**Agencja Oceny Technologii Medycznych i Taryfikacji**

**Wydział Świadczeń Opieki Zdrowotnej**

# Przegląd doniesień naukowych dla iwermektyny w leczeniu oraz profilaktyce COVID-19

Opracowanie analityczne AOTMiT

*Wersja 1.1*

data ukończenia 21.05.2021 r.

| HISTORIA ZMIAN DOKUMENTU | |
|---|---|
| **WERSJA 1.0 (04.02.2021)** | – |
| **WERSJA 1.1 (21.05.2021)** | • Dokument został uzupełniony o następujące badania: Lopez-Medina 2021, Mohan 2021, Beltran-Gonzalez 2021, Kishoria 2020, Shah Bukhari 2021, Pott-Junior 2021, Galan 2021;<br>• Zaktualizowano informacje dot. badania Mahmud 2021 w związku z pojawieniem się publikacji pełnotekstowej, jak również zweryfikowano wyniki badania Okumus 2021, Chowdhury 2021 i Babalola 2021 w związku z pojawieniem się recenzowanych wersji publikacji. |

## KLUCZOWE INFORMACJE

- Iwermektyna (IVM) jest lekiem przeciwpasożytniczym. Stosowanie u ludzi ogranicza się w Polsce do chorób dermatologicznych, tj. trądzik różowaty – lek w postaci kremu (rejestracja URPL). IVM stosowana w formie doustnej nie posiada rejestracji centralnej EMA, ani krajowej URPLWMiPB. Lek jest dopuszczony do stosowania w niektórych państwach, m.in. Francji, Niemczech, Holandii, Austrii, Szwecji.
- Kryteria włączenia do przeglądu spełniło łącznie 21 kontrolowanych prób klinicznych z randomizacją, z czego 19 dotyczyło stosowania iwermektyny w leczeniu COVID-19, jedno dotyczyło stosowania iwermektyny w ramach profilaktyki COVID-19 po kontakcie z zakażonym, a jedno obejmowało zarówno leczenie, jak i profilaktykę COVID-19.
- Do większości badań kwalifikowano pacjentów z łagodnym i umiarkowanym przebiegiem choroby. Iwermektyna stosowana była w monoterapii lub w skojarzeniu z opieką standardową. W 4 badaniach interwencję stanowiła iwermektyna w skojarzeniu z doksycyliną +/- opieka standardowa. W 6 RCTs jako ramię kontrolne stosowano hydroksychlorochinę oraz chlorochinę, a w 1 lopinawir w skojarzeniu z rytonawirem.

  Leczenie:

  - W żadnym z badań, w których porównywano skuteczność iwermektyny (± doksycyklina) z placebo / opieką standardową nie odnotowano istotnych statystycznie różnic w zakresie śmiertelności; wyniki próby klinicznej Lopez-Medina 2021 (największa liczebność grup (238 vs 238), niskie ryzyko błędu systematycznego) również nie potwierdzają skuteczności iwermektyny w COVID-19 (łagodny przebieg choroby).
  - Wyniki metaanalizy AOTMiT (6 RCTs, N=870 pacjentów), przeprowadzonej z wykluczeniem badań, w których ramię kontrolne stanowiła hydroksychlorochina, wskazują że stosowanie IVM +/- opieka standardowa w porównaniu do opieki standardowa +/- placebo nie wiąże się ze znamienną statystycznie redukują ryzyka zgonu. Z uwagi na heterogeniczność włączonych badań, kumulacja wyników obarczona jest wysokim ryzykiem błędu.
  - W badaniu Lopez-Medina 2021 odnotowano istotnie statystycznie wyższy odsetek ciężkich zdarzeń niepożądanych w ramieniu badania z iwermektyną względem pacjentów stosujących placebo.
  - U pacjentów stosujących iwermektynę w skojarzeniu z doksycykliną, w porównaniu do pacjentów stosujących placebo z opieką standardową, istotne statystycznie korzyści odnotowano w zakresie punktów końcowych dotyczących poprawy klinicznej i wyzdrowienia klinicznego, czasu utrzymywania się pozytywnego wyniku testu RT-PCR w 14. dniu (Mahmud 202), jak również czasu do wyzdrowienia (Hashim 2020).
  - W badaniach Ahmed 2020 i Krolewiecki 2020 odnotowano istotne statystycznie różnice na korzyść IVM względem placebo / opieki standardowej w zakresie czasu do eliminacji wirusa / szybkości zaniku wiremii.
  - Analizując wyniki badań należy wziąć pod uwagę ich ograniczenia, wynikające przede wszystkim z: niskiej liczebności prób; regionów geograficznych (Bangladesz, Egipt, Irak, Iran, Indie, Nigeria, Turcja, Argentyna, Hiszpania), w których przeprowadzono badania; sposobu analizy wyników; różnic w charakterystykach wyjściowych pacjentów (nieskuteczność procesu randomizacji); doboru komparatorów, braku informacji o leczeniu stosowanym w ramach opieki standardowej lub publikacji typu *pre-print* (Hashim 2020, Elgazzar 2020, Niaee 2020, Beltran-Gonzalez 2021).
  - Zidentyfikowane, w ramach przeglądu aktualizacyjnego, badania pierwotne nie wpływają na wnioski z wcześniejszej wersji przeglądu.

  Profilaktyka:

  - W grupie pacjentów otrzymujących IVM zaobserwowano znamiennie statystycznie niższy odsetek pacjentów, u których wystąpiły objawy choroby (Shouman 2020), jak również niższy odsetek osób z potwierdzonym RT-PCR zakażeniem (Elgazzar 2020).
- Aktualnie dla iwermektyny w leczeniu COVID-19 toczą się duże badania kliniczne z randomizacją (w Europie i Ameryce Północnej tj. COVIDOUT, IVER-303, PRINCIPLE), których wyniki mogą dostarczyć wiarygodnych danych umożliwiających ponowną analizę jej efektywności w COVID-19.

## 1. CEL

Celem opracowania jest ocena skuteczności i profilu bezpieczeństwa iwermektyny (IVM) stosowanej u pacjentów z COVID-19 oraz w profilaktyce COVID-19.

## 2. METODYKA

Przeprowadzono przegląd systematyczny baz informacji medycznej – PubMed, EMBASE (data ostatniego wyszukiwania 28.01.2021 r.). W celu odnalezienia doniesień jeszcze nieopublikowanych w ww. bazach, przeprowadzono również przegląd baz publikacji typu pre-print – www.medrxiv.org oraz ResearchSquare. W analizie wykorzystano również zasoby bazy COVID-19 (www.covid19.aotm.gov.pl). W aneksie dokumentu zamieszczono strategię wyszukiwania wykorzystywaną na rzecz przeglądu.

W ramach aktualizacji Przeglądu (wersja 1.1), przeprowadzono ponowne wyszukiwanie (data ostatniego wyszukiwania – 14.05.2021), włączając do analizy badania eksperymentalne z grupą kontrolną, oceniające efektywność kliniczną iwermektyny w leczeniu COVID-19, opublikowane po dacie wcześniejszego przeglądu doniesień – wersja 1.0.

Szczegółowe kryteria włączenia badań pierwotnych i wtórnych do przeglądu zestawiono w poniższej tabeli.

**Tabela 1. Kryteria włączenia badań pierwotnych i wtórnych do przeglądu dla iwermektyny**

| | **Kryteria włączenia i wykluczenia** |
|---|---|
| **Populacja** | Pacjenci z COVID-19, pacjenci po kontakcie z zakażonym wirusem SARS-CoV-2 |
| **Interwencja** | Iwermektyna |
| **Komparator** | Inne postępowanie terapeutyczne / zachowawcze / opieka standardowa |
| **Punkt końcowy** | Nie zdefiniowano – wszystkie zdefiniowane w protokołach punkty końcowe dla oceny skuteczności i profilu bezpieczeństwa |
| **Rodzaj badań** | Badania eksperymentalne z grupą kontrolną i randomizacją |

We współpracy z Komitetem Sterującym, nadzorującym prace nad Zaleceniami w COVID-19, zaproponowano poziomy doniesień naukowych w celu określenia stopnia wiarygodności uzyskanych wyników (Tabela 3). Zastosowano również gradację wyniku badania klinicznego przy uwzględnieniu rodzaju analizowanego punktu końcowego (klinicznie istotny/zastępczy punkt końcowy) oraz wielkości efektu (wykazanie różnic istotnych statystycznie na korzyść ramienia badanego lub kontrolnego) – Tabela 2.

**Tabela 2. Istotność wyniku badania pierwotnego**

| |
|---|
| IS różnice na korzyść interwencji – istotny klinicznie punkt końcowy |
| IS różnice na korzyść interwencji – zastępczy punkt końcowy |
| Brak IS różnic pomiędzy ramionami badania |
| IS różnice na korzyść ramienia kontrolnego – zastępczy punkt końcowy |
| IS różnice na korzyść ramienia kontrolnego – istotny klinicznie punkt końcowy |

**Tabela 3. Poziomy dowodów naukowych[1]**

| Poziom | Opis |
|---|---|
| **A** | • Wyniki >1 poprawnie zaprojektowanych RCT, wysoka wiarygodność wyników (reprezentatywność próby, ITT, zaślepienie, właściwa metoda randomizacji),<br>• Metaanaliza poprawnie zaprojektowanych RCTs,<br>• Wyniki ≥1 RCT uzupełnione danymi z wysokiej jakości rejestrów; |
| **B** | • Poprawnie zaprojektowane RCT, wysoka wiarygodność wyników (reprezentatywność próby, ITT, zaślepienie, właściwa metoda randomizacji) |
| **C** | • RCT z nielicznymi (≤2) ograniczeniami metodycznymi (brak zaślepienia, mała liczebność próby, ograniczenia metody randomizacyjnej, zmodyfikowana analiza wyników (mITT)) |
| **D** | • Poprawnie zaprojektowana kontrolowana próba kliniczna bez randomizacji,<br>• Poprawnie zaprojektowanie prospektywne badanie kohortowe,<br>• Poprawnie zaprojektowany rejestr,<br>• Metaanaliza wyżej wymienionych badań pierwotnych. |
| **E** | • Randomizowane lub nierandomizowane próby kliniczne z licznymi (>2) ograniczeniami metodycznymi (brak zaślepienia, mała liczebność próby, niewłaściwa metoda randomizacyjna, brak ITT),<br>• Badania obserwacyjne prospektywne z licznymi ograniczeniami metodycznymi, retrospektywne badania z grupą kontrolną |
| **F** | • Badania eksperymentalne bez grupy kontrolnej, badania obserwacyjne opisowe (serie przypadków) |
| **G** | • Opis przypadku |

[1] Prezentacja przyjętych poziomów wiarygodności na podstawie podejścia ACC/AHA (2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, dostęp online: https://www.ahajournals.org/doi/full/10.1161/CIR.0000000000000678

## 3. WYNIKI

Do przeglądu włączono 21 kontrolowanych prób klinicznych z randomizacją, z czego 1 (Shouman 2020) dotyczyła zastosowania iwermektyny tylko w ramach profilaktyki COVID-19.

W Tabela 4 zestawiono badania pierwotne odnalezione w ramach przeglądu. Opis metodyki i wyników badań przedstawiono w tabelach zamieszczonych w aneksie dokumentu.

W większości badań populację stanowili pacjenci z łagodnym i umiarkowanym przebiegiem choroby, jedynie do 6 badań kwalifikowano również osoby z cięższym przebiegiem COVID-19. Wielkość populacji w ramieniu interwencji tylko w 5 RCTs wynosiła ≥100 osób, największa liczebność próby w grupie interwencji – 238 osób – została uwzględniona w badaniu Lopez-Medina 2021.

W większości odnalezionych badań IVM stosowana była w monoterapii lub w skojarzeniu z opieką standardową (Lopez-Medina 2021, Ahmed 2020, Ravikirti 2021, Chachar 2020, Chaccour 2021, Podder 2020, Krolewiecki 2020, Okumus 2021, Mohan 2021, Beltran-Gonzalez, Kishoria 2020, Shah Bukhari 2021, Pott-Junior 2021). W 4 badaniach interwencję stanowiła iwermektyna w skojarzeniu z doksycyliną +/- opieka standardowa (Ahmed 2020, Mahmud 2021, Hashim 2020, Chowdhury 2021). Postępowanie w ramach opieki standardowej było zróżnicowane i obejmowało m.in. antybiotykoterapię (Podder 2020, Hashim 2020 i Elgazzar 2020, Ravikirti 2021, Okumus 2021), hydroksychlorochinę (Ravikirti 2021, Okumus 2021, Kishoria 2020) czy glikokortykosteroidy (Ravikirti 2021, Hashim 2020, Mahmud 2021, Beltran-Gonzalez 2021).

W 6 RCTs jako ramię kontrolne stosowano hydroksychlorochinę (Elgazzar 2020, Chowdhury 2021, Niae 2020, Galan 2021, Beltran-Gonzalez 2021) oraz chlorochinę (Galan 2021), aw 1 lopinawir w skojarzeniu z rytonawirem (Babalola 2021).

Schemat dawkowania, jak również czas leczenia IVM, był zróżnicowany – w większości badań IVM stosowano w jednorazowej dawce. Maksymalny czas terapii IVM wyniósł 5 dni.

Analizując wyniki RCTs należy uwzględnić liczne ograniczenia metodyczne badań, tj.

- niska liczebność prób (Ahmed 2020, Ravikirti 2021, Chachar 2020, Chaccour 2020, Podder 2020, Krolewiecki 2020, Okumus 2021, Hashim 2020, Chowdhury 2021, Babalola 2021, Mohan 2021, Beltran-Gonzalez 2021, Kishoria 2020, Shah Bukhari 2021, Pott-Junior 2021, Galan 2021);
- wybór hydroksychlorochiny lub chlorochiny jako opcji stanowiącej ramię kontrolne w badaniach (Elgazzar 2020, Chowdhury 2021, Niae 2020, Galan 2021, Beltran-Gonzalez 2021);
- brak zaślepienia (Chachar 2020, Podder 2020, Krolewiecki 2020, Chowdhury 2021, Elgazzar 2020, Okumus 2021, Kishoria 2020, Shah Bukhari 2021) lub brak informacji o zaślepieniu (Hashim 2020);
- brak informacji o leczeniu stosowanym w ramach opieki standardowej, brak szczegółowych informacji o odsetkach pacjentów otrzymujących daną terapię (Mahmud 2021, Chowdhury 2021, Krolewiecki 2020, Chachar 2020, Pott-Junior 2021);
- różnice pomiędzy ramionami badania w wyjściowej charakterystyce pacjentów (Chachar 2020, Babalola 2021, Krolewiecki 2020) – wskazuje na nieskuteczność procesu randomizacji;
- region geograficzny, w którym przeprowadzono badania (Bangladesz, Egipt, Irak, Iran, Indie, Nigeria, Turcja, Argentyna, Hiszpania, Meksyk, Kolumbia, Brazylia);
- brak analizy ITT (Ahmed 2020, Ravikirti 2021, Mahmud 2021, Krolewiecki 2020);
- status publikacji – pre-print (Hashim 2020, Elgazzar 2020, Niaee 2020, Beltran-Gonzalez 2021).

**Tabela 4. Zestawienie włączonych badań pierwotnych dla skuteczności i profilu bezpieczeństwa iwermektyny w COVID-19**

| No. | Study author, year | Country | Population | Intervention arm | N | Control arm | N | Types of analysed endpoints | Blinding | Reliability level |
|---|---|---|---|---|---|---|---|---|---|---|
| **TREATMENT (v 1.0, 4/02/2021)** | | | | | | | | | | |
| **1.** | **Ahmed 2020** | Bangladesh | Mild | IVM (12 mg once daily for 5 days) | 22 | Placebo | 23 | Duration of hospitalization after treatment; Duration to viral clearance; Afebrile, Cough and Sore throat on day 7, Serious adverse drug events | **DB** | **E** |
| | | | | IVM (12 mg single dose) + doxycycline (200 mg on day 1, followed by 100 mg every 12 h for the next 4 days) | 23 | | | | | |
| **2.** | **Ravikirti 2021** | India | Mild-moderate | IVM (12 mg on day 1 and 2) | 55 | Placebo | 58 | Negative RT-PCR; Symptom free; Discharged; Admission to ICU; Invasive Ventilation; In-hospital mortality | **DB** | **E** |
| **3.** | **Chachar 2020** | Bangladesh | Mild | IVM (12 mg at 0, 12, and 24 hours) + symptomatic treatment | 25 | Symptomatic treatment | 25 | Symptomatic on day 7 | **OL** | **E** |
| **4.** | **Chaccour 2021(SAINT)** | Spain | Mild | IVM (single dose of 0.4 mg/kg) | 12 | Placebo | 12 | Positive SARS-CoV-2 PCR – gene E, gene N; Seroconversion (positive IgG); Median of IgG titers; Viral load; Cycle threshold; Fever progression; Cough progression; AEs; SAEs; Drug-related AE; Mortality | **DB** | **E** |
| **5.** | **Podder 2020** | Bangladesh | Mild-moderate | IVM (0.2 mg/kg on the day 1) + usual care | 32 | Usual care | 30 | Time required for the resolution of symptoms; Result of repeat RT-PCR test: positive, negative | **OL** | **E** |
| **6.** | **Krolewiecki 2020** | Argentina | Mild-moderate | IVM (0.6 mg/kg/day for 5 days) + SoC | 30 | SoC | 15 | Viral load reduction in respiratory secretions; The viral load decay rate; Disease progression; AEs, SAEs | **OL** | **E** |
| **7.** | **Mahmud 2021** | Bangladesh | Mild-moderate | IVM (12 mg x1) + doxycycline (100 mg, BD 5 days) + SoC | 200 | Placebo+ SoC | 200 | Early Clinical Improvement; Late Clinical Recovery; Clinical Deterioration; Persistently Positive for RT-PCR of Covid-19, Mortality, SAEs | **DB** | **C** |
| **8.** | **Okumus 2021** | Turkey | Severe | IVM (0.2 mg/kg/day for 5 days) + Soc (hydroxychloroquine, favipiravir, azithromycin) | 36 | SoC (hydroxychloroquine, favipiravir, azithromycin) | 30 | Mortality, Clinical response, adverse events | **OL** | **E** |
| **9.** | **Hashim 2020** | Iraq | Mild-moderate, severe, critical | IVM (0.2 mg/kg per day for 2 days, in some patients third dose 0.2 mg/kg per day was given 7 days after the first dose) + doxycycline + SoC | 70 | SoC | 70 | Time to recovery; Progression of the disease; Mortality | **ND** | **E** |
| **10.** | **Chowdhury 2021** | Bangladesh | Mild-moderate | IVM (0.2 mg/kg single dose) + doxycycline (100 mg BID for 10 days) | 60 | HCQ (400 mg 1st day, then 200 mg BID for 9 days) + Azithromycin (500 mg daily for 5 days) | 56 | Recovery to negative PCR rate; Recovery duration to negative PCR; Duration of symptomatic recovery; New symptoms that may be attributed to drug adverse effect or progression of COVID-19 Adverse effects | **OL** | **E** |
| **11.** | **Elgazzar 2020** | Egypt | Mild-moderate | IVM (0.4 mg/kg, max. 4 tablets (6mg / tablet) once daily dose, for 4 days) + SoC | 100 | HCQ (400 mg every 12 hours for one day followed by 200 mg every 12 hours for 5 days) + SoC | 100 | Duration of hospital stay; Prognosis: improved, progressed, died; Laboratory investigations; RT- PCR conversion | **OL** | **C** |
| | | | Severe | IVM (4 days course of 0.4 mg/kg max.4 tablets (6mg / tablet) once daily dose) | 100 | HCQ (400 mg every 12 hours for one day followed by 200 mg | 100 | | | |

| No. | Study author, year | Country | Population | Intervention arm | N | Control arm | N | Types of analysed endpoints | Blinding | Reliability level |
|---|---|---|---|---|---|---|---|---|---|---|
| **TREATMENT (v 1.0, 4/02/2021)** | | | | | | | | | | |
| | | | | + SoC | | every 12 hours for 9 days) +SoC | | | | |
| **12.** | **Niaee 2020** | Iran | Mild - severe | • IVM, single dose (0.2 mg/kg)<br>• IVM, three doses (0.2 mg/kg)<br>• IVM, single dose (0.4 mg/kg)<br>• IVM, three doses (0.4, 0.2, 0.2 mg/kg) | 120 | • Common regimen (HCQ 200mg/kg 2x per day)<br>• Placebo + common regimen (HCQ 200mg/kg 2x per day) | 60 | Duration of hospital stay; Duration of low $O_2$ saturation; Tachypnea Off; Fever Off; Mortality | **DB** | **E** |
| **13.** | **Babalola 2021** | Nigeria | Mild – moderate, asymptomatic | IVM (6 mg every 84 hours, 2x week) | 21 | Lopinavir / ritonavir daily for 2 weeks | 20 | Time to SARS-CoV-2 negativity; Time sequence of days to negativity; Platelet count – change | **DB** | **E** |
| | | | | IVM (12 mg every 84 hours, for 2 weeks) | 21 | | | | | |
| **v 1.1, 21/05/2021** | | | | | | | | | | |
| **14.** | **Lopez-Medina 2021** | Colombia | Mild | IVM (300 mcg/kg/d for 5 days) | 238 | placebo | 238 | Time to resolution of symptoms, Symptoms resolved, Deterioration by ≥2 points in an ordinal 8-point scale, Fever (≥38 °C) since randomization, Escalation of care since randomization, Duration of care, Deaths, Adverse events | **DB** | **C** |
| **15.** | **Mohan 2021** | India | Mild-moderate | IVM (12 mg, single dose) | 40 | placebo | 45 | Negative RT-PCR, Days to symptom resolution, Change in WHO Ordinal Scale score between daily 0-14, Discharge, Any clinical worsening, Adverse events, Death | **DB** | **E** |
| | | | | IVM (24 mg, single dose) | 40 | | | | | |
| **16.** | **Beltran-Gonzalez 2021** | Mexico | Moderate-severe | IVM (12 mg (if body mass <80kg) or 18 mg (if body mass >80 kg) | 36 | placebo | 37 | Death, Duration of hospitalization, Hospital discharge, Discharge without respiratory deterioration or death, Respiratory deterioration or death | **DB** | **E** |
| | | | | | | HCQ (400 mg every 12h on the first day and subsequently, 200 mg every 12h for 4 days) | 33 | | | |
| **17.** | **Kishoria 2020** | India | Mild/ Asymptomatic | IVM (12 mg, single dose) + SoC | 19 | SoC (5 days: hydroxychloroquine 400 mg twice a day paracetamol 500mg as required, vitamin C 1 tab twice a day) | 13 | PCR negativity, Discharge | **OL** | **E** |
| **18.** | **Shah Bukhari 2021** | Colombia | Mild | IVM (12 mg, single dose) | 50 | standard care (oral vitamin C 500mg once daily, oral vitamin D3 200,000 IU once weekly, and oral paracetamol 500 mg SOS) | 50 | PCR negativity, Adverse side effects | **OL** | **E** |
| **19.** | **Pott-Junior 2021** | Brazil | Mild | ivermectin + SoC: 100 mcg/kg | 7 | SoC | 4 | Undetectable levels of SARS-CoV-2, Time to achieve undetectable viral load, Change in cycle threshold values, Adverse events | **DB** | **E** |
| | | | | ivermectin + SoC: 200 mcg/kg | 14 | | | | | |
| | | | | ivermectin + SoC: 400 mcg/kg | 7 | | | | | |
| **20.** | **Galan 2021** | Brazil | Severe | IVM (14 mg, once daily, total dose 42 mg) | 53 | HCQ (2x400 mg on day 0, and once daily from day 1 to day 4, total dose 2.4 g) | 54 | The need of oxygen supplementation, Duration of oxygen need, Corticosteroid therapy, Duration of corticosteroides | **DB** | **E** |

| No. | Study author, year | Country | Population | Intervention arm | N | Control arm | N | Types of analysed endpoints | Blinding | Reliability level |
|---|---|---|---|---|---|---|---|---|---|---|
| **TREATMENT (v 1.0, 4/02/2021)** | | | | | | | | | | |
| | | | | | | Chloroquine (2x450 mg on day 0, and once daily from day 1 to day 4, total dose 2.7 g) | 61 | treatment, Anticoagulant therapy, ICU admission, Need for vasoactive drugs, Need for invasive ventilation, Death due to COVID complications, adverse events | | |
| **PROPHYLAXIS (v 1.0)** | | | | | | | | | | |
| **21.** | **Elgazzar 2020** | Egypt | Health care and household contacts | IVM (0.4 mg/kg single oral dose before breakfast to be repeated after one week) + PPE | 100 | PPE only | 100 | Confirmed infected subjects by RT-PCR | **OL** | **C** |
| **22.** | **Shouman 2020** | Egypt | Asymptomatic household close contacts | IVM (2 doses 72 hours apart 40-60 kg – 15 mg/day,60-80kg – 18mg/day, >80kg – 24 mg/day) | 203 | No intervention | 101 | Development of Symptoms; Mortality; AEs; SAEs | **OL** | **E** |

HCQ – Hydroxychloroquine; IVM – Ivermectin; ND – no data; PPE – personal protective equipment; AEs – adverse events; SAEs – serious adverse events; DB – double blind; OL - open-label; SB – single-blind; ND – no data

**Podsumowanie wyników badań pierwotnych**

- **Leczenie**

*Iwermektyna vs opieka standardowa / placebo*

**Nie odnotowano istotnych statystycznie różnic w zakresie śmiertelności (Ravikirti 2021, Chaccour 2021, Okumus 2021, Lopez-Medina 2021, Mohan 2021, Beltran-Gonzalez 2021), długości hospitalizacji (Ahmed 2020) oraz punktów końcowych odnoszących się do stanu klinicznego pacjentów tj. progresja choroby, wyzdrowienie, występowania objawów. (Ravikirti 2021, Chachar 2020, Chaccour 2021, Podder 2020, Okumus 2021).**

Istotne statystycznie różnice na korzyść IVM odnotowano w zakresie czasu do eliminacji wirusa / szybkości zaniku wiremii w 5 dniu (Ahmed 2020 – 9,7 vs 12,7 dni / Krolewiecki 2020 – subpopulacja z medianą stężenia IVM w osoczu >160ng/ml – $0,64^{-1}$ vs $0,13^{-1}$ dni) oraz zmniejszenia miana wirusa (Krolewiecki 2020 – 72 vs 42% – subpopulacja z medianą stężenia IVM w osoczu >160ng/ml).

**W jednym badaniu (Lopez-Medina 2021) odnotowano istotnie statystycznie wyższy odsetek ciężkich zdarzeń niepożądanych w ramieniu badania z iwermektyną względem pacjentów stosujących placebo.** W pozostałych badaniach prezentujących wyniki w zakresie profilu bezpieczeństwa (Ahmed 2020, Chaccour 2021, Krolewiecki 2020, Okumus 2021, Pott-Junior 2021) ryzyko występowania działań niepożądanych pomiędzy ramionami badań było zbliżone.

*Iwermektyna + doksycyklina vs opieka standardowa / placebo*

**W żadnym z badań nie odnotowano istotnych statystycznie różnic w zakresie śmiertelności (Mahmud 2021, Hashim 2020) i występowania działań niepożądanych (Mahmud 2021, Ahmed 2020).**

W badaniu Mahmud 2021, u pacjentów stosujących iwermektynę w skojarzeniu z doksycykliną, w porównaniu do pacjentów stosujących placebo z opieką standardową, istotne statystycznie korzyści odnotowano w zakresie punktów końcowych dotyczących czasu do wyzdrowienia (7 vs 9 dni, HR=0,73, 95%CI: 0,06; 0,09), pogorszenia klinicznego (8,7 vs 17,8%, HR=0,43, 95%CI: 0,38; 0,62), poprawy klinicznej w ciągu 7 dni (60,7 vs 44,4%, HR=0,06, 95%CI: 0,004; 0,09) objawowości po 12 dniach (23 vs 37,2%, HR=0,04, 95%CI: 0,03; 0,07) oraz czasu utrzymywania się pozytywnego wyniku testu RT-PCR w 14. dniu (7,7 vs 20%, HR=0,61, 95%CI: 0,44; 0,83). W badaniu Hashim 2020 istotne statystycznie różnice na korzyść interwencji odnotowano jedynie dla czasu do wyzdrowienia (w populacji ogólnej 10,6 vs 17,9 dni; w subpopulacji pacjentów z łagodnym do umiarkowanego nasileniem objawów 6,3 vs 13,7 dni).

*Iwermektyna + doksycyklina vs hydroksychlorochina + azytromycyna*

Nie odnotowano istotnych statystycznie różnic dla analizowanych punktów końcowych tj. m.in. szybkości ustępowania objawów, średniego czasu do uzyskania ujemnego wyniku PCR (Chowdhury 2021).

*Iwermektyna vs hydroksychlorochina*

Istotne statystycznie różnice na korzyść IVM odnotowano w zakresie śmiertelności (Niae 2020, Elgazzar 2020), progresji choroby (Elgazzar 2020), poprawy klinicznej (Elgazzar 2020), długości hospitalizacji (Elgazzar 2020, Niae 2020), czasu do konwersji RT-PCR (Elgazzar 2020) oraz poprawy parametrów laboratoryjnych (Elgazzar 2020).

*Iwermektyna vs lopinawir/rytonawir*

W badaniu Babalola 2020 odnotowano istotnie statystycznie krótszy czas do uzyskania negatywnego wyniku testu RT-PCR względem grupy kontrolnej (6 vs 4,7 dni). W badaniu nie analizowano istotnych klinicznie punktów końcowych.

- **Profilaktyka**

W dwóch badaniach, w których iwermektyna była stosowana w ramach profilaktyki COVID-19 u osób po kontakcie z zakażonym, w grupie pacjentów otrzymujących IVM zaobserwowano znamiennie

statystycznie niższy odsetek pacjentów, u których wystąpiły objawy choroby (Shouman 2020), jak również niższy odsetek osób z potwierdzonym RT-PCR zakażeniem (Elgazzar 2020). Różnice w zakresie występowania działań niepożądanych, jak również pojawiania się poszczególnych objawów (tj. m.in. nudności, zmęczenie, biegunka) były nieistotne statystycznie.

**Tabela 5. Wyniki badań pierwotnych włączonych do przeglądu – leczenie**

| No. | Study author, year / acronym | Reliability level | Test arm, N | Control arm, N | Mortality | Progression | Recovery | Duration of hospital stay | Duration of viral clearance | SARS-CoV-2 negativity | AEs | SAEs |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Ivermectin vs SoC / placebo** | | | | | | | | | | | | |
| 1. | **Ahmed 2020** | **E** | 22 | 24 | | | | | p=0.005 (mean: 9.7 vs 12.7 days) | | | |
| 2. | **Ravikirti 2021** | **E** | 55 | 57 | | Admission to ICU; Invasive Ventilation | Symptom free Discharge | | | Day 6 | | |
| 3. | **Chachar 2020** | **E** | 25 | 25 | | | Symptomatic on day 7 | | | | | |
| 4. | **Chaccour 2021 (SAINT)** | **E** | 12 | 12 | | Fever Cough | | | | Positive SARS-CoV-2 PCR | | |
| 5. | **Podder 2020** | **E** | 32 | 30 | | | Resolution of symptoms – time | | | Negative result of repeat RT-PCR test | | |
| 6. | **Krolewiecki 2020** | **E** | 30 | 15 | | | | | The viral load decay rate (Subgroup with >160ng/ml IVM median plasma concentration) p=0.041 | | | |
| 7. | **Okumus 2021** | **E** | 36 | 30 | | | Clinical response | | | | | |
| 8. | **Lopez-Medina 2021** | **C** | 200 | 198 | | | | | | | | RR=2,97 (95%CI: 1,1; 8,02)^ |
| 9. | **Mohan 2021** | **E** | 80 | 45 | | | | Discharge | | | | |
| 10. | **Beltran-Gonzalez 2021** | **E** | 36 | 37 | | | | | | | | |
| 11. | **Shah Bukhari 2021** | **E** | 41 | 45 | | | | | | W 72 godzinie RR=9,32 (95%CI: 2,29; 37,9), NNT=3^<br>dzień 7 | | |
| 12. | **Kishoria 2021** | **E** | 19 | 13 | | | | Discharge | | | | |
| 13. | **Pott-Junior 2021** | **E** | 27 | 4 | | | | | | | | |
| **Ivermectin + doxycycline vs SoC / placebo** | | | | | | | | | | | | |
| 1. | **Ahmed 2020** | **E** | 23 | 24 | | | | | | | | |
| 2. | **Mahmud 2021** | **C** | 183 | 180 | | HR=0.45 (95%CI: 0.23; 0.85) | HR=0.51 (95%CI 0.32; 0.80) Clinical improvement HR=0.53 (95%CI 0.30; 0.96) | | | Persistently Positive for RT-PCR HR=0.58 (95%CI: 0.44; 0.81) | | |
| 3. | **Hashim 2020** | **E** | 70 | 70 | | | Time to recovery (mean: 10.6 vs 17.9 days) p<0.0001 | | | | | |
| **Ivermectin + doxycycline vs hydroxychloroquine + azhitromycin** | | | | | | | | | | | | |
| 1. | **Chowdhury 2021** | **E** | 60 | 56 | | | Recovery to negative PCR rate | | | | | |
| **Ivermectin +/- SoC vs hydroxychloroquine +/- SoC** | | | | | | | | | | | | |
| 1. | **Elgazzar 2020** | **C** | 100 | 100 | *Mild-moderate* | *Mild-moderate* ^RR=0.05 (95%CI: 0.01; 0.33), NNT=5 | | p<0.001 *Mild-moderate:* 5 vs 15 dni *Severe:* 6 vs 18 dni | Time to RT-PCR conversion p<0.001 | | | |
| | | | 100 | 100 | *Severe* ^RR=0.10 (95%CI: 0.02; 0.42), NNT=6 | *Severe* ^RR=0.13 (95%CI: 0.05; 0.36), NNT=4 | | | | | | |
| 2. | **Niae 2020** | **E** | 120 | 60 | RR=0.18 (95%CI: 0.06; 0.55), NNT=7 | | Tachypnea Off Fever Off | p=0.006 | | | | |

| No. | Study author, year / acronym | Reliability level | Test arm, N | Control arm, N | Mortality | Progression | Recovery | Duration of hospital stay | Duration of viral clearance | SARS-CoV-2 negativity | AEs | SAEs |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Ivermectin vs SoC / placebo** | | | | | | | | | | | | |
| 3. | **Beltran-Gonzalez 2021** | **E** | 36 | 33 | | | | | | | | |
| 4. | **Galan 2021** | **E** | 53 | 54 | | ICU admission | | | | | | |
| **Ivermectin vs chloroquine** | | | | | | | | | | | | |
| 1. | **Galan 2021** | **E** | 53 | 61 | | ICU admission | | | | | | |
| **Ivermectin vs lopinavir/rytonavir** | | | | | | | | | | | | |
| 1. | **Babalola 2020** | **E** | 42 | 20 | | | | | Time to negativity p=0.0066 | | | |

^ Agency's own calculations; AEs – adverse events; SAEs – serious adverse events; SoC – standard of care; RR – risk ratio

**Tabela 6. Wyniki badań pierwotnych włączonych do przeglądu – profilaktyka**

| No. | Study author, year / acronym | Reliability level | Test arm, N | Control arm, N | Development of Symptoms | Confirmed infected subjects by RT-PCR | AEs | Mortality |
|---|---|---|---|---|---|---|---|---|
| 1. | **Elgazzar 2020** | **C** | 100 | 100 | | p<0.05<br>^RR=0.20 (95%CI: 0.04; 0.89), NNT=30 | | |
| 2. | **Shouman 2020** | **E** | 203 | 101 | ^RR=0.13 (95%CI: 0.08; 0.21), NNT=2 | | | |

^ Agency's own calculations; AEs – adverse events; RR – risk ratio

**Analiza skuteczności w zakresie redukcji ryzyka zgonu – leczenie**

W Tabela 7 podsumowano wyniki dla śmiertelności z informacją o poziomie wiarygodności dowodów naukowych.

**Tabela 7. Podsumowanie danych dla skuteczności iwermektyny w zakresie redukcji ryzyka zgonu**

| Badanie | Populacja | Ramię badane, n/N | Ramię kontrolne, n/N | Wynik, parametr względny (95% CI), NNT | Poziom wiarygodności |
|---|---|---|---|---|---|
| **Iwermektyna vs SoC / placebo** | | | | | |
| **Ravikirti 2021** | Mild-moderate | 0/55 | 4/57 | ^RR=0.1 (0.0; 2.1) | **E** |
| **Chaccour 2021** | Mild | 0/12 | 0/12 | - | **E** |
| **Okumus 2021** | Severe | 6/30 | 9/30 | ^RR=0.66 (0.27; 1.64) | **E** |
| **Lopez-Medina** | Mild | 0/238 | 1/238 | ^RR=0.33 (0.01; 6.14) | **C** |
| **Mohan** | Mild-moderate | 0/80 | 0/45 | - | **E** |
| **Beltran-Gonzalez 2021** | Moderate-severe | 5/36 | 6/37 | ^RR=0.86 (0.29; 2.56) | **E** |
| **Iwermektyna + doksycyklina vs SoC / placebo** | | | | | |
| **Mahmud 2021** | Mild-moderate | 0/183 | 3/180 | ^RR=0.14 (0.01; 2.70) | **C** |
| **Hashim 2020** | Mild-critical | 2/70 | 6/70 | ^RR=0.33 (0.07; 1.60) | **E** |
| | Mild-moderate | 0/48 | 0/48 | - | |
| | Severe | 0/11 | 6/22 | OR=0.11 (ND;ND)<br>^RR=1.15 (0.01; 2.40) | |
| | Critical | 2/11 | no patients | - | |
| **Iwermektyna +/- SoC vs hydroksychlorochina +/- SoC** | | | | | |
| **Elgazzar 2020** | Mild, moderate, severe | 2/200 | 24/200 | ^RR=0.08 (0.020; 0.35), NNT=10 | **C** |
| **Niae 2020** | Mild-severe | 4/120 | 11/60 | RR=0.18 (0.06; 0.55), ^NNT=7 | **E** |
| **Galan 2021** | Severe | 12/53 | 12/54 | ^RR=1.02 (0.50; 2.06) | **E** |
| **Beltran-Gonzalez 2021** | Moderate-severe | 5/36 | 2/33 | ^RR=2.29 (0.49; 11.02) | **E** |

^ obliczenia własne Agencji; BD – brak danych; RR – risk ratio

**Z uwagi na heterogeniczność badań w zakresie ciężkości choroby, schematów dawkowania iwermektyny, doboru komparatorów i terapii stosowanych w ramach opieki standardowej, kryteriów kwalifikacji do badań (uwzględnianie pacjentów z różnym nasileniem objawów choroby), metodyki badania – zaślepienie / brak zaślepienia, liczebności prób, sposobu analizy wyników (analiza ITT, mITT lub *per protocol*), analizowanych punktów końcowych i ich definicji, okresu obserwacji, przeprowadzenie kumulacji wyników badań wydaje się nieuprawnione.**

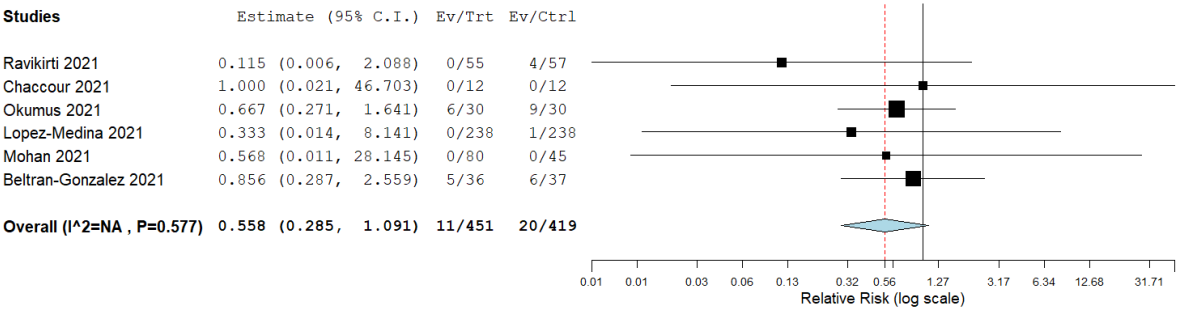
Analitycy AOTMiT przeprowadzili metaanalizę (6 RCTs, N= 870 pacjentów), z wykluczeniem badań, w których ramię kontrolne stanowiła hydroksychlorochina – wyniki dla porównania IVM +/- opieka standardowa vs opieka standardowa +/- placebo wskazują, że zastosowanie iwermektyny nie wiąże się ze znamienną statystycznie redukują ryzyka zgonu (RR=0,56, 95%CI: 0,29; 1,09 – Rysunek 1).

Dodatkowo przeprowadzono analizę z uwzględnieniem stopienia nasilenia choroby tj. łagodny – umiarkowany (4 RCTs, N= 737 pacjentów) – wyniki skumulowane również nie są istotne statystycznie (Rysunek 2).

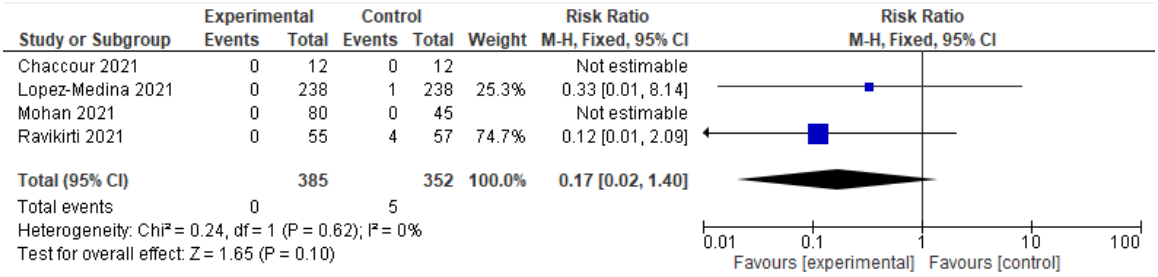
Wyniki metaanalizy przeprowadzonej dla porównania IVM+DOX+SoC vs SoC+/- placebo (2 RCTs, 503 pacjentów) wskazują z kolei, że zastosowanie terapii skojarzonej może wiązać się ze znamienną statystycznie redukcją zgonu – wynik na granicy istotności statystycznej (RR=0,222, 95%CI: 0,049; 0,999 – Rysunek 3).

Do uzyskanych wyników metaanaliz należy podchodzić z ostrożnością (heterogeniczność kliniczna: ciężkość przebiegu COVID-19, leczenie stosowane równolegle; heterogeniczność metodyczna: różne schematy dawkowania iwermektyny, liczebności prób, sposób analizy wyników, okres obserwacji).

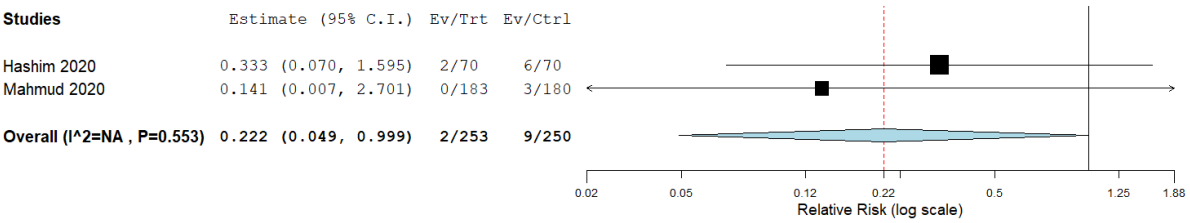
**Rysunek 1. Metaanaliza wyników RCTs (ryzyko zgonu, RR) dla porównania IVM+/-SoC vs PLB/SoC**




**Rysunek 2. Metaanaliza wyników RCTs (RR) dla porównania IVM+/-SoC vs PLB/SoC – populacja *mild-moderate***




**Rysunek 3. Metaanaliza wyników RCTs (RR) dla porównania IVM+DOX+SoC vs SoC+-/placebo**



## 4. DYSKUSJA I WNIOSKI

Kryteria włączenia do przeglądu spełniło łącznie 21 kontrolowanych prób klinicznych z randomizacją, z czego 19 dotyczyło stosowania iwermektyny w leczeniu COVID-19, jedno obejmowało zarówno leczenie jak i profilaktykę COVID-19, jedno dotyczyło stosowania iwermektyny w ramach profilaktyki COVID-19 po kontakcie z zakażonym. W większości badań populację stanowili pacjenci z łagodnym i umiarkowanym przebiegiem choroby, a iwermektyna stosowana była w monoterapii lub w skojarzeniu z opieką standardową. W 4 badaniach interwencję stanowiła iwermektyna w skojarzeniu z doksycykliną +/- opieka standardowa. Efektywność iwermektyny porównywano głównie z placebo ± opieka standardowa, w 6 RCTs w ramieniu kontrolnym stosowano hydroksychlorochinę (Elgazzar 2020, Chowdhury 2021, Niae 2020, Galan 2021, Beltran-Gonzalez 2021) oraz chlorochinę (Galan 2021), a w 1 lopinawir w skojarzeniu z rytonawirem (Babalola 2021).

W żadnym z badań, w których iwermektynę (± doksycyklina) porównywano z placebo / opieką standardową nie odnotowano istotnych statystycznie różnic w zakresie śmiertelności, wyniki próby klinicznej Lopez-Medina 2021 (największa liczebność grup (238 vs 238), niskie ryzyko błędu systematycznego wg Cochrane) również nie potwierdzają skuteczności iwermektyny w COVID-19 (łagodny przebieg choroby). Wyniki badań, w których w ramieniu kontrolnym stosowano hydroksychlorochinę (Elgazzar 2020, Niae 2020) wskazują co prawda na występowanie istotnych statystycznie różnic w zakresie śmiertelności na korzyść ramienia z iwermektyną, jednak z uwagi na możliwy negatywny wpływ hydroksychlorochiny na wyniki, leczenia należy je traktować ze szczególną ostrożnością.

W badaniach, w których porównywano IVM z placebo / opieką standardową, nie odnotowywano również istotnych statystycznie różnic pomiędzy ramionami badania w zakresie istotnych klinicznie punktów końcowych tj. progresja choroby, ustąpienie objawów, odpowiedź na leczenie czy wypis ze szpitala. Z kolei wyniki badania Mahmud 2021, przeprowadzonego z udziałem 400 pacjentów wskazują, że korzyści ze stosowania iwermektyny w skojarzeniu z doksycykliną można zaobserwować w zakresie poprawy klinicznej oraz redukcji ryzyka progresji choroby. Wyniki mniejszych prób klinicznych – Ahmed 2020 i Krolewiecki 2020 – wskazują z kolei, że iwermektyna może wpływać na zmniejszenie miana wirusa oraz skracać czas do uzyskania negatywnego wyniku PCR.

W jednym badaniu (Lopez-Medina 2021) odnotowano istotnie statystycznie wyższy odsetek ciężkich zdarzeń niepożądanych w ramieniu badania z iwermektyną względem pacjentów stosujących placebo. W pozostałych badaniach prezentujących wyniki w zakresie profilu bezpieczeństwa (Ahmed 2020, Chaccour 2021, Krolewiecki 2020, Okumus 2021, Pott-Junior 2021) ryzyko występowania działań niepożądanych pomiędzy ramionami badań było zbliżone.

Analizując wyniki badań pierwotnych włączonych do przeglądu AOTMiT, należy wziąć pod uwagę ich ograniczenia, wynikające przede wszystkim niskiej liczebności prób wpływającej na moc statystyczną badań, regionów geograficznych, w których przeprowadzono badania, sposobu analizy wyników, różnic w charakterystyce wyjściowej pacjentów, doboru komparatorów, braku informacji o leczeniu stosowanym w ramach opieki standardowej, brak szczegółowych informacji o odsetkach pacjentów otrzymujących konkretną terapię, braku publikacji wyników (Shouman 2020 – wyniki badania dostępne tylko na *clinicaltrial.gov*) lub publikacji typu pre-print (Hashim 2020, Elgazzar 2020, Niaee 2020, Beltran-Gonzalez 2021).

Wyniki metaanalizy AOTMiT (6 RCTs, N=870 pacjentów), przeprowadzonej z wykluczeniem badań, w których ramię kontrolne stanowiła hydroksychlorochina wskazują, że stosowanie IVM +/- opieka standardowa w porównaniu do opieki standardowa +/- placebo nie wiąże się ze znamienną statystycznie redukują ryzyka zgonu. Heterogeniczność włączonych badań pierwotnych pozwala stwierdzić, że kumulacja wyników obarczona jest wysokim ryzykiem błędu.

Stosowanie iwermektyny jako profilaktyki COVID-19 oceniano w dwóch, zidentyfikowanych w ramach wyszukiwania, próbach klinicznych z randomizacją, w których w grupie pacjentów otrzymujących IVM zaobserwowano istotnie niższy odsetek pacjentów, u których wystąpiły objawy choroby (Shouman 2020), jak również niższy odsetek osób z potwierdzonym RT-PCR zakażeniem (Elgazzar 2020).

Ponadto, należy mieć na uwadze, w Polsce lek z iwermektyną do stosowania u ludzi dostępny jest wyłącznie w postaci kremu wskazanego do leczenia trądziku różowatego. Lek w postaci tabletek oraz

iniekcji dostępny jest wyłącznie do leczenia weterynaryjnego. IVM stosowana w formie doustnej nie posiada rejestracji centralnej EMA ani rejestracji krajowej URPLWMiPB. Lek jest dopuszczony do stosowania w niektórych państwach, m.in. Francji, Niemczech, Holandii, Austrii, Szwecji.

## Aneks 1 (wersja 1.0, 4.02.2021 r.)

**Tabela 8. Opis metodyki i wyników badania Ahmed 2020 – leczenie**

| Ahmed 2020 | | | | | |
|---|---|---|---|---|---|
| **A five-day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness (International Journal of Infectious Diseases, 26.11.2020)** | | | | | |
| **Methodology** | **Population** | **Intervention 1** | **Intervention 2** | **Control** | **Limitations** |
| Randomized, double-blind, placebo-controlled<br><br>Randomization 1:1:1<br><br>Duration of the study: no data<br><br>Bangladesh | N=75 (72 included in the final analysis)*<br>Adults with mild COVID-19.<br><br>Inclusion criteria: age 18–65 years; admitted to hospital within the last 7 days; presence of a fever (>37.5°C), cough, and/or sore throat; diagnosed positive for SARS-CoV-2 by real-time reverse transcription PCR (rRT-PCR).<br>Exclusion criteria: allergic to ivermectin or doxycycline, or if there was the potential for a drug–drug interaction with ivermectin or doxycycline; had chronic illnesses (e.g., ischemic heart disease, heart failure, documented cardiomyopathy, chronic kidney disease, chronic liver disease); had received ivermectin and/or doxycycline in the last 7 days; were pregnant or lactating; or had participated in any other clinical trial within the last month.<br>The duration of illness before assessment was an average of 3.83 days. | Ni1=24 (22 included in the final analysis)*<br><br>Oral ivermectin alone (12 mg once daily for 5 days) | Ni2=24 (23 included in the final analysis)*<br><br>Oral ivermectin in combination with doxycycline (12 mg ivermectin single dose and 200 mg doxycycline on day 1, followed by 100 mg every 12 h for the next 4 days) | Nc=24 (23 included in the final analysis)*<br><br>Placebo | – Lack of detailed characteristics of patients in study arms;<br>– No detailed results for all analyzed endpoints;<br>– No detailed information about randomization method, blinding and statistical methods;<br>– Supported by Beximco Pharmaceutical Limited, Bangladesh. |
| | Mean age ± SD – yr | 42 | | | |
| | Female sex – % | 54 | | | |
| | Fever at enrolment – n/N (%) | 17/22 (77.3) | 17/23 (73.9) | 19/23 (82.6) | |
| | Cough at enrolment – n/N (%) | 18/22 (81.8) | 19/23 (82.6) | 15/23 (65.2) | |
| | Sore throat at enrolment – n/N (%) | 4/22 (18.2) | 3/23 (13) | 4/23 (17.4) | |

| **Results** | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Outcome** | | | **Intervention 1 (IVM)** | **Intervention 2 (IVM+DOX)** | **Control (PLB)** | **Statistical significance of differences** | |
| **event** | | **follow-up period** | | | | **Relative parameter (95%CI) / p** | **Absolute difference** |
| Duration of hospitalization after treatment – days, mean (95%CI) | | 14 days** | 9.6 (7.7; 11.7) | 10.1 (8.5; 11.8) | 9.7 (8.1; 11.0) | p=0.93 | - |
| Duration to viral clearance – days, mean (95%CI) | All patients | | 9.7 (7.8; 11.8) | 11.5 (9.8; 13.2) | 12.7 (11.3; 14.2) | **IVM vs PLB: p=0.005** | **-** |
| | | | | | | IVM+DOX vs PLB: p=0.123 | - |
| | Patients without co-morbidities | | 9 | - | 13 | **IVM vs PLB: p=0.02** | - |
| Afebrile on day 7 – n/N (%) | | 7 days | 17/17 (100) | 16/17 (94.1) | 16/19 (84.2) | IVM+DOX vs PLB: p=0.35<br>IVM vs PLB: p=0.09 | - |
| Cough at on day 7 – n/N (%) | | | 7/18 (61.1) | 7/19 (63.2) | 9/15 (40 | IVM+DOX vs PLB: p=0.18<br>IVM vs PLB: p=0.23 | - |
| Sore throat on day 7 – n/N (%) | | | 3/4 (75) | 1/3 (33.3) | 3/4 (75) | IVM+DOX vs PLB: p=0.35<br>IVM vs PLB: p=0.09 | - |
| Serious adverse drug events – n | | 14 days** | 0 | 0 | 0 | - | - |
| The mean values of the blood biomarkers (CRP, LDH, procalcitonin, and ferritin) dropped from baseline to day 7 in all three groups and these changes were significant for CRP (p=0.02) and LDH (p=0.01) in the 5-day ivermectin arm and for LDH in the placebo group (p=0.01). | | | | | | | |
| **Author's conclusion: A 5-day course of ivermectin was found to be safe and effective in treating adult patients with mild COVID-19. Larger trials will be needed to confirm these preliminary findings.** | | | | | | | |

DOX – doxycycline; IVM – ivermectin; PLB – placebo; *24 patients were included per study arm.
One patient from each of the ivermectin + doxycycline and placebo groups and two patients in the 5-day ivermectin group withdrew their consent during the study due to family obligations and unwillingness to be tested further; ** After day 14, patients were followed-up weekly until found to be test-negative.

**Tabela 9. Opis metodyki i wyników badania Ravikirti 2021 – leczenie**

| Ravikirti 2021 | | | | | |
|---|---|---|---|---|---|
| **Ivermectin as a potential treatment for mild to moderate COVID-19 – A double blind randomized placebo-controlled trial (medRxiv, 09.01.2021)** | | | | | |
| **Methodology** | **Population** | | **Intervention** | **Control** | **Limitations** |
| Randomized, double-blind, placebo-controlled<br><br>Duration of the study: 01/08/2020 – 31/10/2020<br><br>India | N=115 (112 included in the final analysis)*<br>Adults with mild to moderate COVID-19.<br><br>Inclusion criteria: all patients above the age of 18 admitted with a diagnosis of COVID -19 (on the basis of a positive RT-PCR or Rapid Antigen Test report) at AIIMS, Patna, India with mild or moderate disease as defined by the ministry of health and family welfare guidelines** and not meeting any of the exclusion criteria were considered eligible for the study.<br>Exclusion criteria: known allergy to or adverse drug reaction with Ivermectin; unwillingness or inability to provide consent to participate in the study; prior use of ivermectin during the course of this illness; pregnancy and lactation. | | Ni1=57 (55 included in the final analysis)*<br><br>Ivermectin<br>(12 mg on day 1 and day 2 of admission) | Nc=58 (57 included in the final analysis)*<br><br>placebo | – A conclusive repeat RT-PCR report could not be obtained in 32.1% of the patients. Moreover, as serial RT-PCR tests were not done, the median time to viral clearance in the two groups could not be ascertained;<br>– Most of patients received concomitant treatment;<br>– Small sample; |
| | Mean age ± SD – yr | | 50.7±12.7 | 54.2±16.3 | |
| | Female sex – no (%) | | 15 (27.3) | 16 (28.1) | |
| | COVID-19 disease severity | Mild | 42 (76.4) | 46 (80.7) | |
| | | Moderate | 13 (23.6) | 11 (19.3) | |
| | Comorbidities | Hypertension | 21 (38.2) | 18 (31.6) | |
| | | Diabetes | 21 (38.2) | 19(33.3) | |
| | Treatments | Hydroxychloroquine | 55 (100) | 57 (100) | |
| | | Steroid | 55 (100) | 57 (100) | |
| | | Enoxaparin | 53 (96.4) | 55 (96.5) | |
| | | Antibiotics | 55 (100) | 57 (100) | |
| | | Remdesivir | 12 (21.8) | 11 (19.3) | |
| | | Convalescent Plasma | 8 (14.5) | 7 (12.3) | |
| | | Tocilizumab | 4 (7.3) | 3 (5.3) | |
| | | Other Drugs | 36 (65.5) | 38 (66.7) | |
| | Days since onset of symptoms ± SD | | 6.1±3.6 | 7.9±8.6 | |

| **Results** | | | | | |
|---|---|---|---|---|---|
| **Outcome** | | **Intervention** | **Control** | **Statistical significance of differences** | |
| **event** | **follow-up period** | | | **Relative parameter, RR (95%CI)** | **Absolute difference** |
| Negative RT-PCR on day 6 (*primary outcome*) – n/N (%) | 6 days | 13/55 (23.6) | 18/57 (31.6) | 0.8 (0.4-1.4) | - |
| Symptom free on day 6 – n/N (%) | | 46/55 (83.6) | 51/57 (89.5) | 0.9 (0.8-1.1) | - |
| Discharged by day 10 – n/N (%) | 10 days | 44/55 (80) | 42/57 (73.7) | 1.2 (0.7-1.9) | - |
| Admission to ICU – n/N (%) | ND | 5/55 (9.1) | 6/57 (10.5) | 0.9 (0.3-2.7) | - |
| Invasive Ventilation – n/N (%) | | 1/55 (1.8) | 5/57 (8.8) | 0.2 (0.0-1.7) | - |
| Final outcome: discharge – n/N (%) | | 55/55 (100) | 53/57 (93) | 1.1 (1.0-1.2) | - |
| Final outcome: in-hospital mortality – n/N (%) | | 0/55 (0) | 4/57 (7) | ^0.1 (0.0; 2.1) | - |
| **Author's conclusion: There was no difference in the primary outcome i.e. negative RT-PCR status on day 6 of admission with the use of ivermectin. However, a significantly higher proportion of patients were discharged alive from the hospital when they received ivermectin.** | | | | | |

ICU – Intensive Care Unit; RR- rate ratio; yr – years; ND – no data

*57 were randomised to the intervention arm, 58 to the placebo arm. One patient in either arm was administered ivermectin by the treating team and one patient in the intervention arm was lost to follow up from day 2. Excluding these three patients, 55 patients in the intervention arm and 57 patients in the placebo arm were included in the final analysis. ** Ministry of Health and Family Welfare (Government of India).Clinical Management

| Ravikirti 2021 |
|---|

Protocol: COVID-19 (Version 3, 13/06/2020): Mild COVID-19: No evidence of breathlessness or Hypoxia (normal saturation); Moderate: Breathlessness and/or hypoxia (saturation 90-94% on room air), respiratory rate of 24 or more and no features of severe disease; Severe: Any of the following – Severe respiratory distress, oxygen saturation < 90% on room air, respiratory rate > 30, shock or evidence of a life threatening organ dysfunction; ^ Risk ratio, Agency's own calculations

**Tabela 10. Opis metodyki i wyników badania Chachar 2020 – leczenie**

| Chachar 2020 | | | | | |
|---|---|---|---|---|---|
| **Effectiveness of Ivermectin in SARS-CoV-2/COVID-19 Patients (International Journal of Sciences September, 2020)** | | | | | |
| **Methodology** | **Population** | | **Intervention** | **Control** | **Limitations** |
| Randomized, open-label, single-centre study<br><br>Randomization 1:1<br><br>Duration of the study: 01/05/2020 – 30/06/2020<br><br>Bangladesh | N=50<br>Adults with mild COVID-19.<br><br>Inclusion criteria: All patients diagnosed with COVID-19 infection with positive reverse transcriptase RT-PCR test, who were willing to participate in this study; age of 18-75 years; mild symptoms of Coronavirus disease and RT- PCR positive for SARSCov-2; Ability to take oral medication and were willing to adhere to the drug intake regimen;<br>Exclusion criteria: Known severe allergic reactions to Ivermectin; Pregnancy or breastfeeding; Severe symptoms likely attributed to Cytokine Release Storm; Malignant diseases; Chronic kidney disease; Cirrhosis liver with Child class B or C. | | Ni1=25<br><br>Ivermectin (12 mg stat and then 12 mg after 12 hours and 12 mg after 24 hours)<br>+ symptomatic treatment | Nc=25<br><br>Symptomatic treatment | – Small sample size;<br>– No blinding;<br>– Single-centre study;<br>– Significant differences in baseline characteristic of patients;<br>– No information on the percentage of patients and kind of receiving a symptomatic treatment; |
| | Mean age ± SD – yr | | 40.60 ±17 | 43.08 ± 14.8 | |
| | Male sex – n | | 17 | 14 | |
| | Cough – n* | | 24 | 18 | |
| | Fever – n | | 25 | 24 | |
| | Sore throat – n | | 20 | 14 | |
| | Headache – n | | 20 | 13 | |
| | Dyspnea – n | | 25 | 25 | |
| | Nausea – n | | 6 | 10 | |
| | Vomiting – n* | | 6 | 14 | |
| | Diarrhea – n* | | 4 | 17 | |
| | Myalgia – n | | 23 | 24 | |
| | Loss of taste – n* | | 15 | 5 | |
| | Anosmia – n* | | 15 | 5 | |
| | Hypotension – n | | 2 | 6 | |
| | Comorbidity – n | Diabetes | 11 | 9 | |
| | | Hypertension | 7 | 6 | |
| | | Obesity | 2 | 4 | |
| | | Cardiovascular disease | 2 | 2 | |
| | | Smoking | 9 | 6 | |

| Results | | | | | |
|---|---|---|---|---|---|
| **Outcome** | | **Intervention** | **Control** | **Statistical significance of differences** | |
| **Event** | **follow-up period** | | | **Relative parameter (95%CI) / p value** | **Absolute parameter (95%CI)** |
| Symptomatic on day 7 – n/N (%) | 7 days | 9/25 (36) | 10/25 (40) | p=0.5 | - |
| **Author's conclusion: In Ivermectin's (case group) recovery was almost equal to control group who received only conventional symptomatic treatment, so this is the need of the day that we need to conduct more randomized controlled trials across our country involving major tertiary care health care facilities with larger sample size to assess its efficacy for validating the use of Ivermectin against SARS-CoV-2. Nearly 40 clinical trials are ongoing world over for measuring the outcome of COVID-19 treatment with Ivermectin.** | | | | | |

ND – no data; * – p<0.05

**Tabela 11. Opis metodyki i wyników badania Chaccour 2021 (SAINT) – leczenie**

| Chaccour 2021 (SAINT) | | | | |
|---|---|---|---|---|
| **The effect of early treatment with ivermectin on viral load, symptoms and humoral response in patients with mild COVID-19: a pilot, double-blind, placebo controlled, randomized clinical trial (Lancet, 19.01.2021)** | | | | |
| **Methodology** | **Population** | **Intervention** | **Control** | **Limitations** |
| Randomized, double-blind, single-centre study, phase 2<br><br>Randomization 1:1<br><br>Duration of the study: 31/07/2020-11/09/2020<br><br>Spain | N=24<br>Adults with mild COVID-19. SARS-CoV-2 infected patients who are at low risk of progression to severe disease.<br><br><u>Inclusion criteria:</u> 18-59 years; Consecutive outpatients attending the Emergency Room of the Clínica Universidad de Navarra (Pamplona, Spain) with symptoms compatible with COVID-19, no more than 72 hours of fever or cough and a positive PCR for SARS-CoV-2; Negative pregnancy test for women of child bearing age*; Consent to participate in the study; The patient should, in the investigator's opinion, be able to comply with all the requirements of the clinical trial (including home follow up during isolation)<br><u>Exclusion criteria:</u> Known history of Ivermectin allergy; Hypersensitivity to any component of Stromectol®; COVID-19 Pneumonia (diagnosed by the attending physician; identified in a chest X-ray); Fever or cough present for more than 48 hours; Positive IgG against SARS-CoV-2 by rapid test; The following co-morbidities (or any other disease that might interfere with the study in the eyes of the investigator): Immunosuppression, Chronic Obstructive Pulmonary Disease, Diabetes, Hypertension, Obesity, Acute or chronic renal failure, History of coronary disease, History of cerebrovascular disease, Current neoplasm; Recent travel history to countries that are endemic for Loa loa (Angola, Cameroon, Central African Republic, Chad, Democratic Republic of Congo, Ethiopia, Equatorial, Guinea, Gabon, Republic of Congo, Nigeria and Sudan); Current use of CYP 3A4 or P-gp inhibitor drugs such as quinidine, amiodarone, diltiazem, spironolactone, verapamil, clarithromycin, erythromycin, itraconazole, ketoconazole, cyclosporine, tacrolimus, indinavir, ritonavir or cobicistat. Use of critical CYP3A4 substrate drugs such as warfarin. | Ni1=12<br><br>Ivermectin (Stromectol®, single dose of 400 mcg/kg) | Nc=12<br><br>Placebo | – Small sample size;<br>– Single-centre study;<br>– The placebo tablets did not match ivermectin in appearance, therefore, in order for the clinical team to remain blinded, treatment was administered under direct supervision by a nurse not participating in patient´s care. |
| | Age – median (IQR) | 26 (19-36) | 26 (21-44) | |
| | Male sex – n (%) | 7 (58) | 5 (42) | |
| | Any symptoms – % | 100 | 100 | |
| | Cough – n (%) | 4 (33) | 2 (17) | |
| | Fever – n (%) | 7 (58) | 9 (75) | |
| | Headache – n (%) | 7 (58) | 10 (83) | |
| | Myalgia/general malaise – n (%) | 8 (67) | 6 (50) | |
| | Earliest start of any symptom – hours, median (IQR) | 24 (24-48) | 48 (36-48) | |
| | Earliest start of fever – hours, median (IQR) | 24 (12-24) | 24 (24-48) | |
| | Earliest start of cough – hours, median (IQR) | 24 (16-36) | 10 (8-12) | |
| | CRP – median (IQR) | 0.3 (0.2-0.8) | 0.3 (0.2-0.6) | |
| | Ferritin – median (IQR) | 165.0 (95.5-241.3) | 156.1 (103.1-223) | |
| | IL-6 – median (IQR) | 6.5 (5.1-9.6) | 4.5 (3.0-6.5) | |
| | D-Dimer – median (IQR) | 295 (270-420) | 280 (270-315) | |
| | Viral load – no. (IQR), copies/mL – gene E | $1.7x10^7$ ($5.9x10^6$ – $3.9x10^8$) | $2.7x10^7$ ($8.3x10^5$ – $4.2x10^8$) | |
| | Viral load – no. (IQR), copies/mL – gene N | $3.7x10^8$ ($1.8x10^7$ –$9.3x10^9$) | $3.3x10^8$ ($5.8x10^7$ –$6.7x10^9$) | |

| Chaccour 2021 (SAINT) | | | | | | |
|---|---|---|---|---|---|---|
| **Results** | | | | | | |
| **Outcome** | | | **Intervention** | **Control** | **Statistical significance of differences** | |
| **Event** | | **follow-up period** | | | **Relative parameter, RR (95%CI) / p** | **Absolute parameter** |
| Positive SARS-CoV-2 PCR – n/N (%) (*primary endpoint*) | gene N | Day 7 | 12/12 (100) | 12/12 (100) | - | - |
| | gene E | | 11/12 (91.7) | 12/12 (100) | 0.92 (0.77; 1.09) | - |
| Seroconversion (positive IgG) – n/N (%) | | Day 21 | 12/12 (100) | 12/12 (100) | - | - |
| Median of IgG titers (IQR) | | | 4.7 (3.5-8.9) | 7.5 (4.2-9.3) | p=0.24 | - |
| Adverse events – n/N (%) | | Day 28 | 5/12 (41.7) | 5/12 (41.7) | - | - |
| Severe Adverse Events | | | 0/12 (0) | 0/12 (0) | - | - |
| Viral load – median (IQR), copies/mL | gene E | Day 1 | $1.7x10^7$ ($5.9x10^6$ – $3.9x10^8$) | $2.7x10^7$ ($8.3x10^5$ – $4.2x10^8$) | p=0.64 | - |
| | | Day 4 | $1.6x10^5$ (2820-8.8 $x10^5$) | $4.9x10^5$ ($1.0x10^5$-9.9 $x10^6$) | p=0.25 | - |
| | | Day 7 | 1018 (92-15445) | 23550 (709-2.3 $x10^5$) | p=0.17 | - |
| | | Day 14 | 7 (0-42) | 30 (1-50) | p=0.42 | - |
| | | Day 21 | 1 (0-9) | 0 (0-16) | p=0.49 | - |
| | gene N | Day 1 | $3.7x10^8$($1.8x10^7$ –$9.3x10^9$) | $3.3x10^8$ ($5.8x10^7$ –$6.7x10^9$) | p=1.0 | - |
| | | Day 4 | $2.7x10^5$ (1885-1.0 $x10^6$) | $2.2x10^6$ (73150-3.7 $x10^7$) | p=0.18 | - |
| | | Day 7 | 2255 (938-34650) | 36800 ($4510-6.3x10^5$) | p=0.18 | - |
| | | Day 14 | 86 (0-1235) | 75 (24-710) | p=0.36 | - |
| | | Day 21 | 0 (0-67) | 107 (0-183) | p=0.09 | - |
| Cycle threshold– median (IQR) | gene E | Day 1 | 20 (17-22) | 21 (18-23) | p=0.69 | - |
| | | Day 4 | 27 (25-31) | 26 (22-28) | p=0.20 | - |
| | | Day 7 | 33 (30-35) | 30 (28-32) | p=0.17 | - |
| | | Day 14 | 36 (35-41) | 35 (35-37) | p=0.22 | - |
| | | Day 21 | 38 (36-41) | 41 (37-41) | p=0.28 | - |
| | gene N | Day 1 | 20 (16-22) | 21 (17-22) | p=0.64 | - |
| | | Day 4 | 27 (24-31) | 25 (22-27) | p=0.13 | - |
| | | Day 7 | 32 (30-34) | 29 (27-31) | p=0.11 | - |
| | | Day 14 | 36 (33-41) | 35 (33-35) | p=0.30 | - |
| | | Day 21 | 41 (35-41) | 35 (35-39) | p=0.26 | - |
| **clinicaltrials.gov [2]** | | | | | | |
| Fever progression – n/N (%) | | Day 7 | 1/12 (8.3) | 0/12 (0) | ^3.00 (0,13; 67.06) | - |
| | | Day 14 | 0/12 (0) | 0/12 (0) | - | - |
| Cough progression – n/N (%) | | Day 7 | 5/12 (41.7) | 5/12 (41.7) | - | - |
| | | Day 14 | 1/12 (8.3) | 3/12 (25) | ^0.33 (0.04; 2.77) | - |
| Drug-related Adverse Events – n/N (%) | | Day 7 | 0/12 (0) | 0/12 (0) | - | - |
| All-Cause Mortality – n/N (%) | | Day 28 | 0/12 (0) | 0/12 (0) | - | - |

[2] https://clinicaltrials.gov/ct2/show/results/NCT04390022?term=ivermectin&cond=covid&draw=2 [access: 18/01/2021]

| Chaccour 2021 (SAINT) |
|---|
| **Author's conclusion: The positive signal found in this pilot warrants the conduction of larger trials using ivermectin for the early treatment of COVID-19. Such trials should include patients with risk factors for severe disease as well as patients with pneumonia. The potential for a mechanism of action different to direct antiviral effect also opens the door for pre-exposure prophylaxis in high risk groups.** |

^ Risk ratio, Agency's own calculations

**Tabela 12. Opis metodyki i wyników badania Podder 2020 – leczenie**

| Podder 2020 | | | | | |
|---|---|---|---|---|---|
| **Outcome of ivermectin treated mild to moderate COVID-19 cases: a singlecentre, open-label, randomised controlled study (IMC Journal of Medicine Science, 03.09.2020)** | | | | | |
| **Methodology** | **Population** | | **Intervention** | **Control** | **Limitations** |
| Randomized, open-label controlled study<br><br>Randomization: odd-even methodology applied to registration numbers, in a consecutive fashion of 1:1 ratio<br><br>Enrollment: 01/05/2020–31/07/2020<br><br>Bangladesh | N=62<br>Mild to moderate COVID-19 patients (according to WHO COVID-19 disease severity classification*).<br><br>Inclusion criteria: RT-PCR positive, mild to moderate COVID-19 cases, >18 years of age<br>Exclusion criteria: known pre-existing hypersensitivity to Ivermectin, pregnant and lactating mothers, and patients taking other antimicrobials or hydroxychloroquine | | Ni=32<br><br>Ivermectin 200 mcg/kg on the day 1 of randomization<br>+ usual care | Nc=30<br><br>Usual care | – Small sample size,<br>– No blinding;<br>– Investigators were unable to determine the effect of ivermectin (if any) on the biochemical and haematological parameters of the COVID-19 cases. |
| | | | Symptomatic treatment (usual care) included:<br>• antipyretics,<br>• cough suppressants,<br>• capsule doxycycline (100 mg every 12 hours for seven days) | | |
| | Age (years), mean±SD | | 38.41±11.02 | 39.97±13.24 | |
| | Male, no. (%) | | 23 (71.9) | 21 (70.0) | |
| | Presenting symptoms, no. (%) | Fever | 27 (84.4) | 23 (76.7) | |
| | | Cough | 21 (65.6) | 21 (70.0) | |
| | | Shortness of breath | 6 (18.8) | 6 (20) | |
| | | Sore throat | 3 (9.4) | 11 (36.7) | |
| | | Anosmia | 9 (28.1) | 5 (16.7) | |
| | | Dysgeusia | 1 (3.1) | 2 (6.7) | |
| | | Diarrhoea | 4 (12.5) | 2 (6.7) | |
| | | Myalgia | 14 (43.8) | 8 (26.7) | |
| | | Fatigue | 5 (15.6) | 7 (23.3) | |
| | | Headache | 2 (6.3) | 5 (16.7) | |
| | | Rhinorrhoea | 4 (12.5) | 4 (13.3) | |
| | Severity of illness, no. (%) | Mild | 26 (81.3) | 24 (80.0) | |
| | | Moderate | 6 (18.8) | 6 (20) | |
| | Duration of symptoms of patients in intervention and control arms at the time of enrolment (days), mean± SD | Fever | 3.85±2.11 | 4.00±2.17 | |
| | | Cough | 3.90±1.89 | 3.62±2.27 | |
| | | Shortness of breath | 1.83±1.17 | 3.00±1.27 | |
| | | Fatigue | 3.00±1.41 | 4.71±2.36 | |
| | | Myalgia | 3.25±.96 | 4.50±3.54 | |

| Podder 2020 | | | | | | |
|---|---|---|---|---|---|---|
| **Results** | | | | | | |
| **Outcome** | | | **Intervention** | **Control** | **Statistical variability of differences** | |
| **Event** | | **follow-up period (days)** | | | **Relative parameter (95% CI) / p** | **Absolute parameter** |
| Time required for the resolution of symptoms (days), mean ±SD | Complete recovery* | NA (from the date of enrolment) | 5.31±2.48 | 6.33±4.23 | p>0.05 | - |
| | Fever | | 3.33±2.18 | 3.18±2.61 | p>0.05 | - |
| | Shortness of breath | | 4.83±1.72 | 6.33±3.67 | p>0.05 | - |
| | Fatigue | | 6.00±4.85 | 5.67±3.62 | p>0.05 | - |
| Time required for the resolution of symptoms (days), mean ±SD | Complete recovery* | NA (from the date of onset of illness) | 10.09±3.24 | 11.50±5.32 | p>0.05 | - |
| | Fever | | 6.48±3.39 | 6.43±2.45 | p>0.05 | - |
| | Cough | | 9.23±3.22 | 10.45±3.70 | p>0.05 | - |
| | Shortness of breath | | 6.67±1.86 | 8.86±4.74 | p>0.05 | - |
| | Fatigue | | 9.00±3.61 | 9.57±3.65 | p>0.05 | - |
| Result of repeat RT-PCR test, no./N (%) | Positive | 10 | 2/20 (10) | 1/20(5) | p>0.05<br>^RR=2.00 (0.20; 20.33) | - |
| | Negative | | 18/20 (90) | 19/20 (95) | p>0.05<br>^RR=0.95 (0.79; 1.13) | - |
| **Conclusions: Ivermectin had no beneficial effect on the disease course over usual care in mild to moderate COVID-19 cases.** | | | | | | |

* Symptomatic patients without evidence of viral pneumonia or hypoxia (SpO2 >93% on room air) were considered as a mild disease and patients with clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) but no signs of severe pneumonia, including SpO2≥ 90% on room air were considered as a moderate disease; * Resolution of all symptoms. Some parameters are excluded from the analysis due to inadequate data; ^Agency's own calculations

SD – standard deviation; NA – not applicable; RR – risk ratio

**Tabela 13. Opis metodyki i wyników badania Krolewiecki 2020 – leczenie**

| Krolewiecki 2020 | | | | |
|---|---|---|---|---|
| **Antiviral effect of high-dose ivermectin in adults with COVID-19: a pilot randomised, controlled, open label, multicentre trial (ResearchGate, 11.2020)** | | | | |
| **Methodology** | **Population** | **Intervention** | **Control** | **Limitations** |
| A pilot, randomized, multicenter, controlled, open-label, outcome-assessor blinded clinical trial<br><br>Randomization: 2:1<br><br>Study period: 18/05/2020 –29/09/ 2020<br><br>Argentina | N=45<br>Adult hospitalized patients with mild to moderate COVID-19.<br><br>Inclusion criteria: COVID-19 patients aged 18 to 69 years-old with RT-PCR confirmed infection, hospitalized with disease stages 3 to 5 from the WHO 8-Category ordinal scale of clinical status and no requiring intensive care unit admission; COVID-19 symptoms onset ≤ 5 days at recruitment, absence of use of drugs with potential activity against SARS-CoV-2 (hydroxychloroquine, chloroquine, lopinavir and azithromycin) and available in Argentina during the trial; and those drugs were not permitted during the first week of the trial.<br>Exclusion criteria: the use of immunomodulators within 30 days of recruitment, pregnancy, breast feeding, poorly controlled comorbidities and known allergies to IVM | Ni=30<br>n=20 (efficacy population)<br>n=30 (safety population)<br><br>Ivermectin at 0.6 mg/kg/day for 5 days<br>+ SoC | Nc=15<br>n=12 (efficacy population)<br>n=15 (safety population)<br><br>SoC | – Small sample size,<br>– Only outcome-assessor was blinded;<br>– The finding of 2 distinct populations regarding mean IVM systemic concentrations was identified despite the body weight-based dosing and the indication of administering the drug tablets with meals,<br>– No information on what the standard therapy included. |
| | Age (years), mean±SD | 42.3 ± 12.8 | 38.1 ± 11.7 | |
| | Male, no. (%) | 15 (50) | 10 (67) | |
| | Weight (kilogram), mean±SD | 75.3 ± 15.0 | 79.7 ± 14.4 | |
| | Overweight, no. (%) | 6 (20) | 8 (53) | |
| | Obesity I, no. (%) | 11 (47) | 2 (13) | |
| | Obesity II, no. (%) | 1 (3) | 1 (7) | |
| | Obesity III, no. (%) | 1 (3) | 1 (7) | |
| | Oxygen saturation <94%, no. (%) | 1 (3) | 0 | |
| | Log viral load*** (log10 copies/reaction) | 4.18 ± 1.60 | 5.39 ± 1.56 | |
| | Time from symptoms onset (day) | 3.5 ± 1.0 | 3.6 ± 1.4 | |
| | Body temperature ≥37.5ºC, no. (%) | 4 (13) | 1 (7) | |
| | WHO-ordinal scale, no. (%) – 3 | 29 (97) | 13 (87) | |
| | WHO-ordinal scale, no. (%) – 4 | 1 (3) | 2 (13) | |
| | Ground glass opacities in thoracic imaging, no. (%) | 14 (47) | 6 (40) | |
| | Comorbidities, no. (%) – Hypertension | 3 (10) | 3 (20) | |
| | Comorbidities, no. (%) – Diabetes | 6 (20) | 1 (7) | |
| | Comorbidities, no. (%) – Chronic lung disease/Asthma | 4 (13) | 1 (7) | |

| Krolewiecki 2020 | | | | | | |
|---|---|---|---|---|---|---|
| **Results** | | | | | | |
| **Outcome** | | **Intervention** | | **Control** | **Statistical variability of differences** | |
| **event** | **follow-up period (days)** | **Group 1$ n=11** | **Group 2 $$ n=9** | | **Relative parameter (95% CI) / p** | **Absolute parameter (95% CI)** |
| Viral load reduction in respiratory secretions^^, median (IQR) | 5 | ND | | 42% (31-73) | p>0.05# | - |
| | | 40% (21-46) | 72% (59-77) | | Group 2 vs. Control: p=0.004 | - |
| The viral load decay rate, median (IQR), $d^{-1}$ | 5 | 0.14 (0.10-0.16) | 0.64 (0.31-0.67) | 0.13 (0.09-0.19) | Group 2 vs. Control: p=0.041 | - |
| | | | | | | - |
| Disease progression, no. | 7 | 2 | | 1 | p>0.05# | - |
| Patients with AEs&, no. (%) | ND | 13 (43) | | 5 (33) | ^RR=1,04 (0,48; 2,28) | - |
| Patients with possible/probable related AEs, no. (%) | | 9 (30) | | NA | - | - |
| Patients with SAEs, no. | | 1* | | 0 | - | - |
| Patients with possible/probable related SAEs, no. (%) | | 1 | | 0 | - | - |
| Number of AEs | | 17 | | 5 | - | - |
| Number of possible/probable related AEs | | 11 | | NA | - | - |
| Number of AEs Grade 3/4 | | 3** | | 0 | - | - |
| When mean plasma IVM concentration levels were analyzed in relation to reduction in viral load, a significant positive correlation was identified, with those patients achieving higher mean plasma concentrations of IVM reaching higher reductions in viral load in nasopharyngeal secretions (r: 0·44; p<0·04). This correlation was stronger when the reduction in viral load was related to the IVM exposure corrected by viral load at baseline (r: 0·60; p<0·004). The mean IVM plasma concentration levels also showed a positive correlation with the viral decay rate (r:0·47, p=0·02). | | | | | | |
| **Conclusions: A concentration dependent antiviral activity of oral high dose IVM was identified in this pilot trial at a dosing regimen that was well tolerated. Large trials with clinical endpoints are necessary to determine the clinical utility of IVM in COVID-19.** | | | | | | |

SD – standard deviation; NA – not applicable; SoC - standard of care; IVM – ivermectin; AEs – adverse events; SAEs – serious adverse events; ND – no data; RR – risk ratio

* hyponatremia; ** include the SAE (hyponatremia); ***Efficacy analysis (N=32: Ni=20, Nc=12); $ Subgroup with <160ng/mL IVM median plasma concentration; $$ Subgroup with >160ng/ml IVM median plasma concentration; ^ Agency's own calculations; ^^ by quantitative RT-PCR on upper respiratory tract secretions; & The most frequent adverse event and the only experienced by more than 1 case in the IVM group was rash in 3 (10%) cases (all mild, self-limited and lasting approximately24 h); in the control group, single events of abdominal pain, dizziness, anxiety, anguish, and hyperglycemia (all mild) were reported; # p values <0.05 were considered statistically significant

**Tabela 14. Opis metodyki i wyników badania Mahmud 2021 – leczenie (aktualizacja w wersji 1.1)**

| Mahmud 2021 | | | | |
|---|---|---|---|---|
| **Ivermectin in combination with doxycycline for treating COVID-19 symptoms: a randomized trial (NCT04523831; clnicaltrials.gov, 13.05.2021)** | | | | |
| **Methodology** | **Population** | | **Intervention** | **Control** | **Limitations** |
| Randomized, double-blind, placebo-controlled, phase 3<br><br>Randomization 1:1<br><br>Duration of the study: 01/06/2020 – 30/08/2020<br><br>Bangladesh | N=400 (363 included in the analysis)<br>Adults with mild to moderate COVID-19.<br><br>Inclusion criteria: 18 Years and older; COVID-19 infection, confirmed by RT-PCR test within 3 days from enrollment; mild and moderately severe COVID-19 infected cases; Able to provide informed consent<br>Exclusion criteria: Unable to take oral medication; Pregnant or breast feeding lady; Patients with severe COVID symptoms (defined as tachypnea [>30 breaths/ minute] and hypoxia [oxygen saturation (SpO2) <90%] requiring supplemental oxygen) or admission in ICU or high-dependency units; Alanine Aminotransferase (ALT) or aspartate aminotransferase (AST) more than 5 upper limit of normal (ULN); Known hypersensitivity to Doxycycline or ivermectin or its components. | | Ni1=200 (183 included in the analysis)<br><br>Ivermectin (6 mg 2 tab stat, cap) + doxycycline (100 mg 1 cap BD 5 days)<br>+SoC | Nc=200 (180 included in the analysis)<br><br>Placebo + SoC | – No detailed information on the percentage of patients receiving a specific standard therapy;<br>– Not all of patients completed the study; |
| | | | Standard of care: paracetamol, antihistamines, cough suppressants, vitamins, oxygen therapy according to indication and need, low molecular weight heparin according to indication, appropriate other broad-spectrum antibiotics, remdesivir injection, other antiviral drugs, and other drugs for associated comorbid conditions | | |
| | Mean age ± SD – yr | | 41 ± 14 | 38 ± 12 | |
| | Male sex – n/N (%) | | 123/200 (62) | 112/200 (56) | |
| | Severity – n/N (%) | Mild | 141/200 (71) | 136/200 (68) | |
| | | Moderate | 59/200 (30) | 64/200 (32) | |
| | Time between onset of symptoms and enrollment, median (IQR), day | | 4 (3-5) | 4 (3-5) | |

| Results | | | | | |
|---|---|---|---|---|---|
| **Outcome** | | **Intervention** | **Control** | **Statistical significance of differences** | |
| **event** | **follow-up period** | | | **Relative parameter (95%CI)** | **Absolute parameter (95%CI)** |
| Median recovery time, (IQR), day *(primary outcome)* | - | 7 (4-10) | 9 (5-12) | HR=0.73 (0.60; 0.90) | - |
| Patients responding within 7 days* – n/N (%) | 7 days | 111/183 (60.7) | 80/180 (44.4) | HR=0.06 (0.04; 0.09)<br>^RR=1.41 (1.15; 1.72) | ^^NNT=7 (4; 17) |
| Patients responding within 7–11 days – n/N (%) | 7-11 days | 32/183 (47.1) | 36/180 (52.9) | HR=1.02 (0.77; 1.36) | |
| Patients remaining symptomatic after 12 days – n/N (%) | >12 days | 42/183 (23.0) | 67/180 (37.2) | HR=0.04 (0.03; 0.07)<br>^RR=0.64 (0.46; 0.88) | ^^NNT=8 (5; 21) |
| Increase in stage of severity– n/N (%) | ≥14 days** | 16/183 (8.7) | 32/180 (17.8) | HR=0.43 (0.38; 0.62)<br>^RR=0.51 (0.29; 0.89) | ^^NNT=12 (7; 48) |
| Persistent COVID-19 RT-PCR positivity – n/N (%) | Day 14 | 14/183 (7.7) | 36/180 (20.0) | HR=0.61 (0.44; 0.83)<br>^RR=0.40 (0.22; 0.71) | ^^NNT=9 (6; 19) |
| All-Cause Mortality – n/N (%) | ≥14 days** | 0/200 (0) | 3/200 (1.5) | ^RR=0.14 (0.007; 2.75) | - |
| Adverse drug reaction – n/N (%) | | 9/200 (2.25) | 0/200 (0) | ^RR=19 (1.13; 324.25) | - |
| **Author's conclusion: Patients with mild-to-moderate COVID-19 infection treated with ivermectin plus doxycycline recovered earlier, were less likely to progress to more serious disease, and were more likely to be COVID-19 negative by RT-PCR on day 14. Although additional research on the effects of ivermectin combined with doxycycline is warranted, the safety and efficacy of this combination are favorable compared with current standard of care.** | | | | | |

* Body temperature remains normal for at least 3 days (ear temperature is lower than 37.5 °C); Respiratory symptoms are significantly improved; Lung imaging shows obvious improvement in lesions; There is no co-morbidities or complications which require hospitalization; SpO2, >93% without assisted oxygen inhalation.
** Hospitalized patients were followed from day 1 through day 14 or until discharge or clinical improvement, whichever occurred later
^ Risk ratio; Agency's own calculations; ^^^ Number Needed-to-treat; Agency's own calculations

**Tabela 15. Opis metodyki i wyników badania Okumus 2021 – leczenie (aktualizacja w wersji 1.1)**

| Okumus 2021 | | | | | |
|---|---|---|---|---|---|
| **Evaluation of the effectiveness and safety of adding ivermectin to treatment in severe COVID-19 patients (NCT04646109, BMC Infectious Diseases, 4.05.2021)** | | | | | |
| **Methodology** | **Population** | | **Intervention** | **Control** | **Limitations** |
| Randomized, open-label, multicentre, phase 3<br><br>Randomization 1:1<br><br>Duration of the study: 11/05/2020 – 02/09/2020<br><br>Turkey | N=66<br>Patients with severe COVID-19 pneumonia.<br><br>Inclusion criteria: Patients who were hospitalised with a pre-diagnosis of "severe COVID-19 pneumonia" and thereafter diagnosis of COVID-19 was also confirmed microbiologically with PCR positivity in respiratory tract samples were included into the study. Patients with at least one of the criteria below were accepted as patients with severe COVID-19 pneumonia: 1) Presence of tachypnea ≥ 30/minute, SpO2 level < 90% in room air, PaO2/FiO2 <300 in oxygen receiving patient, 2) Presence of specific radiological finding for COVID-19 in lung tomography (bilateral lobular, peripherally located, diffuse patchy ground glass opacities,<br>3) Mechanical ventilation requirement, 4) Acute organ dysfunction findings; patients with SOFA (sepsis-related organ failure assessment) score >2;<br>Exclusion criteria: <18 years of old; chronic liver or kidney disease; pregnancy; known ivermectin allergy | | Ni1=36<br><br>Ivermectin (0.2 mg/kg/day for 5 days)<br>+ Soc (hydroxychloroquine, favipiravir, azithromycin) | Nc=30<br><br>SoC (hydroxychloroquine, favipiravir, azithromycin) | – Small sample;<br>– No blinding;<br>– No full text publication; results available only on clinicaltrial.gov. |
| | Mean age ± SD – yr | | 58.17 (11.52) | 66.23 (13.31) | |
| | Female sex – n (%) | | 9 (30) | 11 (36.7) | |
| | Symptoms – n (%) | Fever – n (%) | 15 (50) | 13 (43.3) | |
| | | Cough – n (%) | 16 (53.3) | 14 (46.7) | |
| | | Sore throat – n (%) | 3 (10) | 1 (3.3) | |
| | | Dyspnea – n (%) | 23 (76.7) | 19 (63.3) | |
| | | Headache – n (%) | 5 (16.7) | 2 (6.7) | |
| | | Weakness – n (%) | 13 (43.3) | 11 (36.7) | |
| | | Myalgia – n (%) | 9 (30) | 7 (23.3) | |
| | Comorbidities – n (%) | Diabetes Mellitus | 9 (30) | 10 (33.3) | |
| | | Hypertension | 15 (50) | 12 (40) | |
| | | Coronary artery disease | 5 (16.7) | 8 (26.7) | |
| | | Cardiac failure | 0 | 1 (3.3) | |
| | | Chronic obstructive pulmonary disease | 6 (20) | 3 (10) | |
| | | Malignancy | 0 | 1 (3.3) | |
| | | Immunodeficiency | 0 | 1 (3.3) | |

| Okumus 2021 | | | | | |
|---|---|---|---|---|---|
| **Results** | | | | | |
| **Outcome** | | **Intervention** | **Control** | **Statistical significance of differences** | |
| **event** | **follow-up period** | | | **Relative parameter (95%CI)** | **Absolute parameter (95%CI)** |
| Clinical Response – n/N (%) | Day 5 | 14/30 (46.7) | 11/30 (36.7) | p=0.43<br>^RR=1.27 (0.69; 2.33) | - |
| Clinical Response – n/N (%) | Day 10 | 22/30 (73.3) | 16/30 (53.3) | p=0.10<br>^RR=1.38 (0.92; 2.05) | - |
| Mortality – n/N (%) | Mean: 3 months | 6/30 (20) | 9/30 (30) | p=0.37<br>^RR=0.66 (0.27; 1.64) | - |
| Treatment-Related Adverse Events– n/N (%) | Day 5 | 0/30 | 3/30 | - | - |
| **Author's conclusion: According to the findings obtained, ivermectin can provide an increase in clinical recovery, improvement in prognostic laboratory parameters and a decrease in mortality rates even when used in patients with severe COVID-19. Consequently, ivermectin should be considered as an alternative drug that can be used in the treatment of COVID-19 disease or as an additional option to existing protocols.** | | | | | |

ND – no data; ^ – Agency's own calculations

**Tabela 16. Opis metodyki i wyników badania Hashim 2020 – leczenie**

| Hashim 2020 | | | | |
|---|---|---|---|---|
| **Controlled randomized clinical trial on using Ivermectin with Doxycycline for treating COVID-19 patients in Baghdad, Iraq (medRxiv, 27.10.2020)** | | | | |
| **Methodology** | **Population** | **Intervention** | **Control** | **Limitations** |
| Randomized controlled trial<br><br>Recruitment: 01/06/2020–30/09/2020<br><br>Iraq | N=140<br><br>Inclusion criteria: COVID-19 patients diagnosed by clinical, radiological and laboratory PCR testing, at different stages of the disease (mild-moderate, severe, and critical according to WHO guidelines), who were symptomatic for no more than three days for mild-moderate cases, no more than two days after being severe cases, and no more than one day after being critical cases, outpatients or inpatients<br><br>Exclusion criteria: ND | Ni=70<br><br>Ivermectin + Doxycycline + SoC<br><br>IVM 200ug/kg PO per day for 2 days, in some patients third dose 200ug/kg PO per day was given 7 days after the first dose.<br><br>Doxycycline 100mg capsule PO every 12h per day, for 5-10 days, based on the clinical improvement of patients | Nc=70<br><br>SoC | – Randomization method: patients recruited at dates with odd number were allocated to intervention group or control group; no critical patient recruited in this study was allocated to the control group,<br>– Small size of subpopulations at different stages of the disease that makes impossible to achieve statistical power,<br>– No clear information on blinding,<br>– Pre-print |
| | | SoC included:<br>• Acetaminophen 500mg on need<br>• Vitamin C 1000mg twice/ day<br>• Zinc 75-125 mg/day<br>• Vitamin D3 5000IU/day<br>• Azithromycin 250mg/day for 5 days<br>• Oxygen therapy/ C-Pap if needed<br>• Dexamethazone 6 mg/day or methylprednisolone 40mg twice per day, if needed<br>• Mechanical ventilation, if needed | | |
| | Age (years), mean±SD | 50.1±9.3 | 47.2±7.8 | |
| | Male, % | 53 | 51 | |
| | Stage of the disease, no. – Mild-moderate | 48 | 48 | |
| | Stage of the disease, no. – Severe | 11 | 22 | |
| | Stage of the disease, no. – Critical | 11 | 0 | |

| Hashim 2020 | | | | | |
|---|---|---|---|---|---|
| | Median post-infection day for starting therapy, days | Mild-moderate | 3 | 3 | |
| | | Severe | 7 | 7 | |
| | | Critical | 8,5 | NA | |
| | Mean weight (kg), mean±SD | | 79.6±13.2 | 71.5±11.9 | |

| Results | | | | | | |
|---|---|---|---|---|---|---|
| **Outcome** | | | **Intervention** | **Control** | **Statistical variability of differences** | |
| **event** | | **follow-up period (days)** | | | **Relative parameter (95% CI) / p** | **Absolute parameter** |
| Time to recovery, mean±SD (days) | Total | NA | 10.61±5.3 | 17.9±6.8 | **p<0.0001** | - |
| | Mild-moderate | NA | 6.34±2.4 | 13.66±6.4 | **p<0.0001** | - |
| | Severe | | 20.27±7.8 | 24.25 ±9.5 | p=0.29 | |
| | Critical | | 19.77±9.2 | NA | - | - |
| Progression of the disease, n/N (%) | Total | Patients were monitored till recovery or death | 3/70 (4.28) | 7/70 (10) | OR=0.4 (ND; ND), p=0.2<br>^RR=0.43 (0.12; 1.60) | - |
| | Mild-moderate | | 0/48 (0) | 0/48 (0) | - | - |
| | Severe | | 1/11 (9) | 7/22 (31.81) | OR=0.21 (ND;ND), p=0.17<br>^RR=0.29 (0.04; 2.04) | - |
| | Critical | | 2/11 (18.2) | NA | - | - |
| Mortality rate, n/N (%) | Total | | 2/70 (2.85) | 6/70 (7.14) | OR=0.31(ND;ND), p=0.16<br>^RR=0.33 (0.07; 1.60) | |
| | Mild-moderate | | 0/48 (0) | 0/48 (0) | - | - |
| | Severe | | 0/11 (0) | 6/22 (27.27) | OR=0.11 (ND;ND), p=0.14<br>^RR=1.15 (0.01; 2.40) | |
| | Critical | | 2/11 (18.2) | NA | - | - |
| **Authors' conclusions: Ivermectin with doxycycline reduced the time to recovery and the percentage of patients who progress to more advanced stage of disease; in addition, Ivermectin with doxycycline reduced mortality rate in severe patients from 22.27% to 0%; however, 18.2% of critically ill patients died with Ivermectin and doxycycline therapy. Taken together, the earlier administered Ivermectin with doxycycline, the higher rate of successful therapy.** | | | | | | |

SD – standard deviation; NA – not applicable; IVM – ivermectin; MD – mean difference; SoC – standard of care; ND – no data; PO – per oss; RR – risk ratio; ^Agency's own calculations

**Tabela 17. Opis metodyki i wyników badania Chowdhury 2021 – leczenie**

| Chowdhury 2021 | | | | |
|---|---|---|---|---|
| **Comparative Study on Ivermectin-Doxycycline and Hydroxychloroquine-Azithromycin Therapy on COVID-19 Patients (EJMO, 25.02.2021)** | | | | |
| **Methodology** | **Population** | **Intervention** | **Control** | **Limitations** |
| Randomized, open-label<br><br>Randomization 1:1<br><br>Duration of the study: 02/05/2020 – 05/06/2020<br><br>Bangladesh | N=116<br>Adults with mild to moderate COVID-19.<br><br>Inclusion criteria: All patients who tested positive for SARS-CoV-2 infection by RT PCR at Chakoria Upazilla Health Complex, Cox's Bazar; Bangladesh from May 2nd to June 5th, 2020 were initially included in this study;<br>Exclusion criteria: Patients with unstable comorbid conditions like bronchial asthma, COPD, ischemic heart disease, uncontrolled diabetes mellitus, advanced renal and hepatic disease, carcinoma, hospitalized, and Immuno-compromised patients | Ni1=60<br><br>Ivermectin (200µgm/kg single dose)<br>+ Doxycycline<br>(100 mg BID for 10 days) | Nc=56<br><br>Hydroxychloroquine (400 mg 1st day, then 200 mg BID for 9 days) +<br>Azithromycin (500 mg daily for 5 days) | – Small sample;<br>– No blinding;<br>– No detailed information on the percentage of patients receiving a symptomatic treatment;<br>– Outcomes may be biased by additional factors like severity of the disease, lack of cooperation of some participants, and unknown comorbidity. |
| | | All subjects were also provided with symptomatic treatment for fever, headache, cough, myalgia, etc. | | |
| | Mean age ± SD – yr | 35.72 ± 15.1 | 31.91 ± 12.72 | |
| | Female sex – n (%) | 17 (28.33) | 9 (16.07) | |
| | Symptomatic – n (%) | 49 (81.67) | 42 (75) | |
| | Asymptomatic – n (%) | 11 (18.33) | 14 (25) | |

| Results | | | | | | |
|---|---|---|---|---|---|---|
| **Outcome** | | | **Intervention** | **Control** | **Statistical significance of differences** | |
| **event** | | **follow-up period** | | | **Relative parameter (95%CI)** | **Absolute parameter (95%CI)** |
| Recovery to negative PCR rate – n/N (%) | | ND | 60/60 (100) | 54/56 (96.36) | p=0.23 | - |
| Mean recovery duration to negative PCR – days | All patients | | 8.93 (8-13) | 9.33 (5-15) | ND | - |
| | Symptomatic | | 9.06 | 9.74 | p=0.071 | - |
| | Asymptomatic | | 8.36 | 7.92 | p=0.44 | - |
| Mean duration of symptomatic recovery – days | | | 5.93 (5-10) | 6.99 (4-12) | p=0.071 | - |
| New symptoms that may be attributed to drug adverse effect or progression of COVID-19 – n/N (%) | | | 41/60 (63.3) | 30/56 (53.57) | ^RR=1.28 (0.95; 1.72) | - |
| Adverse effects – n/N (%) | | | ND/ND (31.67) | ND-ND (46.42) | - | - |
| **Author's conclusion: The Ivermectin-Doxycycline combination showed a trend toward superiority to the Hydroxychloroquine-Azithromycin combination therapy in the case of patients with mild to moderate COVID19 disease, though the difference in time to becoming symptom-free and the difference in time to negative PCR was not statistically significant. Further study is required on a larger scale with an increase in the duration of Ivermectin treatment.** | | | | | | |

ND – no data; ^ – Agency's own calculations

**Tabela 18. Opis metodyki i wyników badania Elgazzar 2020 – leczenie i profilaktyka**

<table>
<tr><th colspan="10">Elgazzar 2020</th></tr>
<tr><th colspan="10">Efficacy and Safety of Ivermectin for Treatment and prophylaxis of COVID-19 Pandemic (ResearchSquare, 28.12.202)</th></tr>
<tr><th rowspan="2">Methodology</th><th rowspan="2" colspan="2">Population</th><th>Group 1</th><th>Group 2</th><th>Group 3</th><th>Group 4</th><th>Group 5</th><th>Group 6</th><th rowspan="2">Limitations</th></tr>
<tr><th colspan="4">TREATMENT</th><th colspan="2">PROPHYLAXIS</th></tr>
<tr><td rowspan="11">Randomized, multicenter, controlled clinical trial<br><br>Study period: 08/06/2020–15/09/2020<br><br>Egypt</td><td rowspan="3" colspan="2">N=600<br><br>Group 1-4:<br>n=400 symptomatic confirmed COVID-19<br><br>Group 5-6:<br>n=200 health care and household contacts<br><br>Group 1-4:<br><u>Inclusion criteria:</u> diagnosed COVID-19 infection with at least one positive RT-PCR result from nasopharyngeal/oropharyngeal swab, mild, moderate or severe cases*<br><br><u>Exclusion criteria:</u> pregnancy, lactation, and critical cases defined as: occurrence of respiratory failure requiring mechanical ventilation; Presence of shock; other organ failure that requires monitoring and treatment in the ICU</td><td>Ni1=100<br><br>IVM + SoC<br><br>IVM 400 microgram/kg body weight maximum 4 tablets (6mg / tablet) once daily dose, for 4 days</td><td>Ni2=100<br><br>HCQ + SoC<br><br>HCQ 400 mg every 12 hours for one day followed by 200 mg every 12 hours for 5 days</td><td>Ni3=100<br><br>IVM + SoC<br><br>4 days course of IVM 400 microgram/kg body weight maximum 4 tablets (6mg / tablet) once daily dose</td><td>Ni4=100<br><br>HCQ + SoC<br><br>HCQ 400 mg every 12 hours for one day followed by 200 mg every 12 hours for 9 days</td><td>Ni5=100<br><br>IVM + PPE<br><br>IVM400 microgram s/kg single oral dose before breakfast to be repeated after one week</td><td>Ni6=100<br><br>PPE only</td><td rowspan="11">– Pre-print,<br>– No information on blinding</td></tr>
<tr><td colspan="4"><u>SoC including:</u><br>• Azithromycin 500mg OD for 6 days,<br>• Paracetamol 500mg PRN,<br>• Vitamin C 1gm OD,<br>• Zinc 50 mg OD,<br>• Lactoferrin 100mg sachets BID & Acetylcystein 200mg t.d.s<br>• prophylactic or therapeutic anticoagulation if D-dimer > 1000</td><td>-</td><td>-</td></tr>
<tr><td colspan="2">Stage of disease</td><td colspan="2">mild/moderate</td><td colspan="2">severe</td><td colspan="2">NA</td></tr>
<tr><td colspan="2">Age (years), mean±SD</td><td>56.7±18.4</td><td>53.8±21.3</td><td>58.2±20.9</td><td>59.6±18.2</td><td>57.6±18.4</td><td>56.8±18.2</td></tr>
<tr><td colspan="2">Male, %</td><td>72</td><td>67</td><td>68</td><td>74</td><td>75</td><td>72</td></tr>
<tr><td rowspan="4">Comorbidities, %</td><td>Diabetes</td><td>15</td><td>14</td><td>18</td><td>21</td><td>15</td><td>19</td></tr>
<tr><td>Hypertension</td><td>11</td><td>12</td><td>14</td><td>18</td><td>15</td><td>14</td></tr>
<tr><td>IHD</td><td>2</td><td>6</td><td>5</td><td>12</td><td>1</td><td>3</td></tr>
<tr><td>Bronchial asthma</td><td>5</td><td>6</td><td>14</td><td>12</td><td>5</td><td>4</td></tr>
<tr><td colspan="2">Fatigue, dyspnea,%</td><td>54</td><td>52</td><td>86</td><td>88</td><td colspan="2">NA</td></tr>
<tr><td colspan="2">Respiratory failure, %</td><td>0</td><td>0</td><td>38</td><td>40</td><td colspan="2">NA</td></tr>
</table>

| Elgazzar 2020 | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Results** | | | | | | | | | | | | |
| **Outcome** | | | **Group 1** IVM + SoC Mild-moderate | **Group 2** HCQ + SoC Mild-moderate | **Group 3** IVM + SoC Severe | **Group 4** HCQ + SoC Severe | **Group 5** IVM + PPE | **Group 6** PPE | **Statistical variability of differences** | | | |
| **event** | | **follow-up period (days)** | | | | | | | **Relative parameter (95% CI) / p** | | **Absolute parameter** | |
| **TREATMENT RESULTS** | | | | | | | | | | | | |
| **IVM + SoC vs HCQ + SoC** | | | | | | | | | G1 vs G2 | G3 vs G4 | G1 vs G2 | G3 vs G4 |
| Laboratory investigations**, mean ±SD | Hgb (gm/dL) | 7 | 14.2 ± 1.8 | 14.8 ± 2.7 | 13.8 ± 1.2 | 12.6 ± 1.9 | NA | NA | 0.07 | <0.001 | - | - |
| | TLC (X 103/ mL) | | 6.4±2.1 | 7.1±2.3 | 8.9±2.4 | 14.2±3.8 | | | <0.05 | <0.001 | - | |
| | Lymphocyte (%) | | 32.4 ± 6.8 | 28.2 ± 3.9 | 34 ± 6.7 | 24.6 ± 5.8 | | | <0.001 | <0.001 | - | |
| | CRP (mg/l) | | 4.8 ± 2.1 | 8.3 ± 3.6 | 28.6 ± 9.4 | 58.6 ± 24.4 | | | <0.001 | <0.001 | - | |
| | Serum ferritin (ng/ml) | | 94.8 ± 4 | 98.4 ± 54.8 | 104 ± 19.6 | 294 ± 78.6 | | | 0.62 | <0.001 | - | - |
| | D dimer (mg/l) | | 0.54 ± 0.06 | 0.68 ± 0.21 | 0.72 ± 0.12 | 1.86 ± 0.6 | | | <0.001 | <0.001 | - | - |
| | RT-PCR conversion (days) | | 5 ±1 | 10 ± 4 | 6 ± 1 | 12 ± 4 | | | <0.001 | <0.001 | - | - |
| Prognosis##, no. | Improved | 4 | 99 | 74 | 94 | 50 | NA | NA | ^RR=1.34 (1.19; 1.50) | ^RR=1.88 (1.54; 2.30) | ^NNT=4 (3; 6.2) | ^NNT=3 (1.8; 3) |
| | Progressed | | 1 | 22 | 4 | 30 | | | ^RR=0.05 (0.01; 0.33) | ^RR=0.13 (0.05; 0.36) | ^NNT=5 (3.4; 7.9) | ^NNT=4 (2.8; 6.2) |
| | Died | | 0 | 4 | 2 | 20 | | | ^RR=0.11 (0.01; 2.04) | ^RR=0.10 (0.02; 0.42) | - | ^NNT=6 (3.8; 10.3) |
| Hospital stay days | Range | 4 | 4-6 | 6-31 | 4-7 | 9-25 | | | <0.001# | | - | |
| | Mean±SD | | 5 ± 1 | 15 ± 8 | 6 ± 1 | 18 ± 8 | | | | | | |
| **PROPHYLAXIS RESULTS** | | | | | | | | | | | | |
| **IVM + PPE vs PPE** | | | | | | | | | G5 vs G6 | | | |
| Confirmed infected subjects by RT-PCR, no. (%) | | ND | NA | | | | 2 (2) | 10 (10) | <0.05 ^RR=0.20 (0.04; 0.89) | | ^NNT=13 (6.9; 66.2) | |
| **Authors' conclusions: Addition of Ivermectin to standard care is very effective drug for treatment of COVID-19 patients with significant reduction in mortality compared to Hydroxychloroquine plus standard treatment only. Early use of Ivermectin is very useful for controlling COVID 19 infections; prophylaxis and improving cytokines storm.** | | | | | | | | | | | | |

SD – standard deviation; NA – not applicable; IVM – ivermectin; ND – no data; PPE – personal protective equipment; IHD - ischemic heart disease; HCQ – hydroxychloroquine; RR – risk ratio

* **Mild cases**: Patients have mild symptoms such as anosmia, loss of taste, fever or respiratory tract symptoms, gastrointestinal symptoms, etc. and free chest imaging; **Moderate Cases:** Patients have symptoms such as fever, respiratory tract symptoms, gastrointestinal symptoms, etc. and pneumonia manifestations can be seen in chest imaging; **Severe COVID-19 confirmed cases**, fulfilling any of the following criteria:
1. Respiratory rate more than 30/min; 2. Blood oxygen saturation of less than 93%; 3. PaO2/FiO2 ratio of less than 200; 4. Lung infiltrates >50% of the lung fields or rapid progression within 24-48 hours; 5. Patients need respiratory support e.g. high flow oxygen noninvasive or invasive mechanical ventilation.

** Laboratory investigations improvement and/or 2 consecutive negative PCR tests taken at least 48 hours apart

^Agency's own calculations; # Chi-square test; ##There was a highly statistically significant improvement associated with significant reduction in mortality, recovery time, and hospital stay days in groups received Ivermectin ( I & III) compared to those received Hydroxychloroquine ( II & IV) (p-value <0.001, Chi-square test).

**Tabela 19. Opis metodyki i wyników badania Niae 2020 – leczenie**

| Niae 2020 | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Ivermectin as an adjunct treatment for hospitalized adult COVID-19 patients: A randomized multi-center clinical trial (Research Square, 24.11.2020)** | | | | | | | | |
| **Methodology** | **Population** | | **Arm 1** | **Arm 2** | **Arm 3** | **Arm 4** | **Control 1** | **Control 2** | **Limitations** |
| Randomized, multicenter double-blind, placebo-controlled, phase 2<br><br>Randomization 1:1:1:1:1:1<br><br>Duration of the study: 45 days<br><br>Iran | N=180<br>Hospitalized adults with mild to severe COVID-19.<br><br>Inclusion criteria: age >18 years; signed the informed consent; clinical symptoms of suggestive of COVID-19 pneumonia: cough (with or without sputum), fever, pleuritic chest pain or dyspnea; mild to severe COVID-19 disease confirmed by chest computed tomography (CT) scan findings compatible with COVID-19 or positive real-time reverse transcription polymerase chain reaction (RT-PCR).<br>Exclusion criteria: presence of severe immunosuppression (e.g., use of immune-suppressants and HIV positive), pregnant women, chronic kidney disease, malignancy, and indications that the patients were unable and/or unlikely to comprehend and/or follow the protocol. | | Ni1=30<br>(FAS n=30)<br><br>Ivermectin, single dose (200 mcg/kg) | Ni2=30<br>(FAS n=27)<br><br>Ivermectin, three doses (200 mcg/kg) | Ni3=30<br>(FAS n=30)<br><br>Ivermectin, single dose (400 mcg/kg) | Ni4=30<br>(FAS n=29)<br><br>Ivermectin, three doses (400, 200, 200 mcg/kg) | Nc1=30<br>(FAS n=25)<br><br>Common regimen (Hydroxychloroquine 200mg/kg twice per day) | Nc2=30<br>(FAS n=24)<br><br>Placebo + common regimen (Hydroxychloroquine 200mg/kg twice per day) | – No detailed results for all comparisons;<br>– Small samples;<br>– Pre-print |
| | Age [IQR] – yr | | 61 [42-68] | 53 [42-65] | 54 [47-60] | 54 [46-65] | 55 [45-70] | 58 [45-68] | |
| | Female sex – n (%) | | 18 (60) | 11 (36.7) | 14 (46.7) | 17 (56.7) | 14 (46.7) | 16 (53.3) | |
| | Severity on CT – % | negative | 0 | 2 (6.7) | 0 | 0 | 0 | 0 | |
| | | mild | 26.7 | 6.7 | 13.3 | 6.7 | 13.3 | 16.7 | |
| | | mode | 70.0 | 66.7 | 70.0 | 76.7 | 76.7 | 76.7 | |
| | | severe | 3.3 | 20.0 | 16.7 | 16.7 | 10.0 | 6.7 | |

| **Results** | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Outcome** | | | **Arm 1** | **Arm 2** | **Arm 3** | **Arm 4** | **Control 1** | **Control 2** | **Statistical significance of differences** | |
| **event** | | **follow-up period** | | | | | | | **Relative parameter, RR (95%CI) / p*** | **Absolute parameter, (95%CI)** |
| Duration on hospital stay – days [IQR] | | 45 days | 6 [5-7] | 8 [6-9] | 5 [4-7] | 7 [6-10] | 7 [7-9] | 8 [6-11] | **p=0.006** | - |
| Duration of low $O_2$ saturation – days [IQR] | | | 2 [1 - 2] | 3 [2 - 5] | 2 [1 - 4] | 5 [3 - 6] | 3 [2-5] | 4 [2 - 6] | **p=0.025** | - |
| Tachypnea Off – days [IQR] | | | 2 [1 - 3] | 3 [2 - 4] | 3 [3 - 5] | 3 [3 - 5] | 2 [2 - 3] | 3 [2 - 4] | p=0.584 | - |
| Fever Off – days [IQR] | | | 0 [0 - 1] | 0 [0 - 1] | [1 - 1] | 1 [0 - 2] | 0 [0 - 1] | 0 [0 - 1] | p=0.102 | - |
| Death | | | 0 | 3 (10) | 0 | 1 (3.3) | 5 (16.7) | 6 (20) | **p=0.001** | - |
| Risk of mortality | | | 3.3% | | | | 18.3% | | **0.18 (0.06; 0.55)** | **^NNT=7 (4; 22)** |
| **Author's conclusion: Ivermectin as an adjunct reduced the rate of mortality, low $O_2$ duration, and duration of hospitalization in adult COVID 19 patients. The improvement of other clinical parameters showed that the ivermectin, with a wide margin of safety, had a high therapeutic effect on COVID-19.** | | | | | | | | | | |

* Ivermectin arms vs control arms; ^Agency's own calculations

**Tabela 20. Opis metodyki i wyników badania Babalola 2021 – leczenie**

| Babalola 2021 | | | | | | |
|---|---|---|---|---|---|---|
| **Ivermectin shows clinical benefits in mild to moderate COVID19: A randomised controlled double blind dose response study in Lagos (QJM, 18.02.2021)** | | | | | | |
| **Methodology** | **Population** | | **Intervention 1** | **Intervention 2** | **Control** | **Limitations** |
| A proof of concept (PoC), double blind, randomized controlled trial, of a parallel group, dose-response design<br><br>Study duration: May and November 2020<br><br>Nigeria | N=63 (n=62 completed the study)<br><br>Inclusion criteria: COVID 19 PCR proven positive patients, who gave informed, written consent to participate in the study, and were either asymptomatic or had mild/moderate symptoms<br>Exclusion criteria: COVID 19 negative patients, patients who had COVID pneumonia or requiring ventilator therapy, renal failure, thromboembolic complications, or unconscious by reduced Glasgow Coma Scale | | Ni2=21<br><br>Ivermectin 6mg (given every 84 hours) twice a week | Ni2=21<br><br>Ivermectin 12mg (given every 84 hours) for 2 weeks | Nc=20<br><br>Lopinavir / ritonavir daily for 2 weeks | – Slight differences in the baseline Cycle threshold (Ct) values, being lower in the A arm than the other two arms with regards to the ORF and N genes, but similar for the EN gene. |
| | Age (years), mean | | 48.3 | 39.7 | 44.8 | |
| | Male, no. | | 15 | 14 | 14 | |
| | Symptoms | Fever | 30% | 42.8% | 20% | |
| | | Headache | 50% | 57% | 25% | |
| | | Cough | 30% | 19% | 45% | |
| | | Dyspnea | 20% | 23% | 10% | |
| | Comorbidities, no. | Hypertension | 2 | 2 | 5 | |
| | | Diabetes | 1 | 1 | 0 | |
| | SpO2, % | | 97.5 | 96.8 | 95.8 | |
| | Medication, no. | Dexamethasone | 1 | 1 | 2 | |
| | | Zinc | 16 | 17 | 18 | |
| | | Supplemental oxygen use | 0 | 3 | 2 | |
| | | Enoxaparine | 2 | 1 | 1 | |

| **Results** | | | | | | |
|---|---|---|---|---|---|---|
| **Outcome** | | **Intervention 1 (IVM1)** | **Intervention 2 (IVM2)** | **Control (C)** | **Statistical variability of differences** | |
| **event** | **follow-up period (days)** | | | | **Relative parameter (95% CI) / p** | **Absolute parameter (95% CI)** |
| Time to SARS-CoV-2 negativity, mean days (SD) | NA | 6.0 (2.96) | 4.65 (3.2) | 9.15 (7.42) | **IVM1 vs IVM2: p=0.0179** | - |
| | | 5.33 | | | **p=0.0066** | - |
| Time sequence of days to negativity | NA | ND | ND | ND | IVM1 vs C: HR=1.68 (0.87; 3.25) | - |
| | | ND | ND | ND | **IVM2 vs C: HR=2.38 (1.22; 4.65)** | **-** |
| | | ND | ND | ND | **IVM vs C: HR=1.96 (1.09; 3.51)** | **-** |
| Platelet count (000/ml), change (Day 7-Baseline) | 7 | 20.05 | | -64.00 | **-** | **MD=84.06 (5.56; 162.55)** |
| **Authors' conclusions: 12 mg IV regime may have superior efficacy. IV should be considered for use in clinical management of SARS-Cov-2, and may find applications in community prophylaxis in high-risk areas.** | | | | | | |

SD – standard deviation; NA – not applicable; IVM – ivermectin; MD – mean difference; ND – no data

**Tabela 21. Opis metodyki i wyników badania Shouman 2020 – profilaktyka**

| Shouman 2020 | | | | |
|---|---|---|---|---|
| **Use of Ivermectin as a Prophylactic Option in Asymptomatic Family Close Contact for Patient With COVID-19 (ClinicalTrials, NCT04422561, 27.08.2021)[3]** | | | | |
| **Methodology** | **Population** | **Intervention** | **Control** | **Limitations** |
| Open-label randomised study, phase 2/3<br><br>Intervention Model: Sequential Assignment<br><br>Actual Study Start Date: May 31, 2020<br><br>Egypt | N=340 (Actual Enrollment; submitted: August 23, 2020)<br>N=304 (number analyzed)<br><br>Inclusion criteria: age more than 16 years, Asymptomatic household close contacts<br>Exclusion criteria: people previously treated for COVID-19, asymptomatic contacts with who have HRCT chest done and suggestive for COVID-19 infection | Ni=228 (started)<br>N=203 (completed)<br><br>Prophylactic ivermectin (tablets), two doses 72 hours apart<br>40-60 kg – 15mg/day,<br>60-80kg – 18mg/day<br>>80kg – 24mg/day | Nc=112 (started)<br>N=101 (completed)<br><br>No intervention;<br>Contacts who will be only observed without prophylaxis | – No publication provided,<br>– No blinding;<br>– No detailed baseline characteristics,<br>– Outcome measure data not reported for secondary outcome: Development of COVID within 14 days after enrollment. |
| | Age, years, mean (SD) | 39.75 (14.93) | 37.69 (16.95) | |
| | Male, no. (%) | 106 (52.2) | 50 (49.5) | |

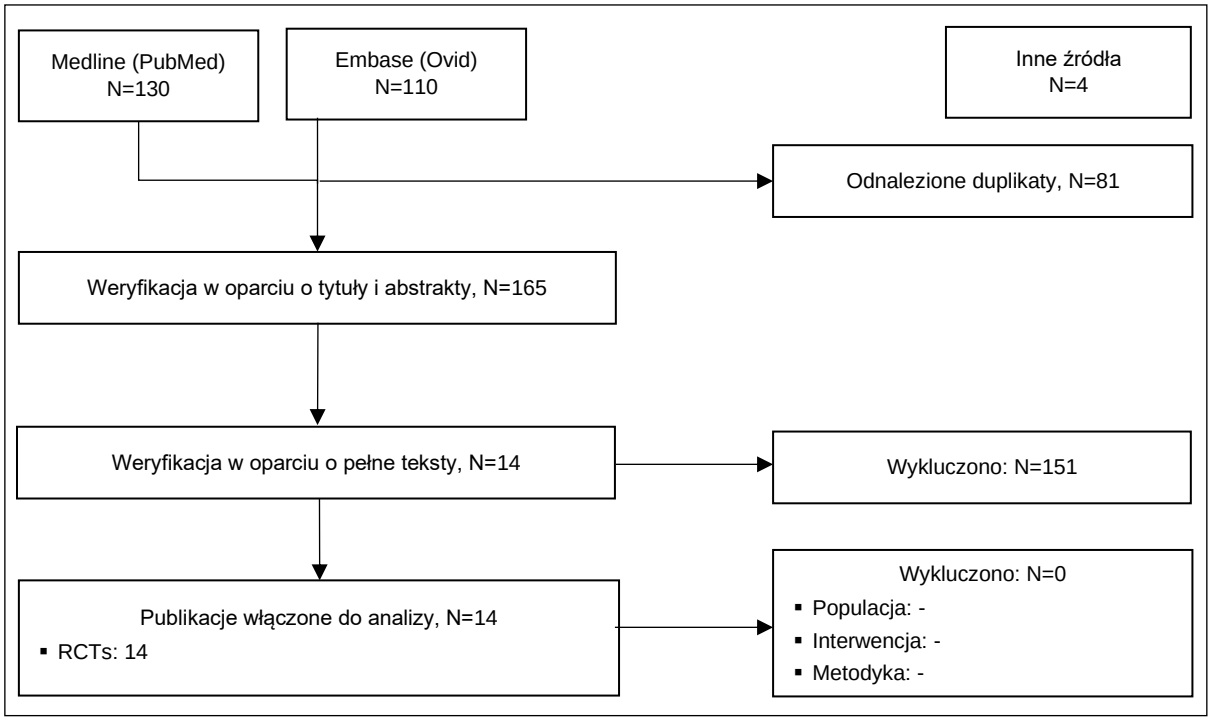
| **Results** | | | | | |
|---|---|---|---|---|---|
| **Outcome** | | **Intervention** | **Control** | **Statistical variability of differences** | |
| **event** | **follow-up period (days)** | | | **Relative parameter (95% CI) / p** | **Absolute parameter (95% CI)** |
| Development of Symptoms*, no. (%) | 14 | 15/203 (7.4) | 59/101 (58.4) | **^RR=0.13 (0.08; 0.21)** | **^NNT=2 (1.6; 2.5)** |
| All-Cause Mortality, n/N (%) | 14 | 0/203 (0) | 0/101 (0) | NA | - |
| Serious Adverse Events, n/N (%) | | 0/203 (0) | 0/101 (0) | NA | - |
| Total adverse events, n/N (%) | | 11/203 (5.42) | 0/101 (0) | ^RR=11.50 (0.68; 193.21) | - |
| Nausea, n/N (%) | | 2/203 (0.99) | 0/101 (0) | - | - |
| Diarrhea, n/N (%) | | 3/203 (1.48) | 0/101 (0) | - | - |
| Burning sensation, n/N (%) | | 1/203 (0.49) | 0/101 (0) | - | - |
| Heart burn, n/N (%) | | 1/203 (0.49) | 0/101 (0) | - | - |
| Abdominal pain, n/N (%) | | 1/203 (0.49) | 0/101 (0) | - | - |
| Fatigue, n/N (%) | | 2/203 (0.99) | 0/101 (0) | - | - |
| Tingling/numbness, n/N (%) | | 1/203 (0.49) | 0/101 (0) | - | - |
| Sleepiness, n/N (%) | | 1/203 (0.49) | 0/101 (0) | - | - |
| **Authors' conclusions: –** | | | | | |

*Symptoms: fever, cough, sore throat, myalgia, diarrhea, shortness of breath; ^ Agency's own calculations
SD – standard deviation; NA – not applicable; RR – risk ratio

[3] https://clinicaltrials.gov/ct2/show/NCT04422561 [access: 19/01/2021]

**Tabela 22. Strategie wyszukiwania w PubMed i Embase**

| **Bazy informacji medycznej** |
|---|
| **Pubmed (data wyszukiwania 28.01.2021)** |
| ((((ivermectin AND (("severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "COVID-19"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2" OR COVID-19 OR "COVID 19" OR COVID19 OR SARS-CoV-2 OR "SARS CoV 2" OR "SARS-CoV 2" OR "SARSCoV 2" OR "SARS CoV-2" OR "SARS CoV2" OR SARS-CoV2 OR SARSCoV-2 OR SARSCoV-2 OR SARS2 OR "SARS 2" OR SARS-2 OR 2019-nCoV OR "2019 nCoV" OR 2019nCoV OR "2019 novel coronavirus" OR "coronavirus disease 2019" OR "coronavirus disease-19" OR "novel coronavirus pneumonia" OR "novel coronavirus disease" OR "novel coronavirus infected disease" OR "novel coronavirus infection pneumonia" OR "novel coronavirus infected pneumonia" OR "new coronovirus disease" OR "new coronavirus infected disease" OR "new coronavirus infection pneumonia" OR "new coronavirus infected pneumonia" OR "Wuhan coronavirus" OR "Wuhan seafood market pneumonia virus" OR "2019-novel coronavirus" OR "2019 new coronavirus" OR "2019-new coronavirus" OR "coronavirus disease-2019" OR SARSCoV2 OR SARSCoV2)) |
| **Embase (data wyszukiwania: 28.01.2021)** |
| ivermectin.ti,ab. and ("severe acute respiratory syndrome coronavirus 2" or COVID-19 or "COVID 19" or COVID19 or SARS-CoV-2 or "SARS CoV 2" or "SARS-CoV 2" or "SARSCoV 2" or "SARS CoV-2" or "SARS CoV2" or SARS-CoV2 or SARSCoV-2 or SARS2 or "SARS 2" or SARS-2 or 2019-nCoV or "2019 nCoV" or "nCoV 2019" or "nCoV-2019" or 2019nCoV or "2019 novel coronavirus" or "coronavirus disease 2019" or "coronavirus disease-19" or "novel coronavirus pneumonia" or "novel coronavirus disease" or "novel coronavirus infected pneumonia" or "Wuhan coronavirus" or "Wuhan seafood market pneumonia virus" or "2019-novel coronavirus" or "2019 new coronavirus" or "2019-new coronavirus" or "coronavirus disease-2019" or SARSCoV2).ti. |




**Rysunek 4. Proces selekcji doniesień, zgodnie z zaleceniami PRISMA (daty wyszukiwania: 28.01.2021)**

## Aneks 2 (wersja 1.1)

**Tabela 23. Opis metodyki i wyników badania Lopez-Medina 2021 – leczenie**

| López-Medina 2021 | | | | | |
|---|---|---|---|---|---|
| **Effect of Ivermectin on Time to Resolution of Symptoms Among Adults With Mild COVID-19 - A Randomized Clinical Trial (JAMA, 4.03.2021)** | | | | | |
| **Methodology** | **Population** | | **Intervention** | **Control** | **Limitations** |
| Single-center, randomized (1:1), double-blind, placebo controlled, phase 2/3<br><br>Colombia<br><br>Study duration: 15.07 – 21.12.2020 | N=476 patients – randomized; 398 – included in primary analysis<br><br>Inclusion criteria: adult men and non–pregnant or breast-feeding women over 18 years of age; SARS CoV2 / COVID 19 disease confirmed by RT-PCR in any of the laboratories that report to the Departmental Health Secretary, approved for the diagnosis of COVID-19 by the National Institute of Health; onset of symptoms began within the previous 7 days and they had mild disease, defined as being at home or hospitalized but not receiving high-flow nasal oxygen or mechanical ventilation (invasive or non-invasive).<br>Exclusion criteria: medical history of liver disease; history of allergy to ivermectin or any of its components; belonging to another clinical trial that evaluates the efficacy of an investigational drug against COVID-19. The use of other treatments outside of clinical trials is allowed; patients who were asymptomatic; severe pneumonia; received ivermectin within the previous 5 days; subjects receiving Warfarin, erdafitinib, or quinidine; hepatic dysfunction or liver function test results more than 1.5 times the normal level. | | Ni=238 – randomized; 200 – included in primary analysis<br><br>Ivermectin 300 mcg/kg/d for 5 days | Nc= 238 – randomized; 198 – included in primary analysis<br><br>Placebo for 5 days | – the study was not conducted or completed according to the original design, and the original primary outcome to detect the ability of ivermectin to prevent clinical deterioration was changed 6 weeks into the trial;<br>– the placebo used in the first 65 patients differed in taste and smell from ivermectin. However, patients from the same household were not included until the placebo with the same organoleptic properties was available, and the lack of effect of ivermectin on the primary outcome was similar when compared with either formulation of placebo;<br>– the study population was relatively young and results may differ in an older population |
| | Age, median (IQR), years | | 37 (29-47.7) | 37 (28.7-49.2) | |
| | Female (%) | | 61 | 55 | |
| | Race or ethnic group (%) | Mixed race[#] | 89,0 | 90,4 | |
| | | Black or African American | 8,0 | 8,1 | |
| | | Colombian native | 3,0 | 1,5 | |
| | Coexisting conditions (%) | Obesity (BMI ≥30) | 18,5 | 19,4 | |
| | | Hypertension | 14,0 | 12,6 | |
| | | Diabetes | 5,0 | 6,1 | |
| | | Thyroid disease | 3,5 | 4,0 | |
| | | Respiratory disease | 3,0 | 3,0 | |
| | | Cardiovascular disease | 2,0 | 1,5 | |
| | | Any coexisting condition | 22,0 | 19,2 | |
| | Medications initiated since symptom onset | NSAIDs | 28,5 | 30,8 | |
| | | Other[##] | 20,5 | 19,2 | |
| | | Macrolides | 13,5 | 11,1 | |
| | | Other antipyretics | 13,0 | 11,6 | |
| | | Nonmacrolide antibiotics | 6,5 | 5,6 | |
| | | Glucucorticoids | 3,0 | 6,1 | |
| | | Other immunomodulating agents | 2,0 | 1,0 | |
| | | Anticoagulants | 0,5 | 3,5 | |

| López-Medina 2021 | | | | | |
|---|---|---|---|---|---|
| | Median time (IQR) from symptom onset to randomization, days | 5 (4-6) | 5 (4-6) | | |
| **Results** | | | | | |
| **Outcome** | | **Ivermectin** | **Placebo** | **Statistical significance of differences** | |
| **event** | **follow-up period** | | | **Relative parameter (95%CI) / p** | **Absolute difference** |
| Time to resolution of symptoms (days), median (IQR) | 21 days | 10 (9-13) | 12 (9-13) | HR=1,07 (0,87; 1,32) | −2 (−4; 2) |
| Symptoms resolved, n/N (%) | | 164/200 (82,0) | 156/198 (79,0) | OR=1,23 (0,75; 2,01) | 3,21 (−4,58; 11,01) |
| Deterioration by ≥2 points in an ordinal 8-point scale** | | 4/200 (2,0) | 7/198 (3,5) | OR=0,56 (0,16; 1,93) | −1,53 (−4,75; 1,69) |
| Fever (≥38 °C) since randomization, n/N (%) | | 16/200 (8,0) | 21/198 (10,6) | OR=0,73 (0,37; 1,45) | −2,61 (−8,31; 3,09) |
| Escalation of care since randomization***, n/N (%) | | 4/200 (2,0) | 10/198 (5.0) | OR=0,38 (0,12; 1,24) | −3,05 (−6,67; 0,56) |
| Duration of care (days), median (IQR) | | 13 (3,5-21) | 6 (3,7-10,7) | - | 7 (−5; 16,5) |
| Deaths | | 0/200 (9) | 1/198 (0,5) | - | - |
| Adverse events, n/N (%) | | 154/200 (77) | 161/198 (81,3) | RR=0,95 (0,86; 1,05)^ | - |
| Serious adverse events, n/N (%) | | 2/200 (1) | 2/198 (1,1) | RR=0,99 (0,14; 6,96)^ | - |
| Discontinuation of treatment due to AE, n/N (%) | | 15/200 (7,5) | 5/198 (2,5) | RR=2,97 (1,1; 8,02)^ | NNT=21 (11; 141)^ |
| **Post-hoc analysis** | | | | | |
| Escalation of care occurring ≥12 h since randomization | 21 days | 4/200 (2,0) | 6/198 (3,0) | OR=0,65 (0,18; 2,36) | −1,0 (−4,11; 2,05) |
| Duration of care (days), median (IQR) | | 13 (3,5-21) | 8 (4,2-13,2) | - | 5 (−8,5; 16) |
| Emergency department visits or telemedicine consultations, n/N (%) | | 16/200 (8,0) | 13/198 (6,6) | OR=1,24 (0,56; 2,74) | 1,43 (−3,67; 6,54) |
| **Author's conclusion: Among adults with mild COVID-19, a 5-day course of ivermectin, compared with placebo, did not significantly improve the time to resolution of symptoms. The findings do not support the use of ivermectin for treatment of mild COVID-19, although larger trials may be needed to understand the effects of ivermectin on other clinically relevant outcomes.** | | | | | |

# refers to an individual of mixed European/Colombian native heritage; ## Acyclovir, antidiarrheals, antiemetics, antihistamines, antiparasitics, antispasmodics, antitussives, natural or homeopathic medications, proton pump inhibitors, and salbutamol

*defined as the first day during the 21 days of follow-up in which the patient reported a score of 0.; **Ordinal scale: 0 = no clinical evidence of infection; 1 = not hospitalized and no limitation of activities; 2 = not hospitalized, with limitation of activities, home oxygen requirement, or both; 3 = hospitalized, not requiring supplemental oxygen; 4 = hospitalized, requiring supplemental oxygen; 5 = hospitalized, requiring nasal high-flow oxygen, noninvasive mechanical ventilation, or both; 6 = hospitalized, requiring extracorporeal membrane oxygenation, invasive mechanical ventilation, or both; and 7 = death; ***Escalation of care defined as new-onset hospitalization in the general ward or intensive care unit or new-onset supplementary oxygen requirement for more than 24 hours.

^Agency's own calculation

**Tabela 24. Opis metodyki i wyników badania Mohan 2021 – leczenie**

| Mohan 2021 | | | | | | |
|---|---|---|---|---|---|---|
| **Ivermectin in mild and moderate COVID-19 (RIVETCOV): a randomized, placebo-controlled trial (ResearchSquare, 02/02/2021)** | | | | | | |
| **Methodology** | **Population** | | **Intervention 1** | **Intervention 2** | **Control** | **Limitations** |
| Randomized, double-blind, placebo-controlled<br><br>India<br><br>Randomization 1:1:1<br><br>Duration of the study: no data | N=157 (125 patients were included in mITT analysis)<br>Adults with mild to moderate COVID-19.<br><br>Inclusion criteria: age >18 years; diagnosed (based on a positive result on either SARS-CoV-2 reverse transcription-polymerase chain reaction (RT-PCR) or the rapid antigen test); non-severe COVID-19 (i.e. room air saturation (SpO2) >90%, no hypote.<br>Exclusion criteria: pregnancy or lactation; known hypersensitivity to ivermectin; chronic kidney disease with creatinine clearance <30 mL/min; elevated transaminase levels (>5 x upper limit of normal); myocardial infarction or heart failure within 90 days prior to enrolment, prolonged corrected QT interval (>450 ms) on electrocardiogram; any other severe comorbidity as per investigator's assessment, no informed consent. | | Ni1=40<br><br>Oral ivermectin (12 mg single dose) | Ni2=40<br><br>Oral ivermectin (24 mg single dose) | Ni3=45<br><br>placebo | – Modified intention-to-treat analysis<br>– Single center study with a relatively small sample size |
| | Mean age ± SD – yr | | 36.3 | 34.3 | 35.3 | |
| | Male sex – % | | 87.5 | 92.5 | 86.2 | |
| | Severity – % | Mild | 67.5 | 60 | 64.4 | |
| | | Moderate | 32.5 | 40 | 35.6 | |
| | WHO Ordinal Scale at baseline – % | 3 | 87.5 | 95 | 93.3 | |
| | | 4 | 12.5 | 5 | 6.7 | |
| | Asymptomatic at the time of enrolment (%) | | 27.5 | 22.5 | 17.7 | |
| | Duration of symptoms prior to enrolment (days), median (IQR) | | 5 (3-7) | 4 (3-7) | 4 (3-6) | |

| **Results** | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Outcome** | | | **Intervention 1** | **Intervention 2** | **Control** | **Statistical significance of differences** | |
| **event** | | **follow-up period** | | | | **Relative parameter (95%CI) / p** | **Absolute difference** |
| Negative RT-PCR in mITT population | | Day 3 | 7/40 (17.5) | 3/40 (7.5) | 7/45 (15.6) | p= 0.42 | - |
| | | Day 5 | 14/40 (35) | 19/40 (47.5) | 14/45 (31.1) | p= 0.30 | - |
| | | Day 7 | 13/36 (36.1) | 16/36 (44.4) | 16/42 (38.1) | p= 0.79 | - |
| Days to symptom resolution#, mean (SD) | | | 4.76 (2.44) | 4.26 (2.65) | 4.58 (2.94) | p= 0.77 | - |
| Change in WHO Ordinal Scale score between daily 0-14, n (%) | No change | Day 14 | 3 (7.5) | 2 (5) | 5 (11.1) | p= 0.67 | - |
| | Decrease by 1 | | 0 | 1 (2.5) | 1 (2.2) | | |
| | Decrease by 2 | | 32 (80) | 35 (87.5) | 37 (82.2) | | |
| | Decrease by 3 | | 5 (12.5) | 2 (5) | 2 (4.4) | | |
| Discharge – n/N (%) | | Day 14 | 38/40 (95) | 37/40 (92.5) | 39/45 (86.7) | p= 0.42 | - |
| Any clinical worsening ## | | | 2 (5) | 3 (7.5) | 5 (11.1) | p= 0.65 | - |
| Adverse events – n/N (%) | | | 8 (16.3) | 6 (11.8) | 6 (11.5) | p = 0.76 | - |
| Serious adverse events – n/N (%) | | | 0 | 0 | 0 | - | - |
| Death – n | | | 0 | 0 | 0 | - | - |
| **Author's conclusion: In patients with mild and moderate COVID-19, a single administration of Ivermectin elixir (either 24 mg or 12 mg) demonstrated a trend towards higher proportion of RT-PCR negativity at day 5 of enrolment.** | | | | | | | |

**Tabela 25. Opis metodyki i wyników badania Beltran-Gonzalez 2021 – leczenie**

| Beltran-Gonzalez 2021 | | | | | | |
|---|---|---|---|---|---|---|
| **Efficacy and safety of Ivermectin and Hydroxychloroquine in patients with severe COVID-19. A randomized controlled trial (Preprint; MedRxiv, 23.02.2021); NCT04391127** | | | | | | |
| **Methodology** | **Population** | | **Intervention 1** | **Intervention 2** | **Control** | **Limitations** |
| RCT, double-blind<br><br>Patients with QT interval ≥ 500 ms randomized to IVM or PLB, patients with an interval < 500 ms to IVM, HCQ or PLB<br><br>Country: Mexico | N=106<br>Non-critically ill patients with pneumonia secondary to COVID-19 and fulfilling hospitalization criteria<br><u>Inclusion criteria:</u><br>– positive RT-PCR for SARS-CoV-2 by nasal and oropharyngeal swabbing<br>– pneumonia, diagnosed by X-ray or HR-CT<br>– recently established hypoxemic respiratory failure or acute clinical deterioration of pre-existing lung or heart<br><u>Exclusion criteria:</u><br>– required high oxygen volumes (face mask >10 L/ min)<br>– predictors of a poor response to high-flow oxygen nasal prong therapy<br>– required mechanical ventilation | | Ni1=36<br>Ivermectin (IVM)<br><br>12 mg (if body mass <80kg) or 18 mg (if body mass >80 kg) | Ni2=33<br>Hydroxychloroquine (HCQ)<br><br>400 mg every 12h on the first day and subsequently, 200 mg every 12h for 4 days | Nc=37<br>Placebo (calcium citrate)<br><br>2 tablets every 12h on day 1, then 1 tablet every 12h for 4 days | – Limited number of patients per group;<br>– Pre-print status of publication;<br>– No data on follow-up period |
| | | | • All hospitalized patients received thromboprophylaxis with low molecular weight heparin or unfractionated heparin.<br>• Dexamethasone, 6 mg IV every 24h, for 10 days or until discharge, in patients requiring oxygen therapy | | | |
| | Age [years] mean (±SD) | | 56 (16.5) | 48.9 (15.3) | 53.8 (16.9) | |
| | Male, % | | 58.3 | 66.6 | 62.1 | |
| | $SatO_2$, mean (±SD) | | 83 (8) | 86 (9) | 83 (8) | |
| | Concomitant medications, % | Antibiotics | 61.1 | 45.4 | 50 | |
| | | Thromboprophylaxis | 100 | 90.9 | 94.5 | |
| | | Steroids | 58.3 | 63.6 | 51.3 | |
| | Comorbidities, % | Hypertension | 33.3 | 24.2 | 37.8 | |
| | | Chronic kidney disease | 5.5 | 6.1 | 2.7 | |
| | | COPD | 5.5 | 3 | 10.8 | |
| | | Diabetes Mellitus | 25 | 33.3 | 43.2 | |

| **Results** | | | | | | |
|---|---|---|---|---|---|---|
| **Outcome** | | **IVM** | **HCQ** | **PLB** | **Statistical variability of differences** | |
| **event** | **follow-up period (days)** | | | | **relative parameter* (95% CI)/p** | **absolute parameter** |
| Death, n/N (%) | ND | 5/36 (13.8) | 2/33 (6) | 6/37 (16.2) | <u>IVM vs PLB:</u><br>^RR=0.86 (0.29; 2.56)<br><u>IVM vs HCQ:</u><br>^RR=0.98 (0.84; 1.15) | - |
| Duration of hospitalization [days], med (IQR) | NA | 6 (4–11) | 7 (3–9) | 5 (4–7) | p=0.43 | - |
| Hospital discharge, n/N (%) | ND | 32/36 (88.8) | 30/33 (90.9) | 34/37 (91.8) | <u>IVM vs PLB:</u><br>^RR=0.97 (0.83; 1.12)<br><u>IVM vs HCQ:</u><br>^RR=0.98 (0.84; 1.15) | - |
| Discharge without respiratory deterioration or death, n/N (%) | | 27/36 (75) | 26/33 (78.7) | 27/37 (72.9) | <u>IVM vs PLB:</u><br>^RR=1.03 (0.78; 1.35)<br><u>IVM vs HCQ:</u><br>^RR=0.95 (0.74; 1.23) | - |

| Beltran-Gonzalez 2021 | | | | | | |
|---|---|---|---|---|---|---|
| Respiratory deterioration or death, n/N (%) | | 8/36 (22.2) | 6/33 (18.1) | 9/37 (24.3) | IVM vs PLB:<br>^RR=0.91 (0.40; 2.11)<br>IVM vs HCQ:<br>^RR=1.22 (0.48; 3.15) | - |
| **Authors' conclusions: In non-critical hospitalized patients with COVID-19 pneumonia, neither ivermectin nor hydroxychloroquine decreases the number of in-hospital days, respiratory deterioration, or deaths.** | | | | | | |

**Tabela 26. Opis metodyki i wyników badania Kishoria 2020 – leczenie**

<table>
<tr><th colspan="5">Kishoria 2021</th></tr>
<tr><th colspan="5">Ivermectin as adjuvant to hydroxycholoroquine in patients resistant to standard treatment for SARS-CoV-2: results of an open-label randomized clinical study (Indian Journal Of Research 08.2020)</th></tr>
<tr><th>Methodology</th><th>Population</th><th>Intervention</th><th>Control</th><th>Limitations</th></tr>
<tr><td rowspan="4">Single-center, randomized, open-label<br><br>India<br><br>Study duration: no data</td><td rowspan="2">N=32<br>Hospitalized COVID-19 patients.<br><br><u>Inclusion criteria</u>: patients aged 18 years and above; positive test after completion of standard care treatment for SARS-CoV-2 confirmed by reverse transcriptase–polymerase-chain-reaction (RT-PCR) assay; mild/ asymptomatic; no comorbidities rendering high-risk patients; informed consent obtained<br><u>Exclusion criteria:</u> Allergy or hypersensitivity to ivermectin and/or its inactive ingredients; respiratory distress or requiring intensive care; used immunosuppressants (including systemic corticosteroids) in the last 30 days; known HIV infection with CD4 count <300 cell/ L; pregnancy or lactating patients; medical conditions such as malabsorption syndromes affecting proper ivermectin absorption; autoimmune disease and/or decompensated chronic diseases; Uncontrolled, intercurrent diseases including renal impairment, hepatic impairment, symptomatic congestive heart failure, unstable chest angina or heart arrhythmia; treated in any other study in the previous 30 days; concomitant administration of enzyme inducers (such as carbamazepine) that could affect the effectiveness of the drug and those receiving CYP3A4 substrates (such as statins) due to the risk of increased toxicity</td><td>Ni= 19<br><br>Ivermectin (12mg single dose)<br>+ SoC</td><td>Nc= 13<br><br>SoC</td><td rowspan="4">– Lack of detailed information on baseline characteristics of patients;<br>– Small sample</td></tr>
<tr><td colspan="2">standard of care:<br>5 days: hydroxychloroquine 400 mg twice a day paracetamol 500mg as required, vitamin C 1 tab twice a day</td></tr>
<tr><td>Age, mean</td><td>39.5</td><td>37.0</td></tr>
<tr><td>Female (%)</td><td>26.3</td><td>30.7</td></tr>
<tr><th colspan="5">Results</th></tr>
<tr><th colspan="2">Outcome</th><th rowspan="2">Ivermectin</th><th rowspan="2">Placebo</th><th colspan="2">Statistical significance of differences</th></tr>
<tr><th>event</th><th>follow-up period</th><th>Relative parameter (95%CI) / p</th><th>Absolute difference</th></tr>
<tr><td>PCR negativity, n/N (%)</td><td>Day 3</td><td>8/19 (42.2)</td><td>6/13 (46.2)</td><td>^RR=0.91 (0.41; 2.01)</td><td>-</td></tr>
<tr><td>Discharged patients at end of study</td><td>ND</td><td>8/19 (42.2)</td><td>6/13 (46.2)</td><td>^RR=0.91 (0.41; 2.01)</td><td>-</td></tr>
<tr><td colspan="5">Author’s conclusion: In summary,this open label randomized study of patients with COVID-19 found that the use of a regimen containing hydroxychloroquine and ivermectin was associated with no evidence of benefit in comparison to hydroxychloroquine alone. However, it was observed that ivermectin was well tolerated with no serious drug related adverse event thus a large sample sized randomized clinical trial may be initiated to further investigate its efficacy as anti-viral agent inCOVID19.</td></tr>
</table>

**Tabela 27. Opis metodyki i wyników badania Galan 2021 – leczenie**

| Galan 2021 | | | | | | |
|---|---|---|---|---|---|---|
| **Phase 2 randomized study on chloroquine, hydroxychloroquine or ivermectin in hospitalized patients with severe manifestations of SARS-CoV-2 infection (Pathogens and Global Health)** | | | | | | |
| **Methodology** | **Population** | | **Intervention** | **Control** | | **Limitations** |
| Randomized, double-blind, single-center, placebo controlled, phase 2<br><br>Brazil<br><br>Study duration: 1/05/2020 – 16/07/2020 | N=168 patients<br><br><u>Inclusion criteria</u>: laboratory test confirming infection by SARS-CoV-2 (positive serologic test IgM or rt-PCR); hospitalized with a clinical, epidemiological, and radiological picture compatible with COVID-19; over 18 years old; present a severe form of the disease characterized by one of the following clinical signs: dyspnea, tachypnea (>30 bpm), peripheral oxygen saturation <93% (pulse oximeter evaluation), PaO2/FiO2 ratio <300, or infiltrate pulmonary>50% of the parenchyma seen on chest tomography or chest radiography.<br><br><u>Exclusion criteria:</u> under 18 years old; indigenous people; patients not fluent in Portuguese; unable to understand the objectives and methods of the study; critically ill patients who are not accompanied by legal representatives; those who reject participation in the study; patients with cardiac arrhythmia that include prolongation of the QT interval; previous use of any of the medications surveyed for more than 24 h. | | Ni= 53<br><br>Ivermectin (14 mg once at day 0 + 1 placebo tablet at day 0, and once daily from day 1 to day 2, + 1 placebo tablet daily from day 3 to 4, total dose 42 mg. For participants with body weight <55 kg, IVM dose was adjusted to 10 mg each dose. | Nc1=54<br><br>Hydroxychloroquine 2x400 mg on day 0, and once daily from day 1 to day 4, total dose 2.4 g | Nc2=61<br><br>Chloroquine 2x450 mg on day 0, and once daily from day 1 to day 4, total dose 2.7 g | – High percentage of Hispanic origin people (78,9%)<br>– High percentage of patients with corticosteroids therapy |
| | Age, mean ± SD | | 53.2 (±17.3) | 54.8 (±15,5) | 51.9 (±14.0) | |
| | Male (%) | | 60.7 | 56.8 | 57.8 | |
| | Coexisting conditions (%) | Hypertension | 42.8 | 45.2 | 42.1 | |
| | | Diabetes | 28.5 | 24.5 | 28.5 | |
| | | Chronic renal failure | 4.0 | 0 | 4.0 | |
| | | Previous pulmonary disease | 3.7 | 5.5 | 3.7 | |
| | | Cancer | 4.0 | 3.7 | 4.0 | |

| Galan 2021 | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Results** | | | | | | | |
| **Outcome** | | | **Ivermectin** | **Hydroxychloroquine** | **Chloroquine** | **Statistical significance of differences** | |
| **event** | | **follow-up period** | | | | **Relative risk (95%CI) / p value** | **Absolute difference** |
| The need of oxygen supplementation (%) | | nd | 52/53 (88.4) | 49/54 (90.2) | 54/61 (88.5) | ns | - |
| Duration of oxygen need (days) (SD) | | - | 8.1 (±2.0) | 7.8 (±2.1) | 7.9 (±2.3) | - | - |
| Corticosteroid therapy (%) | | nd | 51/53 (97) | 54/54 (100) | 60/61 (98) | ns | - |
| Duration of corticosteroides treatment (days) (SD) | | - | 6.9 (±1.7) | 6.8 (±2.0) | 7.2 (±1.8) | - | - |
| Anticoagulant therapy (%) | | nd | 16/53 (30.4) | 18/54 (32.9) | 22/61 (36.7) | ns | - |
| ICU admission (%) | | | 15/53 (28.0) | 11/54 (21.1) | 14/61 (22.4) | ns | - |
| Need for vasoactive drugs (%) | | | 14/53 (26.0) | 11/54 (21.1) | 12/61 (20.6) | ns | - |
| Need for invasive ventilation (%) | | | 13/53 (23.5) | 11/54 (21.1) | 20.6 | ns | - |
| Death due to COVID complications | | nd | 12/53 (23.0) | 12/54 (22.2) | 13/61 (21.3) | IVM vs HCQ: 1.02 (0.50; 2.06)<br>IVM vs. CQ: 1.06 (0.53; 2.12) | - |
| Adverse events (%) | Arrhythmia (clinically significant) | nd | 0 | 0 | 0 | - | - |
| | Elevated liver Transminases G1/G2 | | 8/53 (14.2) | 8/54 (15.2) | 8/61 (13.4) | ns | - |
| | Elevated liver Transminases G3/G4 | | 1/53 (11.2) | 6/54 (10.2) | 5/61 (8.5) | ns | - |
| | Anemia (hemoglobin < 8 g/dL) | | 6/53 (7.8) | 3/54 (5.5) | 3/61 (5.2) | ns | - |
| | Leukopenia (<1500/mm$^3$) | | 1/53 (2.2) | 3/54 (5.5) | 2/61 (3.2) | ns | - |
| **Author's conclusion:** Although CQ. HCQ or ivermectin revealed a favorable safety profile. the tested drugs do not reduce the need for supplemental oxygen. ICU admission. invasive ventilation or death. in patients hospitalized with a severe form of COVID-19. | | | | | | | |

IVM – ivermectin; nd – no data; ns – no significant difference between the three groups

**Tabela 28. Opis metodyki i wyników badania Shah Bukhari 2021 – leczenie**

| Shah Bukhari 2021 | | | | | |
|---|---|---|---|---|---|
| **Efficacy of Ivermectin in COVID-19 Patients with Mild to Moderate Disease (MedRxiv, 5.02.2021)** | | | | | |
| **Methodology** | **Population** | | **Intervention** | **Control** | **Limitations** |
| Single-center, randomized, open-label<br><br>Pakistan<br><br>Colombia<br><br>Study duration: 15.03 – 15.06.2020 | N=100 (86 included in the analysis)<br><br><u>Inclusion criteria</u>: 15-65 years; any gender; COVID-19 positive, proven by RT-PCR; Mild (fever <38oC quelled without treatment with or without cough, no dyspnea, no gasping, no chronic disease, no imaging findings of pneumonia) to moderate (fever, respiratory symptoms, imaging findings of pneumonia) severity of the disease; consent for trial, stated their willingness to comply with all study procedures, agreed for admission for the trial period (14 days); able to take oral medication<br><u>Exclusion criteria:</u> Positive pregnancy test (all females were tested); severe symptoms likely due to cytokine release syndrome; uncontrolled co-morbidities; malignant diseases; diabetes mellitus; chronic kidney disease; cirrhosis liver with CPT class B or C; immunocompromised; history of ivermectin allergy; patients taking CYP 3A4 inhibitors or inducers; oxygen requirements equivalent to FiO2 ≥50% in moderate severity patients | | Ni= 50 (41 included in the analysis)<br><br>Ivermectin 12mg at administration | Nc= 50 (45 included in the analysis)<br><br>standard care<br>(oral vitamin C 500mg once daily, oral vitamin D3 200,000 IU once weekly, and oral paracetamol 500 mg SOS) | – No information about concomitant treatment<br>– The duration and severity of individual symptoms and time of resolution of these symptoms were not studied<br>– Most of the patients were lost to follow up after the trial period concluded and very few could be traced back to assess for any potential adverse reaction that may have occurred due to treatment with ivermectin, hence prolonged safety of drug could not be established.<br>– Publication status - preprint |
| | Age, mean ± SD | | 42.24 ± 12.0 | 38.98 ± 12.61 | |
| | Female (%) | | 9,8 | 20 | |
| | Coexisting conditions (%) | Diabetes | 14,6 | 8,9 | |
| | | Hypertension | 12,2 | 15,6 | |
| | | Ischemic heart disease | 7,3 | 4,4 | |

| **Results** | | | | | |
|---|---|---|---|---|---|
| **Outcome** | | **Ivermectin** | **Placebo** | **Statistical significance of differences** | |
| **event** | **follow-up period** | | | **Relative parameter (95%CI) / p** | **Absolute difference** |
| PCR negativity, n/N (%) | 72 hours | 17/41 (41,1) | 2/45 (4,4) | RR=9,32 (2,29; 37,9)^ | NNT=3 |
| | 7 days | 20/41 (49,9) | 18/45 (40,0) | RR=1,21 (0,76; 1,97)^ | - |
| | 14 days | 4*/41 | 25/45 (55,6) | * | - |
| Adverse side effects | 14 days | - | - | - | - |
| | 28 days | - | - | - | - |
| **Author's conclusion: In the intervention arm, early viral clearance was observed in patients without experiencing any side effects. These are of importance because high viral load and prolonged viremia can potentially trigger the immune dysregulation phase leading to more severe disease, and the requirement of treatment escalation.** | | | | | |

**Tabela 29. Opis metodyki i wyników badania Pott-Junior 2021 – leczenie**

| | Pott-Junior 2021 | | | | | |
|---|---|---|---|---|---|---|
| | Use of ivermectin in the treatment of Covid-19: A pilot trial (NCT04431466, ELSEVIER, 09.03.2021) | | | | | |
| **Methodology** | **Population** | **Intervention 1** | **Intervention 2** | **Intervention 3** | **Control** | **Limitations** |
| RCT, double-blind, phase 2a<br><br>Brazil | N=32<br><br>Inclusion criteria: 18 years and older; an Eastern Cooperative Oncology Group (ECOG) score of 0-1; a National Early Warning Score (NEWS) of 0-4; and had SARS-CoV-2 infection confirmed by real-time reverse transcription polymerase chain reaction (RT-PCR) testing performed on nasopharyngeal swab specimens.<br>Exclusion criteria: Not able to ingest / absorb the drug orally through spontaneous ingestion or by gastro / enteral tubes; any clinical observation (clinical / physical evaluation) or laboratory findings which, in the investigators opinion, would have put the patient at risk to participate in the study; any abnormal ECG findings that require additional evaluation; known hypersensitivity to the drug components used during the study; pregnancy or breastfeeding; body weight less than 15 kg; an estimated glomerular filtration rate (CKD-Epidemiology Collaboration, CKD-EPI) below 30 mL/min; and values of aspartate aminotransaminase (AST) or alanine aminotransaminase (ALT) 5-fold above the upper limit of normality. | N1=7<br><br>Ivermectin + SoC: 100 mcg/kg | N2=14<br><br>Ivermectin + SoC: 200 mcg/kg | N3=7<br><br>Ivermectin + SoC: 400 mcg/kg | N4=4<br><br>SoC | – Small sample<br>– No detail information on intervention used as standard of care |
| | Age [years] mean (±SD) | 50 ±9 | 49 ± 13.5 | 47 ± 22.9 | 54.2 ±9.6 | |
| | Female, % | 66.7 | 35.7 | 57.1 | 54.8 | |
| | Time from symptom onset to hospital admission, days | 7 | 8 | 9 | 9.5 | |
| | Concomitant medications, % – LMWH – intermediary dose | 16.7 | 35.7 | 0 | 25 | |
| | Concomitant medications, % – Antibiotics | 16.7 | 35.7 | 100 | 75 | |
| | Concomitant medications, % – Steroids | 16.7 | 35.7 | 14.3 | 75 | |

| **Results** | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Outcome** | | **IVM 100** | **IVM 200** | **IVM 400** | **SoC** | **Statistical variability of differences** | |
| **event** | **follow-up period (days)** | | | | | **relative parameter* (95% CI)/p** | **absolute parameter** |
| Undetectable levels of SARS-CoV-2* – n/N (%) | | 3/6 (50) | 10/14 (71.4) | 4/7 (57.1) | 2/3 | - | - |
| Time to achieve undetectable viral load, days | - | 6 | 5 | 5 | 6 | - | |
| Total adverse events – n/N (%) | | 1/7 (16.7) | 5/14 (35.7) | 1/7 (14.3) | 2/4 (50) | - | - |
| **Authors' conclusions: Ivermectin is safe in patients with SARS-CoV-2, reducing symptomatology and the SARS-CoV-2 viral load. This antiviral effect appears to depend on the dose used, and if confirmed in future studies, it suggests that ivermectin may be a useful adjuvant to the SOC treatment in patients with mild COVID-19 symptoms.** | | | | | | | |

*Defined as defined as two consecutive SARS-CoV-2 RT-PCR tests with negative results (Ct above 40) within 7 days of the start of study dosing period.

Comment: Due to very low sample AOTMiT did't calculate parameters

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