Terapias Avanzadas:
Implicaciones, Avances y Nuevas Necesidades en el Ámbito asistencial

Mesa Terapias SuperHumanizadas

64 Congreso SEFH
Sevilla Octubre 2019

Ana Clopés Estela
Instituto Catalán de Oncología

Medicamentos de Terapias avanzadas

Según EMA:

"medicines for human use that are based on genes and cells…and offer groundbreaking new opportunities for the treatment of disease and injury"

Según EMA:

1. Medicamentos terapia génica
2. Medicamentos terapia celular somática
3. Medicamentos ingeniería tisular
4. Terapias combinadas

Según FDA:

1. Medicamentos terapia génica
2. Medicamentos terapia celular

EMA y FDA:

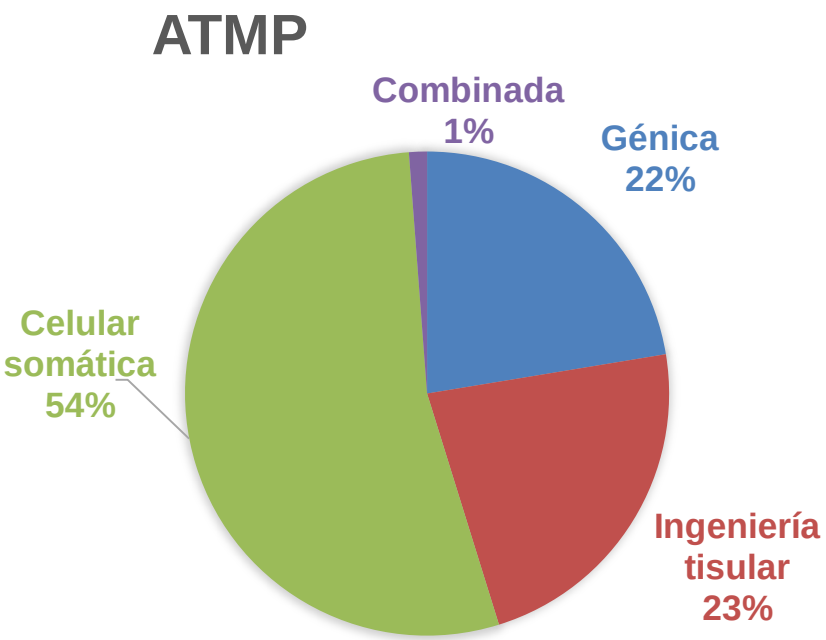
Para clasificar ATMP-proceso de las células implica manipulación que altera las características biológicas

Aunque el termino de manipulación difiere entre las agencias

Medicamentos de Terapias avanzadas

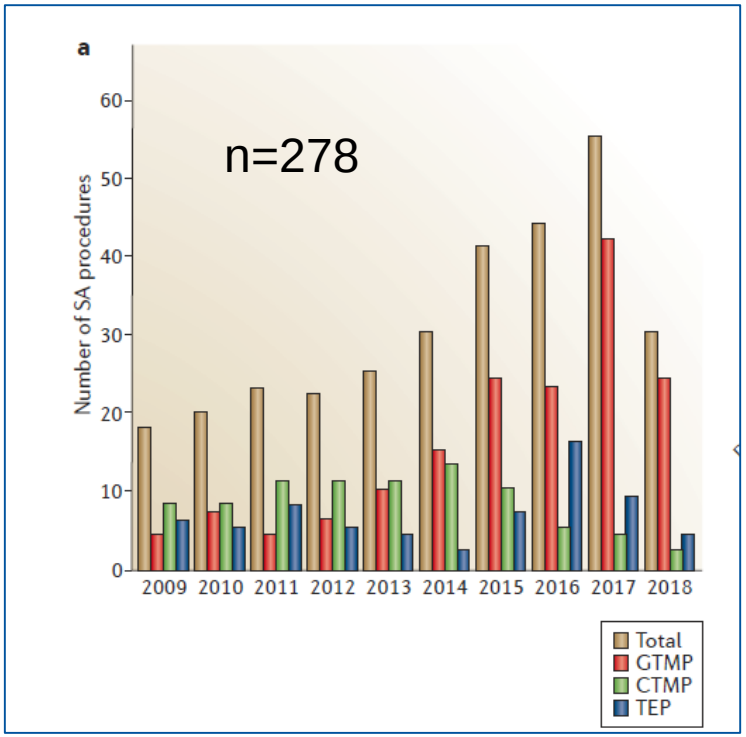
Proporción de subgrupos de ATMP en EC

Clinical trials were searched in the following databases: EudraCT, ClinicalTrials.gov, and ICTRP .



Hanna et al. Journal Market Access & Health Policy 2017

Experiencia de evaluación de ATMPs en EMA 2009-2018



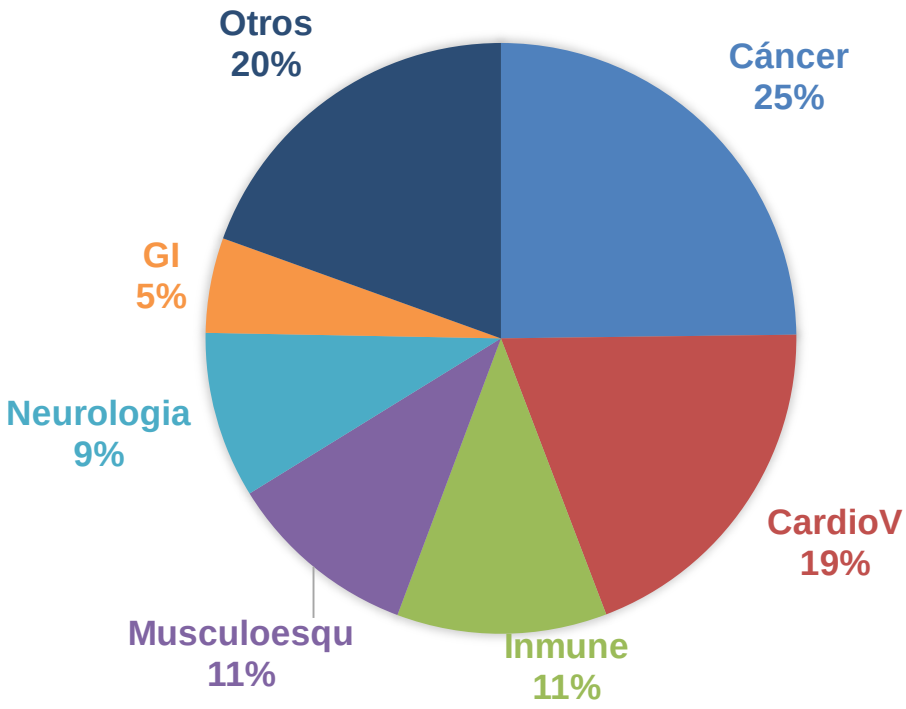
Barkholt et al. Nat Rev Drug Discov 2019 Jan;18:8-9

Category of ATMP as defined by European regulation EC No. 1394/2007.
GTMP= terápia génica/ CTMP= terapia celular/ TEP=terapia de ingeniería de tejidos

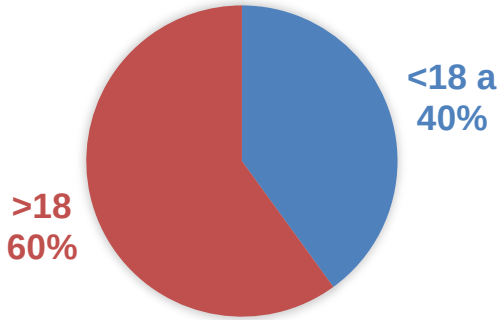
Medicamentos de Terapias avanzadas

Características de las ATMPs en Desarrollo o comercializadas en Europa

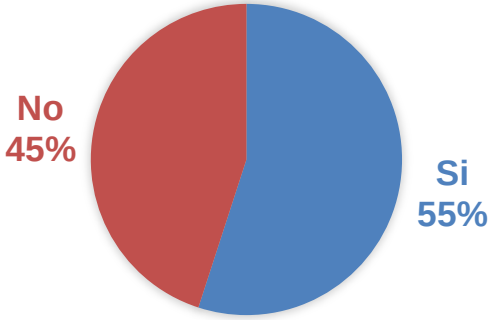
INDICACIÓN



EDAD



HUÉRFANO



Medicamentos de Terapias avanzadas:

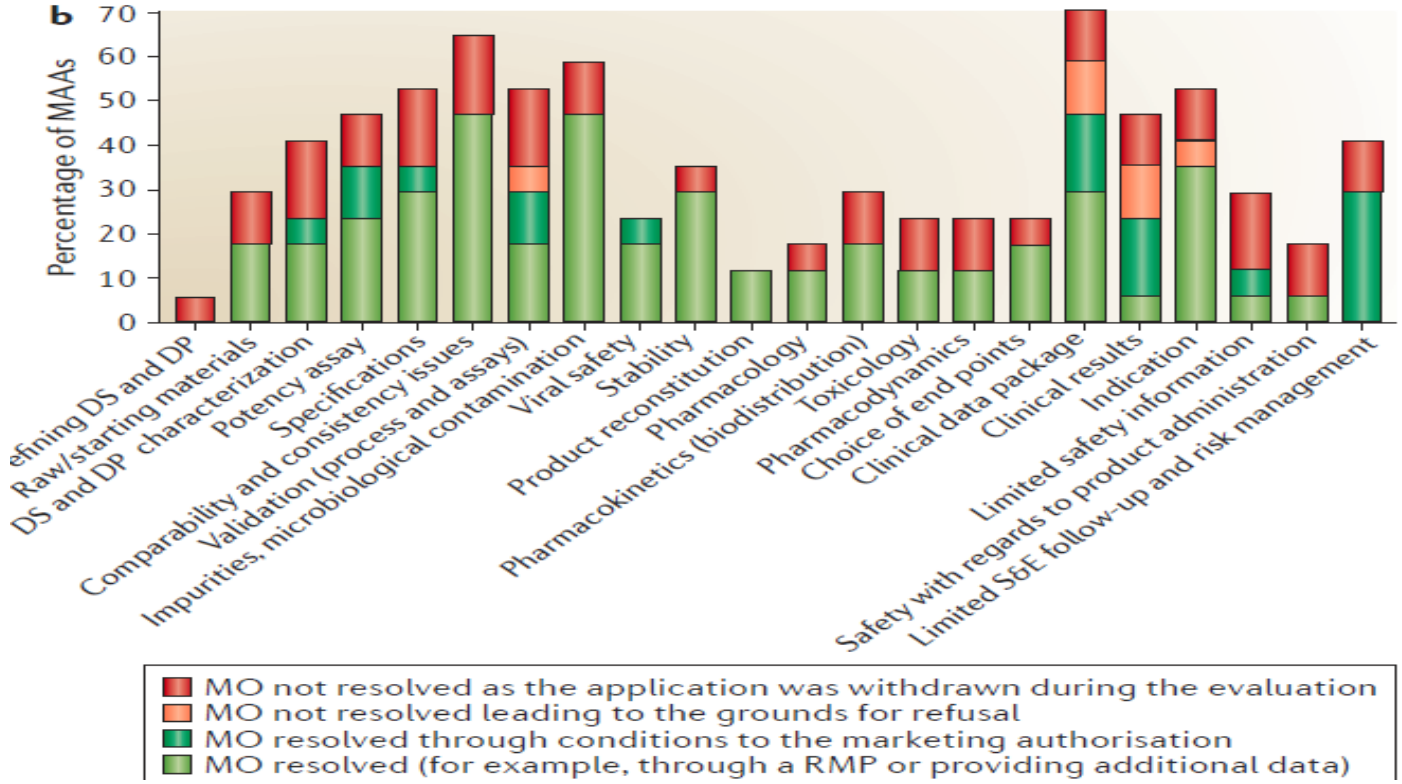
Retos

Retos

Regulatorios

Experiencia de evaluación de ATMPs en EMA 2009-2018

Características de las objeciones mayores (MOs) elevadas durante la evaluación de las solicitudes a EMA de 2007-2018.



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Regulatorios

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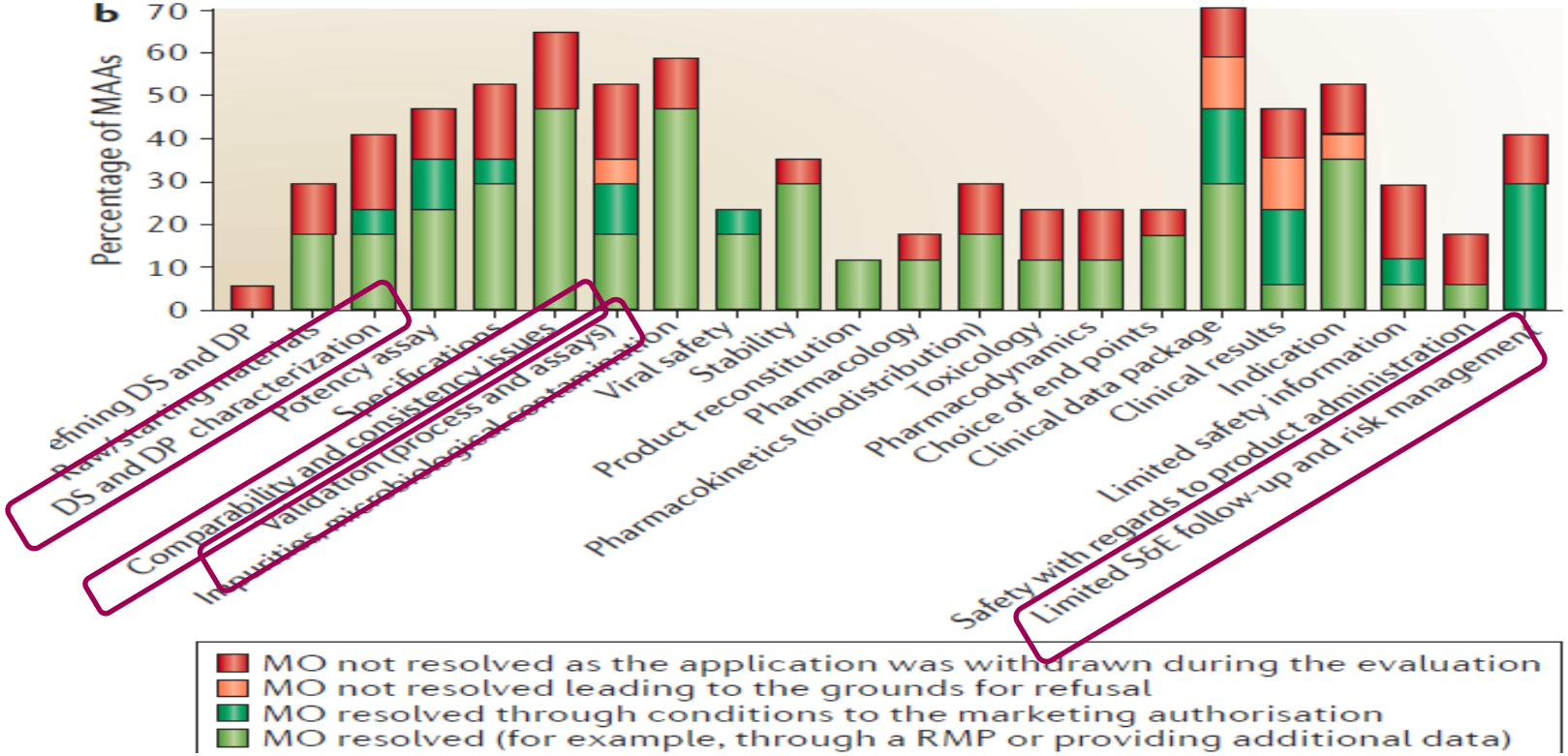

EMA ha generado herramientas adicionales a la designación PRIME que ayudan a desarrolladores en informe robusto

Barkholt et al. Nat Rev Drug Discov 2019 Jan;18:8-9

Retos

Regulatorios

European Commission

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

European Commission-DG Health and Food Safety and European Medicines Agency Action Plan on ATMPs

The term "advanced therapy medicinal products" ("ATMPs") is used to designate gene therapies, somatic cell therapies and tissue engineered products.

In the EU, these products are governed by Regulation 1394/2007 on advanced therapy medicinal products ("ATMP Regulation"). The cornerstone of the Regulation is that a marketing authorisation

Incluye: Interaction with EUnetHTA / Collaboration in the frame of the EMA-EUnetHTA 2017-2020 Work Plan started.

The 2014 report on the application of ATMPs[1], concluded that the Regulation had protected patients from unsound treatments. However, it also recognised shortcomings and identified actions to help translate scientific progress into medicinal products available to patients. Such shortcomings were also discussed in a multi-stakeholder workshop organised by the EMA on 27 May 2016 and certain

FDA

FDA's Efforts to Advance the Development of Gene Therapy

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By: Peter Marks, M.D., Ph.D., Director, Center for Biologics Evaluation and Research

FDA Voices: Perspectives From FDA Leadership and Experts

FDA Voices on Policy

FDA Voices on Consumer Safety and Enforcement

FDA Voices on Medical Products

FDA Voices on Food

Content current as of: 05/01/2019

Gene therapy has been on the horizon for several decades and has now become a reality in the United States. There are now three approved products: two cell-based gene therapies for cancers of the blood (Kymriah and Yescarta) and one directly-administered gene therapy (Luxturna) for an inherited disorder of the retina of the eye. Numerous gene therapy products are in development to address unmet medical needs, such as those for the treatment of diseases ranging from

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/human-gene-therapy-rare-diseases

https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-quality-non-clinical-clinical-aspects-medicinal-products-containing-genetically-modified_en.pdf

Científicos

Retos

Evaluación y posicionamiento terapéutico

- *Jönsson et al. Advanced therapy medicinal products and health technology assessment principles and practices for value-based and sustainable healthcare*
  - Método
    - Panel de expertos en metodología HTA en Europa
    - Revisión e identificación de potenciales retos en la aplicación de los principios y practices de HTA aplicado a ATMPs
  - Resultados: Se identifican retos en 7 áreas:
    1. Incertidumbres
    2. Tasa de decuento
    3. Valor social vs beneficio en salud incremental esperado
    4. Impacto presupuestario
    5. Datos de vida real
    6. Impacto ético
    7. Seguridad

Científicos

Retos

Evaluación y posicionamiento terapéutico

- Jönsson et al. *Advanced therapy medicinal products and health technology assessment principles and practices for value-based and sustainable healthcare*
  - **Se priorizan 3 áreas específicas relevantes**

1. **Incertidumbres**
2. **Tasa de decuento en evaluación económica**
3. **Valor social vs beneficio en salud incremental esperado**
4. Impacto presupuestario
5. Datos de vida real
6. Impacto ético
7. Seguridad

Científicos

Retos

Evaluación y posicionamiento terapéutico

1. INCERTIDUMBRES

Peltzamn desarrolló la teoría del Mercado farmacéutico:

Oferta y demanda: en el proceso de introducción de un nuevo medicamento se puede realizar 2 errores

Error tipo 1- admitir un fármaco no Efectivo /no Seguro/no CE

Error tipo 2- retrasar el acceso

Científicos

Retos

Evaluación y posicionamiento terapéutico

1. INCERTIDUMBRES

Error tipo 1- admitir un fármaco no efectivo /no Seguro/no CE

Error tipo 2- retrasar el acceso

Situación ATMPs ➡ PRESIÓN

1. Grupos específicos de población
2. Enfermedad grave
3. Opciones limitadas de tratamiento
4. Basado en conocimiento enfermedad
5. Posibilidad curativa

Científicos

Retos

Evaluación y posicionamiento terapéutico

1. INCERTIDUMBRES

a) Efectividad del producto vs eficacia

b) Eficacia/efectividad comparada con otras alternativas

c) Efectividad a largo plazo

d) Relación coste-efectividad

e) Impacto presupuestario

Retos

Científicos

Evaluación y posicionamiento terapéutico

2. Factor tiempo en EVALUACIÓN ECONÓMICA

- La tasa de descuento formaliza el ajuste a valores futuros. Es un parámetro crucial pero que se asigna sin mucha justificación. Las agencias HTA en Europa aplica 3-5% para costes y 1,5 y 5% para beneficio

- Una tasa menor se aplica para tecnologías lejos en el tiempo, es decir que favorecerán generaciones futuras
- ATMPs es probable que sean intervenciones con alto coste que ocurre años antes que el beneficio en salud emerge
- Debido a esta distribución temporal entre costes y beneficios, la selección de la tasa de descuento puede tener un efecto en la estimación del coste-efectividad

➢ **Se debe aplicar unas reglas diferentes para ATMPs?**

Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies

NICE
National Institute for Health and Care Excellence

Survival extrapolations

A cure point between 2 years and 5 years with excess mortality after a cure is plausible but further long-term data are needed

3.13 The company's revised base case after consultation assumed that patients alive after 2 years were functionally cured and had mortality rates similar to those of the general population without any excess mortality risk after a cure.

Gompertz distribution is appropriate to model the survival benefit for salvage chemotherapy but other extrapolations are plausible

3.15….
The committee concluded that a single parametric survival model applying a Gompertz curve to overall survival data for patients who did or did not have subsequent stem cell transplant was appropriate to model survival benefit for salvage chemotherapy, but that other extrapolations may also be plausible

Acceso y Financiación

Retos

Científicos

3. Valor social vs beneficio en salud incremental esperado

- Toma de decisiones en salud es complejo y debe estar basado en valores, pero que debe incluir?

- ATMPs deben tener diferente criterio?

- ATMPs podrían disponer de elementos adicionales no incluidos en concepto valor-coste/QUALY ?
  1. Enfermedades sin alternativas
  2. Ultra-huerfanas
  3. Curabilidad?

➢ Opción: se utilice valor como coste-utilidad pero recogiendo todo el potencial de la ATMPS

Un reflexión desde UK

House of Lords Science and Technology Committee *analizó si habían barreras a la traslación y comercialización de ATMPs*

En respuesta NICE realiza un informe específico

- Los métodos actuales y los métodos de decisión son aplicables
- La cuantificación de la incertidumbre en la decisión es clave en la toma de decisión
- Cuando la incertidumbre es importante, los nuevos modelos de financiación tienen un papel importante y pueden facilitar el acceso en término de concepto tiempo

Exploring the assessment and appraisal of regenerative medicines and cell therapy products

Produced by Centre for Health Technology Evaluation, National Institute for Health and Care Excellence (NICE)

Authors Nick Crabb, Programme Director, Scientific Affairs
Andrew Stevens, Technology Appraisals Committee Chair

Acknowledgements:

Cell and Gene Therapy Catapult staff are thanked for their substantial support, including providing initial evidence summaries on the example products, hosting technical meetings, providing members for the Project Advisory Group and providing ad-hoc support throughout the project.

Hettle R, et al Health Technol Assess. 2017 Feb;21(7):1-204.

Acceso y Financiación

Retos

Científicos

- Jönsson et al. *Advanced therapy medicinal products and health technology assessment principles and practices for value-based and sustainable healthcare*
  - **Se proponen recomendaciones**

- Contratos basados en resultados o cobertura condicional dónde datos aportados disminuirán incertidumbres
- Registros de resultados a largo plazo de los ATMPs que deben ser:
  1. Independiente
  2. Inclusivos a todas las tecnologías, poblaciones e indicaciones
  3. Internacional

- Consenso internacional respecto factor tiempo en EE


OUTCOME
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OUTLOOK | CANCER IMMUNOTHERAPY

PERSPECTIVE

Share your values

Paying for cancer immunotherapy will require new ways of cooperation

cott Ramsey.

It is important to consider two issues that are pertinent to costly new medical treatments: budgetary impact and value.

Barriers to value-based pricing or PBRSAs may be falling-for example Medicare and Medicaid announced a PBRSAs programme for tisangenlecleucel.

I
people with cancer
The price of cancer
to $18,000 a month –
ventional chemothera
chemotherapy, even y
tion treatments involv
some, including nivolu
are already being used in the clinic, pushing costs even higher.

side the United States.
most immunotherapy
nses
will
that
uch
ped
under the term performance-based risk-sharing agreements

D HUTCHINSON CANCER RESEARCH CENTER

Ramsey S. Nature 2017; December 552: S78

Logísticos y Técnicos

Retos

Prácticas de Seguridad

En el caso de Medicamentos de Terapias Avanzadas (CART's, TIL's...)

Fabricación industrial

Vs

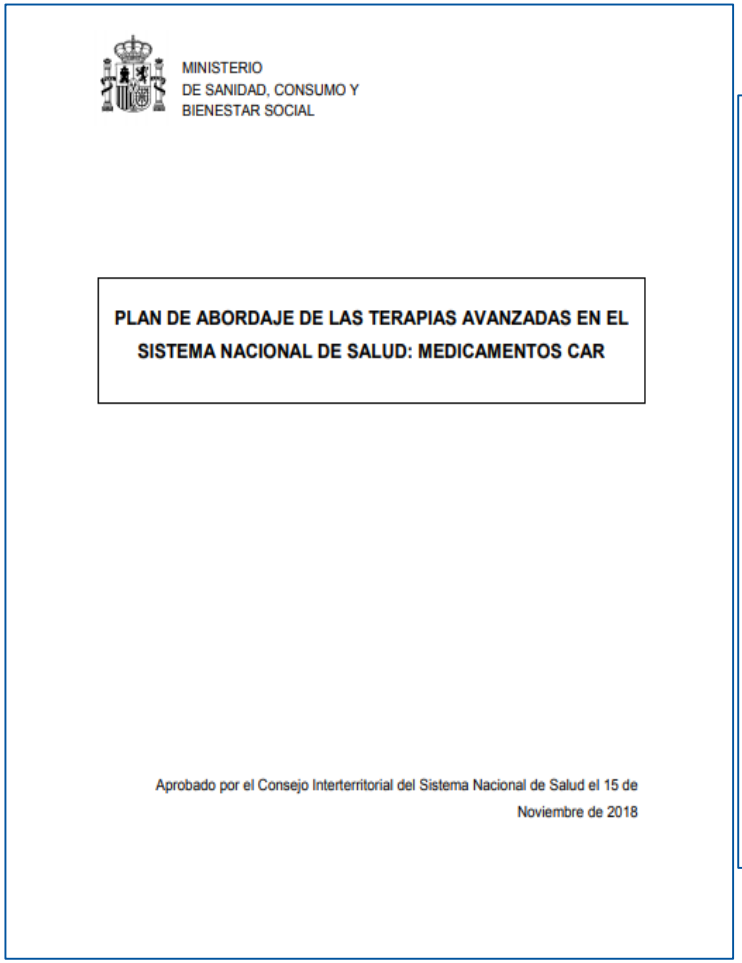
Fabricación in house

i. Reglamento CE 1394/2007 Parlamento Europeo y Consejo sobre medicamentos de terapia avanzada
ii. Directiva 2001/83/CE se establece código comunitario sobre medicamentós uso humano
iii. Exención hospitalària: RD 477/2014 por el que se regula la autorización de medicamentos de terapia avanzada de fabricación no industrial
iv. RD 1/2015 se aprueba texto refundido Ley garantías y uso racional de medicamentos y PS

Logísticos y Técnicos

Retos

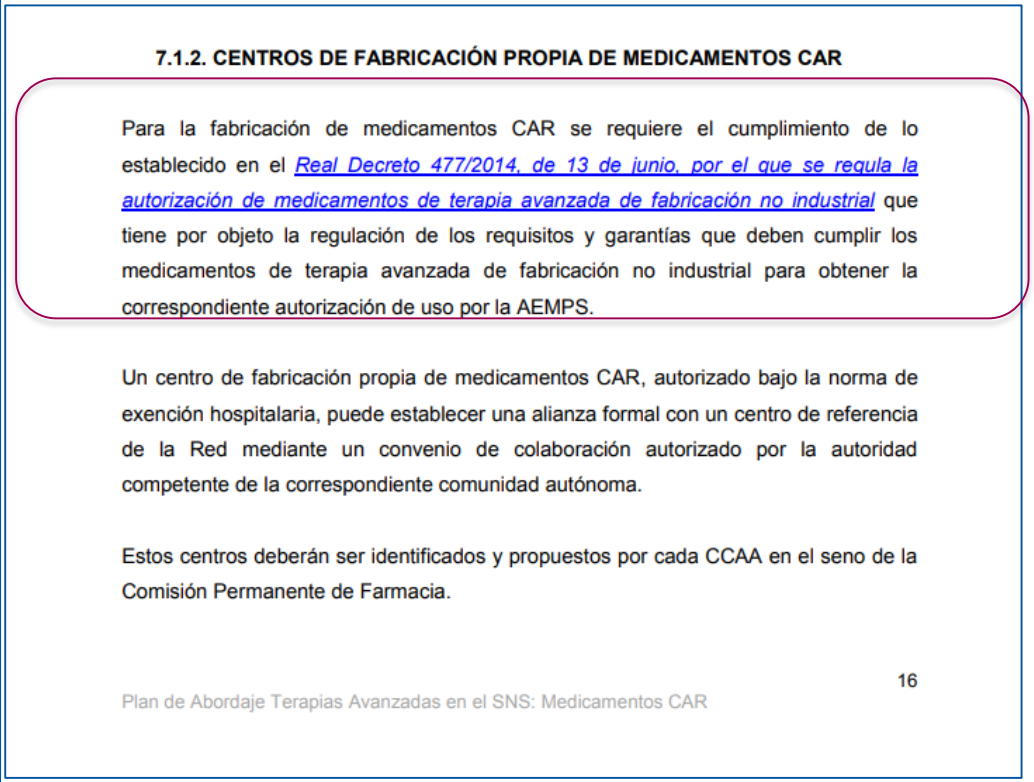
Plan de abordaje TA en el SNS



MINISTERIO
DE SANIDAD, CONSUMO Y
BIENESTAR SOCIAL

PLAN DE ABORDAJE DE LAS TERAPIAS AVANZADAS EN EL SISTEMA NACIONAL DE SALUD: MEDICAMENTOS CAR

Aprobado por el Consejo Interterritorial del Sistema Nacional de Salud el 15 de Noviembre de 2018



7.1.2. CENTROS DE FABRICACIÓN PROPIA DE MEDICAMENTOS CAR

Para la fabricación de medicamentos CAR se requiere el cumplimiento de lo establecido en el *Real Decreto 477/2014, de 13 de junio, por el que se regula la autorización de medicamentos de terapia avanzada de fabricación no industrial* que tiene por objeto la regulación de los requisitos y garantías que deben cumplir los medicamentos de terapia avanzada de fabricación no industrial para obtener la correspondiente autorización de uso por la AEMPS.

Un centro de fabricación propia de medicamentos CAR, autorizado bajo la norma de exención hospitalaria, puede establecer una alianza formal con un centro de referencia de la Red mediante un convenio de colaboración autorizado por la autoridad competente de la correspondiente comunidad autónoma.

Estos centros deberán ser identificados y propuestos por cada CCAA en el seno de la Comisión Permanente de Farmacia.

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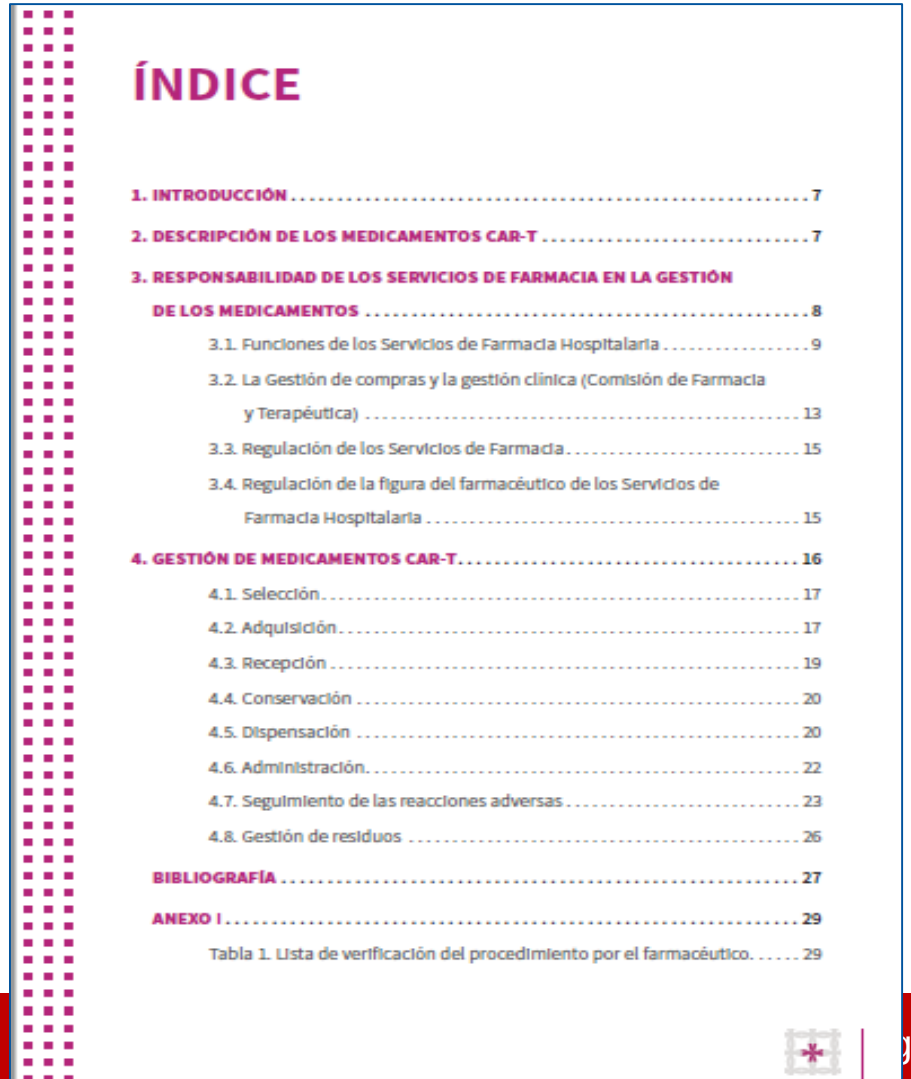
Plan de Abordaje Terapias Avanzadas en el SNS: Medicamentos CAR

Retos

Logísticos y Técnicos

Procedimiento de Gestión de Medicamentos CART



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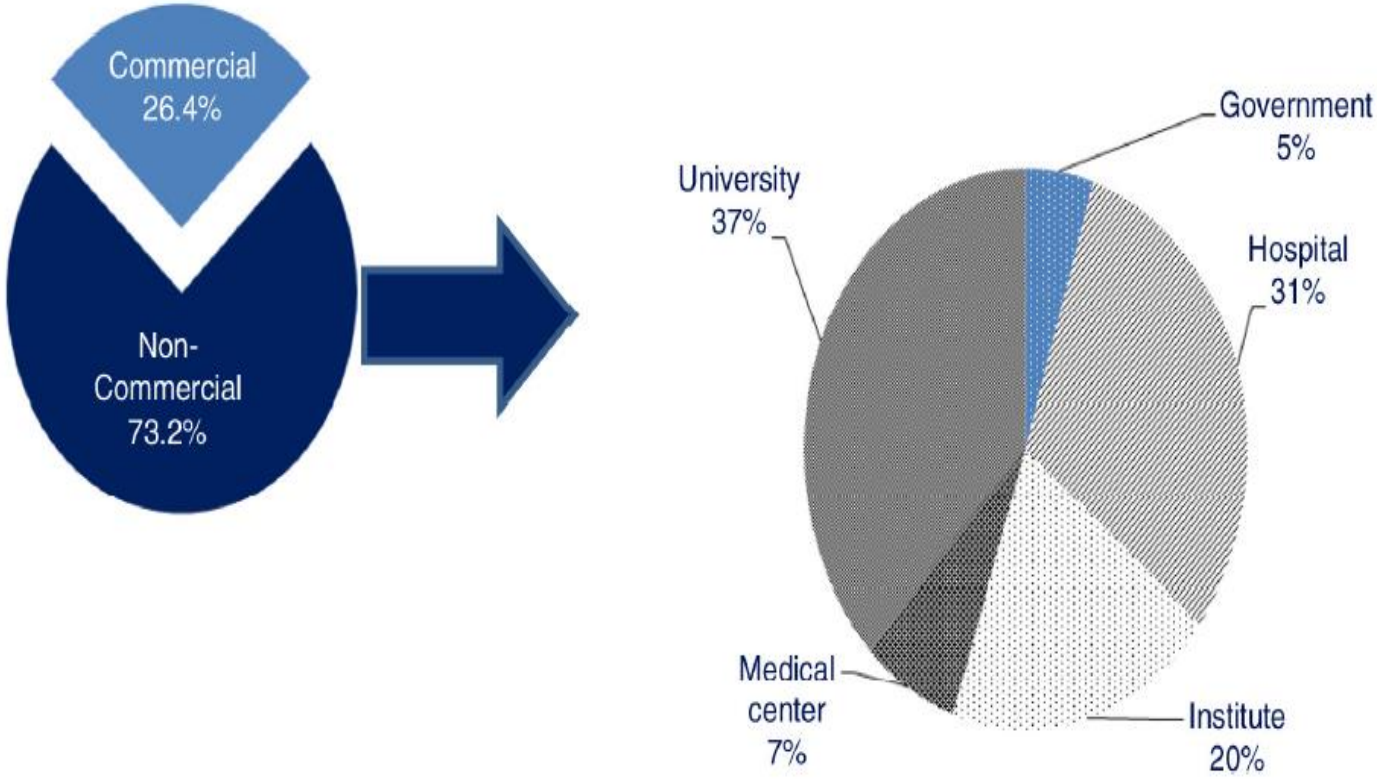
Distribución promotor Ensayos Clínicos de ATMPs



Hanna et al. Journal Market Access & Health Policy 2017

Logísticos y Técnicos

Retos

Carcedo califica de “acuerdo histórico” la aprobación de NC1, la primera terapia celular 100% pública

¿Quieres saber lo último de...

Agencia Española de Medicamentos y Productos Sanitarios (Aemps) | Brexit | Cartera de Servicios | Comisiones de Farmacia | Compra centralizada | Comunidad de Madrid | Consejo Interterritorial del SNS (CISNS) | Desabastecimiento | Efectividad | Eficacia

Logísticos y Técnicos

Retos

Prácticas de Seguridad

En el caso de Medicamentos de Terapia Avanzada (CART's, TIL's...)

Fabricación in

house

Trazabilidad
Programa de Gestión de riesgos

i. Reglamento CE 1394/2007 Parlamento Europeo y Consejo sobre medicamentos de terapia avanzada
ii. Directiva 2001/83/CE se establece código comunitario sobre medicamentós uso humano
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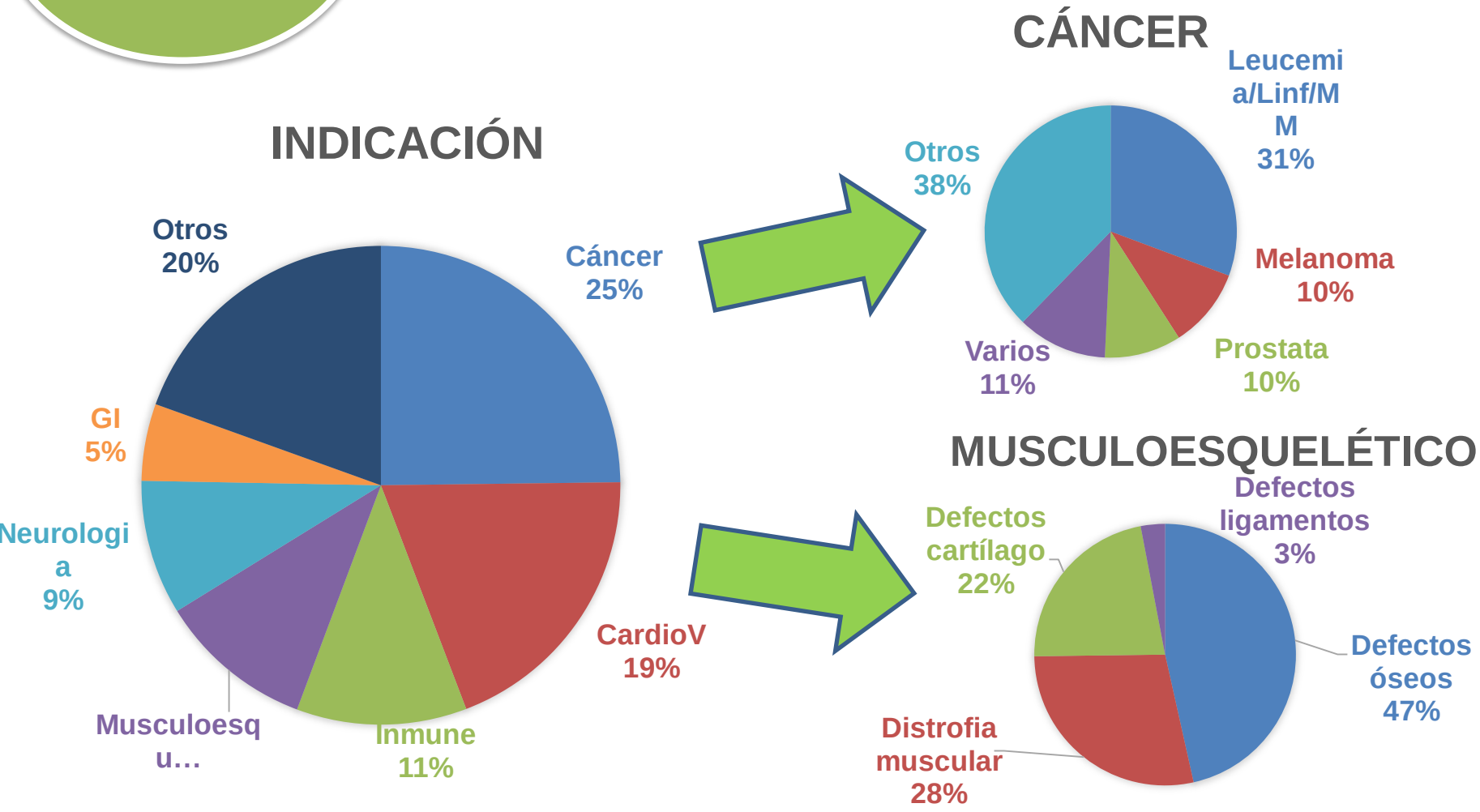

Retos

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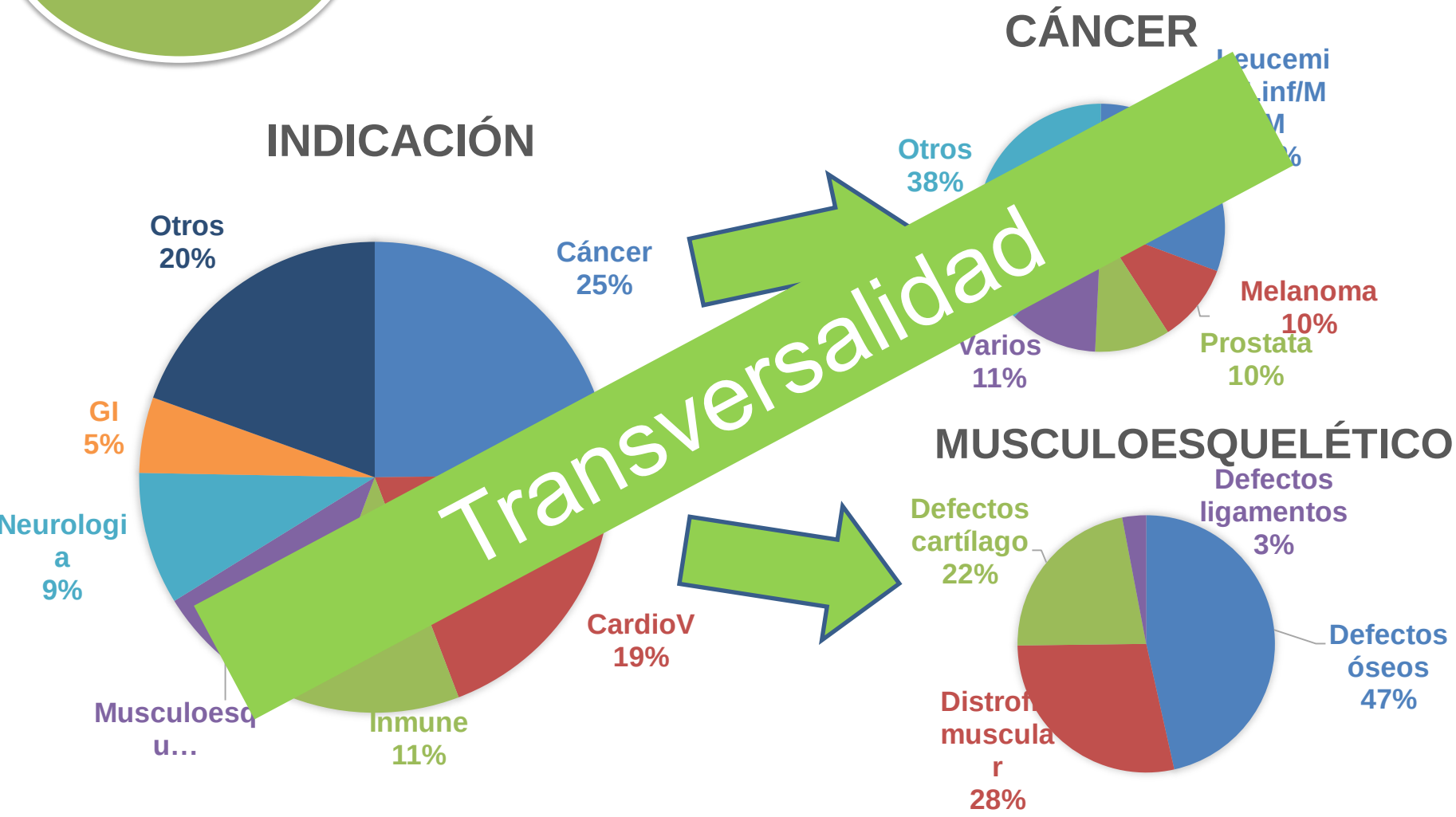

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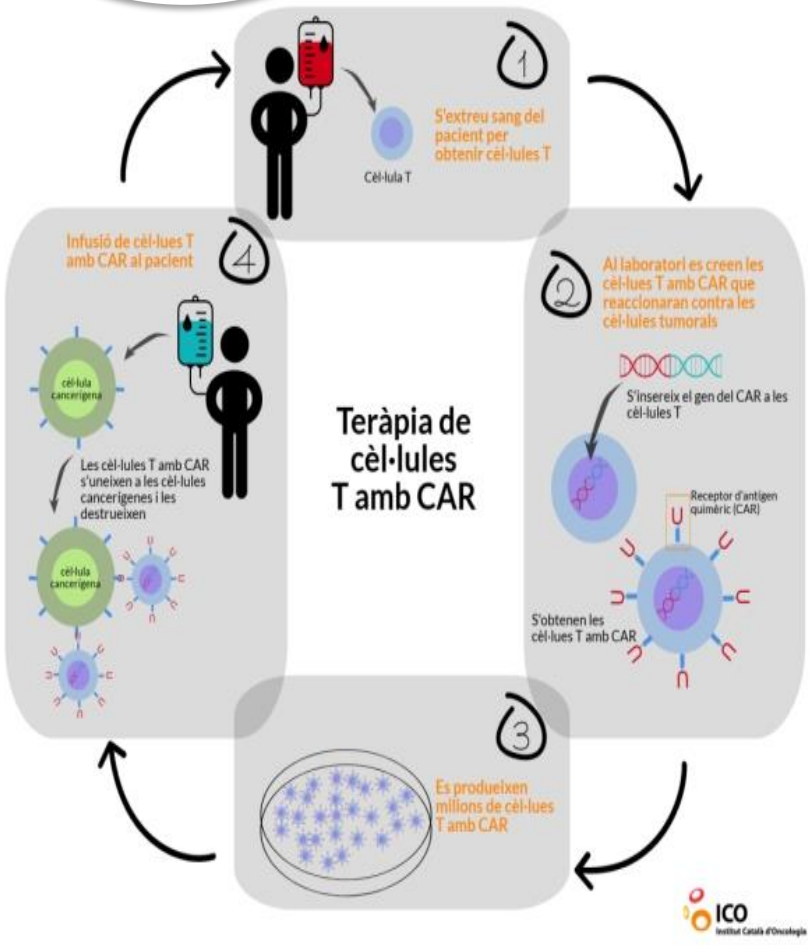

- Complejidad del proceso
- Complejidad del tratamiento

- Optimización de la farmacoterapia individualizada
- Evaluación de resultados
- Equipos multidisciplinares para decisiones complejas

Apuntes para la discusión

Medicamentos de Terapias avanzadas:

Retos


OPPORTUNITY

Inteligencia colaborativa

Gracias

Generalitat de Catalunya
Departament de Salut

ICO
Institut Català d'Oncologia

http://ico.gencat.cat

ICO L'Hospitalet
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ICO Badalona
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ICO Girona
Hospital Doctor Trueta
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ICO Camp de Tarragona e ICO Terres de l'Ebre
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Hospital Verge de la Cinta
C. De les Esplanetes, 14 43500 Tortosa

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SCIENCE MEDICINES HEALTH

Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products

6.6 Efficacy

Existing guidelines for the specific therapeutic area (e.g. cancer, rare diseases**) should be followed** with regards to study design (e.g. choice of endpoints, choice of comparator, inclusion/exclusion criteria). **Any major deviation(s) from these guidelines should be justified.**

Ideally, randomised controlled and blinded confirmatory studies should be conducted. However this may **not always be possible** and other controls (i.e. historical controls, patient's own control) could be acceptable. The guideline on clinical trials in small populations provides guidance on the choice of control groups. The applicant has to justify the approach scientifically.

…

The efficacy studies should be designed to ***demonstrate efficacy in the target population***, to support the proposed posology, and to evaluate the duration of the therapeutic effect of the GTMP.

https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-quality-non-clinical-clinical-aspects-medicinal-products-containing-genetically-modified_en.pdf

Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products

6.6 Efficacy

…

Clinically meaningful endpoints which include previously validated or generally accepted surrogate endpoints are generally required to demonstrate efficacy.

In certain situations the use other endpoints is possible provided that there is a correlation between this endpoint and the clinical meaningfully outcome. **However a clinically meaningful endpoint has to be investigated in the long term follow up.**

Another important aspect is the **timing of the efficacy assessment** which may be different to conventional medicinal products and therefore the schedule of clinical evaluation should be planned accordingly.

If the intended outcome of the treatment is the long-term persistence and functionality of the transgene expression product (e.g. genetic diseases), this should be reflected with an adequate duration of follow-up. **The design and duration of follow-up has to be specified also considering potential loss of efficacy and might be completed, post-marketing if justified.**

…

Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products

7.6. Clinical Safety

…

The risk of the therapeutic procedure as a whole, including

i) the risk associated with cell procurement in an autologous setting

ii) the risk of administration procedures

iii) the risk of any required concomitant therapy e.g. the use of immunosuppressive therapy

As for any other biological product, there is a **risk of infection from unknown adventitious agents**; therefore patients should be monitored for signs of infections.

The **risk of delayed adverse reactions** and of decreasing efficacy for genetically modified cells is related to the actual **risk profile of the vector used for the genetic modification of the cell, the nature of the gene product, the life-span (persistence) of the modified cells, and the biodistribution**.

In relation to a possible **life-long persistence of genetically modified stem or progenitor cells**, special risk for delayed effects associated with the integrated vector and its expressed products should be considered (e.g.oncogenesis, immunogenicity or vector reactivation).

If there is a **risk of late onset of an adverse event** e.g. development of leukemia, measures have to be put in place to mitigate this risk e.g. treatment plan, back-up transplant.

FDA's Efforts to Advance the Development of Gene Therapy

FDA Voices: Perspectives From FDA Leadership and Experts

FDA Voices on Policy

FDA Voices on Consumer Safety and Enforcement

FDA Voices on Medical Products

FDA Voices on Food

By: Peter Marks, M.D., Ph.D., Director, Center for Biologics Evaluation and Research

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https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products

https://www.fda.gov/news-events/fda-voices-perspectives-fda-experts/fdas-efforts-advance-development-gene-therapy

- **FDA guidance Human Gene therapy rare disease**
  - The **randomized, concurrent-controlled trial** is generally considered the ideal standard for establishing effectiveness and providing treatment-related safety data.
  - **Single-arm trial using historical controls**, sometimes including an initial observation period, **may be considered** if there are feasibility issues with conducting a randomized, controlled trial.
  - If use of a type of single-arm trial design with a historical control is necessary, then **knowledge of the natural history of disease** is critical.
  - Adequate measures to minimize **bias** should be undertaken. The preferred approach to minimize bias is to use a study design that includes blinding.
  - **Patient experience** data may provide important additional information about the clinical benefit of a GT product

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/human-gene-therapy-rare-diseases

- **FDA guidance Human Gene therapy rare disease**
  - Because of the unique nature of the mechanism of action involving genetic manipulation, a potential exists for **serious long-term effects** that may not be apparent during development or even at the time of an initial licensure.
- **FDA guidance long-term follow after administration human GT**
  - To understand and mitigate the risk of a delayed adverse event, subjects in gene therapy trials **may be monitored for an extended period of time**, which is commonly referred to as the "long term follow-up" (LTFU) period (of a clinical study).

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/human-gene-therapy-rare-diseases

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/long-term-follow-after-administration-human-gene-therapy-products