

The GITER group and the treatment of rare diseases in Spain

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Introduction:

As a result of the measures taken by the Spanish government to support the patients of rare diseases, thematic research networks were created, including REPIER (Epidemiological Network on Rare Diseases Research) that focuses its research on the knowledge of rare diseases, including its therapy, with the aim of improving the guidelines of government actions. For this purpose exists a specific group within this network, the Rare Diseases Therapeutics Research Group (GITER).

Methods:

Based on the database developed by the group, we determine whether there are drugs designated as orphans by the EMEA, FDA and the Japanese Agency for the selected diseases and expand in which development stage these drugs are. Next we carry out a meta-analysis of published papers on treatment of the selected diseases. We search for information in the following databases and web pages: Medline, medicine and Medscape between the years 1994-2007 (information is mostly from 2001-2007). To analyze the cost of treatment we outline the procedures in the three selected diseases, which represent the three types of methodology used by the group. In the case of porphyria the study is done through the information obtained in a sample of patients, through a questionnaire developed by the GITER group and REPIER coordinator group and distributed in collaboration with FEDER. In the case of Addison's disease, we determine a therapeutic guidance through information obtained from a hospital that treated a small group of patients (4)*, contrasted with data from meta-analysis. In the case of aniridia, considering the dosage obtained from meta-analysis, we estimate the cost of treatment. Methods used in the study of treatment costs of every disease are shown in the specific section.

Objectives:

Introducing some of the findings on the utilization and treatment costs of rare diseases carried out by the GITER group of REPIER. To do this we put forward the results obtained in 3 diseases, Porphyria, Addison disease and Aniridia

Results about GITER data base

The GITER database contains information on medicines for rare diseases. For every product it is specified: the indication, the mechanism of action, the regulatory agency (FDA, EMA or Japanese), clinical trial phase and if it is approved and marketed the name of the country where it is available, finally it is collected the sponsor and the address of it. When a drug has been designated for more than one regulatory agency, EMEA will be prioritized on FDA and on the Japanese agency. Currently there is data of 412 orphan drugs for 478 indications. The figures 1 and 2 show the percentages of drugs designated and authorized by the different Agencies, as well as indications.

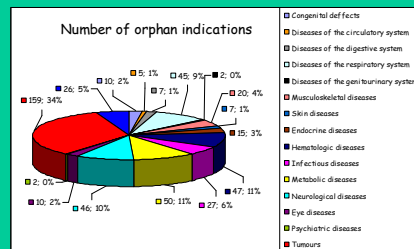
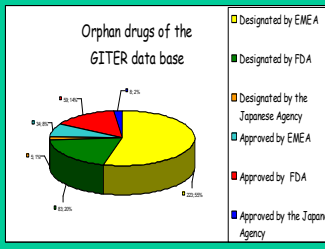


Table 1 shows the information contained in the database of the GITER group on designated orphan drugs for porphyria and Addison disease. It does not exist any orphan drug specific for the Addison disease, but there are some for those who suffer from renal failure with Addison disease. There are not orphan drugs for Aniridia.

There is only one orphan drug designated and marketed: the hemin, indicated for Acute Porphyria, the women are in clinical trials.

Orphan drug (Trade name)	Orphan	Agency (EMA/FDA/Japanese)	Phase	Mechanism of action	Market in Spain / Clinical phase	
Recombinant Human Porphobilinogen Synthetase (Normesang)	Yes	Zymenex A/S	Designated EMEA 22/06/2002 FDA 09/09/2004	Acute intermittent porphyria	Substitutive therapy of enzyme	II
Hemin (Prohemine)	Yes	Orphan Europe	Designated FDA 01/03/2008	Acute porphyria	Reduce synthesis of porphyrins	Marketed in Spain (12/08/2008)
Hemin (Prohemine)	Yes	Abbott Laboratories	Approved FDA 20/07/1983	Acute porphyria	Reduce synthesis of porphyrins	Marketed in EEU (20/07/1983)
Hematin (Sopranelin LA)	Yes	Anderson, Karl E, M.D. University of Texas Medical Branch	Designated FDA 03/05/1991	Acute porphyria	Marketed in EEU to treat porphyria (04/08/2007) III	
L-cysteine	Yes	Brigham and Women's Hospital Boston	Designated FDA 22/09/2004	Erythroid Protoporphyrin IX	Reduce photosensitivity	III
Tinamin disodium base/ tinadifil	Yes	Orphan	Designated EMA 12/08/2002	Skin porphyria	Sun blocker	II
Proxeterone (DHE A)	Yes	Medicon Healthcare AB	Designated EMEA 28/07/2003	Treatment of adrenal insufficiency	Replacement therapy	III
Hydrocortisone (Hydrocortisone Tablets)	Yes	DucCort	Designated EMEA 22/09/2006	Treatment of adrenal insufficiency	Replacement therapy	II/III
Hydrocortisone (Hydrocortisone release tablet)	Yes	Pharos Pharmaceuticals	Designated EMEA 20/03/2007	Treatment of adrenal insufficiency	Replacement therapy	II

Results about the utilization and the cost of treatment

Porphyrias

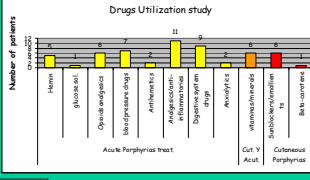
Aniridia

Overview (5):

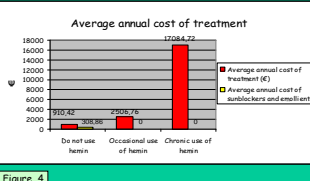
Overview: The porphyrias are a group of disorders of the heme biosynthesis pathway that present with acute neurovisceral symptoms, skin lesions or both.

Method: In a previous work (1) the utilization of drugs (figure 3) and the financing by the National Health System (NHS) has been analyzed. The present paper extends the study looking into the financing of sun blockers by the Autonomous Communities and the estimated cost of treatment (2). The annual cost per product was derived from the dosage, assessing the number of units per year and the packaging, having determined in that way the annual cost of each product. It has been possible to calculate the individual patient's annual cost of medication, and thus, to obtain the average annual cost per patient (Figure 4).

The patients were divided into two subgroups the first including those who use the hemin only occasionally, the second those using it on a chronically. In the first case, the cost was calculated on the basis of one crisis per year* (3). In skin or mixed porphyrias, the approximate average cost of sun blockers was considered separately, based on the consumption of 2 tubes per month*.



Results and discussion: Of the 26 patients who responded to the survey, 19 specified their treatment. There is a high cost of treatment in patients who use hemin chronically because they suffer from frequently recurring acute attacks(4) Regarding NHS funding of treatment, in acute porphyrias, drugs are partially or fully funded by the NHS; in porphyrias with skin symptoms sun blockers, emollients, beta-carotene and sunglasses are not funded by the NHS, but may be included in specific situations. In the case of sun blockers, the agreements between the Official Pharmaceutical Colleges and the Health Services of the Autonomous Communities were reviewed to check if they could be compounded and funded by the NHS. The results are shown in table 2.



Andalusia: It is possible to compound sun blockers in community pharmacies and they are funded by NHS through visa prescriptions.

Basque Country: Requires visa prescriptions for products with active sun blockers but only for Lupus Erythematosus.

Murcia, Castilla y Leon, Castilla La Mancha, Galicia, Navarra, Canary Islands, Madrid, Balearic Islands, Asturias, Catalonia and Valencia: Preparations with sun blockers can be made, but only to be used with other active compounds in pathological processes requiring photo protection.

Cantabria, Extremadura and Aragon: Not allowed to compound sun blocker products in community pharmacies.

Autonomous Community	Funding Status
Andalusia	Yes (with visa)
Basque Country	Yes (with visa)
Murcia, Castilla y Leon, Castilla La Mancha, Galicia, Navarra, Canary Islands, Madrid, Balearic Islands, Asturias, Catalonia and Valencia	Yes (with other compounds)
Cantabria, Extremadura and Aragon	No

Conclusions: As expected the cost of treatment for porphyrias rises considerably when patients use hemin (Normesang®) chronically because this is a new drug and it is very difficult to obtain for its extractive origin. In the case of skin porphyrias almost all Spanish patients assume the cost in sun blockers and only in one Autonomous Community are funded by NHS. In the case of Addison's Disease, the sample is not wide enough to allow reach a conclusion on the treatments currently underway in Spain, but there is a great variety in the cost of the replacement therapy with hydrocortisone.

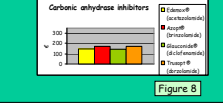
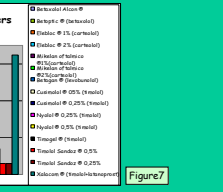
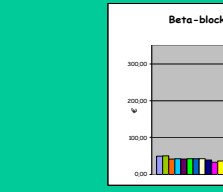
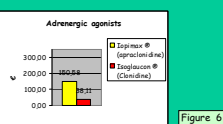
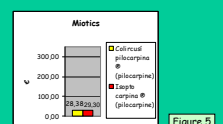
The variety of drug treatment makes it difficult to establish a standard cost of the drug treatment for aniridia glaucoma.

Agreements:
* To The Porphyrias Spanish Association.
** To the Hospital Pharmacy Service of the "Virgen de las Nieves" Hospital, Granada

Method: We select 27 drugs that by their features (indications / contraindications) might be suitable for the treatment of aniridia glaucoma. For purposes of calculating the annual cost, we consider the theoretical number of daily administered drops according to each leaflet and the total number of drops per bottle. The number of drops per bottle is calculated from literature search. For drugs with no bibliographic reference we make an approximate estimate of its volume. Once we get the number of bottles used per patient and year we estimate of the annual cost.

Results and discussion:
1- Treatment of aniridia glaucoma according to medical literature:
A) Miotics: they are the first choice in the preventive treatment of glaucoma. pilocarpine is administered.
B) Adrenergic agonists: they have the disadvantage of causing mydriasis and are contraindicated in closed-angle glaucoma, with the exception of clonidine: apraclonidine, brominidine, dipivefrin.
C) Beta-blockers: they are the treatment of choice in open-angle glaucoma. timolol, betaxolol, levobunolol, carteolol are used.
D) Carbonic anhydrase inhibitors: They are the only ones who can be administered orally, but only in resistant cases. Acetazolamide, brinzolamide, dichlorfenamide and dorzolamide are used.
E) Prostaglandin derivatives: These drugs have been more recently introduced in the treatment of glaucoma, although its use has not been fully evaluated: Latanoprost, bimatoprost, travoprost are used.

2- Annual cost of the pharmacological treatment: (Figures 5-9)
The treatment of choice with miotics turned out to be the cheapest, followed by beta-blockers and adrenergic agonists; next are the carbonic anhydrase inhibitors, which are only administered and are not the first choice. Finally, we find prostaglandin derivatives, which are the most expensive but which are viewed as a last choice, and have not been fully assessed in aniridia glaucoma. There is a similar cost for drugs in the same group, except for Timogel® for which the increased cost is due to the advantage that it is once daily administered, and Zipimax® (apraclonidine), with a marketing authorization later than that of clonidine (Zipolaclo®) and therefore, with higher price(6). In the case of Xalacom® (timolol/latanoprost) the higher cost is due to the association of a beta-blocker and a prostaglandin derivative. Patients may also require low vision aids which vary greatly depending on the patients and their characteristics; and include magnifying glasses and microscopic lenses, among others. The cost to patients varies depending on the funding by the insurer.



Addison Disease

Overview (7): Addison's disease is a disorder caused by an adrenal cortex failure, which leads to a deficiency of mineralocorticoid and glucocorticoid hormones. This disease has a slow and gradual course. Symptoms may include muscle weakness, weight loss and skin hyperpigmentation.

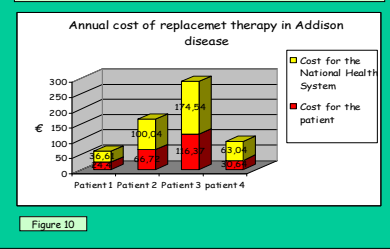
Method: It is compared the treatment indicated on the medical literature with the treatment administered to the 4 patients*. The cost of the replacement therapy is estimated from prices fixed on 2007.

Results and discussion:
1. **Meta-analysis of the treatment:** The treatment established in medical literature consists of replacement therapy with glucocorticoids and mineralocorticoids and increased administration of salt, thus achieving the goal of controlling symptoms. There is no consensus among authors on the regime of therapy and dosage. We can describe treatment regimes as follows:
A) Some authors recommend hydrocortisone alone, since this product presents both glucocorticoid and mineralocorticoid properties.
B) Other authors believe that hydrocortisone is not enough and a mineralocorticoid must be administered together, primarily fludrocortisone.
C) Finally, several authors think that prednisone can be administered instead of hydrocortisone, together with a mineralocorticoid.

2. **Annual cost of the replacement therapy:** The medication regime used in the sample of patients consists of the administration of a mineralocorticoid (fludrocortisone) and a glucocorticoid, preferably hydrocortisone rather than prednisone. No orphan drug was used, although it must be said that data collection dates from the years 2002 and 2003. None of the four patients was under medication with hydrocortisone alone. Instead, we found a patient who was treated with prednisone, hydrocortisone and fludrocortisone (table 3). We did not find a significant interannual variation. There were many differences in the dosage and frequency of administration between patients.

Drug	Number of patients	0-2	2-6	6-14	14-18	>18
Fludrocortisone	4				1	3
Hydrocortisone	3				1	2
Prednisone	2				1	1

Figure 10 shows the annual cost of the replacement therapy of the sample. Party is funded by NHS.



References:
(1) Alsina C, Bonet F, Martín-Anríbas C, Posada M, Bel E. "Análisis de la Utilización de medicamentos en una muestra de pacientes afectados de porfirias en España". III Congreso Internacional de Medicamentos Huérfanos y Enfermedades Raras. Sevilla, 14 al 17 de febrero de 2007.
(2) Alsina Armengol, C. "Tratamiento de los enfermos afectados de Porfiria: Análisis de la utilización de medicamentos y otros productos farmacéuticos y coste del tratamiento". Trabajo realizado para obtener el título de Diploma de Estudios Avanzados (DEA), del departamento de Farmacia y Tecnología Farmacéutica de la Universidad de Barcelona. Director del trabajo: Dra. Elvira Bel Prieto. Julio 2007 (not publish).
(3) Morales Ortega X, Wolff Fernandez C, Leal Ibarra T, Monte Navarro N, Armas-Merino R. Crisis porfirica. Experiencia con 30 episodios. Medicina (Buenos Aires). 1999; 59:23-27
(4) Anderson K E, Collins S. Open-label study of hemin for acute porphyria: clinical practice implications. The American Journal of Medicine. 2006;119(9): 801.e19-801.e24.
(5) De Andrés Lázaro, A. M. "Aniridia: estudio de los tratamientos y costos orientados". Trabajo práctico presentado en la Facultad de Farmacia de la Universidad de Barcelona. Director: Dra. Elvira Bel Prieto. Enero 2006 (no publish).
(6) Nürsen Yüksel, Cenap Güler, Yusuf Çağlar and Orhan Elilob. Apraclonidine and clonidine: a comparison of efficacy and side effects in normal and ocular hypertensive volunteers. International Ophthalmology. Setiembre 1992; 16(4-5):337-342.
(7) Barceló Giro J. "Malaltia d'Addison: anàlisi de tractaments i aproximació de costos". Trabajo práctico presentado en la Facultad de Farmacia de la Universidad de Barcelona. Director: Dra. Elvira Bel Prieto. Setiembre 2007 (no publish).