Access to innovative therapies in rare diseases – Evaluation challenges of single arm trials with external control arm : FDA versus French HAS evaluations between 2018 and 2024

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BACKGROUND

The need for innovative therapies is increasingly raising for rare diseases. Unfortunately, randomized controlled trials (RCTs) in orphan drug development programs often face significant methodological challenges. That's why licensing of new treatments could be based on evidence from phase II/III single arm trials (SAT) with external control arms (ECA). Outcomes in patients receiving the test treatment during the RCT are compared to outcomes in a group of people external to the trial that had not received the same treatment [a].

OBJECTIVES

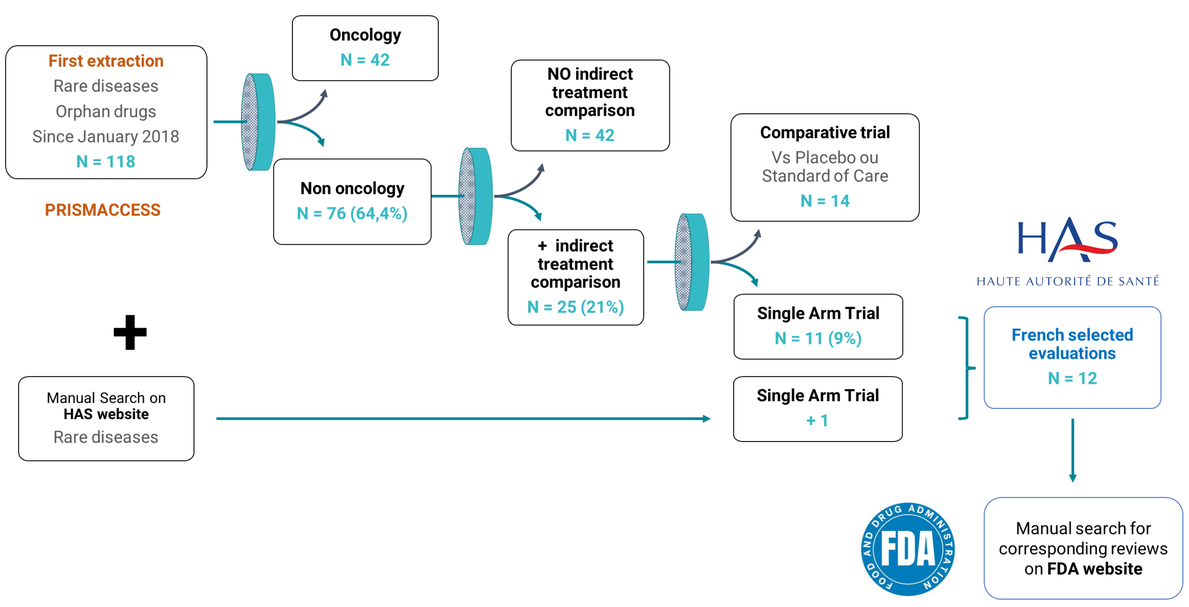
Both FDA (American Food and Drug Administration) and HAS (French National Authority for Health) have published nonbonding recommendations concerning externally controlled trials [a,b]. In the absence of a clearly defined framework, this analysis * aims to understand the evaluation challenges of SAT with ECA in rare diseases between 2018 and 2024, identify differences between these two agencies and provide a roadmap for the construction of externally controlled trials.

* *Pharmacy thesis - 2024*

METHODOLOGY

A targeted search of rare condition (non-oncology) submissions was performed on PRISMACCESS© database. From this list, only dossiers with a pivotal study based on SAT with an indirect treatment comparison (ITC) were selected. One last review was added to this list, after a search on HAS website

Figure 1 : Reviews selection flow chart



In the absence of an official methodological grid for the validation of an ITC, it was considered in this project that an ITC was refused if :

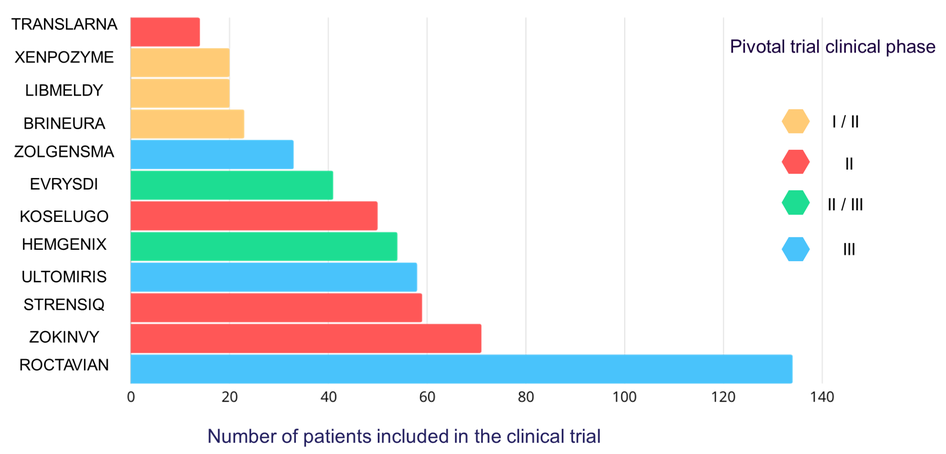
- not detailed in the review or ;
- there is an explicit mention "The comparison will not be detailed because of its methodological weaknesses" or "No conclusion can be drawn from this ITC"

RESULTS

– A total of 12 SAT with ECA-based submissions were identified between 2018 and 2024 [Figure 1] : 5 in metabolic diseases, 4 in neurology and 3 in hematology.

– Submission were based in nearly 60% of cases on phase I / II studies results. Not surprisingly, with small patient samples (maximum 134 patients) due to the rarity of the diseases and the resulting recruitment challenges. [Figure 2]

Figure 2 : Pivotal trials characteristics (Clinical phase & number of patients included)



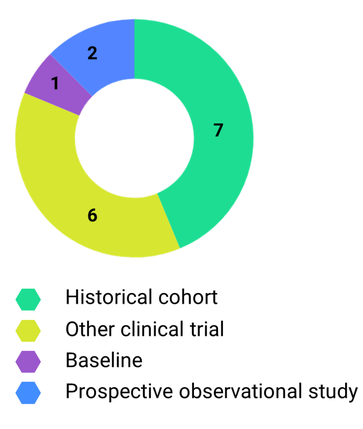
– 3/12 molecules did not submit an ITC to the FDA . Those ITC were rejected by the HAS

– 7/12 assesments were convergent between the 2 HTA agencies : 4 rejections / 3 acceptance

– 2/12 reviews were different (EVRYSDI ®, HEMGENIX ®) : in both dossier, a post hoc comparison was submitted, that was systematically refused by the HAS, but accepted by the FDA.

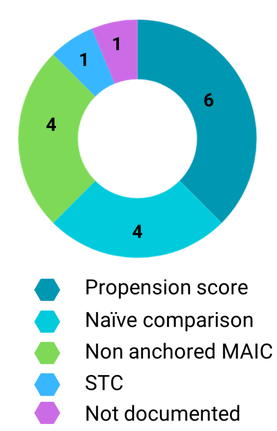
– 16 ITC were submitted using different sources of data : Historical cohorts, other clinical trials, baseline, observational studies [Figure 3] .

Figure 3 : Source of the ECA



– To increase comparability between patients of the experimental trial and the ECA, matching techniques (MAIC) and propensity score wheigting analysis were applied in 10 comparisons [Figure 4] . Naïve comparisons were also used in 4 ITC, but systematically rejected by both agencies.

Figure 4 : ITC methods



DISCUSSION

Both agencies tend to have similar methodological requirements as found in their recommendations, with a greater flexibility of FDA regarding the post hoc nature of the comparison.

Main methodological considerations
Uncontrolled open-label clinical trials with a small sample size
Even though, inherent to the rarity of the disease, these two points were raised in all reviews. Study populations were very small (at maximum 134 patients, [Figure 2]) to draw reliable conclusions. These samples were further reduced after matching with the control population.
Anticipating the clinical trial design and the choice of the ECA
Anticipation is one of the key requirements : both FDA and HAS higlighetd this point in their draft guidance. This avoids selective choice of the ECA that could falsly favor the experimental treatment. Any post-hoc comparison was rejected by the french HAS. Early advice is probably a good solution but unfortunately no guarantee of success.
External control quality and comparability of study populations
In order to reduce bias, it's recommended to use an ECA with : ▪ Available individual data (ID) rather than aggregated data (AD) ▪ Comprehensive collection of clinical and demographic data (Systematic identification of all confounding factors) ▪ Concurrent control ; if not possible and a historical cohort is available, make sure that the natural history of the disease is well understood and treatment options has not changed. ▪ Follow-up period and index date comparable to the current trial ▪ Relevant clinical endpoints that can be assessed in both cohorts (ECA and experimental trial)
Appropriate ITC method
Comparison is not problematic if it's the only available source of data and is well justified. Naïve comparison was not accepted. Propensity score matching is used when ID are available. Otherwise, a well conducted MAIC, STC or NMA, could provide relevant data.
Handling missing data
Missing or incomplete information can concern the ECA or / and the experimental trial. It's important to identify the nature and the mechanism of missing data to apply appropriate method (prefer imputation methods with robust statistical model rather than simple imputation methods)

CONCLUSION

While RCTs remain the gold standard, SAT with ECA seem to be more suitable in rare diseases, though they have methodological weaknesses often criticized by HTA bodies. Collaboration to establish a validated framework would be crucial to increase the acceptability of those studies that should not be seen as an option to accelerate commercialization at a lower cost.

Moreover, with the emergence of artificial intelligence, potential for clinical methodologies is even greater, positioning synthetic controls as a promising option.

Early planning, appropriate selection of the control arm and control of confounding factor are key tools to mitigate potential sources of bias.

REFERENCES

a. *FDA : Considerations for the design and conduct of externally controlled trials for Drug and Biological products (Feb 2023)*
b. *HAS : Rapid access to innovative medicinal products while ensuring relevant health technology assessment. Position of the French National Authority for health*