The influence of investigator initiated studies in the COVID-19 pandemic

Jenny Novotny-Devenport

Department of Biostatistics, Roche Basel

Outline

- The Race
- Investigator Initiated Studies
- Case Study
- Learnings


THE AMAZING
RACE

“An invisible assassin is stalking the entire globe causing mayhem, havoc, disease and deaths, forcing panicked people to stay home even at the cost of livelihoods and leaving behind a trail of shattered economies and battered societies.

As the world grapples with the huge fallout from this pandemic invasion by novel coronavirus, the scientific communities are racing against time to invent and initiate clinical trials of vaccines and drugs to halt the menace by any means.”

Source: https://thefinancialexpress.com.bd/views/columns/search-for-covid-19-cure-1586962981.
Search for Covid-19 cure, Helal Uddin Ahmed | Published: April 15, 2020 21:03:01.

IN DEPTH | INFECTIOUS DISEASES

Race to find COVID-19 treatments accelerates

Kai Kupferschmidt, Jon Cohen

+ See all authors and affiliations

Science 27 Mar 2020:
Vol. 367, Issue 6485, pp. 1412-1413
DOI: 10.1126/science.367.6485.1412

Researchers want to avoid repeating the mistakes of the 2014–16 West African Ebola epidemic, in which willy-nilly experiments proliferated but randomized clinical trials were set up so late that many ended up not recruiting enough patients. “The lesson is you start trials now,” says Arthur Caplan, a bioethicist at New York University's Langone Medical Center. “Make it a part of what you're doing so that you can move rapidly to have the most efficacious interventions come to the front.”

Off-label use of medicines for COVID-19

https://www.who.int/publications-detail/off-label-use-of-medicines-for-covid-19-scientific-brief

Scientific brief
31 March 2020

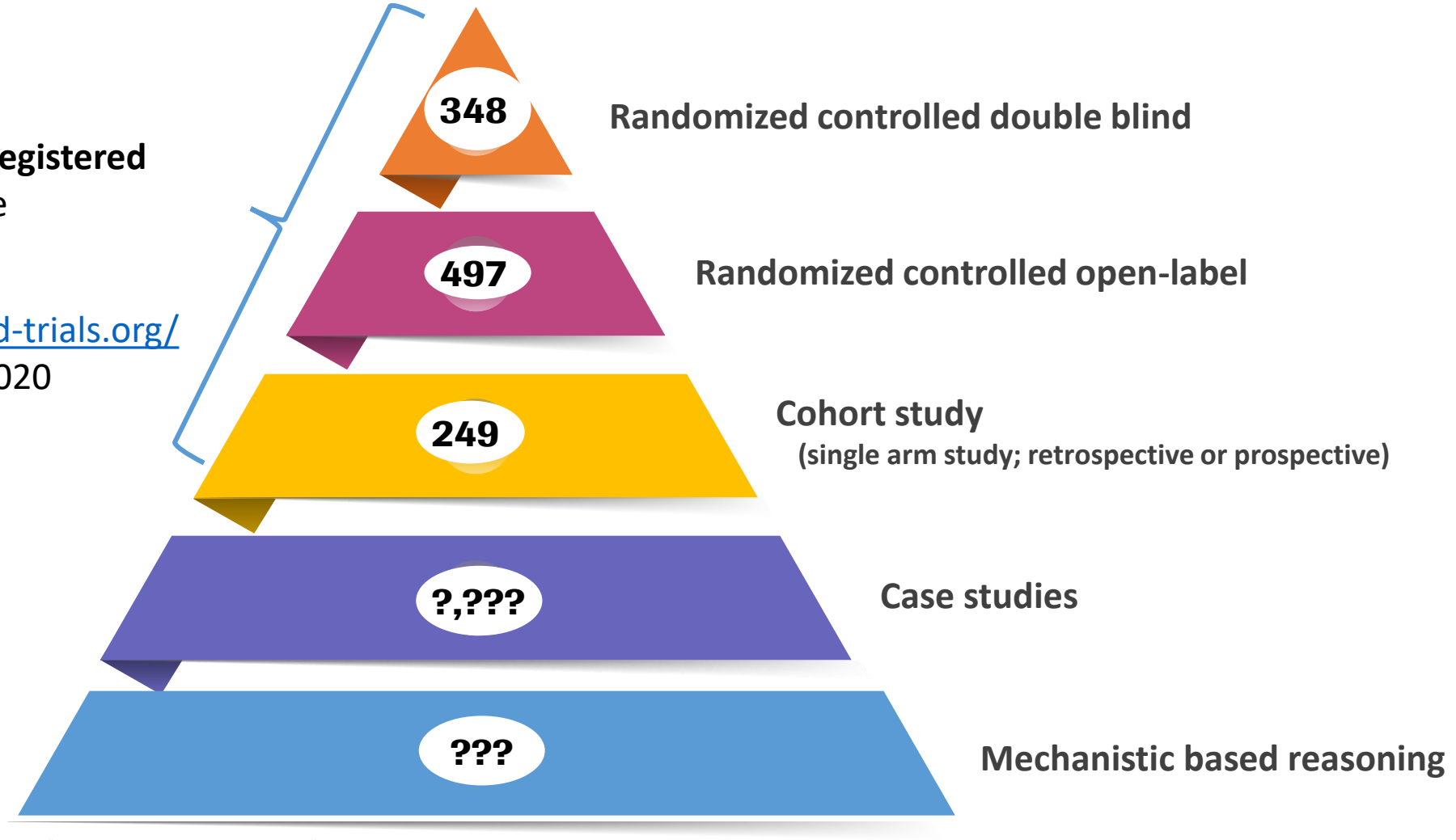
World Health Organization

- No pharmaceutical products have yet been shown to be safe and effective for the treatment of COVID-19.
- Off label use is occurring.
- Stockpiling medicines approved for other indications for off-label use in pandemic should be avoided (don’t create shortages).
- There are mechanisms to offer individual patients experimental treatments on an emergency basis outside of clinical trials (in compliance with local regulatory and legal requirements), but clinical trials are the preferred mechanism

The Explosion in Registered Studies

> 1000 COVID-19 Trials Registered
Mostly in Feb – April range

Source: https://www.covid-trials.org/
data downloaded 19May2020



Adapted from: OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence". Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653

Investigator Initiated Studies

What	Clinical studies **initiated and managed** by a non-pharmaceutical company researchers (eg., individual investigators, institutions, collaborative or cooperative groups).
Why	Enhance understanding of products (eg., answer pragmatic questions in current indication, evaluate potential of new indication, etc.)
How	• **As trial sponsor, the researcher is responsible for the legal and regulatory requirements and** for the **conduct and management of the study.** • The pharmaceutical company *may* support the study through drug supply, funding, material and/or information, as allowed under local laws and regulations, provided that they align with the company defined areas of strategic interest.
Criteria	Scientific rigor, technical expertise, operational capabilities, ability to fulfill safety / regulatory requirements, commitment to transparency / publication

Data/statistical issues in IIS and academic trials*

(drug agnostic)

- Missing data
  - inability to collect / compile in database
  - handling for analysis
- Inconsistent application of inclusion / exclusion criteria for analysis populations
- Shifts in sample size (both directions, mainly for pragmatic reasons)
- Evolution in endpoints and/or criteria for comparisons
- Ambiguity in assumptions for sample size estimation, adaptation, and planned modeling
- Shifts in timelines (both directions)

* No implication that these issues are present in all studies, just that when issues arise these are most common

Case Study: Tocilizumab

Current Indications:

Rheumatoid Arthritis (RA)

- Adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more DiseaseModifying Anti-Rheumatic Drugs (DMARDs).

Giant Cell Arteritis (GCA)

- Adult patients with giant cell arteritis.

Polyarticular Juvenile Idiopathic Arthritis (PJIA)

- Patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis.

Systemic Juvenile Idiopathic Arthritis (SJIA)

- Patients 2 years of age and older with active systemic juvenile idiopathic arthritis.

Cytokine Release Syndrome (CRS)

- Adults and pediatric patients 2 years of age and older with chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome.

Case Study: Tocilizumab (Timelines)

- February 2020: First investigator initiated study using tocilizumab in severe/critical COVID-19 infected patients (single arm case series N=21)
- March 2020: China adds tocilizumab to its treatment guidelines for COVID-19
- On the basis the Chinese findings, many requests from health authorities wanting to co-sponsor trials with investigators came in
- March 19 Roche initiates randomized double blind controlled trial

Case Study – Tocilizumab, Early IIS Results

March: China IIS, 21 patient case series (ChinaXiv: 202003.00026v1)

- Tocilizumab is an effective treatment in severe patients of COVID-19, which provided a new therapeutic strategy for this fatal infectious disease.

April: French open-label RCT Press Release

(https://www.aphp.fr/contenu/tocilizumab-improves-significantly-clinical-outcomes-patients-moderate-or-severe-covid-19)

- Tocilizumab improves significantly clinical outcomes of patients with moderate or severe COVID-19 pneumonia…. These results should be confirmed independently by additional trials. Given the pandemic context, the investigators and sponsor felt ethically obligated to disclose this information, pending peer review and while continuing to increased longer follow-up.

May Italy (13May)

https://www.aifa.gov.it/web/guest/-/studio-tocivid-19-risultati-incoraggianti-anche-se-non-definitivi

- The non-comparative clinical study on tocilizumab was carried out in emergency conditions, in a context of high expectations and absence of effective treatments. This is the first study approved by AIFA during the Covid19 emergency. For ethical reasons, it was decided to make the treatment available for all patients who in clinical judgment could benefit from it, with the prospect of starting randomized comparative studies as soon as possible. The results suggest a moderate reduction in mortality.

Right now annecdotes, observational studies, and IIS are dominating the media

ELSEVIER

European Journal of Internal Medicine
Available online 21 May 2020
In Press, Corrected Proof

Original article

Off-label use of tocilizumab for the treatment of SARS-CoV-2 pneumonia in Milan, Italy

ELSEVIER

Journal of Clinical Virology
Available online 15 May 2020, 104444
In Press, Journal Pre-proof

Profiling COVID-19 pneumonia progressing into the cytokine storm syndrome: results from a single Italian Centre study on tocilizumab versus standard of care

ELSEVIER

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original article

Impact of low dose tocilizumab on mortality rate in patients with COVID-19 related pneumonia

Ruggero Capra[a,*], Nicola De Rossi[a], Flavia Mattioli[b], Giuseppe Romanelli[c], Cristina Scarpazza[d], Maria Pia Sormani[e], Stefania Cossi[a]

FOX News reported on a 34-year-old hospitalized COVID-19 patient who has returned home after receiving Actemra.

Boston Globe reported on Boston Children's Hospital admitting 13 children for COVID-19 and that therapies like hydroxychloroquine, remdesivir, and Actemra have been used

CNN featured an interview with a Queens gastroenterologist who is recovering from severe COVID-19, Dr. Arnold Weg. As his lungs were filling up with fluid, his doctors treated him with Actemra, which he credits with avoiding intubation. He then received remdesivir and is now recovering at home

Italian outlet *MonzaToday* reports that Actemra is being tested in less severe COVID-19 patients at Vimercate Hospital. Giuseppe Danilo Vighi, head of general medicine at the hospital, comments on the progress so far: "The first results seem encouraging, even if transitory. The treatment must be accompanied by a pharmacological maintenance strategy".

And it’s not just regular media touting the early results

medRxiv is receiving many new papers on coronavirus SARS-CoV-2. A reminder: these are preliminary reports that have not been peer-reviewed. They should not be regarded as conclusive, guide clinical practice/health-related behavior, or be reported in news media as established information.

COVID-19 SARS-CoV-2 preprints from medRxiv and bioRxiv

3738 Articles (2993 medRxiv, 745 bioRxiv)

Subject Areas

https://connect.medrxiv.org/relate/content/181

What are we learning?

- In past and current pandemics, we repeatedly see the demand for treatments to address patient needs NOW
- In emergency situations, documentation requirements of trials may exceed capacity
- It is possible—even for big pharma-- to move faster and get trial programs/protocols approved quickly.
- There is a huge demand / opportunity for collaboration with investigators, institutions, local / national health authorities.
- Randomized, controlled, trials are still needed (duh!); and where relevant, with blinding to increase confidence in clinical endpoints

What can we do to help the next wave?

- Curate external control arms
- Create / promote simple, standardized data collection tools
- Advance R&D preparedness and effective collaboration frameworks before new pan / epidemics occur
  - Industry collaborations—Is 1 drug at a time by each sponsor the right way to go?
  - Collaborations with noncommercial entities—to expedite timelines, optimize feasibility, etc.
- Other ideas?