Randomized building blocks: A plea to provide best evidence in trials under sample size restrictions

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Restricted sample sizes:  
A common occurrence in rare diseases

• Rare diseases (Dupont & Van Wilder 2011):  
  • Less than five people per 10 thousand people affected  
  • Over 6000 rare diseases  
  • Up to 30 million patients in Europe affected  

• Regulation 141/2000 on orphan medicinal products:  
  Patients with such conditions deserve the same quality, safety and efficacy in medicinal products as other patients

• Comparisons of trials in rare and non-rare diseases: (Bell & Tudur Smith 2014)  
  → Anticipated and actual recruitment numbers are lower in rare disease trials  
     (41 vs 76, 29 vs. 62 (median))  
  → Majority of trials in rare diseases are single-arm trials (63% vs 29%)
Fanconi Anemia and oral lesions

Fanconi Anemia (FA): rare inherited chromosomal instability syndrome

- a predisposition to cancers

- risk of head and neck squamous cell carcinoma (SSC) increased by 500-fold (Kutler et al. 2003)

- Lesions in the oral cavity (leukoplakia and erythroplakia) often progress to SSC

- Chemotherapy not possible due to chromosome instability

- Hope: therapy option that resolves oral lesions

Pioglitazone: Prevention of the development of malignant tumors?

Pioglitazone
- Oral hypoglycemic medication administered in type 2 diabetes mellitus
- Safe risk profile

Single-arm trial (Miller et al. 2015)
- n=21 non-FA patients with oral lesions
- Pioglitazone
  - twice daily for 12 weeks
- Partial or complete involution of oral lesions
- 2004-2008

Assumption:
Pioglitazone effective in FA
Pioglitazone in FA: study design based on available information

Planning of a randomized trial

- prospective, placebo-controlled, double-blind, monocentric

- Pioglitazone is efficacious in resolving oral lesions in FA patients

- Binary Responder Criterion (partial or complete involution)

- Placebo effect based on expert opinion (spontaneous remission rate)
Pioglitazone in FA:
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Placebo effect based on expert opinion (spontaneous remission rate)

“Nobody would participate in a placebo-controlled trial, since it is already clear that pioglitazone is effective!”

| placebo   | 68 |
| treatment effect | 63 |

Assumptions response rate (%) pioglitazone placebo treatment effect
Pioglitazone in FA:
Updated knowledge while study planning was still ongoing

RCT (NCI 2016)
• N = 52 non-FA patients with oral lesions
  • Pioglitazone vs placebo
    • once daily for 24 weeks
  • Partial or complete involution of oral lesions
• Terminated due to slow accrual
  • 2010-2014, reported 2016

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Pioglitazone in FA: lessons learned

Single-arm trial

Clinical equipoise was perceived to be lost!

Reluctance against RCT …. 
… although wrong assumptions were made
→ Pioglitazone and placebo response misestimated
→ Treatment effect overestimated

Suspected reason:
→ (Latent) patient selection
→ Patient characteristics lead to a good prognosis

RCT

Only way to check our assumptions

Population characteristics and treatment effect are distinguishable:
→ Response rate of control group characterizes study population
→ Difference between treatment and control group leads to unbiased effect estimate
→ Risk/benefit profile directly assessable

Unfortunately, it was felt that further investigations are not necessary due to the perceived setback
Pioglitazone in FA: underlying problem

• (Implicit) assumption in single-arm trials:
  • Outcome in the control group fully known and not subjected to patient selection or temporal effect
  • Only acceptable if the natural history (development/course) of disease is fully understood and constant over time

• Best evidence can be generated through RCTs!
  • Even under sample size restriction …
    … it is possible to obtain an unbiased estimate
    … characterize the study population
    … assess internal validity
Pioglitazone in FA: global perspective

(1) New research question

Interpretable results add up to overall evidence

Small RCT → RCT based on prior evidence → Appropriate evidence for decision

(2) Single-arm trial → Single-arm trial

Not interpretable results

RCT Based on single-arm trials

Unsufficient evidence for decision

(Lasch et al. 2017)
Randomized building blocks - future research

- Combination of results
- Meta-Analysis
- Adaptive design (two-stage designs, …)
- Extrapolation concepts
References

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