69 CONGRESO NACIONAL
SOCIEDAD ESPAÑOLA DE FARMACIA HOSPITALARIA

A CORUÑA
17-19 OCT 24

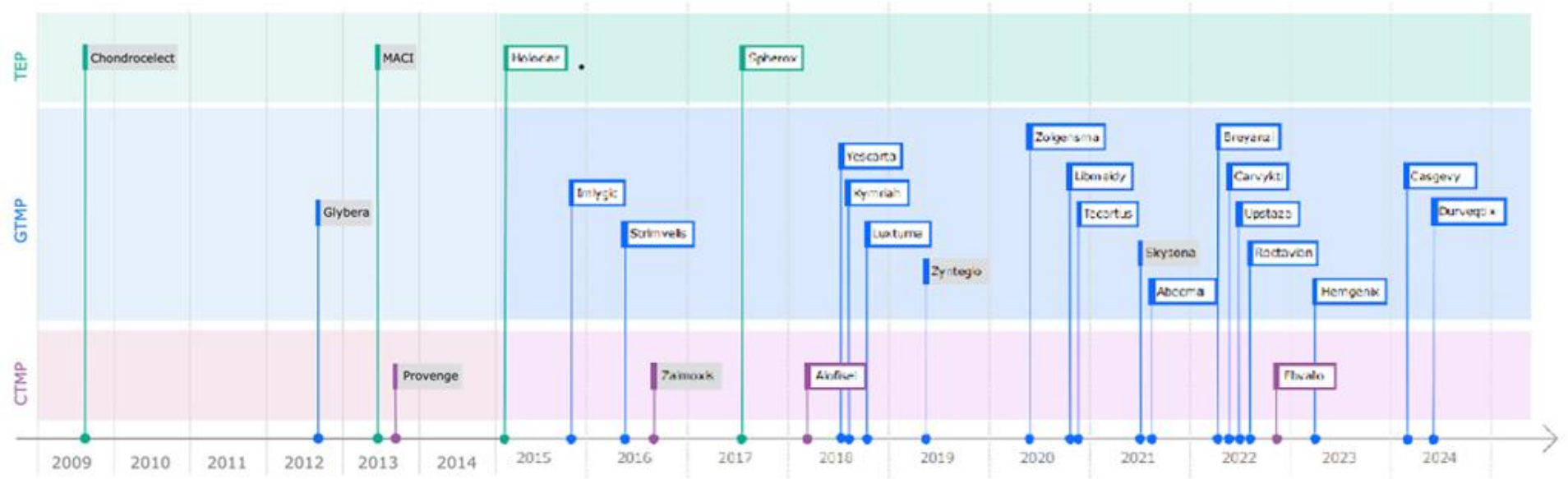
RETOS DE LOS SERVICIOS DE FARMACIA ANTE LOS MEDICAMENTOS DE TERAPIA AVANZADA: AHORA O NUNCA

MTAs DISPONIBLES: EFICACIA, SEGURIDAD Y PROTOCOLOS FARMACOCLÍNICOS

Joan Vinent Genestar
Jefe de la Unidad de Farmacia Oncológica
Pediatric Cancer Center Barcelona
Hospital Sant Joan de Déu

sefh
Sociedad Española de Farmacia Hospitalaria

MTAs aprobados por la EMA



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A CORUÑA 17-19 OCT 24

TEP Tissue engineered product
GTMP Gene therapy medicinal product
CTMP Cell therapy medicinal product
Withdrawn / Marketing authorisation not renewed

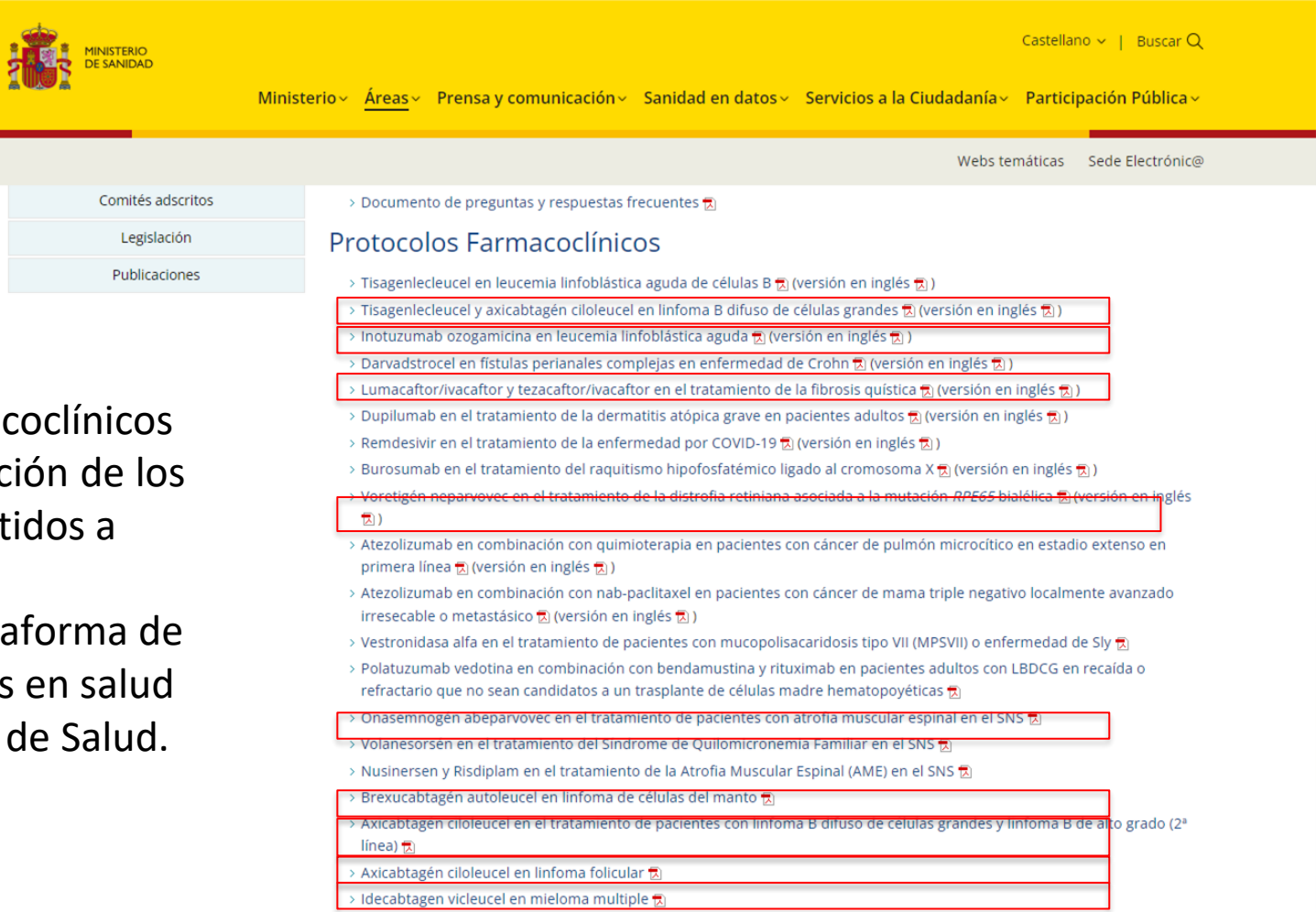
Advanced therapy medicinal products

EMA

MTAs con autorización de uso por la AEMPS mediante la cláusula de exención hospitalaria

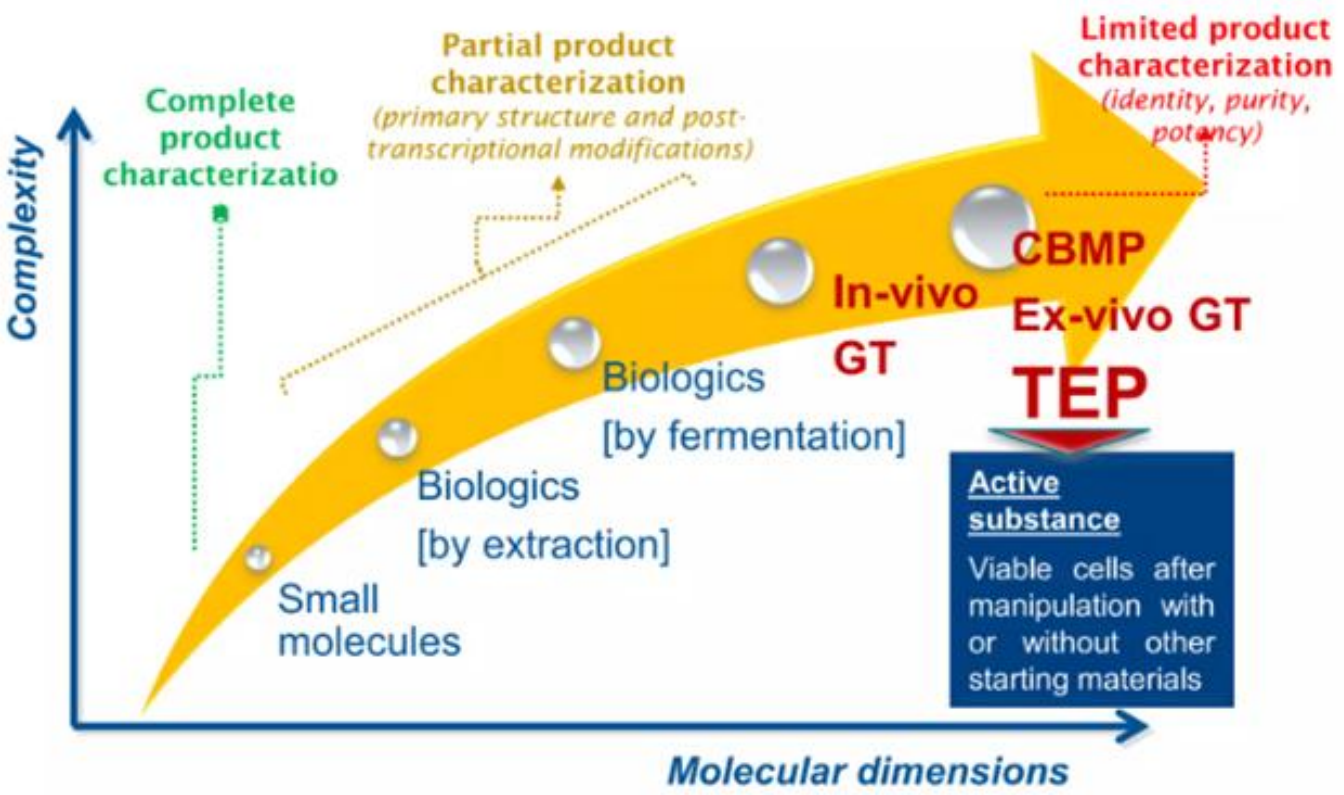
Nombre	Titular de la autorización de uso	Fecha autorización de uso	Ficha técnica	Prospecto	Material de prevención de riesgos
NC1 – Suspensión celular en plasma autólogo 100-300×10^6 células, jeringa precargada	Hospital Universitario Puerta de Hierro Majadahonda	29-01-2019	Ficha técnica	Prospecto	
ARI-0001 Dispersión para perfusión que contiene 0,1-1×10^6 células/kg	Hospital Clínic de Barcelona	01-02-2021	Ficha técnica	Prospecto	
CEMTROCELL 50.000 células/microlitro – Suspención para implantación	Clínica Cemtro S.A.	31-10-2023	Ficha técnica	Prospecto	
Piel humana obtenida por ingeniería de tejidos 1,0-1,5 x 10^6 / 1,5-3,0 x 10^6 células / lámina apósito impregnado	Hospital Universitario Virgen del Rocio – Sevilla	06-06-2024	Ficha técnica	Prospecto	
ARI0002H 13,5-720 X 10^6 Células dispersión para perfusión	Hospital Clínic de Barcelona	08-08-2024	Ficha técnica	Prospecto	

https://www.aemps.gob.es/medicamentos-de-uso-humano/medicamentos-de-fabricacion-no-industrial/terapias-avanzadas/listado-de-autorizacion-de-uso/

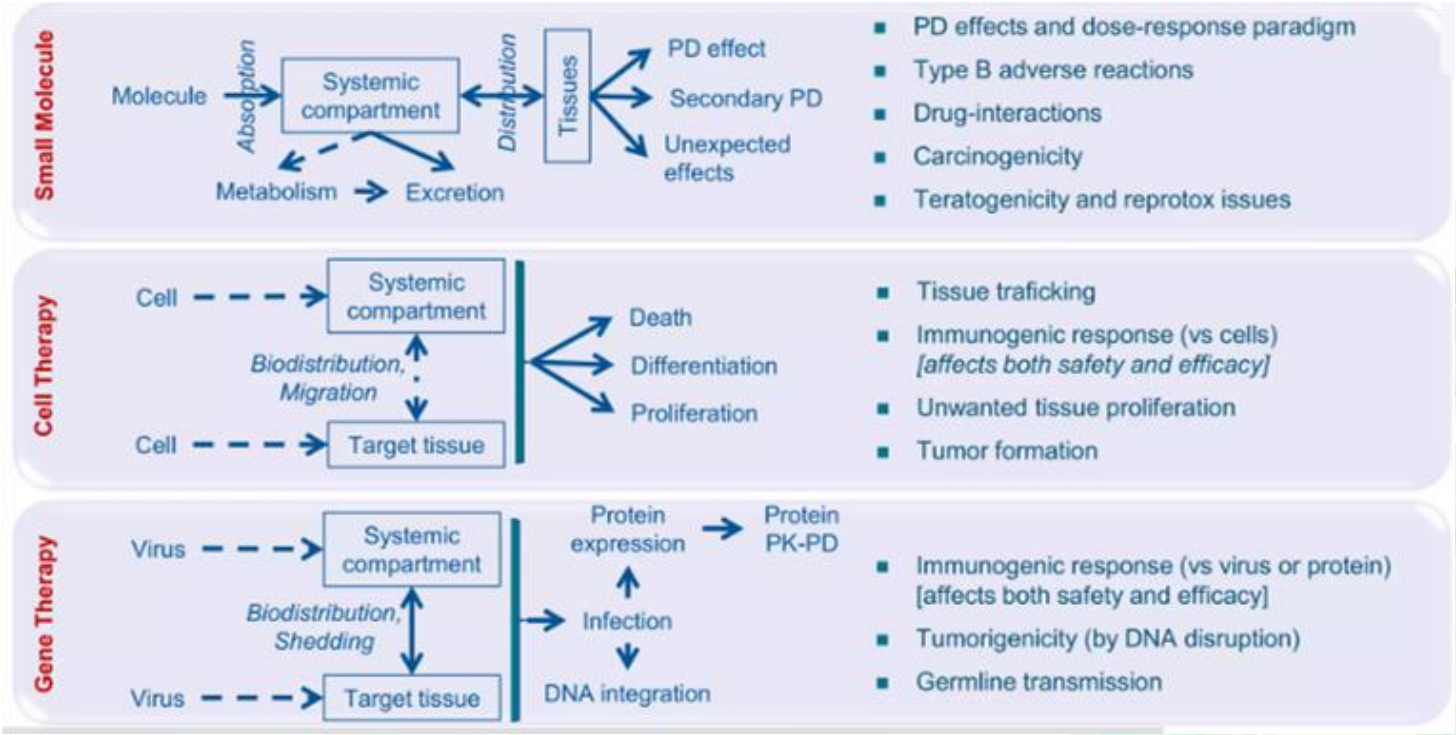


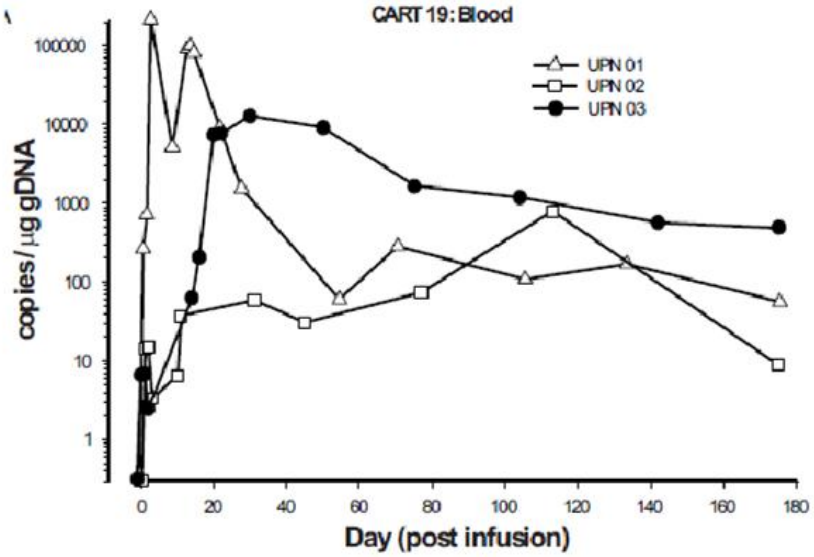
Los protocolos farmacoclínicos que marcan la utilización de los medicamentos sometidos a seguimiento a través de Valtermed, la plataforma de registro de resultados en salud del Sistema Nacional de Salud.

https://www.sanidad.gob.es/areas/farmacia/infoMedicamentos/valtermed/home.htm


Complete product characterizatio
Partial product characterization
(primary structure and post-transcriptional modifications)
Limited product characterization
(identity, purity, potency)
Complexity
Small molecules
Biologics [by extraction]
Biologics [by fermentation]
In-vivo GT
CBMP
Ex-vivo GT
TEP
Active substance
Viable cells after manipulation with or without other starting materials
Molecular dimensions

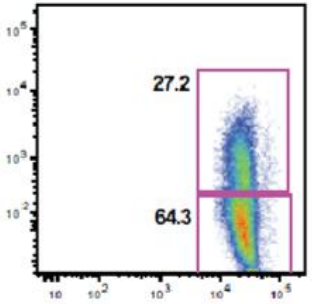
PKPD


Small Molecule
Molecule
Absorption
Systemic compartment
Distribution
Tissues
PD effect
Secondary PD
Unexpected effects
Metabolism
Excretion
PD effects and dose-response paradigm
Type B adverse reactions
Drug-interactions
Carcinogenicity
Teratogenicity and reprotox issues
Cell Therapy
Cell
Systemic compartment
Biodistribution, Migration
Cell
Target tissue
Death
Differentiation
Proliferation
Tissue traficking
Immunogenic response (vs cells)
[affects both safety and efficacy]
Unwanted tissue proliferation
Tumor formation
Gene Therapy
Virus
Systemic compartment
Biodistribution, Shedding
Virus
Target tissue
Protein expression
Protein PK-PD
Infection
DNA integration
Immunogenic response (vs virus or protein)
[affects both safety and efficacy]
Tumorigenicity (by DNA disruption)
Germline transmission



CART19 cells proliferate 2 to 4 log10 in all patients in vivo

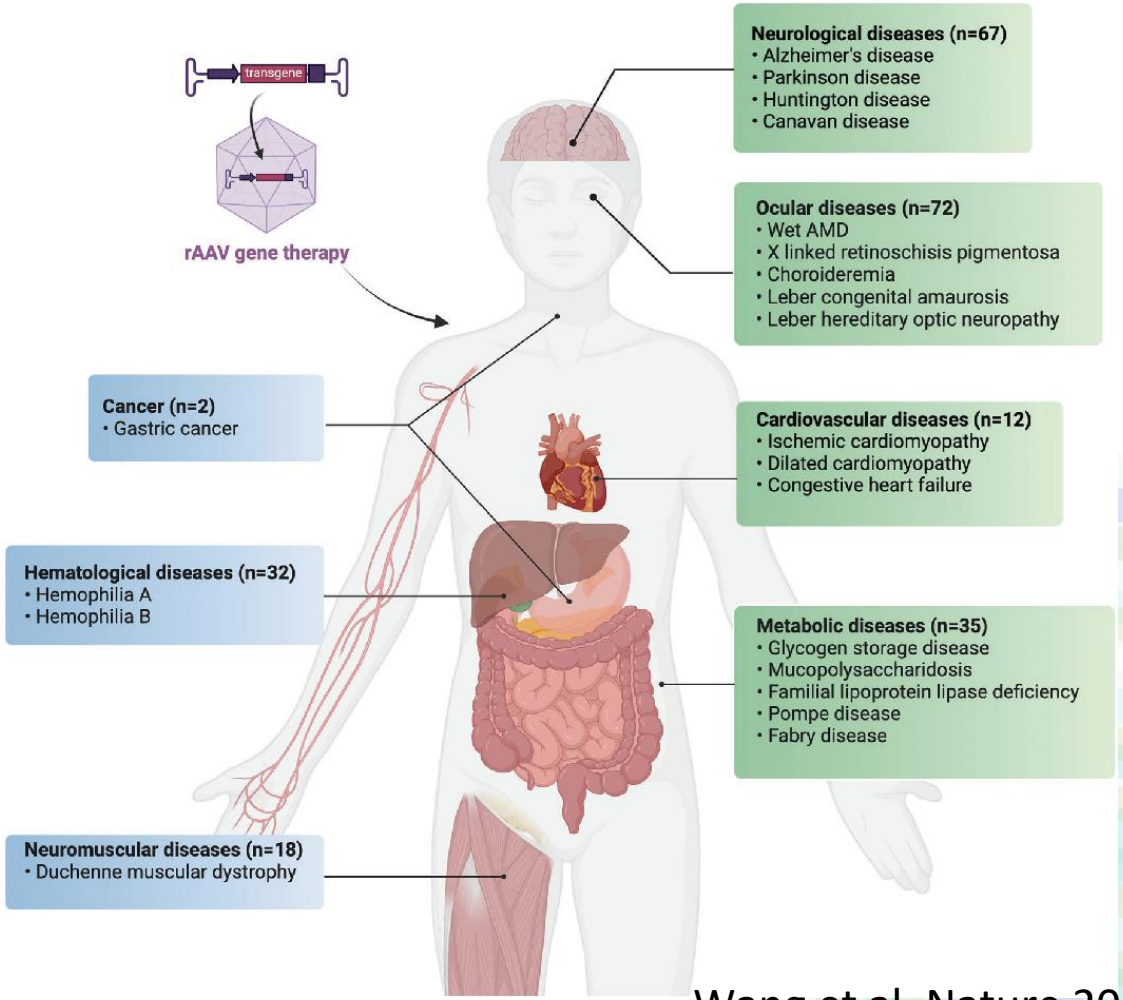
CD8 Day 56



1. Sustained delivery with a single infusion!
2. CARs expressed for at least 10+ years

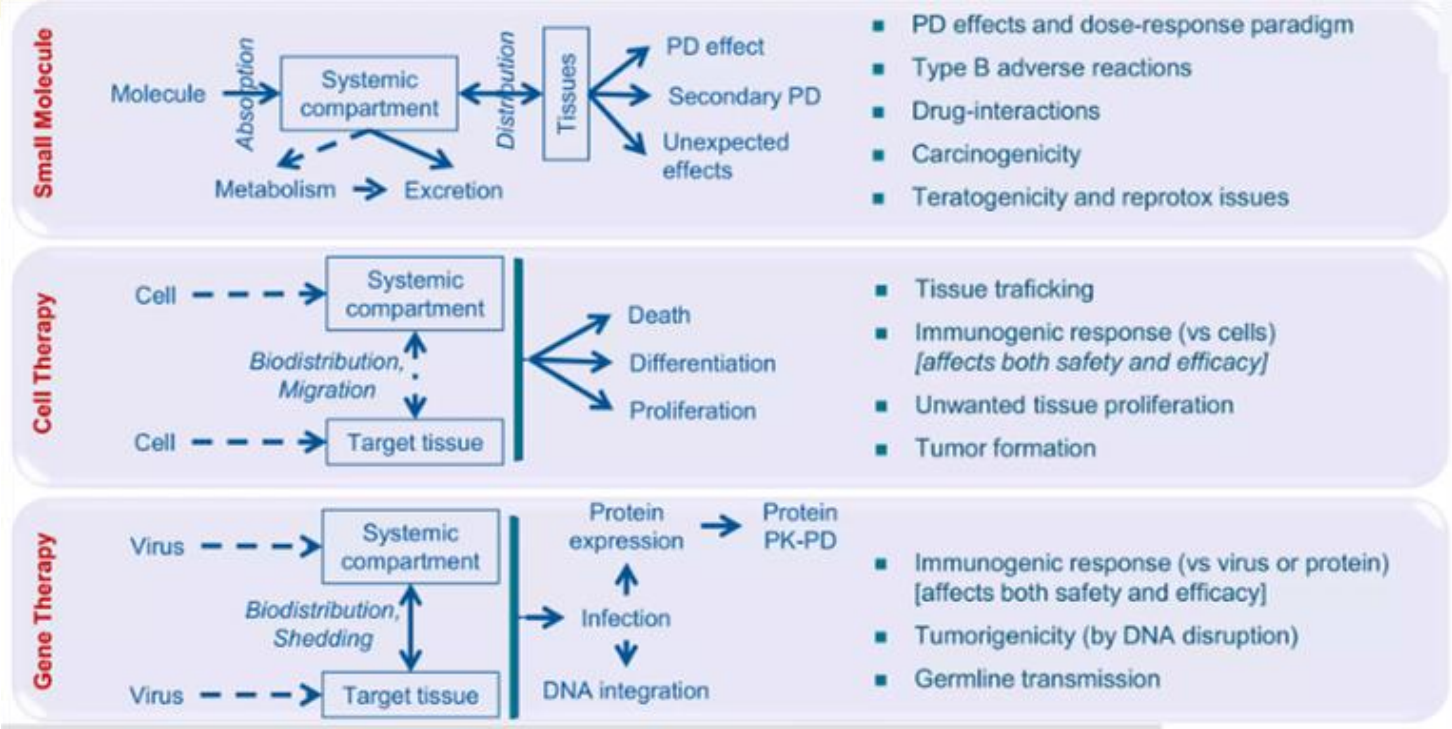
Porter NEJM 2011
Kalos STM 2011

AAV han emergido como uno de los vectores más habituales.



Wang et al. Nature 2024

EFICACIA Y SEGURIDAD



DESARROLLO CLÍNICO

- Población
- Intervención
- Diseño del estudio
- Resultados
- Evidencia de práctica clínica real

POBLACIÓN

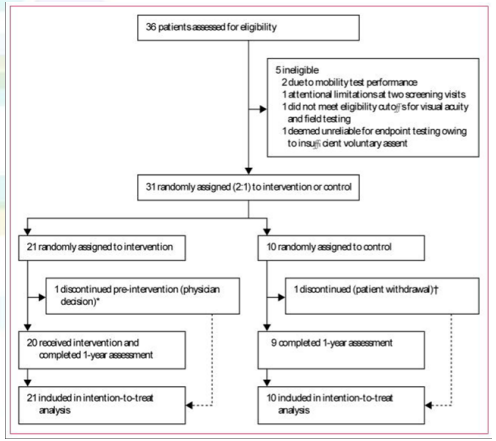
- La mayoría de los ECs con MTAs se han centrado en enfermedades raras y ultrararas, como hemos visto en las autorizaciones de la EMA.
- Los estudios tienen tamaños de muestra pequeños.

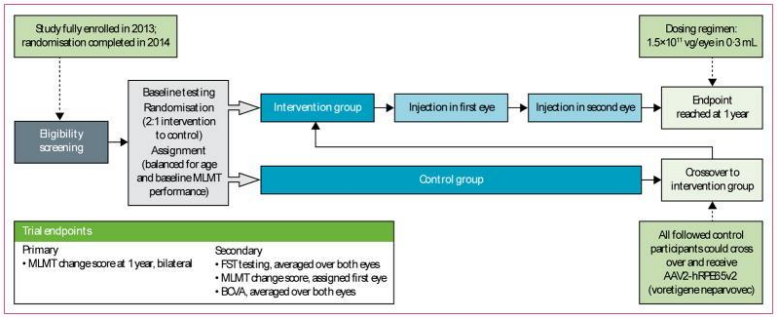
AMAUROSIS CONGÉNITA DE LEBER II (RPE65)

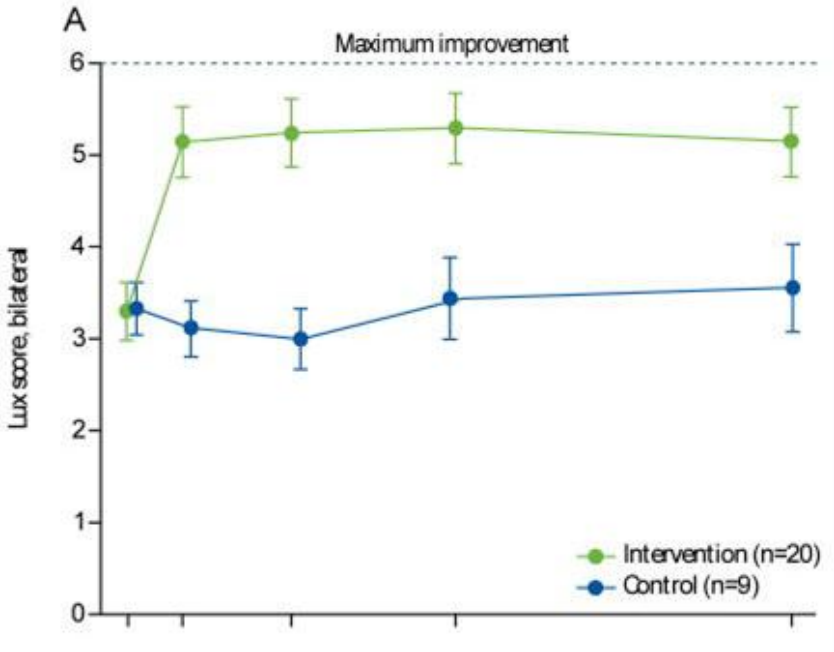
- Enfermedad congénita de la retina. por mutación bialélica del gen RPE65.
- Autosómica recesiva 1/100 mil RN.
- Pérdida progresiva de visión, nistagmus, hipermetropía.
- Ayudas ópticas (filtros contraste, lupas para magnificar visión cercana.

https://luxturna.com/about-luxturna/

VORETRIGÉN NEPARVOVEC (LUXTURNA®)







Media de la prueba de movilidad luminiscente bilateral (MLMT)

Russel S et al. Lancet 2017

VORETRIGÉN NEPARVOVEC (LUXTURNA®)

MINISTERIO DE SANIDAD

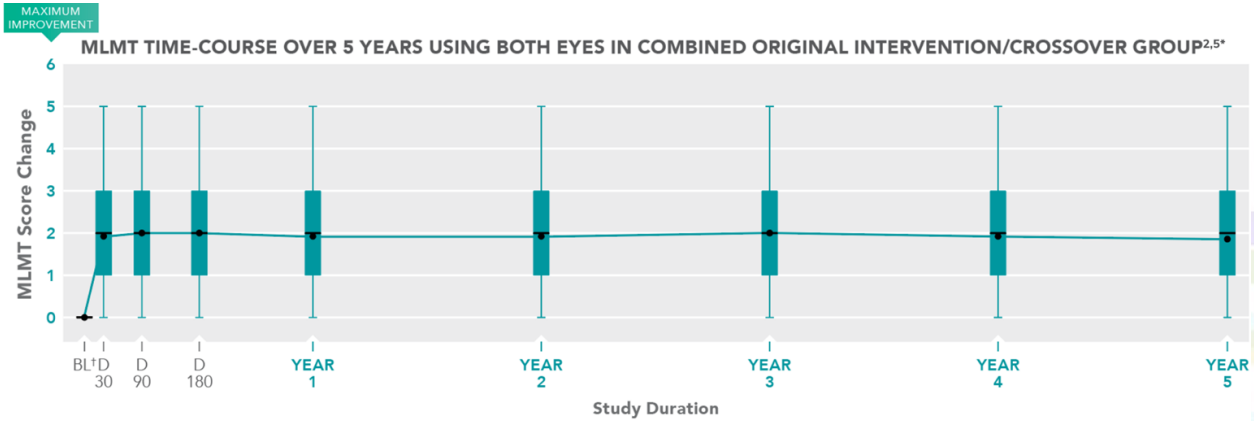
SECRETARÍA DE ESTADO DE SANIDAD

DIRECCIÓN GENERAL DE CARTERA COMÚN DE SERVICIOS DEL SNS Y FARMACIA

PROTOCOLO FARMACOCLÍNICO DEL USO DE VORETIGÉN NEPARVOVEC EN EL TRATAMIENTO DE LA DISTROFIA RETINIANA ASOCIADA A LA MUTACIÓN RPE65 BIALÉLICA EN EL SISTEMA NACIONAL DE SALUD

Aprobado por la Comisión Permanente de Farmacia

04/05/2021



ELIANA: TISAGENLECLEUCEL (KYMRIAH®)

TABLE 1. Patient Demographics and Clinical Characteristics

Characteristic	All Patients (N = 79)	Post-Infusion alloSCT (n = 17)	No Post-Infusion alloSCT (n = 62)
Age, years, median (range)	11 (3-24)	9 (4-21)	12 (3-24)
Sex, male, No. (%)	45 (57)	13 (77)	32 (52)
Prior HSCT, No. (%)	48 (61)	6 (35)	42 (68)
Previous lines of therapy, No., median (range)	3 (1-8)	2 (2-4)	3 (1-8)
Disease status, No. (%)			
Primary refractory	6 (8)	1 (6)	5 (8)
Relapsed	73 (92)	16 (94)	57 (92)
Morphologic blast count in bone marrow, %, median (range)[a]	74 (5-99)	84 (9-99)	72 (5-96)
CNS status classification, No. (%)			
CNS-1[b]	68 (86)	16 (88)	52 (84)
CNS-2	10 (13)	1 (6)	9 (15)
Unknown	1 (1)	0	1 (2)
High-risk genomic lesions,[c] No. (%)	30 (38)	9 (53)	21 (34)
Down syndrome, No. (%)	6 (8)	1 (6)	5 (8)

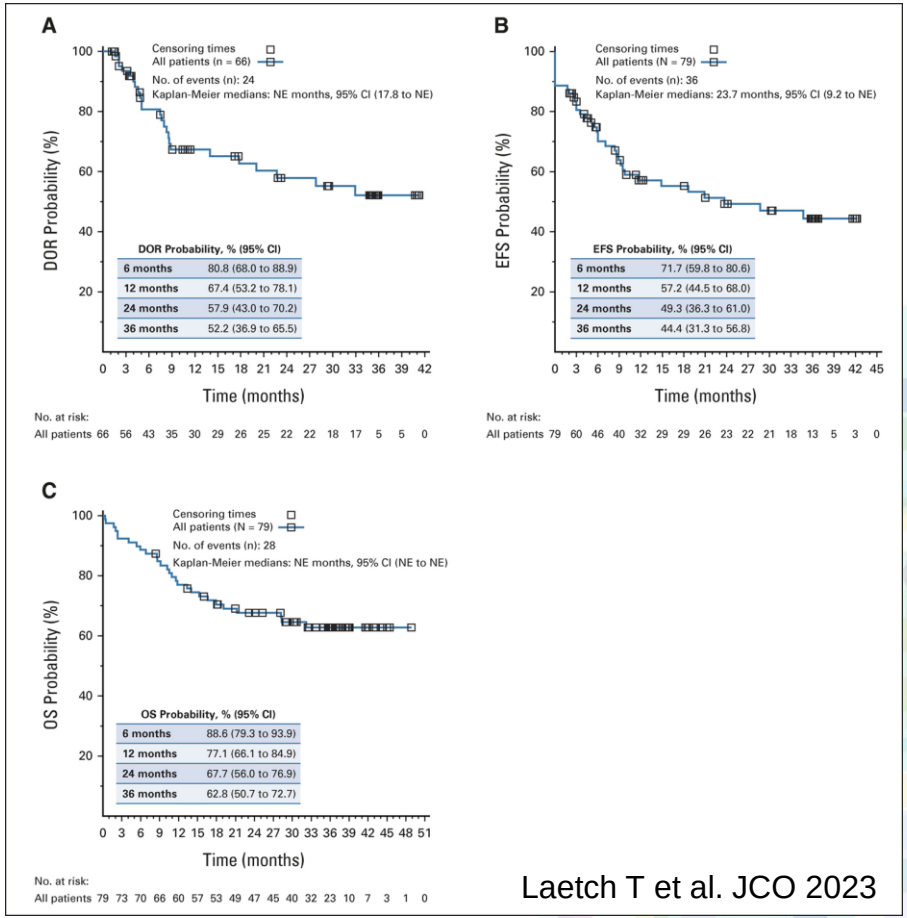
NOTE. Baseline demographics, clinical characteristics, and serum biomarkers constitute the last nonmissing observation prior to tisagenlecleucel infusion. Baseline is defined as the most current assessment on or prior to the date of enrollment.

Abbreviations: alloSCT, allogeneic stem cell transplant; HSCT, hematopoietic stem cell transplant.

[a]Morphologic blast count in bone marrow is the maximum from biopsy or aspirate prior to enrollment.

[b]One patient was CNS-1 prior to infusion and subsequently CNS-3 by unscheduled assessment on day 13 post infusion.

[c]BCR-ABL1, MLL rearrangement, hypoploidy, lesions associated with BCR-ABL1–like gene signature, or complex karyotype (≥ 5 unrelated abnormalities).



Laetch T et al. JCO 2023

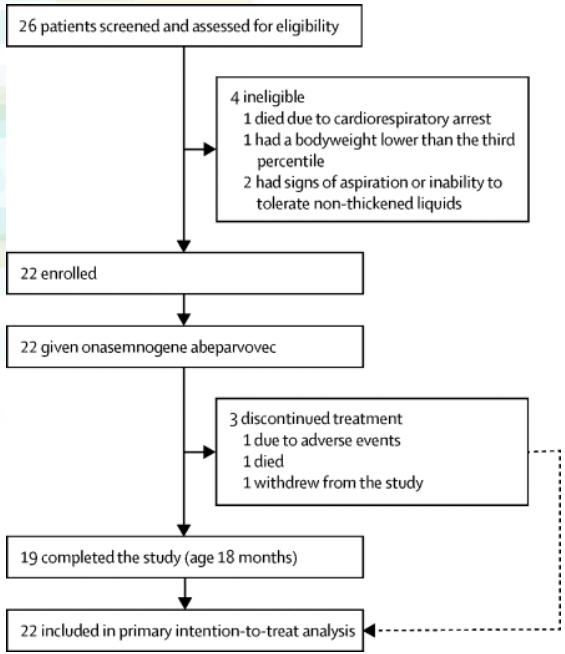
69 CONGRESO NACIONAL SOCIEDAD ESPAÑOLA DE FARMACIA HOSPITALARIA
A CORUÑA 17-19 OCT 24

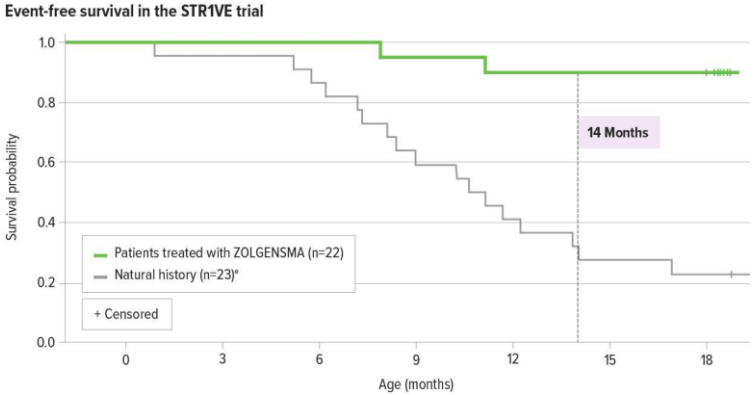
ATROFIA MUSCULAR ESPINAL (AME)

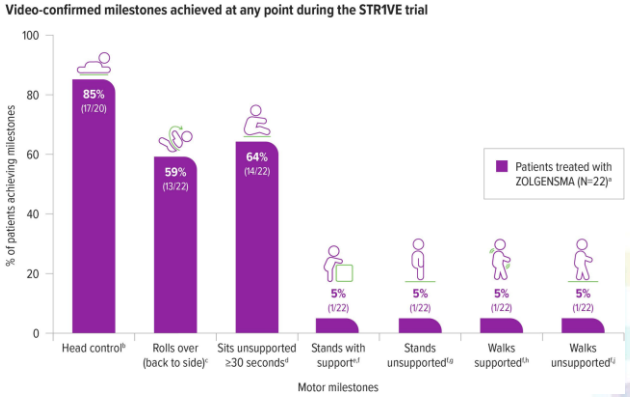
- Enfermedad congénita autosómica recesiva 1/10 mil RN.
- Degeneración de las motoneuronas y atrofia progresiva proximal.
- Alteración del gen SMN1
- Tipo 1, infantil (50-60%), 2c SMN2 (73%) y 3c SMN2 (20%)
- Debilidad muscular, hipotonía generalizada, no llegan a sostener cabeza ni consiguen sedestación.
- Soporte ventilatorio y nutricional

https://www.zolgensma-hcp.com/understanding-sma/what-is-sma/

STR1VE: ONASEMNOGENE ABEPARVOVEC (ZOLGENSMA®)







Day W J et al. Lancet Neurol 2021

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A CORUÑA 17-19 OCT 24

PROTOCOLO FARMACOCLÍNICO ZOLGENSMA®

Excluye pacientes presintomáticos con 3 copias del gen SMN2 debido a una falta percibida de datos de esta población de pacientes, a pesar que este grupo está cubierto el la FT.

PROTOCOLO FARMACOCLÍNICO DEL TRATAMIENTO CON ONASEMNOGÉN ABEPARVOVEC (ZOLGENSMA®) EN PACIENTES CON ATROFIA MUSCULAR ESPINAL EN EL SISTEMA NACIONAL DE SALUD.

Aprobado por la Comisión Permanente de Farmacia

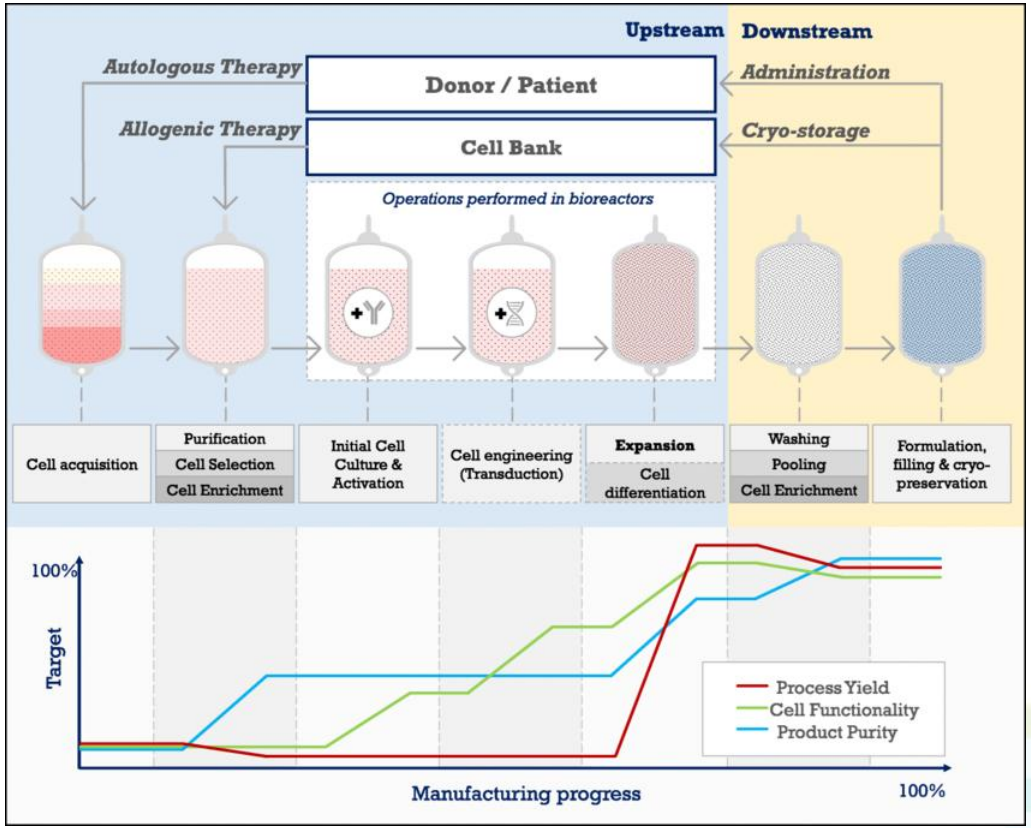
08/04/2022

https://www.sanidad.gob.es/areas/farmacia/infoMedicamentos/valtermed/docs/20220408_Protocolo_farmacoclinico_Zolgensma_AME.pdf

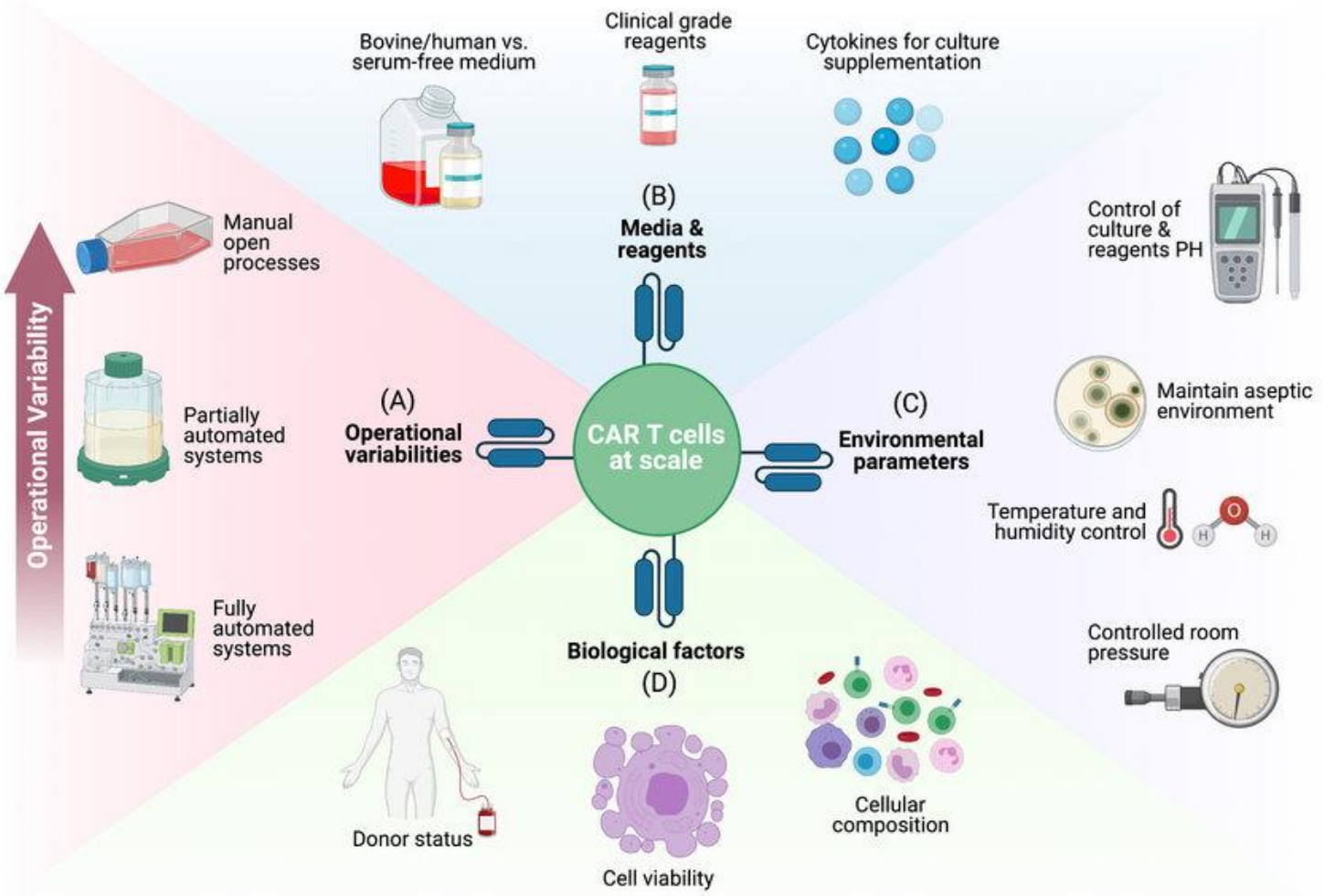
INTERVENCIÓN

- Procesos de fabricación complejos
- En que momento tratar en el curso de la enfermedad (*treatment timing*)
- Requerimientos específicos para el tratamiento
- Alto coste inicial

COMPLEJIDAD EN LA FABRICACIÓN



Herwig C et al. J Biol Engineering 2021



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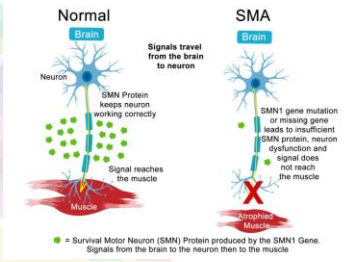
A CORUÑA 17-19 OCT 24

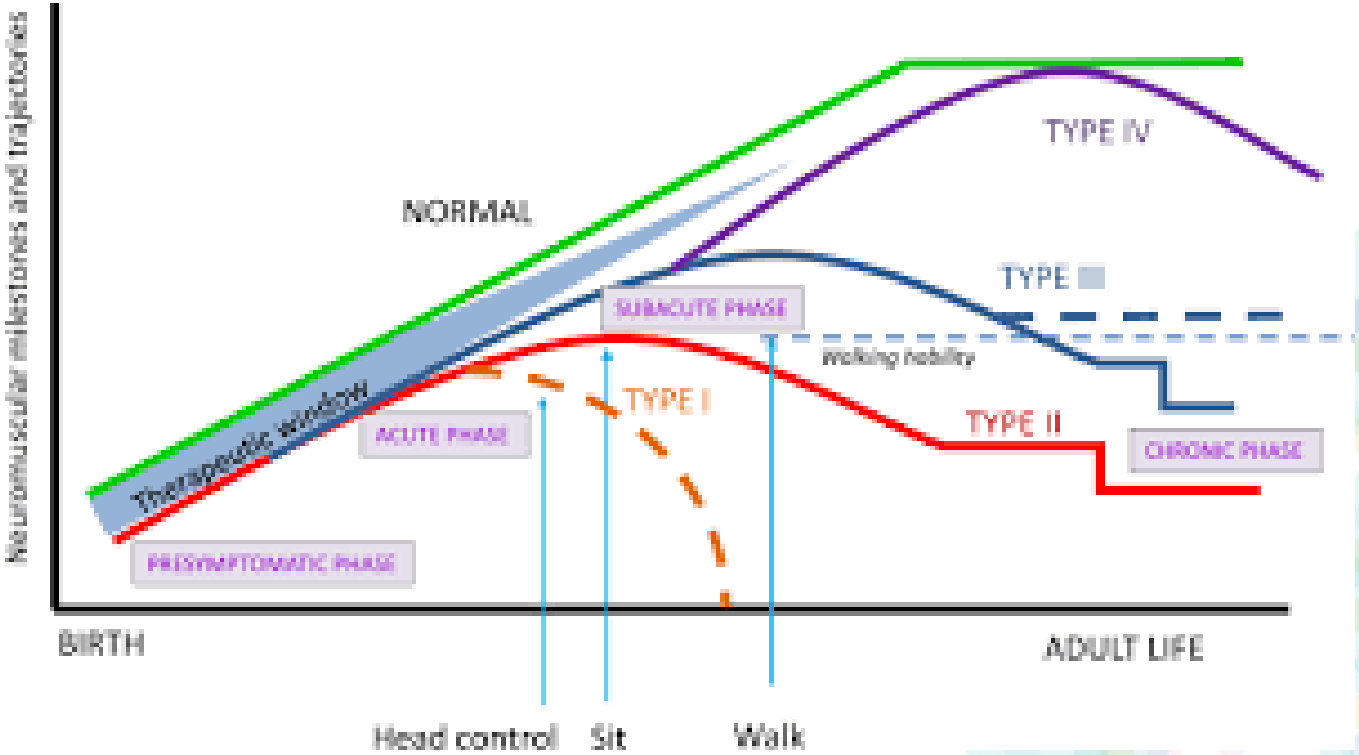
Test/ Time to perform	Instruments/ Reagents	Reason to perform	Release Specs	Commentary and expert opinion
Cell viability assay <1 hr	Flow Cytometry. 7-AAD dye Also, vis trypan blue	· % of live cells · For dose calculation	≥70%	Technologists indicated that ≥70% has been a threshold for most academic products, while ≥80% is not uncommon for commercial. If viability is less than threshold, a product can still be administered to patients upon physician approval, but only under compassionate use (i.e., provided at no charge). Viability assessment using trypan blue, using a product surrogate vial, must be performed on T0, prior to product distribution and release
CAR+ % <1 day	Flow Cytometry. Staining for CAR, CD4, CD8, CD45	· % cells with CAR · Dose calc	N/A	Calculated as sum of %CD4+CAR+ and %CD8+CAR+. Experts said that many products have ~50% transduction efficiency and that they clear products with ≥10%. Cohort dose is recorded on the CoA.
Endotoxin <1 hr	EndoSafe PTS device. LAL water	Level of endotoxin	≤5.00 EU/kg	Endotoxin is released from the membranes of gram-negative bacteria. It can cross blood-brain barrier and cause fever
Microorganisms of final product <1 hr or 14 d	BacT Alert bottles (14 days) or STAT Gram stain (<1hr)	Presence of bacteria, fungi, yeast, mycobacteria	No bacteria or fungus after 14 d	Fresh products must be analyzed by gram stain (due to time constraints). When products have contamination with microorganisms, they are either discarded or given with a high dose of antibiotics in life-saving cases
Mycoplasma, <1 day	qPCR, mycocensor kit	Presence of mycoplasma	Negative	Mycoplasma comprises several species and is hard to detect due to the lack of cell walls
Replication Competent virus <1 day	PCR	Presence post transduction	Negative	Lentiviral vectors, used to transduce T cells, are designed to minimize replication competence

https://bioheights.com/car-t-release-testing-basics/

CUANDO TRATAR

- Para algunas enfermedades, lo ideal sería administrar la terapia génica cuando el paciente aún es asintomático antes que la patología sea irreversible. (población incidente vs prevalente)
- Los protocolos farmacoclínicos pueden establecer criterios de inclusión y exclusión en pacientes con enfermedad avanzada.





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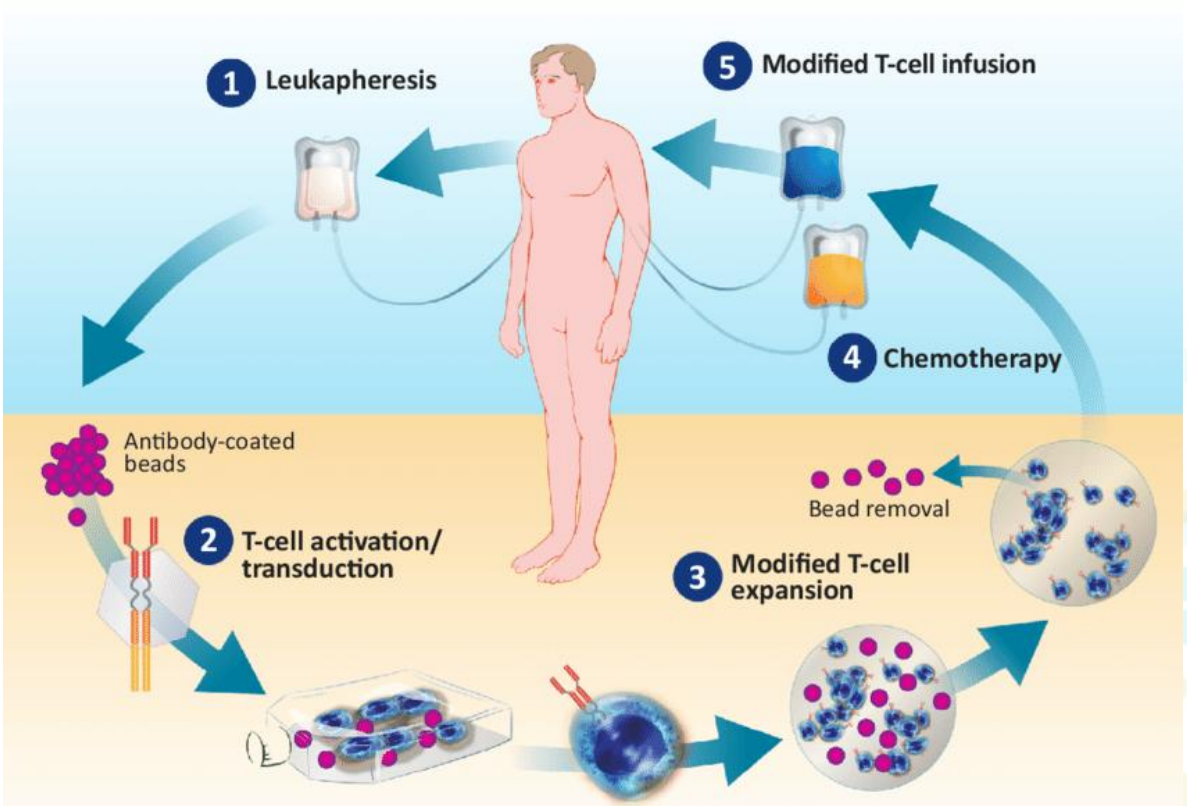
SOCIEDAD ESPAÑOLA DE FARMACIA HOSPITALARIA
A CORUÑA 17-19 OCT 24

CUANDO TRATAR

- A veces la estrecha ventana de tratamiento puede hacer que ECs controlados sean poco éticos o inviables para MTAs en tales indicaciones.
- Otro factor a tener en cuenta es el tiempo entre recolección de las células, fabricación y re infusión, especialmente en el caso de terapia génica ex vivo, por el potencial deterioro del estado del paciente.

CAR T AUTÓLOGO



REQUERIMIENTOS ESPECIFICOS

- Los MTAs son medicamentos que requieren criopreservación, con caducidades cortas y periodos de validez una vez descongelados muy cortos.
- Requisitos específicos para el almacenamiento y transporte.
- Errores en la manipulación pueden tener consecuencias irreversibles y la pérdida de oportunidades de tratamiento para los pacientes.

DISEÑO DEL ESTUDIO

- Baja potencia estadística
- Falta datos comparativos/dificultad de hacer comparaciones directas.
- Diseño abierto
- Duración del seguimiento

RESULTADOS

- Magnitud del beneficio clínico. (¿cura? ¿remisión? ¿diferencia clínicamente significativa?)
- Resultados basados en variables subrogadas para medir el beneficio a largo plazo.

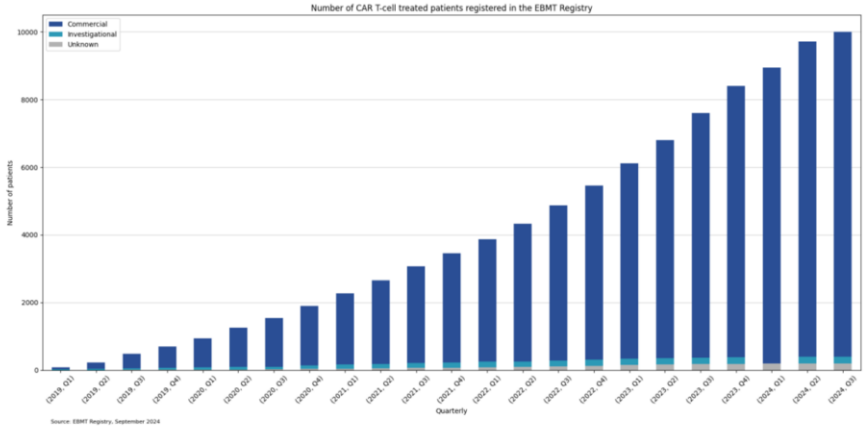
Registro EBMT CAR T

EBMT

PRESS RELEASE

The EBMT reaches major milestone: 10,000 CAR-T treated patients registered in its Registry

Barcelona, Spain - 9 September 2024 - The EBMT is proud to announce that its Registry has achieved a landmark milestone of 10,000 chimeric antigen receptor T-cell (CAR-T) therapy patients. This significant achievement underscores the growing impact and advancement of CAR-T therapy in the treatment of haematological malignancies.

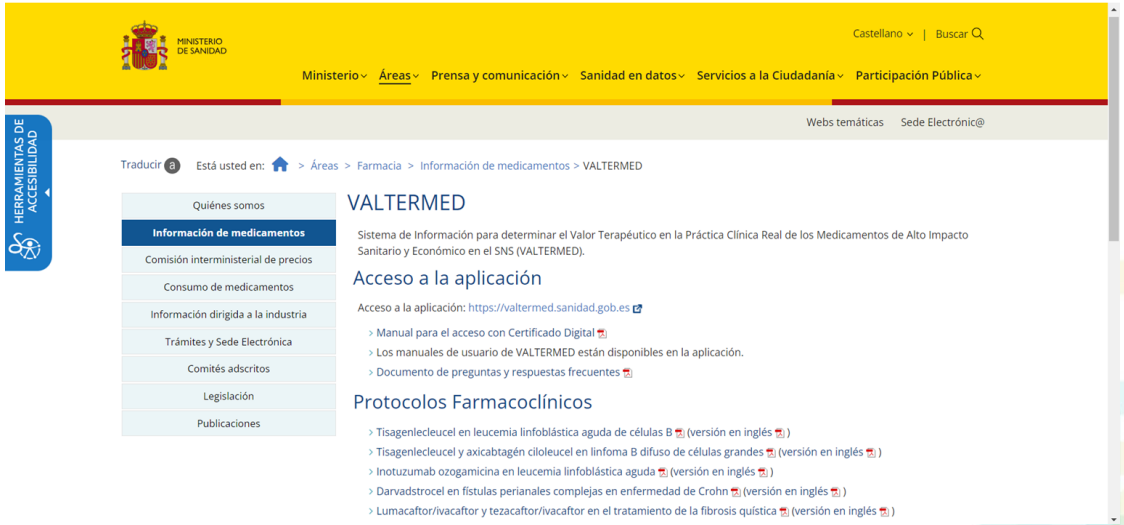


69 CONGRESO NACIONAL SOCIEDAD ESPAÑOLA DE FARMACIA HOSPITALARIA

A CORUÑA 17-19 OCT 24

EVIDENCIA EN PRÁCTICA CLINICA REAL

- Necesidad de evidencia post autorización



EVALUACIÓN ECONÓMICA

- Los MTAs generalmente se administran en 1 o 2 dosis, y requieren seguimiento a largo plazo.
- Beneficios a largo plazo que no va a ser posible medir a partir de los EC por su corta duración. (RWE, registros)
- Altos costes iniciales que presentan mayor riesgo financiero comparado con los medicamentos convencionales.
- Nuevos modelos de financiación y accesibilidad basados en resultados en salud.

IMPACTO DE LOS MTAs EN LOS SFH

- Gobernanza (acreditación de centros, auditorias, JACIE o la gestión del medicamento a nivel local eg. CFyT, CB, FV, financiación, UC/ECs)
- Clínicos (verificación tratamiento, seguridad y FV)
- Logísticos (recepción, custodia, dispensar +/- preparar)

MINISTERIO DE SANIDAD, CONSUMO Y BIENESTAR SOCIAL

SECRETARÍA GENERAL DE SANIDAD Y CONSUMO

DIRECCIÓN GENERAL DE CARTERA BÁSICA DE SERVICIOS DEL SNS Y FARMACIA

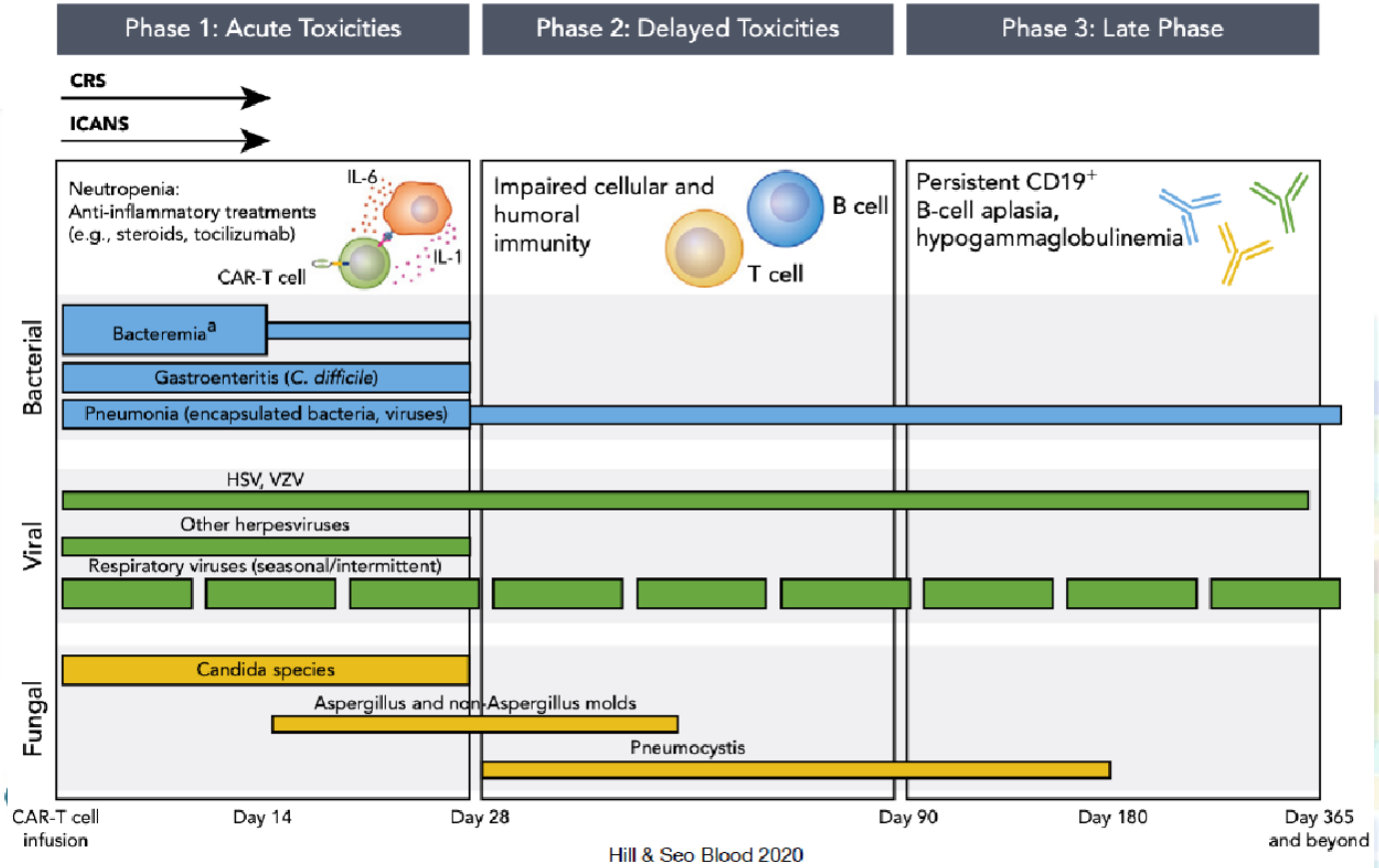
PROTOCOLO CLÍNICO PARA EL MANEJO DE LOS EFECTOS ADVERSOS GRAVES EN PACIENTES TRATADOS CON MEDICAMENTOS QUE CONTIENEN CÉLULAS T CAR (CHIMERIC ANTIGEN RECEPTOR) ANTI-CD 19 (CART-19)

Desarrollado por el grupo de expertos en la utilización de medicamentos CAR del "Plan de abordaje de las terapias avanzadas en el SNS: medicamentos CAR"

Remitido a la Comisión Permanente de Farmacia y a la Comisión de Prestaciones, Aseguramiento y Financiación para aportaciones

Validado por el grupo de trabajo institucional

Aprobado por el Consejo Interterritorial del Sistema Nacional de Salud (8 de mayo de 2019)



Hill & Seo Blood 2020

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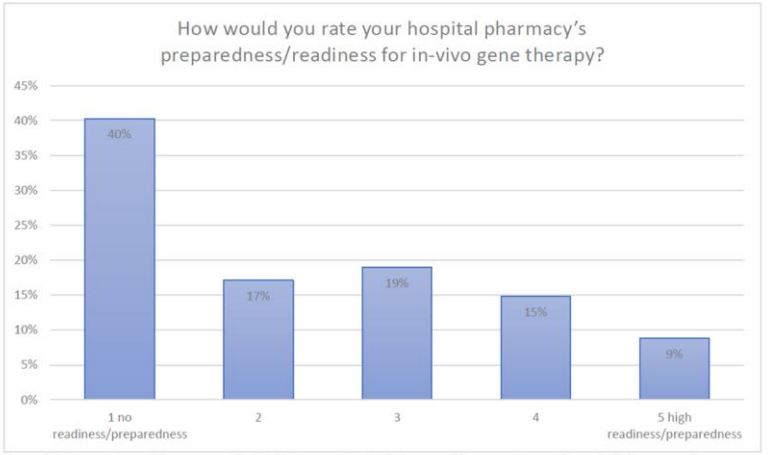

Figure 3: Percentage of responses (n=216) to question 4 "How would you rate your hospital pharmacy's preparedness/readiness for in-vivo gene therapy?"

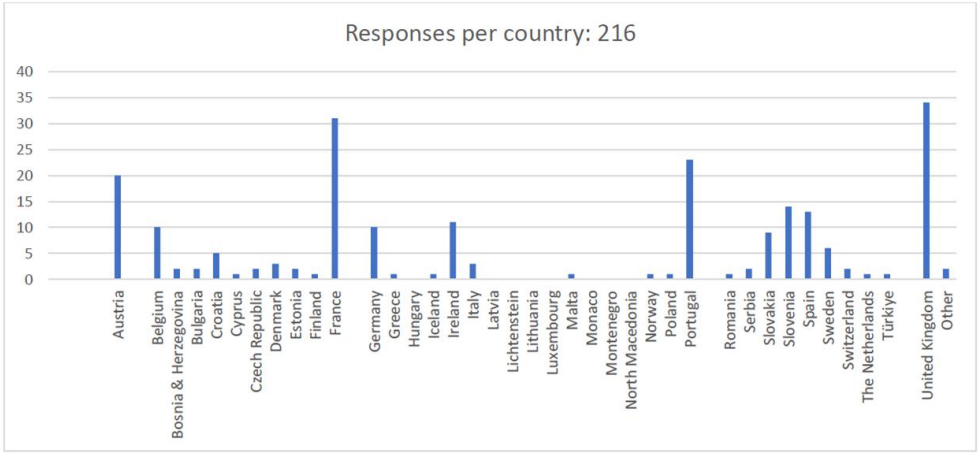

Figure 1: Overview of the country from the respondents that participated in the Survey

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Original research

European Association of Hospital Pharmacists (EAHP) guidance on the pharmacy handling of in vivo gene therapy medicinal products

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ABSTRACT

Gene therapy is becoming increasingly prevalent, with new gene therapy medicinal products (GTMPs) being approved for use every year. Hospital pharmacists are expected to prepare and dispense these products, but there is substantial heterogeneity in the availability of up-to-date, practical guidance at a national level in Europe. Many institutions have no or very limited experience in handling GTMPs. As such, there is a need for updated, practical guidance to aid hospital pharmacy teams in developing institutional standard operating procedures (SOPs) for the safe handling of GTMPs across the entire workflow. Here, we present the European Association of Hospital Pharmacists' updated guidance on the handling of GTMPs, developed by a team of recognised experts from around Europe. Each aspect of the GTMP handling process is addressed, including receipt and storage, dispensing and reconstitution, transportation, administration, waste disposal, decontamination of spills and accidental exposure. A series of figures are provided to aid the development of practical workflows. This guidance document is intended as a framework to help develop institutional SOPs and should always be used in conjunction with local regulations.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Gene therapy is becoming increasingly prevalent and hospital pharmacists are expected to handle both investigational and approved gene therapy medicinal products as and when required. However, there is substantial heterogeneity in the level of experience of hospital pharmacy teams and in the availability of up-to-date, practical guidance for handling these products.

WHAT THIS STUDY ADDS

⇒ Updated guidance is provided to assist hospital pharmacy teams in developing institutional standard operating procedures for the handling of gene therapy medicinal products, in conjunction with local regulations.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This updated guidance will enable the safe and appropriate handling of gene therapy medicinal products in a more standardised manner across Europe, for both experienced hospital pharmacy teams and those who are new to handling these therapies.

INTRODUCTION

This European Association of Hospital Pharmacists (EAHP) guidance document for the handling of gene therapy medicinal products (GTMPs) outlines practical considerations for the hospital pharmacy handling of GTMPs. The term 'handling' encompasses receipt and storage, dispensing and reconstitution, transportation, administration, waste disposal, spills and accidental exposure. Practical experience from a committee of experts and published evidence were used in the development of these guidelines. All committee members provided feedback on these recommendations, which were then subsequently validated and approved by external experts.

These guidelines cover both European Commission (EC)-approved GTMPs and products under investigation in clinical trials. However, it is important to note that these guidelines are of a general nature and intended as a framework to aid the development of institutional standard operating procedures (SOPs), especially when policy-making committees may have difficulty accessing credible guidance on which to base their recommendations.[1] As such, national regulations and the Summary of Product Characteristics/relevant clinical trial documents should always be consulted for country- and product-specific requirements.

This document is an update on the EAHP guidance on the handling of gene medicines, published in 2007,[2] and takes into account the substantial advances in GTMP technology and marketing approval being granted for a number of GTMPs in Europe.

OVERVIEW OF THE GUIDANCE DEVELOPMENT PROCESS

This guidance document was developed by a Special Interest Group convened by the EAHP to update the EAHP's Guidance on the Pharmacy Handling of Gene Medicines[2] and gain insight into the preparedness of hospital pharmacy departments for the delivery of in vivo GTMPs.[3] The original guidance was developed by a steering committee of representatives from the EAHP in 2007, representing

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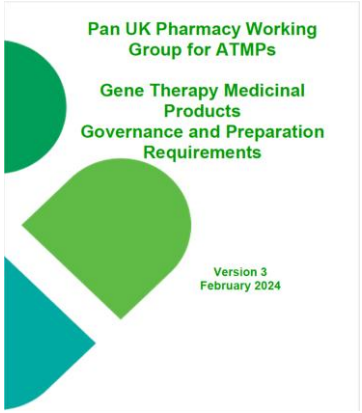

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https://gruposdetrabajo.sefh.es/terapias-avanzadas/contacta-al-grupo

CONCLUSIONES

- Cambio disruptivo en el campo de la terapéutica afectando a los modelos asistenciales.
- Oportunidad de tratamiento para enfermedades raras, convirtiéndose en una potencial cura o mejora de la calidad de vida.
- Múltiples desafíos en el desarrollo clínico que afectan a la evaluación de la seguridad y eficacia.
- Son fármacos con efectos secundarios diferentes , y a largo plazo, lo que requiere una estrecha FV
- Incertidumbre genera riesgo financiero, nuevos modelos de pago por resultados.

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Gracias por su atención

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