Real World Evidence and HTA – Experiences with IQWiG

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Overview

- Some definitions
- IQWiG and RWD
- Examples
- Final remarks
§ 5 (7) Size of additional benefit

- Major
- Considerable
- Minor
- Not quantifiable
- No additional benefit
- Benefit lower than benefit of GBA-defined comparator
Confidence in benefit (IQWiG Methods paper 5.0 chapter 3.1.4)

- **Proof**
  - Statistical significance in ≥ 2 RCTs with high confidence in benefit

- **Hint**
  - Statistical significance in one RCT with high confidence in benefit or in ≥ 2 RCTs with moderate confidence in benefit

- **Clue**
  - Statistical significance in one RCT with moderate confidence in benefit or in ≥ 2 RCTs with low confidence in benefit

- **No confidence**
AMNOG - Principle

Studies with the highest evidence to be reported

- If RCTs available, then these are to be reported
- If no RCT is available, the studies with next highest evidence to be reported
  - E.g. single-arm studies
  - E.g. non-randomized studies
What is meant by RWE?

- Real world data vs. Real world evidence
- RWD = Data used for decision making that is not collected in RCTs
- RWD can be obtained when the drug is marketed => as request with time restriction of decision by G-BA

Evidence level

- 1 = RCT (or meta-analyses based on RCTs)
  - Internal validity => causal relationship can be concluded

- 2 to 4 = observational studies (cohort / case control studies and case series)
  - Timely relationship can be concluded
  - External validity
  - Low costs
  - No randomization => treatment effect depends on similarity of groups
Issues with RWD

- Statistically
  - Many sources of bias
    - selection bias, missingness not at random, etc.
  - No causal interpretation possible

- Non-statistically
  - Generation of data
  - Transparency
  - Validity
  - Data quality
RWD in AMNOG

- Main application in AMNOG dossier
  - prevalence and incidence in Module 3
  - Patient pathways and use of drugs
    - maybe relevant in price negotiations
  - Supportive data in Module 4

- Single-arm trials
  - In absence of RCTs
  - Accepted in special circumstances
    - HepC and HIV applications (historical comparisons)
    - Vismodegib
RWD – IQWiG position

- RCTs are study designs with least issues
- All other designs are worse
  - Huge effort needed to control for confounders
  - Issues in literature search (search terms, filters)
  - RWD not necessarily with higher external validity
  - External validity is useless, if based on low quality data
  - Effectiveness cannot be assessed by RWD
    - Even should not be assessed at all

Most publications of RWD state that they need to be confirmed in RCTs…

Requirements on RWD not defined

Adaptive pathways regarded doubtful

Registries most often do not collect QoL data

RWD is needed for

- The assessment of prevalence and incidence
- Cost of the comparators and/or best supportive care

Vismodegib – Module 4

- Studies included by Roche
  - SHH4476g (ERIVANCE, Phase II, single-arm, pivotal)
  - MO25616 (STEVIE, Phase II, single-arm)
  - Study SHH4811g (US-EAP, Expanded access study, single-arm)
  - Study SHH3925g (Phase I, single-arm)
  - Extension study of patients from Phase I and II
  - RegiSONIC (observational, single-arm)
  - NIELS (observational, single-arm)
  - Viscusi and Hanke 2015 (observational, single-arm)

Source: Nutzendossier zu Vismodegib
Studies included by Roche

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=> No data on the comparison to BSC

Source: IQWiG Nutzenbewertung zu Vismodegib
Vismodegib – G-BA

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=> **Clue for a minor benefit**

Source: Tragende Gründe des G-BA zu Vismodegib
Asfotase Alfa – G-BA assessment

- Long-term Enzym-replacement therapy in patients with hypophosphotasia (age < 18, orphan)

- Study program
  - Single-arm intervention trials (Methodological issues)
  - Historical comparisons with two observational studies not accepted
  - One RCT (ENB-009-10), placebo-controlled (high potential for bias due to open-label design, issues with statistical test strategies)

- Limited evidence available
  => Prospective registry (EMA)
  => Prospective registry data with all German patients (G-BA)

Source: Tragende Gründe des G-BA zu Asfotase alfa
Sebelipase Alfa – G-BA assessment

- Long-term Enzym-replacement therapy in patients with LAL-deficite (orphan)
- Study program
  - Single-arm intervention trial (N=9)
  - Single-arm retrospective observational study (N=25)
- Limited evidence available
  => Prospective registry (EMA)
  => Prospective registry data with all German patients (G-BA)

Source: Tragende Gründe des G-BA zu Sebelipase alfa
Idebenon – G-BA assessment

- Visual deficits with LHON
- Study program
  - RCT (RHODOS, Phase II, N=85), placebo-controlled, but methodological issues
  - RHODOS observational Follow-up
  - Expanded Access Programm
  - Historical Case Record Survey
- Limited evidence available especially on long-term safety
  => Prospective registry (EMA)
  => Prospective registry (G-BA, time-restriction 2 years)

Source: Tragende Gründe des G-BA zu Idebenon
Pragmatic trials - a way out…?

- **Pragmatic trial**
  - Aim to maximize generalizability to a broader setting
  - **Four domains**
    - Study population
    - Setting of the trial
    - Operationalization of the intervention and chosen comparator
    - Outcome measure
  - **Comparison of randomized groups of patients**
    - That are similar to the target population
    - Setting as in real world

Source: Groebbee et al. 2017: Pragmatic trials and real world evidence: Paper 1. Introduction, J of Clin Epi 88: 7-13); GetReal Initiative
Final remarks

- IQWiG and G-BA use data of the highest evidence level
- If RCTs or at least interventional trials are available, RWD will not be taken into account
- If for orphan drugs the available evidence is sparse, a registry may be demanded by G-BA
  - Strategic implications for the company with regards to set-up, timing, etc.
  - G-BA may be asked for advice early on, if a registry is requested by EMA
Thank you!