RBD-specific Polyclonal F(ab´)_2 fragments of equine antibodies improve survival in severe patients hospitalized with COVID-19

Fernando Goldbaum
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R&D Biotech private company, founded in 2009 in Buenos Aires, Argentina

Insud pharma is the main shareholder of the company

It develops vaccines and products for human health.

Inmunova’s main technology:

- **IMC®**: stands for Immuno Multi Carrier, a proprietary recombinant platform for vaccine delivery
- Development of immunogens and therapeutic hyperimmune sera
Hemolytic Uremic Syndrome (HUS) occurs after an infection of the digestive tract by Shiga toxin *Escherichia coli (STEC)* bacterium, which might be found in meat, dairy products, vegetables and juices.

HUS affects predominantly children and is a life-threatening disease characterized by acute renal failure (uraemia), haemolytic anaemia, and a low platelet count (thrombocytopenia).

It is a medical emergency with 5% mortality rate and most common cause of sudden short-term-acute-kidney failure in children.

No current treatment exist for prevention or treatment of this disease. Only supportive measures
INM-004  An innovative product to prevent the onset of HUS

**Product:** Anti-Shiga toxin - by using a novel proprietary immunogen, we have generated equine immunoglobulin fragments that neutralize 8 variants of Shiga toxins.

**Phase 1 clinical trial** successfully finished during 2018

**Phase 2/3 clinical trial** launched during 2019
Orphan Drug status

➢ April 2018 EMA grants ODD
➢ August 2019 FDA grants ODD
➢ February 2020 FDA grants Rare Pediatrics Disease designation.
Anti SARS-CoV-2 hyperimmune sera: a product based on previous developments
CoviFab® In vitro activity

- Neutralizing capacity of INM005 greater than 1/20,000 in vitro

- Absence of Fc fragment could prevent ADE and exacerbated inflammatory reactions

- Excellent safety profile: use in early stages of the disease

- Manufacturing process can be scaled up
RBD-specific polyclonal F(ab')_2 fragments of equine antibodies in patients with moderate to severe COVID-19 disease: a randomized, multicentre, double-blind, placebo-controlled, adaptive phase 2/3 clinical trial

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- Sample size:
  - 242 patients
  - SOC event rate 70%, alpha 0.025, power 80%, absolute effect size 15%

- Interim analysis by CMD: it was performed after 156 patients (64.5%) with 28 days of follow-up. Possibility of re-estimating sample size to 314 if necessary depending on the rate of the event in the control arm.
Albeit not having reached the primary endpoint, we found clinical improvement of hospitalized patients with SARS-CoV-2 pneumonia, particularly those with severe disease.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>INM005 (N=118)</th>
<th>Placebo (N=123)</th>
<th>Risk difference or Hazard Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
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<tr>
<td>Improvement in at least two categories in WHO ordinal clinical scale at day 28 or discharge</td>
<td>106 (89.8%)</td>
<td>104 (84.5%)</td>
<td>Risk difference, 5.28% (-3.95 to 14.50)</td>
<td>0.15</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
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<tr>
<td>Time to achieve improvement in at least two categories on the ordinal clinical scale (days)</td>
<td>14.2 ± 7</td>
<td>16.3 ± 0.7</td>
<td>1.31 (1.00 to 1.74)</td>
<td>0.05</td>
</tr>
<tr>
<td>Improvement in at least two categories in WHO ordinal clinical scale at day 28* (%)</td>
<td>87.3 ± 3.1</td>
<td>79.7 ± 3.6</td>
<td>··</td>
<td>0.08</td>
</tr>
<tr>
<td>Improvement in at least two categories in WHO ordinal clinical scale or discharge at day 7* (%)</td>
<td>64.1 ± 4.4</td>
<td>58.3 ± 4.5</td>
<td>··</td>
<td>0.26</td>
</tr>
<tr>
<td>Improvement in at least two categories in WHO ordinal clinical scale or discharge at day 14* (%)</td>
<td>87.3 ± 3.1</td>
<td>79.7 ± 3.6</td>
<td>··</td>
<td>0.05</td>
</tr>
<tr>
<td>Time until discharge (days)</td>
<td>8.7 ± 0.6</td>
<td>10.2 ± 0.7</td>
<td>1.26 (0.96 to 1.66)</td>
<td>0.09</td>
</tr>
<tr>
<td>Improvement in the ordinal scale for clinical status scale (AUC)**</td>
<td>60.5 ± 41.7</td>
<td>73.7 ± 49.4</td>
<td>-13.14 (-1.56 to -24.72)</td>
<td>0.02</td>
</tr>
<tr>
<td>Mean category at day 7***</td>
<td>3.1 ± 1.7</td>
<td>2.7 ± 1.7</td>
<td>0.63 (0.36 to 1.13)</td>
<td>0.19</td>
</tr>
<tr>
<td>Mean category at day 14***</td>
<td>2.4 ± 2.2</td>
<td>1.7 ± 1.8</td>
<td>0.52 (0.29 to 0.96)</td>
<td>0.03</td>
</tr>
<tr>
<td>Mean category at day 21***</td>
<td>2.1 ± 2.3</td>
<td>1.5 ± 1.9</td>
<td>0.54 (0.30 to 0.99)</td>
<td>0.05</td>
</tr>
<tr>
<td>Mean category at day 28***</td>
<td>1.9 ± 2.5</td>
<td>1.4 ± 2.1</td>
<td>0.80 (0.44 to 1.46)</td>
<td>0.99</td>
</tr>
<tr>
<td>Time until discharge from ICU (days)</td>
<td>24.7 ± 0.8</td>
<td>23.6 ± 0.8</td>
<td>0.67 (0.35 to 1.28)</td>
<td>0.22</td>
</tr>
<tr>
<td>Patients requiring ICU admission at day 28* (%)</td>
<td>12.7 ± 3.1</td>
<td>17.8 ± 3.5</td>
<td>··</td>
<td>0.11</td>
</tr>
<tr>
<td>Patients requiring invasive mechanical ventilation at day 28* (%)</td>
<td>9.3 ± 2.6</td>
<td>13.9 ± 2.9</td>
<td>··</td>
<td>0.20</td>
</tr>
<tr>
<td>Overall mortality* (%)</td>
<td>6.9 ± 2.3</td>
<td>11.4 ± 2.9</td>
<td>··</td>
<td>0.19</td>
</tr>
<tr>
<td>Risk to disease progression***</td>
<td>17 (14.4%)</td>
<td>29 (23.5%)</td>
<td>0.54 (0.28 to 1.05)</td>
<td>0.07</td>
</tr>
</tbody>
</table>
The area under the curve of the WHO scale values was significantly lower in the INM005 group than in the placebo.

The average of the WHO scale shows on day 7 an improvement in patients who received INM005, the difference increases to 14 and 21 days (odds ratio [95% CI]: 0.63 [0.36-1.13], 0.53 [0.29-0.96], and 0.54 [0.29-0.99], respectively).
Mortality Incidence:
placebo = 11.4%, vs active = 6.7%
p = 0.19

- No significant difference in mortality incidence
- Mortality decreases a 39% in the active arm compared with placebo
Findings in the study population treated with INM005

- No statistically significant difference in the improvement of 2 points or discharge at day 28 (primary endpoint)
- Statistically Significant clinical improvement throughout the 28-day period of the clinical trial.
- Statistically Significant improvement of 2 points in the WHO scale at days 14 and 21.
- Statistically significant difference in time to achieve improvement in at least 2 points in the WHO scale or discharge (16 vs 14 days)
- A Statistically Significant decrease in the number of events associated to the progression of COVID-19 in 33% of the patients.
- A decrease of 39% in the mortality rate
- A decrease of 33% in the number of ICU admissions.
- A decrease of 36% in the requirement of MV.

Adequate safety profile, according to the products $F(ab')_2$
In November 2020 we were at a difficult crossroads

A single RCT showing clear trends

**What to do?**

A new RCT???
The RCT testing cocktail of mAbs in severe patients using the Recovery platform began on September 2020 and finished on June 2021

Ask for EUA and increase data on safety and efficacy of our immunotherapy in “real life”

In the case of Inmunova we could get probably a nice paper but little practical application

Excellent safety profile, choice to benefit thousands of patients, observational studies
ANMAT granted the EUA of CoviFab® to treat hospitalized COVID-19 severe patients on December 2020

- Drug traceability
- Informed consent
- Approval for 1 year

Plan for monitoring efficacy and safety of CoviFab® in a web-based platform

- List of patients and adverse events
- Efficacy assessment at day 21 post treatment
- Time to event: hospital stay, disease progression, and hospital discharge
- Proportion of patients requiring ICU, MV and deaths
- Data about clinical improvement
Patients treated with CoviFab® February to August 10 2021

- 17 states

- 221 health institutions

- 8,501 patients registered

- According to projections most than 20,000 treated patients
CoviFab® shows an excellent safety profile

- **Related events**
  - 7623 patients
  - 1% related events
  - 6 anaphylactic reactions
  - Frequency less than 1:1,300
21-day cohort with closed data
5.722 patients, 86% Severe

- Severe patients
  - Intensive Care Unit: 24 to 32%
- Severe patients
  - Mechanical Ventilation: 20 to 28%
- Severe patients
  - Death: 20 to 30%
Efectiveness and Safety of CoviFab® after ANMAT’s EUA

Retrospective Cohort Study

- Htal. Campaña Corrientes
- 400 severe patients treated with CoviFab® vs 400 historic controls
  - Feb-April 2021
  - Dec 2020- Jan 2021

- **Primary Endpoint**: Mortality
- **Secondary Endpoints**: ICU %, MV %
- **Results**: next days
Delayed production of neutralizing antibodies correlates with fatal COVID-19

La aparición tardía de Acs neutralizantes correlaciona con la falta de clearence viral en pacientes fallecidos (Lucas et al., Yale School of Medicine, https://doi.org/10.1101/2020.12.18.20248331)
Seronegative severe patients would most benefit from passive immunotherapies.

Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial

Running title: REGEN-COV for COVID-19

RECOVERY Collaborative Group*

Research Paper
RBD-specific polyclonal F(ab)₂ fragments of equine antibodies in patients with moderate to severe COVID-19 disease: A randomized, multicenter, double-blind, placebo-controlled, adaptive phase 2/3 clinical trial
Real world data exhibit a trend very similar or better to that observed in the clinical trial, with the number of patients being treated now is 70 times higher.

In the next days we will be confirming this trend with a retrospective cohort study.

CoviFab® *in vitro* neutralizes variant P.1 (Manaus) and variant B.1.1.7 (UK) with a similar capacity to the pandemic variant.

CoviFab® is a safe product that meets the challenges of the current pandemic situation.

ANMAT decision to grant EUA for CoviFab® was right
Thanks!

Questions?