Dear colleagues,

Yesterday, I started a series of overviews on COVID treatment, taking a bit of a distance from the omicron tsunami (of cases and preprint publications), because I would like to understand were we stand with therapy almost two years into the pandemic. As always, I'm triggered by curiosity, but also by questions from colleagues, including those in regulatory agencies or in general practice, who wonder what you can do to prevent or relieve (mild/moderate) COVID and prevent deterioration into severe disease (hospitalization, ICU, death…)

As you already know: the answers are not straightforward, there is, as yet, no magic bullet…. And, from my "distant" perspective, it is very difficult to judge the quality of the many clinical trials, sometimes on very unexpected compounds. **Therefore I would love hearing from those of you who see real patients and have hands-on experience with some of these drugs.**

In Episode 221, I discussed the "forerunners" of the to be expected "classical" antivirals: the polymerase inhibitor **Molnupiravir** (Merck) and the protease inhibitor **Paxlovid** (Pfizer).

- Clearly, the original enthusiasm for Molnupiravir has been lowered by the not so brilliant final results of the phase 3 trial (after more optimistic preliminary press release) and the fear for mutagenic effect.
- Paxlovid may be more active and the SARS-CoV-2 compound Nirmatrelvir or PF-07,321,332 in the combination is a highly specific, with a broad activity against many Coronaviruses, but:
    - No formal phase 3 results have been published
    - The Ritonavir "enhancer" could cause quite some drug toxicity in elderly, treated with "polypharmacy" (see 221-9).

I will come back on other candidates in these drug classes under development in later episodes.

The other interesting class are the **monoclonal antibodies**. As you know several companies, including Regeneron, Lilly, Astra-Zeneca and VIR, had very promising antibodies, mostly in combinations of pairs. I discussed recent findings with omicron in Episode 219. Clearly, Regeneron and Lilly are "out", while Sotrovimab (VIR) and one of the Astra-Zeneca mAbs (Cilgavimab) lose activity, but could probable still be used in a prophylactic setting, while using them therapeutically would most probably rapidly favor resistant mutations. But new very active mAbs were also proposed e.g. ZCB11 (Ep 219-7) or RBT-083 (Ep 219-9). However, they are still in an early preclinical phase

In the present Ep 222, I turn my attention to <u>"repurposed" drugs</u>, with some focus on use in outpatients.

First, I will NOT come back on the "old workhorses" such as hydro chloroquine, azithromycin, ivermectin or systemic interferon. We have passed that station for COVID and those trains go nowhere in my opinion. Ep 222-A, B, C is a copy of the position of NIH, which I fully endorse.

I will discuss the **local corticoid budesonide** (used in allergic asthma), the **anti-inflammatory colchicine** (used for gout), the **specific serotonin reuptake inhibitors** SSRI (ant-depressants with anti-inflammatory potential) and **inhalation type 1 interferon**. Is any of these products promising to be used in an outpatient setting to mitigate COVID symptoms and prevent deterioration?

<u>BUDESONIDE</u>

<u>Rationale:</u> The favorable effect of high dose systemic corticoids in hospitalized COVID patients has been well established, with as a potential explanation that they block the "hyperinflammation". **The**

question is whether local (inhaled or nasally applied) lower dose corticoids in ambulatory patients could be useful to prevent hospitalization.

Ep 222-1: Ramakrishnan Lancet Resp Dis April 2021 **STOIC**: Inhaled budesonide (2 X 800 µg per day with phase 2, open-label, community based randomised controlled trial with 70 participants in each arm: within 7 days of the onset of mild COVID-19 symptoms.

- The primary outcome (**need for hospitalization**) occurred in 11 (**15%**) participants in the usual care group and two (**3%**) participants in the budesonide group (p=0·009).
- **Clinical recovery was 1 day shorter** in the budesonide group (median 7 days *vs* 8 days ; log-rank test p=0·007).
- The mean proportion of **days with a fever** in the first 14 days was **lower** in the budesonide group (2%, SD 6) than the usual care group (8%, SD 18; Wilcoxon test p=0·051): less use of antipyretics in budesonide group (p= 0.025).
- **Persistent symptoms** at day 14 and 28: fewer in budesonide group
- However: **Blood oxygen** saturations and **SARS-CoV-2 load**, measured by cycle threshold, were **not different** between the groups.

Ep 222-2: Ly-Mee Yu Lancet Aug 2021 : Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (**PRINCIPLE)**: a randomised, controlled, open-label, adaptive platform trial:

Subjects = aged 65 years or older or 50 years or older with comorbidities, and unwell for up to 14 days with suspected COVID-19 but not admitted to hospital: 787 in the budesonide group, 1069 in the usual care group, and 974 receiving other treatments.

- **Self-reported recovery** was 3 days shorter (11.8 vs 14.7 days)
- **Hospitalisation or death:** 6.8 % vs 8.8 %

Interpretation Inhaled budesonide improves time to recovery, with a chance of also reducing hospital admissions or deaths (although our results did not meet the superiority threshold), in people with COVID-19 in the community who are at higher risk of complications.

Ep 222-3: Critical remarks on PRINCIPLE in Lancet Dec 2021:
- Based on self-reporting
- How compliant?
- Non-significant reduction in important « composite » primary outcome of hospitalisation + death….
- Could rather high doses of inhaled budesonide (400 µg) be replaced by lower (200 µg) of intranasal administration with less systemic exposure (less chances on adrenal suppression)?

Ep 222-4: The latter point is supported by a retrospective study in Cleveland, where the use of intranasal corticosteroids was associated with lower risk of hospitalization, ICU admission and death. Obviously, these data need to be confirmed in a prospective randomized control study.

Conclusion: There is a clear trend of a beneficial symptomatic effect, but it is not spectacular, especially not on “hard outcomes”, such as viral load, blood oxygen, death…

COLCHICINE

Ep 222-5: COLCORONA Tardiff Lancet Resp Med 2021: a phase 3, randomised, double-blinded, adaptive, placebo-controlled, multicentre trial with colcchine for 27 days in patients at least 40 years old and had at least one high-risk characteristic with PCR(+) within 24 hours. (> 2200 patients in colchicine and placebo arm)

- Primary outcome hospitalization or death: 4.6 % colchicine vs 6.0 in placebo (p= 0.042).
- Pneumonia in 2.9 % colchicine vs 4.1 % placebo (p= 0.021).
- Diarrhea (side effect) in 13.7 % colchicine vs. 7 % placebo (p < 0.001).

Interpretation: *Given the absence of orally administered therapies to prevent COVID-19 complications in community-treated patients and the benefit of colchicine in patients with PCR-proven COVID-19, this* ***safe and inexpensive anti-inflammatory agent could be considered for use in those at risk of complications****. Notwithstanding these considerations,* ***replication*** *in other studies of PCR-positive community-treated patients is recommended.*

Ep 222-6: PRINCIPLE trial on 156 patients with high risk, taking colchicine for 14 days was stopped for futility. *Colchicine did not improve time to recovery in people at higher risk of complications with COVID-19 in the community.*

Ep 222-7: Kow Meta-analysis on colchicine effect Immunity Inflammation and Disease Oct 2021

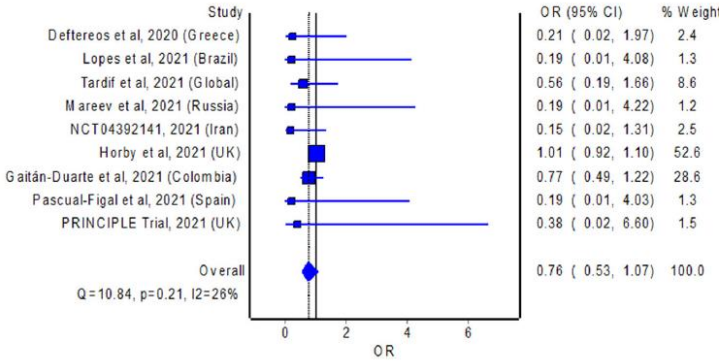

FIGURE 1 Pooled odds ratio of mortality between colchicine users and non-colchicine users with coronavirus disease-2019. CI, confidence interval; OR, odds ratio

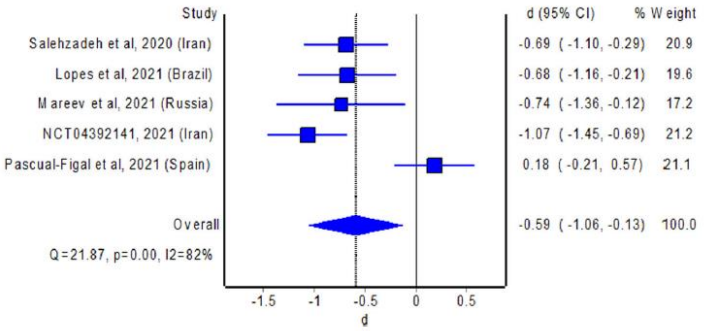

FIGURE 2 Pooled standardized mean difference of duration of hospital stay between colchicine users and non-colchicine users with coronavirus disease-2019. CI, confidence interval

No significant difference in mortality (pooled OR = 0.76; 95% CI: 0.53–1.07),
Significant reduction in the duration of hospital stay (mean difference = −0.59; CI: −1.06 to −0.13).

However, the authors express “some concerns” for bias in practically all the studies.

Conclusion: A bit similar as for budesonide: most probably some symptomatic relieve, but little evidence on hard outcomes

FLUVOXAMINE:

Fluvoxamine a **selective serotonin re-uptake inhibitor (SSRI)**, used as antidepressant, with also anti-inflammatory effects and it may have also anti-viral effects, according to in vitro data?

Ep 222-8: in the TOGETHER randomized platform study, a Brazilian substudy compared 2 groups of appr. 750 high risk PCR(+) symptomatic adults, treated with Fluvoxamine or not. The drug **reduced the risk for emergency hospitalization and death each by 30 % in the intention-to-treat analys**is and by 76 resp 91 % in the "per protocol" analysis.

Ep 222-9: Oskotsky in JAMA Open Large retrospective on several SSRI and **risk of mortality**

Analyzing electronic health records of 83 584 patients diagnosed with COVID-19, including 3401 patients who were prescribed SSRIs, a reduced relative risk of mortality RR, 0.92 [95%CI, 0.85-0.99 *was found to be associated with the use of SSRIs—specifically **fluoxetine and fluvoxamine*** **RR, 0.74 [95%CI,0.55-0.99].**

Ep 222-10**:** Hoertel explains the various proposed mechanisms and favors clinical use.

Ep 222-11: Facente review in drugs Oct 2021

In both the STOP COVID and Seftel and Boulware studies, ***no*** **participant** who received fluvoxamine experienced the primary adverse outcome—**respiratory deterioration** (in the case of STOP COVID) or **hospitalization** (Seftel and Boulware)—
compared with 8.3% or 12.5% of participants in the control arm, respectively.

Conclusion: Clearly, also more evidence is needed…

INTERFERON INHALATION: a very logical candidate:

- since type 1 interferon deficiency has a clear-cut role in the pathogenesis of COVID
- IFN acts locally
- Systemic IFN is too "toxic"

Ep 222-12: A retrospective Chinese "phase 2a" study in the beginning of the epidemic, using 5 million units of IFN-alpha 2b twice daily I hospitalized patients showed **a 64% reduction in "composite outcome": risk on mechanical ventilation, ICU admission and death**. From subgroup analysis, it was very evident that treatment should start as early as possible….

Ep 222-13: A prospective randomized double blind placebo controlled study in UK, using 6 million units of IFN beta 1a for two weeks in hospitalized patients. There is a clear-cut improvement, but certainly not significantly for all parameters.

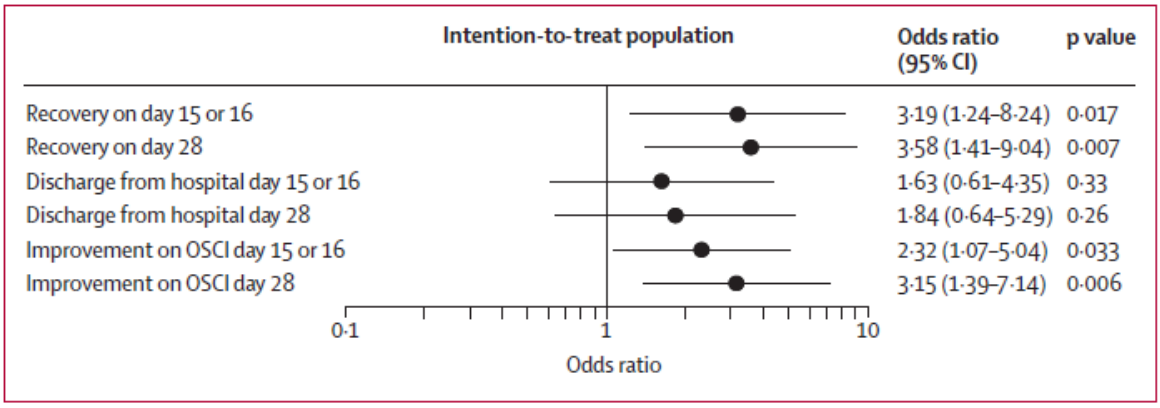

Figure 2: **Odds ratios of recovery (OSCI ≤1), hospital discharge, and improvement**
Odds ratios of recovery (defined as unchanged post-baseline OSCI score of 0 or 1), hospital discharge, and improvement on the WHO OSCI on days 15 or 16 (end-of-treatment visit) and on day 28 (follow-up visit) are shown. Comparisons were made between the SNG001 group (n=48) and placebo group (n=50) in the intention-to-treat population. OSCI=Ordinal Scale for Clinical Improvement.

Conclusion: At first view, one could take these results as "promising preliminary evidence", but… both studies date back in 2020. One would expect that a genuine phase 3 trial should have been done and published in the meantime.

GENERAL CONCLUSION:

1) Inhaled/nasal corticosteroids and/or oral colchicine presumable have favorable effects on symptoms of outpatients with mild-moderate COVID and may shorten the disease duration and the risk on hospitalisation. Whether they have a significant effect on "hard outcomes" is more questionable.
2) The same applies to SSRI, but I would be more reluctant to use them, as they are psychopharmaca in the first place and their mechanism of action against COVID remains questionable. More data is needed to convince me.
3) Although appealing at first view, inhaled type 1 interferon is certainly not ready to be used outside of well-controlled clinical trials.

Curious to read your reactions !

Best wishes,

Guido