EULAR review

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#EULAReview23

Sociedad Española de Reumatología

Enfermedades Autoinmunes Sistémicas: Vasculitis, Miopatías y Otras Conectivopatías

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BENRALIZUMAB FOR EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS (EGPA): RESULTS FROM A EUROPEAN MULTICENTER STUDY ON 121 PATIENTS

A. Bettiol[1], I. Mattioli[1], M. L. Urban[1], F. Bello[1], R. Padoan[2], M. Groh[3], G. Lopalco[4], A. Egan[5], V. Cottin[6], P. Fraticelli[7], C. Crimi[8], S. Del Giacco[9], J. Schroeder[10], L. Moi[11], D. Jayne[12], A. Vaglio[13], G. Emmi[1]

Objetivos:

- Evaluar eficacia y seguridad benralizumab cohorte europea multicéntrica GEPA

Métodos:

- GEPA tto benralizumab; 28 centros European EGPA Study
- Resultados eficacia y seguridad 3, 6 y 12 m de tto
- **RC**:
  - ausencia actividad enfermedad (BVAS=0)
  - PD≤4 mg
- **Respiratory outcomes:** asma, ORL y función pulmonar

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Resultados:

- **121 GEPA**
- benralizumab (30 mg/4 semanas x 3 → 8 s)

	Benralizumab beginning (t0)	3 months	p-value (t3 vs t0)	6 months	p-value (t6 vs t0)	12 months	p-value (t12 vs t0)
N patients	*121*	*121*		*101*		*85*	
Complete response	-	15/96 (15.6%)		23/87 (26.4%)		32/69 (46.4%)	
BVAS, median (IQR)	3 (2-8)	0 (0-2)[n=96]	<0.001*	0 (0-2)[n=87]	<0.001*	0 (0-1)[n=69]	<0.001*
Respiratory involvement							
Pulmonary	114 (94.2)	43/111 (38.7)	<0.001*	36 (35.6)	<0.001*	33 (38.8)	<0.001*
ENT	85 (70.3)	54/111 (48.6)	<0.001*	46 (45.5)	<0.001*	40 (47.1)	<0.001*

- 19 pc **eventos adversos** (3 hospitalización)

Conclusión:

- **Benralizumab** (dosis asma eosinofílica), podría ser **eficaz** y controlar:
  - **manifestaciones respiratorias** GEPA
  - **actividad general** enfermedad

THE BURDEN OF MULTIMORBIDITY IN ANCA-ASSOCIATED VASCULITIS: A COHORT STUDY

Z. Wallace[1,2,3], X. Fu[1,2], S. Srivatsan[1,2], Z. Williams[1,2], C. Cook[1,2], J. Hanberg[4], J. H. Stone[2,3], H. Choi[1,2,3], Y. Zhang[1,2,3]

Objetivos:

- Determinar la carga de multimorbilidad en VAA.

Métodos:

- **Cohorte VAA Mass General Brigham** (MGB) de 2002-2019
- **Comparadores sin enfermedad reumática sistémica** se identificaron MGB y se compararon con los casos (10:1) por fecha inicio, edad, sexo y raza.
- **Definición MM**: presencia ≥ *2* de 37 *condiciones crónicas,* identificadas códigos ICD-9/10 ≥ *2 veces/* ≥ *30 días*
- **Excluyeron:**
  - **manifestaciones VAA**
  - condiciones presentes **≥ 6 m antes de inicio del tto**
- 1º proporción de casos y comparadores con MM método Aalen-Johansen (riesgos competitivos muerte y pérdida durante seguimiento)
- 2º modelo de regresión Cox estimar HR de MM en casos vs comparadores y tiempo de supervivencia medio restringido para estimar días libres de MM en casos vs comparadores
- 3º análisis de clases latentes para caracterizar clusters de morbilidad entre personas con MM.

THE BURDEN OF MULTIMORBIDITY IN ANCA-ASSOCIATED VASCULITIS: A COHORT STUDY

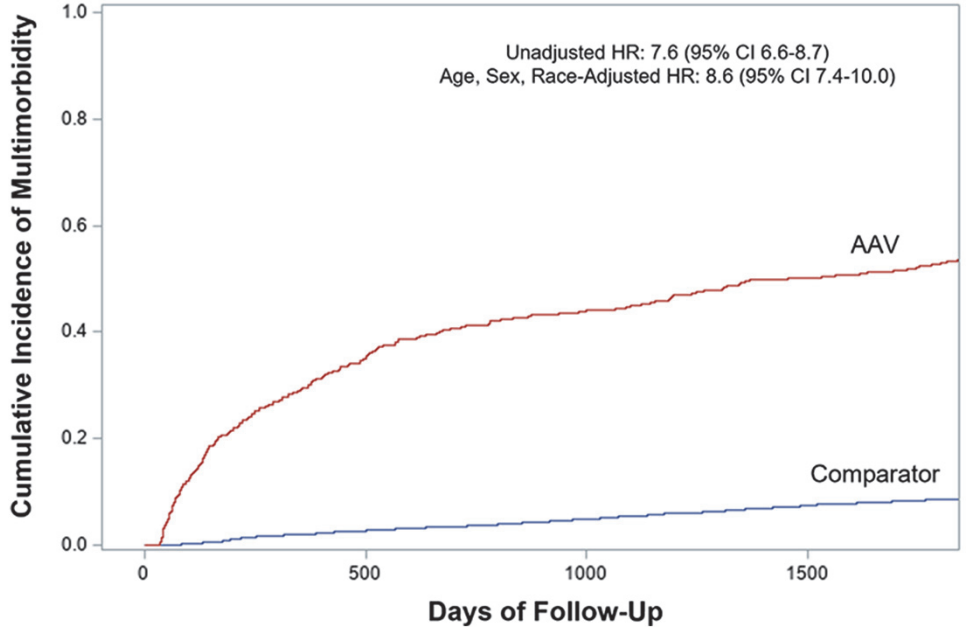
OP0305 (2023)

Z. Wallace[1,2,3], X. Fu[1,2], S. Srivatsan[1,2], Z. Williams[1,2], C. Cook[1,2], J. Hanberg[4], J. H. Stone[2,3], H. Choi[1,2,3], Y. Zhang[1,2,3]

Resultados:

	AAV Cases	Comparators
N	547	5259
Age (mean, SD)	59 (17)	59 (17)
Female (%)	39%	39%
Race		
White	88%	92%
Black/African American	2%	2%
Asian	1%	1%
Other	2%	2%
Unknown	3%	1%
BMI (mean, SD)	28.3 (6.9)	28.5 (7.3)
Proportion with Multimorbidity		
Year 1	37.8%	5.7%
Year 2	50.7%	8.7%
Year 3	54.4%	11.8%
Year 4	61.4%	14.9%
Year 5	66.2%	19.1%
Days Free from Multimorbidity*		
Year 1	282	353
Year 2	489	696
Year 3	666	1028
Year 4	823	1353
Year 5	963	1671
*Adjusted for age, sex, race		
Promedio días sin MM	963.4	1670.5 (p<0,001)
mediana seguimiento	102m	66m

Figure: The Risk of Multimorbidity in AAV vs Comparators



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OP0305 (2023)

Resultados:

1 año

1A 76%	1B 24%
HTA DLP	DOLOR

2 años

2A 82%	2B 18%
	< CV PULMONAR

5 años

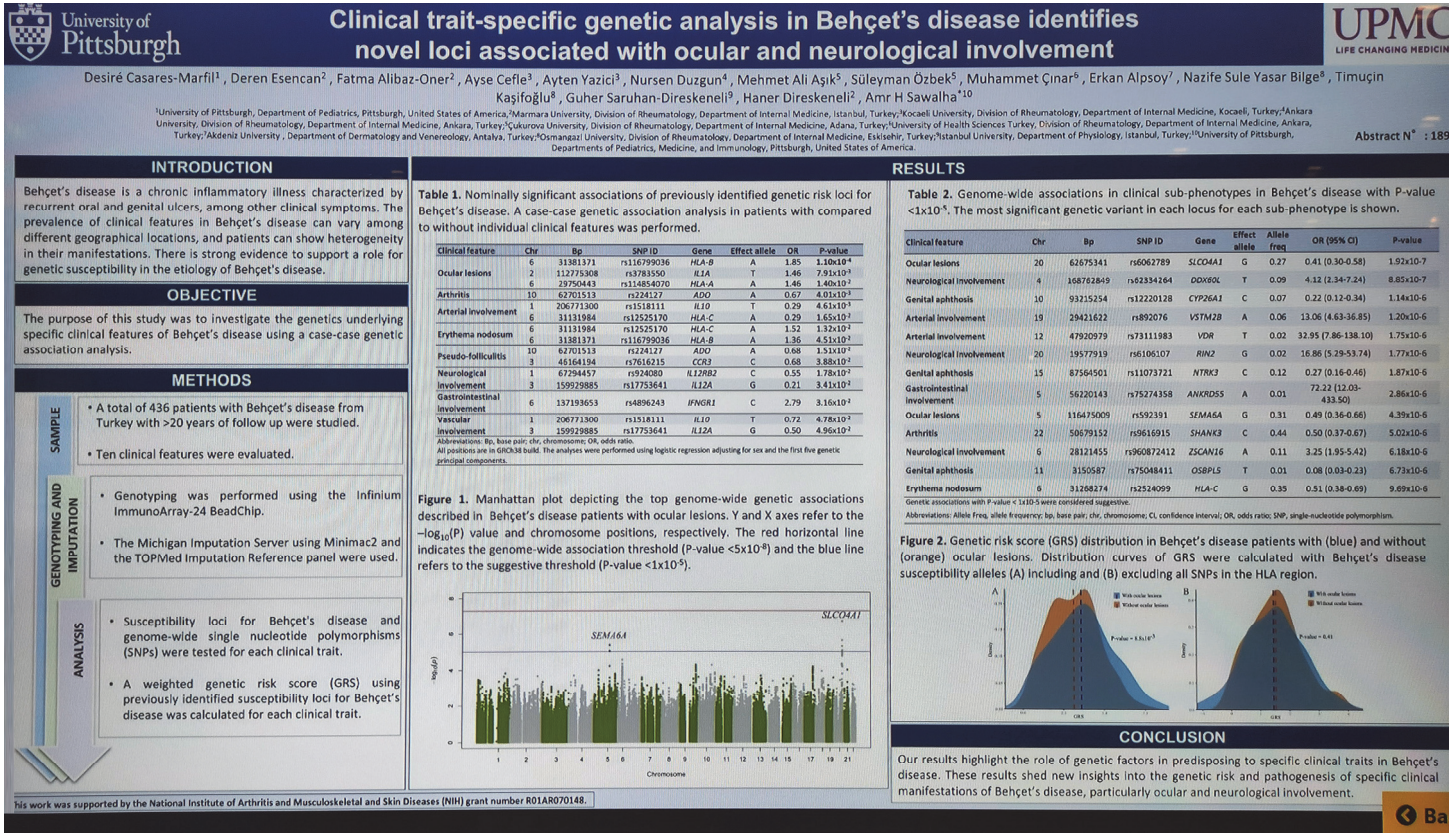
5A 81%	5B 11%	5C 8%
HTA DLP	CV PULMONAR	TOXICIDAD GC

Conclusiones:

- VAA ↑ carga MM y > riesgo MM que población general.
- MM en VAA: clusters de morbilidad varían curso enfermedad y reflejan ↑ impacto enfermedad y su tto.
- Necesario desarrollo intervenciones prevenir MM y minimizar su impacto.
- Estos hallazgos → futuras investigaciones para mejorar atención y resultados pacientes VAA.

CLINICAL TRAIT-SPECIFIC GENETIC ANALYSIS IN BEHÇET'S DISEASE IDENTIFIES NOVEL LOCI ASSOCIATED WITH OCULAR AND NEUROLOGICAL INVOLVEMENT

D. Casares-Marfil[1], D. Esencan[2], F. Alibaz-Oner[2], A. Cefle[3], A. Yazici[3], N. Duzgun[4], M. A. Aşik[5], S. Özbek[5], M. Çinar[6], E. Alpsoy[7], N. S. Yasar Bilge[8], T. Kaşifoğlu[8], G. Saruhan-Direskeneli[9], H. Direskeneli[2], A. H. Sawalha[10]



University of Pittsburgh

Clinical trait-specific genetic analysis in Behçet's disease identifies novel loci associated with ocular and neurological involvement

UPMC LIFE CHANGING MEDICIN

Desiré Casares-Marfil[1], Deren Esencan[2], Fatma Alibaz-Oner[2], Ayse Cefle[3], Ayten Yazici[3], Nursen Duzgun[4], Mehmet Ali Aşik[5], Süleyman Özbek[5], Muhammet Çinar[6], Erkan Alpsoy[7], Nazife Sule Yasar Bilge[8], Timuçin Kaşifoğlu[8], Guher Saruhan-Direskeneli[9], Haner Direskeneli[2], Amr H Sawalha[*10]

[1]University of Pittsburgh, Department of Pediatrics, Pittsburgh, United States of America, [2]Marmara University, Division of Rheumatology, Department of Internal Medicine, Istanbul, Turkey; [3]Kocaeli University, Division of Rheumatology, Department of Internal Medicine, Kocaeli, Turkey; [4]Ankara University, Division of Rheumatology, Department of Internal Medicine, Ankara, Turkey; [5]Çukurova University, Division of Rheumatology, Department of Internal Medicine, Adana, Turkey; [6]University of Health Sciences Turkey, Division of Rheumatology, Department of Internal Medicine, Ankara, Turkey; [7]Akdeniz University , Department of Dermatology and Venereology, Antalya, Turkey; [8]Osmangazi University, Division of Rheumatology, Department of Internal Medicine, Eskisehir, Turkey; [9]Istanbul University, Department of Physiology, Istanbul, Turkey; [10]University of Pittsburgh, Departments of Pediatrics, Medicine, and Immunology, Pittsburgh, United States of America.

Abstract N° : 189

INTRODUCTION

Behçet's disease is a chronic inflammatory illness characterized by recurrent oral and genital ulcers, among other clinical symptoms. The prevalence of clinical features in Behçet's disease can vary among different geographical locations, and patients can show heterogeneity in their manifestations. There is strong evidence to support a role for genetic susceptibility in the etiology of Behçet's disease.

OBJECTIVE

The purpose of this study was to investigate the genetics underlying specific clinical features of Behçet's disease using a case-case genetic association analysis.

METHODS

SAMPLE

- A total of 436 patients with Behçet's disease from Turkey with >20 years of follow up were studied.
- Ten clinical features were evaluated.

GENOTYPING AND IMPUTATION

- Genotyping was performed using the Infinium ImmunoArray-24 BeadChip.
- The Michigan Imputation Server using Minimac2 and the TOPMed Imputation Reference panel were used.

ANALYSIS

- Susceptibility loci for Behçet's disease and genome-wide single nucleotide polymorphisms (SNPs) were tested for each clinical trait.
- A weighted genetic risk score (GRS) using previously identified susceptibility loci for Behçet's disease was calculated for each clinical trait.

RESULTS

Table 1. Nominally significant associations of previously identified genetic risk loci for Behçet's disease. A case-case genetic association analysis in patients with compared to without individual clinical features was performed.

Clinical feature	Chr	Bp	SNP ID	Gene	Effect allele	OR	P-value
Ocular lesions	6	31381371	rs116799036	*HLA-B*	A	1.85	1.10×10^{-4}
	2	112775308	rs3783550	*IL1A*	T	1.46	7.91×10^{-3}
	6	29750443	rs114854070	*HLA-A*	A	1.46	1.40×10^{-2}
Arthritis	10	62701513	rs224127	*ADO*	A	0.67	4.01×10^{-3}
Arterial involvement	1	206771300	rs1518111	*IL10*	T	0.29	4.61×10^{-3}
	6	31131984	rs12525170	*HLA-C*	A	0.29	1.65×10^{-2}
Erythema nodosum	6	31131984	rs12525170	*HLA-C*	A	1.52	1.32×10^{-2}
	6	31381371	rs116799036	*HLA-B*	A	1.36	4.51×10^{-2}
Pseudo-folliculitis	10	62701513	rs224127	*ADO*	A	0.68	1.51×10^{-2}
	3	46164194	rs7616215	*CCR3*	C	0.68	3.88×10^{-2}
Neurological involvement	1	67294457	rs924080	*IL12RB2*	C	0.55	1.78×10^{-2}
	3	159929885	rs17753641	*IL12A*	G	0.21	3.41×10^{-2}
Gastrointestinal involvement	6	137193653	rs4896243	*IFNGR1*	C	2.79	3.16×10^{-2}
Vascular involvement	1	206771300	rs1518111	*IL10*	T	0.72	4.78×10^{-2}
	3	159929885	rs17753641	*IL12A*	G	0.50	4.96×10^{-2}

Abbreviations: Bp, base pair; chr, chromosome; OR, odds ratio.
All positions are in GRCh38 build. The analyses were performed using logistic regression adjusting for sex and the first five genetic principal components.

Figure 1. Manhattan plot depicting the top genome-wide genetic associations described in Behçet's disease patients with ocular lesions. Y and X axes refer to the $-\log_{10}$(P) value and chromosome positions, respectively. The red horizontal line indicates the genome-wide association threshold (P-value $<5\times10^{-8}$) and the blue line refers to the suggestive threshold (P-value $<1\times10^{-5}$).

Table 2. Genome-wide associations in clinical sub-phenotypes in Behçet's disease with P-value $<1\times10^{-5}$. The most significant genetic variant in each locus for each sub-phenotype is shown.

Clinical feature	Chr	Bp	SNP ID	Gene	Effect allele	Allele freq	OR (95% CI)	P-value
Ocular lesions	20	62675341	rs6062789	*SLCO4A1*	G	0.27	0.41 (0.30-0.58)	1.92x10-7
Neurological involvement	4	168762849	rs62334264	*DDX60L*	T	0.09	4.12 (2.34-7.24)	8.85x10-7
Genital aphthosis	10	93215254	rs12220128	*CYP26A1*	C	0.07	0.22 (0.12-0.34)	1.14x10-6
Arterial involvement	19	29421622	rs892076	*VSTM2B*	A	0.06	13.06 (4.63-36.85)	1.20x10-6
Arterial involvement	12	47920979	rs73111983	*VDR*	T	0.02	32.95 (7.86-138.10)	1.75x10-6
Neurological involvement	20	19577919	rs6106107	*RIN2*	G	0.02	16.86 (5.29-53.74)	1.77x10-6
Genital aphthosis	15	87564501	rs11073721	*NTRK3*	C	0.12	0.27 (0.16-0.46)	1.87x10-6
Gastrointestinal involvement	5	56220143	rs75274358	*ANKRD55*	A	0.01	72.22 (12.03-433.50)	2.86x10-6
Ocular lesions	5	116475009	rs592391	*SEMA6A*	G	0.31	0.49 (0.36-0.66)	4.39x10-6
Arthritis	22	50679152	rs9616915	*SHANK3*	C	0.44	0.50 (0.37-0.67)	5.02x10-6
Neurological involvement	6	28121455	rs960872412	*ZSCAN16*	A	0.11	3.25 (1.95-5.42)	6.18x10-6
Genital aphthosis	11	3150587	rs75048411	*OSBPL5*	T	0.01	0.08 (0.03-0.23)	6.73x10-6
Erythema nodosum	6	31268274	rs2524099	*HLA-C*	G	0.35	0.51 (0.38-0.69)	9.69x10-6

Genetic associations with P-value < 1x10-5 were considered suggestive.
Abbreviations: Allele freq, allele frequency; bp, base pair; chr, chromosome; CI, confidence interval; OR, odds ratio; SNP, single-nucleotide polymorphism.

Figure 2. Genetic risk score (GRS) distribution in Behçet's disease patients with (blue) and without (orange) ocular lesions. Distribution curves of GRS were calculated with Behçet's disease susceptibility alleles (A) including and (B) excluding all SNPs in the HLA region.

CONCLUSION

Our results highlight the role of genetic factors in predisposing to specific clinical traits in Behçet's disease. These results shed new insights into the genetic risk and pathogenesis of specific clinical manifestations of Behçet's disease, particularly ocular and neurological involvement.

This work was supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIH) grant number R01AR070148.

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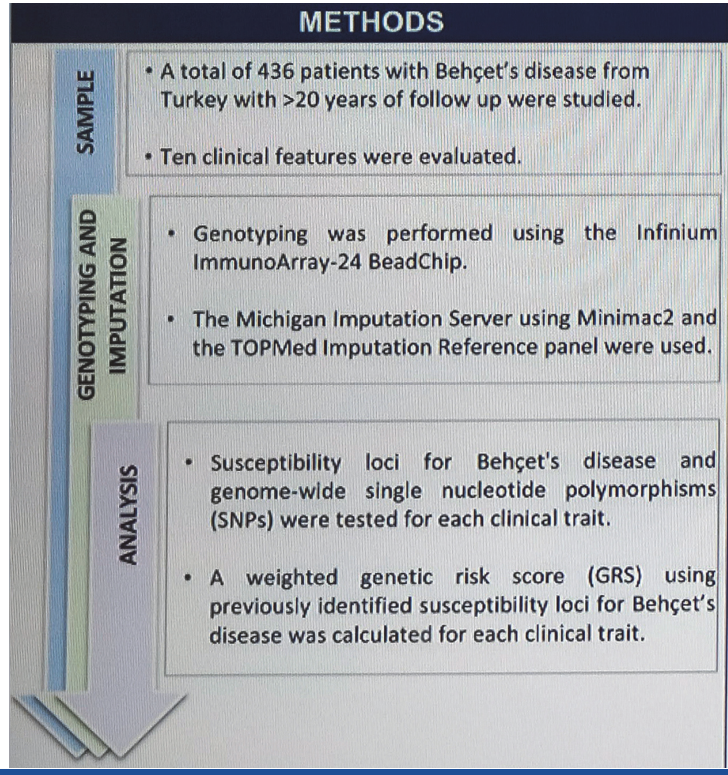
Objetivos:

- Investigar **genética subyacente** a **características clínicas específicas EB** grupo pacientes con > 5 años seguimiento

Métodos:

- **436 EB** Turquía
- Genotipado **Infinium ImmunoArray-24 BeadChip**
- Imputación y medidas de control de calidad
- Analizan los **loci susceptibles** para **EB** y **SNPs** para cada **rasgo clínico**
- **Score de riesgo genético ponderado** para cada característica clínica utilizando loci susceptible para EB identificados previamente.



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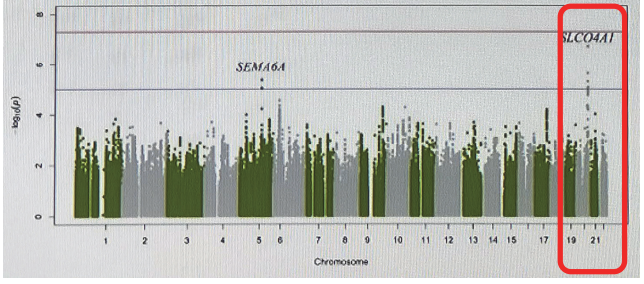
Resultados:

- **Asociación genética** entre **lesiones oculares y HLA-B/MICA** (rs116799036: OR=1,85, IC 95%=1,35-2,52, valor p=1,1x10).
- **Puntuación riesgo genético** significativamente **>** **EB + lesiones oculares** vs no afectación ocular (variación genética región HLA)
- **Nuevos loci** genéticos **predisponen** a **características clínicas** específicas EB
- **Asociaciones + significativas**:
  - *afectación ocular* → *SLCO4A* (rs6062789: OR=0,41 (IC 95%=0,30-0,58), valor de p=1,92x10)
  - *afectación NRL* → *DDX60L* (rs62334264: OR= 4,12 (IC del 95%: 2,34 a 7,24), valor de p = 8,85x10)

Figure 1. Manhattan plot depicting the top genome-wide genetic associations described in Behçet's disease patients with ocular lesions. Y and X axes refer to the $-\log_{10}(P)$ value and chromosome positions, respectively. The red horizontal line indicates the genome-wide association threshold (P-value $<5x10^{-8}$) and the blue line refers to the suggestive threshold (P-value $<1x10^{-5}$).



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Genital aphthosis	11	3150587	rs75048411	*OSBPL5*	T	0.01	0.08 (0.03-0.23)	6.73x10-6
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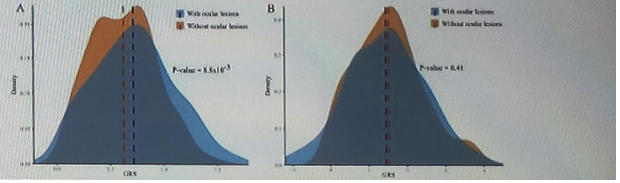

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Conclusión:

- Resultados enfatizan papel **factores genéticos** en **predisposición** a **manifestaciones clínicas específicas EB**
- Podría arrojar luz adicional sobre **heterogeneidad**, **patogenia** y **variabilidad presentación** de EB **≠ poblaciones**

FIRST EVIDENCE FOR EFFICACY OF CAR-T CELL TREATMENT IN REFRACTORY ANTISYNTHETASE SYNDROME

J. Taubmann[1,2], F. Müller[2,3], S. Boeltz[1,2], J. Knitza[1,2], S. Völkl[2,3], M. Aigner[2,3], A. Kleyer[1,2], I. Minnopoulou[1,2], F. Locatelli[4], M. A. D'agostino[5], R. Gary[2,3], S. Krestchmann[2,3], S. Kharboutli[2,3], D. Mougiakakos[2,3,6], G. Krönke[1,2], M. Andreas[2,3], G. Schett[1,2]

First evidence for efficacy of CAR-T-cell treatment in refractory antisynthetase syndrome

EULAR POS1238

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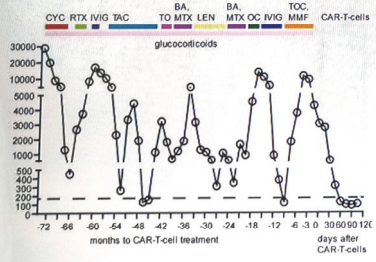
Introduction

Idiopathic inflammatory myopathies (IMM) are a heterogenic group of rare autoimmune diseases classified by muscle inflammation (myositis). Autoantibodies against (tRNA) synthetases (e.g. anti-Jo-1) are a hallmark of a subgroup called antisynthetase syndrome (ASS), that affects muscles, joints, skin and lung. ASS can be very severe and life-threatening needing effective and fast treatment. Due to its rarity and heterogeneity medical management remains challenging.

Cases

Compassionate use program for two anti-Jo-1 positive ASS patients (patient 1: 41year old male, patients 2: 43year old female) with severe ASS showing organ involvement and resistance to multiple immune suppressive treatments to prove safety and efficacy of anti CD 19 CAR-T-cell therapy. Both patients presented with active myositis. Patient 1 did not respond to five different immunosuppressive treatments including cyclophosphamide and rituximab (publication QR-code), patient 2 did not respond to 11 treatments including cyclophosphamide, rituximab and ocrelizumab (Figure 1, creatinine kinase concentrations before and after treatment with CD19 CAR-T-cells and the timing of previous treatments in patient 2).



Anti CD19 CAR-T-cell therapy

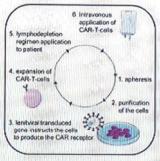


Figure 2) Autologous CD19 CAR-T-cells were prepared from leukapheresis specimen after enrichment of T-cells and transfection with MB-CART19.1 lentiviral vector (Miltenyi) encoding for a 4-1BB based CAR targeting CD19. Cells were expanded for 12 days and 1 million CAR-T-cells/kg body weight were administered as a single intravenous infusion after standard conditioning therapy with cyc/flu, as described previously [1, 2, 3]. All disease related treatments were stopped before CAR-T-cell administration.

Results

CAR-T-cell treatment was well tolerated. Only mild CRS (grade I) was observed in both patients. Patient 2 had signs of mild self-limited ICANS (grade I, discrete ataxia) for a few days after CAR-T-cell treatment. In patient 1, CAR-T cells expanded to a maximum of 60 cells/µl on day 8, in patient 2 max. 1524 cells/µl on day 8. Expansion of CAR-T cells paralleled with the complete depletion of circulating B-cells. B-cell aplasia lasted for 119 days in patient 1 and 93 days in patient 2. Both patients experienced normalization in creatine kinase level (CK), major clinical improvement according to the 2016 TIS and could stop all immunosuppressive therapy. At the latest follow up (+ 365 days and + 180 days) both patients were in drug-free remission.

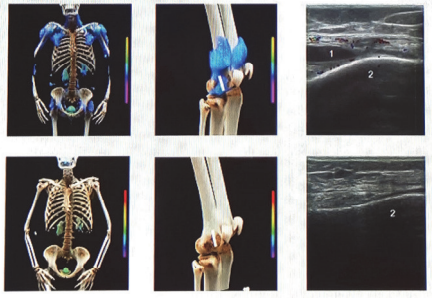


Figure 3) Cinematic rendering reformatted upper body FAPI-PET-CT scans (done in patient 2) at baseline (top) and follow up (bottom) showing a significant reduction in (left) muscle and (middle) joint fibroblast activity (blue). (right) Correlating knee ultrasound showing resolution of edema (1).

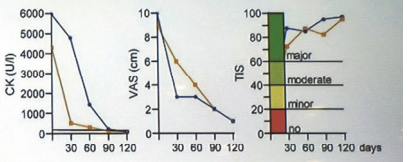


Figure 4) Concentrations of serum creatinine kinase (CK), patient 1 (blue dots) with baseline CK levels of 5969 U/l (norm <170 U/l) and 70 U/l at +120 days; patient 2 (orange squares) with baseline CK at 4298 U/l and 94 U/l at + 120 days (left graph); Patient global assessment using visual analogue scale (VAS) [0.0 – 10.0 cm] (middle); Disease activity assessed with the ACR/EULAR total improvement score (TIS), showing cutoffs for major, moderate, minor, or no improvement (right) in days after CAR-T-cell treatment.

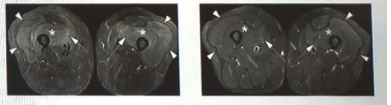


Figure 5) Follow-up MRI (right) shows complete resolution of signal changes and normalization of muscle signal in the same locations, i.e. M. vastus lateralis (arrowheads), M. vastus medialis (arrows) and M. vastus intermedius (asterisks).

Conclusion

Taken together, these data suggest that CD19 CAR-T-cell therapy provides a possibility to intercept with severe ASS leading to drug-free remission, resolution of muscle and lung inflammation and abrogation of disease-associated autoimmunity.

[1] Mouglakakos D. et al., N Engl J Med 2021; [2] Mackensen A. et al., Nat Med 2022; [3] Mueller F. et al., The Lancet 2023; The case was supported by the Deutsche Forschungsgemeinschaft (FOR2886, CRC1181 and TRR221), the Bundesministerium für Bildung und Forschung (BMBF; MASCARA), the European Union (ERC Synergy grant 4D Nanoscope, ERC Consolidator grant INSPIRE) and the IMIfunded project RTCure. We thank S. Milteryi for fruitful discussions, D. Werner and J. Hofer for assistance, and Dr. Klaus Engel (Siemens Healthineers, Erlangen) for cinematic rendering of FAPI PET CT images. Disclosures: none declared

FIRST EVIDENCE FOR EFFICACY OF CAR-T CELL TREATMENT IN REFRACTORY ANTISYNTHETASE SYNDROME

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Objetivos:

- Evaluar administración c CD19 **CAR-T** es **tolerable** y **efectiva SAS refractario** y **grave**

Métodos:

- Se administran 1 millón c CAR-T/kg en infusión ev única después de CFM/fludarabina
- Todos ttos enfermedad se suspendieron
- Seguimiento hospitalario
  - primeros 10 d
  - semanal/1 m
  - mensual/3 m

Evaluación:

- ***Tolerabilidad*** **:** monitorización sd liberación citoquinas (SLC) y el sd Neurotoxicidad asociado a c inmunoefectoras
- ***Eficacia***: niveles CK, buena respuesta según 2016 ACR/EULAR total improvement score (TIS), imágenes musculares y pulmonares y suspensión todos IS (GC)

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Resultados:

	Paciente 1	Paciente 2
Sexo, edad	♂ 41 años	♀ 43 años
Afectación muscular	miositis activa CK ↑	
Afectación otros órganos	cutánea y pulmonar	cutánea, pulmonar y articular
Tto IS previo	5 IS (CFM y RTX)	10 IS (CFM, RTX y ocrelizumab)
Tolerancia	SLC leve	SLC leve SNCIE leve autolimitado
Expansión máx c CAR-T día 8	60 células/µl	1524 células/µl
Aplasia células B	119 días	Aplasia (día 60)
CK	9305 → 70 U/l	3055 → 311 U/l
2016 ACR/EULAR total improvement score (TIS)	mejoría clínica importante	
Suspensión IS	Si	
TAC pulmón/RMN muscular	resolución inflamación alveolar Ausencia cambios inflamatorios músculos	
Último seguimiento	120 días Remisión sin IS	60 días Remisión sin IS
Ac anti-Jo1	331 → 25 UI	?

Conclusiones:

- Terapia c CAR-T brinda posibilidad interceptar ASS grave: remisión libre fármacos, resolución inflamación muscular y pulmonar y anulación autoinmunidad asociada a enfermedad.

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