関節リウマチの治療
~Sarilumab~

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1. SarilumabのLandmark study
   - -MOBILITY
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3. 有効性
4. 安全性と免疫原性

Clinical and epidemiological research

OPEN ACCESS

EXTENDED REPORT

Sarilumab, a fully human monoclonal antibody against IL-6Rα in patients with rheumatoid arthritis and an inadequate response to methotrexate: efficacy and safety results from the randomised SARIL-RA-MOBILITY Part A trial

Tom W J Huizinga,[1] Roy M Fleischmann,[2] Martine Jasson,[3] Allen R Radin,[4] Janet van Adelsberg,[4] Stefano Fiore,[5] Xiaohong Huang,[5] George D Yancopoulos,[4] Neil Stahl,[4] Mark C Genovese[6]

- MTX-IRにSAR+MTXはPBOに対してACR20を達成.
- 用量依存性に効果あり.

[Ann Rheum Dis. 2014 Sep;73(9):1626-34.]

＊Phase II, randomised, double-blind,placebo-controlled, multicentre, dose-ranging study.

MTX-IR(n=360)にSAR+MTXがPBOに対して12w時点でのACR 20 response rate(primary)を検証.

Secondary outcome: ACR50,70 response rate, ベースラインからの疾患活動性変化(DAS28,HAQなど)

SAR: **100**mg qw or q2w, **150**mg qw or q2w, **200mg** q2w vs PBO

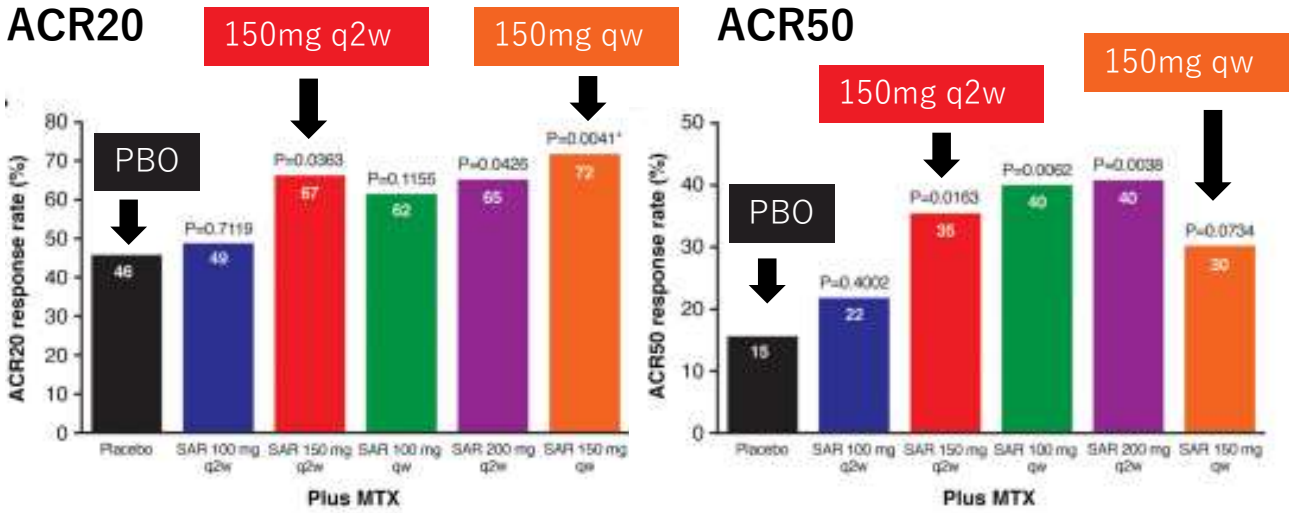
● 12週ACR20 response rate

150mg qw 72%(p=0.0041) vs PBO 46.2%

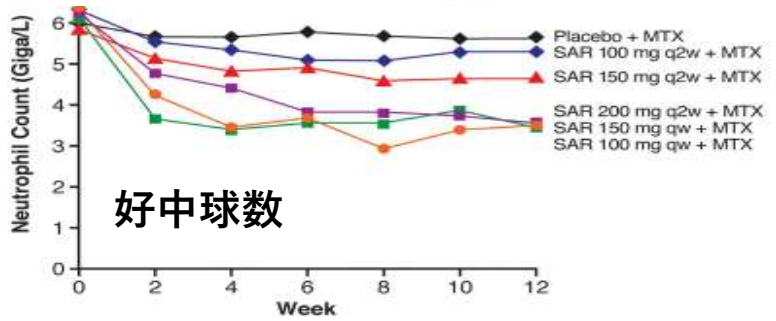
150mg q2w 67%(p=0.0363) vs PBO 46.2%

200mg q2w 65%(p=0.0426) vs PBO 46.2%

ACR 50,70も150mg q2w(300mg/月)以上で高い奏効率.



- 100mg q2wは12w目に血中濃度ゼロ.
- IL-6は上昇.



・重篤な有害事象の発生率に用量依存傾向は見られなかった.

・用量依存的に好中球は減少. 感染症とは関連せず.

・150mg q2w以上でPBOより感染症は多い.

Sarilumab Plus Methotrexate in Patients With Active Rheumatoid Arthritis and Inadequate Response to Methotrexate

Results of a Phase III Study

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■ MTX-IRでSAR+MTXはPBOよりACR20, HAQ-DI, mTSSに有効

[Arthritis Rheumatol. 2015 Jun;67(6):1424-37.]

＊multicenter, randomized, double-blind, placebo-controlled study.

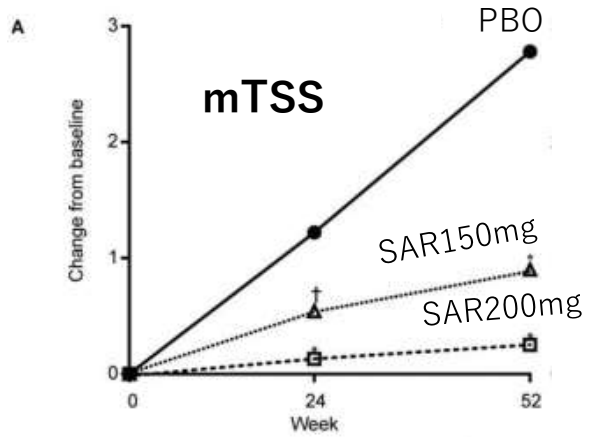
MTX-IR(n=1197)に対してSAR+MTXが24w時点でのACR 20 response rate, 16週時点でのHAQ-DIの変化, 52w時点でのmTSSを検証.

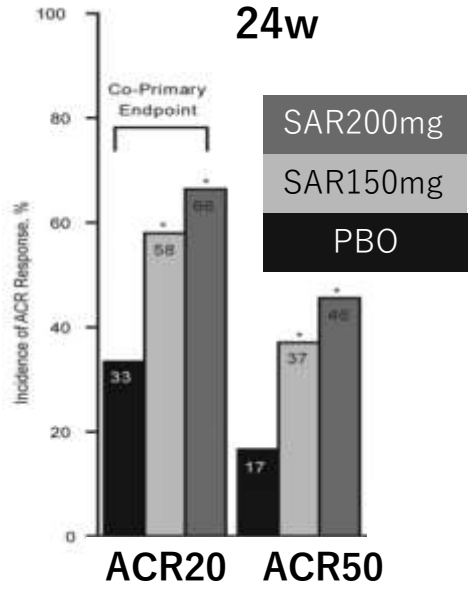
SAR:**150**mg q2w or **200**mg q2w vs PBO.

- ACR20 at 24w, HAQ-DI at 16w, mTSS at 52wはSAR群(150or200)で有意差あり(p=0.0001)
- ACR50,70もPBOと比較して有効.

	Placebo + MTX (n = 398)	Sarilumab 150 mg every 2 weeks + MTX (n = 400)	Sarilumab 200 mg every 2 weeks + MTX (n = 399)
Signs and symptoms			
ACR20 response at week 24, % (no./total)†	33.4 (133/398)	58.0 (232/400)‡	66.4 (265/399)‡
ACR core set of disease activity measures, adjusted mean change from baseline at week 24, using MMRM			
Swollen joint count (of 66 joints assessed)	−6.6 ± 0.45	−10.6 ± 0.42‡	−11.3 ± 0.42‡
Tender joint count (of 68 joints assessed)	−10.1 ± 0.69	−16.9 ± 0.66‡	−17.4 ± 0.66‡
Patient's global assessment by VAS, mm	−15.7 ± 1.36	−28.3 ± 1.29‡	−32.9 ± 1.28‡
Physician's global assessment by VAS, mm	−24.6 ± 1.23	−37.5 ± 1.17‡	−40.3 ± 1.16‡
Patient's assessment of pain by VAS, mm	−15.4 ± 1.42	−28.5 ± 1.35‡	−31.8 ± 1.34‡
HAQ DI	−0.3 ± 0.03	−0.6 ± 0.03‡	−0.6 ± 0.03‡
CRP, mg/dl	−0.0 ± 0.12	−1.3 ± 0.12‡	−1.7 ± 0.12‡
ACR20 response at week 52, % (no./total)	31.7 (126/398)	53.5 (214/400)‡	58.6 (234/399)‡
Major clinical response (ACR70 response maintained for 24 weeks), % (no./total)†	3.0 (12/398)	12.8 (51/400)‡	14.8 (59/399)‡
DAS28-CRP response at week 24, % (no./total)			
Score <2.6†	10.1 (40/398)	27.8 (111/400)‡	34.1 (136/399)‡
Score ≤3.2	16.8 (67/398)	39.8 (159/400)‡	49.1 (196/399)‡
CDAI response (score ≤ 2.8) at week 24, % (no./total)	5.0 (20/398)	10.3 (41/400)‡	13.8 (55/399)‡
Physical function			
HAQ DI, adjusted mean change from baseline at week 16, using MMRM†	−0.29 ± 0.03	−0.53 ± 0.03‡	−0.55 ± 0.03‡
HAQ DI response (MCID ≥0.3), no. (%)			
At week 16	169 (42.5)	215 (53.8)‡	229 (57.4)‡
At week 24	133 (33.4)	204 (51.0)‡	205 (51.4)‡
At week 52	104 (26.1)	188 (47.0)‡	190 (47.6)‡
Radiographic progression			
Mean change from baseline in SHS at week 52, using rank ANCOVA†	2.78 ± 7.73	0.90 ± 4.66‡	0.25 ± 4.61‡
No radiographic progression, % (no./total)			
At week 24	39.7 (158/398)	46.3 (185/400)	56.6 (226/399)‡
At week 52†	38.7 (154/398)	47.8 (191/398)‡	55.6 (222/398)‡

- 重篤な感染症: 150 mg 2.6%, 200mg 4.0%, PBO 2.3%.
- 好中球減少(500~1000):150mg 5.1%, 200mg 7.8%
- 多くの有害事象は軽症から中等症.
- Adverse eventは用量依存性.






Efficacy and safety of sarilumab monotherapy versus adalimumab monotherapy for the treatment of patients with active rheumatoid arthritis (MONARCH): a randomised, double-blind, parallel-group phase III trial

- SAR monoの有用性を証明.
- ADAよりもDAS28-ESRを改善.

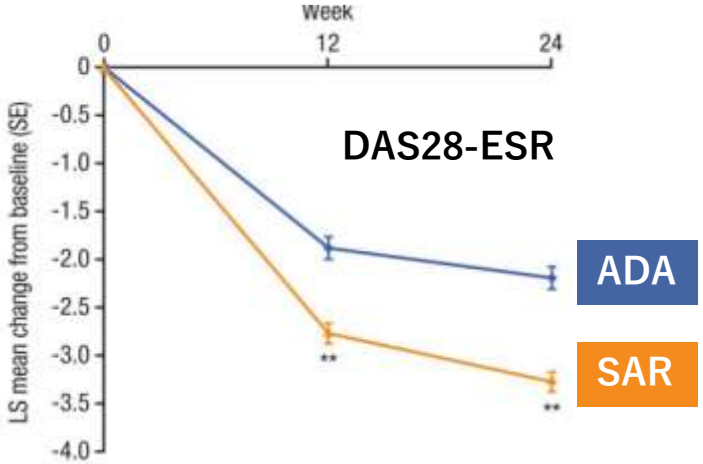
[Ann Rheum Dis. 2017 May;76(5):840-847.]

＊multicentre, randomised, active-controlled,double-blind, double-dummy, phase III superiority trial

MTX-IR or intolerantに対する**ADA** 40mg q2w mono(n=185) **vs SAR** 200mg q2wmono(n=184).

Primary: 24wでのDAS28-ESRの変化, Secondary: DAS28-ESR<2.6など

16wで効果不十分ならADA q2w→qwにdose up可能.



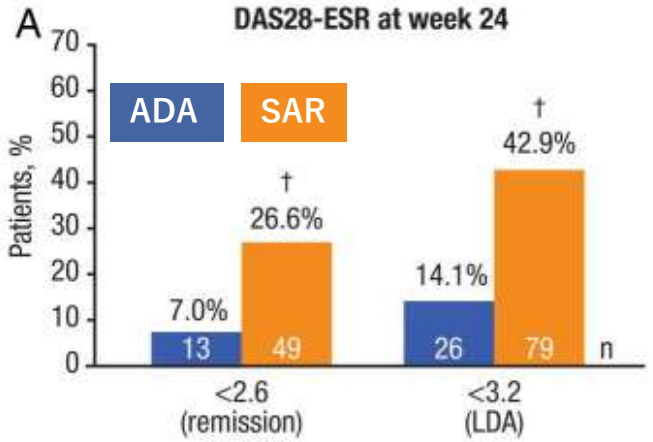


Table 3 Safety results

n (%)	Adalimumab 40 mg q2w (n=184)*	Sarilumab 200 mg q2w (n=184)
Overall results		
Patients with any AE	117 (63.6)	118 (64.1)
Patients with any SAE	12 (6.5)	9 (4.9)
Patients with any AE that led to treatment discontinuation	13 (7.1)	11 (6.0)
AEs (≥3% in any treatment group)		
Infections	51 (27.7)	53 (28.8)

- 12w,24wでDAS28-ESRの低下率 SAR>ADA(p<0.0001).
- LDA, remission率もSARが高い.

- ACR20/50/70(all p≤0.0074)
  SAR: 71.7%/45.7%/23.4% vs ADA: 58.4%/29.7%/11.9%
- HAQ-DI, SF-36 PCS, FACIT-FもSAR>ADA

- Adverse eventと中止率はSAR=ADA.
- 好中球減少はSAR>ADA, 感染症は同等.
- SARの抗体は13例, 中和抗体はなし.

TARGET study

TNFi-IRからSARの変更は有用

Sarilumab and Nonbiologic Disease-Modifying Antirheumatic Drugs in Patients With Active Rheumatoid Arthritis and Inadequate Response or Intolerance to Tumor Necrosis Factor Inhibitors

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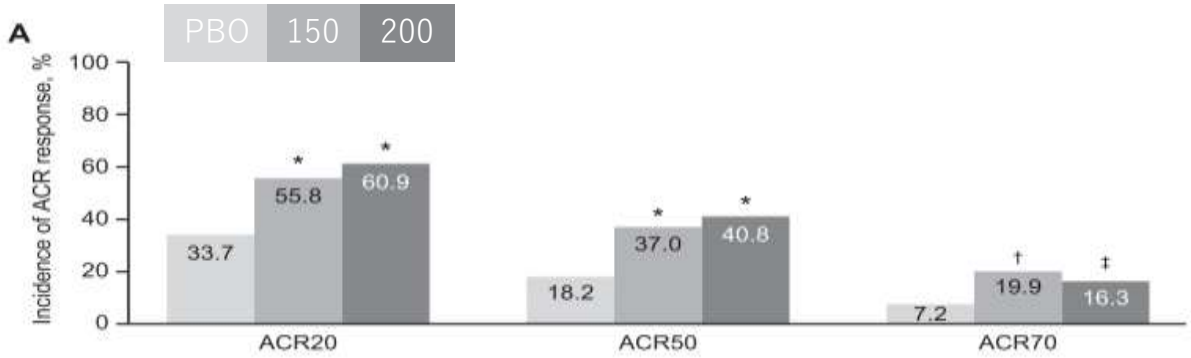
[Arthritis Rheumatol. 2017 Feb;69(2):277-290.]

TNFi-IR(n=546)に対してSARの有効性を検証した研究.

＊3-arm, multicenter, randomized, double-blind, placebo-controlled, phase III study

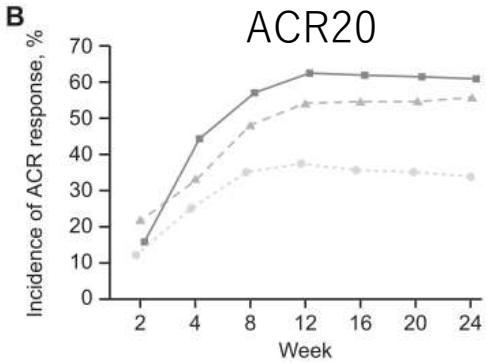
SAR 150mg or 200mg or **PBO**＋csDAMRDs(MTX, LEF, SASP, HCQ).

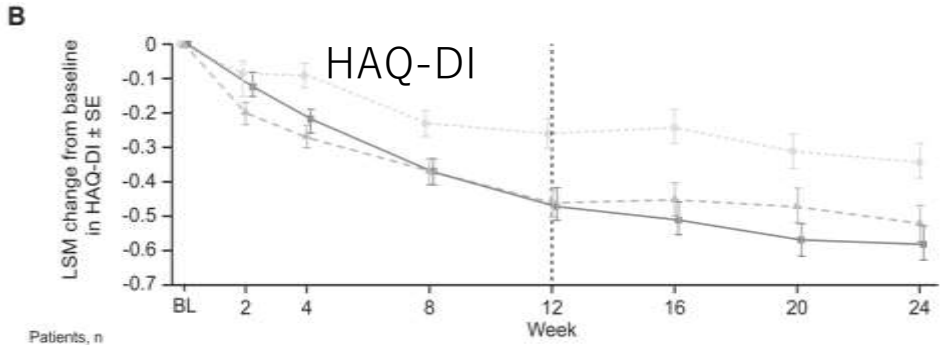
Primary:24w時点でのACR20 responseと12w時点でのHAQ-DIの変化.



	Placebo plus csDMARD(s) (n = 181)	Sarilumab 150 mg every 2 weeks plus csDMARD(s) (n = 181)	Sarilumab 200 mg every 2 weeks plus csDMARD(s) (n = 184)
Patient-years of exposure	65.0	69.8	72.5
AEs	90 (49.7)	119 (65.7)	120 (65.2)
Serious AEs	6 (3.3)	6 (3.3)	10 (5.4)
AEs leading to treatment discontinuation	8 (4.4)	14 (7.7)	17 (9.2)
AEs leading to death	1 (0.6)	0	0
AEs according to system organ class			
Infections and infestations	48 (26.5)	40 (22.1)	56 (30.4)
Urinary tract infection	12 (6.6)	6 (3.3)	13 (7.1)
Nasopharyngitis	9 (5.0)	11 (6.1)	7 (3.8)
Pharyngitis	3 (1.7)	2 (1.1)	6 (3.3)
Upper respiratory tract infection	6 (3.3)	4 (2.2)	6 (3.3)
Blood and lymphatic disorders	9 (5.0)	25 (13.8)	29 (15.8)
Neutropenia	2 (1.1)	23 (12.7)	23 (12.5)
Thrombocytopenia	0	0	5 (2.7)
Leukopenia	0	2 (1.1)	3 (1.6)
Anemia	5 (2.8)	0	1 (0.5)

- 24wのACR20/50/70, 12wのHAQ-DIはPBOと有意差あり.
- 8w目までにACR20, HAQ-DIは4週目までに有意差を達成.





- PBOよりAEは多い.
- SAR中止理由は, 感染症, 好中球減少, 肝機能障害.
- GI perforationなし.
- 抗SAR抗体:150mg 6.1%, 200mg 4.9%

ASCERTAIN study

SARとTCZの安全性と忍容性は同等

Safety and tolerability of subcutaneous sarilumab and intravenous tocilizumab in patients with rheumatoid arthritis

Paul Emery[1], Juan Rondon[2], Janie Parrino[3], Yong Lin[4], Claudia Pena-Rossi[4], Hubert van Hoogstraten[4], Neil M. H. Graham[3], Nancy Liu[4], Anne Paccaly[3], Richard Wu[3,*] and Alberto Spindler[5]

[Rheumatology (Oxford). 2019 May 1;58(5):849-858.]

- ASCERTAIN study: TNFi-IR(n=202)に**SAR**(150,200)と**TCZ iv**の安全性と忍容性を評価した研究.

＊international, multicentre, 24-week, randomized, double-blind, double-dummy, parallel-group, three-arm study.

- Study 1309: MTX-IR(n=101)にSARとTCZ ivのPK, PD, 好中球数などを観察する研究.

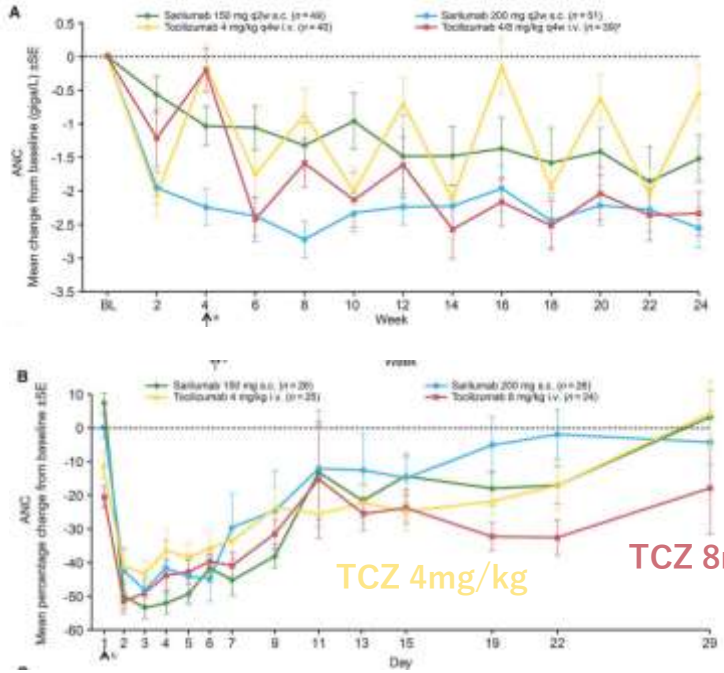
- adverse eventsは, 2つの研究でSARとTCZは同等.
- 重篤な有害事象もほぼなし.

有害事象	ASCERTAIN			Study 1309			
AE	Tocilizumab q4w i.v. + csDMARDs (n = 102)[a]	Sarilumab 150 mg q2w s.c. + csDMARDs (n = 49)	Sarilumab 200 mg q2w s.c. + csDMARDs (n = 51)	Tocilizumab 4 mg/kg i.v. + MTX (n = 25)	Tocilizumab 8 mg/kg i.v. + MTX (n = 24)	Sarilumab 150 mg s.c. + MTX (n = 26)	Sarilumab 200 mg s.c. + MTX (n = 26)
AE	68 (66.7)	33 (67.3)	36 (70.6)	8 (32.0)	12 (50.0)	10 (38.5)	12 (46.2)
SAE	7 (6.9)	1 (2.0)	3 (5.9)	0	1 (4.2)	0	0
Serious infection	2 (2.0)	0	1 (2.0)	0	0	0	0
AE leading to death	1 (1.0)	0	0	0	0	0	0
AE leading to treatment discontinuation	4 (3.9)	6 (12.2)	8 (15.7)	0	0	0	0
ANC[b]							
0.5-<1.0, giga/l	1 (1.0)	2 (4.2)	5 (9.8)	3 (12.0)	6 (25.0)	4 (15.4)	6 (23.1)
<0.5, giga/l	0	1 (2.1)	0	0	0	0	1 (3.8)
ALT[b]							
>3-5 × ULN	3 (3.0)	2 (4.3)	2 (3.9)	0	1 (4.2)	0	1 (3.8)
>5 × ULN	0	0	1 (2.0)	0	1 (4.2)	0	0
Platelet count[b]							
<100, giga/l	0	1 (2.1)	0	0	0	2 (7.7)	0

ASCERTAINでは, 好中球減少(<1000)はSAR>TCZ(平均変化は同じ.) Study 1309は同等だが, 用量依存性に減少.

- 投与数時間後から好中球は低下している.
- SARのみで血小板低下(<10万)あり.

好中球減少の変化



- 投与直前までに好中球数は上昇する傾向.
- SARはベースラインまで早く戻る.
- TCZ 4mgは戻るが, 8mg/kgは戻らず.


RESEARCH Open Access

Sarilumab plus methotrexate in patients with active rheumatoid arthritis and inadequate response to methotrexate: results of a randomized, placebo-controlled phase III trial in Japan

日本人もMTX-IRにSARが有効.

[Arthritis Res Ther. 2019 Mar 20;21(1):79.]

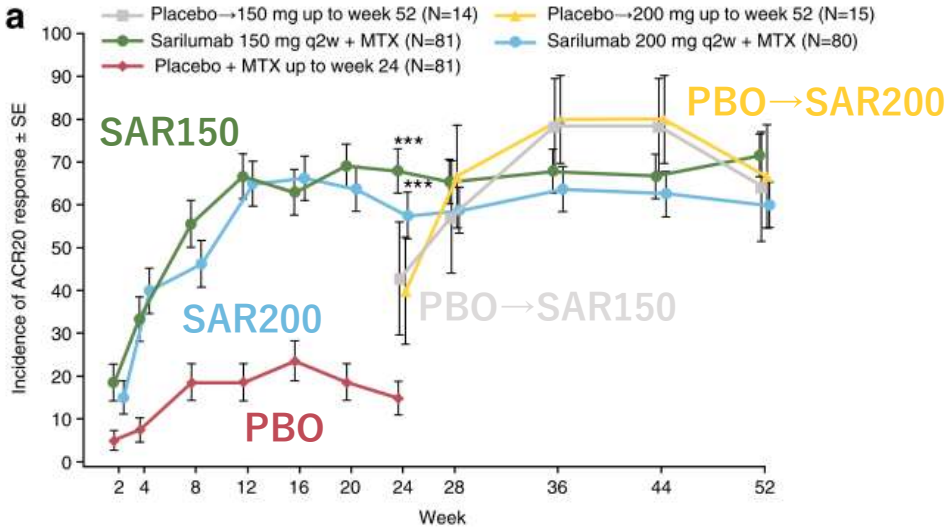
日本人(n=243)＊multicenter,randomized, 52-week, parallel-group study.

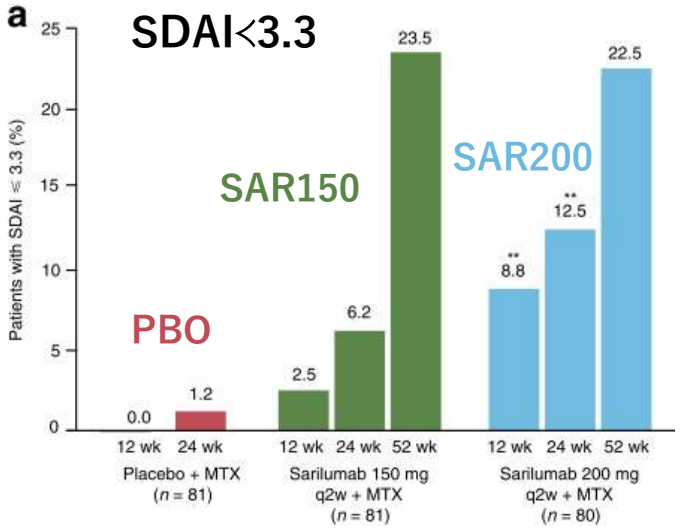
24wは盲検化, 以降の28wはPBOはSAR150mg or 200mgに切り替え.

TNFi使用歴があれば除外.

MTX-IRに**SAR**150mg, 200mgで24週時点でのACR20を評価.

- ACR20 at 24w:150mg 67.9%, 200mg 57.5%, PBO 14.8%(p<0.001).
- PBOからSAR切り替え後の52wもACR20は150mg 64%, 200mg 66%.
- ACR50/70も同様に効果あり.





- SDAI<3.3やCRP<0.02の割合は200mg群で多い(post hoc).
- PBOの半数はrescue.

- 安全性
- 150mgと200mgで安全性は同等.
- AEでGI perforationなし.
- 感染症：鼻咽頭炎・上気道炎
- 好中球減少(感染と関連せず):

  >1000 150mg 42%, 200mg 46.3%.

  <1000 150mg 13.6%, 200mg 7.5%.

HARUKA study

Non MTX-csDMARDs+SARの有効性と安全性.

Sarilumab monotherapy or in combination with non-methotrexate disease-modifying antirheumatic drugs in active rheumatoid arthritis: A Japan phase 3 trial (HARUKA)

Hideto Kameda[a], Kazuteru Wada[b], Yoshinori Takahashi[b], Owen Hagino[c], Hubert van Hoogstraten[d], Neil Graham[e] and Yoshiya Tanaka[f]

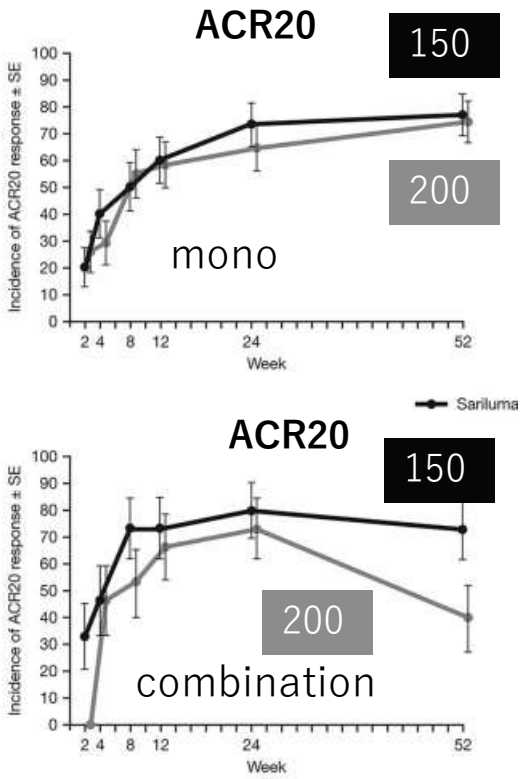
[Mod Rheumatol. 2020 Mar;30(2):239-248.]

MTX-IRに対して**SAR mono** or **SAR**+non-MTXの**csDMARDs**の有効性と安全性を検証.

＊multicenter,randomized, double-blind, 52-week study.

4群(n=91): SAR mono (150mg, 200mg), combination of SAR (150mg, 200mg) + nonMTX csDAMRDs.

Primaryは長期の安全性. SecondaryはACR20/50/70, HAQ-DIなど



- Monoとcombinationとも150と200でACR20/50/70の反応率は同等.
- 頻度の高いTEAEは鼻咽頭炎と好中球減少.
- 重篤な有害事象は, 150-mono 3.3%, 200-mono 6.5%, 150-comb 0%, 200-comb 20%
- 最も多い重篤な有害事象は感染症, zoster, 肺炎, 眼窩周囲膿瘍など.
- 好中球<500はいない

	Sarilumab			
	150 mg q2w (n= 30)	200 mg q2w (n= 31)	150 mg q2w + non-MTX csDMARDs (n= 15)	200 mg q2w + non-MTX csDMARDs (n= 15)
AEs	25 (83.3)	28 (90.3)	14 (93.3)	13 (86.7)
Serious AEs	1 (3.3)	2 (6.5)	0	3 (20.0)
AEs leading to permanent treatment discontinuation	1 (3.3)	0	2 (13.3)	5 (33.3)
AEs leading to death	0	0	0	0
Most frequent AEs by system organ class and preferred term				
Infections and infestations	21 (70.0)	16 (51.6)	5 (33.3)	6 (40.0)
Nasopharyngitis	13 (43.3)	14 (45.2)	4 (26.7)	5 (33.3)
Gastroenteritis	1 (3.3)	1 (3.2)	2 (13.3)	0
Blood and lymphatic disorders	2 (6.7)	5 (16.1)	5 (33.3)	4 (26.7)
Neutropenia	1 (3.3)	3 (9.7)	5 (33.3)	3 (20.0)
Nervous system disorders	4 (13.3)	3 (9.7)	1 (6.7)	3 (20.0)
Dizziness	2 (6.7)	1 (3.2)	0	2 (13.3)
Respiratory, thoracic and mediastinal disorders	7 (23.3)	4 (12.9)	0	2 (13.3)
Oropharyngeal pain	3 (10.0)	2 (6.5)	0	0
Gastrointestinal disorders	9 (30.0)	10 (32.3)	3 (20.0)	5 (33.3)
Stomatitis	3 (10.0)	4 (12.9)	3 (20.0)	4 (26.7)
Hepatobiliary disorders	1 (3.3)	5 (16.1)	1 (6.7)	0
Hepatic function abnormal	1 (3.3)	4 (12.9)	1 (6.7)	0
Musculoskeletal and connective tissue disorders	6 (20.0)	5 (16.1)	6 (40.0)	1 (6.7)
RA	4 (13.3)	2 (6.5)	1 (6.7)	0
General disorders and administration site conditions	3 (10.0)	9 (29.0)	3 (20.0)	1 (6.7)
Injection site erythema	1 (3.3)	6 (19.4)	0	1 (6.7)
Injury, poisoning and procedural complications	6 (20.0)	4 (12.9)	4 (26.7)	3 (20.0)
Contusion	2 (6.7)	0	3 (20.0)	0

	Sarilumab			
	150 mg q2w (n= 30)	200 mg q2w (n= 31)	150 mg q2w + non-MTX csDMARDs (n= 15)	200 mg q2w + non-MTX csDMARDs (n= 15)
Absolute neutrophil count, n (%)				
Grade 1: ≥1.5 Giga/L to < LLN	8 (26.7)	8 (25.8)	0	1 (6.7)
Grade 2: ≥1 to <1.5 Giga/L	6 (20.0)	9 (29.0)	3 (20.0)	8 (53.3)
Grade 3: ≥0.5 to <1 Giga/L	2 (6.7)	4 (12.9)	5 (33.3)	3 (20.0)
Grade 4: <0.5 Giga/L	0	0	0	0

Sample sizeが少ない, 離脱者++.

1. SarilumabのLandmark study
   - -MOBILITY
   - -NOMARCH
   - -TARGET
   - -ASCERTAIN
   - -KAKEHASI
   - -HARUKA
2. Open Label Extension
3. 有効性
4. 安全性と免疫原性

MOBILITY

Two years of sarilumab in patients with rheumatoid arthritis and an inadequate response to MTX: safety, efficacy and radiographic outcomes

Mark C. Genovese[1], Janet van Adelsberg[2,*], Chunpeng Fan[3], Neil M. H. Graham[2], Hubert van Hoogstraten[3], Janie Parrino[2], Erin K. Mangan[2], Alberto Spindler[4], Tom W. J. Huizinga[5] and Désirée van der Heijde[5]; for the EXTEND study investigators

2年間で重篤な有害事象の増加なく, 有効性を維持し関節破壊を抑制.

[Rheumatology (Oxford). 2018 Aug 1;57(8):1423-1431.]

MOBILITY studyのopen label extension(OLE) study.

2年間延長され,有効性と安全性を検証.

OLE studyでは, 全ての患者がSAR200mg q2w+MTXに変更.

- Safety

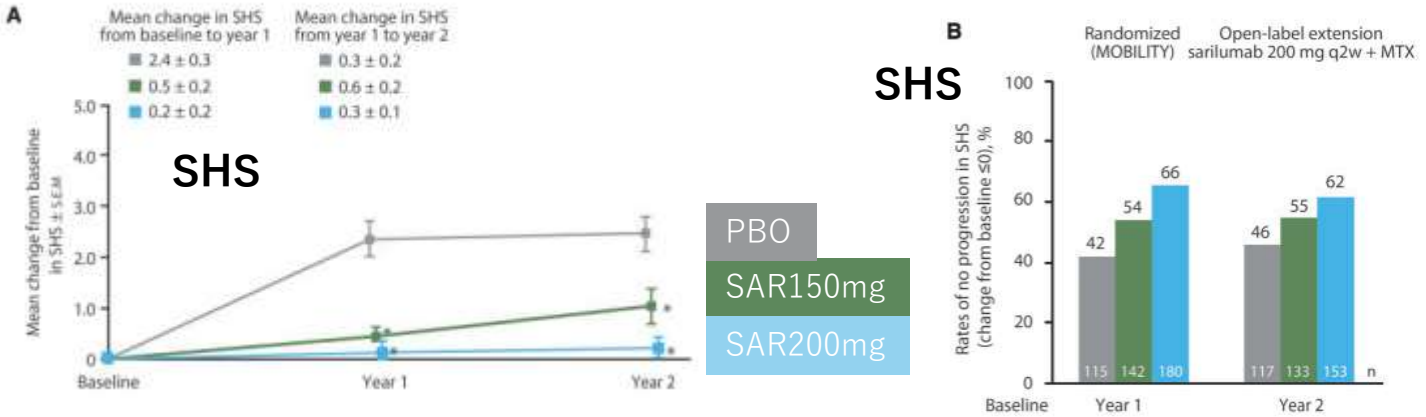
好中球減少症(20.6 events/100PY)

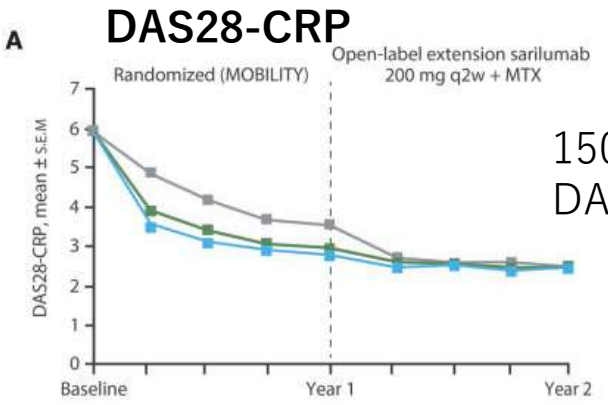
注射部位紅斑(20.2events/100PY)

上気道感染症(9.6 events/100PY).

GI perforation(0.1 events/100 PY, 2名の憩室炎の内, 1名)

	MOBILITY			EXTEND (OLE)		
		Sarilumab			Sarilumab	
	Placebo + MTX (n=398)	150 mg q2w + MTX (n=400)	200 mg q2w + MTX (n=399)	Placebo + MTX (n=307)	150 mg q2w + MTX (n=300)	200 mg q2w + MTX (n=294)
Female, n (%)	321 (81)	319 (80)	337 (84)	246 (80)	241 (80)	246 (84)
Age, mean (s.d.), years	50.9 (11.2)	50.1 (11.9)	50.8 (11.8)	50.8 (10.7)	50.3 (11.8)	50.2 (11.6)
Prior biologic DMARD use, n (%)	86 (22)	87 (22)	84 (21)	71 (23)	75 (25)	64 (22)
Duration of RA, mean (range), years	9 (0–44)	10 (0–45)	9 (0–34)	9 (0–44)	10 (0–45)	9 (0–34)
Seropositive for RF, n (%)	336 (84)	345 (87)[a]	328 (83)[a]	260 (85)	261 (88)[b]	250 (85)[b]
Seropositive for anti-CCP autoantibody, n (%)	340 (85)	359 (90)[c]	337 (85)[c]	264 (86)	273 (91)	255 (87)[d]
Tender joint count (0–68), mean (s.d.)	26.8 (13.7)	27.2 (14.1)	26.5 (14.5)	26.8 (13.6)	27.4 (14.4)	26.9 (14.4)
Swollen joint count (0–66), mean (s.d.)	16.7 (9.3)	16.6 (9.0)	16.8 (9.7)	17.1 (9.4)	16.7 (9.2)	17.0 (9.5)
CRP, mean (s.d.), mg/l	20.5 (23.0)	22.5 (23.1)	22.2 (23.8)	20.1 (22.1)	22.8 (24.0)	21.5 (20.6)
DAS28-CRP, mean (s.d.)	5.9 (0.9)	6.0 (0.9)	6.0 (0.9)	5.9 (0.9)	6.0 (0.9)	6.0 (0.9)
HAQ-DI, mean (s.d.)	1.6 (0.7)	1.6 (0.6)	1.7 (0.6)	1.6 (0.7)	1.6 (0.6)	1.7 (0.6)





150→200mgに変更でもDAS28-CRPに差はない.

- 2年間で200mgq2wが最もX線変化が少ない(150mgよりも).
- PBO→SARで進行も止まる.
- 最初からSAR200mg(150mg:55%)なら62%は2年間進行せず

- 好中球, 血小板, 肝機能障害があれば200→150mgに減量
- 200→150mgで好中球減少の患者割合は55.1%→14.3%に改善.
- 89.4%が2年間の延長試験を完遂できた.

SAR mono 48wの安全性とADA→SARの有効性.

[RMD Open. 2019 Oct 18;5(2):e001017.]

MONARCH trialのopen label extension(OPE) study.

SAR mono群の最大48wの有効性と安全性を検証(n=320).ADA群はSAR200mg q2wに変更.

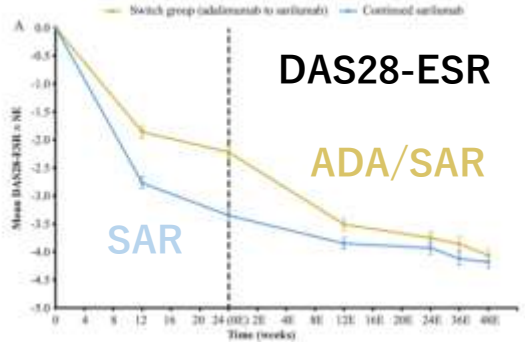
- 最も一般的なadverse eventは

感染症(ADA/SAR: 41.9%, 66.4/100 PY; SAR: 35.8%、53.2/100 PY)

好中球減少症 (ADA/SAR: 13.5%, 27.8/100 PY; SAR: 12.7%, 28.5/100 PY)

注射部位反応 (ADA/SAR: 9.0%, 39.8/100 PY, SAR：10.3%, 55.4/100 PY).

- GI perforationなし.
- 好中球減少:ADA/SAR 57.7%, SAR 56.4%.



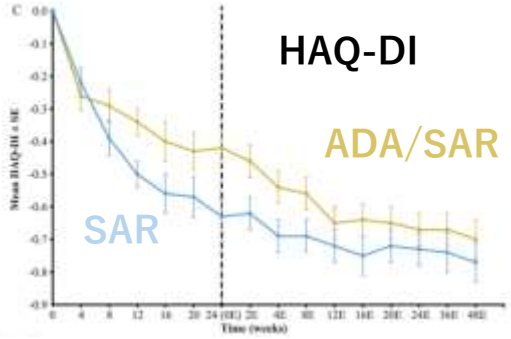


Table 2 TEAEs reported during the OLE

OLE period (as of March 2017)	Patients, n (%)		n_e (n_e/100 PY)	
	Adalimumab/sarilumab (n=155)	Sarilumab/sarilumab (n=165)	Adalimumab/sarilumab (PY=165.7)	Sarilumab/sarilumab (PY=182.4)
Any TEAE	118 (76.1)	117 (70.9)	443 (267.4)	420 (230.2)
Any treatment-emergent SAE	17 (11.0)	6 (3.6)	25 (15.1)	8 (4.4)
Any TEAE leading to death	2 (1.3)	1 (0.6)	3 (1.8)	1 (0.5)
Any TEAE leading to permanent treatment discontinuation	10 (6.5)	12 (7.3)	12 (7.2)	15 (8.2)
AESI type				
Infection	65 (41.9)	59 (35.8)	110 (66.4)	97 (53.2)
Serious infection	3 (1.9)	0	3 (1.8)	0
Opportunistic infection	3 (1.9)	1 (0.6)	3 (1.8)	1 (0.5)
Tuberculosis	1 (0.6)	0	1 (0.6)	0
Leucopenia	21 (13.5)	22 (13.3)	46 (27.8)	56 (30.7)
Thrombocytopenia	3 (1.9)	1 (0.6)	5 (3.0)	1 (0.5)
Hepatic disorders	10 (6.5)	13 (7.9)	15 (9.1)	20 (11.0)
Diverticulitis/GI perforation	0	0	0	0
GI ulceration	0	0	0	0
Elevation in lipids	4 (2.6)	6 (3.6)	4 (2.4)	7 (3.8)
Hypersensitivity	8 (5.2)	7 (4.2)	16 (9.7)	8 (4.4)
Anaphylaxis	0	0	0	0
Injection-site reaction	14 (9.0)	17 (10.3)	66 (39.8)	101 (55.4)
Malignancy	3 (1.9)	0	4 (2.4)	0
Malignancy excluding NMSC	3 (1.9)	0	4 (2.4)	0
Lupus-like syndrome	0	0	0	0
Demyelinating disorder	0	0	0	0

・ADA/SAR群はSAR群のDAS28-ESRに近づく傾向あり.

・CDAIのLAD 41名が, ADA/SAR群となり, 73%がOPE 48wにLDAを維持.

・SAR群は48wまでDAR28-ESR/CRPの継続的で持続的な改善を維持.

TARGET study

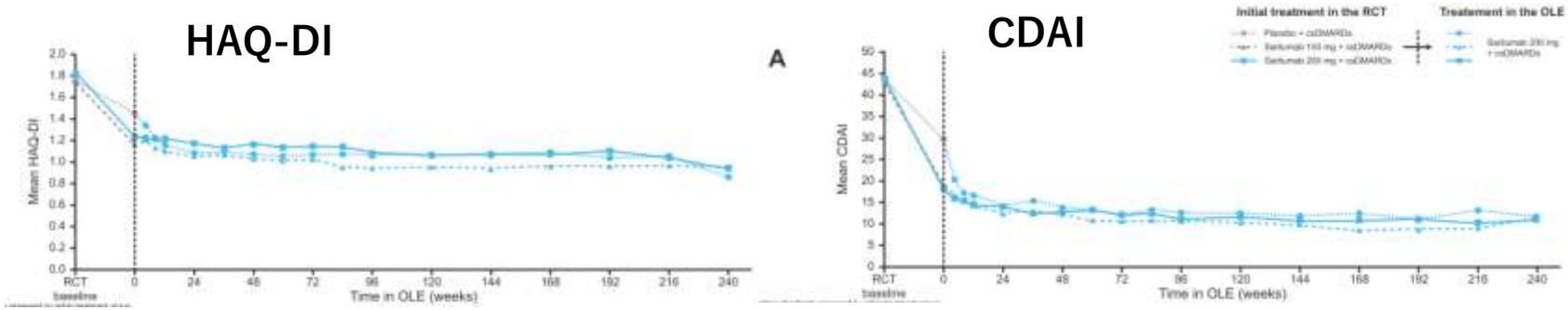
5年間の有効性と安全性を証明.

Long-term safety and efficacy of sarilumab over 5 years in patients with rheumatoid arthritis refractory to TNF inhibitors

Roy Fleischmann[1], Mark C. Genovese[2], Karina Maslova[3], Henry Leher[4], Amy Praestgaard[5] and Gerd R. Burmester[6]

[Rheumatology (Oxford). 2021 Nov 3;60(11):4991-5001.]

- TARGET studyのopen label extension study.
- 5年間の有効性と安全性を評価(n=454). 24w終了後にSAR200mgに変更.



- CDAI, HAQ-DIは5年間維持.

- 一般的なAEは, 好中球減少, 注射部位反応, 上気道炎.
- 重篤な感染症: 3.9/100PY
- GI perfoationなし.
- 好中球減少は200→150mgの減量で81%の例で改善(疾患活動性は悪化するかもしれない).

過去に1つ以上のTNFi-IRがある方がよりAEが多い
(290.6/PY vs 197.9/PY).

	RCT (Week 24)			RCT+OLE
	Placebo + csDMARDs (*n* = 181)	Sarilumab 150 mg q2w + csDMARDs (*n* = 181)	Sarilumab 200 mg q2w + csDMARDs (*n* = 184)	Any sarilumab dose[a] + csDMARDs (*n* = 521)
Cumulative total AE observation period, PY	68.9	75.1	77.2	1654.8
Summary, *n* (%) [n_E/100 PY]				
Any AE	90 (49.7) [339.8]	119 (65.7) [460.6]	120 (65.2) [493.4]	481 (92.3) [160.4]
Any treatment-emergent SAE	6 (3.3) [13.1]	6 (3.3) [9.3]	10 (5.4) [16.8]	146 (28.0) [10.2]
Any AE leading to discontinuation	8 (4.4) [11.6]	14 (7.7) [21.3]	17 (9.2) [28.5]	132 (25.3) [8.1]
Deaths[b]	1 (0.6) [1.5]	0	0	5 (1.0) [0.3]
AEs with incidence rate ≥2 per 100 PY with any sarilumab dose, *n* (%) [n_E/100 PY]				
Neutropenia	2 (1.1) [2.9]	23 (12.7) [43.9]	23 (12.5) [41.4]	104 (20.0) [15.3]
Injection-site erythema	0	11 (6.1) [43.9]	7 (3.8) [22.0]	29 (5.6) [11.9]
Nasopharyngitis	9 (5.0) [13.1]	11 (6.1) [16.0]	7 (3.8) [9.1]	71 (13.6) [7.9]
Accidental overdose[c]	5 (2.8) [7.3]	7 (3.9) [12.0]	9 (4.9) [11.7]	78 (15.0) [7.7]
Urinary tract infection	12 (6.6) [18.9]	6 (3.3) [8.0]	13 (7.1) [20.7]	78 (15.0) [7.7]
Pruritus generalized	0	1 (0.6) [6.7]	3 (1.6) [3.9]	5 (1.0) [7.3]
Upper respiratory tract infection	6 (3.3) [10.2]	4 (2.2) [5.3]	6 (3.3) [7.8]	66 (12.7) [6.7]
RA	8 (4.4) [13.1]	3 (1.7) [4.0]	4 (2.2) [6.5]	66 (12.7) [5.9]
Injection-site pruritus	0	4 (2.2) [13.3]	5 (2.7) [14.2]	17 (3.3) [5.0]
ALT increased	2 (1.1) [2.9]	5 (2.8) [6.7]	10 (5.4) [13.0]	47 (9.0) [4.3]
Hypertension	4 (2.2) [7.3]	3 (1.7) [4.0]	8 (4.3) [10.4]	61 (11.7) [4.2]
Cellulitis	1 (0.6) [1.5]	3 (1.7) [5.3]	3 (1.6) [3.9]	38 (7.3) [3.0]
Hypertriglyceridaemia	3 (1.7) [4.4]	11 (6.1) [16.0]	5 (2.7) [6.5]	32 (6.1) [2.5]
Headache	7 (3.9) [10.2]	5 (2.8) [6.7]	6 (3.3) [7.8]	31 (6.0) [2.1]

ASCERTAIN study

TCZ→SARの切り替えも有効性と安全性を維持.

Subcutaneous Sarilumab in Patients With Rheumatoid Arthritis who Previously Received Subcutaneous Sarilumab or Intravenous Tocilizumab: An Open-Label Extension of a Randomized Clinical Trial

Paul Emery,[1] Hubert van Hoogstraten,[2] Karthinathan Thangavelu,[3] Erin Mangan,[4] Gregory St John,[4] and Patrick Verschueren[5]

[ACR Open Rheumatol. 2020 Nov;2(11):672-680.]

ASCERTAIN trial(TNFi-IRにSAR vs TCZivのRCT)のopen label extend(OLE) trial.

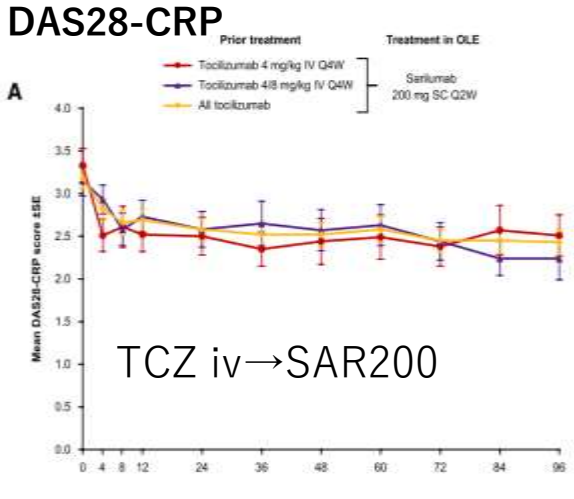
SARの5年間の有効性と安全性を検証. TCZ iv or PBOはSARに変更.

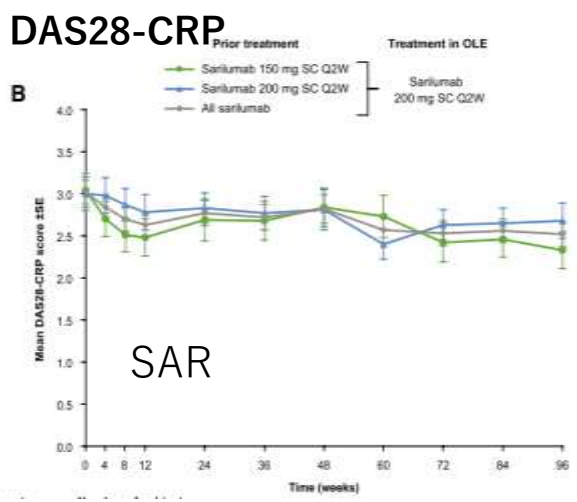
- SAR継続, TCZ→SARで安全性は同等.
- 最も一般的なAEは, 好中球減少症(全体で19.4/100PY), 上気道感染症(8.8/100PY), 尿路感染症(6.6/100PY).
- 重篤な感染症: 3.3/100PY
- 好中球減少はグループ間で同等. <500なし.

- DAS28-CRP, CDAI, HAQ-DIの平均スコアは, 切り替え群とSAR継続群で, 96週維持.
- OLE開始時に疾患活動性が低い患者 (DAS28-CRP<3.2 または CDAI≤10)では, 低い疾患活動性を維持.

Table 2. Investigator-reported AEs

	Treatment During the RCT, Before Switch to Sarilumab 200 mg SC Q2W in the OLE					
	All patients (n = 168)	Sarilumab 150 mg SC Q2W (n = 37)	Sarilumab 200 mg SC Q2W (n = 38)	Tocilizumab 4 mg/kg IV Q4W[a] (n = 35)	Tocilizumab 4/8 mg/kg IV Q4W[b] (n = 38)	All tocilizumab[c] (n = 93)
Cumulative total AE observation period, PY	273.7	61.2	63.6	56.7	57.4	149.0
Summary,[a] n (%) [n/100 PY]						
Any AE	137 (81.5) [276.2]	31 (83.8) [376.0]	30 (78.9) [291.0]	25 (71.4) [195.6]	33 (86.8) [250.8]	76 (81.7) [228.9]
SAE	32 (19.0) [15.7]	11 (29.7) [22.9]	5 (13.2) [9.4]	7 (20.0) [19.4]	7 (18.4) [13.9]	16 (17.2) [15.4]
AE leading to permanent discontinuation[a]	21 (12.5) [7.7]	4 (10.8) [6.5]	5 (13.2) [7.9]	5 (14.3) [8.8]	6 (15.8) [10.5]	12 (12.9) [8.1]
AE leading to death	3 (1.8) [1.1]	1 (2.7) [1.6]	1 (2.6) [1.6]	1 (2.9) [1.8]	...	1 (1.1) [0.7]
AEs with incidence ≥ 10% in any group,[a] n (%) [n/100 PY]						
Neutropenia	24 (14.3) [19.4]	3 (8.1) [9.8]	5 (13.2) [12.6]	5 (14.3) [28.2]	7 (18.4) [15.7]	16 (17.2) [26.2]
Upper respiratory tract infection	20 (11.9) [8.8]	6 (16.2) [14.7]	4 (10.5) [6.3]	5 (14.3) [10.6]	4 (10.5) [7.0]	10 (10.8) [7.4]
Urinary tract infection	15 (8.9) [6.6]	5 (13.5) [11.4]	2 (5.3) [3.1]	3 (8.6) [5.3]	5 (13.2) [10.5]	8 (8.6) [6.0]
Injection-site erythema	15 (8.9) [30.3]	4 (10.8) [44.1]	5 (13.2) [59.8]	2 (5.7) [14.1]	3 (7.9) [15.7]	6 (6.5) [12.1]
Rheumatoid arthritis	15 (8.9) [6.9]	3 (8.1) [4.9]	4 (10.5) [9.4]	2 (5.7) [3.5]	3 (7.9) [8.7]	8 (8.6) [6.7]
Viral upper respiratory tract infection	14 (8.3) [6.2]	4 (10.8) [9.8]	3 (7.9) [4.7]	1 (2.9) [1.8]	3 (7.9) [5.2]	7 (7.5) [5.4]
Back pain	11 (6.5) [4.4]	4 (10.8) [6.5]	2 (5.3) [4.7]	...	4 (10.5) [7.0]	5 (5.4) [3.4]
Diarrhea	9 (5.4) [3.3]	2 (5.4) [3.3]	1 (2.6) [1.6]	1 (2.9) [1.8]	4 (10.5) [7.0]	6 (6.5) [4.0]
Fall	6 (3.6) [2.2]	5 (13.5) [8.2]	...	...	1 (2.6) [1.7]	1 (1.1) [0.7]
Headache	6 (3.6) [2.2]	4 (10.8) [6.5]	...	...	2 (5.3) [3.5]	2 (2.2) [1.3]





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Sarilumab monotherapy *vs* sarilumab and methotrexate combination therapy in patients with rheumatoid arthritis

Gerd R. Burmester [1], Vivian P. Bykerk[2], Maya H. Buch [3,4], Yoshiya Tanaka [5], Hideto Kameda[6], Amy Praestgaard[7], Hubert van Hoogstraten[8], Antonio Fernandez-Nebro[9] and Thomas Huizinga[10]

MTXの併用で臨床的な効果に差はない.

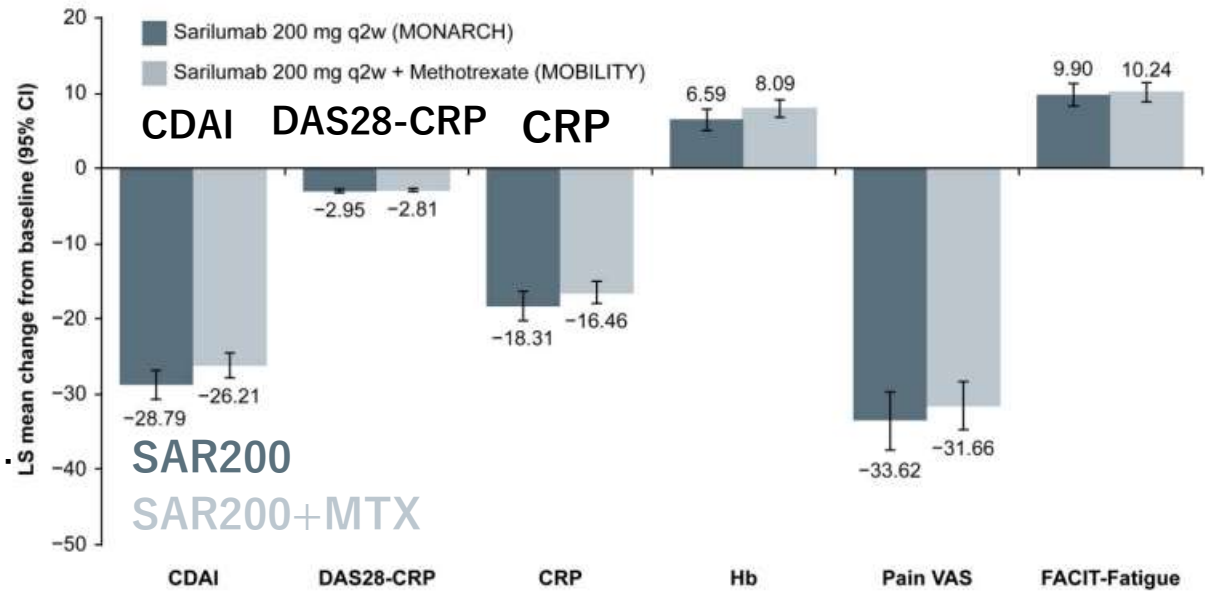
[Rheumatology (Oxford). 2022 May 30;61(6):2596-2602.]

MTX-IR/INTで評価したMOBILITY and MONARCH trialから, SAR mono vs SAR+MTXを比較したpost hoc解析.
SARは200mg q2w, MTX 6~25mg/週. MONARCH(n=184), MOBILITY(n=399)
統計学的評価でMMRM modelを使用.

ベースラインの比較で, 民族, 地域, BMI, RF, CCP抗体, 腫脹関節数, CRP, CDAI, GCsの併用で差あり(P<0.05).

- **CDAI** LDA: mono 42% vs combination 43%.
- **DAS28-CRP** LDA: mono 52% vs combination 49%.
- CRP<10: mono 85% vs combination 73%.
- HbのMCID: mono 26% vs combination 38%.
- Pain VASのMCID: mono 73% vs combination 64%.
- FACIT-fatigueのMCID: mono 66% vs combination 61%.

FIG. 1 Adjusted comparisons of LS mean change from baseline at week 24 using MMRM[a]



● monoとcombinationで臨床的な有効性に差はなかった.

*minimal clinically important difference (MCID)

Association of High Serum Interleukin-6 Levels With Severe Progression of Rheumatoid Arthritis and Increased Treatment Response Differentiating Sarilumab From Adalimumab or Methotrexate in a Post Hoc Analysis

Anita Boyapati,[1] Sergio Schwartzman,[2] Jérôme Msihid,[3] Ernest Choy,[4] Mark C. Genovese,[5] Gerd R. Burmester,[6] Gordon Lam,[7] Toshio Kimura,[1] Jonathan Sadeh,[8] David M. Weinreich,[1] George D. Yancopoulos,[1] and Neil M. H. Graham[1]

IL-6高値は, ADAやMTXよりもSARの効果が高い.

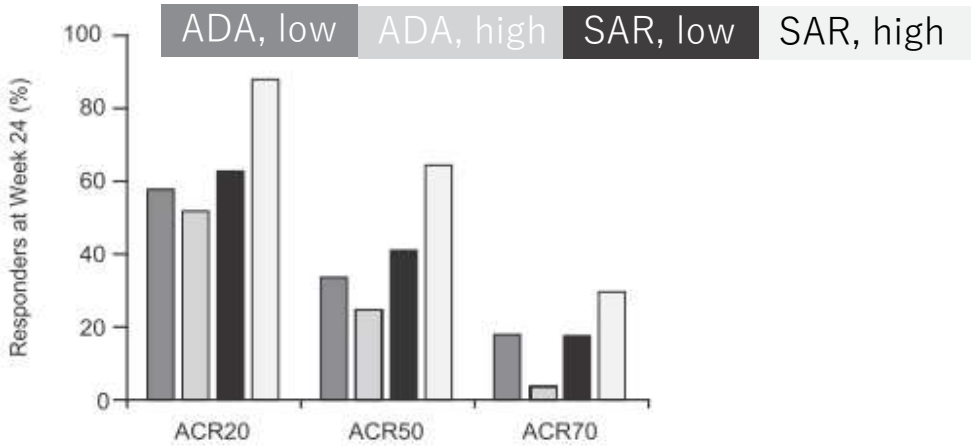
[Arthritis Rheumatol. 2020 Sep;72(9):1456-1466.]

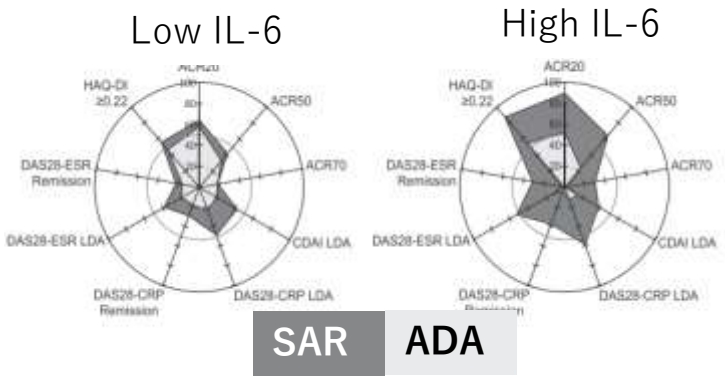
MONARCHとMOBILITYで, ベースラインのIL-6が, 臨床的な有効性とPROを予測できるかを検証したpost hoc解析.

- MONARCH trial

SAR IL-6 highの高値の方が, SAR IL-6 lowよりACR 20/50/70などの反応が良い.

SAR IL-6 high>ADA IL-6 highで臨床効果が高い.

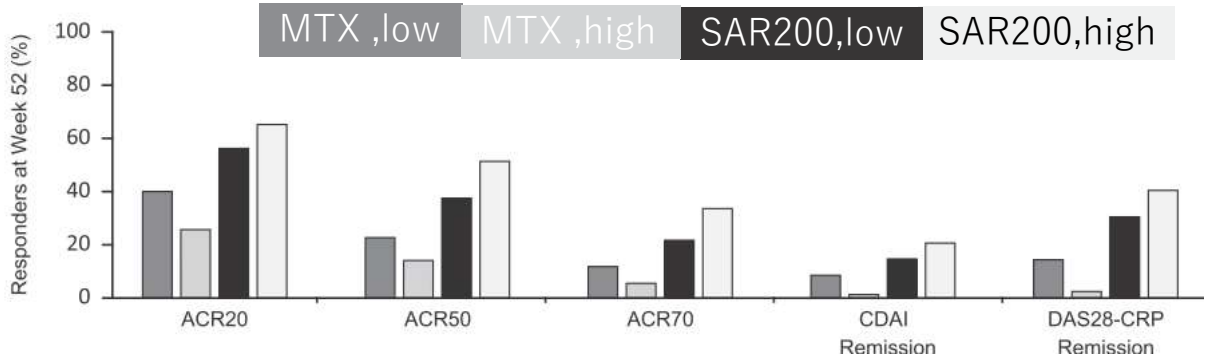


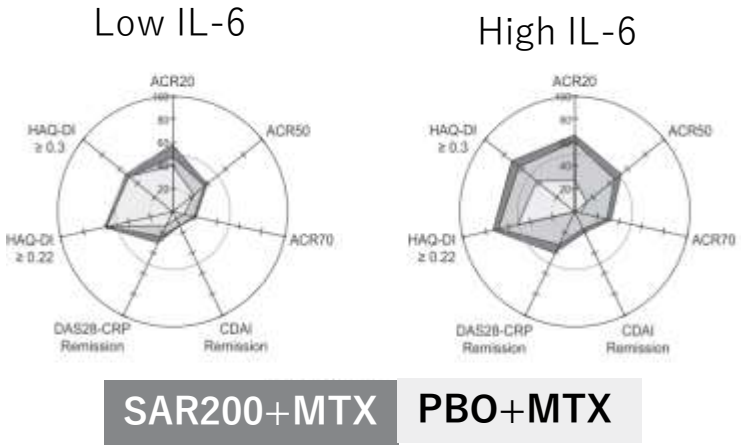


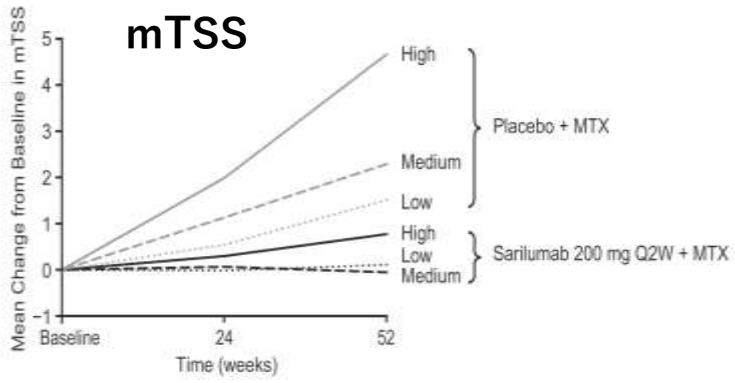
- MOBILITY trial.

-52wのACR 20/50/70: SAR IL-6 high>low.

-52wのmTSS進行: SAR200mg+MTX IL-6 high>low.







Differences in the strength of inhibition of interleukin-6 signalling by subcutaneous sarilumab and tocilizumab in rheumatoid arthritis patients

S. Saito, K. Suzuki, K. Yoshimoto, Y. Kondo, J. Kikuchi, H. Hanaoka, Y. Kaneko, T. Takeuchi

Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan.

TCZとのIL-6 signal blockadeの違い

[Clin Exp Rheumatol. 2023 Jul;41(7):1451-1455.]

TCZ or SARは, IL-6/STAT3シグナル伝達を阻害する.

pSTAT3陽性CD4+T細胞を測定することで, TCZおよびSARによるIL-6シグナル伝達阻害の強度を評価した研究.

TCZ or SAR or MTX投与でCDAI≦10の患者を対象.

- 100ng/mlのrecombinant human IL-6で刺激した後のpSTAT3陽性CD4+T細胞の割合(A)

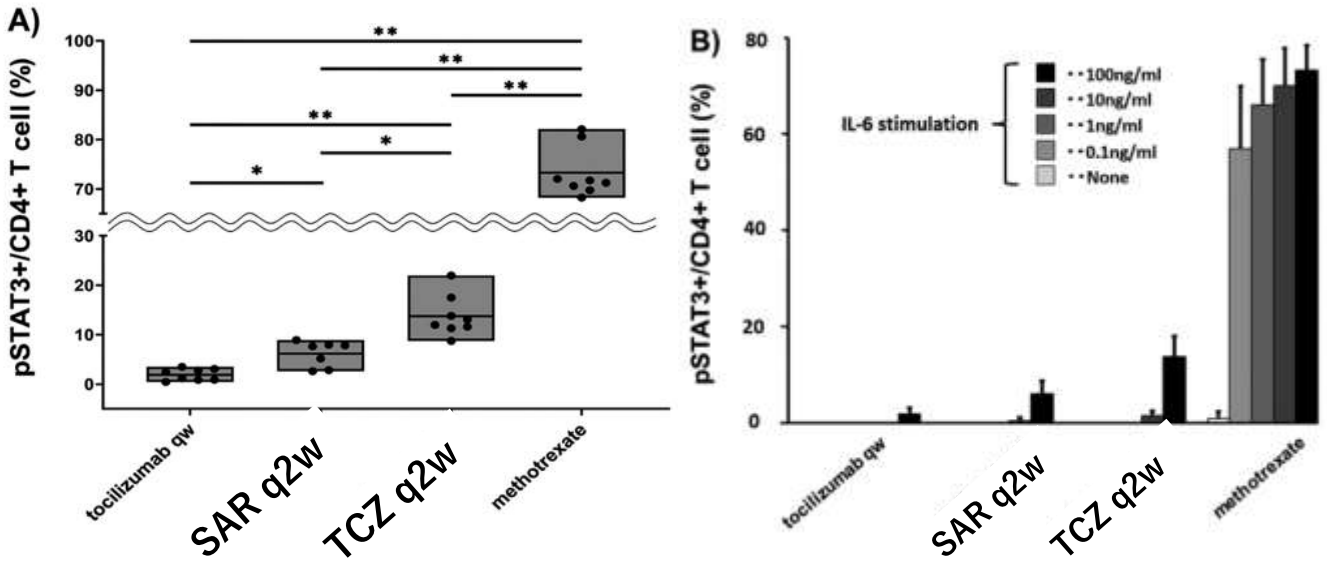
TCZ qw 1.8% [0.9–3.0] vs SAR q2w 7.7% [2.9–8.0] vs TCZ q2w 12.5% [11.4–16.6] vs MTX 71.5% [68.0–78.5]

- 各濃度別のrhIL-6の刺激で生じるpSTAT3陽性CD4+T 細胞の割合(B)

100ng/ml: TCZ qw<SAR q2w<TCZ q2w<MTX

- SAR 200 mg q2wは, TCZ 162mg sc q2wよりも有意に強いIL-6/STAT3シグナル伝達の阻害を示した.

*血中濃度を測っていない.
*滑膜ではわからない.
*臨床効果の影響は不明.



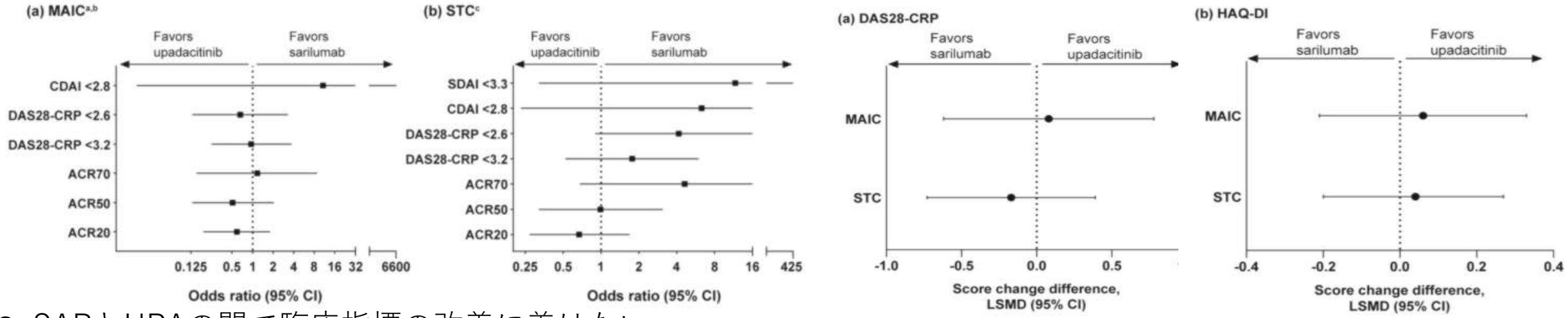
Clinical Efficacy of Sarilumab Versus Upadacitinib Over 12 weeks: An Indirect Treatment Comparison

Thomas Huizinga · Ernest Choy · Amy Praestgaard · Hubert van Hoogstraten · Patrick R. LaFontaine · Patricia Guyot · Daniel Aletaha · Ulf Müller-Ladner · Yoshiya Tanaka · Jeffrey R. Curtis · Roy Fleischmann

1つ以上のbDMARDs-IRに対して, SARとUPAは同等の効果

[Rheumatol Ther. 2023 Jun;10(3):539-550.]

- SARのTARGET trialとUPAのSELECT-BEYOUND trial(両試験ともbDMARDs-IR)のデータでmatching-adjusted indirect comparison (MAIC)とsimulated treatment comparison (STC)解析を行い有効性を間接的に比較検証した研究.



- SARとUPAの間で臨床指標の改善に差はない.

CDAI<2.8: MAIC OR=10.8 (95% CI 0.0–6597.6), STC OR=6.3 (95%CI 0.2–170.4).

DAS28-CRP<2.6: MAIC OR=0.7 (95%CI 0.1–3.3), STC OR=4.2 (95%CI 0.9–19.3).

- SARとUPAで, ベースから12週目までのDAS28-CRPとHAQ-DIのスコア変化の差はない.

DAS28-CRP: MAIC 0.1 (95% CI -0.6-0.8), STC -0.2 (95%CI -0.7-0.4)

HAQ-DI: MAIC 0.1 (95%CI -0.2 to 0.3), STC 0.0 (95%CI -0.2 to 0.3).

Disproportionate articular pain is a frequent phenomenon in rheumatoid arthritis and responds to treatment with sarilumab

Ernest Choy [1]*, Vivian Bykerk[2], Yvonne C. Lee[3], Hubert van Hoogstraten[4], Kerri Ford[5], Amy Praestgaard[6], Serge Perrot[7], Janet Pope [8], Anthony Sebba[9]

SARは, ADAより疼痛緩和に有効かもしれない.

[Rheumatology (Oxford). 2023 Jul 5;62(7):2386-2393.]

disproportionate articular pain(DP): 関節損傷・炎症による痛みと患者が感じる痛みとの乖離.

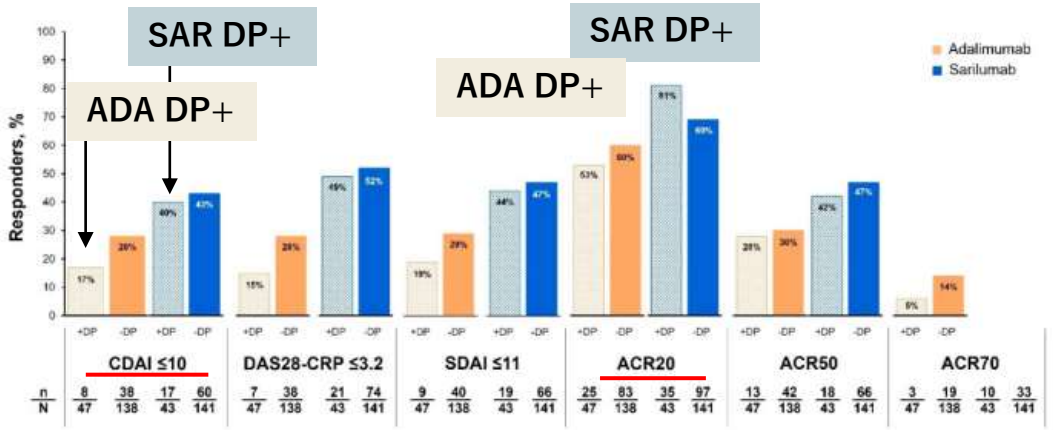
DPは, “TJC28-SJC28≥7”と定義.

DPの有病率, DPに対するSARの効果, 疾患活動性と DPの関連性を検証した研究.

3つのRCT(MOBILITY, TARGET, MONARCH)とその延長試験が対象.

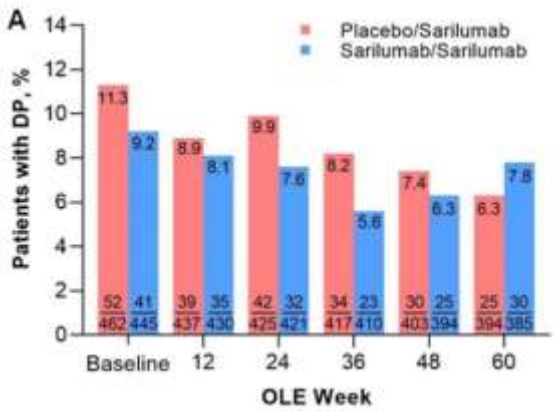
Outcome: 治療12w,24w後のDPの持続割合, ベースのDPの状態に応じた24週のACR20/50/70, CDAI≤10など.

- DPの有病率：約20%
- DP+は, TJC28, CDAI, DAS28-CRP, pain VASが高い.

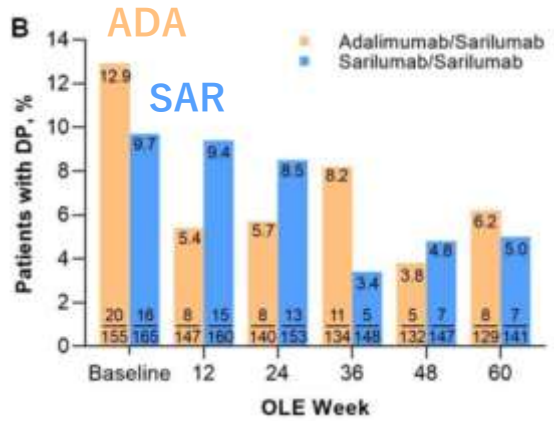


[MONARCH trial]

[MOBILITY/TARGET trial]



[MONARCH trial]



OLEで, SAR>ADA, SAR>PBOでDPが低下.

- 3つのRCTでは, SAR>PBO/ADAでDPの減少率が高い.
- ベースのDPの有無で, 臨床指標の反応率に差はない.
- ベースのDPの有無に関わらず, Pain VAS低下はSAR>PBO/ADA

1. SarilumabのLandmark study
   - -MOBILITY
   - -NOMARCH
   - -TARGET
   - -ASCERTAIN
   - -KAKEHASI
   - -HARUKA
2. Open Label Extension
3. 有効性
4. 安全性と免疫原性

Long-term safety and efficacy of sarilumab with or without background csDMARDs in rheumatoid arthritis

Gerd R. Burmester [1,*], Vibeke Strand [2], Alan J. Kivitz[3], Chih-Chi Hu[4], Sheldon Wang[4], Hubert van Hoogstraten[4], Gabriella L. Klier[4], Roy Fleischmann[5]

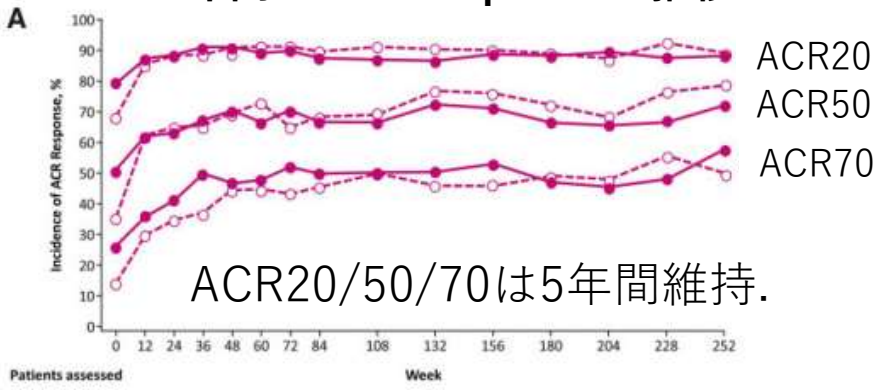
5つのRCTで長期の安全性と有効性を検証

[Rheumatology (Oxford). 2023 Feb 2;kead062.]

- 5つののRTC(n=2341), [NCT01217814, ASCERTAIN, TARGET, MOBILITY, and ONE]から SAR-monoやwith csDMARDsの有効性と安全性を評価.

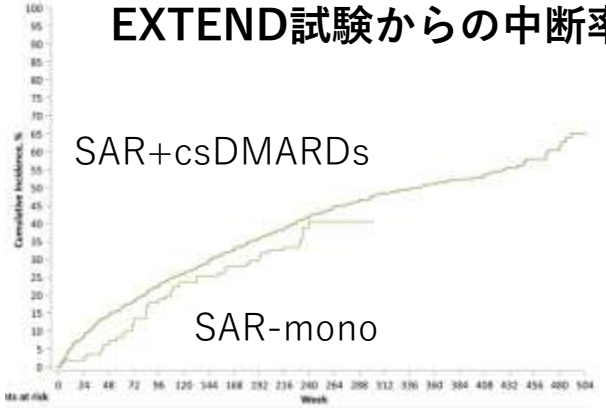
- SAEの発生率(/100PY): mono 8.8, +csDMARDs 12.3, Continuation(OLEでmono継続) 6.0, switch 10.3(OLEでADA→SAR).
- 重篤な感染症, SAR中止のAEは, SAR+csDMARDsで多い傾向.
- 最も多いadverse eventは感染症(鼻咽頭炎, 上気道炎, 気管支炎).
- 好中球減少は10-20%で発生. 好中球数と感染症発生率に関連はない.
- 日和見感染ではVZVが多い.
- GI perforationはSAR+csDMARDs群で0.2%と非常に低い.
- 抗SAR抗体陽性率は全体で5.7%～7.3%.

5年間のACR responseの推移



ACR20/50/70は5年間維持.

EXTEND試験からの中断率



	EXTEND				MONARCH OLE			
	Sarilumab Monotherapy		Sarilumab + csDMARD		Continuation		Switch	
	N = 111[a]	PY = 464.3[b]	N = 1910[a]	PY = 8758.5[b]	N = 165[a]	PY = 612.7[b]	N = 155[a]	PY = 552.7[b]
Any TEAE	98 (88.3)	584 (125.8)	1760 (92.1)	14 839 (169.4)	143 (86.7)	975 (159.1)	135 (87.1)	879 (159.0)
≥5 events/100 PY in either group								
Neutropenia	18 (16.2)	**64 (13.8)**	351 (18.4)	**796 (9.1)**	28 (17.0)	**68 (11.1)**	31 (20.0)	**82 (14.8)**
Injection site erythema	0	0	111 (5.8)	**751 (8.6)**	15 (9.1)	**189 (30.8)**	11 (7.1)	**31 (5.6)**
Nasopharyngitis	14 (12.6)	**26 (5.6)**	249 (13.0)	390 (4.5)	30 (18.2)	**48 (7.8)**	30 (19.4)	**59 (10.7)**
Upper respiratory tract infection	16 (14.4)	21 (4.5)	305 (16.0)	**576 (6.6)**	21 (12.7)	**33 (5.4)**	15 (9.7)	19 (3.4)
≥2 doses in <11 days[c]	20 (18.0)	22 (4.7)	331 (17.3)	**497 (5.7)**	21 (12.7)	28 (4.6)	18 (11.6)	26 (4.7)
Bronchitis	12 (10.8)	19 (4.1)	218 (11.4)	305 (3.5)	20 (12.1)	**32 (5.2)**	21 (13.5)	**31 (5.6)**
RA	17 (15.3)	**32 (6.9)**	254 (13.3)	389 (4.4)	11 (6.7)	**18 (2.9)**	12 (7.7)	20 (3.6)
Any SAE	27 (24.3)	41 (8.8)	617 (32.3)	1081 (12.3)	25 (15.2)	37 (6.0)	31 (20.0)	**57 (10.3)**
≥0.3 events/100 PY in either group								
OA	2 (1.8)	**2 (0.4)**	45 (2.4)	**52 (0.6)**	1 (0.6)	1 (0.2)	4 (2.6)	**5 (0.9)**
Pneumonia	1 (0.9)	1 (0.2)	52 (2.7)	**55 (0.6)**	2 (1.2)	**2 (0.3)**	3 (1.9)	**4 (0.7)**
Cholelithiasis	0	0	24 (1.3)	**24 (0.3)**	2 (1.2)	**2 (0.3)**	2 (1.3)	**2 (0.4)**
RA	1 (0.9)	1 (0.2)	32 (1.7)	**33 (0.4)**	2 (1.2)	**3 (0.5)**	1 (0.6)	1 (0.2)
Atrial fibrillation	2 (1.8)	**3 (0.6)**	9 (0.5)	11 (0.1)	0	0	1 (0.6)	1 (0.2)
Atrial flutter	0	0	3 (0.2)	4 (0.0)	0	0	1 (0.6)	**5 (0.9)**
Pulmonary embolism	2 (1.8)	**3 (0.6)**	10 (0.5)	10 (0.1)	1 (0.6)	1 (0.2)	0	0
Clostridium difficile infection	2 (1.8)	**2 (0.4)**	1 (<0.1)	1 (0.0)	NR	NR	NR	NR
Cellulitis	0	0	21 (1.1)	**24 (0.3)**	NR	NR	NR	NR
Haemorrhagic stroke	2 (1.8)	**2 (0.4)**	0	0	NR	NR	NR	NR
TEAEs leading to discontinuation	15 (13.5)	16 (3.4)	496 (26.0)	553 (6.3)	22 (13.3)	27 (4.4)	20 (12.9)	23 (4.2)
≥0.3 events/100 PY in either group leading to discontinuation								
Herpes zoster	1 (0.9)	1 (0.2)	32 (1.7)	**32 (0.4)**	1 (0.6)	1 (0.2)	4 (2.6)	**4 (0.7)**
ALT increased	0	0	41 (2.1)	**41 (0.5)**	1 (0.6)	1 (0.2)	1 (0.6)	1 (0.2)
Neutropenia	0	0	39 (2.0)	**39 (0.4)**	2 (1.2)	**2 (0.3)**	1 (0.6)	1 (0.2)
Injection-site erythema	0	0	6 (0.3)	6 (0.1)	2 (1.2)	**2 (0.3)**	0	0
Hepatic enzyme increased	NR	NR	NR	NR	2 (1.2)	**2 (0.3)**	0	0
TEAEs leading to death	2 (1.8)	3 (0.6)	40 (2.1)	52 (0.6)	5 (3.0)	6 (1.0)	3 (1.9)	4 (0.7)
Adverse events of special interest								
Infections	61 (55.0)	168 (36.2)	1246 (65.2)	3974 (45.4)	85 (51.5)	243 (39.7)	92 (59.4)	255 (46.1)
Serious Infections	6 (5.4)	8 (1.7)	225 (11.8)	288 (3.3)	4 (2.4)	4 (0.7)	9 (5.8)	12 (2.2)
Opportunistic	0	0	74 (3.9)	80 (0.9)	3 (1.8)	3 (0.5)	7 (4.5)	8 (1.4)
Infections								
Tuberculosis	0	0	7 (0.4)	7 (0.1)	0	0	1 (0.6)	1 (0.2)
Leukopenia	22 (19.8)	72 (15.5)	431 (22.6)	1087 (12.4)	29 (17.6)	73 (11.9)	31 (20.0)	82 (14.8)
Thrombocytopenia	1 (0.9)	6 (1.3)	96 (5.0)	152 (1.7)	3 (1.8)	3 (0.5)	3 (1.9)	7 (1.3)
Hepatic disorders	8 (7.2)	10 (2.2)	329 (17.2)	550 (6.3)	24 (14.5)	40 (6.5)	13 (8.4)	18 (3.3)
Diverticulitis/potential GI perforations[d]	2 (1.8)	2 (0.4)	28 (1.5)	36 (0.4)	1 (0.6)	1 (0.2)	0	0
Lower GI	0	0	4 (0.2)	4 (<0.1)	0	0	0	0
Perforations								
GI ulcerations	1 (0.9)	1 (0.2)	24 (1.3)	26 (0.3)	1 (0.6)	1 (0.2)	2 (1.3)	2 (0.4)
Elevation in lipids	5 (4.5)	5 (1.1)	272 (14.2)	405 (4.6)	8 (4.8)	8 (1.3)	10 (6.5)	10 (1.8)
Hypersensitivity	12 (10.8)	16 (3.4)	194 (10.2)	296 (3.4)	19 (11.5)	22 (3.6)	13 (8.4)	16 (2.9)
Anaphylaxis	0	0	1 (<0.1)	1 (0.0)	0	0	0	0
Injection site reactions	2 (1.8)	2 (0.4)	171 (9.0)	1279 (14.6)	19 (11.5)	197 (32.2)	15 (9.7)	70 (12.7)
Malignancy	2 (1.8)	3 (0.6)	45 (2.4)	49 (0.6)	3 (1.8)	3 (0.5)	6 (3.9)	7 (1.3)
Malignancy excluding NMSC	2 (1.8)	3 (0.6)	35 (1.8)	35 (0.4)	3 (1.8)	3 (0.5)	6 (3.9)	7 (1.3)
Lupus-like syndrome	0	0	6 (0.3)	6 (0.1)	0	0	0	0
Demyelinating disorders	0	0	0	0	0	0	0	0
MACE[e]	3 (2.7)	3 (0.6)	45 (2.4)	50 (0.6)	1 (0.6)	1 (0.2)	2 (1.3)	2 (0.4)
VTE	2 (1.8)	3 (0.6)	24 (1.3)	33 (0.4)	1 (0.6)	1 (0.2)	1 (0.6)	1 (0.2)
DVT	0	0	19 (1.0)	20 (0.2)	0	0	1 (0.6)	1 (0.2)
PE	2 (1.8)	3 (0.6)	12 (0.6)	13 (0.1)	1 (0.6)	1 (0.2)	0	0

Immunogenicity of sarilumab and impact on safety and efficacy in Japanese patients with rheumatoid arthritis: analysis of two Phase 3 randomised clinical trials

Yoshiya Tanaka[a,*], Toshiya Takahashi[b], Mariko Sumi[c], Owen Hagino[d], Hubert Van Hoogstraten[e], Christine Xu[f], Naoto Kato[g] and Hideto Kameda[h]

抗薬物抗体の出現は, 有効性・安全性と関連せず

[Mod Rheumatol. 2022 Jul 1;32(4):686-695.]

日本人(KAKEHASIとHARUKA)でのSARの免疫原性を評価した研究.

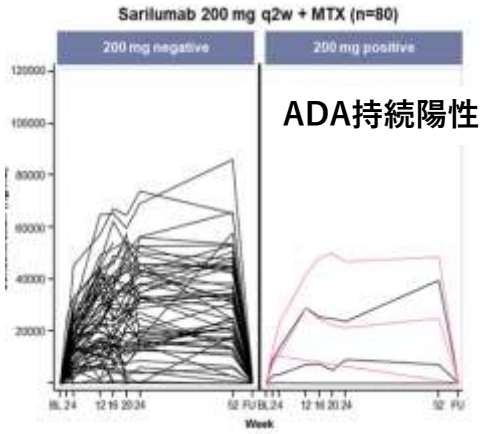
- 抗薬物抗体(anti-drug antibody, ADA)出現率

KAKEHASI: 150+MTX 6.2%(持続陽性 2.5%), 200+MTX 7.5%(持続陽性 3.8%). 中和抗体は200群で1名(1.3%)のみ.

HARUKA: 150-mono 16.7%, 200-mono 6.5%(両群とも持続陽性, 中和抗体なし), +csDMARDs 0%

- MTXなどのcsDMARDs併用の方がADAの出現率が低いかもしれない.

	KAKEHASI		HARUKA		J-Pool	
Response during sarilumab treatment	Sarilumab 150 mg q2w + MTX ($n = 81$)	Sarilumab 200 mg q2w + MTX ($n = 80$)	Sarilumab 150 mg q2w monotherapy ($n = 30$)	Sarilumab 200 mg q2w monotherapy ($n = 31$)	Sarilumab 150 mg q2w initial dose ($n = 140$)	Sarilumab 200 mg q2w initial dose ($n = 185$)
ADA negative, *n* (%)	76 (93.8)	74 (92.5)	25 (83.3)	29 (93.5)	130 (92.9)	172 (93.0)
ADA positive, *n* (%)	5 (6.2)	6 (7.5)	5 (16.7)	2 (6.5)	10 (7.1)	13 (7.0)
Peak titre, median (min: max)	30 (30 : 30)	30 (30 : 30)	30 (30 : 30)	30 (30 : 30)	30 (30 : 30)	30 (30 : 30)
Persistent positive response, *n* (%)	2 (2.5)	3 (3.8)	0	0	2 (1.4)	4 (2.2)
NAb, *n* (%)	0	1 (1.3)	0	0	0	1 (0.5)
Non-NAb, *n* (%)	2 (2.5)	2 (2.5)	0	0	2 (1.4)	3 (1.6)
Transient positive response, *n* (%)	3 (3.7)	3 (3.8)	5 (16.7)	2 (6.5)	8 (5.7)	9 (4.9)
NAb, *n* (%)	0	0	0	0	0	0
Non-NAb, *n* (%)	3 (3.7)	3 (3.8)	5 (16.7)	2 (6.5)	8 (5.7)	9 (4.9)



- ADA陽性は, 陰性と比べてSARの血中濃度が低い.

- ADA+は, 過敏反応と注射部位反応が多い傾向.

Preferred term, *n* (%)	ADA negative ($N = 302$)	ADA positive ($N = 23$)
Hypersensitivity reactions	54 (17.9)	8 (34.8)
Injection-site reactions	33 (10.9)	4 (17.4)

- ADAの有無と有効性の低下

	KAKEHASI (sarilumab 150 mg or 200 mg + MTX)		HARUKA (monotherapy)	
No. of patients (%)	ADA-negative ($n = 150$)	ADA-positive ($n = 11$)	ADA-negative ($n = 54$)	ADA-positive ($n = 7$)
Lack of efficacy[a]	18 (12.0)	1 (9.1)	1 (1.9)	0
Loss of efficacy[b]	4 (2.7)	0	0	0

Safety and effectiveness of sarilumab in Japanese patients with rheumatoid arthritis refractory to previous treatments: An interim analysis of a post-marketing surveillance

Hideto Kameda[a,*], Sadatomo Tasaka[b], Toshiya Takahashi[c], Katsuhisa Suzuki[d], Naoki Soeda[e] and Yoshiya Tanaka[f]

日本のPMS dateの報告

[Mod Rheumatol. 2023 Jun 10;road055. Online ahead of print]

日本での636例, 52wのpost-marketing surveillance.

- Adverse drug reactionは25.1%, severeは7.1%.
- 主に, 血球減少(白血球), 感染症, 脂質異常症, アレルギー反応が大半を占める.
  血球異常の大半は回復.
  感染症は, 蜂窩織炎と肺炎. 適切な治療で治癒.
- 好中球数<1.96×10^{3}は, >と比較しても感染症は増えない.
- 3例(0.4%)で腸管穿孔あり
- DAS28-CRP<2.3の割合がSAR開始後12か月まで上昇傾向.

Table 5. ADRs considered serious infections classified by lowest neutrophil count (below or above the lower limit of normal; 1.96 × 10^3/μl).

Priority survey item[a] Event term (PT)	Minimum ANC value at or above the lower limit of normal,[b] *n* (%) *N* = 345[c]	Minimum ANC value less than the lower limit of normal,[b] *n* (%) *N* = 292[c]
Serious infections (ADRs)	11 (3.2)	5 (1.7)
Cellulitis	1 (0.3)	3 (1.0)
Pneumonia	2 (0.6)	2 (0.7)
Diverticulitis	3 (0.9)	0
Pneumonia bacterial	2 (0.6)	0
Infectious pleural effusion	2 (0.6)	0
Bacteraemia	1 (0.3)	0
Urinary tract infection	1 (0.3)	0
Pseudomonas infection	1 (0.3)	0

Table 3. Priority surveillance items (safety analysis set).

Priority survey item[a,b]	Safety analysis set, *N* = 678, *n* (%) Serious	Nonserious	Total
Serious haematologic disorders[c]	23 (3.4)	0 (0.0)	23 (3.4)
Serious infections (including tuberculosis)[d]	17 (2.5)	0 (0.0)	17 (2.5)
Hepatic dysfunction[e]	0 (0.0)	10 (1.5)	10 (1.5)
Serious hypersensitivity reaction[f]	7 (1.0)	0 (0.0)	7 (1.0)
Intestinal perforation[g]	3 (0.4)	0 (0.0)	3 (0.4)
Interstitial lung disease[h]	3 (0.4)	0 (0.0)	3 (0.4)
Cardiovascular event[i]	1 (0.2)	1 (0.2)	2 (0.3)
Reactivation of hepatitis B virus[j]	0 (0.0)	0 (0.0)	0 (0.0)
Malignant tumour[k]	0 (0.0)	0 (0.0)	0 (0.0)

	ADRs[a] (*N* = 678) Serious	Total
Number (%) of patients with ADRs	48 (7.1)	170 (25.1)
White blood cell count decreased	1 (0.2)	30 (4.4)
Neutrophil count decreased	3 (0.4)	11 (1.6)
Stomatitis	0 (0)	11 (1.6)
Injection site reaction	0 (0)	9 (1.3)
Leukopenia	7 (1.0)	7 (1.0)
Dyslipidaemia	0 (0)	7 (1.0)
Abnormal hepatic function	0 (0)	6 (0.9)
Injection site erythema	0 (0)	6 (0.9)
Injection site pruritus	0 (0)	6 (0.9)
Nasopharyngitis	0 (0)	5 (0.7)
Pneumonia	4 (0.6)	4 (0.6)
Cellulitis	4 (0.6)	4 (0.6)
Interstitial lung disease	3 (0.4)	3 (0.4)
Diverticulitis	3 (0.4)	3 (0.4)
Pneumonia bacterial	2 (0.3)	2 (0.3)
Infectious pleural effusion	2 (0.3)	2 (0.3)
Pancytopenia	2 (0.3)	2 (0.3)
RA	2 (0.3)	2 (0.3)
Urinary tract infection	1 (0.2)	2 (0.3)
Purulent synovitis	1 (0.2)	1 (0.2)
Pseudomonas infection	1 (0.2)	1 (0.2)
Bacteraemia	1 (0.2)	1 (0.2)
Agranulocytosis	1 (0.2)	1 (0.2)
Thrombocytopenia	1 (0.2)	1 (0.2)
Anaphylactoid reaction	1 (0.2)	1 (0.2)
Facial paralysis	1 (0.2)	1 (0.2)
Trigeminal palsy	1 (0.2)	1 (0.2)
Shock	1 (0.2)	1 (0.2)
Large intestinal perforation	1 (0.2)	1 (0.2)
Erythema multiforme	1 (0.2)	1 (0.2)
Panniculitis	1 (0.2)	1 (0.2)
Seronegative arthritis	1 (0.2)	1 (0.2)
Fasciitis	1 (0.2)	1 (0.2)
Osteoarthritis	1 (0.2)	1 (0.2)
Asthenia	1 (0.2)	1 (0.2)
Compression fracture	1 (0.2)	1 (0.2)