1   Safety and efficacy of a MEURI Program for the use of high dose ivermectin in COVID-

2   19 patients

3   Short Title: A MEURI Program with ivermectin for COVID-19

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Abstract

Background

In the absence of antiviral alternatives, interventions under research for COVID-19 might be offered following guidelines from WHO for monitored emergency use of unregistered and experimental interventions (MEURI). Ivermectin is among several drugs explored for its role against SARS-CoV-2, with a well-known safety profile but conflicting data regarding clinical utility for COVID-19. The aim of this report is to inform on the results of a MEURI Program of high-dose ivermectin in COVID-19 carried out by the Ministry of Health of the Province of La Pampa, Argentina.

Methods

COVID-19 subjects, within 5 days of symptoms onset were invited to participate in the program, which consisted in the administration of ivermectin 0.6 mg/kg/day for 5 days plus standard of care. Active pharmacosurveillance was performed for 21 days, and hepatic laboratory assessments were performed in a subset of patients. Frequency of Intensive Care Unit (ICU) admission and COVID-19-related mortality of subjects in the ivermectin intention to treat group were compared with that observed in inhabitants of the same province during the same period not participating in the program.

Results

From 21232 subjects with COVID-19, 3266 were offered and agreed to participate in the ivermectin program and 17966 did not and were considered as controls. A total of 567 participants reported 819 adverse events (AEs); 3.13% discontinued ivermectin due to adverse. ICU admission was significantly lower in the ivermectin group

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42   compared to controls among participants ≥40 year-old (1.2% vs 2.0, odds ratio 0.608;

43   p=0.024). Similarly, mortality was lower in the ivermectin group in the full group

44   analysis (1.5% vs 2.1%, odds ratio 0.720; p=0.029), as well as in subjects ≥ 40 year-

45   old (2.7% vs 4.1%, odds ratio 0,655; p=0.005).

Conclusion

47   This report highlights the safety and possible efficacy of high dose ivermectin as a

48   potentially useful intervention deserving public health-based consideration for COVID-

49   19 patients.

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Introduction

COVID-19 constitutes a public health emergency at a global scale since its appearance in Wuhan, China, in December 2019 (1). By August 2021, over 200 million cases and 4 million deaths have been reported worldwide (2). Vaccine rollout campaigns, which currently offer the best hopes for pandemic control, are a key targeted pharmacologic intervention for containment of disease spread and impact on the incidence of severe cases (3,4).

Despite having an asymptomatic or mild course in most cases, COVID-19 constitutes a significant burden on health systems unprepared to cope with outbreaks requiring, among other things, massive testing capacity for rapid case detection and isolation, expansion of intensive care unit (ICU) capacity and case management guidelines for a previously unknown pathogen. This public health crisis has been, and still is, more profound in countries with weaker health systems (5).

The unprecedented progress in vaccine development has not been matched by the development of antiviral molecules, either new or repurposed, that could contribute to the treatment or prevention of COVID-19. With convalescent plasma, monoclonal antibodies, hydroxychloroquine and antiretrovirals among many molecules tested in-vitro and in observational and clinical trials, different treatment guidelines only agree in the use of corticosteroids, thromboprofilaxis and respiratory support, none of them an antiviral, in their recommendations (6,7).

Ivermectin (IVM) is an endectocide drug widely used for the treatment and control of onchocerciasis and lymphatic filariasis through mass drug administration programs, which has a wide therapeutic index and a benign safety profile (8,9). Besides its known

78   uses, it has been evaluated as an antiviral, demonstrating in vitro activity against zika,

79   rabies and dengue among other viruses (10). In the case of dengue, a recently

80   published randomized clinical trial from Thailand showed positive although

81   inconclusive results (11). For SARS-CoV-2, early on the pandemic, the report of the

82   antiviral activity of IVM in Vero cells cultures sparked widespread interest in the

83   potential utility of this oral, safe and affordable drug against COVID-19 (12). However,

84   after over a year of several publications addressing this question, there is a lack of

85   clear evidence for or against the use of IVM in COVID-19 patients (6,13). With at least

86   two completed double-blind randomized clinical trials (RCTs) showing no effect in

87   clinical endpoints, other smaller randomized trials using higher doses identified

88   significant antiviral effects (14–18). That undefined landscape is summarized by the

89   current NIH COVID-19 treatment Guidelines stating that there is insufficient data to

90   recommend either for or against the use of IVM in COVID-19 patients (6).

91   In 2016, the World Health Organization (WHO) issued the Guidance for Managing

92   Ethical Issues in Infectious Diseases Outbreaks, with the aim of complementing

93   existing guidance on ethics in public health in situations of great uncertainty and

94   including recommendations for the use of unproven interventions outside clinical trials,

95   which based on a WHO response developed in the context of the outbreak of Ebola

96   Virus Disease in Western Africa in 2014 are called "monitored emergency use of

97   unregistered and experimental interventions" (MEURI) (19). These interventions apply

98   when no proven effective treatments exist, it is not possible to initiate clinical trials

99   immediately, existing preliminary data supports the intervention, relevant regulatory,

100   ethical and scientific authorities approve such use, resources are available to minimize

101   risks and patient´s informed consent is obtained. Proper monitoring and timely sharing

102   of the results with the wider medical and scientific community are also requirements

103   to MEURI activities.

104   The aim of this report is to inform about the satisfactory safety and efficacy results of

105   a MEURI Program for the use of high dose IVM in COVID-19 patients, carried out by

106   the Ministry of Health of the Province of La Pampa, in the Patagonian region of

107   Argentina.

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109   Methods

110   MEURI Program for the use of high dose IVM in COVID-19
111   patients.

112   By the end of January 2021, the Ministry of Health of the Province of La Pampa

113   (Argentina) authorized the implementation of a MEURI program based on the use of

114   high dose IVM in COVID-19 adult patients (older than 18 year-old). In order to be able

115   to participate, subjects had to be able to provide written informed consent, have a

116   confirmed diagnosis of COVID-19 infection (by means of RT-PCR or antigen test) and

117   symptoms onset within 5 days before entering the program. Exclusion criteria included

118   pregnancy, breast feeding, hypersensitivity to IVM or acute allergic states, and active

119   use of warfarin. Women with child-bearing potential were eligible if they were taking

120   effective contraceptive measures before entering the program and agreed to continue

121   with these measures for at least 30 days after receiving the last dose of IVM.

122   Meanwhile ambulatory and inpatient subjects were allowed to participate (as long as

123   they accomplished all inclusion criteria and had no exclusion criteria), admission to

ICU was considered an exclusion criteria. Every member of the health staff of the Province of La Pampa was instructed to invite to participate in the program to every COVID-19 patient identified within the first five days of symptoms onset. However, participation in the program was voluntary, and physicians could decide not to include subjects in the program based on their medical criteria.

Ethical approval was obtained from the Provincial Ethics Committee of La Pampa, and participating individuals provided written informed consent.

Intervention

Participants were evaluated at program entry with complete medical history and a brief physical exam. At the beginning of the program, safety laboratory assessments before and at the end of treatment were mandatory. However, after a preliminary safety analysis that triggered an amendment approved by the Ethics Committee, these assessments were no longer mandatory and could be performed or not, based on medical judgment.

Patients received oral treatment with IVM for 5 consecutive days within 30 minutes of food ingestion, preferentially of high fat content, at approximately 24 h intervals. IVM 6 mg, 9 mg and 18 mg tablets were used, combined to in all cases at a dose of 0.6 mg/kg/day based on baseline weight rounding to the lower full (6 mg) dose. There were no specific guidelines regarding medical management of COVID-19 infection for the participants in the IVM program, which was the same as for the rest of the population.

Safety Assessment

146 Active pharmacosurveillance was performed during the first 21 days after treatment

147 start by means of the completion of a follow up chart, and safety assessment was

148 based in all subjects that participated in the program in which follow up safety data

149 was reported.

Hepatic safety assessment

151 Hepatic safety assessment was based on the analysis of hepatic lab exams performed

152 before and after IVM treatment in a subset of patients, and consisted of laboratory

153 determinations of alanine aminotransferase (ALT), aspartate aminotransferase (AST),

154 alkaline phosphatase (ALP) and total bilirubin levels. Drug induced liver injury was

155 defined according to the Latin American Association for Study of the liver definition,

156 that includes (i) ALT elevation ≥5 ULN, (ii) ALP elevation ≥2 ULN (in the absence of

157 known bone pathology driving the increase in ALP level) or (iii) ALT ≥3 ULN and

158 simultaneous elevation of total bilirubin concentration above 2 ULN (20).

Efficacy analysis

160 In order to estimate the efficacy of the implementation of the program, the clinical

161 evolution of the subjects in the IVM intention to treat (ITT) group was compared with

162 that observed in inhabitants of the same province during the same analyzed period

163 (from January 20, 2021 to May 20 2021) who did not participate in the program (control

164 group, C). To identify them, the analysis of the National Health Surveillance System

165 (SNVS 2.0) was used, which records, among other events, the notification of COVID-

166 19 cases, their clinical and demographic characteristics and the respective laboratory

167 studies, in a mandatory, nominal and immediate way, according to a national

168 regulation.

Given that the registration methodology differs between the one used in the IVM-monitored intervention program and the one used for registering subjects and events in SNVS 2.0 database, it was decided to consider variables not dependent on the registration method in the system for the efficacy analysis. Specifically, the primary objectives of the evaluation were the analysis of the impact of the program on the frequency of ICU admission and COVID-19-related death. It should be noted that both ICU admission and death registration is carried out centrally, so their identification is independent of the type of follow-up carried out.

In order to compare the clinical course of both groups, subjects under 18 years of age and pregnant women were excluded from the analysis.

In the univariate efficacy analysis, subgroup analysis was performed according to age group (subjects ≥ 18 year old -whole sample- or subjects ≥ 40 year old), immunization status (excluding subjects with at least one vaccine dose) and mean IVM prescribed dose.

Statistical analysis-

Baseline characteristics of the two groups (C and IVM) were compared by means of Student`s T- test and Chi square. The clinical evolution was evaluated by Chi square Test and logistic regression analysis. Whenever possible, number needed to treat (NNT) values for IVM were estimated for the end points of ICU admission and death. The NNT values were estimated as the inverse of the difference in estimated absolute risk between control and IVM groups. In all cases, p-values <0.05 were considered statistically significant. All analysis were performed with GraphPad Prism version 9.1.0 for Windows (La Jolla, California).).

Results

Recruitment

A total of 21232 non-pregnant adults were identified as COVID-19 positive between Jan 20 2021 and May 20 2021. Of these, 3266 agreed to participate in the program and received at least one dose of IVM, and were included in the ITT analysis group. A group of 17966 subjects that did not participate in the program were included in the C group. Descriptive characteristics of the population are presented in Table 1.

Safety follow up data was obtained from 2613 subjects that participated in the program and were included in the Safety Analysis Group. Of these, 1022 were followed with post-treatment hepatic lab exams, and were included in the Hepatic Safety Analysis group (Fig 1).
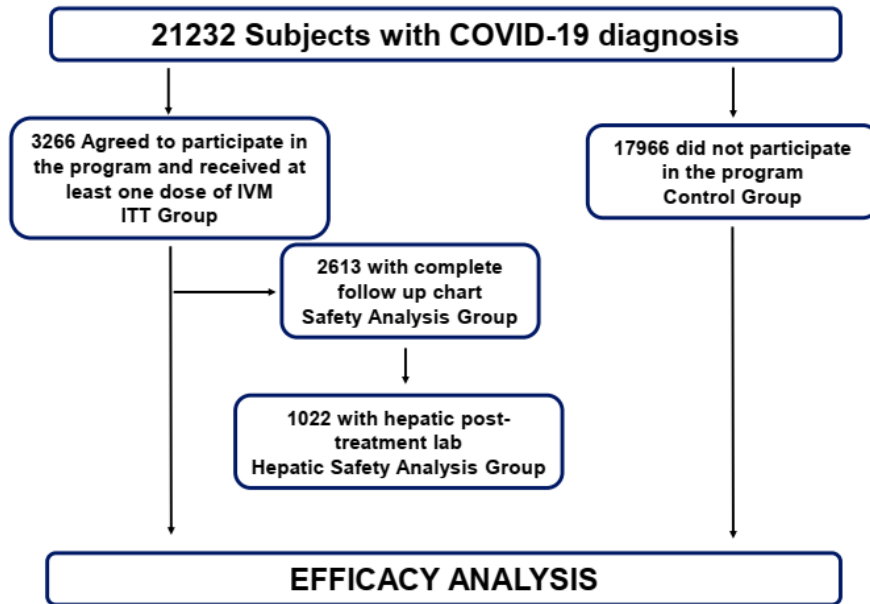
211 **Fig 1. Flow diagram of the MEURI Program for the use of high dose IVM in**

212 **ambulatory COVID-19 patients.**

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224   **Table 1. Descriptive characteristics of the sample.**

VARIABLE	CONTROL GROUP (n=17966)	IVERMECTIN GROUP (n=3266)
AGE (years +/- SD)	42.30±16,65	43.81±15,47**
SEX	52.8% FEMALE 47.2% MALE	50.6% FEMALE[#] 49.4% MALE
COMPLETE IMMUNIZATION	323 (1.8%)	59 (1.8%)
INCOMPLETE IMMUNIZATION	1417 (8.0%)	271 (8.5%)
CARDIOVASCULAR DISEASE	1792 (10.0%)	344 (10.5%)
COPD	1177 (6.6%)	244 (7.5%)
HYPERTENSION	1583 (8.8%)	551 (16.9%)**

DIABETES	1579 (8.8%)	315 (9.6%)
NEOPLASM	269 (1.5%)	63 (1.9%)
OBESITY	2241 (12.5%)	1182 (36.2%)**

225 COPD: Chronic obstructive pulmonary disease

226 Complete immunization: subjects with complete vaccine scheme at least 14 days

227 before symptoms onset

228 Incomplete immunization: subjects with the first vaccine dose (of a two-dose scheme)

229 received at least 14 days before symptoms onset

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232 # $p < 0,05$ vs Control group

233 * $p < 0,01$ vs Control group

234 ** $p < 0,001$ vs Control group

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Safety Analysis

237 A total of 2613 participants were included in the safety assessment. Five hundred sixty

238 seven (567) participants reported 819 adverse events (AEs). Eighty-two subjects (3.13

239 %) discontinued IVM due to adverse events and all AEs resolved after treatment

240 discontinuation. The most common AEs were diarrhea, followed by visual disorders,

241 dizziness, abdominal pain, headache and nausea (Table 2). Although many of the

242 symptoms presented during treatment resemble COVID, they were all assumed to be

243 related to IVM treatment.

244

245 **Table 2.** Safety analysis among subjects receiving ivermectin (n 2613). The table

246 shows adverse events reported in more than 0.5% of subjects

.ADVERSE EVENT	N (%)
Diarrhea	155 (5.93%)
Visual disorders	136 (5.2%)
Dizziness	120 (4.59%)
Abdominal pain	91 (3.48%)
Headache	73 (2.79%)
Nausea	78 (2.98%)

Anorexia	31 (1.19%)
Vomiting	30 (1.15%)
Heart rate elevation	18 (0.69%)
Rash	16 (0.61%)
Blood pressure elevation	15 (0.57%)
Pruritus	14 (0.53%)
Insomnia	14 (0.53%)
Drowsiness	14 (0.53%)

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Hepatic safety analysis

249 Although there was a small but statistically significant increase in ALT, AST and total

250 bilirubin values after IVM treatment (Table 3), among 1022 subjects that were followed

251 up with laboratory determinations after IVM treatment, only one presented liver

252 enzyme values compatible with low grade drug induced liver injury, that lead to drug

253 discontinuation on day 4 of treatment. According to medical records, this subject had

254 abnormal baseline ALT and AST values (AST 240 U/l, ALT 375 U/l, Total Bilirrubin

255 0,63 mg/dl and the values peaked to AST 366 U/l ALT 630 U/l total bilirrubin 0.8 mg/dl

256 and returned to AST 111 U/l, ALT 214 U/l and total bilirrubin 0.62 mg/dl. Considering

257 the total hepatic safety sample (n=1022), this represents an incidence of 0.98/1000

258 treated subjects.

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260 **Table 3.** Hepatic safety analysis.

VARIABLE	PRE-TREATMENT	POST-TREATMENT
AST (n=1000)	34.07±29.59 U/l	36.15±31.35 U/l **
ALT (n=988)	25.67±14.93 U/l	27.61±25.07 U/l **
Total bilirrubin (N=966)	0.44±0.24 mg/dl	0.47±0.24 mg/dl **
Alkaline phosphatase (n=1000)	146.32±77.27 U/l	120.60±93.33 U/l **

261 ** $p < 0.001$ vs pre-treatment values.

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263 # Program´s efficacy

264   In order to evaluate the program´s efficacy, the clinical evolution of subjects in the

265   IVM-ITT analysis group (n= 3266) was compared with 17966 subjects that did not

266   participate in the program (C group).

267   In the whole sample analysis, there was a non-significant tendency towards lower ICU

268   admission in the IVM-ITT group compared with C (0.9% vs 1.2%, odds ratio 0.738)

269   (95% CI 0.497-1.097, NNT 333, NS). Mortality rate was significantly lower in the IVM-

270   ITT group (1.5% vs 2.1%) with an odds ratio of 0.720 (95% CI 0.535-0.969, NNT 172,

271   (p=0.029) (Fig 2 A).

272   Regarding clinical evolution of subjects ≥ 40 year old (C n= 9022; IVM-ITT n=1851),

273   ICU admission was significantly lower (1.2% vs 2.0, with an odds ratio of 0.608 (95%

274   CI 0.393-0.940), NNT 128, (p=0.024). Mortality rate was significantly lower (2.7% vs

275   4.1%, with an odds ratio of 0.655 (95% CI 0.485-0.884), NNT 74, (p=0.005) (Fig 2 B).
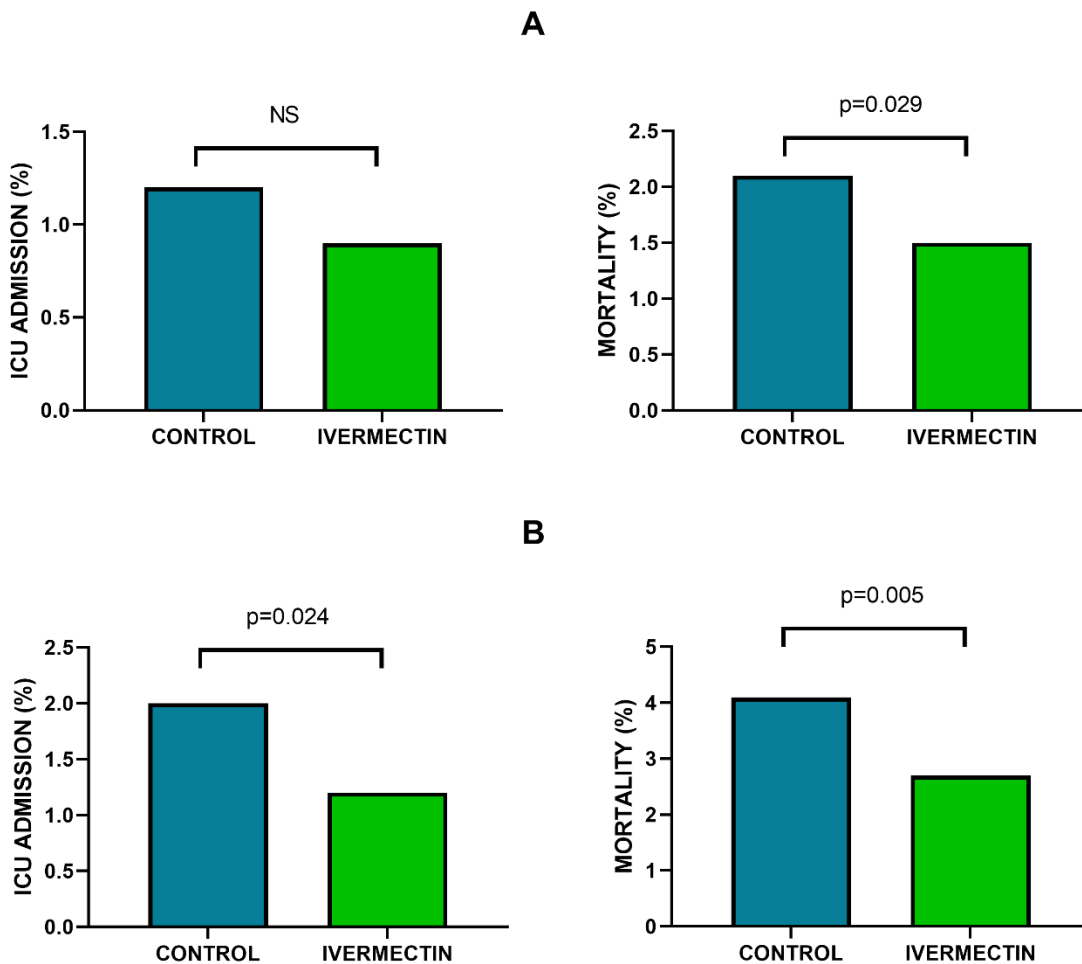
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283   **Fig 2**. ICU admission and mortality in IVM-ITT and C groups. Fig 2A: Analysis of all

284   subjects ≥18 year-old (C n= 17966; IVM-ITT n=3266); Fig 2B: Analysis of all subjects

285   ≥40 year-old (C n= 9022; IVM-ITT n=1851).

A

B

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287   In the analysis of all non-immunized subjects (C: n= 16226; IVM: n=2936), there was

288   a non-significant tendency towards lower ICU admission in the IVM-ITT group

289   compared with C (0.7% VS 1.1%, odds ratio 0.639 (95% CI 0.406-1.005, NNT 250;

290   p=0.051). Mortality rate was significantly lower in the IVM-ITT group (1.1% vs 1.7%,

291   with an odds ratio of 0.628 (95% CI 0.434-0.907, NNT 158; p=0.012).

292   Regarding clinical evolution of non-immunized subjects ≥ 40 year old (C n=7463 and

293   IVM-ITT n=1556), ICU admission was significantly lower (1.0% vs 2.1%, with an odds

ratio of 0.487 (95% CI 0.290-0.816, NNT 95;p=0.005). Mortality rate was significantly lower (2.1% vs 3.6%), with an odds ratio of 0.566 (95% CI 0.391-0.820, NNT 66;p=0.002).

A total of 2895 subjects in the IVM group had complete data regarding weight-based ivermectin dose information (of 3266 subjects assigned to IVM, 146 had missing data regarding the prescribed dose, and 335 had missing body weight data).

Mean IVM prescribed dose was 44.15±11.83 mg/day, mean IVM prescribed dose per kg of body weight was 0.54±0,09 mg/kg/day . Based on these values, two IVM groups were created: Low-dose IVM (with prescribed dose lower than 0.54 mg/kg/day, n=1157) and High-dose IVM (with a prescribed dose equal or higher than 0.54 mg/kg/day, n=1738). No significant differences were observed between groups regarding descriptive characteristics (age, gender, immunization status and comorbidities; data not shown).

In the whole sample analysis of High-dose IVM vs Low-dose IVM, there was a non-significant tendency towards lower ICU admission in the IVM-ITT group compared with C (0.6% vs 1.2%), with an odds ratio of 0.472 (95% CI 0.209-1.067; p=0.065). There were no significant differences in mortality rate (1.2 vs 1.6%) -odds ratio of 0.733 (95% CI 0.392-1.369;NS).

Regarding clinical evolution of subjects with an age of ≥ 40 year old (Low-dose IVM n=645 and High-dose IVM n=1016, there was a non significant tendency towards lower ICU admission in the High-dose IVM group (0.8% VS 1.7%)-with an odds ratio of 0.457 (95% CI 0.183-1.143;p=0.086). There were no significant differences in mortality rate (2.1% VS 2.9%) -odds ratio of 0.695 (95% CI 0.371-1.304;NS).

317   In the analysis of all subjects receiving High-dose IVM (n= 1738) vs C (n=17966), ICU

318   admission was significantly lower in the High-dose IVM group compared with C (0.6%

319   vs 1.2%), with an odds ratio of 0.494 (95% CI 0.261-0.934), NNT 172, (p=0.027).

320   Similarly, mortality rate was lower in the High-dose IVM group compared with C (1.2

321   vs 2.1%) -odds ratio of 0.566 (95% CI 0.364-0.881, NNT 111;p=0.01).

322   Regarding clinical evolution of subjects with an age of ≥ 40 year old (C n=9212; IVM-

323   ITT n=1016), ICU admission was significantly lower in the High-dose IVM group

324   compared with C (0.8% vs 2.0%), with an odds ratio of 0.383 (95% CI 0.188-0.780,

325   NNT 81;p=0.006). Similarly, mortality rate was lower in the High-dose IVM group

326   compared with C (2.1 vs 4.1%) -odds ratio of 0.498 (95% CI 0.319-0.776, NNT 50;

327   p=0.002).

328   The logistic regression analysis was performed after adjusting for sex, age,

329   immunization status and comorbidities, and IVM treatment remained negatively

330   associated with ICU admission rate and mortality rate (Fig 3).

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337 **Fig 3**. ICU admission and mortality in patients receiving ivermectin within MEURI

338 program vs Control after controlling for other variables by multiple logistic regression

339 analysis. Age was considered as a continuous variable. Subjects were considered

340 immunized after 14 days of their last vaccine dose. ** p<0.001; * p<0.01.

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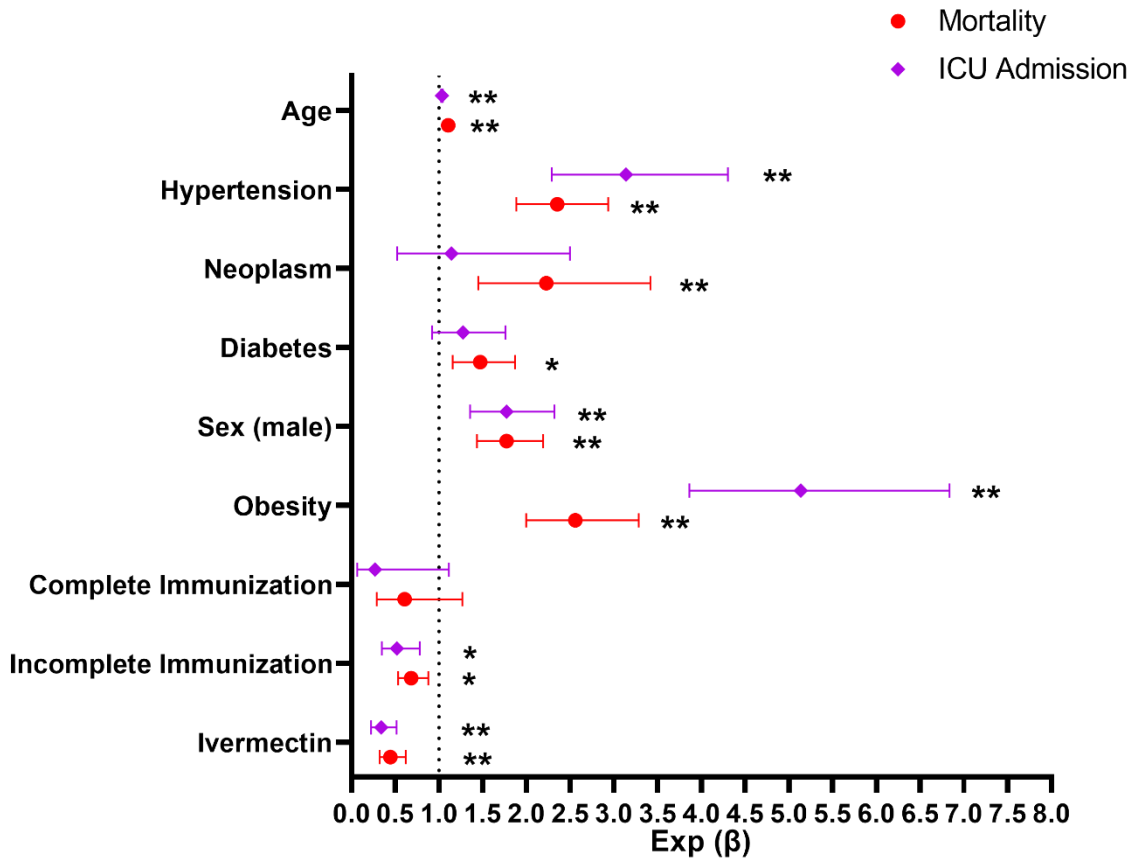
Discussion

343 This report of a monitored intervention program with ivermectin in COVID-19 patients

344 provides observational data on a significant number of adult patients that through the

345 incorporation of clinical and demographic data from a large number of patients from

346 the same province and period but not participating in the program (control group)

347 allowed a comparison and analysis of hard clinical endpoints as are admission to ICU

348 and death. This comparison provides results that suggest a significant positive clinical

349 impact of this intervention that, in the context of a lack of proven antiviral alternative

350 treatments for ambulatory patients against COVID-19, the safety, availability and

351 affordability of IVM and the growing concerns on vaccine efficacy against emerging

352 variants of SARS-CoV-2, deserves consideration as a potential tool for case

353 management.

354 The approach taken in the Province of La Pampa for the use of IVM through a MEURI

355 Program supported and leaded by the provincial Ministry of Health was based on

356 preliminary but inconclusive data on efficacy and a more solid reference base on the

357 safety of the drug, even at higher doses than those approved for other indications in

358 Argentina, as strongyloidiasis and scabies (21). With the incorporation of over three

359 thousand cases that completed treatment and follow up, including 1022 with clinical

360 laboratory monitoring, this intervention program contributes the largest analysis on the

361 safety of high dose ivermectin at a regimen of 600 µg/kg/day for 5 consecutive days.

362 This regimen was selected based on a proof-of-concept trial that identified a significant

363 antiviral activity against SARS-CoV-2 in a subgroup of participant who achieved high

364 IVM median plasma concentrations without any significant safety issues (16). In view

365 of that seemingly dose response antiviral effect, participants of our program were

366 advised to ingest the daily doses of IVM after a meal with adequate fat content in view

367 of the lipophilic nature of IVM (12,22) . The favorable safety profile of this regimen of

368 high dose IVM in a setting with conditions for high oral bioavailability confirms prior

369 communications with smaller sample sizes, on the safety of these regimens and allows

370 to focus in exploring the clinical efficacy of these regimens for a variety of clinical

371 indications for which IVM is in pre-clinical and clinical development as a repurposed

372 drug including COVID-19, dengue, trichuriasis and malaria. The finding of a single

373 case of clinically significant increase in liver enzymes, in an individual with baseline

374 abnormal values highlights these clinical and laboratory findings and provides

375 evidence for the design of simplified MEURI Programs, should they be considered

376 appropriate.

377 The controversial findings around the efficacy of IVM in COVID-19 is currently

378 preventing from making firm recommendations to clinicians. The situation is worsened

379 by confusing messages through social and traditional media plus articles from peer-

380 reviewed journals that are published and afterwards retracted as well as the

381 uncontrolled use of medical and veterinary products by the population (23). Meta-

382 analyses that included studies with a variety of regimens have reached different

383 interpretations and conclusions, preventing the achievement of consistent findings

384 (13,24–26). In this context, a MEURI Program appears as the mean to attempt

385 monitored and controlled use of a treatment not approved for the indication but with

386 preliminary results of adequate safety and potential efficacy. While the impossibility to

387 perform clinical trials was not an absolute situation at the time of the design of our

388 Program, the means and capacities of a provincial Ministry of Health were beyond the

389 scope and resources available.

390 The role of IVM against SARS-CoV-2 is supported by the biologic plausibility based

391 on in vitro and in vivo studies of mechanistic analyses and antiviral effects. Its

392 proposed antiviral mechanism is thought to be mediated by its ability to inhibit the

393 nuclear import of viral proteins mediated by IMPa/b1 heterodimer, and the promotion

394 of defense mechanisms such as pyroptosis in infected epithelial cells, suggesting its

395 possible role as a broad spectrum antiviral agent (27). These proposed effects might

396 explain the antiviral activity against SARS-CoV-2 reported by our group and Biber et

397 al, in two small randomized controled trials (16,18). However, randomized clinical trials

398 published on this topic have shown a lack of efficacy regarding clinical outcomes.

399 Lopez Medina et al. reported on the failure to show a significant effect of 300 µg/kg of

400 IVM for 5 consecutive days versus placebo in symptom´s resolution among 400

401 patients with mild disease recruited during the first week of COVID-19 in a single

402 center in Colombia (14). This trial, that was originally designed to demonstrate

403 improvement of 2 points in WHO Ordinary Scale but suffered from fewer than

404 estimated events, included a population with a median age of 37 year-old and

405 administered IVM on an empty stomach, as indicated by the manufacturer, which

406 probably prevented from maximizing oral biovailability of this highly lipophilic drug. In

407 the study from Vallejos et al. in Argentina (15), 501 patients with mild early COVID-19

408 infection were randomized to receive placebo or IVM for two consecutive days at up

409 to 200 µg/kg (the currently approved dose for other indications). Neither hospitalization

410 (primary outcome) nor other secondary outcomes including polymerase chain reaction

411 test negativity and safety outcomes showed statistically significant differences

412 between groups in this population with fewer events than estimated a priori and a

413 mean age of 42 year-old (SD ± 15.5).

414 The seemingly contrasting efficacy results between our analysis of an intervention

415 program versus the double-blind, placebo-controlled RCTs might not be discordant at

416 closer look with reasons laying in several factors pertaining to IVM regimens,

417 population size and outcomes; but potential bias in our results is another possibility to

418 be considered and explored. The IVM regimen used in our program provided a higher

419 total exposure to the drug through a higher dose per day, longer treatment (compared

420 to the trial by Vallejos) and administration with food, which while equally safe might

421 have allowed reaching drug levels at the relevant tissues above the threshold required

422 for an antiviral activity resulting in better clinical outcomes. This postulated dose effect

423 has been observed in other studies and the high levels achieved in lungs and

424 nasopharyngeal mucosa were seen in an animal model (28). In terms of the

425 populations included in the analyses, it is relevant to consider that both RCTs reached

426 fewer primary endpoints than estimated for the sample size calculation;

427 notwithstanding those potential limitations, which might have been affected by the age

428 of the population recruited to those trials, neither adjustments nor secondary outcomes

429 identified any significant clinical findings. Despite sound trial methodology, failure to

430 demonstrate the effect of an intervention might reside in contextual elements as is the

431 recruitment of subjects at very low risk of achieving the primary outcome regardless

432 of the use of an intervention (29,30), as might have been the case in both RCTs as

433 well as our observational analysis, which due to the significantly larger population size,

434 was able to identify a statistically significant treatment effect in admission to ICU and

435 death in restricting the analysis to those >40 year-old.

436 Statistically significant differences in observational studies should be viewed with

437 caution since the clinical and public health relevance of those results might not be

438 judged as relevant despite the statistics. Based on that, NNT ratios provide an indicator

439 that could inform clinicians and policy makers on the value and convenience of this

440 intervention. Effect size is another element to be considered in the evaluation of an

441 intervention, since the ability of trials to rule-out the effect of an intervention grows in

442 the required sample size in direct relationship to the decrease in the effect size, with

443 direct implications in the feasibility of a clinical trial and the convenience of an

444 intervention (31). In the present analysis, as expected, NNT related to ICU admission

445 and mortality prevention differed significantly between subgroups, with a lower NNT in

446 higher risk groups, as subjects older than 40 year-old.

447 As an observational intervention, our analyses are susceptible to bias, which constitute

448 the most significant limitation of this report and a major concern in COVID-19 in view

449 of the multitude of publications of studies and observations designed, run and

450 published at unprecedented speed (32). The risk of confounding factors introducing

451 bias in the comparison between groups cannot be completely ruled out, although

452 several measures were taken to minimize its occurrence, like the verification of

453 balanced age distribution, vaccination status and prevalence of comorbidities, with a

454 special attention paid to current oncologic processes that could identify patients with

455 terminal disease. In reference to it, in a sub-analysis that excluded individuals with

456 current oncologic processes the differences between IVM and C groups remained

457 significant (data not shown). Survivor bias was assessed and controlled in a sub-

458 analysis (data not shown) through the exclusion from the analysis of all individuals in

459 the control groups whose death occurred within the first 4 days since diagnosis, since

460 those individuals were in all likelihood not offered the intervention, maintaining a

461 significant association in favor of IVM in terms of mortality frequency in the higher risk

462 groups (non-immunized subjects older than 40 year-old). In order to limit the mortality

463 assessment to death related to COVID-19 in the C group, deaths were only considered

464 for the analysis when occurring during the original hospital admission or within a month

465 after discharge. Regarding the possible influence of differences in the prevalence of

466 comorbidities between groups, it is important to highlight that, meanwhile most

467 comorbidities were balanced between groups, a higher percentage of participants in

468 the IVM group reported hypertension and obesity compared to C. Although these

469 differences could be attributed to methodological differences in the identification of

470 comorbidities, should they be real, describe a higher risk of disease progression and,

471 consequently, would not explain the better outcomes observed in this group.

472 A per-protocol analysis including only individuals that completed the whole treatment,

473 which could provide information of the full potential of the regimen was not performed

474 since individuals on therapy that had their treatments interrupted at hospital admission

475 were identified and given that situation, performing a per-protocol analysis would have

476 given biased results that would wrongfully inflate the efficacy of the intervention.

477 One limitation of the present work is the absence of a detailed record of the refusal of

478 patients to participate in the IVM program. Specifically, since the start of the program

479 in January 2021, every physician in the province was authorized to offer this treatment

480 to patients who met the inclusion criteria. However, the inclusion of patients was left

481 to the discretion of the treating physician and to the acceptance by the patient. For this

482 reason, the non-inclusion of patients in the IVM program could be due both to the

483 refusal of patients to receive treatment after it was offered, to non-compliance with the

484 inclusion criteria, or to the decision by the treating physician not to offer this treatment

485 option. Unfortunately, no information is available to confirm the reason for not including

486 each individual patient.

487 When looking at our findings in the context of the results and conclusions of rigorous

488 RCTs, other observational clinical studies, virologic .and molecular biology studies for

489 the evaluation of IVM in COVID-19, we conclude on the plausibility and potential

490 clinical utility of IVM at higher doses than currently approved, optimizing its

491 bioavailability but with a relatively moderate effect size in high-risk population groups.

492 Without safety concerns at the doses used in our program, this report highlights IVM

493 as an intervention that deserves a dispassionate, careful, public health-based

494 consideration for the treatment of patients during present COVID-19 pandemic until

495 superior therapeutic alternatives become available and affordable, and highlights the

496 importance of performing adequately powered RCTs in order to confirm our findings.

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