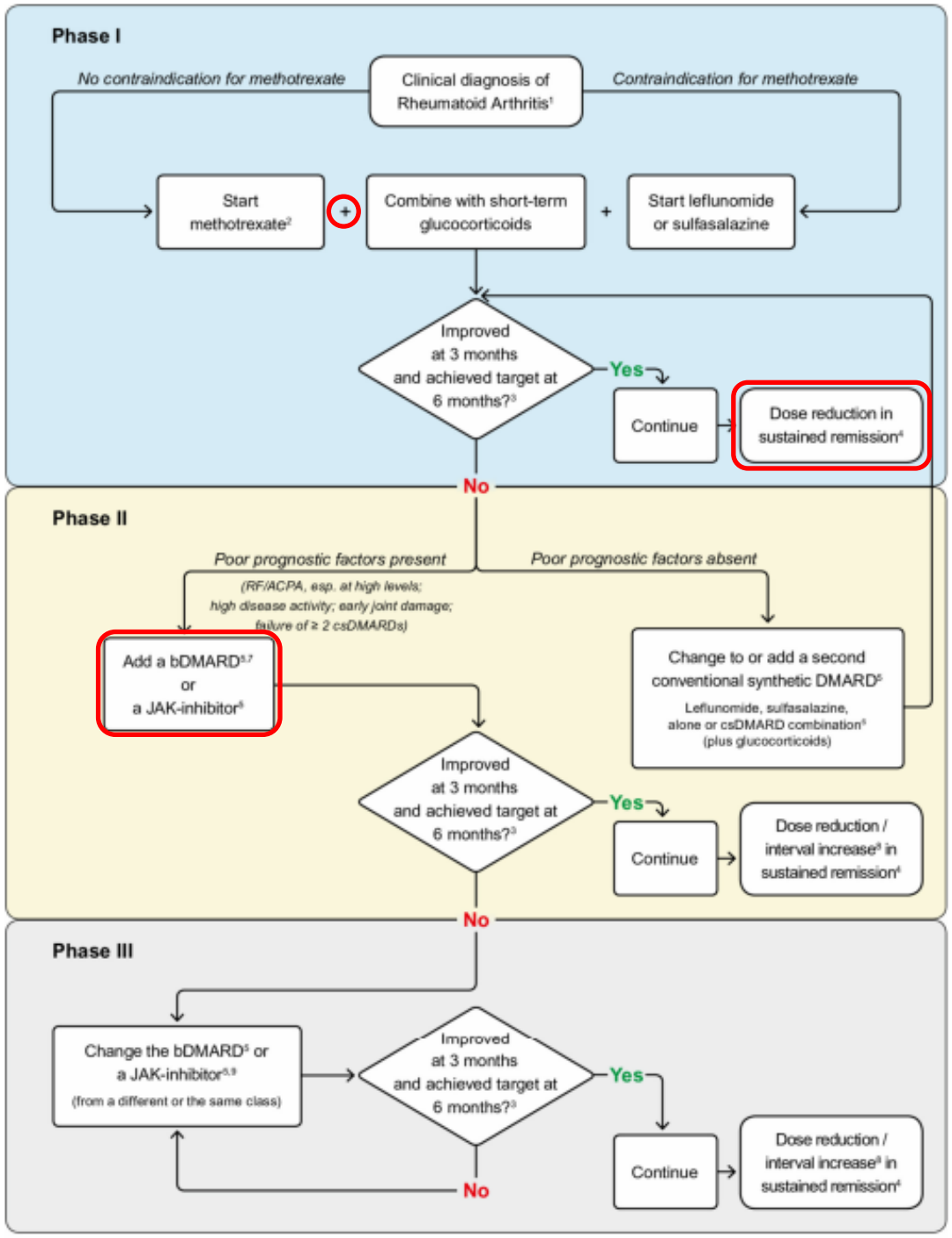
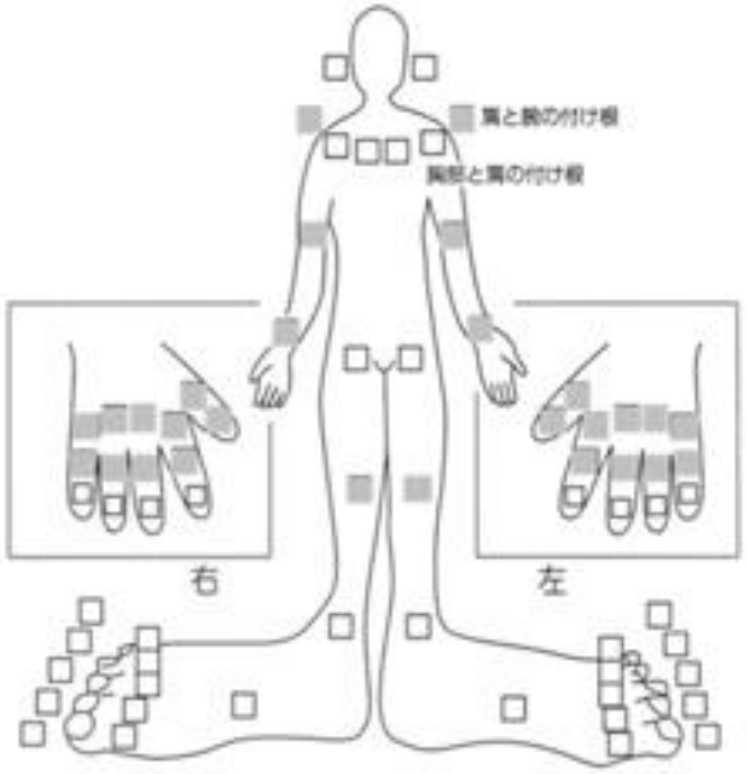


RAの
総合疾患活動性指標

(A) DAS28, SDAI, CDAI で評価する関節



A) 灰色で塗りつぶした 28 関節を評価する。

表 1　総合疾患活動性指標の種類と定義

評価法	定義（計算式）
DAS28	0.56x√TJC28+0.28x√SJC28+0.70xIn(ESR)+0.014xPGA(mm)
SDAI	TJC28+SJC28+PGA(cm)+PhGA(cm)+CRP(mg/dL)
CDAI	TJC28+SJC28+PGA(cm)+PhGA(cm)
HRAS38	SJS38+CRP(mg/dL)+PGA(mm)
DAS	0.54x√Ritchie53+0.065x√SJC44+0.33xIn(ESR)+0.0072xPGA(mm)
RAPID3	PGA (cm)+PainVAS(cm)+MDHAQ

表 2　各疾患活動性指標の基準値

評価法	活動性評価			
	高度	中等度	軽度	寛解
DAS28 (ESR)	>5.1	3.2-5.1	<3.2	<2.6
DAS28 (CRP)	>4.1	2.7-4.1	<2.7	<2.3
SDAI	>26	11-26	<11	<3.3
CDAI	>22	10-22	<10	<2.8
HRAS38	>100	50-100	<50	<10
DAS	>3.7	2.4-3.7	<2.4	<1.6
RAPID3	>4	2-4	<2	<1

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Risk profiling for a refractory course of rheumatoid arthritis

Manuel Bécède[a], Farideh Alasti[a], Irina Gessl[a], Lukas Haupt[b], Andreas Kerschbaumer[a], Uriel Landesmann[a], Michaela Loiskandl[a], Gabriela M. Supp[a], Josef S. Smolen[a,b], Daniel Aletaha[a,*]

Clinical and epidemiological research

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EXTENDED REPORT

Biologic refractory disease in rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis

Lianne Kearsley-Fleet,[1] Rebecca Davies,[1] Diederik De Cock,[1] Kath D Watson,[1] Mark Lunt,[1] Maya H Buch,[2,3] John D Isaacs,[4] Kimme L Hyrich,[1,5] the BSRBR-RA Contributors Group

RHEUMATOLOGY

Rheumatology 2018;57:1135–1144
doi:10.1093/rheumatology/kex349
Advance Access publication 4 October 2017

Review

Difficult-to-treat rheumatoid arthritis: an area of unmet clinical need

Maria J. H. de Hair[1], Johannes W. G. Jacobs[1], Jan L. M. Schoneveld[1] and Jacob M. van Laar[1]

D2Tの様々な定義

1剤以上のb-DMARDを含む3剤以上のDMARDを使用してもLDA (低疾患活動性) に入らない18カ月以上治療しているRA

=> 17%がD2T-RA

種類によらず2剤以上のb-DMARD無効例

=>バイオを導入患者の6%がD2T-RA

2剤以上のb-DMARD無効例

実際には2014-2018年に以下を含む60の文献に difficult-to-treat RAに関連する記述、定義があり

Supplementary Table 1. Summary of selected articles

No	Ref	Definition in text	Treatment failure	Study type	Study topic
1	Álvaro-Gracia JM, Jover JA, García-Vicuña R, *et al*. Intravenous administration of expanded allogeneic adipose-derived mesenchymal stem cells in refractory rheumatoid arthritis (Cx611): results of a multicentre, dose escalation, randomised, single-blind, placebo-controlled phase Ib/IIa clinical trial. *Ann Rheum Dis* 2017;**76**:196–202.	refractory RA (failure to at least two biologicals)	≥2bDMARDs	RCT	Efficacy of Cx611 vs placebo
2	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;**0**:1–8.	bDMARD refractory on the date they started their third class of bDMARD	≥2bDMARDs	Cohort	Quantify frequency and identify associated factors
3	Buch MH. Defining refractory rheumatoid arthritis. *Ann Rheum Dis* 2018;:annrheumds-2017-212662.	failure of at least one anticytokine (TNF and/or IL-6 directed) and one cell-targeted (B cell depletion and/or T cell costimulation blockade) bDMARD	≥2bDMARDs: 1TNFi/IL6, 1B-cell/T-cell	Editorial	Defining refractory RA
4	Genovese MC, Kremer J, Zamani O, *et al*. Baricitinib in Patients with Refractory Rheumatoid Arthritis. *N Engl J Med* 2016;**374**:1243–52. doi:10.1056/NEJMoa1507247	one or more TNF inhibitors and discontinued treatment because of an insufficient response after 3 months or more or because of unacceptable side effects. Patients who had received other biologic DMARDs could also participate	≥1bDMARDs	RCT	Efficacy of baricitinib vs placebo
5	Genovese MC, Kremer JM, Kartman CE, *et al*. Response to baricitinib based on prior biologic use in patients with refractory rheumatoid arthritis. *Rheumatology (Oxford)*. 2018;**57**:900–8.	previously received one or more TNF inhibitor and discontinued treatment because of either insufficient response or intolerance	≥1bDMARDs	RCT	Efficacy of baricitinib vs placebo
6	Smolen JS, Kremer JM, Gaich CL, *et al*. Patient-reported outcomes from a randomised phase III study of baricitinib in patients with rheumatoid arthritis and an inadequate response to biological agents (RA-BEACON). *Ann. Rheum. Dis.* 2017;**76**:694–700.	≥1 tumour necrosis factor inhibitors (TNFis) or other biological disease-modifying antirheumatic drugs (bDMARDs).	≥1bDMARDs	RCT	PROs in patients receiving baricitinib vs placebo
7	Feist E, Burmester GR. Small molecules targeting JAKs--a new approach in the treatment of rheumatoid arthritis. *Rheumatology (Oxford)*. 2013;**52**:1352–7.	patients resistant to biologics	bDMARDs	Review	JAKi as a new treatment option
8	Duriez P, Vandepapelière P, Miranda P, *et al*. Therapeutic vaccination with TNF-Kinoid in TNF antagonist-resistant rheumatoid arthritis: a phase II randomized, controlled clinical trial. *PLoS One*. 2014;**9**:e113465.	adults with RA who previously experienced secondary failure of TNF antagonists	≥2TNFi	RCT	Efficacy of TNF-Kinoid vaccination
9	Williams JH, Hülmacher MM, Zierhut ML, *et al*. Comparative assessment of clinical response in patients with rheumatoid arthritis between PF-05280586, a	active rheumatoid arthritis refractory to anti-tumour necrosis factor therapy on a	≥1TNFi + MTX	RCT	Efficacy of RTX vs biosimilar RTX

Nagy G Ann Rheum Dis 2021; 80: 31-35 suppl

CONCISE REPORT

Characteristics of difficult-to-treat rheumatoid arthritis: results of an international survey

Roodenrijs NMT, et al. Ann Rheum Dis 2018;77:1705–1709

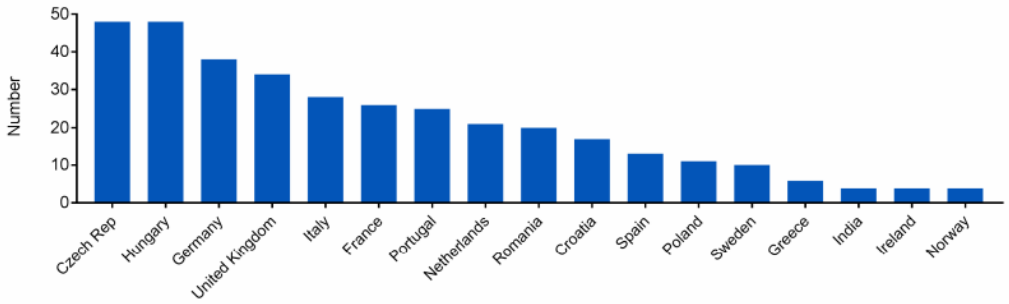
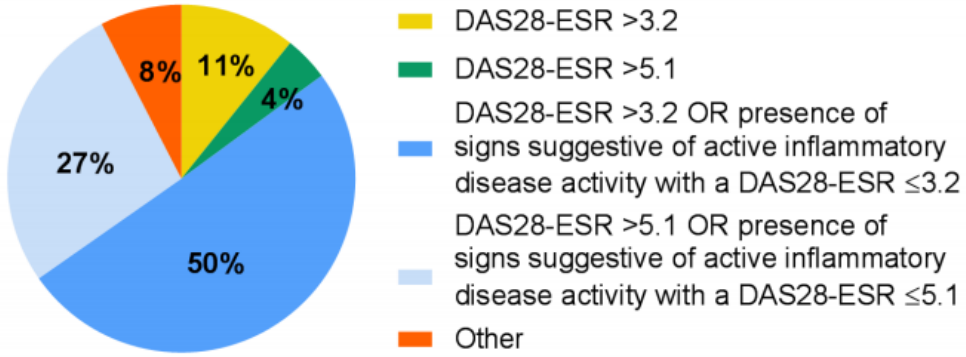


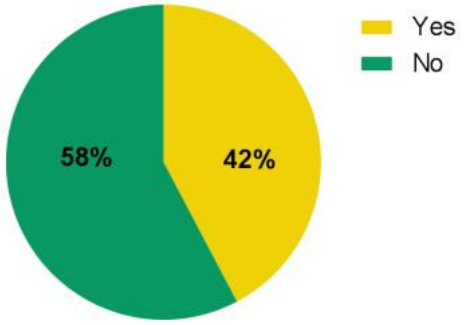
Figure 1 Number of respondents per country.

A. What should be the definition for not well-controlled disease in the definition of difficult-to-treat RA?



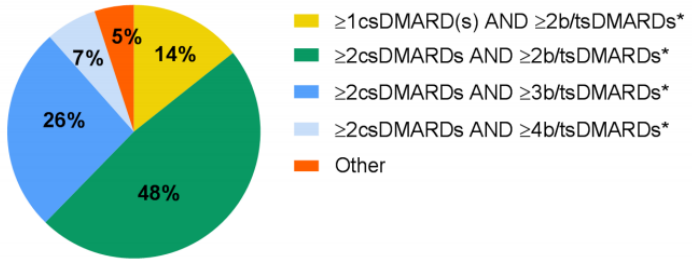
Total responses = 409

B. Would you include fatigue in the definition of not well-controlled disease?

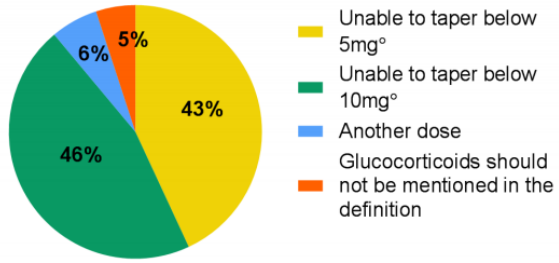


Total responses = 396

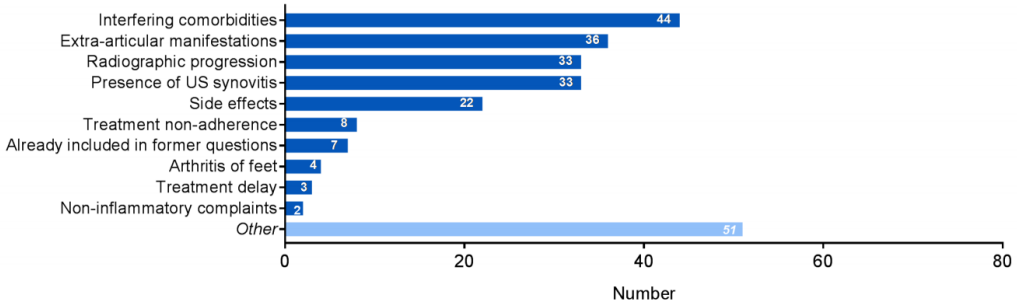
C. Which and how many antirheumatic drugs should at least be tried with insufficient effect for the definition of difficult-to-treat RA?



D. Treatment with glucocorticoids should be mentioned in the criteria for difficult-to-treat RA as follows:



E. Additional characteristics of difficult-to-treat RA



方法

・32人のメンバー（リウマチ専門医26名、患者2人、医療専門家1人、心理学者1人、薬剤師1人、作業療法士1人）が話し合いで決めた。

・文献検索による60のD2Tの定義と先のInternational Surveryをもとに Steering Committee がDraftをつくり、Task Forceに諮り修正を加え、合意を諮った。

・Task Forceは関節症状と関節外症状どちらも含めるべきという点で一致した。

Box 1 EULAR definition of difficult-to-treat RA

1. Treatment according to European League Against Rheumatism recommendation and failure of ≥2 b/tsDMARDs (with different mechanisms of action)* after failing csDMARD therapy (unless contraindicated).†
2. Signs suggestive of active/progressive disease, defined as ≥1 of:
   a. At least moderate disease activity (according to validated composite measures including joint counts, for example, 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).‡
   e. Well-controlled disease according to above standards, but still having RA symptoms that are causing a reduction in quality of life.
3. The management of signs and/or symptoms is perceived as problematic by the rheumatologist and/or the patient.

日本語訳

1. ヨーロッパリウマチ学会推奨治療に従って、（禁忌でない限り）通常の抗リウマチ薬治療を行って後（作用機序の異なる）２剤以上の生物学的製剤もしくはJak阻害薬を用いても治療がうまくいかない。

2. 活動性、進行性の病態を示す以下の症状を１つ以上もつこと
   a. 少なくとも中等度以上の疾患活動性（DAS28-ESR>3.2もしくはCDAI>10といった検証済みの総合疾患活動性指標を用いる）をもつ
   b. 臨床所見（急性期反応や画像所見を含む）や活動性を示す症状（関節症状と関節外症状）
   c. ステロイドをPSL 7.5mgより減量できないこと
   d. 急激な骨破壊（RRP）（活動性徴候の有無を問わず）
   e. 標準治療により活動性はよく抑えられているのに、QOLを低下させるようなRA関連の症状が続いている。

3. 臨床所見や症状が問題がある、とリウマチ専門医か患者が捉えている。

解説（１．治療歴）

- **b/t DMARD failureの数は2つ**とすることで全員の合意を得た
- 治療期間は1年以上とすることが妥当（Eular recommendationsを踏襲するとそのくらいになる）
- 「**社会的・経済的な理由で治療中止したことを除く**」ということが追記された

解説（2. 活動性/症候性 病態の特徴）

- a (**中等度疾患活動性以上 eg. DAS-ESR≧3.2**)には異議なし
- bでは、DAS-ESR <3.2であっても、**活動性を示す所見（関節症状以外も含める）があれば、D2Tとする**ことで合意。急性反応蛋白や画像所見のほか、血管炎、心外膜炎、強膜炎、糸球体腎炎(?)も含める。
- cでは、**ステロイド減量困難をD2Tの定義に加える**ことをほとんどの人が同意。PSL <10mgとするかPSL <5mgとするかで割れた(46% vs 43%)。その中間(**PSL <7.5mg**)をとった。
- dではRRP（X線での急激な悪化）も含めている。臨床的に異常なしでもX線が進行することがあると（全員が合意）。
- eの文言を挿入することには全員一致。線維筋痛症症状や倦怠感もRAに伴う症状に含まれるが、倦怠感を含めるべきではないという意見も58%あり、倦怠感に言及することは避けた。

解説（3. この状況を問題と思っているかどうか）

- 患者もしくは医師が問題視（problematic)していることが条件

PSL 5mgで安定していて医師も患者も満足ならD2T-RAではないなど。