Schwenke Consulting:
Strategies and Solutions in Statistics

Real World Evidence and HTA – Experiences with IQWiG

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Overview

- Some definitions
- IQWiG and RWD
- Examples
- Final remarks

Amount of additional benefit

- **§ 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

- **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 ment 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 retriction 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

Source: Windeler J (2015): Real World data – ein Gewinn für die Nutzenbewertung?; Herbstsymposium 2015

RWD – IQWiG position

- 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

Source: Windeler J (2015): Real World data – ein Gewinn für die Nutzenbewertung?; Herbstsymposium 2015

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

Vismodegib – IQWiG

- Studies included by Roche
  - SHH4476g (ERIVANCE, Phase II, single-arm, pivotal)
  - MO25616 (STEVIE, Phase II, single-arm)
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  - Viscusi and Hanke 2015 (observational, single-arm)

=> No data on the comparison to BSC

Source: IQWiG Nutzenbewertung zu Vismodegib

Vismodegib – G-BA

- 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)

=> 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 expecially 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!