Hospital Universitario La Paz

SaludMadrid

Comunidad de Madrid

UNIVERSIDAD AUTONOMA DE MADRID

IdiPAZ Instituto de Investigación Hospital Universitario La Paz

Esquemas de la TSE en la enfermedad de Fabry

Grupo de Enfermedades Minoritarias

Dra. Mónica López Rodríguez

Servicio Medicina Interna

1898..... 1998

TRATAMIENTO SINTOMÁTICO

Crisis de dolor neuropático y acroparestesias: carbamacepina, gabapentina o fenitoína.

Angioqueratomas: terapia láser con argón.

Afectación renal: control estricto de la tensión arterial con IECA o ARA-II (también en proteinuria). Si progresa a IR terminal, diálisis o trasplante renal.

Prevención de accidentes cerebrovasculares: sí antiagregación (anticoagulación?)

Síntomas gastrointestinales: dieta pobre en grasas, procinéticos, espasmolíticos.

***Kidney Int* 2002;61:249-55**

TERAPIA DE SUSTITUCIÓN ENZIMÁTICA (DESDE 2001)

Agalsidasa Alfa (Replagal®)

Obtención	Recombinación genética
Dosis	0,2 mg/Kg de peso
Vía	Intravenosa
Velocidad de administración	40 minutos
Intervalo	Cada 2 semanas

Agalsidasa Beta (Fabrazyme®)

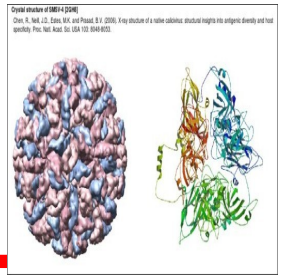
Obtención	Origen animal
Dosis	1 mg/kg de peso
Vía	Intravenosa
Velocidad de administración	15 mg/hora (inicial). Aprox 2 horas
Intervalo	Cada 2 semanas

JAMA 2001;285:2743-2749.
Am J Hum Genet 2001;68:711-722.

TERAPIA DE SUSTITUCIÓN ENZIMÁTICA (DESDE 2001)


Ehh,
What's Up,
Doc?

JUNIO 2009… PROBLEMAS EN LA PRODUCCIÓN DE FABRAZYME



www.wccpda.org/Pages/Arc × | Virus closes Genzyme plant, × | www.wccpda.org/Pages/Archives/M.Wiebe%20Adventitious%20Virus%20Talk%20WCC%20PDA%2006%2017%2010.pdf

More Headlines

Virus closes Genzyme plant, holds up drugs for 8,000 … Boston Globe, June 17, 2009

Genzyme's plight leaves patients uneasy … Boston Globe, June 18, 2009

After a virus invades, Genzyme scrubs down … Boston Globe, June 25, 2009

Genzyme Plant Shutdown Could Mean up to $300M in Lost Sales … Genetic Engineering News, July 2, 2009

Genzyme Rival, Actelion, Seeks to Fill Void Created by Cerezyme Shortage … Xconomy.com, July 9, 2009

Genzyme Corporation hit by Shareholder Class Action Lawsuit … PR-inside.com, July 29, 2009

Shire's Gaucher Drug Passes Key Trial, Putting More Heat on Genzyme

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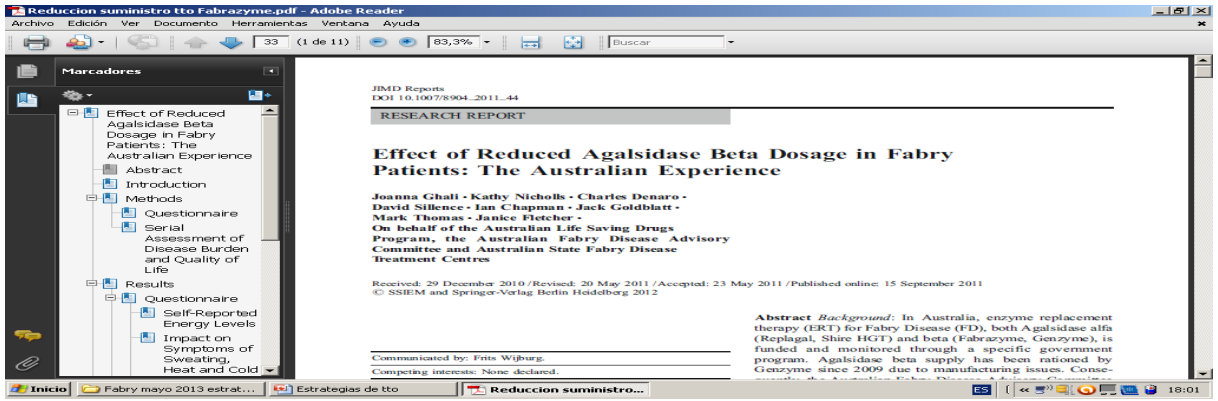
TSE: reducción dosis Agalsidasa Beta



Reduccion suministro tto Fabrazyme.pdf - Adobe Reader

Marcadores

- Effect of Reduced Agalsidase Beta Dosage in Fabry Patients: The Australian Experience
  - Abstract
  - Introduction
  - Methods
    - Questionnaire
    - Serial Assessment of Disease Burden and Quality of Life
  - Results
    - Questionnaire
      - Self-Reported Energy Levels
      - Impact on Symptoms of Sweating, Heat and Cold

JIMD Reports
DOI 10.1007/8904_2011_44

RESEARCH REPORT

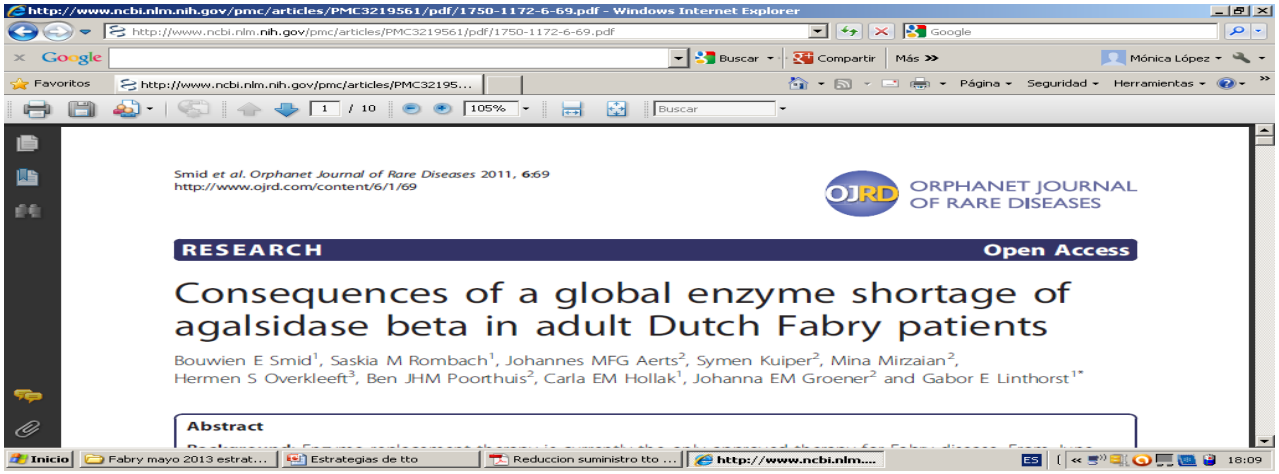
Effect of Reduced Agalsidase Beta Dosage in Fabry Patients: The Australian Experience

Joanna Ghali · Kathy Nicholls · Charles Denaro · David Sillence · Ian Chapman · Jack Goldblatt · Mark Thomas · Janice Fletcher · On behalf of the Australian Life Saving Drugs Program, the Australian Fabry Disease Advisory Committee and Australian State Fabry Disease Treatment Centres

Received: 29 December 2010 / Revised: 20 May 2011 / Accepted: 23 May 2011 / Published online: 15 September 2011

Abstract *Background*: In Australia, enzyme replacement therapy (ERT) for Fabry Disease (FD), both Agalsidase alfa (Replagal, Shire HGT) and beta (Fabrazyme, Genzyme), is funded and monitored through a specific government program. Agalsidase beta supply has been rationed by Genzyme since 2009 due to manufacturing issues. Conse-

Communicated by: Frits Wijburg.
Competing interests: None declared.



http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3219561/pdf/1750-1172-6-69.pdf - Windows Internet Explorer

Smid *et al. Orphanet Journal of Rare Diseases* 2011, 6:69
http://www.ojrd.com/content/6/1/69

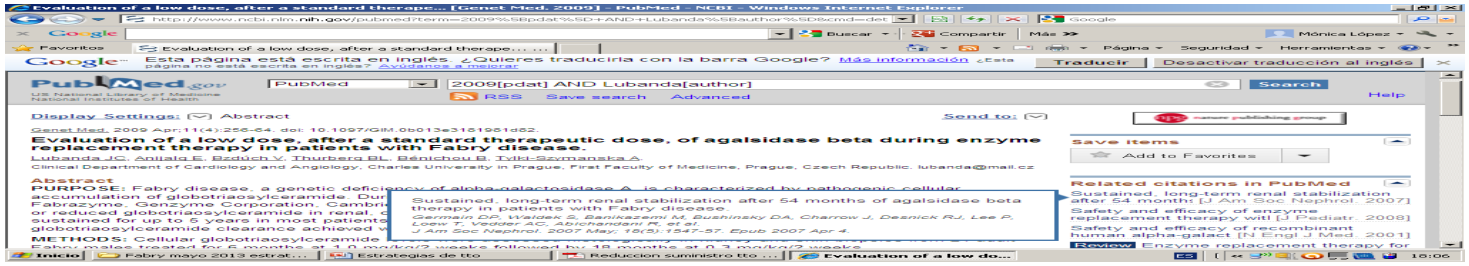
ORPHANET JOURNAL OF RARE DISEASES

RESEARCH Open Access

Consequences of a global enzyme shortage of agalsidase beta in adult Dutch Fabry patients

Bouwien E Smid[1], Saskia M Rombach[1], Johannes MFG Aerts[2], Symen Kuiper[2], Mina Mirzaian[2], Hermen S Overkleeft[3], Ben JHM Poorthuis[2], Carla EM Hollak[1], Johanna EM Groener[2] and Gabor E Linthorst[1*]

Abstract



Evaluation of a low dose, after a standard therapeu... [Genet Med. 2009] - PubMed - NCBI - Windows Internet Explorer

PubMed — 2009[pdat] AND Lubanda[author] — Search

Display Settings: Abstract — Send to:

Genet Med. 2009 Apr;11(4):256-64. doi: 10.1097/GIM.0b013e3181981d52.

Evaluation of a low dose, after a standard therapeutic dose, of agalsidase beta during enzyme replacement therapy in patients with Fabry disease.

Lubanda JC, Anilala E, Bzdúch V, Thurberg BL, Bénichou B, Tylki-Szymanska A.

Clinical Department of Cardiology and Angiology, Charles University in Prague, First Faculty of Medicine, Prague, Czech Republic. lubanda@mail.cz

Abstract

PURPOSE: Fabry disease, a genetic deficiency of alpha-galactosidase A, is characterized by pathogenic cellular accumulation of globotriaosylceramide. Dur... Fabrazyme, Genzyme Corporation, Cambri... or reduced globotriaosylceramide in renal... sustained for up to 6 years in most patients... globotriaosylceramide clearance achieved w...

Sustained, long-term renal stabilization after 54 months of agalsidase beta therapy in patients with Fabry disease.
Germain DP, Waldek S, Banikazemi M, Bushinsky DA, Charrow J, Desnick RJ, Lee P, Loew T, Vedder AC, Abichandani R, et al.
J Am Soc Nephrol. 2007 May; 18(5): 1547-57. Epub 2007 Apr 4.

METHODS: Cellular globotriaosylceramide ... Fabry patients treated for 6 months at 1.0 mg/kg/2 weeks followed by 18 months at 0.3 mg/kg/2 weeks ...

Save Items — Add to Favorites

Related citations in PubMed

Sustained, long-term renal stabilization after 54 months [J Am Soc Nephrol. 2007]
Safety and efficacy of enzyme replacement therapy with [J Pediatr. 2008]
Safety and efficacy of recombinant human alpha-galact [N Engl J Med. 2001]
Review: Enzyme replacement therapy for

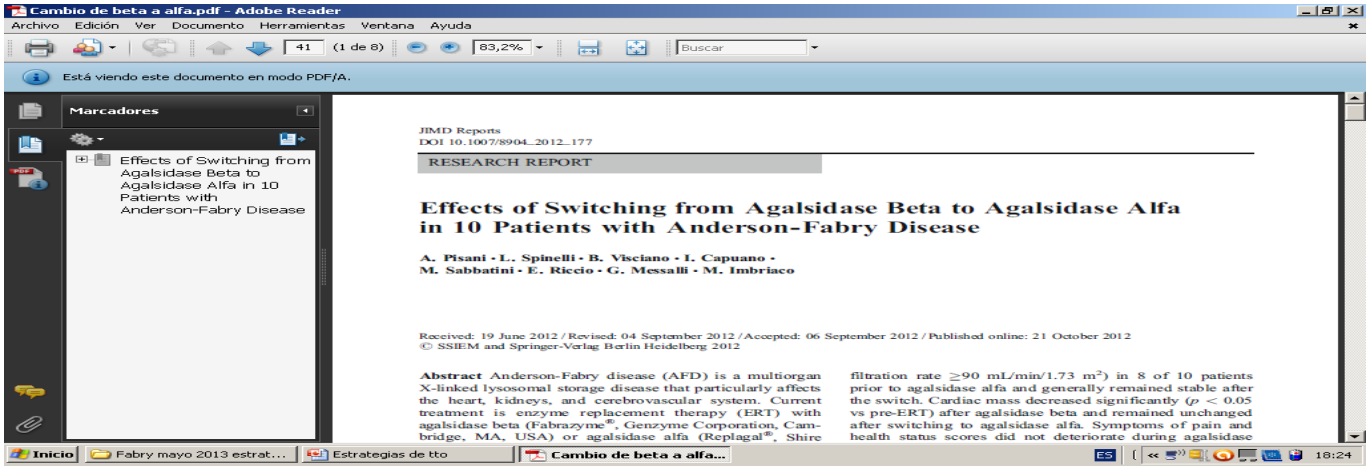
TSE: reducción dosis Agalsidasa Beta

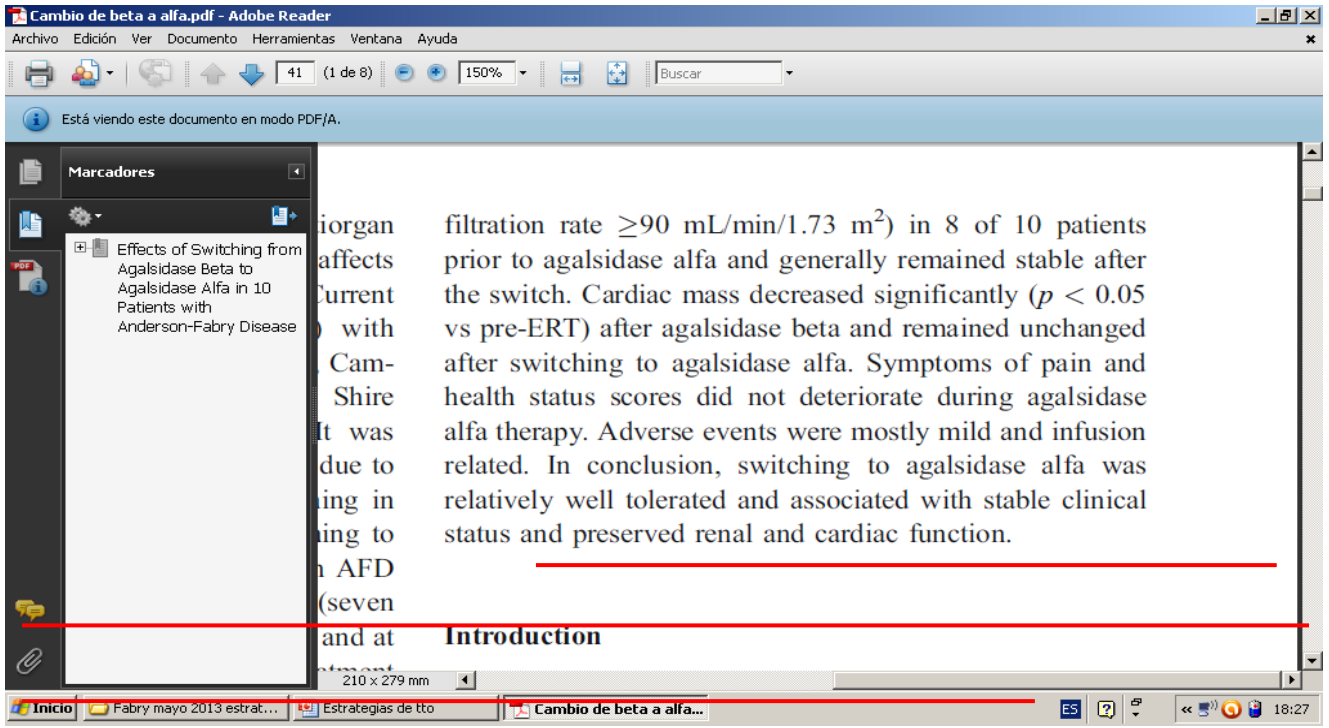
- **Empeoramiento de los síntomas subjetivos de QoL**

- **No incremento en incidencia de eventos clínicos, pero sí incremento en los depósitos de lysoGb3 (¿recurrencia actividad de la enfermedad?)**

- **Evidencia de deterioro aclaramiento Gb3 en algunos pacientes con reducción dosis de 1mg/kg a 0,3 mg/kg**

TSE: cambio a Agalsidasa Alfa





www.ema.europa.eu/docs/e
www.ema.europa.eu/docs/en_GB/document_library/Press_release/2010/10/WC500098370.pdf

The CHMP also noted that monitoring plasma or urine GL-3 levels does not appear to add value to the clinical management of the patients while on a lower dose.

The updated CHMP temporary treatment recommendations for Fabrazyme are as follows:

- Patients who require enzyme replacement therapy for Fabry disease should be prescribed the authorised dose of either Fabrazyme (1.0 mg/kg once every two weeks) or Replagal (0.2 mg/kg once every two weeks).
- Low doses of Fabrazyme should be limited to those patients who are stable and prefer to remain on a low dose.
- Patients and prescribers are advised that a deterioration of the condition has been observed in patients on the lower dose. Pain, cardiac manifestations and deafness are the usual manifestations of Fabry disease progression.

These recommendations do not change the currently approved product information for Fabrazyme.

The supply shortage of Fabrazyme began in June 2009 and was caused by a series of manufacturing problems at the production site in Allston Landing, in the United States of America. Because the current productivity at Allston Landing is still lower than expected, supply of Fabrazyme will not return to normal before the second half of 2011, according to Genzyme.

The CHMP remains concerned about the continued supply shortages of Genzyme's medicines and is closely monitoring the implementation of their improvement measures to prevent similar manufacturing and quality problems in the future.

EMA-FABRAZYME 2010.pdf
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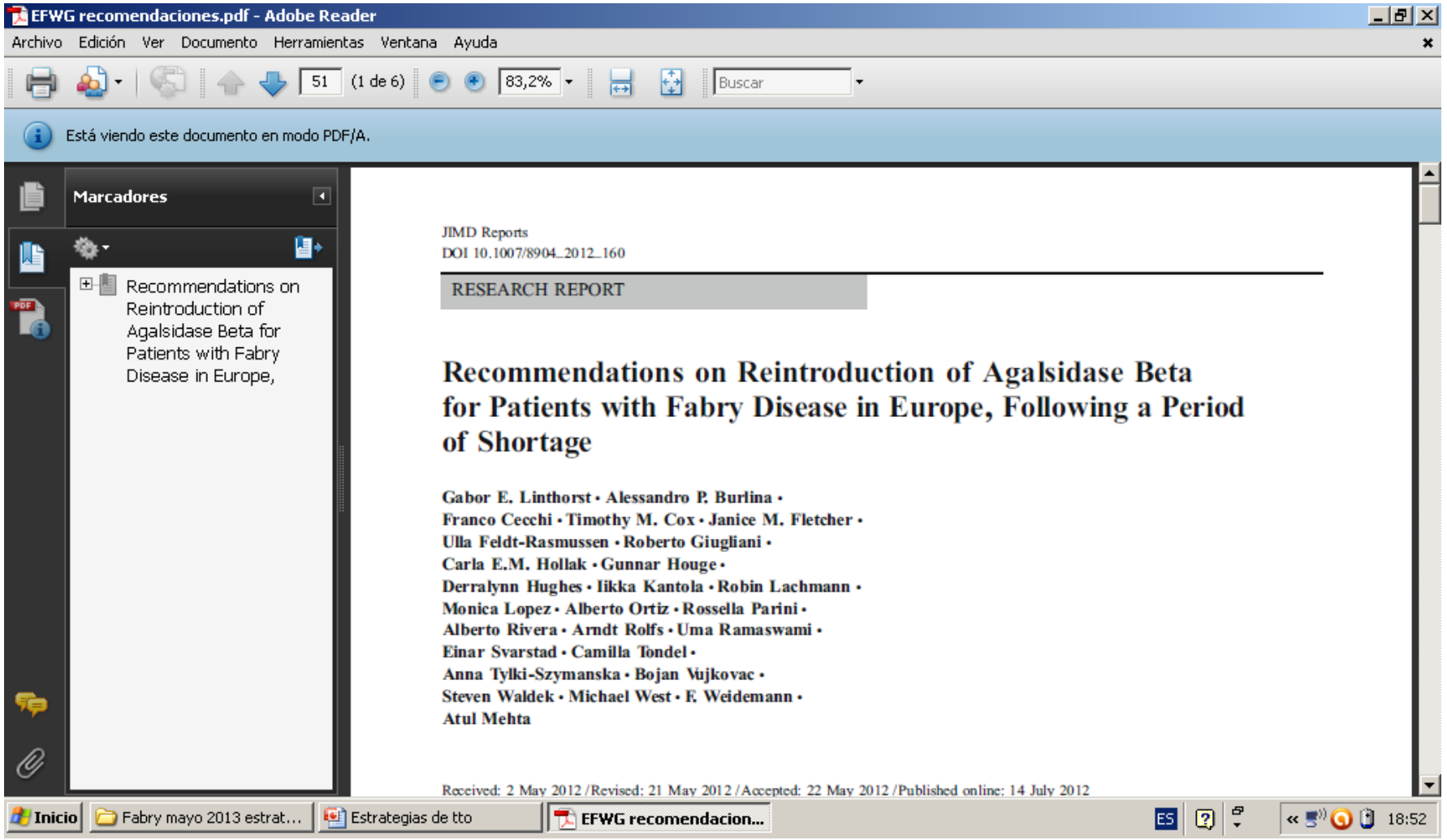
TSE: 2009-2012



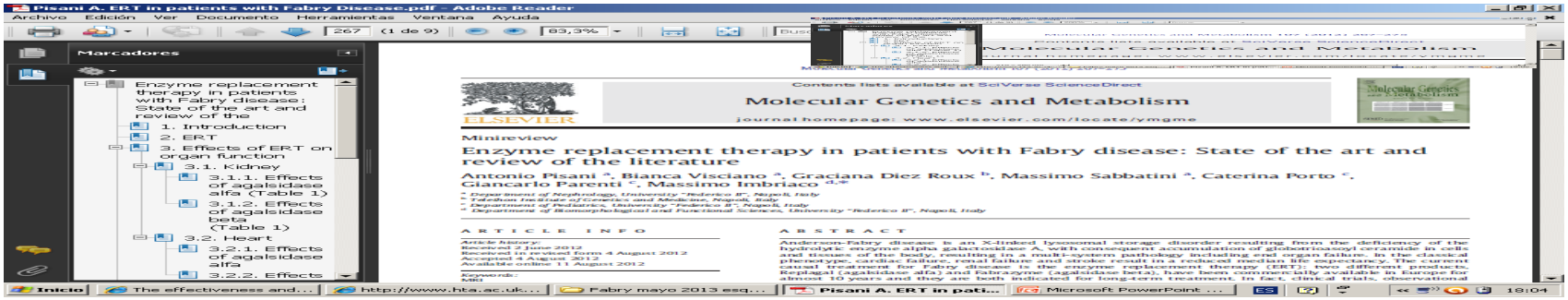
¿EFICACIA Y SEGURIDAD DE LA TSE?

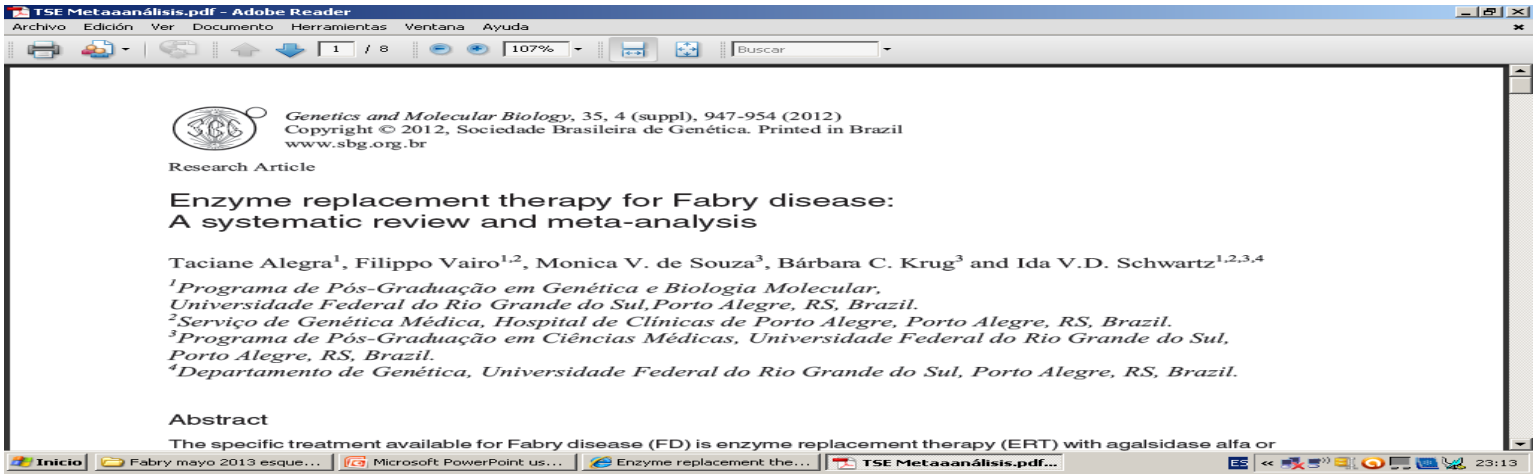
ANTICUERPOS

- **Positividad para IgG con agalsidasa alfa y beta (mayor con beta)**
- **Positividad para IgE sólo con agalsidasa beta**
- **¿Repercusión en la clínica, en los AA y en la respuesta al tratamiento?**

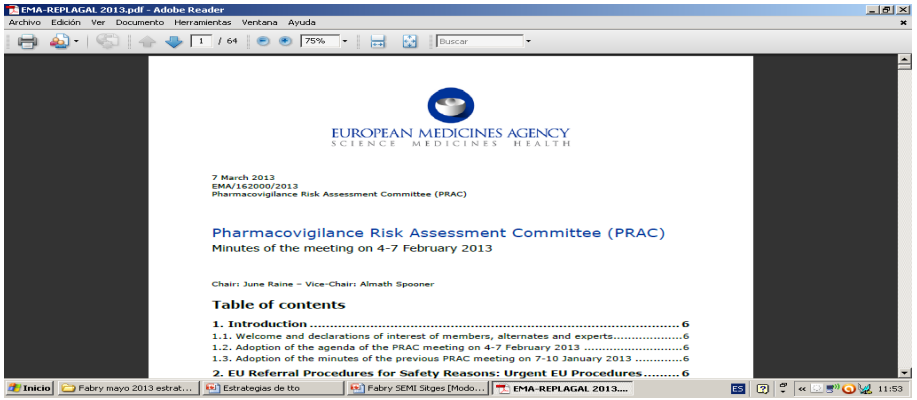
¿EFICACIA Y SEGURIDAD DE LA TSE?

COMPARACIÓN AMBOS TTOS ENZIMÁTICOS





NO EXISTEN DIFERENCIAS SIGNIFICATIVAS ENTRE AGALSIDASA ALFA (0,2 mg/kg) Y AGALSIDASA BETA (1 mg/kg)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EUROPEAN MEDICINES AGENCY
7 March 2013
EMA/162000/2013
Pharmacovigilance Risk Assessment Committee (PRAC)
Pharmacovigilance Risk Assessment Committee (PRAC)
Minutes of the meeting on 4-7 February 2013
Chair: June Raine – Vice-Chair: Almath Spooner
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the RMP for the above mentioned medicines.
6. Assessment of Periodic Safety Update Reports (PSURs)
6.1. Agalsidase alfa – REPLAGAL (CAP)
• Evaluation of a PSUR procedure
Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)
Background
Agalsidase alfa is used to treat long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry Disease (α-galactosidase A deficiency).
Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Replagal, a centrally authorised medicine containing agalsidase alfa, and issued a recommendation on its marketing authorisation.
Summary of recommendation(s) and conclusions
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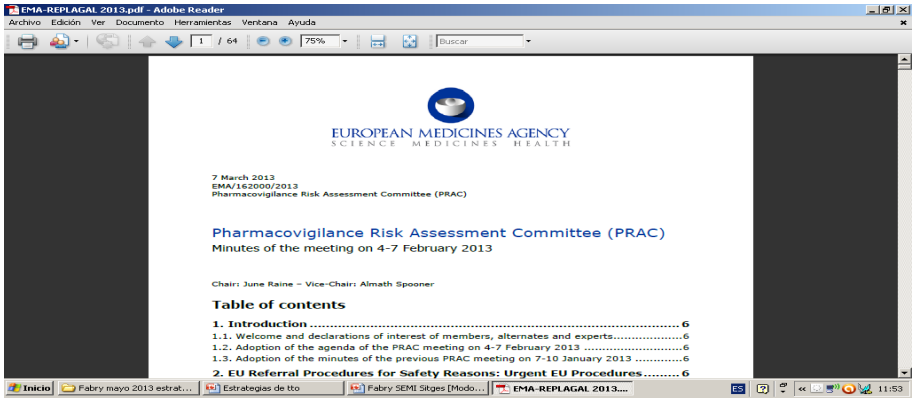

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diagnosis of Fabry Disease (α-galactosidase A deficiency).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Replagal, a centrally authorised medicine containing agalsidase alfa, and issued a recommendation on its marketing authorisation.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Replagal (agalsidase alfa) in the approved indication(s) remains favourable.
- The PRAC recommended the maintenance of the current terms of the marketing authorisation.
- In the next PSUR, the MAH should continue to closely monitoring several ADRs including cardiac adverse events reported in relation to infusion-related reactions.
- The MAH is requested to provide additional assessment of the cardiac adverse events reported in relation to infusion-related reactions within 2 months.

The frequency of submission of PSURs should remain once yearly and the next PSUR should be submitted to the EMA within 70 days of the data lock point.

6.2. *Aripiprazole – ABILIFY* (CAP)

- Evaluation of a PSUR procedure

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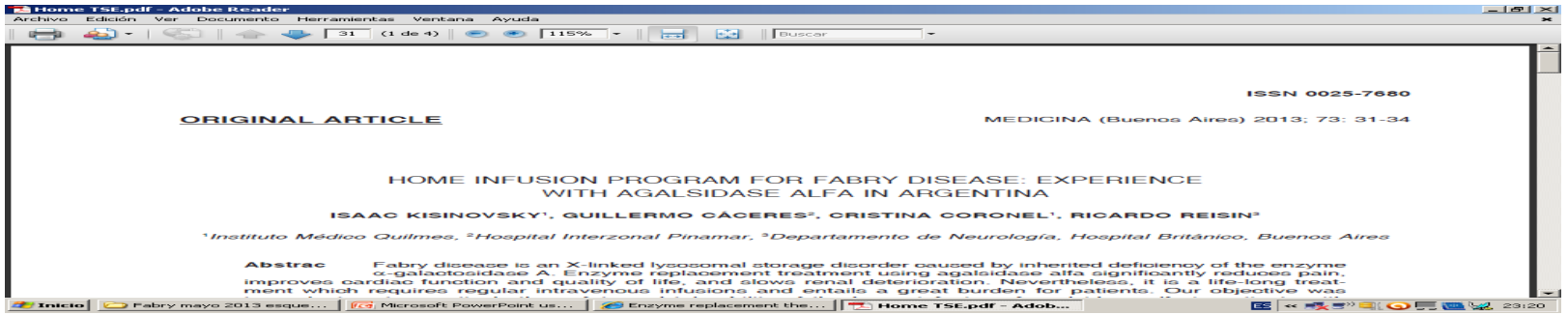
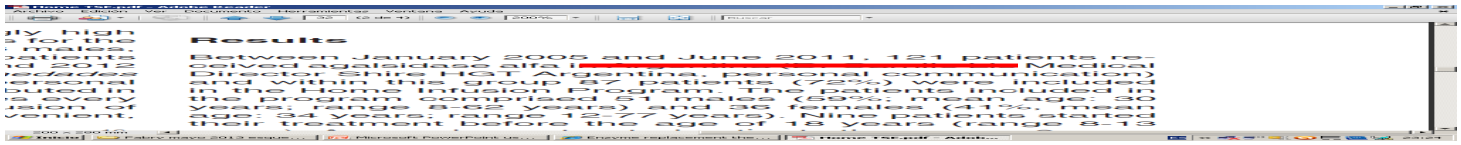
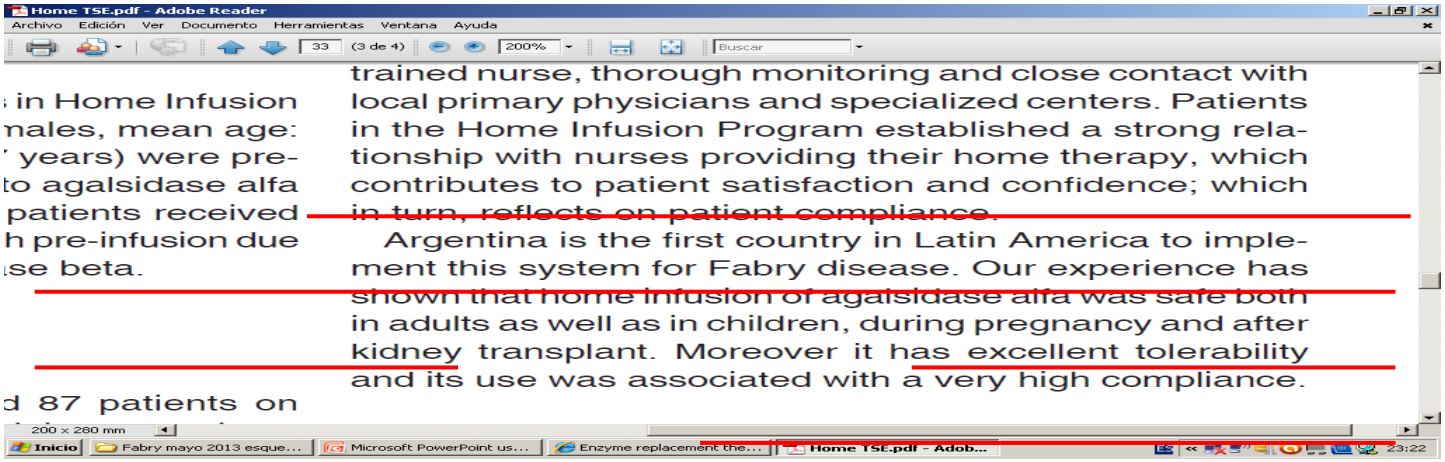
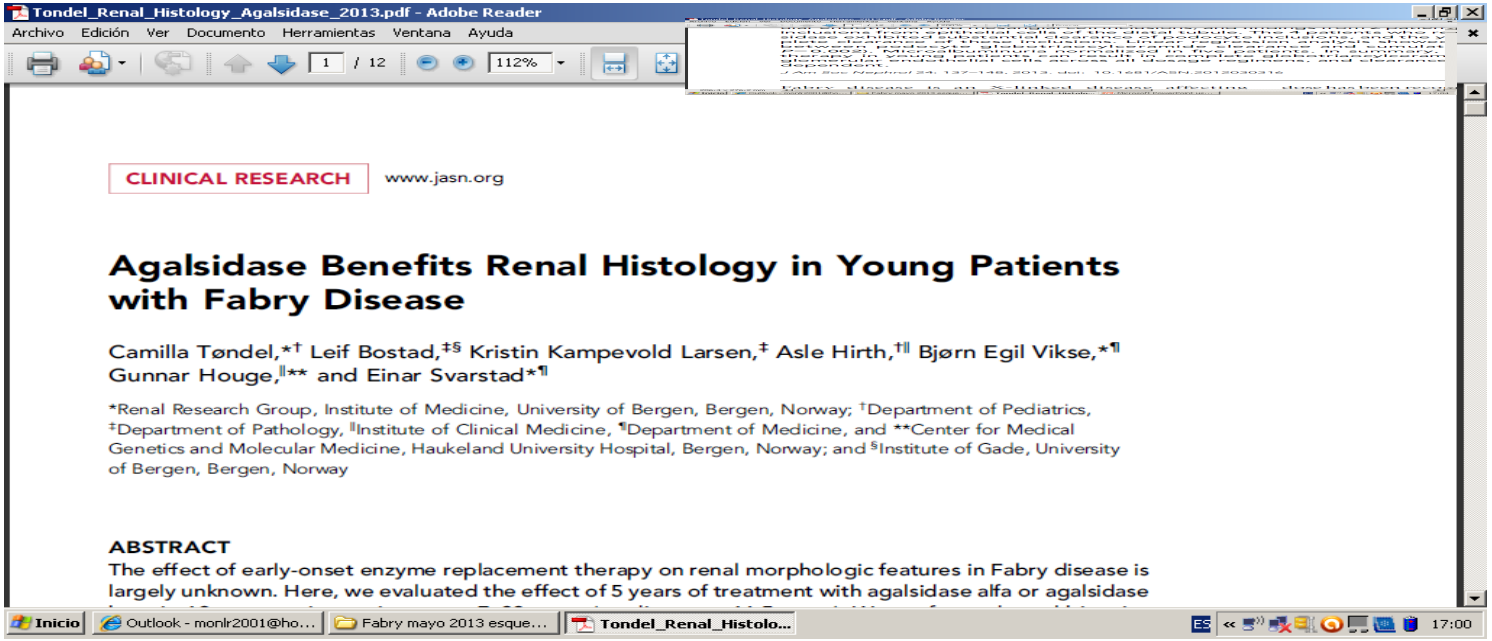
TSE, INFUSIÓN DOMICILIARIA





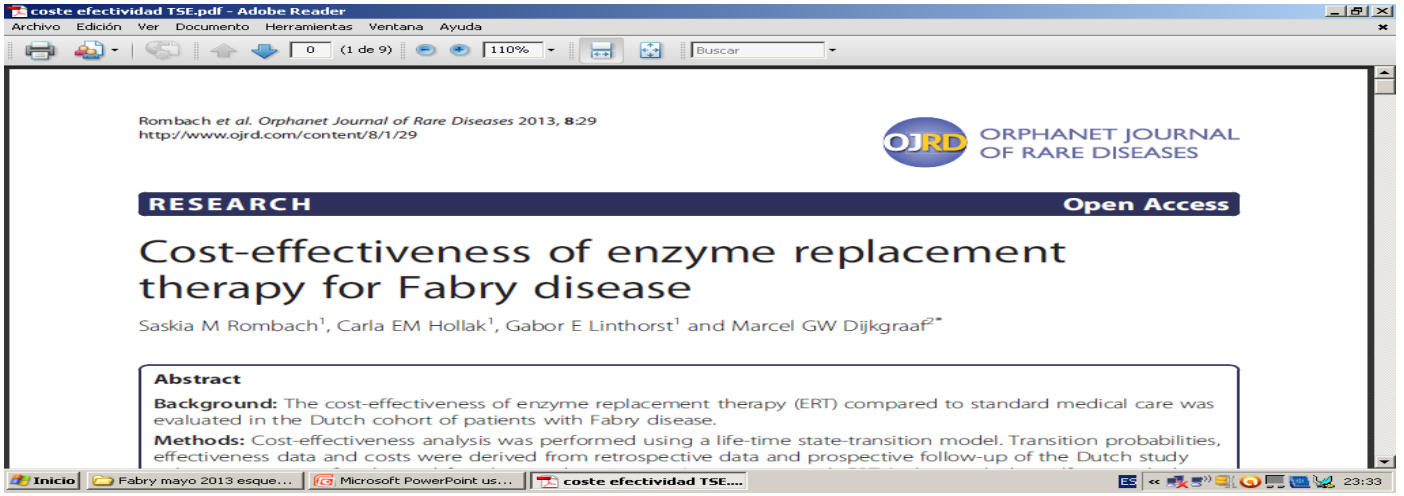


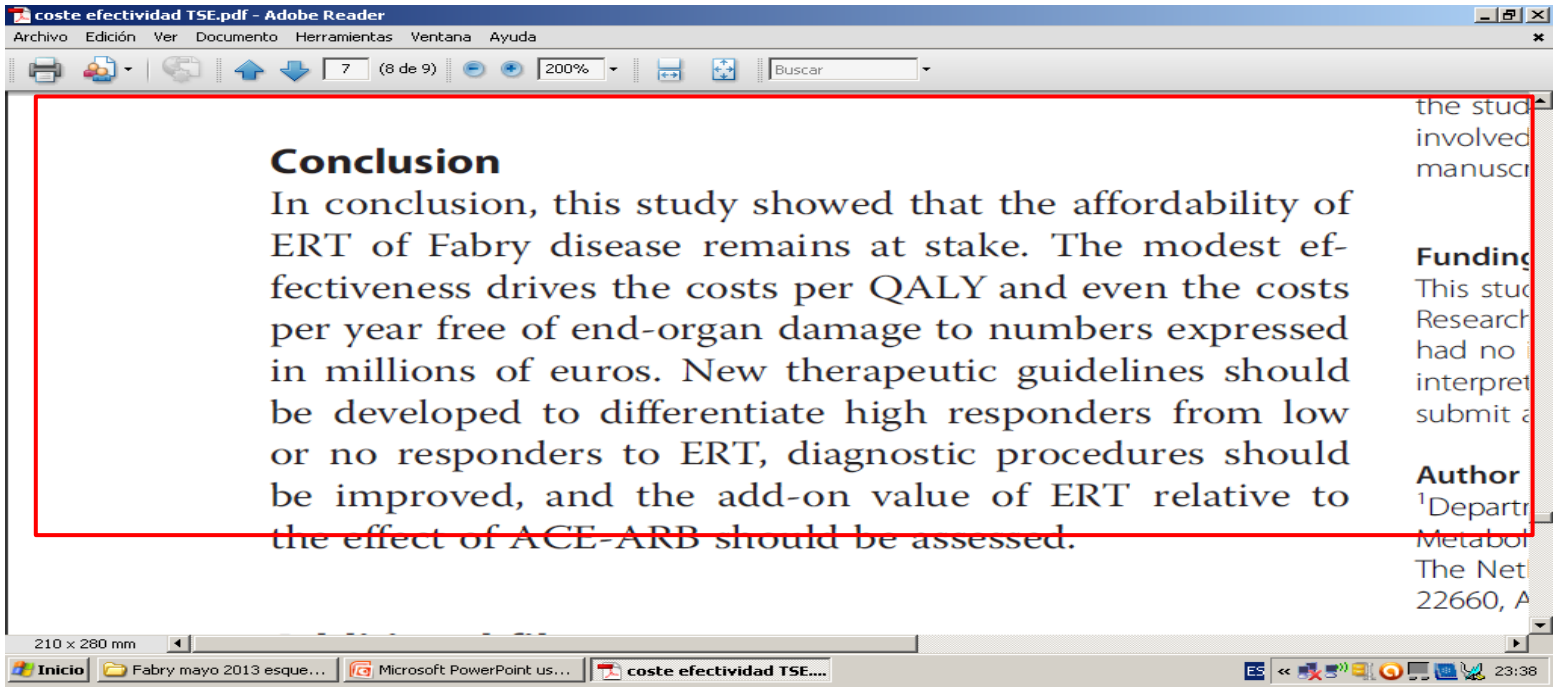
TSE, EFECTOS HISTOLÓGICOS RENALES



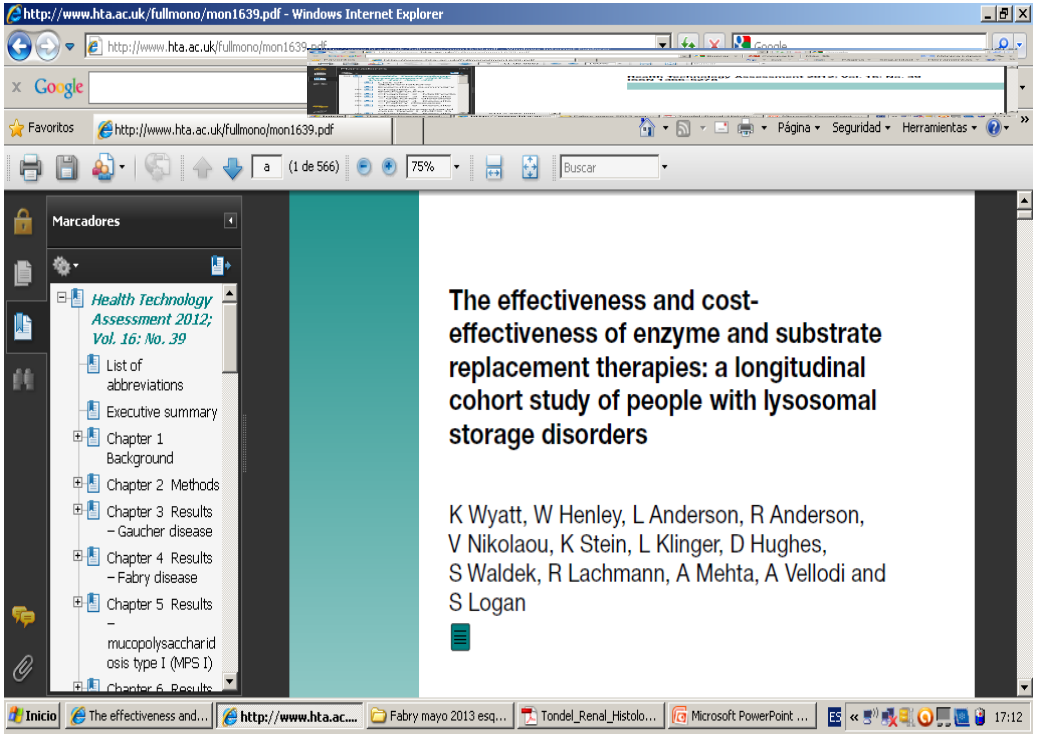
- Aclaramiento de GL3 en los podocitos renales de pacientes Fabry jóvenes
- Mayor aclaramiento con mayor dosis del enzima (alfa o beta)
- No hubo progresión de la enf. renal en ningún grupo.
- ¿Relación entre podocitos y disfunción de células renales?
- ¿Aplicabilidad clínica?

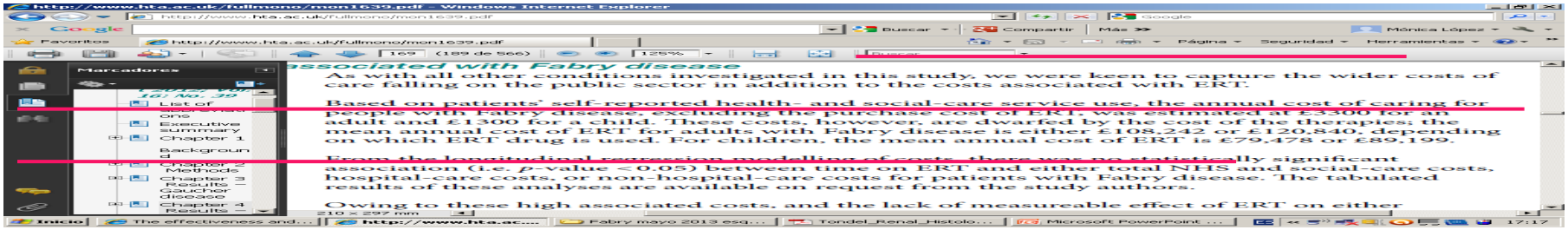
TSE: COSTE-EFECTIVIDAD

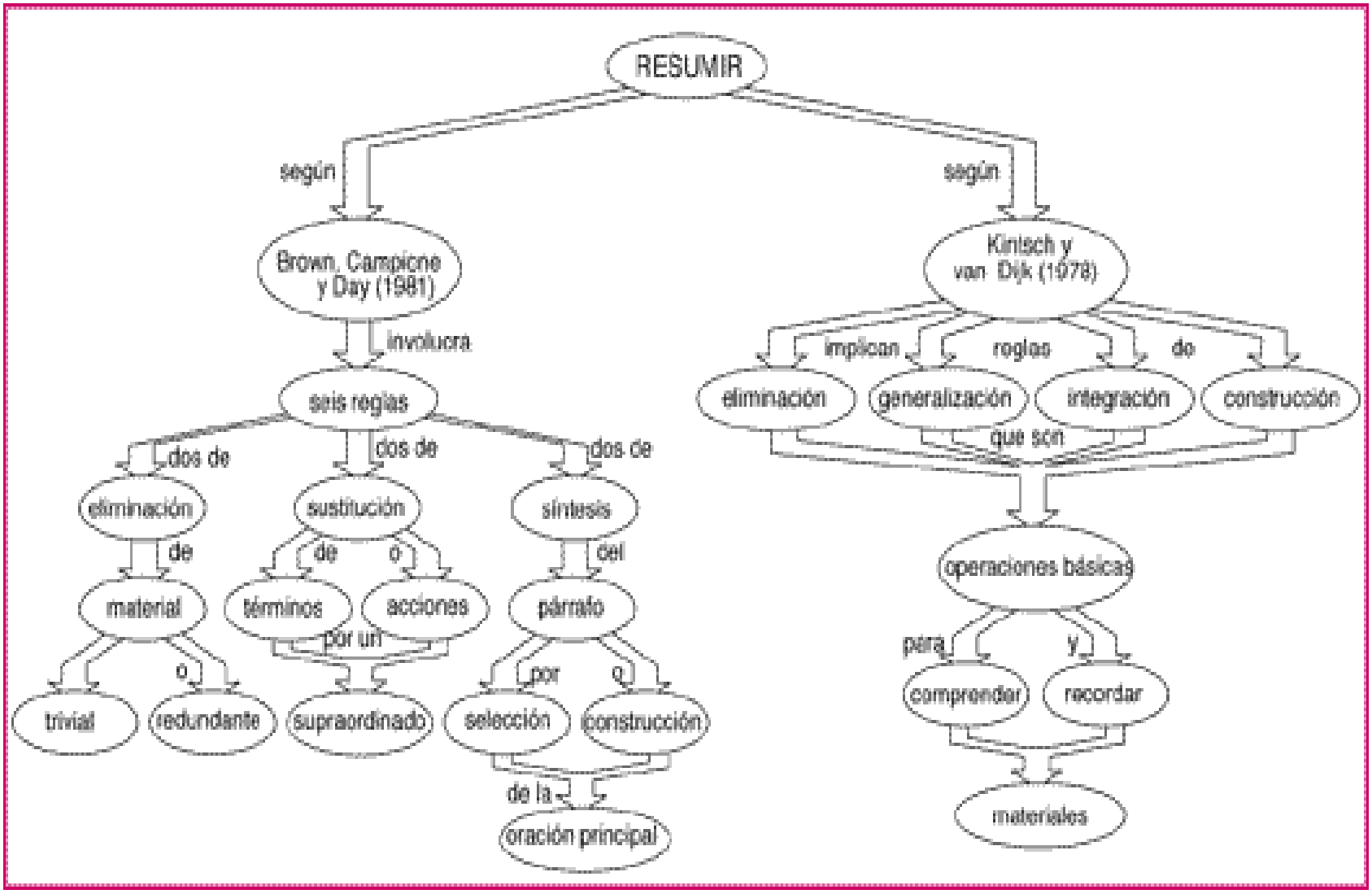




TSE: COSTE-EFECTIVIDAD






RESUMIR
según
Brown, Campione y Day (1981)
involucra
seis reglas
dos de
eliminación
de
material
trivial
redundante
dos de
sustitución
de
o
términos
acciones
por un
supraordinado
dos de
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del
párrafo
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de la
oración principal
según
Kintsch y van Dijk (1978)
implican
reglas
de
eliminación
generalización
integración
construcción
que son
operaciones básicas
para
y
comprender
recordar
materiales

EN RESUMEN…

1. **La TSE sigue siendo el único tratamiento para la enfermedad de Fabry que ha demostrado eficacia.**

2. **Tras el déficit de suministro de agalsidasa beta, han aparecido "nuevas" pautas de tratamiento con dosis inferiores a las aprobadas por las autoridades (EMA, FDA), que no han demostrado la misma eficacia.**

3. **La situación europea y mundial de crisis económica hace replantear la relación coste-efectividad de este tipo de tratamientos, más allá de las decisiones clínicas.**