膠原病 Journal Club

2024/04/23

Effects of tapering conventional synthetic disease-modifying antirheumatic drugs to drug-free remission versus stable treatment in rheumatoid arthritis (ARCTIC REWIND): 3-year results from an open-label, randomised controlled, non-inferiority trial

Kaja E Kjørholt, Nina Paulshus Sundlisæter*, Anna-Birgitte Aga, Joseph Sexton, Inge C Olsen, Hallvard Fremstad, Cristina Spada, Tor Magne Madland, Christian A Høili, Gunnstein Bakland, Åse Lexberg, Inger Johanne Widding Hansen, Inger Myrnes Hansen, Hilde Haukeland, Maud-Kristine Aga Ljoså, Ellen Moholt, Till Uhlig, Tore K Kvien, Daniel H Solomon, Désirée van der Heijde, Espen A Haavardsholm†, Siri Lillegraven†*

Lancet Rheumatol. 2024; 6(5): e268-e278.

膠原病・リウマチ内科

竹内　遼

Recommendation

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

11. After glucocorticoids have been discontinued and a patient is in sustained remission, dose reduction of DMARDs (bDMARDs/tsDMARDs* and/or csDMARDs) may be considered.

EULAR recommendation

グルココルチコイドを中断後、6か月寛解すれば、
DMARDs(bDMARDs、tsDMARDs、csDMARDs)の減量を考慮すべき

Ann Rheum Dis 2023; 82: 3-18.

Previous report

MTX or ETN中止 RCT

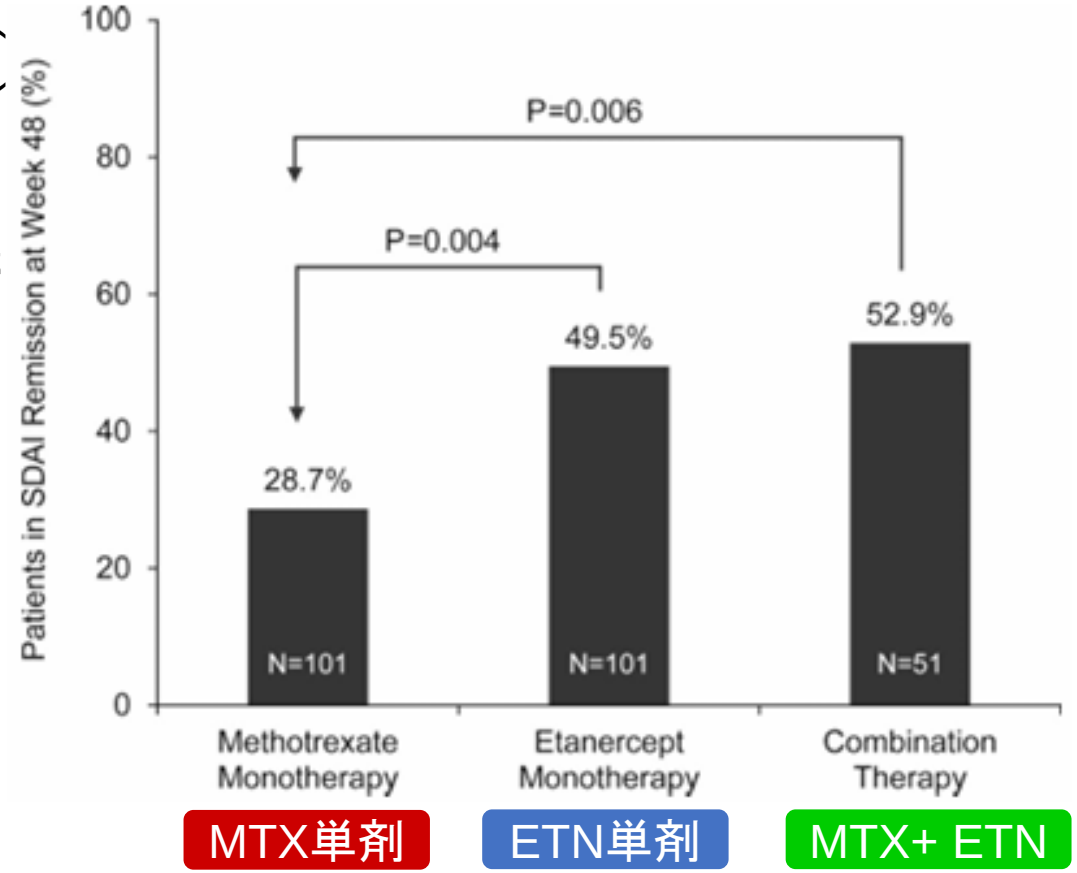
Arthritis & Rheumatology
Vol. 73, No. 5, May 2021, pp 759–768
DOI 10.1002/art.41589

American College of Rheumatology
Empowering Rheumatology Professionals

Etanercept or Methotrexate Withdrawal in Rheumatoid Arthritis Patients in Sustained Remission

Jeffrey R. Curtis,[1] Paul Emery,[2] Elaine Karis,[3] Boulos Haraoui,[4] Vivian Bykerk,[5] Priscilla K. Yen,[3] Greg Kricorian,[3] and James B. Chung[3]

48週におけるSDAI寛解の割合(%)



48週におけるSDAI寛解の割合(%)

- MTX単剤 28.7% (p=0.006 [vs MTX+ETN])
- ETN単剤 49.5% (p=0.004 [vs MTX+ETN])
- MTX+ ETN 52.9%

先にメトトレキサートを中止した方が、
エタネルセプトを先に中止するよりも
SDAI寛解を維持できる

Arthritis Rheumatol 2021; 73: 759–68.

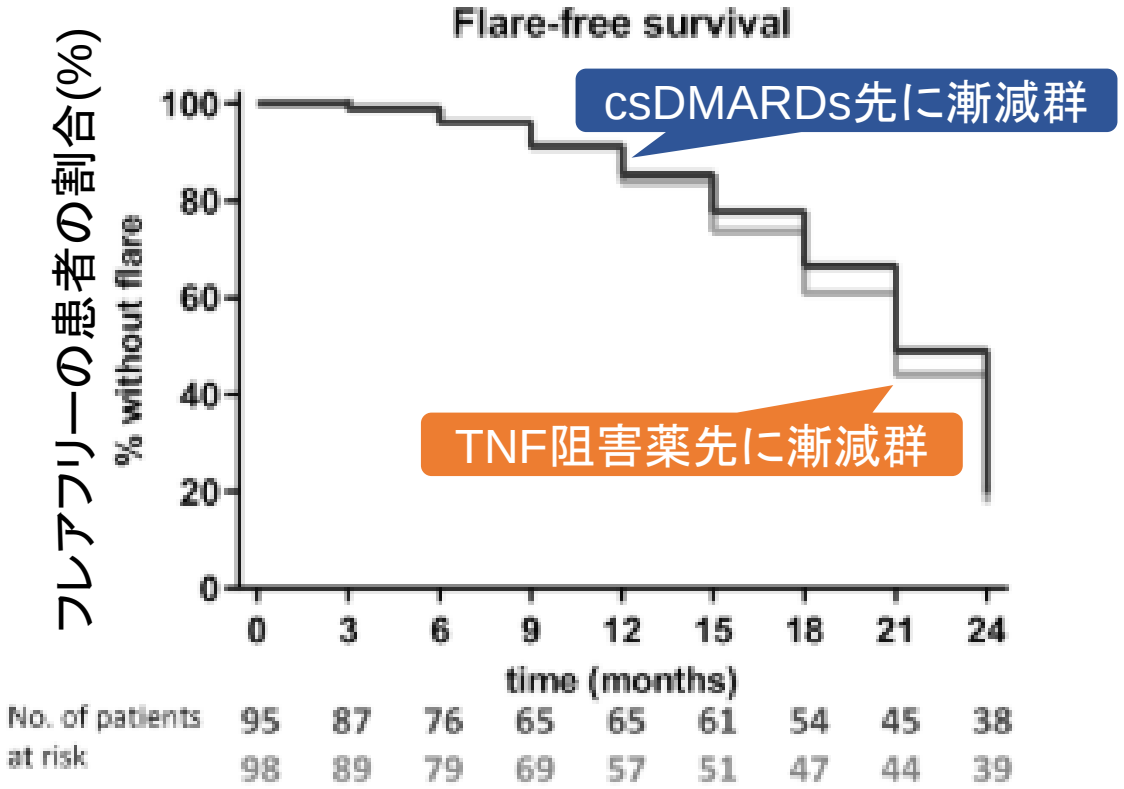
Previous report

csDMARDsとTNFiの漸減順番 RCT (TARA trial)

CLINICAL SCIENCE

Tapering towards DMARD-free remission in established rheumatoid arthritis: 2-year results of the TARA trial

Elise van Mulligen ,[1] Angelique E Weel,[1,2,3] J M Hazes,[1]
Annette van der Helm-van Mil ,[1,4] Pascal Hendrik Pieter de Jong[1]



24か月におけるフレアフリーの割合(%)

- csDMARDs先に漸減群 39%
- TNF阻害薬先に漸減群 38%
  (p=0.48)

csDMARDs、TNF阻害薬の漸減順番は
フレアフリー率に影響しない

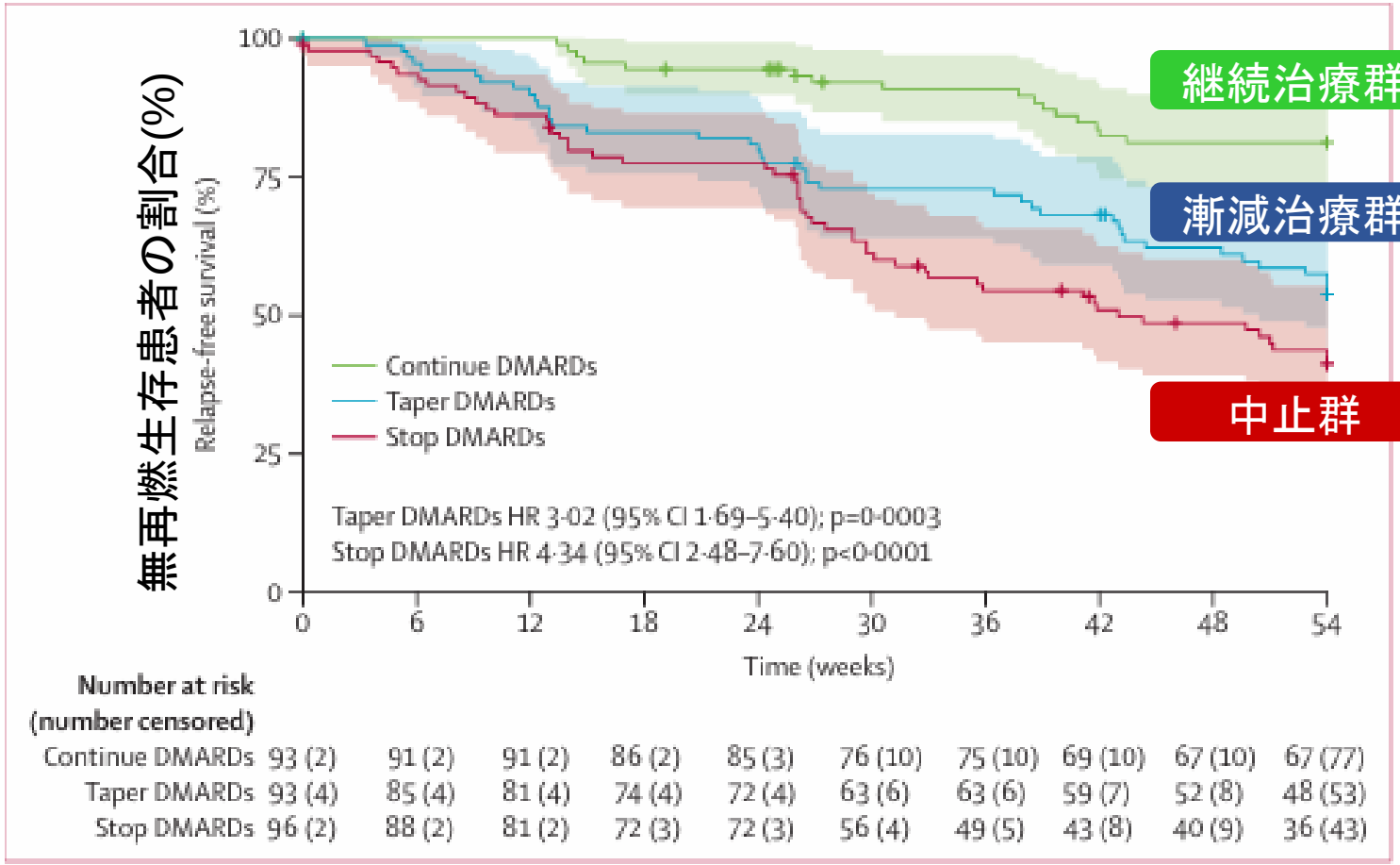
Ann Rheum Dis 2020; 79: 1174–81.

Previous report

DMARDsの減量phase3 RCT (RETRO)

Treatment tapering and stopping in patients with rheumatoid arthritis in stable remission (RETRO): a multicentre, randomised, controlled, open-label, phase 3 trial

Koray Tascilar, Melanie Hagen*, Arnd Kleyer, David Simon, Michaela Reiser, Axel J Hueber, Bernhard Manger, Matthias Englbrecht, Stephanie Finzel, Hans-Peter Tony, Florian Schuch, Stefan Kleinert, Joerg Wendler, Monika Ronneberger, Camille P Figueiredo, Jayme F Cobra, Martin Feuchtenberger, Martin Fleck, Karin Manger, Wolfgang Ochs, Matthias Schmitt-Haendle, Hanns-Martin Lorenz, Hubert Nuesslein, Rieke Alten, Klaus Kruger, Joerg Henes, Georg Schett, Juergen Rech*



52週における無再燃生存患者の割合

- 継続治療群 81.2%
- 漸減治療群 58.6%
- 中止群 43.3%

(Logrank trend 検定; p=0.0005)

DMARDsを漸減しても
約60%で52週寛解を維持できる

Lancet Rheumatol. 2021; 3: e767-77.

Previous report

csDMARDsの減量phase3 RCT (ARCTIC REWIND) 12か月における結果

JAMA | Original Investigation

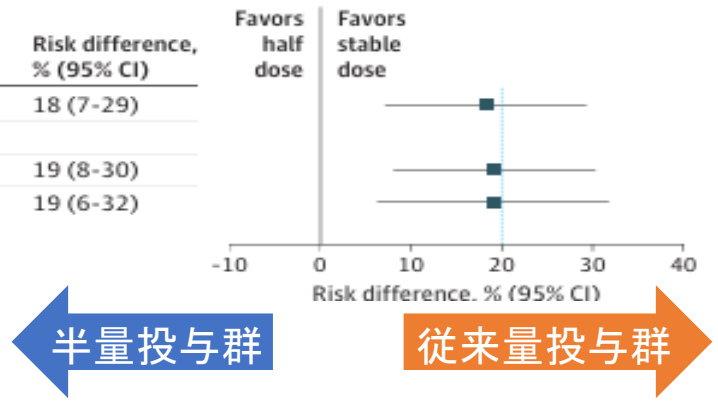
Effect of Half-Dose vs Stable-Dose Conventional Synthetic Disease-Modifying Antirheumatic Drugs on Disease Flares in Patients With Rheumatoid Arthritis in Remission

The ARCTIC REWIND Randomized Clinical Trial

Siri Lillegraven, MD, MPH, PhD; Nina Paulshus Sundlisæter, MD, PhD; Anna-Birgitte Aga, MD, PhD; Joseph Sexton, PhD; Inge C. Olsen, PhD; Hallvard Fremstad, MD; Cristina Spada, MD; Tor Magne Madland, MD, PhD; Christian A. Høili, MD; Gunnstein Bakland, MD, PhD; Åse Lexberg, MD; Inger Johanne Widding Hansen, MD; Inger Myrnes Hansen, MD; Hilde Haukeland, MD; Maud-Kristine Aga Ljoså, MD; Ellen Moholt, RN, Msc; Till Uhlig, MD, PhD; Daniel H. Solomon, MD, MPH; Désirée van der Heijde, MD, PhD; Tore K. Kvien, MD, PhD; Espen A. Haavardsholm, MD, PhD

Figure 2. Flare Rate Within 12 Months (Primary Outcome) in Half-Dose vs Stable-Dose Antirheumatic Drug Treatment

	csDMARD group, No./total No. (%)		
	Half dose	Stable dose	Risk difference, % (95% CI)
Primary analysis[a] フレア率	19/77 (25)	5/78 (6)	18 (7-29)
Additional analyses of primary outcome			
Randomized and initiated therapy[b]	20/78 (26)	5/78 (6)	19 (8-30)
Methotrexate monotherapy[c]	18/66 (27)	5/61 (8)	19 (6-32)



12か月におけるフレア率

- 半量投与群 25%
- 従来量投与群 6%

(p=0.003)

半量投与群は従来量投与群よりも12か月におけるフレアが多かった

JAMA 2021; 325: 1755–64.

Methods

P 2010年ACR/EULARの分類基準を満たすRAで、12か月以上寛解している18-80歳の患者

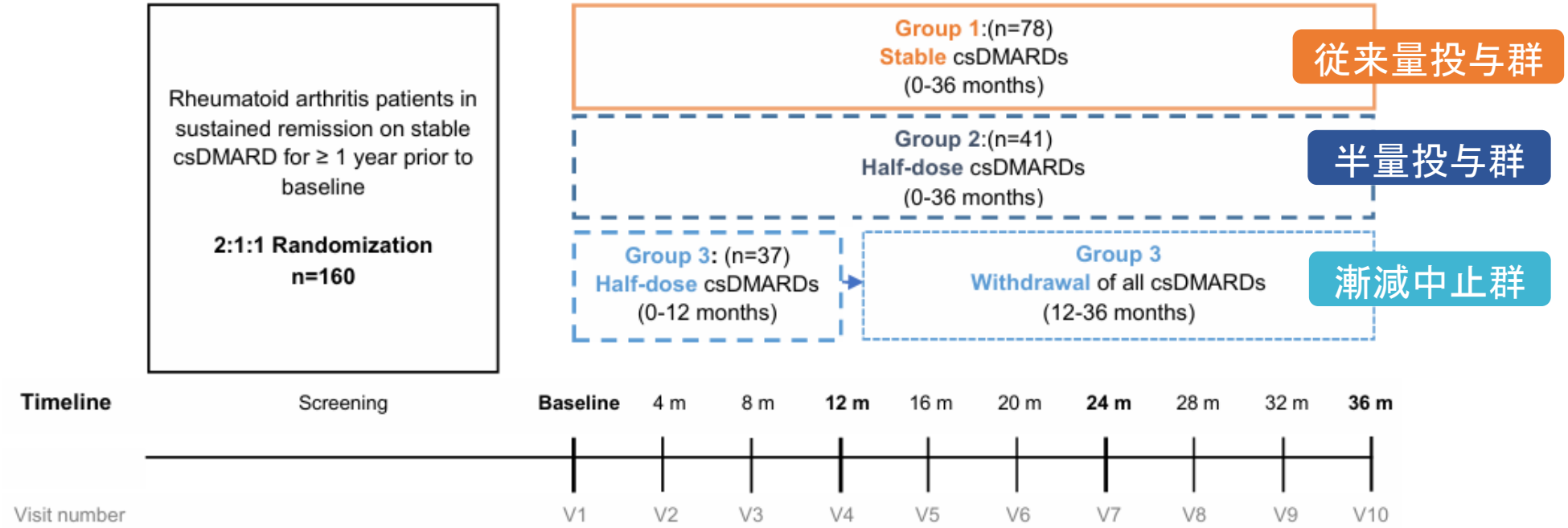
I 従来の半量でcsDMARDsを投与する群
従来の半量で12か月csDMARDs投与後12-36か月で漸減中止する群

C 従来のcsDMARDs治療群

O 36か月のフレアフリー生存率
36か月のACR-EULAR Boolean寛解のリスク差

csDMARDs
メトトレキサート(MTX)、スルファサラジン(SASP)、ヒドロキシクロロキン(HCQ)、レフルノミド(LEF)のうち3剤以下の組み合わせ

フレア
- DAS が1.6以上
- DASが以前の外来より0.6以上増加した場合
- 44関節中少なくとも2関節以上の腫脹



Outcome

Primary Outcome:

- 36か月における
  フレアフリー生存率
  ACR-EULAR Boolean寛解のリスク差

Secondary Outcome:

- DAS寛解、ACR-EULAR Boolean寛解
- DAS28、SDAI、CDAIなどの疾患活動性指標
- 腫脹関節数や圧痛関節数
- CRP、ESR
- 医師VASや患者VAS
- van der Heijde modified Sharp Score
- 超音波検査におけるグレースケール、パワードップラー
- 有害事象

適格基準

2010年 ACR/EULAR分類基準を満たすRA

- 18-80歳の患者
- 2010年1月1日以降に診断
- DAS、DAS28で12か月以上寛解
- 18か月以内の受診で2回連続寛解状態の記載
- 12か月間csDMARDsが変更されていない
- 5mg以下のグルココルチコイド量

除外基準

- 腎障害
- 肝障害
- 大きな合併症

  重篤な悪性腫瘍、重篤な糖尿病、重症感染症、制御不能な高血圧、重篤な心血管疾患(NYHA Ⅲ、Ⅳ)
- 白血球減少、血小板減少
- 妊娠、授乳中
- 活動性結核
- 精神障害、アルコール濫用、薬物濫用

Results

患者背景

	従来治療群 Stable-dose (n=78)	半量投与群 Half-dose (n=41)	漸減中止群 Half-dose 0–12 months, then withdrawal (n=37)
Age, years	55·1 (11·8)	57·0 (12·9)	53·8 (10·9)
Sex			
Female	50 (64%)	30 (73%)	24 (65%)
Male	28 (36%)	11 (27%)	13 (35%)
Time since first swollen joint, years	3·4 (2·6–4·4)	3·1 (2·3–4·5)	3·2 (2·4–4·0)
Current smoker	14 (18%)	5 (12%)	8 (22%)
BMI (kg/m²)	25·7 (22·8–28·4)	25·9 (23·5–28·3)	25·4 (24·1–27·8)
Positive for anti-citrullinated peptide antibodies	57 (73%)	32 (78%)	31 (84%)
Positive for rheumatoid factor	54 (69%)	26 (63%)	27 (73%)
Medication			
Methotrexate monotherapy	61 (78%)	35 (85%)	31 (84%)
Methotrexate monotherapy oral	51 (65%)	26 (63%)	26 (70%)
Methotrexate monotherapy subcutaneous	10 (13%)	9 (22%)	5 (14%)
Methotrexate, sulfasalazine, and hydroxychloroquine	10 (13%)	3 (7%)	3 (8%)
Methotrexate dose in users, mg/week	19·0 (4·7)	19·7 (4·3)	19·5 (4·0)
Sulfasalazine dose in users, mg/day	1769 (438)	1625 (750)	1500 (577)
Hydroxychloroquine dose in users, mg/day	400 (0)	400 (0)	360 (89)
Leflunomide dose in users, mg/day	20·0 (NA)	20·0 (NA)	0 (NA)
Prednisolone	0	2 (5%)	2 (5%)
Prednisolone dose in users, mg/day	0 (0)	3·8 (1·8)	3·1 (2·7)

抗CCP抗体陽性が7～8割、RF陽性が6～7割程度

大部分の患者でメトトレキサートが投与されており、
中央値が19mg/w程度

Results

患者背景

	従来治療群	半量投与群	漸減中止群
Measures of disease activity			
Disease Activity Score	0·8 (0·4)	0·8 (0·3)	0·8 (0·3)
Simplified Disease Activity Index	0·8 (0·5–1·6)	0·8 (0·3–1·9)	1·0 (0·5–2·1)
ACR–EULAR Boolean remission	61 (78%)	28 (68%)	23 (62%)
Simplified Disease Activity Index remission	73 (94%)	34 (83%)	33 (89%)
Swollen-joint count§	0·0 (0·0)	0·0 (0·0)	0·0 (0·0)
Tender-joint count (Ritchie Articular Index)	0·0 (0·0–0·0)	0·0 (0·0–0·0)	0·0 (0·0–0·0)
Erythrocyte sedimentation rate, mm/h (normal value <17mm/h in women and <12mm/h in men)	7·0 (4·0–14·0)	7·0 (5·0–11·0)	7·0 (3·0–14·0)
C-reactive protein, mg/L (normal value <4 mg/L)	2·0 (1·0–3·0)	2·0 (1·0–3·0)	2·0 (1·0–5·0)
Global assessment (0–10)			
Patient	0·4 (0·1–1·0)	0·3 (0·1–1·0)	0·5 (0·1–1·1)
Physician	0·1 (0·0–0·4)	0·0 (0·0–0·2)	0·0 (0·0–0·5)
Functional outcomes			
PROMIS Physical Function	56·1 (7·4)	55·0 (7·8)	56·0 (7·2)
Fatigue VAS (0–100 mm)	5·5 (1·0–24·0)	10·0 (2·0–25·0)	8·0 (1·0–34·0)
Joint pain VAS (0–100 mm)	3·0 (1·0–9·0)	3·0 (1·0–10·0)	5·0 (1·0–10·0)
Radiographic joint damage			
Total van der Heijde modified Sharp score	1·0 (0·0–4·5)	1·0 (0·5–3·5)	1·0 (0·0–2·0)
van der Heijde Sharp Erosion score	0·5 (0·0–2·5)	1·0 (0·5–2·0)	0·5 (0·0–1·0)
van der Heijde Sharp Joint Space Narrowing score	0·0 (0·0–2·0)	0·0 (0·0–1·0)	0·0 (0·0–0·0)
Ultrasound outcomes			
Total power Doppler signal score	0·0 (0·0–0·0)	0·0 (0·0–0·0)	0·0 (0·0–0·0)
Total grey scale score	1·0 (0·0–2·0)	1·0 (0·0–3·0)	1·0 (0·0–3·0)
No power Doppler signal in any joint*	72 (94%)	38 (93%)	34 (92%)

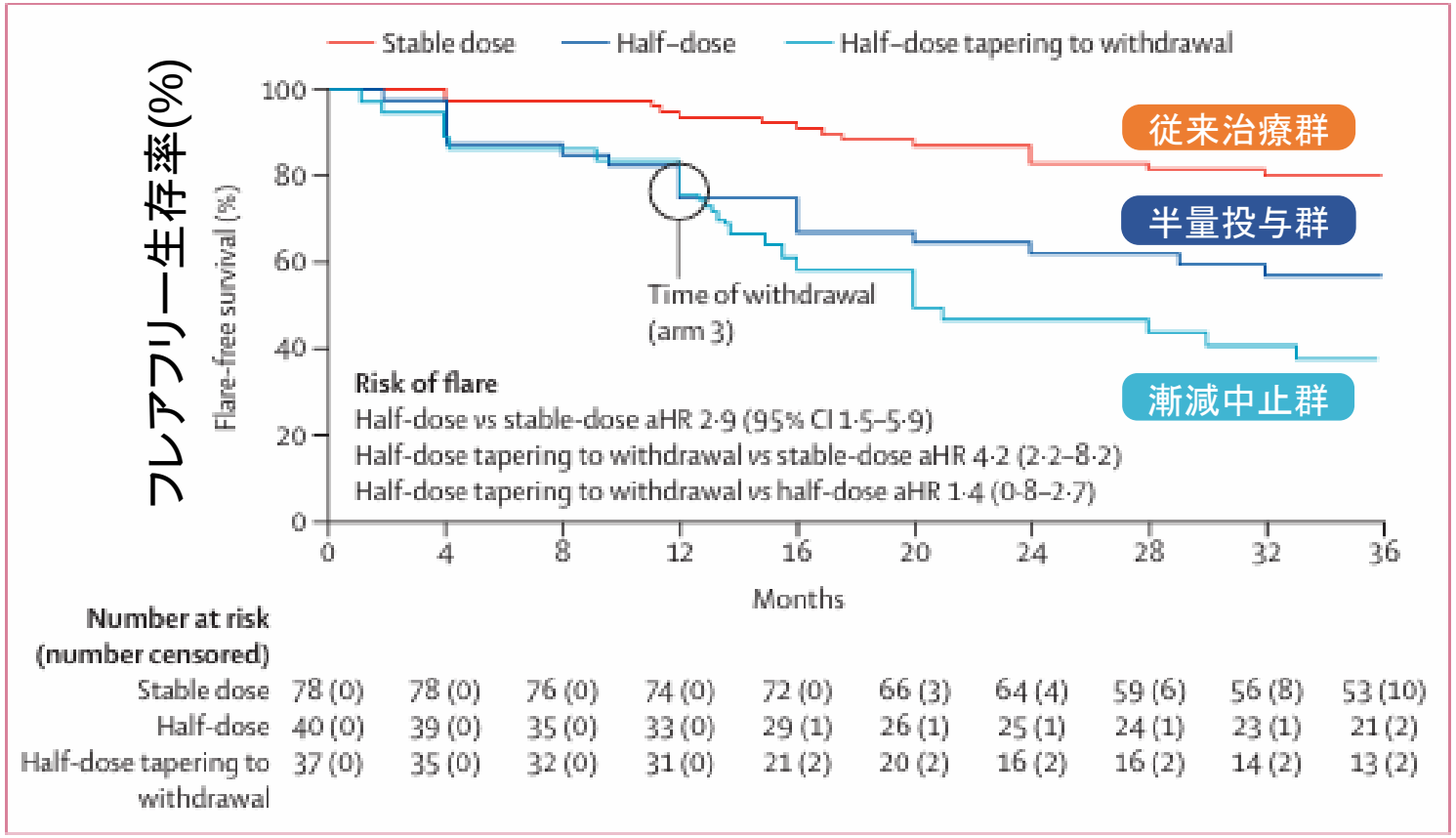
大部分の患者がDAS寛解、SDAI寛解、ACR-EULAR Boolean寛解を満たしている

Van der Heijde modified sharp scoreもどの群も1程度

超音波検査で約90%がPD乗らなかった

Results

Primary endpoint: フレアフリー生存率



80%

57%

38%

- 36か月におけるフレアフリー生存率

従来治療群 80%、半量投与群 57%、漸減中止群　38%

- フレアリスク比

半量投与群は従来治療群と比べて aHR 2.9 (95%CI 1.5-5.9)

漸減中止群は従来治療群と比べて aHR 4.2 (95%CI 2.2-8.2)

フレアフリー生存率は
半量投与群、漸減中止群ともに
従来治療群より有意に低く、
非劣性は示されなかった。

Results

Primary endpoint: 36か月におけるACR-EULAR Boolean寛解

	Remission (unadjusted)			Absolute risk difference*		
	Stable-dose	Half-dose	Half-dose 0–12 months, then withdrawal	Half-dose vs stable-dose†	Half-dose 0–12 months, then withdrawal vs stable-dose†	Half-dose 0–12 months, then withdrawal vs half-dose†
ACR-EULAR Boolean remission						
12 months	56/77 (73%)‡	25/39 (64%)	22/36 (61%)§	−10·3 (−25·2 to 4·5)¶	NA	NA
24 months	47/73 (64%)	21/37 (57%)	20/35 (57%)	−6·7 (−26·0 to 12·6)	−6·2 (−25·6 to 13·1)	0·4 (−21·9 to 22·8)
36 months	55/67 (82%)§	25/36 (69%)	19/34 (56%)§	−11·2 (−29·2 to 6·9)	−24·8 (−43·8 to −5·8)	−13·7 (−35·7 to 8·3)

Data are n/N (%) or absolute risk difference (95% CI) in the per-protocol population. ACR=American College of Rheumatology. EULAR=Alliance of Associations for Rheumatology. NA=Not applicable (same treatment the first 12 months). *Absolute risk difference, calculated with mixed-effect logistic regression with random effects for both patient and study centre, in latter to account for the centre stratification. †Reference group. ‡One patient did not attend the 1-year visit (but attended visits afterwards), and is excluded in the denominator. §One patient did not take blood samples, and is excluded in the denominator. ¶The two groups using half-dose for the first year pooled in this analysis.

Table 2: Remission at 12, 24, and 36 months

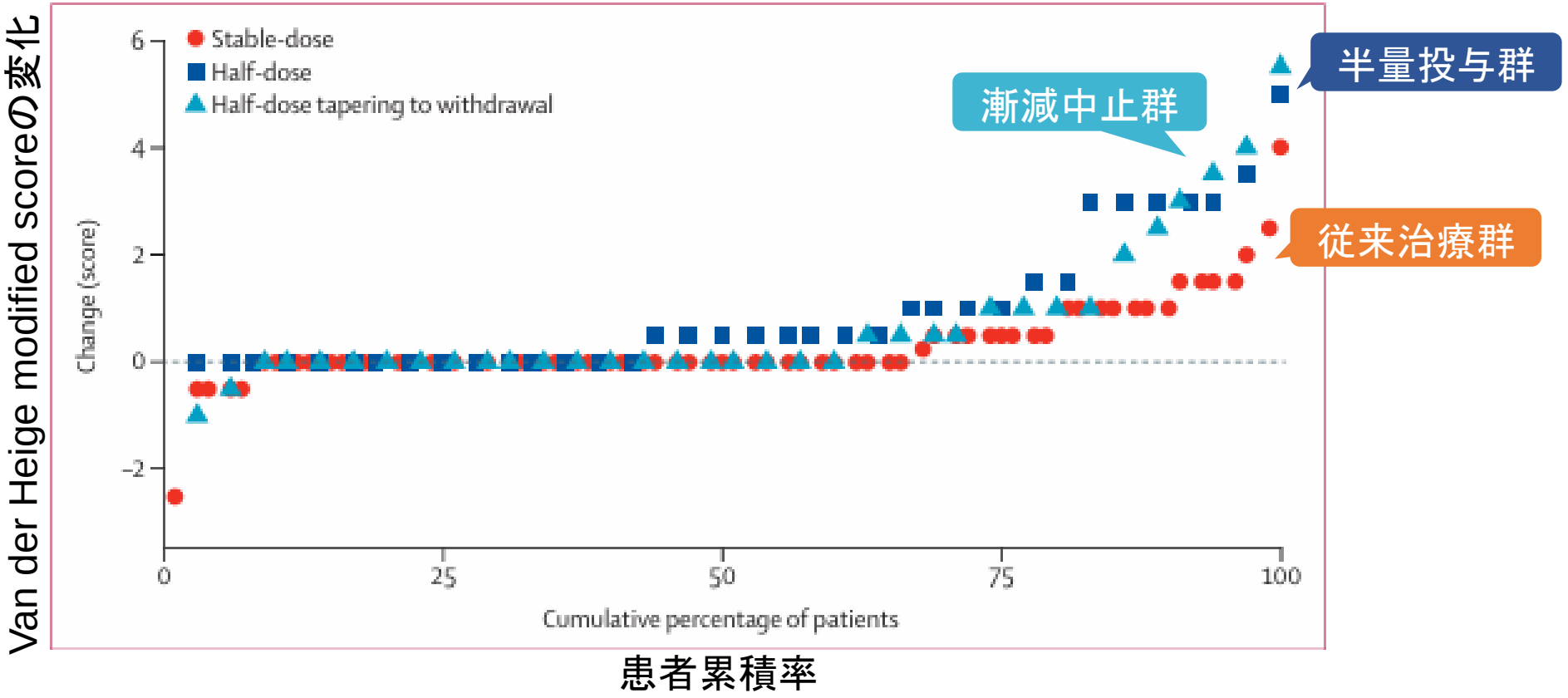
- 半量投与群 vs 従来治療群
  ACR−EULAR Boolean寛解のリスク差
  -11.2 (95%CI -29.2 to -6.9)

- 漸減中止群 vs 従来治療群
  ACR−EULAR Boolean寛解のリスク差
  -24.8 (95%CI -43.8 to -5.8)

半量投与群、漸減中止群ともに、
従来治療群よりも
ACR−EULAR Boolean寛解になりにくい

Results

Secondary endpoint: van der Heidge modified score



- **36か月におけるVan der Heige modified scoreの変化**

中央値：従来治療群 0.0 (0.0-0.5)、半量投与群 0.5 (0.0-1.3)、漸減中止群 0.0(0.0-1.0)

半量投与群が従来治療群より関節の損傷が進行

Results

有害事象

	従来治療群 Stable-dose (n=78)	半量投与群 Half-dose (n=40)	漸減中止群 Half-dose 0–12 months, then withdrawal (n=37)
Patients with ≥1 adverse events	65 (83%)	36 (90%)	36 (97%)
Patients with ≥3 adverse events	39 (50%)	19 (48%)	13 (35%)
Number of adverse events per person	2·8 (2·1)	3·0 (2·6)	2·3 (1·5)
Patients with serious adverse events	13 (17%)	4 (10%)	6 (16%)
Adverse events of special interest			
Any type of infection*	40 (51%)	20 (50%)	13 (35%)
Gastrointestinal symptoms†	14 (18%)	7 (18%)	9 (24%)
Cancer‡	2 (3%)	0	3 (8%)
Death	1 (1%)	0	0

- 有害事象
  従来治療群 83%、半量投与群 90%、漸減中止群 97%
- 重篤な有害事象
  従来治療群 17%、半量投与群 10%、漸減中止群 16%
- 感染症
  従来治療群 51%、半量投与群 50%、漸減中止群 35%

有害事象に大きな差はなし

Discussion

- 持続寛解期にある関節リウマチ患者において、半量投与群、漸減中止群ともに、フレアフリー生存率は従来治療群と比較して非劣性は証明されなかった

- 関節X線では従来のcsDMARDsの治療群の方が半量投与群より関節破壊の進行は有意に少なかった

Limitation

- 非盲検試験である
- メトトレキサートの治療を受けていない患者に一般化できない
- 異なる段階的な漸減方法や突然の中止を行った場合には、結果が異なる可能性がある
- 半量投与群と漸減中止群との間でflareリスクに有意差がなかったのは、検出力が不十分で可能性がある