Journal Club 2024/9/3　　by Dr.大村

CD19 CAR T-Cell Therapy in Autoimmune Disease — A Case Series with Follow-up

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今回はSLEのみに着目します

N Engl J Med 2024, 390: 687

Introduction

・CAR-T療法はB細胞系悪性腫瘍を中心に治療成績が向上している
・多くの自己免疫疾患でもB細胞が病態の中心にある
・現在の治療では長期の寛解はまだまだ困難が多く、drug free寛解はさらに困難だが、CAR-T療法にはその可能性がある

現在保険適応のCAR-T療法

商品名	メーカー	承認年（日本）	主な対象疾患	
キムリア	ノバルティス（スイス）	2019年	B細胞性白血病 B細胞リンパ腫	CD19が標的
プレヤンジ	Juno Therapeutics（米国）	2019年	大細胞型B細胞リンパ腫 濾胞性リンパ腫	CD19が標的
イエスカルタ	ギリアド（米国）	2021年	大細胞型B細胞リンパ腫	CD19が標的
アベクマ	Celgene（米国）	2022年	多発性骨髄腫	BCMAが標的
カービクティ	ヤンセンファーマ（ベルギー）	2022年	多発性骨髄腫	BCMAが標的

ARTICLES　nature medicine

Anti-CD19 CAR T cell therapy for refractory systemic lupus erythematosus

Andreas Mackensen, Fabian Müller, Dimitrios Mougiakakos, Sebastian Böltz, Artur Wilhelm, Michael Aigner, Simon Völkl, David Simon, Arnd Kleyer, Luis Munoz, Sascha Kretschmann, Soraya Kharboutli, Regina Gary, Hannah Reimann, Wolf Rösler, Stefan Uderhardt, Holger Bang, Martin Herrmann, Arif Bülent Ekici, Christian Buettner, Katharina Marie Habenicht, Thomas H. Winkler, Gerhard Krönke and Georg Schett

Nature Medicine | VOL 28 | October 2022 | 2124–2132 |

の続報にあたります

CAR-T細胞とは

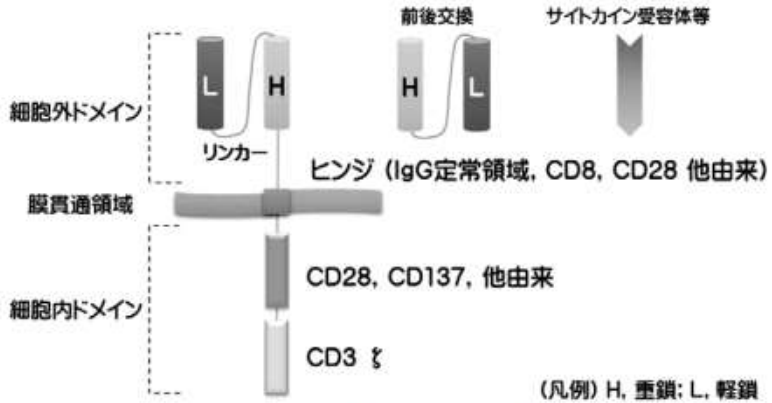
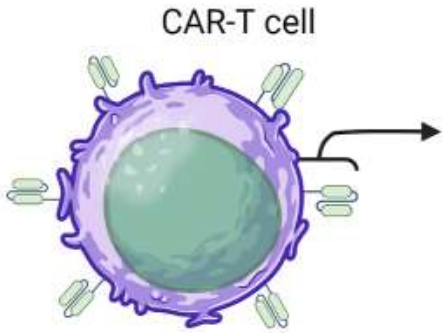
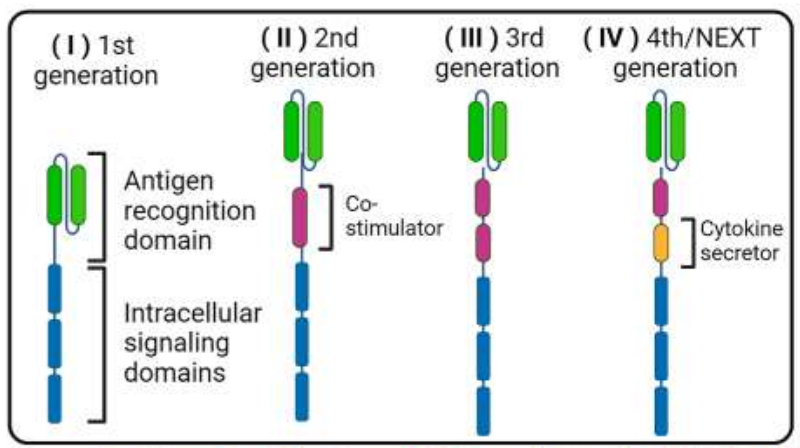


図1　キメラ抗原受容体（CAR）の構造

日本輸血細胞治療学会誌 第65巻 第 6 号





Seminars in Arthritis and Rheumatism 67 (2024) 152479

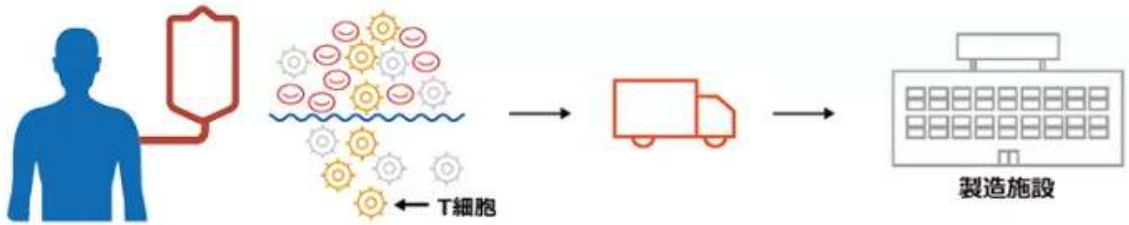
CAR-T療法の流れ

CAR-T細胞療法のプロセス

CAR-T細胞療法は高度に個別化された治療法です。次のようなプロセスを、患者さんごとに行います。

1. 患者さんの細胞の採取

患者さんからT細胞を採取します。採取された患者さんのT細胞は、CAR-T細胞の製造施設に送られます。

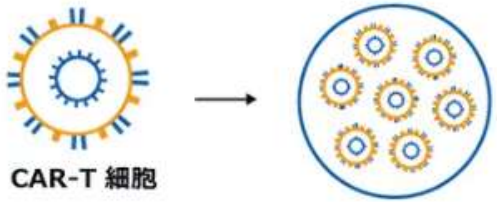


2. T細胞の改変

製造施設では、特定の抗原を発現するがん細胞を認識し攻撃するよう、患者さんのT細胞を改変します。

3. 細胞の増殖

改変されたT細胞（CAR-T細胞）は、特定のがんと闘うのに十分な数まで増やされます。



4. 品質検査

CAR-T細胞は、厳しい品質検査を経て、最終製品として患者さんの治療施設に送られます。

5. リンパ球除去化学療法

患者さんの白血球レベルを下げることで、体がCAR-T細胞を受け入れやすくするために、リンパ球除去化学療法を行います。

6. CAR-T細胞の投与

CAR-T細胞を患者さんの血液に戻します。CAR-T細胞の投与は1回のみの治療で行われます。

7. がん細胞を攻撃

CAR-T細胞は、患者さんの体内で特定の抗原を発現するがん細胞に付着して、攻撃をしかけます。

https://www.novartis.com/jp-ja/research-development/car-t

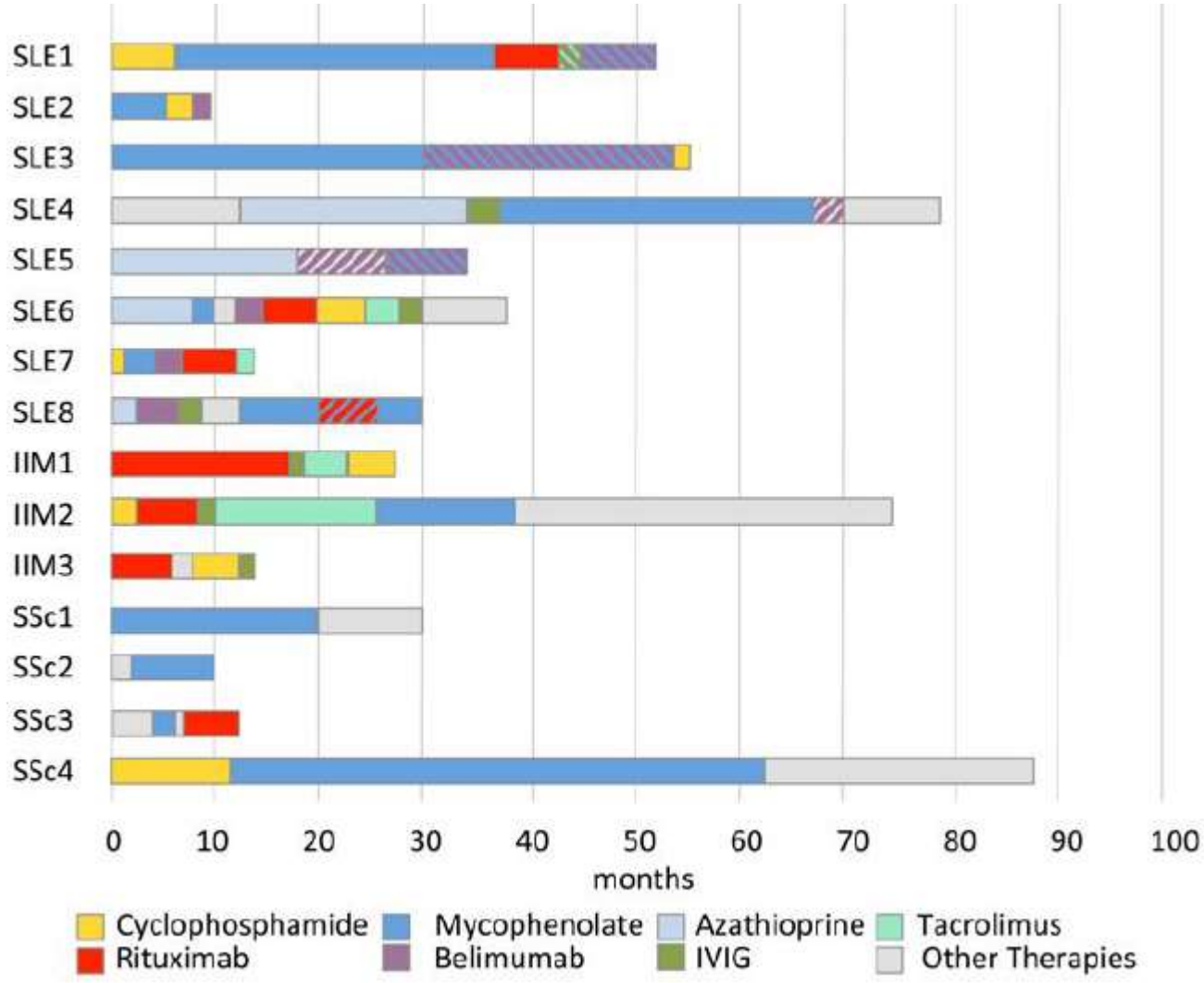
Inclusion Criteria

- SLEの診断を受けている
- 重篤で進行性の経過
- 生検でactiveな糸球体腎炎の証明
- 少なくとも２つの免疫抑制療法に抵抗性

Exclusion Criteria

- 18歳未満
- 妊娠授乳中
- 理解できない方
- 1つ以上の自己免疫疾患を合併している

Suppl. Figure 1　主な治療種類と期間

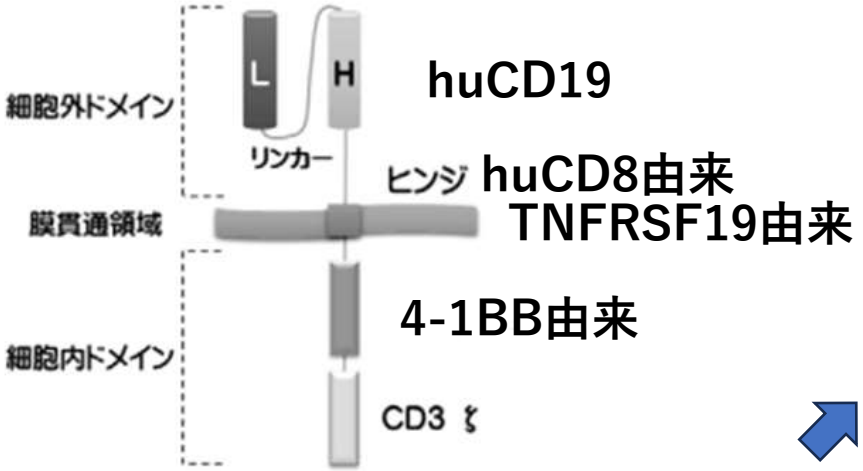


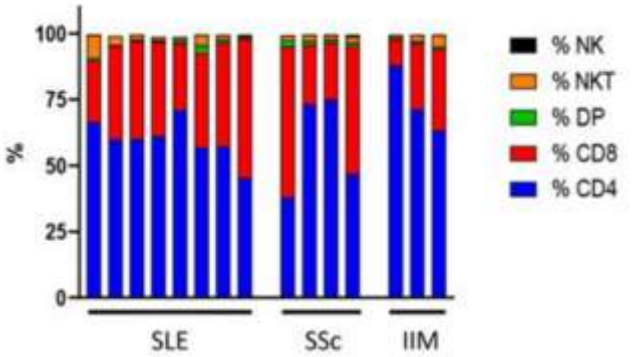
メディアン5種類の免疫抑制療法

Procedure

- Leukapheresis at Day -14
- Manufacturing CAR-T from Day -13 to Day -1
- Chemotherapy at day -5 and day -3
- CAR-T arrive at Day 0 and start infusion

本試験で用いられたCAR-T





Suppl. Fig 2

Leukapheresis前に
・T細胞標的療法は3週前から中止
・PSL量は10mg/日以下へ減量

化学療法は
Fludarabine 25mg/m2/d i.v. on days -5,-4,-3.
IVCY 1000mg/m2/d i.v. on day -3

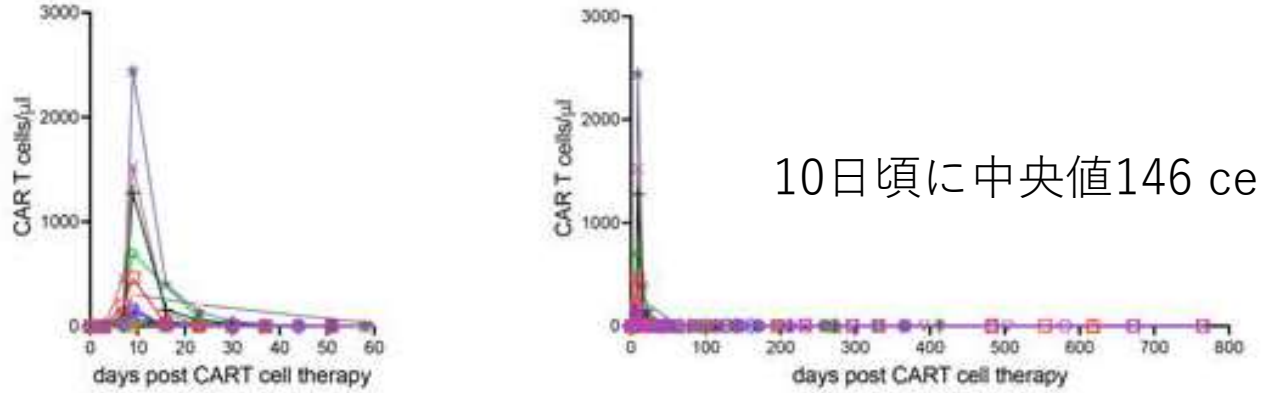
培養方法
PBMC max 1.5x10^9 cells
IL-7, IL-15を含む培養液で12日間培養
Lentivirusによる遺伝子導入では、1x10^8 cellsを用い、抗CD3とCD28刺激しつつ。

CAR-T投与は1x10^6/kgを投与
予防投与としてacyclovir, Cotrimoxazolを最低3ヶ月

・Cytokine release syndrome (CRS) 連日注意
・Immune effector cell-associated neurotoxicity (ICANS) 10日間注意

CAR-T細胞の推移とB細胞の推移

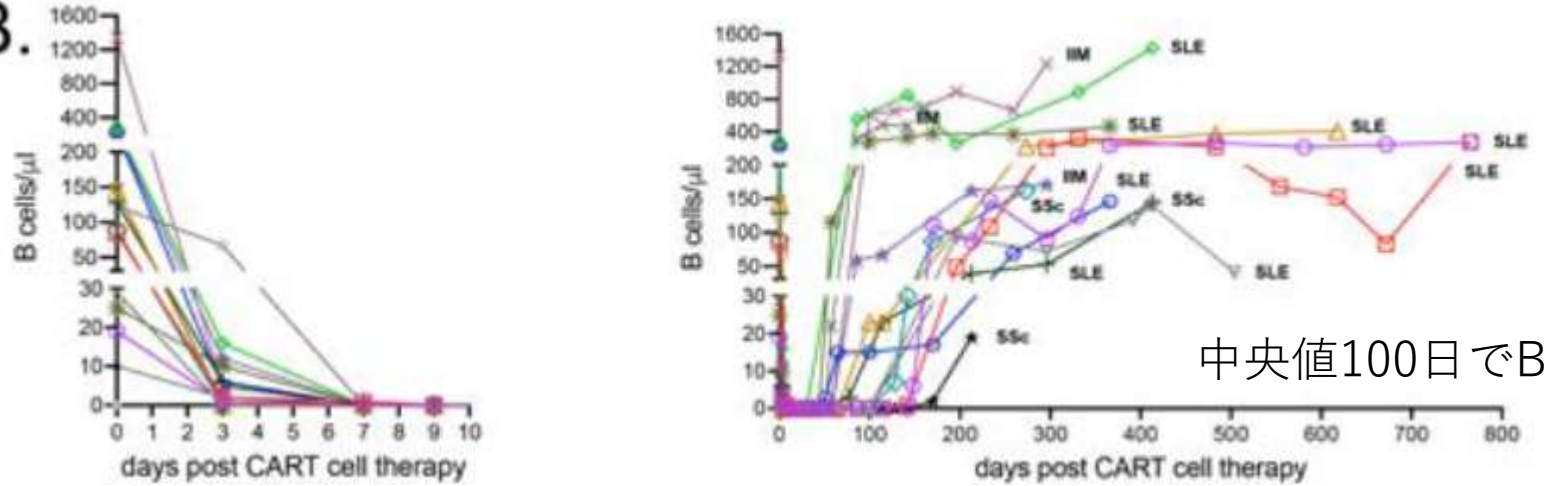
A. Suppl. Fig 3A　投与したCAR-T細胞の動き



10日頃に中央値146 cells/ulまで増殖し、以後ほぼ消失する

Suppl. Fig 3B　CAR-T投与後のB細胞の動き

B.



中央値100日でB細胞は再出現し、以後増加

SLE 患者背景

Table 1. Characteristics of 15 Patients with Autoimmune Disease at Baseline.*

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Age (yr)	20	23	22	24	18	38	33	35
Sex	F	M	F	F	F	F	F	F
Disease	SLE	SLE	SLE	SLE	SLE	SLE	SLE	SLE
Disease duration (yr)	4	1	6	9	3	18	1	20
Follow-up (mo)	29	25	21	19	15	15	12	6
Autoantibodies								
Lead	dsDNA	dsDNA	dsDNA	Sm	dsDNA	dsDNA	dsDNA	dsDNA
Co-lead	—	Sm	—	—	Sm	Sm	—	—
Other	—	—	PCNA	Ro60	Ku	Ro52/60	RNP	RNP
Organ involvement								
Skin	+	+	+	+	+	+	+	+
Kidney	+	+	+	+	+	+	+	+
Nephritis (WHO grade)	III	III	IV	III–V	III–V	IV	IV	IV
Lungs	+	0	+	+	0	0	0	+
Heart	+	0	0	+	0	0	0	0
Bone marrow	+	0	0	0	+	+	0	0
Muscles	0	0	0	0	0	0	0	0
Joints	0	+	+	+	+	+	0	+
Treatments								
Glucocorticoids	+	+	+	+	+	+	+	+
HCQ	+	+	+	+	+	+	+	+
Mycophenolate	+	+	+	+	+	+	+	+
Methotrexate	0	0	0	+	0	+	0	+
Azathioprine	0	0	0	+	+	+	0	+
CPM	+	+	+	0	0	+	+	0
Tacrolimus	+	0	0	0	0	+	+	0
Rituximab	+	0	0	0	0	+	+	+
Belimumab	+	+	+	+	+	+	+	+
IVIG	0	0	0	0	0	0	0	0
Other	0	0	0	LEF	0	+‡	0	+§

SLEDAI 中央値 13 (9.3-16)
少なくとも１つのBILAG Aあり
全員がIII/IVのLN

GCの量は記載なし
臓器障害は現在か、歴が不明

Fig. 1A

SLE 8名全員がdrug free寛解に

CAR-T投与6カ月後の状態

A Short-Term Efficacy of CD19 CAR T-Cell Therapy in Autoimmune Disease

Patient No.	1	2	3	4	5	6	7	8
Disease	SLE							
DORIS Remission	+	+	+	+	+	+	+	+*
LLDAS	+	+	+	+	+	+	+	+*
SLEDAI-2K Score	0	0	0	0	0	0	0	0
ACR–EULAR Major Clinical Response Normalization of CK Level Change in EUSTAR-AI Score Change in mRSS	N/A							
Glucocorticoid-free State	+	+	+	+	+	+	+	+*
No Immunosuppressive Drugs	+	+	+	+	+	+	+	+*

Fig. 1B

CAR-T投与24カ月までの活動性推移

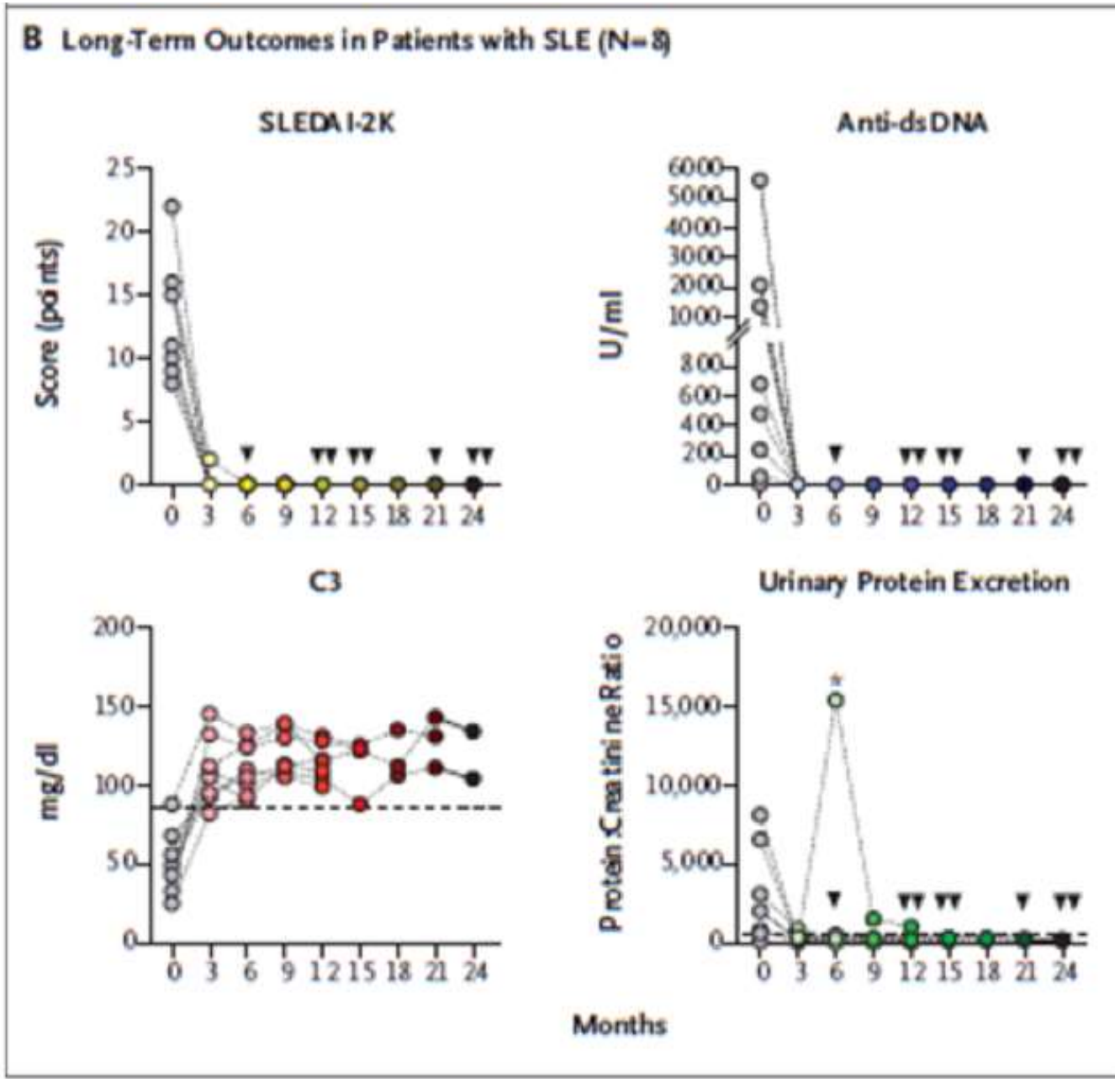


Fig. 2A

自己抗体の治療前後の変化

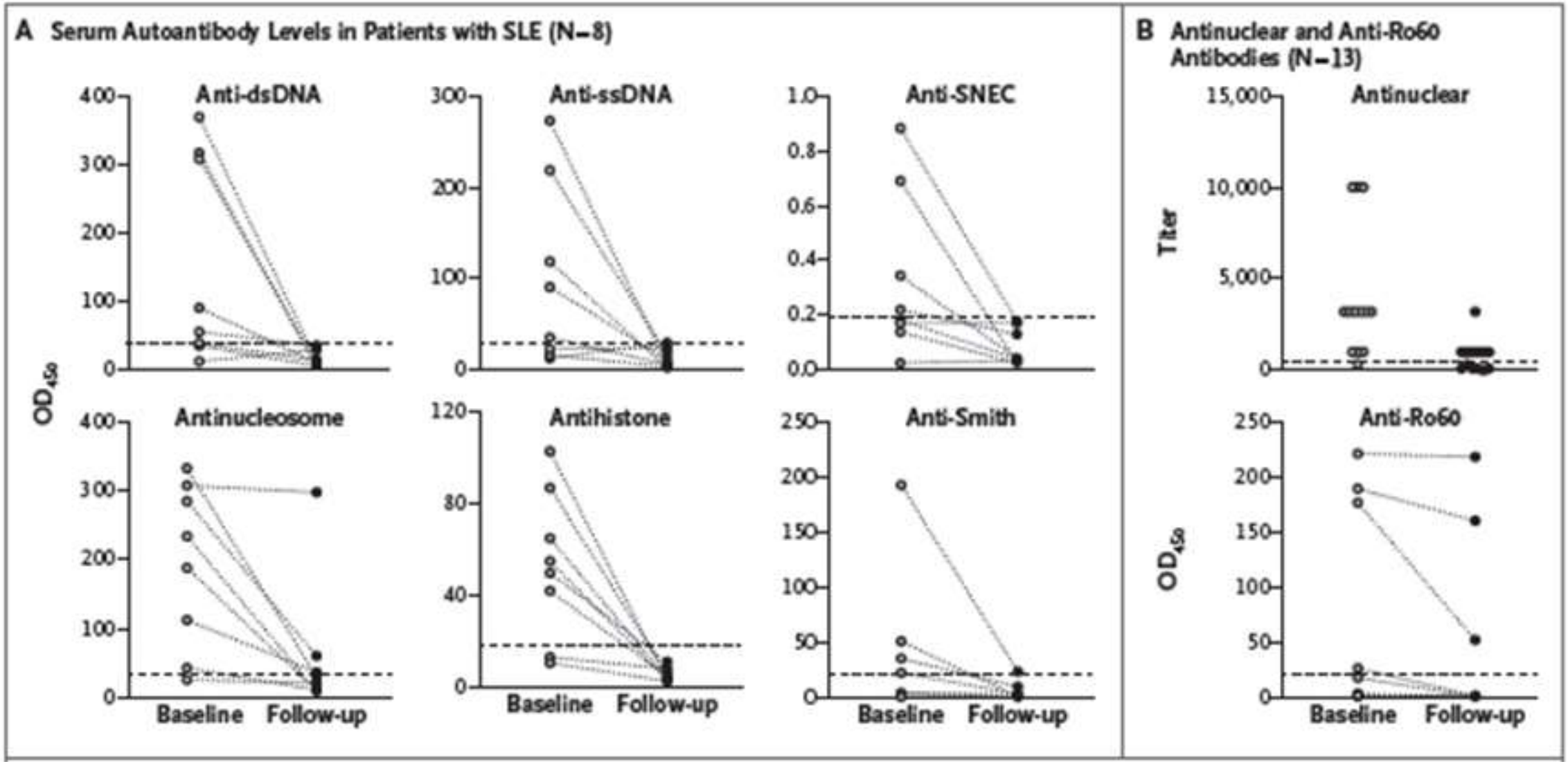


Fig. 2D

ワクチン抗体価の治療前後の変化

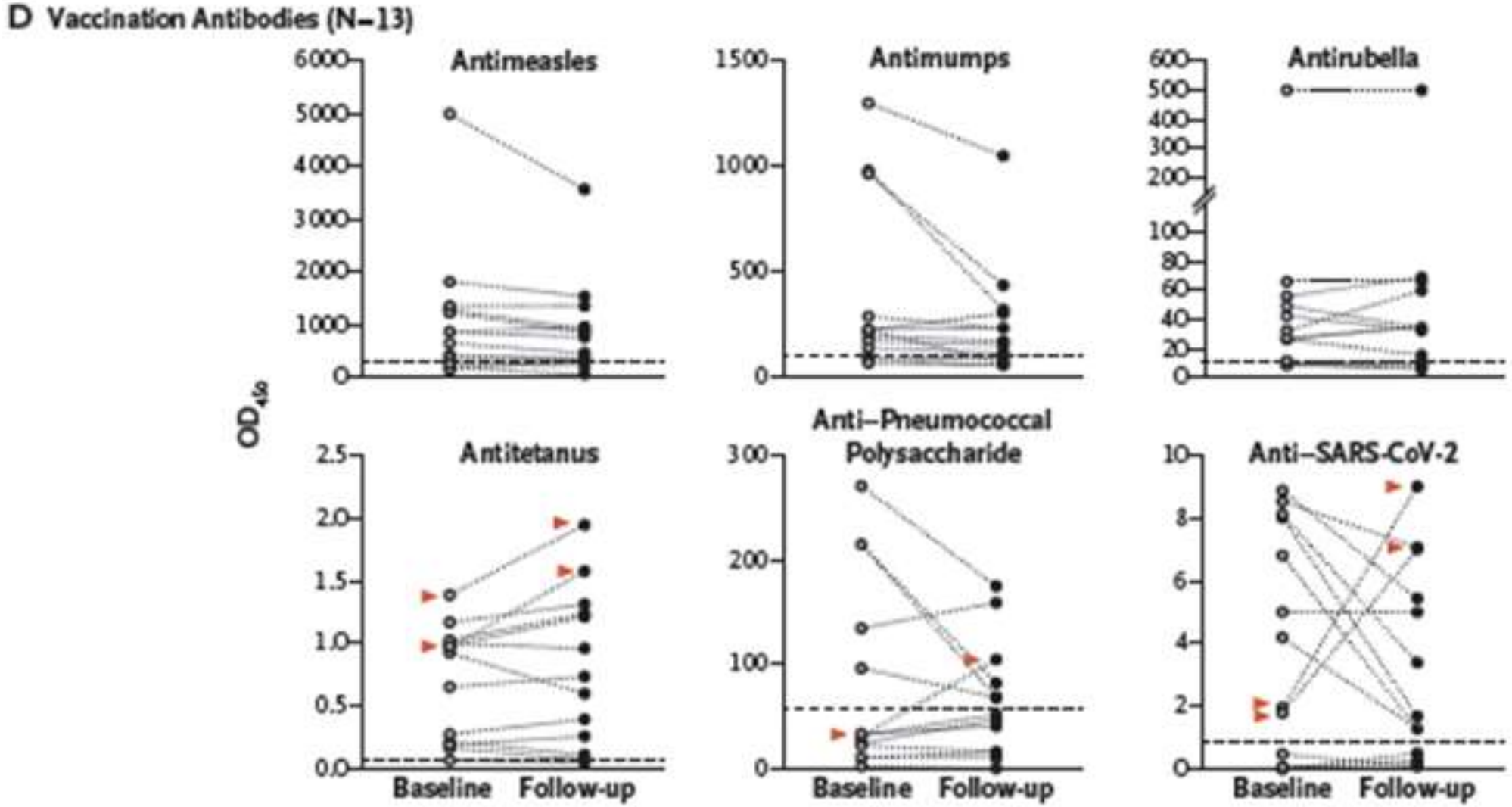
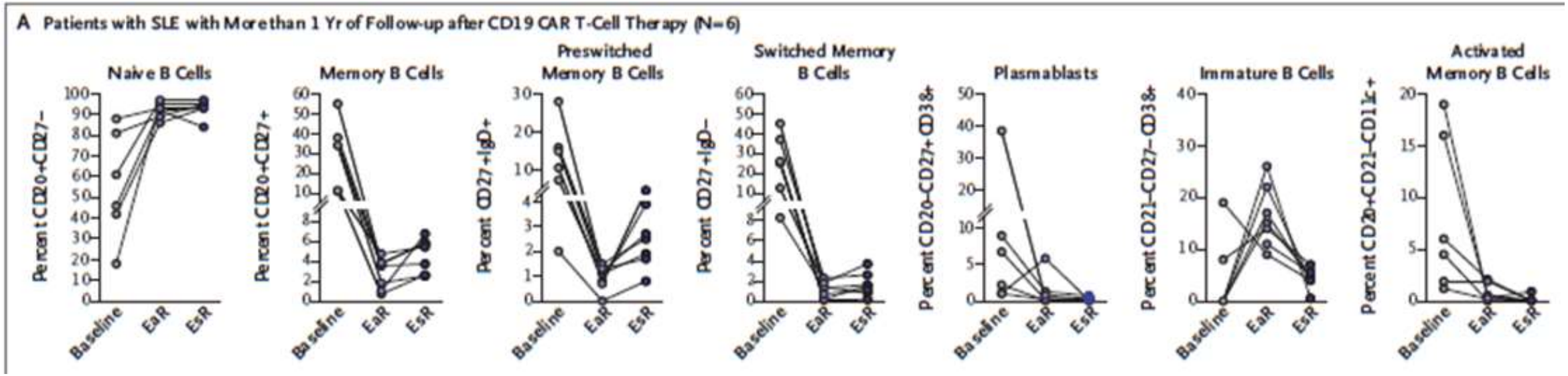
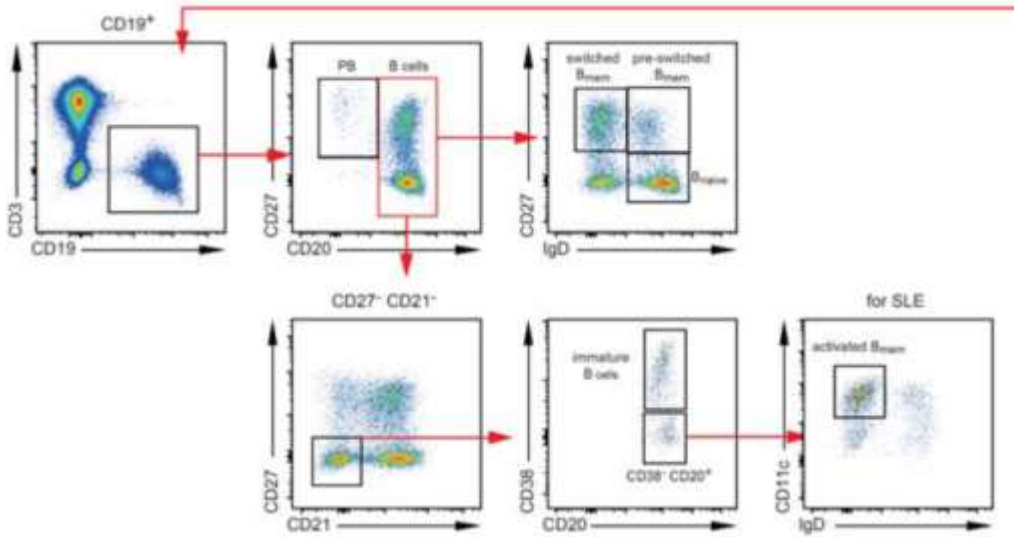


Fig. 3A

B細胞サブセットの治療前後の変化





EaR: Early Reconstitution 4カ月後
EsR: Established Reconstitution 1年後

短期間の安全情報

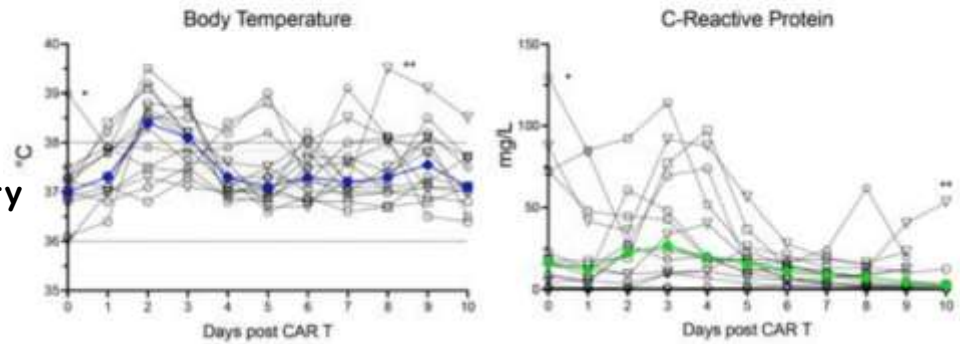
10人が発熱（grade 1）

Table 2. Short-Term Safety of CD19 CAR T-Cell Therapy in Autoimmune Disease.*

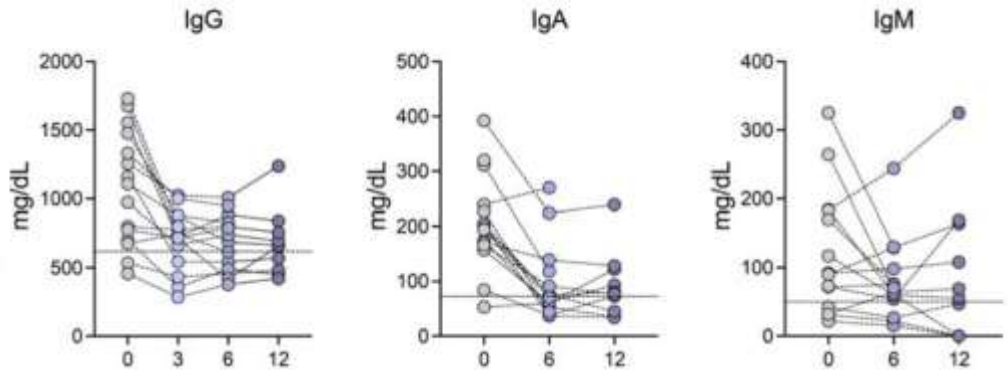
Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12	Patient 13	Patient 14	Patient 15
Disease	SLE	SLE	SLE	SLE	SLE	SLE	SLE	SLE	IIM	IIM	IIM	SSc	SSc	SSc	SSc
CRS (grade)	0	1	1	1	0	1	0	1	1	1	2	1	1	1	0
ICANS (grade)	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
Bone marrow toxicity†	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
TOC treatment	0	0	0	+	0	+	0	+	+	+	+	0	0	0	0
GLC treatment	0	0	0	0	0	0	0	0	0	+	0	0	0	0	0
Low IgG	+	+	+	0	0	0	0	+‡	+‡	0	0	0	0	0	0
IgG substitution	0	+	0	0	0	0	0	+	0	0	0	0	0	0	0

*CAR denotes chimeric antigen receptor, CRS cytokine release syndrome, GLC glucocorticoid, and ICANS immune-effector cell–associated neurotoxicity syndrome.
†Bone marrow toxicity was defined as persisting grade 2 or higher thrombocytopenia, leukopenia, or granulocytopenia at or beyond day 28 after CD19 CAR T-cell therapy.
‡Patients 8 and 9 had preexisting hypogammaglobulinemia due to previous rituximab exposure.

A. Suppl. Fig. 9　B.



C. Suppl. Fig. 11 **免疫グロブリン推移**



CRS: Cytokine Release syndrome

ICANS: Immune effector Cell-Associated Neurotoxicity

発熱、CRP上昇はcommon

長期間の安全情報

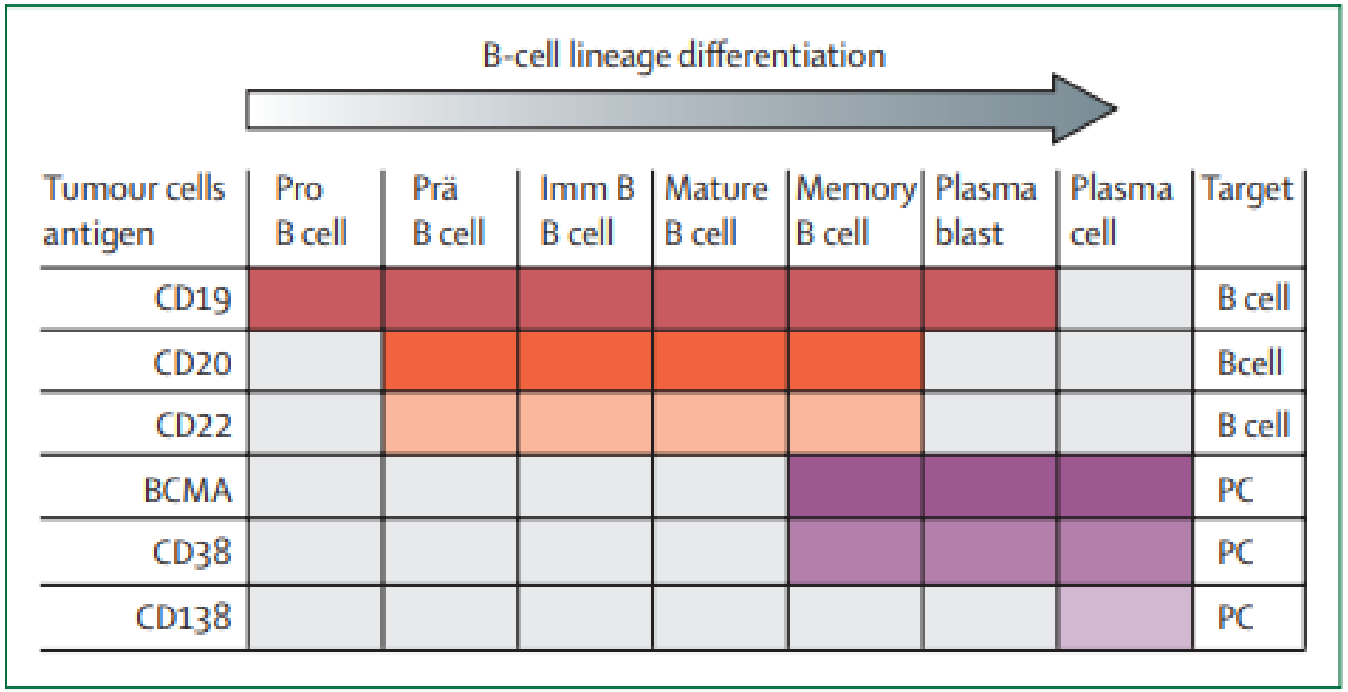
Table 3. Long-Term Safety of CD19 CAR T-Cell Therapy in Autoimmune Disease.*

Patient No.	Disease	<3 Months	3–6 Months	6–12 Months	>12 Months
1	SLE	UTI	0	0	URTI (nonspecified)
2	SLE	0	0	URTI (SARS-CoV-2†)	URTI (nonspecified)
3	SLE	URTI (SARS-CoV-2)	0	URTI (nonspecified)	URTI (SARS-CoV-2) and herpes zoster
4	SLE	0	0	0	Otitis
5	SLE	0	URTI (SARS-CoV-2†)	0	0
6	SLE	0	URTI (SARS-CoV-2† and RSV)	URTI (SARS-CoV-2†)	URTI (nonspecified)
7	SLE	0	0	0	
8	SLE	Pneumonia	0		
9	IIM	0	Enteritis (nonspecified)	0	0
10	IIM	0	Herpes simplex	0	0
11	IIM	URTI (nonspecified)	0		
12	SSc	0	URTI (*Haemophilus influenzae*)	0	0
13	SSc	0	Cellulitis	Herpes zoster	
14	SSc	URTI (SARS-CoV-2†)	0		
15	SSc	0			

Discussion

・SLE8例全例でdrug free寛解が得られ、2年間再燃はない
・IVCY+fludarabineが短期的に影響した可能性は否定できないが多くはIVCY-IR患者で、Fludarabineも投与量は決して多くない
・memory B細胞、plasmablastが消失し、naive B細胞が出現。
いわゆるリセットされた状態
・CRS, ICANSとも軽微で、感染症の頻度も少なかった
・免疫グロブリンの低下も中等度にとどまった
・ワクチン関連免疫グロブリンは実質低下しなかった。
再ワクチン接種が必要かの議論は必要

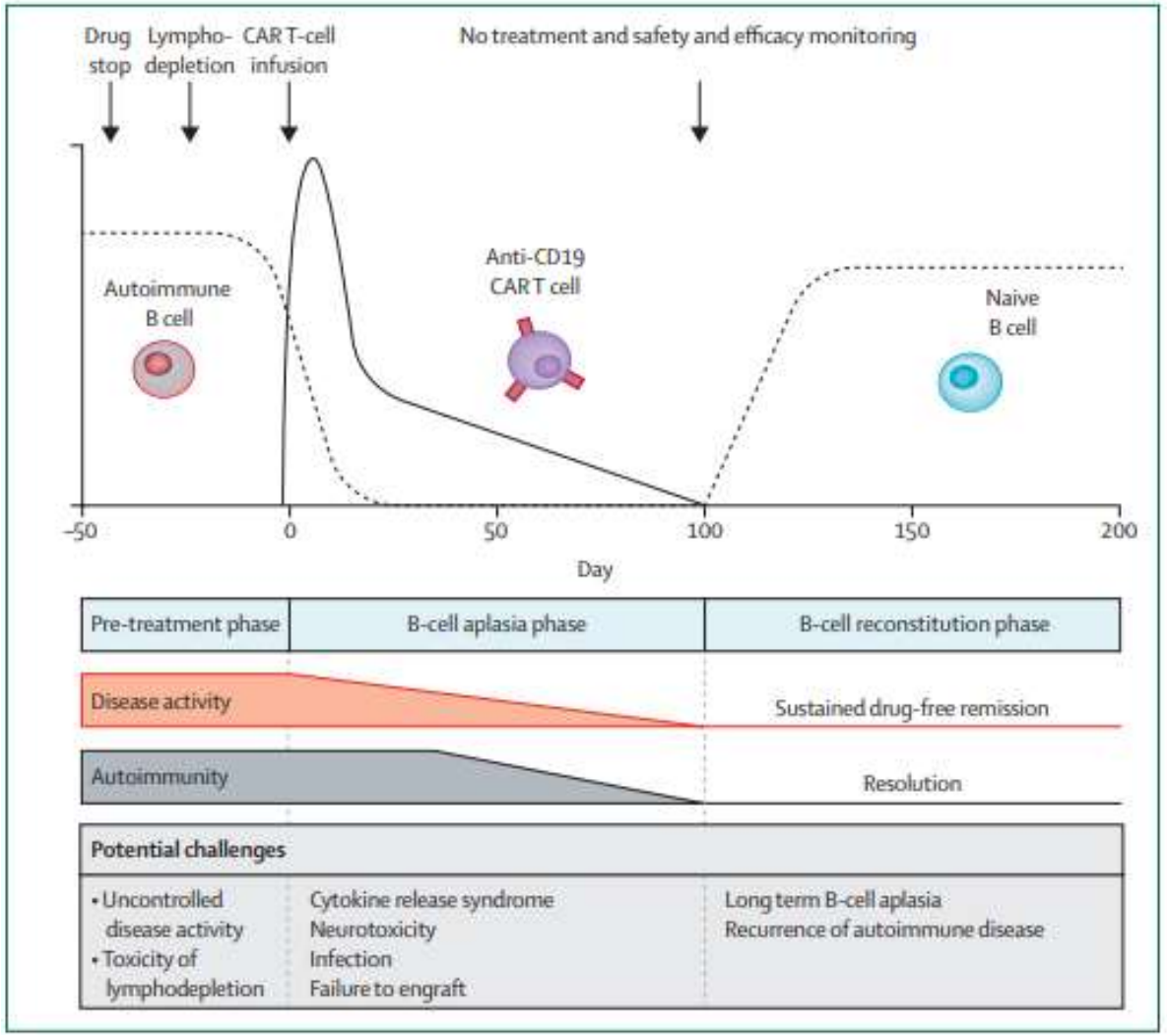
B細胞分化と表面抗原



Tumour cells antigen	Pro B cell	Prä B cell	Imm B B cell	Mature B cell	Memory B cell	Plasma blast	Plasma cell	Target
CD19								B cell
CD20								Bcell
CD22								B cell
BCMA								PC
CD38								PC
CD138								PC

Schett G et al., Lancet 2023; 402: 2034–44

B細胞のreconstruction



おまけ。最近出たSLE CAR-T 13例の報告

Systemic lupus erythematosus

CLINICAL SCIENCE

BCMA-CD19 compound CAR T cells for systemic lupus erythematosus: a phase 1 open-label clinical trial

Weijia Wang,[1] Shanzhi He,[1] Wenli Zhang,[2] Hongyu Zhang,[2] Vincent M DeStefano,[3] Masayuki Wada,[3] Kevin Pinz,[3] Greg Deener,[3] Darshi Shah,[3] Nabil Hagag,[3] Min Wang,[1] Ming Hong,[1] Ronghao Zeng,[1] Ting Lan,[1] Yu Ma,[4] Fugui Li,[1] Yingwen Liang,[1] Zhencong Guo,[1] Chanjuan Zou,[1] Mingxia Wang,[1] Ling Ding,[1] Yupo Ma,[3] Yong Yuan [1]

Ann Rheum Dis 2024;0:1–11. doi:10.1136/ard-2024-225785

BCMA, CD19両方に対するcompound CAR (cCAR) T療法
CD19-CARとBCMA-CARは独立して表出

CD19⁺B cellとCD19⁻BCMA⁺ long-lived plasmacyteを除去

13人のLN（1人V型を含む）Pt#1, #2はML合併
年齢中央値31歳（16-58歳）、
GC, HCQ全例、MMF 8/11, CY 6/11, BEL 7/11,TAC 4/11
SLEDAIは平均10.6から2.7に改善
11/13がmedication-free remission (MFR).
うち6人は1ヶ月で達MFR成
9/13 DORIS寛解、12/13 LLDAS達成（3-6ヶ月後）

Table 1 Baseline characteristics

	Pat. 3	Pat.4	Pat.5	Pat.6	Pat.7	Pat.8	Pat.9	Pat.10	Pat.11	Pat.12	Pat.13
Demographics											
Age (years)	29	46	32	36	20	23	23	16	31	36	17
Sex (female/male)	F	F	F	M	F	M	F	M	F	F	F
Disease duration (years)	6	21	7	10	4	8	4	2	13	12	1
Disease activity SLEDAI-2K (score)	8	10	10	8	12	10	8	12	15	16	8
Laboratory values											
Baseline haemoglobin (113–151g/L)	94	107	114	91	107	110	113	79	62	58	119
Baseline white cell count (3.69–9.16×10⁹ N/L)	2.8	2.58	3.0	1.4	4.4	4.3	2.1	7.1	2.7	3.1	5.0
Baseline lymphocytes (0.8–4.0×10⁹ N/L)	0.7	0.3	0.7	0.30	0.5	0.7	0.2	1.4	0.1	0.4	1.0
Baseline platelets (101–320×10⁹ N/L)	116	168	241	383	250	201	195	416	68	260	298
Baseline C3 (0.9–1.8 mg/dL)	1.1	0.7	1.0	0.52	0.7	0.7	0.5	0.6	0.5	0.3	1.1
Baseline anti-dsDNA (0–10 U/mL)	4.3	203.54	64.7	5.1	48.5	1.2	396.0	20.7	46.6	12.8	2.9
Baseline ANA (0–18 U/mL)	76.4	109.6	267.6	154.5	23.3	21.5	72.2	3.1	300	58.3	308
Proteinuria (28.0–141.0 mg/24 hours)	14 417.2	2742.5	457.5	2852.5	201.0	628.5	104.0	2143.0	3736.8	6780.6	71.0
eGFR (≥90mL/min/1.73 m²)	134.4	166.2	136.9	72.94	192	55.2	135.6	142.3	84.1	83.7	232.4
Urine protein/creatine ratio	1.35	1.23	0.38	3.39	0.24	0.4	0.15	1.75	1.7	0.6	0.25
Other autoantibodies	PO, SSA/Ro60	PO, U1-snRNP,SSA/Ro60	PO, Sm, U1-snRNP, SSA/Ro52, SSA/Ro60	SSA/Ro52,	U1-snRNP, SSA/Ro52, SSA/Ro60	SSA/Ro60	AHA, NUC	/	PO, U1-snRNP, NUC	U1-snRNP	PO, U1-snRNP,SSA/Ro52, SSA/Ro60,
Organ involvement											
Renal biopsy stage	IV/V	V	IV/V	IV/V	IV/V	IV	IV	IV/V	IV/V	IV/V	III/V
Skin (presence/absence)	–	–	–	+	+	–	–	–	–	+	–
Other (presence/absence)	Heart	–	HEM	Heart	–	–	Joint	HEM	HEM	HEM	–
Treatments (at screening)											
Glucocorticoid pulses (yes/no)	+	+	+	+	+	+	+	+	+	+	+
Hydroxychloroquine (yes/no)	+	+	+	+	+	+	+	+	+	+	+
MMF (yes/no)	+	–	+	+	+	+	–	+	+	+	–
Cyclophosphamide (yes/no)	–	+	–	+	+	+	–	–	+	–	+
Belimumab (yes/no)	+	+	+	–	–	+	–	–	+	+	+
Other (yes/no)	TAC	–	–	THAL	TAC	–	MTX, THAL	TAC	TET	TAC	–

AHA, anti-histone antibody; ANA, anti-nuclear antibody; C3, complement factor C3; dsDNA, double stranded DNA; eGFR, estimated glomerular filtration rate; HEM, haematologic abnormalities of SLE; MMF, mycophenolate mofetil; MTX, methotrexate; NUC, anti-nucleosome antibodies; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; TAC, tacrolimus; TET, tetacep; THAL, thalidomide; U1-snRNP, anti-U1 micronbonucleoprotein antibody.

Table 2 SLEDAI-2K score

SLEDAI-2K	LN stage	Pre-CAR medicines	Baseline	1 month	3 months	6 months	1–4 years
Pat.3	IV-G (A)+V	S, HCQ, MMF, B, TAC	8	8	4	0	0
Pat.4	V	S, HCQ, CTX, B	10	4	4	4	4
Pat.5	IV-G (A/C) +V	S, HCQ, MMF, B	10	0	0	0	0
Pat.6	IV-G (A/C) +V	S, HCQ, MMF, CTX, THAL	8	8	4	4	4
Pat.7	IV-G (A)+V	S, HCQ, MMF, CTX, TAC	12	0	0	0	
Pat.8	IV-G (A/C)	S, HCQ, MMF, CTX, B	10	0	0	0	
Pat.9	IV-G (A/C)	S, HCQ, MTX, THAL	8	0	0	0	
Pat.10	IV-G (A)+V	S, HCQ, MMF, TAC	12	8	4	0	
Pat.11*	IV-G (A)+V	S, HCQ, MMF, TAC, B	15	8	4	–	
Pat.12	IV-G (A/C) +V	S, HCQ, MMF, B, TAC	16	12	10	4	
Pat.13	III-G (A)+V	S, HCQ, CTX, B	8	0	0	0	
Mean			10.6	4.4	2.7	1.2	

抗RNP抗体、抗Sm抗体、抗SS-A抗体も陰性化

Fig 1

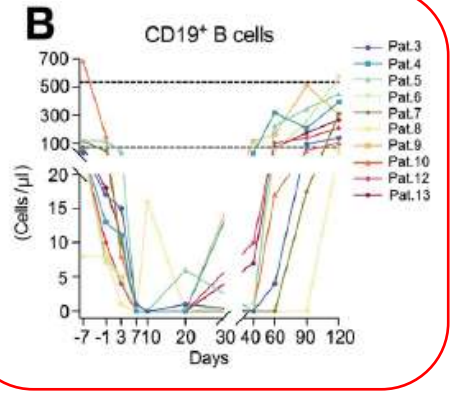


Fig 2

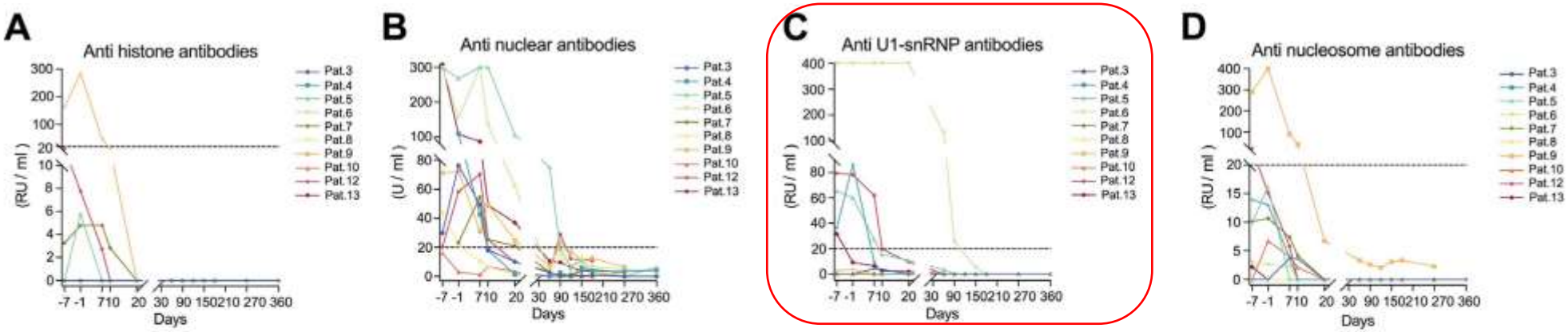
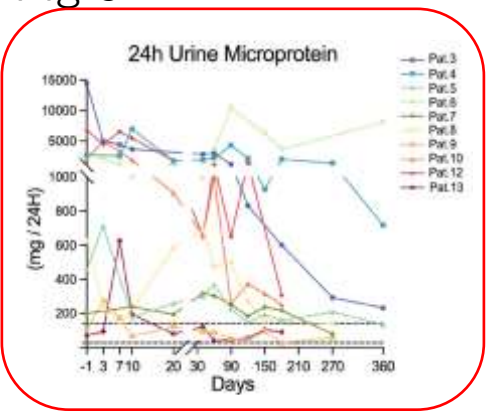
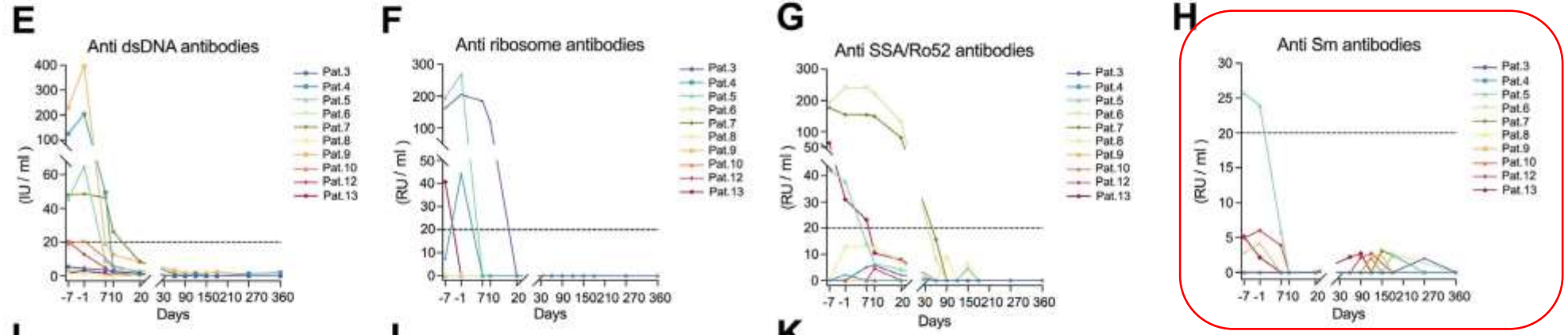
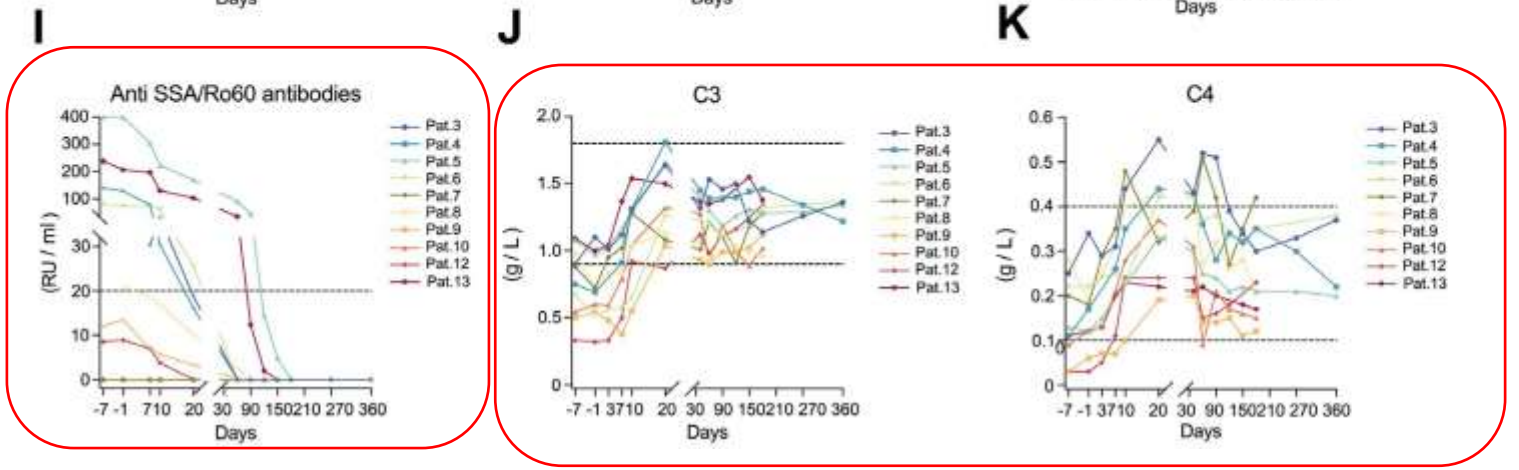


Fig 3



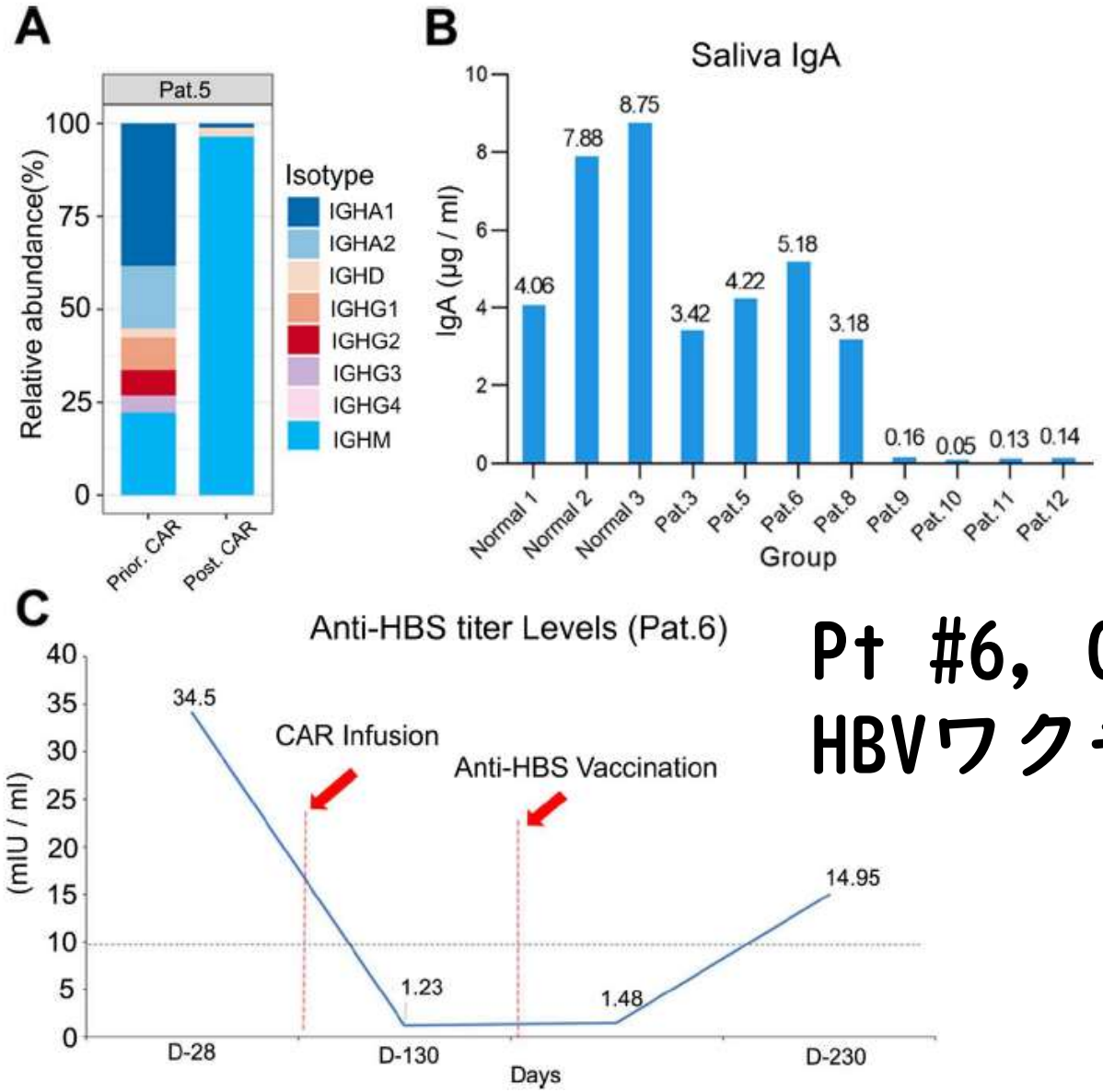




B細胞は40-120日で回復

SLE活動性もほぼ全例で正常化

Pt #5のB cell reset　　唾液中IgA量（CAR-T導入8カ月後）



Pt #6, CAR-T後
HBVワクチン再接種

副作用

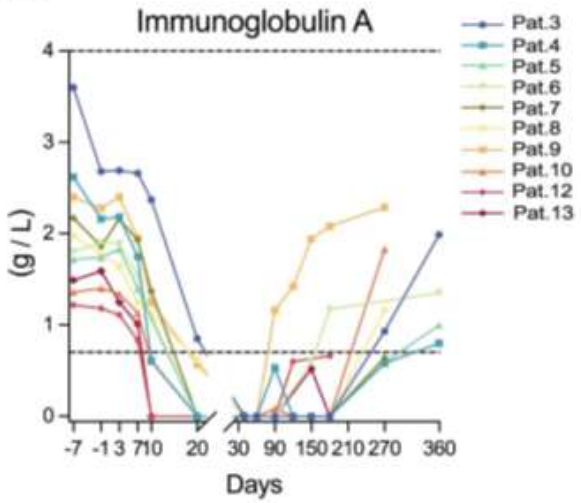
軽微なものが多い

ただ、
Covid肺炎が30%

	Any grade (all patients)	Grade 3 or higher	Any grade (all patients)	Grade 3 or higher
	30 days post-cCAR		>30 days post-cCAR	
AE haematologic				
Leucopenia	5 (50.0%)	2 (20.0%)	0 (0%)	0 (0%)
Neutropenia	4 (40%)	2 (20.0%)	0 (0%)	0 (0%)
Anaemia	5 (50.0%)	0 (0%)	0 (0%)	0 (0%)
Thrombocytopaenia	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Lymphocytopenia	4 (40.0%)	1 (10.0%)	0 (0%)	0 (0%)
Leucocytosis	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Neutrophilia	0 (0%)	0 (0%)	0 (0%)	0 (0%)
AE gastrointestinal				
Nausea and vomiting	1 (10.0%)	0 (0%)	0 (0%)	0 (0%)
Diarrhoea	0 (0%)	0 (0%)	0 (0%)	0 (0%)
AE infectious				
Upper respiratory infection	0 (0%)	0 (0%)	0 (0%)	0 (0%)
COVID infection (N=8)				
COVID related to pneumonia	0 (0%)	0 (0%)	3 (30.0%)	3 (30.0%)
Urinary infection	0 (0%)	0 (0%)	1 (10.0%)	0 (0%)
Pneumonia	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Oral herpes	0 (0%)	0 (0%)	0 (0%)	0 (0%)
AE other				
Influenza-like symptoms	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Fever	8 (80.0%)	0 (0%)	0 (0%)	0 (0%)
Hypotension	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Expectoration	0 (0%)	0 (0%)	0 (0%)	0 (0%)
AST increased	0 (0%)	0 (0%)	0 (0%)	0 (0%)
ALT increased	0 (0%)	0 (0%)	0 (0%)	0 (0%)
APTT prolonged	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Coagulation disorder	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Haematuria	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hypocalcaemia	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hypokalaemia	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Blood fibrinogen decreased	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Myocardial strain	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hypogammaglobulinaemia	10 (100%)	0 (0%)	9 (90.0%)	0 (0%)
Cytokine release syndrome	9 (90.0%)	0 (0%)	0 (0%)	0 (0%)
Neurologic toxic effect	0 (0%)	0 (0%)	0 (0%)	0 (0%)

免疫グロブリンは結構下がる

A.



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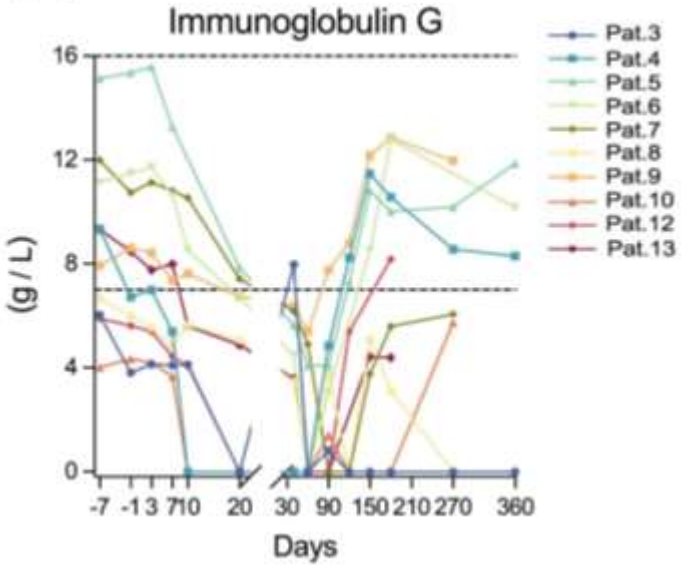

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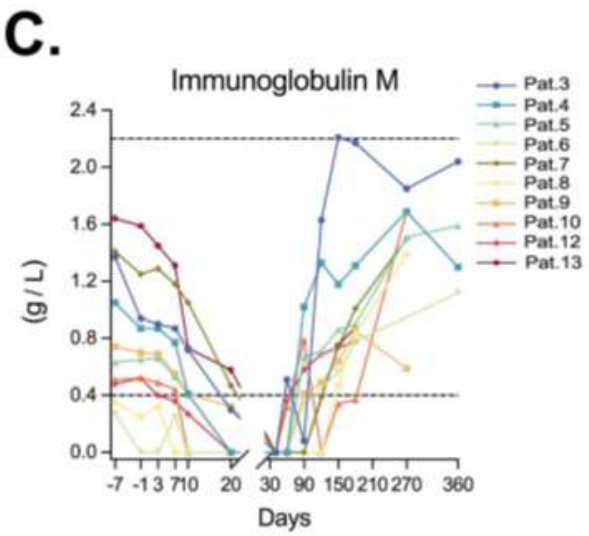

	Infusion time (Days post cCAR)	Total Immunoglobulin (2.5g/50ml)	Indications
Pat. 3	33d	20g	Fever
	234d	5g	Low immunoglobulin
Pat. 4	15d	5g	
	161d	5g	
Pat. 5	151d	5g	
Pat. 6	N/A	N/A	N/A
Pat. 7	129d	5g	Low immunoglobulin
Pat. 8	81d	5g	
	131d	5g	
	133d	5g	
	135d	5g	
Pat. 9	71d	5g	
Pat. 10	53d	5g	
	54d	5g	
Pat. 11	48d	20g	In complete resetting patient
	49d	20g	
	50d	20g	
Pat. 12	8d	5g	Low immunoglobulin
	49d	5g	
Pat. 13	N/A	N/A	N/A

以上、SLEに対するCAR-T療法の結果をまとめました