Off-label use and the information needs of patients with rare diseases

François Houÿez

Director of Treatment Information & Access

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Behcet's syndrome community

map @ 3 months: 900/1348 patients indicated their location

RareConnect.org
A PARTNERSHIP OF EURORDIS AND NORD

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Many reported 5 different misdiagnoses before Behçet's Disease.

What are the consequences of misdiagnosis?

59.28% Innappropiate treatments

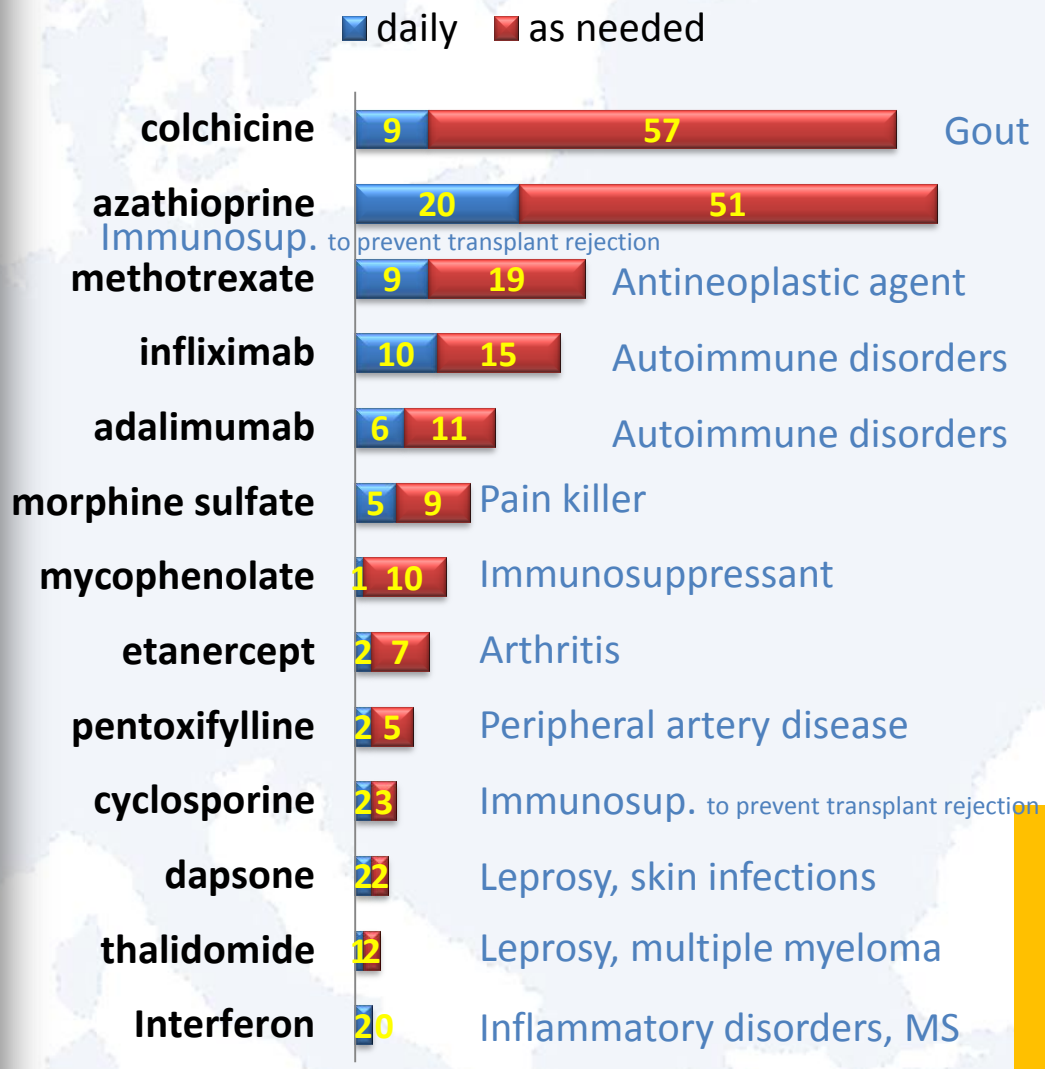
HELP Misunderstanding from family 54.12%

Issues with employment 37.67%

Treatments used by participants

- Prednisone
- Colchicine
- Azathioprine
- Methotrexate

Q11 What medications are you currently taking for Behcet's syndrome?



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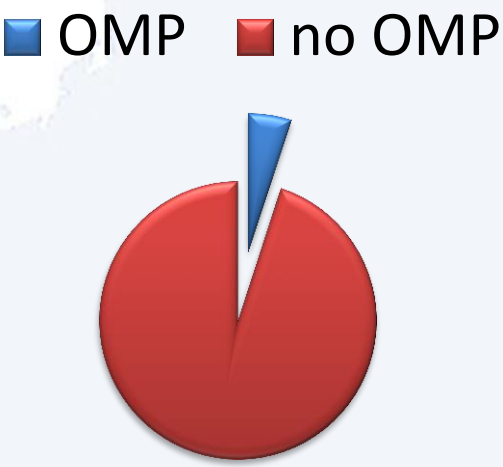
Innovation, innovation, innovation

- 105 orphan drug indications granted
  - Not all active (market withdrawals)
- Covering ~ 5% of rare diseases



- 95% of rare diseases treated empirically
  - Off-label use
  - Symptomatic treatments
  - N-A-T-C and other not-evaluated treatments

Our proposals

- Off-Label use in the absence of standard of diagnosis and care:
  - Most needed: benefit/risk information for each off-label use
- In the absence of evidence
  - EMA Scientific Advice Group for RD treatments for a case by case scientific opinion
  - Consultation with COMP
- GOLUP: Good Off-Label Use Practices
  - Life-threatening / severely debilitating condition
  - Standard treatment failure or non-availability
  - No other (on-label) treatment (Unmet medical need)
  - Some evidence in the literature & experts
  - Reporting of positive/negative results

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Action plan 2015 onwards

- New survey ”Tell us how you’re taking your treatment”
  - 19 languages
  - 2000+ responses expected, 31 countries
  - Aligned with the EC research on off-label use (Call for Tender to come)
  - Submitted to INSERM IRB / response 9 June
- Interviews with the consultant (EC Call for Tender)
- Creation of a larger database of treatments for RD (including devices, off-label)
- Analysis of the environment and national measures for OL (e.g. RTU, mandatory substitution…)

Concerns

- Informed Consent
  - One more! (compassionate use, clinical trial, drugs with ▼ or RMP, complex surgical interventions, registries, surveys…)
  - How much time left for medicine?
  - Legal value?
- Off-label use is a very efficient way of treating patients and making medical progress
  - Freedom to prescribe any authorised product should be protected and let at the discretion of the doctor/patient
- Access versus incentives for industry to develop new indications with authorised products?

Measures to contain pharmaceutical costs
(May 2014, 7th ECRD Berlin)

- Measure:
  - Obligation to prescribe medicines using the active substance name only, not the brand name
  - Adopted in SP, SW, BE, CY, DK, DE, GR, PO, RO
  - Objective: to use generics (when applicable) more than genuine medicines

- Colateral effect
  - A medicine exists for a common indication – originator name
  - A company invests: new indication for a rare disease (CTs) – new name
  - If cheapest is dispensed (originator), how to gain return on investments?
  - Legality of the measure?

CAMPAIGN FOR ACCESS To MEDICINES FOR PEOPLE WITH RARE DISEASES
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Price comparison of selected medicines for common and rare indications in Belgium in 2011

Active substance name	Brand name common disease	Unit dose	Cost per unit dose	Marketing date	Brand name rare disease	Unit dose	Cost per unit dose	Marketing date	Price difference
aztreonam	Azactam	4,000 mg	58.88	1984	Cayston	225 mg	131.52	2004	x 40
Celecoxib	Celebrex	200 mg	0.96	2000	Onsenal	800 mg	4.05	2001	x 1.05
Chenodeoxycholic acid	Chenofalk	750 mg	2.01	1975	Xenbilox	750 mg	23.76	-	x 11
Cladribine	Leustatin	8 mg	315.32	1991	Litak	2 mg	356.91	2001	x 4.5
Dexrazoxane	Cardioxane	1,500 mg	867.87	2000	Savene	500 mg	10,140.5	2001	x 35
Everolimus	Certican	0.25 mg	2.33	2006	Afinitor	10 mg	265.80	2007	x 2.5
Histamine	Histamine	1 mg	0.75	1970	Ceplene	1 mg	150.00	2005	x 200
Sildenafil	Viagra	50 mg	19.14	2002	Revatio	60 mg	29.10	2003	x 1.3
Tadalafil	Cialis	10 mg	13.27	2004	Adcirca	20 mg	15.45	-	x 0.6
Tobramycin	Obracin	240 mg	12.78	1996	Tobi	300 mg	44.17	2003	x 2.8
Carbidopa / levodopa	Sinemet	75 mg/ caps	0.36	2000	Duodopa	500 mg/ infusion	116.66	2001	X 49

Disputes

- Poland
  - Article 4 of the Law on Medicinal Products of 6 September 2001, as amended by the Law of 30 March 2007
  - Dispenses with the requirement for a marketing authorisation for medicinal products from abroad
    - which have the same active substances
    - the same dosage and the same form as those having obtained a marketing authorisation in Poland
    - on condition that, in particular, the price of those imported medicinal products is competitive in relation to the price of products having obtained such authorisation

What does the Court of Justice say?

- Allowing the placing on the market of a non-authorised product or off-label use of a product for financial considerations is not permissible
- Granting of marketing authorisations must take account exclusively of considerations relating to the protection of public health
  - *The conditions for withdrawal of an authorisation must be interpreted in accordance with the general principle, identified in the case-law, that protection of public health must unquestionably take precedence over economic considerations*
  - *(see, in particular, order in Case C-180/96 R United Kingdom v Commission [1996] ECR I-3903 paragraph 93, and the judgment in Case C-183/95 Affish [1997] ECR I-4315, paragraph 43)*

Legal concerns on measures taken by MS

EUCOPE
European Confederation of Pharmaceutical Entrepreneurs AISBL

Off-label Use for financial consideration not permissible

Judgment of the Court of Justice of 29 March 2012 in Commission v Poland (Case C-185/10):

"32 More specifically, as regards the derogation referred to in Article 5(1) of Directive 2001/83, the Court has already pointed out that the possibility of importing non-approved medicinal products, provided for under national legislation implementing the power laid down in that provision, must remain exceptional in order to preserve the practical effect of the marketing authorisation procedure (see, to this effect, Case C-143/06 Ludwigs-Apotheke [2007] ECR I 9623, paragraphs 33 and 35).

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Off-label Use for financial consideration not permissible

"37 Where medicinal products having the same active substances, the same dosage and the same form as those which the doctor providing treatment considers that he must prescribe to treat his patients are already authorised and available on the national market, there cannot in fact be a question of 'special needs', within the meaning of Article 5(1) of Directive 2001/83, necessitating a derogation from the requirement for a marketing authorisation under Article 6(1) of that directive."

"38 Financial considerations cannot, in themselves, lead to recognition of the existence of such special needs capable of justifying the application of the derogation provided for in Article 5(1) of that directive." (emphasis added)

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Italian off label policy development

- Italy's medicines agency (AIFA) permits off-label drug use to be reimbursed even if an alternative authorised treatment is available (June 2014)
- Previously, such use was reimbursable only if the product was included in AIFA's approved drug list and where no alternative authorised treatment was available.
- Changes in the law flout EU rules on marketing authorisations for drugs.
- The Court of Justice of the EU has clearly underlined in [a 2012 case] that (i) exceptions to the marketing authorisation requirement have to be interpreted narrowly and (ii) that financial considerations in themselves cannot justify such an exception

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France off label policy

- France submitted its draft decree *on Off Label use for economic reasons* to the European commission to check compliance with EU law, which has since been approved. (July 2014)
- Now, the draft decree is passing through the hands of the Council of State for double checking.
- If off label use is encouraged, companies will be unlikely to go through the long and costly process of market authorization for new therapies. Putting patients at risk using poorly tested treatments and hindering development of new therapies.

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Questions to you

- Substitution of a prescribed product by a less expensive product with the same active substance can help a higher number of patients receiving treatment

→Substitution can favour access

- Substitution of a prescribed product by a less expensive product with the same active substance prevents industry of generating returns on investments

→Substitution can stop new treatments: no more incentives for drug repurposing (new indication) in RD

EURORDIS Drug Information Transparency and Access 'DITA' task force members

- Claudie Baleydier, Friedreich Ataxia, FRA
- Juan Fuertes, Primary Pulmonary Hypertension, SPA
- Ellen van Veldhuizen, Addison Disease Org., NLD
- Rainald von Gizycki, Pro Retina, GER
- Danijela Szili, Rett synd., HUN
- Luc Matthyssen, Pulmonary Hypertension, BEL
- Sigurður Jóhannesson, Alternating Hemoplagia of Childhood, ICE
- Isabel Fernandez, FEDER, SPA
- François Houÿez, Anne-Mary Bodin, EURORDIS, Paris
- Rob Camp, EURORDIS, SPA
- Lise Murphy, Marfan syndrome, SWE
- Inge Schwersenz, Neuromuscular SMA, GER
- Vesna Stojmirova, Life with Challenges, FYROM
- Thomas Sannié, Association for Haemophilia, FRA
- Oliver Timmis, Alkaptonuria Society, GBR
- Christine Lavery, Muco-polysaccharidosis Society, GBR
- Russel Wheeler, LHON, UK
- Richard West, Behcet Society, GBR
- Tatiana Foltanova, Slovakian Alliance for RD

Marketing Authorisation Requirement

- Article 6(1) of Directive 2001/83:
  - *No medicinal product may be placed on the market of a Member State unless a marketing authorisation has been issued by the competent authorities of that Member State in accordance with this Directive or an authorisation has been granted in accordance with Regulation (EC) No 726/2004.*
- The **therapeutic indication is the most determinative part of the SmPC and the safety and efficacy of the product is only confirmed for that use**. In line with this aspect, the public assessment reports must contain a justification for the authorisation of the medicine for each therapeutic indication (Article 21(4) of Directive 2001/83)

Exceptions to the Marketing Authorisation Requirement

- **Exceptions in Directive 2001/83**
  - **Article 3,** e.g. magistral formula, officinal formula, investigational medicinal products
  - **Article 5,** e.g. medicinal products supplied in response to a bona fide unsolicited order or products that are temporarily authorised in response to the suspected or confirmed spread of pathogenic agents etc.
  - **Article 7** (refers to radiopharmaceuticals)

  and in Article 83 of Regulation 726/2004.
- Exceptions apply where **there is a specific medical need** that cannot be met by properly authorised medicinal products