Registries, trial data & the real world

Innovate, assess, access

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Disclaimer: Slides reflect presenters personal opinion

HIV: A lot went well

- Expanded access / compassionate use (FDA, 1987)
- Accelerated approval life threatening conditions (FDA, 1992)
- Use of surrogate markers instead of clinical end points in pivotal trials (EMA, NVP approval 1997)
- New criteria for conditional approval (Gilead first to apply, access 12 months accelerated)
- **Lazarus effect on dying patients & HIV cohort studies in place to proof cost-effectiveness of expensive treatment**
- Cross-Atlantic lobbying for pivotal trial including 2 NCE, ending exposure to monotherapies & multidrug resistance 2007
- Single tablet regimens for convenience and adherence, while having single compounds to control toxicities, resistance and adapt drug levels, FDA: 27 NCE & 14 combos 1987-2017
- Tiered pricing & voluntary licences supporting global access

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HCV – the silent epidemic

- DAA and combination treatment: Biggest scientific breakthrough for patients since HAART introduction
- Much shorter treatment cycles, much less toxicity, a lot more effective & cheaper than previous gold standard
- Interaction with regulators and industry since 2007
- **Despite tremendous benefit DAA: bumpy reimbursement, access limitations even in UK & CH while patients continue to die**
- **Interesting: HTA bodies assessment in conflict (German IQWiG versus HAS & Scottish Medicines Consortium; Scotland faster than NICE) – apparent methodological discrepancies and challenges**
- **Difficult: convince health authorities about systemic impact condition & to commit to strategic infectious diseases treatment strategies**
- System focus too much on cost containment & for perfection; fails on robustness. Result: insecurity about treatment uptake on all sides.

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HCV – what makes it so different?

- **Disease progression very slow**
- **Patient population diverse – IDU, healthcare system infections, tattoo studios, haemophilia, perinatal & sexual transmission, mono- & co-infection**
- **Weak epidemiological data – WHO expected 180’000’000, now down to 71’000’000. CH estimate 80’000 down to 40’000-50’000**
- Diverse treating physicians: gastroenterologists, hepatologists, ID specialists, addiction specialists. Most patients in GP care.
- **Patient groups diverse, weaker or not existing**
- **Collaboration professionals/patients low level**
- **Research progress very fast: SoC until 2012 35% effective after 9 months & big side effect burden; today 95% in 8-12 weeks, no side effects**
- Old SoC treatment of last resort. DAA treatment ideally earlier

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HCV – what makes it so different? (2)

- "Cost effective" does not mean cheap
- Health systems only look at total cost. Disease burden high in many countries
- QALY & QoL gain in treated patients not considered
- **Almost no cohorts/registries in place to provide data**
- Up to 90% of persons infected unaware of status

How did systems react?

USA

- Gilead caused global turmoil announcing 1’000$ pill. Senate hearing on pricing, poisoning climate beyond Hep C. Slow treatment uptake in most affected populations (veterans, prisoners, former IDU). Screening strategy in place.

Portugal, Scotland

- High system awareness, treatment strategies implemented quickly. Portugal: early deal with Gilead & low price agreement.

Australia

- Hep-C buyers club importing generics from India. Government concludes deal with all manufacturers, commitment to treat 50’000 patients per year at 3’435AU$

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How did systems react? (2)

Switzerland

- Patients treated old SoC, 2001-2014: 14’488, SVR 64%, cost per treatment (48wk) 30’000 CHF
- FOPH unable to negotiate volume deal
- Price setting using “prevalence model” – does not pay out
- Rationing DAA access via limitations, first to F3 & F4
  - Patients treated 2015: 2’000-2’300, SVR 95%
- Widening access to F2 leads to less patients treated (!)
  - Patients treated 2016: 1’900, SVR 95%
  - Current price Harvoni 12wk: 50’000
- CH clinics report no access for 20%-50% HCV-patients (2017)
  - Patients import generics from India, pay themselves (ca 1’500 CHF)
- FOPH refused supporting hepatitis strategy development
- Efforts to delay access continue until Oct 1, 2017

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PCSK9 inhibitors

- **Human monoclonal antibodies, new class of cholesterol lowering drugs, more effective than statins. Evolocumab single injection per month.**
- **High cost, US 14’500 p y, Switzerland 6’700 CHF**
- FDA restricted label to familial hypercholesterolemia, CH also restricted label hypercholesterolemia & statin intolerance
- Cost effectiveness studies say that price would have to drop by 2/3, but even at this price, burden for health systems would be huge
- **Amgen decided against drug registry**
- **Possible remedy could be Scandinavian cardiovascular disease registries**
- Currently no remedy in sight – has industry developed an orphan drug for a large indication?

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General systemic problems

- Complex system with many actors
- **Regulatory approvals more transparent (EMA, less Swissmedic), not accepted by everybody** (Cochrane review HCV)
- EMA regulatory system evolving (PRIME, Adaptive Pathways)
- System turning global & has new players (India, China)
- **Health expenses considered as cost, not an investment. No or insufficient instruments to model cost & QoL effectiveness for new interventions**
- Philosophical question: More regulation or more dialogue?
- Narrow focus on cost containment but little concern about system robustness & stability
- **Price setting system laid out for medicines with daily intake – new models needed for interventions taken once or short term & providing long lasting effect**
- Price driver: insecurity on all sides

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General systemic problems, ctd

- **Medicines regulation harmonisation in Europe a success, blueprint for HTA harmonisation**
- Systems pay for useless interventions (mammography, prostate screening), but lack money for new & useful things
- Medicines labels too static, pricing review also rather static
  - Pricing should be tied to label changes
- **Public debate about orphan medicines needed**
  - **Few patients, expensive treatment but many orphan diseases**
- **Much needed medicines disappear because price is too low, – example: benzathine, long acting penicillin for treating syphilis**
  - SoC for syphilis, on WHO Essential Medicines list, not registered in CH

Registries vs randomisation – a conflict?

- Randomised study: gold standard to understand something precise rather quickly
- Understanding your patient? Disease registries needed
- However, disease registry a good base for running randomised studies
- Example: Integrase inhibitors mono treatment
  - Randomised trials unsuccessful in some countries
  - Despite this, Swiss HIV cohort to continue a study
  - Specific population in cohort with very early treatment start. No failure in this group so far
  - Control arm established within cohort
  - No company could run such a study
  - Patients know the risk, but trust established within cohort over many years

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Acronyms used

- NVP: Nevirapine
- NCE: Novel chemical entity
- DAA: Direct acting antivirals
- HAART: Highly active antiretrovirals
- IDU: Injecting drug users
- ID: Infectious diseases
- GP: General practitioner
- SoC: Standard of care
- QALY: Quality adjusted life years
- QoL: Quality of life
- SVR: Sustained viral response
- FOPH: Federal Office for Public Health
- F1, F2, F3, F4: Fibrosis stages

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