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Clinical decisions in Hepatology: The pirfenidone case analysis

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The approval of potentially effective treatments for serious and life-threatening conditions represents a particularly difficult arena for drug developers, regulators and physicians. Hanging in the balance is the need to provide a timely treatment alternative to an otherwise untreatable and serious condition, while also assuring that the proposed treatment is sufficiently safe to preserve the overall wellbeing of the patient. This is a particularly difficult decision, as weighting the risk and benefits must be done fast and over a much finer scale than in situations where effective treatments are available.

Recently, the Federal Commission for the Protection against Sanitary Risk in Mexico (COFEPRIS) approved the use of pirfenidone for the treatment of lung and liver fibrosis (Register 154M2013). This is an important advance for patients with idiopathic pulmonary fibrosis, for which four randomized clinical trials of adequate quality, a meta-analysis and a cost-effectiveness analysis are available.[1] However, some concerns remain as individuals participating in these clinical trials may not be wholly representative, the cost-efectivenes anaylisis could be uncertain for some subgroups, and stop rules could apply.[1] Nonewithstanding, available data seems robust enough to use pirfenidone in lung fibrosis under careful surveillance.

Pirfenidone's use for liver fibrosis is not as certain. Despite some experimental data to confer biological plausibility,[2] there are still no randomized blinded clinical trials to confirm the safety and efficacy of this drug. The information about its use in clinical practice is based in a case series with a small and underpowered sample size,[3] and has not been replicated by other groups. Additionally, in a recent meta-analysis including 1,073 patients pirfenidone was associated with neurologic, gastrointestinal, and dermatologic adverse events, as well as with early termination of treatment (number needed to harm for discontinuation of 16; 95%CI 9.5-35.7).[4] It is clear that the evidence supporting pirfenidone's efficacy is scarce, compared to the evidence available regarding its potential side effects.

Pirfenidone's approval presents a unique opportunity to review the tenants that should direct the approval of a promissory drug for a severe and life-threatening condition, as many important lessons could be learned.

Translational medicine under serious and life-threatening conditions.

Translational medicine represents a switch in the paradigm of medical research.[5] Under translational medicine the scientific community is expected to:

- Integrate basic research to clinical practice.
- Develop knowledge oriented to solve clinical problems.

There are several phases to achieve these aims: discovery, development and characterization, clinical utility, implementation, and social impact. Each of these phases must be guided by the scientific method under rigorous attachment to ethical principles, in order to avoid unnecessary exposure of patients to harmful adverse events. For this reason 93% of research projects in the field of translational medicine in the U.S. are at the development and characterization phase.[6] Serious and life-threatening conditions add pressure to the translational process, often lowering the threshold for evidence, which does not necessarily translate into health gains for the patient. In Europe fast approved drugs have not shown significant improvements in survival, safety or quality of life, and cost much more than standard treatments.[7] The clinician must know that under these circumstances (in which only low quality clinical data are available) it is necessary to inte-

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grate the opinion of experts from several fields such as statistics, epidemiology, psychometrics, economics, and decision sciences, among others,[8] to reach stronger conclusions about these drugs.

Small sample size

In a recent analysis, published studies with small sample sizes were prone to exaggerate the beneficial effects of interventions. This effect is the result of the complex interaction between lack of precision derived from a small sample size and publication bias, which tends to favor the publication of small studies if the results are large and statistically significant. The overestimation of the beneficial effects ranged from 12% to 32%, which could have a major clinical impact when interventions are transferred from research to practice, particularly because these small sample studies are considered far from the real clinical setting.[9]

The case-series used to justify pirfenidone's use in liver fibrosis included only 15 patients (12 Ishack value = 4) and 5 showed improvements after treatment. If we were to conduct a randomized control trial of pirfenidone against placebo to statistically detect a 30% reduction in fibrosis, with 80% power, and 0.05 alpha, a total of 116 patients would be required. Working back the formula, if only 15 patients were included in a randomized placebo controlled trial the power of this hypothetical study would only be of 15.2%. It is necessary to emphasize that most of the times clinical decisions are based in a single, large, well-designed clinical trial; yet, when this is not possible, more than one trial must be considered to evaluate the consistency of results across sample sizes and methodological limitations.[10]

Non randomized trials (repeated measures designs)

The randomized trial is the ideal method for determining whether an intervention does more good than harm. Randomization minimizes the chances of confounding, a major limitation of observational studies. However, when initial hypothesis are explored repeated measures designs are used. During repeated measures designs each experimental unit (e.g., subject) is tested in more than one experimental condition.[11] The characteristics of the sample under study are very important, particularly to avoid concluding that the treatment has an effect when it actually does not (type I error). These factors are: the population distribution, the population covariance structure, the number of levels of the within-subjects factor, and the sample size. A particularly relevant issue is posed by normally and non normally distributed response measures, as it is extremely difficult to avoid type I errors under non-normally distributed data, requiring larger sample sizes ($n > 100$). Thus, when clinicians use this design in a small sample, such as the case series of pirfenidone in liver fibrosis, conclusions should be tempered against the possibility of exposing patients to futile interventions that may be accompanied by very real adverse events.[11]

Finally, an overall evaluation of the evidence of an intervention must be condensed in a simple structure for the practitioner looking to make fast but grounded patient-centered decisions. Clear and reasonably sources for evidence-based interventions are available to the practitioner through several options, such as the Centre for Evidence-based Medicine at Oxford University (http://www.cebm.net/). For pirfenidone in liver fibrosis the level of evidence is 4, indicating a clear urgency for more research.

Liver cirrhosis is and will be an important public health issue.[12] The scientific community, society, and government are obligated to search for answers to limit the impact of this disease. However, the use of low-quality evidence, with no consideration towards potential biases, to hastily approve a treatment could endanger our patients. It is important for everyone involved to properly evaluate the implications of a proposed new drug, differentiating between legal, biological, medical and epidemiological validity, particularly when a fragile population is involved.

We are happy for the approval of pirfenidone for treatment of lung fibrosis. However, we remain cautious about its approval for liver fibrosis, as evidence to weight the benefits and harms is yet insufficient.

It is essential to develop clear and sound guidelines for fast-track approval of drugs indicated for serious and life-threatening conditions in Mexico. Relevant experience might be drawn from the breakthrough therapy designation program by the FDA in the US, were most applications have been denied due to insufficient clinical data.[13] Despite the authorization for commercial use, from a scientific standpoint gastroenterologists and hepatologists should consider pirfenidone use in liver fibrosis experimental, and safety issues must be followed very closely. Patients receiving pirfenidone for liver fibrosis should be thoroughly informed of the risks of harm and the uncertainty of benefit associated with this experimental application.[14]

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