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Predicting Flare in Patients With Rheumatoid Arthritis in Biologic Induced Remission, on Tapering, and on Stable Therapy

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膠原病・リウマチ内科　Journal Club 2024.05.21　加地　紫苑

Background　DMARDsは漸減・中止できるのか？

Review

Tapering biologic and conventional DMARD therapy in rheumatoid arthritis: current evidence and future directions

Georg Schett,[1] Paul Emery,[2] Yoshiya Tanaka,[3] Gerd Burmester,[4] David S Pisetsky,[5] Esperanza Naredo,[6] Bruno Fautrel,[7] Ronald van Vollenhoven[8]

Ann Rheum Dis. 2016 Aug;75(8):1428-37.

【DMARDsの漸減基準】
(a)臨床的寛解状態（DAS28＜2.6, DAS44＜1.6, SDAI＜3.3, CDAI＜2. 8; ACR/EULAR寛解）
(b)連続した3回の診察で記録された≧6ヵ月の持続的寛解
(c)過去6ヵ月間，DMARDsの種類・用量が安定し
(d)グルココルチコイドを使用していない

→ACPAの陰性化や”深い”寛解, 即ち関節エコーや血中炎症マーカーの正常化が有用かもしれない

RHEUMATOLOGY
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Original article

Defining remission in rheumatoid arthritis: does it matter to the patient? A comparison of multi-dimensional remission criteria and patient reported outcomes

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Rheumatology (Oxford). 2020 Jan 1;59(1):213-223.

- DAS28の臨床的寛解は炎症の消失を反映するわけではない
- 画像，免疫学的所見を含めたMulti-dimensional remission(MDR)は患者立脚型アウトカム(PROs)と関連

Background　早期RAにおけるT cell subsets

Basic and translational research

EXTENDED REPORT

An immunological biomarker to predict MTX response in early RA

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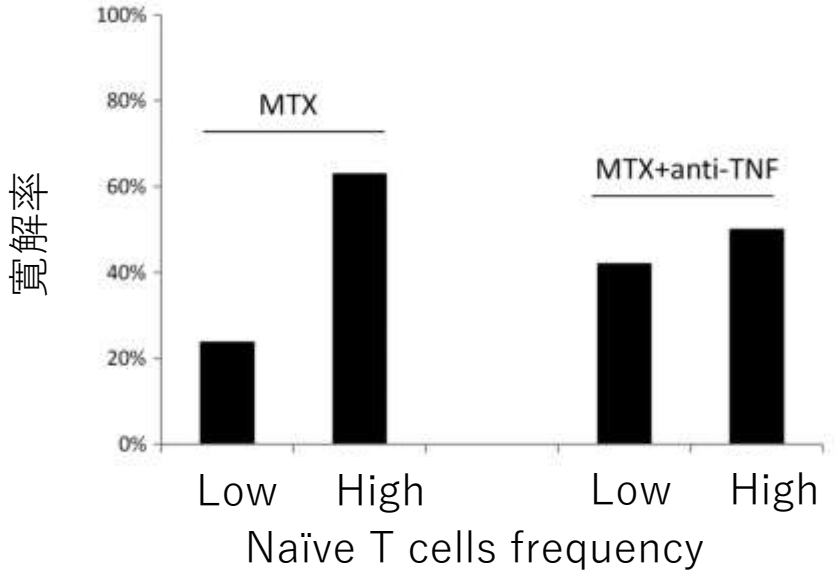
Table 1 Early RA cohort description at baseline

Pilot cohort (frozen PBMC)	*Early RA (n=38)*	*HC (n=35)*
Age (years)*	58 (45, 66)	48 (32, 60)
Gender (M/F)	14/24	15/20
Symptom duration (months)*	5 (3, 10)	
RF (pos/neg)	26/12	
ACPA (pos/neg)†	18/16	
CRP (mg/L)*	18 (9, 58)	
TJC*‡	12 (6, 23)	
SJC*‡	10 (5, 15)	
HAQ*‡	11 (6, 13)	
RAQoL*‡	17 (9, 22)	
DAS28*	6.21 (4.81, 6.69)	
Naïve (% CD4T-cells)	4.1 (2.7, 10.0)	11.2 (5.9, 13.9)
IRC (% CD4T-cells)*	29.0 (21.1, 35.5)	2 (0.9, 7.4)
Treg (% CD4T-cells)*	2.6 (1.7, 3.6)	5.4 (4.1, 8.0)

- 早期RAは健常人と比べ,
  - 末梢血Naïve $CD4^+$ T cellsの減少,
  - Inflammatory related cells (IRCs)の増加
  - regulatory T cells (Tregs)の減少が報告されている.

- 早期RAのNaïve T cell frequencyが高い方が
  （MTX単剤 or MTX+anti-TNF）治療6か月後の寛解率が高い
  →早期RAの治療反応性予測因子として有効.



Ann Rheum Dis. 2014 Nov;73(11):2047-53.

本論文のPICO

P RA（2010 ACR/EULAR criteriaを満たす）
2014-2020にb-DMARD療法を導入, GCs導入なし
DAS28-CRP<2.6の寛解状態を6ヶ月以上認めた123例

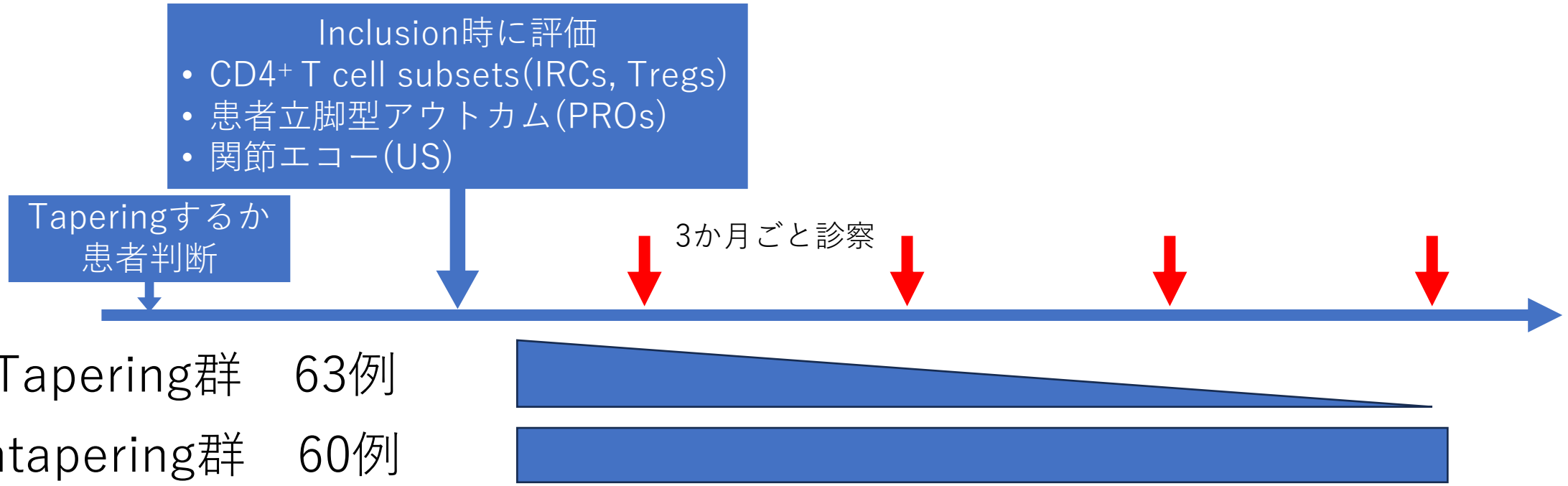
I 3ヶ月ごとにb-DMARDsを漸減/中止（63例）；**Tapering群**

C b-DMARDsを継続（60例）；**Nontapering群**

O 12ヶ月後の再燃率 (DAS28-CRP≧2.6 かつGCs導入 and/or 治療再開†)

† Tapering群

Study design



T-cell subsets:

Naïve $CD4^+$ cells, T-regulatory cells(Tregs), nflammatory related cells(IRCs)をフローサイトメトリで測定

[Normalized Naïve/Treg %] = [観測値] - [同年齢の健常人での期待値(下記)]

[expected naïve %] = -0.63 x [age] +66.6 (rho=0.850, p<0.0001)
[expected Treg %] = +0.061 x [age] +1.83 (rho=0.554, p=0.001)

PROs: VAS (PGA, disease activity(DA), 疲労, 疼痛）, HAQ-DI, RAQoL scores

US: 26関節(両手，2-3PIP+MP, 両肘，両膝，1-5MTP)をGS, PDそれぞれ0-3のスコアで評価

b-DMARDsの漸減プロトコルと内訳

	Baseline Dose	Taper 1	Taper 2	Taper 3	Taper 4
DRUG	0 months	3 months	6 months	9 months	12months
Etanercept	50mg/week	25mg/week	25mg/2 weeks	25mg/4 weeks	Stop
	25mg/week	25mg/2 weeks	25mg/4 weeks	Stop	-
	25mg/2 weeks	25mg/4 weeks	Stop	-	-
Adalimumab	40mg/2 weeks	40mg/4 weeks	40mg/8 weeks	40mg/16 weeks	Stop
	40mg/4 weeks	40mg/8 weeks	40mg/16 weeks	Stop	-
	40mg/8 weeks	40mg/16 weeks	Stop	-	-
Infliximab	Variable	Half dose	Double time interval	Double time interval	Stop
Certolizumab	200mg/2 weeks	200mg/ 4 weeks	200mg/8 weeks	200mg/16 weeks	Stop
Golimumab	Variable	Every 4 weeks	Every 8 weeks	Every 16 weeks	Stop
Tocilizumab (SC)	162mg/2 weeks	162mg/4 weeks	162mg/8 weeks	162mg/16 weeks	Stop
Tocilizumab (IV)	Variable	Half dose	Double time interval	Double time interval	Stop
Abatacept (SC)	125mg/week	125mg/2 weeks	125mg/4 weeks	125mg/8 weeks	Stop
Abatacept (IV)	Variable	Half dose	Double time interval	Double time interval	Stop

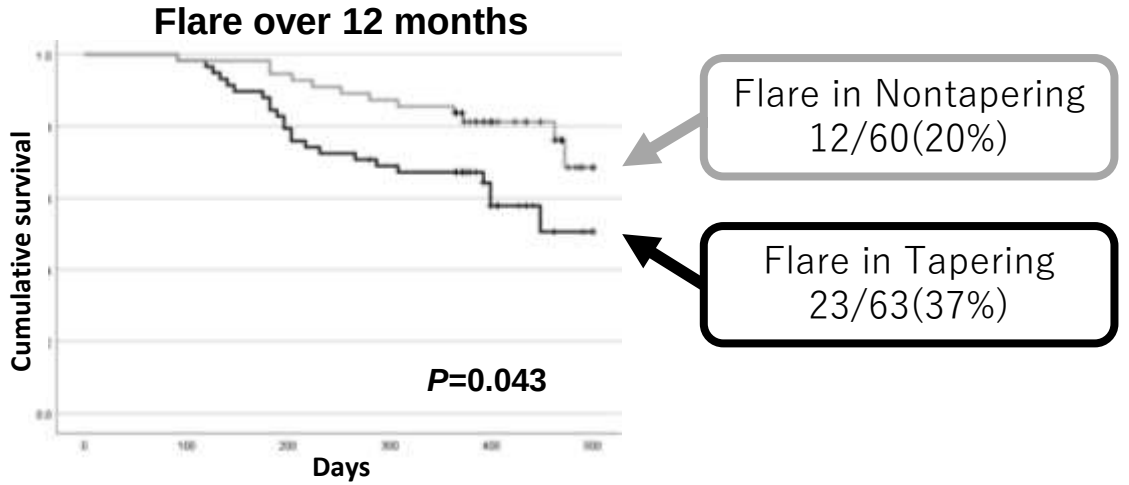
TNF inhibitors n=107/123(92%), TCZ n= 8/123(6.5%), ABT n= 2/123(1.6%)

Results　12か月後の再燃率はTapering群で高い

Table 1. Baseline characteristics of tapering vs nontapering cohort*

	Missing data, n	Tapering cohort (n = 63)	Nontapering cohort (n = 60)	*P* value
Demographic variables				
Female, n (%)	0	37 (59)	39 (65)	0.474
Age, median (IQR), y	0	56 (49 to 66)	59 (53 to 70.5)	0.631
Disease duration, median (IQR), mo	1	104.8 (61.5 to 163.5)	97 (54.8 to 157.2)	0.933
Remission duration, median (IQR), mo	0	21.5 (10.5 to 40.7)	17 (7.9 to 25.1)	0.049
RF$^+$, n (%)	0	39 (62)	29 (48)	0.130
ACPA$^+$, n (%)	0	53 (84)	46 (77)	0.297
Smoking (never), n (%)				
Never	7	29 (48)	22 (39)	
Ever		31 (52)	34 (61)	0.327
Missing		3	4	
Clinical variables, median (IQR)				
TJC28	0	0 (0)	0 (0 to 1)	0.148
SJC28	0	0 (0)	0 (0)	0.115
CRP level,[a] mg/L	0	<5 (<5)	<5 (<5)	0.382
ESR, mm/h	5	8 (4 to 16)	7 (3.5 to 15)	0.375
EMS, min	1	0 (0 to 5)	0 (0 to 5)	0.240
PRO variables, median (IQR)				
VAS PGA	0	10 (3 to 22)	19.5 (10 to 29)	0.068
VAS pain	2	4 (2 to 10)	8.5 (2.25 to 22.75)	<0.0001
VAS DA	3	4 (1 to 10)	5 (3 to 18)	<0.0001
VAS fatigue	3	11 (4 to 35)	12 (4 to 23)	0.204
HAQ-DI	1	0 (0 to 0.875)	0 (0 to 0.625)	0.322
RaQoL	1	1 (0 to 8)	1 (0 to 5)	0.420
Ultrasound variables, median (IQR)				
Total PD	23	0 (0 to 2)	0 (0 to 0)	0.021
Total GS	23	13 (11 to 26)	14 (5 to 19)	0.019
T cell variables, median (IQR)				
Normalized naive	28	9.4 (−5.7 to 21.7)	11.7 (1.3 to 21.7)	0.929
Normalized Tregs	27	−1.0 (−3.1 to −0.33)	−1.1 (−2.3 to −0.2)	0.151
IRCs	26	1.8 (0.8 to 2.8)	1.1 (0.4 to 3.3)	0.504
Flare data				
Loss of remission (3vDAS28 ≥2.6)		23 (35%)	12 (20%)	0.043

*Total n = 123. ACPA, anti-citrullinated protein antibodies; CRP, C-reactive protein; DA, disease activity; EMS, early morning stiffness; ESR, erythrocyte sedimentation rate; GS, grayscale synovial hypertrophy score; HAQ-DI, health assessment questionnaire disability index; IQR, interquartile range; IRC, inflammation-related cell (percentage of total CD4+T cells); PD, power Doppler score; PGA, patient global assessment of disease; RAQoL, rheumatoid arthritis quality of life questionnaire; RF, rheumatoid factor; SJC28, swollen joint count out of 28 joints; T cell subsets, naive CD4+T cells (normalized percentage of total CD4+T cells); TJC28, tender joint count out of 28 joints; Treg, regulatory T cell (normalized percentage of total CD4+T cells); VAS, visual analog scale.
[a]CRP <5 mg/L = lowest detectable limit.



TaperingはNontapering群と比べ
- VAS-pain/DAが低く，
- 寛解期間が長く，US所見がある(多重検定補正で有意差なし)

Tapering群の
- 3例(4.8%)がDrug-free達成
- 9例(5.7%)は寛解だったがtaperingを中断

Tapering群での再燃例と寛解維持例の比較

再燃　　寛解維持

Table 2. Univariate analysis of baseline characteristics associated with flare/loss of DAS28 remission*

	Flare (n = 23), 37%	Stable remission (n = 40), 63%	*P* value	OR (95% CI), *P* value	AUC (95% CI), *P* value
Demographic variables					
Female, n (%)	14 (61)	23 (58)	0.794	1.150 (0.404 to 3.273), 0.794	0.483 (0.334 to 0.632), 0.825
Age, median (IQR), y	63.0 (56.0 to 68.0)	58.5 (47.5 to 69.5)	0.307	1.028 (0.985 to 1.073), 0.204	0.578 (0.437 to 0.719), 0.307
Disease duration, median (IQR), months	97.9 (59.5 to 201.1)	104.8 (66.4 to 161)	0.732	1.000 (0.996 to 1.003), 0.764	0.526 (0.370 to 0.682), 0.732
Remission duration, median (IQR), months	19.6 (9.3 to 33.2)	22.6 (12.3 to 44)	0.141	1.000 (0.985 to 1.016), 0.970	0.437 (0.283 to 0.591), 0.414
RF$^+$, n (%)	16 (73)	23 (56)	0.342	0.592 (0.200 to 1.755), 0.344	0.560 (0.413 to 0.707), 0.428
ACPA$^+$, n (%)	19 (83)	34 (85)	0.803	1.193 (0.299 to 4.762), 0.803	0.488 (0.338 to 0.638), 0.875
Smoking, n (%)		n = 37	0.951	1.033 (0.365 to 2.929), 0.951	0.504 (0.353 to 0.656), 0.958
Never	11 (48)	18 (49)			
Ever	12 (52)	19 (51)			
Clinical variables, median (IQR)					
TJC28	0 (0)	0 (0 to 0.8)	0.150	0.625 (0.253–1.546), 0.309	0.425 (0.280–0.570), 0.325
SJC28	0 (0)	0 (0)	0.689	1.773 (0.106–29.760), 0.691	0.509 (0.359–0.659), 0.903
CRP level,[a] mg/L	<5 (<5 to 9.3)	<5 (<5)	<0.0001	1.312 (1.077 to 1.599), 0.007	0.701 (0.543 to 0.849), 0.009
ESR, mm/h	20.5 (76.5 to 35)	9 (5 to 15.5)	0.035	1.049 (0.996 to 1.999), 0.0.083	0.734 (0.555 to 0.849), 0.002
EMS, min	0 (0 to 1.3)	0 (0 to 1.5)	0.899	1.000 (0.970 to 1.030), 0.982	0.493 (0.341 to 0.644), 0.077
Patient-reported outcome variables, median (IQR)					
VAS PGA	10 (4.0 to 19.0)	13.5 (3.3 to 24.3)	0.577	0.987 (0.957 to 1.018), 0.412	0.458 (0.313 to 0.602), 0.578
VAS pain	5 (2.0 to 8)	3 (1 to 7.8)	0.409	0.998 (0.973 to 1.022), 0.844	0.563 (0.417 to 0.708), 0.412
VAS DA	3 (1.0 to 12)	3 (1.0 to 10)	0.880	0.992 (0.970 to 1.015), 0.511	0.511 (0.363 to 0.660), 0.881
VAS fatigue	11 (3.0 to 32.0)	11 (3.3 to 35.0)	0.983	0.993 (0.976 to 1.010), 0.421	0.498 (0.353 to 0.644), 0.983
HAQ-DI	0.1(0 to 0.9)	0 (0 to 0.1)	0.103	0.963 (0.875 to 1.061), 0.451	0.610 (0.457 to 0.762), 0.149
RaQoL	2 (1 to 4.0)	1 (0 to 2)	0.091	0.983 (0.943 to 1.026), 0.434	0.626 (0.482 to 0.770), 0.098
US variables, median (IQR)					
Total PD	0 (0 to 2)	0 (0 to 1.8)	0.739	0.991 (0.973 to 1.009), 0.322	0.523 (0.365 to 0.680), 0.764
Total GS	14 (12 to 21)	13 (9 to 21.8)	0.847	1.004 (0.957 to 1.054), 0.863	0.515 (0.364 to 0.665), 0.847
Immunologic (T cell variables), median (IQR)					
Normalized naive	8.9 (−7.7 to 20.8)	9.4 (−5.7 to 23.1)	0.191	0.972 (0.932 to 1.013), 0.177	0.380 (0.203 to 0.557), 0.191
Normalized Tregs	−2.4 (−3.9 to −1.5)	−0.80 (−2.3 to 0.2)	<0.0001	0.319 (0.160 to 0.633), 0.001	0.206 (0.095 to 0.318), <0.0001
IRCs	3.1 (1.1 to 4.6)	1.3 (0.8 to 2.0)	0.054	1.782 (1.113 to 2.856), 0.016	0.688 (0.531 to 0.811), 0.027

再燃例では寛解維持例と比較してCRP，ESRが高く，Tregsが少なく，IRCsが多い

Tapering群での再燃予測因子の探索; Tregs, CRP, IRCs

ステップワイズ法によるロジスティック回帰分析

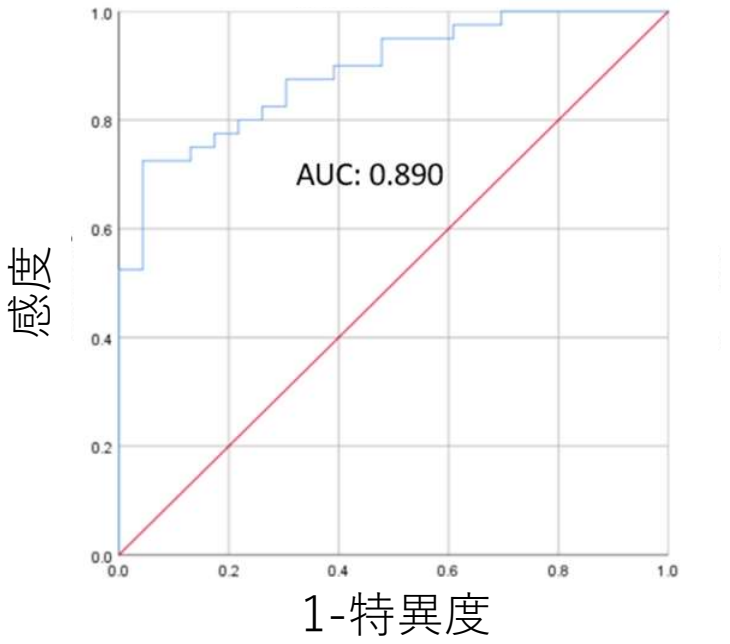
Table 3. Modeling the prediction of flare in the tapering cohort*

Variables	Step 1 Tregs	Step 2 CRP	Step 3 IRCs
Tregs, OR (95% CI), *P* value	0.469 (0.293–0.751), 0.002	0.371 (0.198–0.694), 0.002	0.350 (0.172–0.709), 0.004
CRP level, OR (95% CI)		1.714 (1.161–2.529), *P* = 0.007	1.871 (1.191–2.940), *P* = 0.007
IRCs, OR (95% CI)			1.577 (1.020–2.458), *P* = 0.044
Accuracy	71.4%	76.2%	81.7%
SEN	47.71%	65.2%	69.5%
SPE	85%	86.5%	89.2%
PPV	64.7%	75%	80%
NPV	74%	80%	82.5%
AUROC	0.764	0.862	0.890
95% CI	0.634–0.894	0.774–0.950	0.813–0.967
P value	<0.0001	<0.0001	<0.0001

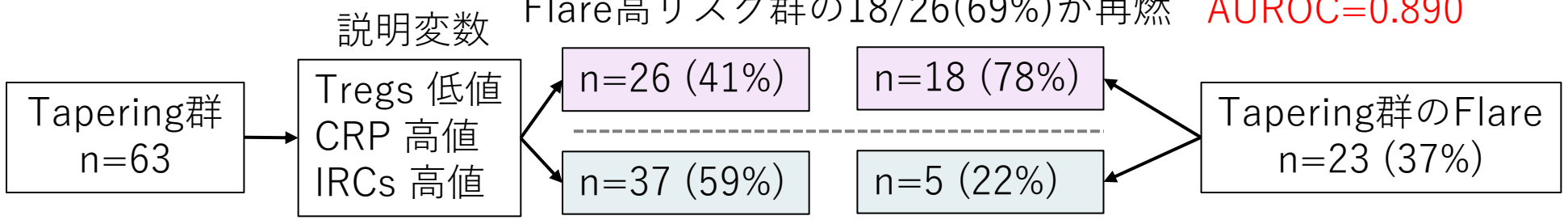
*AUROC, area under the receiving operator curve; CRP, C-reactive protein; IRC, inflammation-related cell; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value; SEN, specificity; SPE, sensitivity; Treg, regulatory T cell; 95% CI, 95% confidence interval.

SEN=感度, SPE=特異度, Accuracy=陽性尤度比（SEN/1-SPE）, PPV=陽性的中率

ROC曲線



【最終的なモデル】Tregs, CRP, IRCs
感度69.5%, 特異度89.2%, 陽性的中率80%
AUROC=0.890



Nontapering群での再燃例と寛解維持例の比較

	再燃 Flare (*n* = 12) 20%	寛解維持 Stable Remission (n = 48) 60%	*P* value	OR (95% CI), *P* value	AUROC (95% CI), *P* value
Demographic variables					
Female, n (%)	9 (75)	30 (63)	0.417	1.800 (0.430 to 7.532), 0.421	0.438 (0.260 to 0.615), 0.438
Age, median (IQR), y	65 (59 to 71)	59 (53 to 69)	0.136	1.049 (0.984 to 1.119), 0.140	0.640 (0.496 to 0.783), 0.073
Disease duration, median (IQR), months	124.1 (43.9 to 260)	107.3 (58.6 to 160.2)	0.706	1.003 (0.997 to 1.009), 0.313	0.535 (0.317 to 0.754), 0.706
Remission duration, median (IQR), months	11.8 (6.5 to 25)	16.9 (9.0 to 26.5)	0.401	1.007 (0.975 to 1.040), 0.671	0.418 (0.207 to 0.629), 0.401
RF^+, n (%)	5 (42)	24 (50)	0.605	1.400 0.389 to 5.033), 0.606	0.458 (0.276 to 0.641), 0.657
$ACPA^+$, n (%)	10 (83)	36 (75)	0.542	0.600 (0.115 to 3.133), 0.545	0.543 (0.364 to 0.720), 0.657
Smoking, n (%)			0.184	0.360 (0.100 to 1.364), 0.135	0.379 (0.196 to 0.561), 0.201
Never	7 (58)	15 (31)			
Ever	5 (42)	29 (60)			
Clinical variables, median (IQR)					
TJC28	1.5 (0 to 3)	0 (0)	0.004	2.081 (1.228 to 3.536), 0.006	0.713 (0.528 to 0.897), 0.024
SJC28	0 (0)	0 (0)	0.859	1.000 (0.297 to 3.362), 1.000	0.491 (0.308 to 0.675), 0.926
CRP level,[a] mg/L	<5 (<5 to 22)	<5 (<5)	0.552	1.035 (0.931 to 1.152), 0.520	0.465 (0.284 to 0.647), 0.712
ESR	10.5 (7 to 30)	7 (3.3 to 25)	0.057	1.043 (1.005 to 1.083), 0.028	0.701 (0.528 to 0.826), 0.033
EMS	0 (0 to 8.8)	0 (0 to 5)	0.501	0.996 (0.956 to 1.038), 0.851	0.553 (0.367 to 0.739), 0.573
Patient-reported outcome variables, median (IQR)					
VAS PGA	22 (14.3 to 38)	15.2 (8.5 to 28)	0.165	1.024 (0.988 to 1.061), 0.194	0.630 (0.455 to 0.805), 0.166
VAS pain	19 (8.1 to 28.5)	8.5 (3 to 20.8)	0.038	1.042 (0.998 to 1.087), 0.060	0.719 (0.579 to 0.856), 0.020
VAS DA	16 (10.3 to 35.8)	8.5 (3.3 to 18)	0.057	1.021 (0.995 to 1.050), 0.096	0.717 (0.576 to 0.857), 0.021
VAS fatigue	10 (4.3 to 58)	14 (7 to 40)	0.643	0.992 (0.971 to 1.013), 0.432	0.457 (0.249 to 0.664), 0.644
HAQ-DI	0.25 (0 to 0.8)	0 (0 to 0.8)	0.740	1.105 (0.343 to 3.566), 0.867	0.529 (0.345 to 0.712), 0.760
RaQoL	2 (0.3 to 7.7)	1 (1 to 5)	0.826	1.018 (0.890 to 1.163), 0.800	0.520 (0.331 to 0.709), 0.832
Ultrasound variables, median (IQR)					
Total PD	1 (0 to 3)	0 (0)	0.001	1.749 (1.045 to 2.927), 0.033	0.734 (0.559 to 0.908), 0.013
Total GS	17 (10 to 24)	14 (6 to 20)	0.237	1.052 (0.971 to 1.136), 0.197	0.622 (0.440 to 0.796), 0.196
Immunologic (T cell variables), median (IQR)					
Normalized naive	0.7 (−9.3 to 7.4)	12.5 (2.4 to 25.7)	0.022	0.923 (0.910 to 0.997), 0.032	0.295 (0.136 to 0.455), 0.029
Normalized Tregs	−2.8 (−4 to 0.1)	−0.9 (−2.0 to −1.2)	0.133	0.628 (0.379 to 1.040), 0.070	0.349 (0.152 to 0.544), 0.108
IRCs	2.9 (2.2 to 9.2)	1.0 (0.4 to 3)	0.382	1.1014 (0.851 to 1.187), 0.866	0.604 (0.408 to 0.801), 0.383

再燃例では寛解維持例と比較して，TJC28が高く，VAS painが高く，Naïve T cellsが少ない

Nontapering群での再燃予測因子の探索；PD, TJC, VAS pain

ステップワイズ法によるロジスティック回帰分析

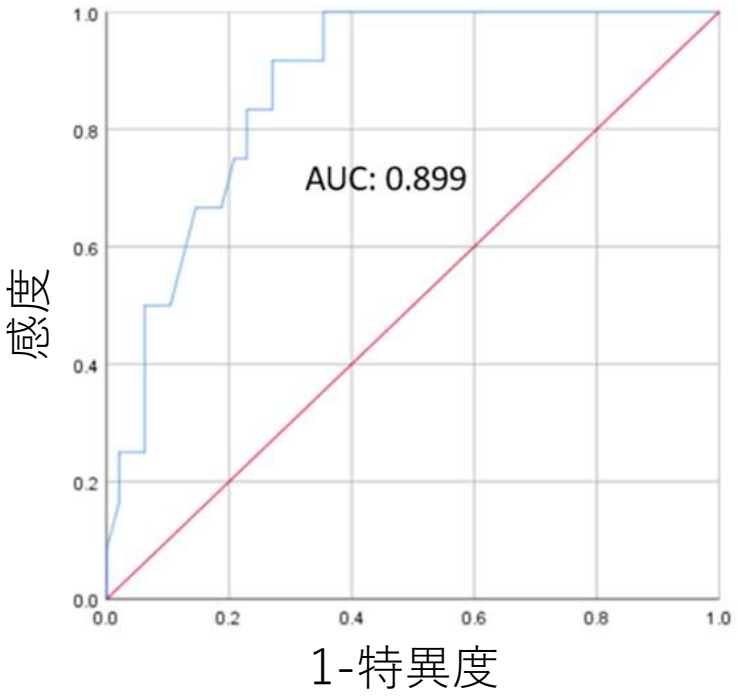
Table 5. Modeling the prediction of flare in the nontapering cohort*

Variables	Step 1 TJC	Step 2 PD score	Step 3 VAS pain
TJC, OR (95% CI), *P* value	2.007 (1.186–3.398), 0.009	2.304 (1.159–3.367), 0.006	2.124 (1.192–3.785), 0.011
Total PD, OR (95% CI), *P* value		1.975 (1.159–3.367), 0.012	2.394 (1.321–4.337), 0.004
Pain, OR (95% CI), *P* value			1.067 (1.007–1.132), 0.029
Accuracy	82.1%	82.1%	82.1%
SEN (%)	84.4%	85.4%	87%
SPE (%)	66.7%	62.5%	55.5%
PPV (%)	95.5%	93%	91%
NPV (%)	33.3%	41.7%	45.5%
AUROC	0.713	0.876	0.899
95% CI	0.528–0.897	0.788–0.964	0.803–0.997
P value	0.002	<0.0001	<0.0001

*AUROC, area under the receiving operator curve; NPV, negative predicted value; OR, odds ratio; PD, power Doppler; PPV, positive predicted value; SEN, sensitivity; SPE, specificity; TJC, tender joint count; 95% CI, 95% confidence interval.

Step3の説明変数を加えるとSPE, PPVは減少

ROC曲線



【最終的なモデル】TJC, PD score, VAS pain
感度87%, 特異度55.5%, 陽性的中率91%
AUROC=0.899

関節エコーのPower Doppler(PD), TJC, VAS painがNontapering群での再燃因子

Discussion

- DAS28寛解持続するb-DMARDs投与RA患者で, b-DMARDs漸減 (Tapering) 群はNontapering群よりも再燃率が高かった.

- Tapering群の再燃予測因子としてTregs低値, CRP高値, IRCs高値が抽出された.
  低リスク群でb-DMARDsを漸減しても, Nontapering群より再燃率が低かった.

- Nontapering群の再燃予測因子として関節エコーのPD, TJC, VAS painが挙がった.
  ➡ DAS28寛解でも疼痛遷延した状態を反映（疼痛のためPtが漸減を選択しない）

- b-DMARDsで寛解が得られているRAでは，安定したCRP低下がみられた場合,
  b-DMARDsの漸減が検討に値する.

Limitation

- ランダム化できていない(患者に選択を委ねている)
- コホートの規模が小さい
- フローサイトメトリのデータ欠損
- Follow up期間がCOVID-19パンデミックと重なり対面診療が制限された
- 関節エコーの施行者間で結果のばらつきが生じうる
- 各b-DMARDsやcsDMARDs併用療法の患者間での比較検討は行なっていない