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Feature Covid-19

Covid-19: The inside story of the RECOVERY trial

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Re: Covid-19: The inside story of the RECOVERY trial

Dear Editor

16th June has been a landmark day in the fight against the COVID-19 pandemic

The beneficial effects of dexamethasone in COVID-19 patients, as an interim result from the RECOVERY trial, was welcomed throughout the world as the first glimpse of the light at the end of the tunnel. It is a real breakthrough in this pandemic when more than half a million people have lost their lives .We are still learning about the behaviour of this disease and an effective vaccine or antiviral agent is not yet available.
The results came out amidst conflicting results published in leading medical journals, on drugs like hydroxychloroquine and some antiviral drugs. The politicians and the pharmaceutical industry were making their own recommendations, confusing the general public [1][2][3][4].

Credit goes to the investigators of the RECOVERY trial and all patients who participated, showing to the world the power of randomised trials in testing the efficacy of a drug.

The result is particularly important for developing countries where support for intensive care is needed. The benefit was so clear (reduction of mortality by 1/3rd in ventilated patients and by 1/5th in patients on oxygen),that trial had to

be halted. There was no evidence of harm so far hence dexamethasone has become a standard of care for severely ill COVID-19 patients. However it's misuse in earlier milder phase of the illness has to be discouraged.

Review of immunosuppressive treatments in COVID -19 disease and the rationale for choosing dexamethasone

Dexamethasone has both anti-inflammatory as well as immunosuppressive properties, thought to be dose dependent and perhaps linked to the timing of dexamethasone administration [5].It is likely that, at the doses used in the RECOVERY trial, dexamethasone will have mainly anti-inflammatory activity . Corticosteroids are generally avoided in pneumonias as it is thought that it may worsen the underlying pneumonia due to immunosuppression. Previous experience from other corona viral diseases like Severe Acute Respiratory Syndrome 1 (SARS- coV-1) and Middle Eastern Respiratory Syndrome (MERS-coV) was not encouraging. Recent reports published in The Lancet as well as the World Health Organization (WHO) and The Centers for Disease Control and Prevention (CDC), USA also specifically advised against the use of corticosteroids in COVID-19 as immunomodulators. [6][7][8][9][12][13]. In contrast, the recent multinational Surviving Sepsis Guideline in COVID-19, recommends giving steroids in patients with severe COVID-19 on mechanical ventilation with adult respiratory distress syndrome (ARDS) [10]. Dexamethasone has been found to be effective in ARDS due to a variety of other conditions [11]. While in COVID-19 patients there are mixed results [14][16][17][15]. Another interesting observation is the under-representation of COPD, asthma and rheumatological disorders initially (the conditions where patients are likely to be on some immunosuppression like steroids), suggesting that low doses of glucocorticoids may be protective [18][19][20][21].

A recent meta-analysis of the use of corticosteroids in COVID-19 shows that prior to the RECOVERY trial, there are five published series on corticosteroids in COVID-19, mostly retrospective. Barring one trial, common theme has been a benefit with low dose steroids and improvement in hospital stay as well as reduction in incidence of intubation or progression to ARDS [22].

What about results of other glucocorticoids in COVID-19 disease?

Methyl prednisolone has been proven to show efficacy in a number of retrospective observational studies both in Europe as well as China and was still in the treatment protocol in the National Health commission and state administration of traditional Chinese medicine for severe COVID-19 infection. This was based on two small retrospective studies in China [23] and a retrospective Spanish study on 463 patients with COVID-19 also showed benefit [24].

Interesting to know how steroids may benefit in COVID-19 disease

There are two pathophysiological phases of this illness. The first is the initial immune reaction (triggered by viral replication) which aims to control the viral replication. Steroids in physiological doses may prime the immune response; larger doses may supress the immunity and enhance viral replication [25]. It is observed that ARDS in COVID-19 develops in the second week of the illness [26] (triggered by pro-inflammatory cytokines and macrophage activation) hence the timing of steroid use is very important, perhaps administering steroids towards 2nd week of the illness may be more logical.

What about trials of other immunosuppressants in COVID-19 disease?

A Chinese study on patients with inflammatory bowel disorders, who had been on immunosuppressants, showed a very low incidence of COVID-19 infection initially in the pandemic[27]. This suggested a possible protective role of immunosuppression. There are a number of other molecules under evaluation. Toxilicimab is a potent anti-IL6 molecule and is highly effective in cytokine storm post CAR-T cell therapy in lymphomas and, together with interleukin-6 blockade, has also been tested in COVID-19 [28][29].

Similarly, molecules like BTK (Bruton tyrosine kinase inhibitors), which inhibit macrophage activation and signalling are thought to modulate inflammation and presumed to be protective. An improvement has been shown in a small single arm clinical trial of a BTK inhibitor acalabrutinib in 19 COVID-19 patients (50% of patients on mechanical ventilation were discharged, 75% on O2 therapy improved) [30].

Similarly, other immunosuppressants like ruxolitinib (a Janus-associated Kinase inhibitor), normally used in myeloproliferative disorders, is also thought to have anti-inflammatory potential [31]. These have been tested in a randomised trial on 44 patients with COVID-19 infection, with faster clinical improvement and suppression of inflammatory markers [32].

Conclusion and important questions for Recovery investigators

It is intriguing to know the benefit of dexamethasone in different genetic/ethnic groups and the effect of co-founding factors like co-morbidities, age, sex, any added benefit with anti-viral drugs and effect on coagulopathy. While WHO is still advocating a cautious approach on prescribing steroids, the Infectious Diseases Society of America (IDSA) have already included low dose dexamethasone (6 mg daily for 10 days) in their guidelines for patients requiring respiratory support. Although the preliminary results of this trial have been just published on 17th July 2020 in NEJM [33], earlier announcement of the results has already saved lives.

16th June will therefore be acclaimed as a landmark day in the history of this pandemic.

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Competing interests: No competing interests

20 July 2020
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Re: Covid-19: The inside story of the RECOVERY trial

Dear Editor,

When a randomised clinical trial or the arm of such a trial is stopped prematurely because of an effect, positive or negative, an immediate answer behind the change is essential.

There is an obligation on the Chief Investgators and the Trial Steering Commitee (TSC) to inform the investigators why the enrollment has been stopped and in which direction the benefit or harm has been observed.

This must happen well before any peer reviewed publication appears given the time lags even with fast track publication that are encountered.

I speak from experience: as Chief Investigator of the MRC International Subarachnoid Aneurysm Trial (ISAT) published in 2002 (reference Lancet 2002).

The trial compared coiling and clipping for ruptured cerebral aneurysms. After 2143 patients of a target 2500 had been enrolled over 7 years the Data Monitoring Commitee (DMC) informed us that their stopping rules had been met. The unblinded analysis that they had reviewed showed that the primary outcome, reduction of death or dependency in the coiling arm, had reached 3 standard deviations. (P = 0.001).
Central telephone randomisation was stopped on 2nd May 2002. That evening I received a telephone call from a colleague trying to randomise a patient with a ruptured cerebral aneursym into the trial.
I explained that the trial had been halted by the Steering committee on grounds of clinical benefit. His question therefore was how do I treat my patient tomorrow, craniotomy and clipping or endovascular coiling? I explained that

there was significant clinical benefit in the coiled allocation so the patient should be coiled. The interim results did not appear in the literature until 5 months later in October 2002.

The benefits of coiling that were observed and size of the absolute and relative risk reduction of death or dependency were announced to the investigators and clinical community the next week at a large International Meeting.

Trials such as ISAT and Recovery have already been through a rigorous peer review process of the protocol and are supervised by an Independent Data Monitoring comittee.

When trials are stopped because they demonstrate highly significant benefit there is an ethical obligation to inform the investigators and the clinical community as soon as possible. Waiting for the full peer-review publication process is neither feasible nor ethical.

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Reference:
Lancet: 360: p 1261 -1340 26th October 2002.
International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial

Competing interests: No competing interests

13 July 2020
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Dose Related Toxicity of Hydroxychloroquine

Dear Editor
The story behind the dosage of Hydroxychloroquine used in the RECOVERY trial gets curiouser and curiouser. David Jayne drew attention to the potentially lethal dose of the drug used in the trial.

Martin Landray, has defended the dosage used. He told the BMJ, that the dose was arrived at using “detailed pharmacokinetic models” developed by Nick White and his team “to rapidly achieve drug levels that might be high enough to kill the virus but not so high as to trigger toxicity”. Landray went on to say the work is now published in a preprint on medRxiv.

The preprint article does not appear to be the basis on which the dosage used in the trial was decided. It merely states, in retrospect, that “the majority of chloroquine regimens trialled in COVID-19 should not cause serious cardiovascular toxicity”.

The real reason patients were given such high doses of Hydroxychloroquine remains the proverbial riddle, wrapped in a mystery, inside an enigma. The authors of the BMJ’s feature article note the criticisms from scientists about lack of transparency in the trial. If this is not addressed, it will erode trust in such trials.

Competing interests: No competing interests

12 July 2020
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The swashbuckling conquest of "Recoveryland'

Dear Editor,

The Politics is reported to have followed the Science. What if the Science has rushed off in an unhelpful direction, with the consumption of finite resources?
The political problem with Covid19 has never been mortality, it was and remains (in the event of a second spike) the continued availability of medical resources that now include exhausted staff. By targeting hospital mortality above hospital usage as a primary outcome has the trial satisfied the science but missed the national political objective of 'protecting the NHS'?
The leaders of the trial have, indeed, done as they see fit and collected a vast trial resource but, rather like colonial invaders, they have laid claim to lands and collected the immediately and easily available low hanging fruits. In doing that they appear to have missed the prospect that their resource may be subject to outside influence by those with competing interests (Was a Hydroxychloroquine arm included on the grounds of scientific promise or Presidential marketing?. Did the reported lack of availability of Remdesivir for the trial support a lucrative exclusive contract with the US Government).
On the face of it the interventions chosen for Recovery appear to have been decided 'on the hoof' as the new 'owners' of the trial patients rode apace to establish themselves in 'Recoveryland'. Even if Remdesivir was excluded because the manufacturer offered only a limited supply, was that not undue influence? Did participants' informed consent extend to supply issues (which reflect the inability of non-Chinese manufacturers to provide 5G components)?
Interventions that might potentially prevent and reduce hospital stays have been proposed. SARS-COV-2 has the characteristics of acting as a proxy for Angiotensin II in that it accesses pulmonary ACE2 (1,2) which would normally prevent the smooth muscle in alveolar vessels and bronchiolar walls to stimulation via the PDE5 pathway (cough and reduced pa02) (3). Angiotensin II has been shown to reduce taste sensation in rodents (and also to induce microemboli) (4,5). There has been much debate about ACE inhibitors (which target Angiotensin II creating ACE1 receptors rather than the 'cleansing' ACE2 receptors favoured by COVID19) but the obvious theoretical benefits of cheap and available ARAs appear to have been ignored (6). The potential for early intervention with widely available and inexpensive PDE5 inhibitors (to prevent Angiotensin II mediated cough and reduced oxygenation) to protect the health resource.
Is it not time for well-meaning but politically naive 'scientific frontiersmen' to consider the responsibility that goes with their apparently monopoly of research resource by reconsidering both inputs (candidate interventions) on the basis of evidence based argument and outcomes (to include use of health resource and post-infection recovery of individuals) on the basis of their economic cost to the nation?

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Competing interests: No competing interests

11 July 2020
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Re: Covid-19: The inside story of the RECOVERY trial

Dear Editor

I and many others stand in awe of the breadth, range and speed of the RECOVERY trial, and it is a huge credit to the UK's research infrastructure and global reputation. Martin Landray and Peter Horby and many, many others need to be hugely congratulated on their drive, and the NIHR too has responded with unusual zeal and speed to this existential challenge.

Was this a perfect trial? Hardly. Was it fundamentally flawed, no, not in my opinion. We should remember that this pandemic wave came "from nowhere" and yet a trial was ready in record time. A few rough edges might be understood. The charge that the therapeutic choices were focussed on anti-virals and anti-inflammatories, a highly pragmatic and sensible decision taken at speed.

Of course, the fascinating and poorly understood thrombotic challenges have become apparent, as Beverley Hunt OBE points out, but really this was later and not so evident at the outset. This should be a focus for a second wave, were we to have one.

Sometimes the best is the enemy of the good, and a lot of the criticisms seem to me to be sour grapes ("why did they do x and not y), and general nickpickery which is frankly of limited value in the present setting.

What I would say is that can we please bottle and manufacture more of the flexibility and agility shown by the NIHR and MHRA and others; something we can usefully use after this pandemic was subsided, but would allow a leaner, more agile research infrastructure to operate going forwards. Much as has been the hope expressed by many that clinical services can retain local decision-making and autonomy to make important change at speed, hardly a hallmark of the NHS overall.

Well done RECOVERY!

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Competing interests: No competing interests

08 July 2020
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