Mishaps in drug regulatory processes: Insights into drugs approved by DCGI for COVID-19 treatment

A public viewpoint

8th National Bioethics Conference Program

Based on bits and pieces compiled from here and there by Siddhartha Das, Malini Aisola

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Regulatory provisions of current interest

- Accelerated approval process for clinical trials
- Restricted emergency use (REU) authorization for marketing and sale of drugs

Public & doctors have no clue what “restricted emergency use” means: if it means that there’s
  - suggestive evidence to grant drug for marketing and sale for given indication then large well-blind RCT (Phase III) cannot be waived.
  - sufficient evidence on efficacy of the drug for given indication then why not full approval?

In USA, EUA is defined & approved products come with explicit conditions/facts to inform all stakeholders.
In India, pertinent results and protocol description need not be in public domain either.
- How do doctors prescribe such drugs?
- How do patients give informed consents?
REU approved drugs for COVID-19


Remdesivir:

- SOLIDARITY (WHO) and ACTT-1 (US): No reduction in mortality for severe cases. No significant clinical benefit.
- ACTT-1: Potential benefit in recovery time for section of moderate-to-severe cases. No significant reduction in mortality (high-flow oxygen or ventilation). (SOLIDARITY result differs; clinical benefit still under scrutiny)
Recommendations by SEC on Favipiravir proposals by Glenmark:

- **24.04.20:** to conduct clinical trial (Phase III) with 150 patients (90 mild + 60 moderate). Approval to be based on data from this trial & trials abroad.

- **On 18.06.20:**
  - REU granted while trial was ongoing;
  - to submit complete report on trial within 3 months;
  - to conduct active PMS on first 1000 patients to access the safety as well as efficacy.

- **22.07.20:** Phase III results submitted for normal marketing approval but SEC opined to continue with REU and conduct PMS on 1000 patients at the earliest.

- **20.05.20:** to conduct clinical trial (superiority study) for Umifenovir + Favipiravir vs Favipiravir in moderate patients. [09.10.20: NO superiority, 1 death in trial].
Efficacy & Safety of Favipiravir in Mild-to-Moderate COVID-19: **Open-Label** RCT, Phase 3

- Included asymptomatic cases, only 69.4% symptomatic patients.
- “Lack of statistical significance on the primary endpoint.”
- Adverse events were observed in 36% of favipiravir and 8% of control patient.
- Paper itself defines mild disease as symptoms not requiring any or minimal therapeutic intervention.
- 10 authors: 1 local trial site PI, 9 (includes corresponding author) Glenmark Pharma employees; Glenmark funded; Published on 08.11.20.
- Claims protocol approved by IEC & DCGI (April 26, 2020), which seems contrary to SEC’s recommendation on 24.04.20 (90 mild and 60 moderate).

Favipiravir NOT included in Clinical Management Protocol: COVID-19 by MOHFW, India.
Biocon presented Phase II (open-label RCT) proposal on 08.04.20. 1st enrollment on 01.05.20. CTRI has sample size 30 (20 treatment +10 control).

On 28.05.20, SEC noted protocol violations during trial:
1. Interim analysis was NOT part of the protocol.
2. Randomization was NOT proper.

On 18.06.20, protocol amendment accepted for ongoing Phase II trial (v3.0 to v5.0).

REU granted on 10.07.20 after recommendation from SEC (the same day) with waiver of Phase III (trial for efficacy testing).

30.07.20: Phase IV on 300 patients. Safety to be only primary endpoint.

Itolizumab NOT included in Clinical Management Protocol: COVID-19 by MOHFW, India.
Itolizumab: Lack of data integrity?

Itolizumab: Unsettling oversights & discrepancies in data disclosures

1 out of 2 patients replaced off Itolizumab arm died in 9 days.

Only 1 female in Itolizumab arm. Unacceptable gender disparity in drug approval.
Itolizumab: A saga of misinformation?

Itolizumab: Retrospective changes to trial design?

Pre-18.08.20, ONLY 1 primary endpoint. Post-18.08.20, CTRI has 6 primary endpoints.

<table>
<thead>
<tr>
<th>Biological Division</th>
<th>Details of Primary endpoint of mortality, other key endpoints of lung function such as improvement in PaO2 and O2 saturation were presented. Key inflammatory markers IL-6, TNFα etc were presented to have been reduced significantly with the drug</th>
</tr>
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<tbody>
<tr>
<td>BIO/CT/20/00037 Itolizumab 25 mg/5 mL solution for intravenous infusion in vials</td>
<td>M/s Biocon Biologics India Limited</td>
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</table>

26.11.20: Phase IV to include clinical outcome efficacy as PE along with safety. ≈ 2000 patients received Itolizumab under REU.

Conclusions:

- Primary endpoint of mortality was statistically highly significant in favor of Itolizumab arm
- Other key endpoints of lung function such as improvement in PaO2 and O2 saturation were statistically significant in favor of Itolizumab arm
- Key inflammatory markers IL-6 and TNFα are significantly reduced by Itolizumab thereby preventing hyper-inflammation
- Itolizumab is safe in COVID19 patients, Infusion reactions are manageable with slowing infusion rate
- Itolizumab effectively controls hyper-activation of the immune system in response to Covid19 virus and prevents morbidity and mortality related to cytokine storm

SEC for COVID-19, Dated 10.07.2020

COVID-19

Mishaps in drug approvals
Itolizumab: Unsolvable riddles

- Was Itolizumab trial over by 07.07.20? A patient’s video during press brief on July 13 implies NO.
- 21.09.20: Post approval (supplement) change permission to mfg for sale Itolizumab Inj (r-DNA origin) 100 mg/vial lyophilized powder. Listed under ”new drug” for approved indications.
- Backed down from conducting global Phase III trial 2 weeks back.
- 01.12.20: pre-print on Phase II trial is released with lots of contradictory and dubious claims.
  1. 5 patients tested for safety (non-RCT) before RCT enrollment.
  2. Conducted per-protocol analysis; 4 primary endpoints.
  3. Claims to have DSMB & approvals from IECs/CDSCO; Biocon funded.
  4. 2 prominent authors from AIIMS Delhi, yet Itolizumab NOT mentioned in “FAQs on COVID-19 from AIIMS e-ICUs” (01.09.20).
On Saturday, Indian authorities approved Biocon’s drug itolizumab for treating moderate to severe Covid-19 patients. The story of how itolizumab—a medicine to treat skin rash psoriasisemerged as a ‘repurposed’ treatment for Covid-19 began in Mumbai. Dr Hemant Thacker was the first doctor in Mumbai to be called by Biocon executive chairperson Kiran Mazumdar-Shaw in early May to carry out a clinical trial. In an interview with TOI, he talks about the drug’s “90% success” in the ICUs at Bhatia Hospital in Tardeo and Breach Candy Hospital.

Q: It is oft repeated that there are no specific treatments for Covid-19. What prompted you to undertake a clinical trial with itolizumab, a drug made in India?

A: Covid hit the scene real hard by about April 10 and I got into the thick of Covid patients by April second week. We didn’t know much about the virus and had few drugs—azithromycin, doxycycline and tocilizumab, a monoclonal antibody supplied by a couple of companies. Tocilizumab was expensive at Rs 70,000, but we were